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Research Article

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Investigation of anti neutrophil cytoplasmic antibody presence with indirect immunofluorescence and enzyme-linked immunosorbent assay

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Abstract

Anti-neutrophil cytoplasmic antibodies (ANCA) are a family of autoantibodies that react with proteins expressed mainly in cytoplasmic granules of polymorphonuclear neutrophil granulocytes (PMNs). The ANCA test is used to diagnose small vessel vasculitis and to monitor inflammatory activity. ANCA was initially detected using indirect immunofluorescence (IIF), which allowed differentiation of different patterns, such as p-ANCA (perinuclear) and c-ANCA (cytoplasmic). It is now common to detect antibodies by immunochemical assays using purified proteins, such as Enzyme-Linked Immunosorbent Assay (ELISA). In our study, we evaluated ANCA test results studied with IIF and ELISA methods and recorded patient diagnoses in the system. Serum samples of 4524 patients who were thought to have autoimmunity in their etiology were evaluated for ANCA presence. In accordance with the recommendation of the manufacturer (Euroimmun AG, Lübeck, Germany), serum IFA technique was evaluated for the presence of p-ANCA, c-ANCA. ELISA test (Alegria, Orgentec) was used to detect antibodies against MPO and PR3. The number of ANCA IIF positive patients was 525(11.6%). When we look at the distribution of ANCAs, 275(52.5%) formalin sensitive pANCA, 95 (18%) formalin resistant pANCA, 60 formalin sensitive cANCA(11.5%), 95(18%) formalin resistant cANCA. 18 (3.4%) of ANCA IIFA positives had PR3 antigen and 22 (4.1%) had significant antibody elevation against MPO antigen., ANCA IIF positive samples, according to the diagnosis of information registered in the operating system, consist of 424 (80.8%) autoimmune and inflammatory diseases according to disease groups, 36 (6.9%) malignancies, 18 (3.4%) infectious diseases, 47 (8.9%) are other diseases which are not included in these groups. ANCA is a determinant for many diseases, especially vasculitis. ANCA, which we found in a large number of different disease groups, was found to be an indicator that should be used in the diagnosis and follow-up of many autoimmune and inflammatory diseases.

Keywords: antineutrophilcytoplasmic antibodies, immunofluorescence, proteinase 3, myeloperoxidase

1. Introduction

Anti-neutrophil cytoplasmic antibodies (ANCA) are IgG autoantibodies directed mainly against the components of primary granules of neutrophils and monocyte lysosomes. Although several antigenic targets have been identified, those ANCA directed to proteinase 3 (PR3) or myeloperoxidase (MPO) are clinically relevant, whereas the importance of other ANCA remains unknown. Although ANCA can be found in multiple autoimmune diseases, the recognition that proteinase 3 (PR3) and myeloperoxidase (MPO) are the dominant autoantigens in small-vessel vasculitis has linked ANCA testing with the so-called ANCA-associated vasculitides (AAV; granulomatosis with polyangiitis, microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis) (1). ANCA also occur in 30-40% of patients with eosinophilic granulomatosis with polyangiitis (EGPA) and anti-GBM disease, but is uncommon in other forms of vasculitis. ANCA with different specificities have been described with varying frequencies in diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis, inflammatory bowel disease, endocarditis, chronic infections and hematopoietic malignancies. ANCA can also develop as an adverse event during pharmacological treatment (2). ANCA was initially detected by indirect immunofluorescence (IIF) in ethanol-fixed neutrophils that appeared as two major patterns as granular cytoplasmic staining (CANCA) or perinuclear staining (P-ANCA). Today, it is common to detect antibodies by immunochemical analyses such as ELISA that use purified proteins as antigens (3,4). The minimum requirements for AAV screening with IIF on neutrophils stabilized with ethanol and, if positive, follow up with antigen-specific enzyme-linked immunosorbent assays (ELISA) enabling detection of PR3- and MPO-ANCA (5). In our study, we evaluated only the test results studied in our immunology laboratory between January 2016 and July 2018 and the patient's diagnostic records.

2. Materials and Methods

In this study, results obtained from serum samples to be studied sent to the Immunology Laboratory of Ondokuz Mayıs University Faculty of Medicine between January 2016-July 2018 and patient diagnoses recorded in the system were retrospectively examined. Serum samples of 4524 patients who

were considered to have autoimmunity in etiology were evaluated in terms of their presence. In accordance with the proposal of the manufacturer (Euromun AG, Lübeck, Germany), serums were irrigated at 1/10 for P-ANCA, c-ANCA with IFA technique. The samples were brought to room temperature before they were studied and worked in accordance with the application procedures of the manufacturer. In these slides, three different areas were evaluated for each sample by solid phase consisting of hep-2 cells, human granulocytes and formalin flaked with ethanol and human granulocytes. In addition to the ANCA, these areas allowed the study of the anti-nuclear antibody (ANA) positivity. In this way, all the fields were evaluated in terms of the separation of two antibodies from each other. Human granulocytes fixed with ethanol were used to differentiate between cANCA or pANCA.P-ANCA formaldehyde resistance status was evaluated with formaldehyde fixated neutrophils. ELISA test (Alegria, Orgentec) was used to detect antibodies against MPO and PR3. This study was found ethically appropriate by the Ondokuz Mayıs University Clinical Research Ethics Committee on 11.03.2021 with the decision number OMUKAEK 2021/68.

3. Results

In our study, the results of 4524 patients whose serum samples were tested for ANCA IFA who were admitted to the Immunology Laboratory of Ondokuz Mayıs University Hospital between January 2016 and July 2018 were evaluated retrospectively. The number of ANCA IFA positive patients without recurrence was 525 (11.6%). The distribution of ANCAs was 275 (52.5%) formalin sensitive pANCA, 95 (18%) formalin resistant pANCA, 60 (11.5%) formalin sensitive cANCA, 95 (18%) formalin resistant cANCA. In 18 (3.4%) of the ANCA IFA positive samples, significant antibody level was detected against PR3 antigen and MPO antigen in 22 (4.1%). Of the ANCA-positive patients, 222 (%42.2) were male and the average age was 47.1 and the number of female positive patients was 303 (%47.8) and the average age was recorded as 49,03. When we classified ANCA IFA positive samples according to disease groups based on information registered in the hospital information system, there were 424 (80.8%) autoimmune and inflammatory diseases, 36 (6.9%) malignancies, 18 (3.4%) infectious diseases, 47 (8.9%) are the other diseases that are not included in these groups (Fig. 1). Of the autoimmune and inflammatory diseases, 27 (6.3%) were chronic lung disease, 13 (3.4%) were chronic liver disease, 54 (12.7%) were chronic renal failure, 89 (20%, 9) were diabetes mellitus, 31 (7.1%) were inflammatory bowel disease, 21 (4.9%) were connective tissue disease, 34 (8%) were rheumatoid arthritis, 23 (5.4%) were systemic lupus erythematosus, 16 (3.7%) were iridocyclitis, 5 (1.1%) were ankylosing spondylitis, 11 (2.1%) were Wegener granulomatosis, 2 (0.4%) were microscopic polyangiitis Takayasu's arteritis, 1 (0.2%) was temporal arteritis, 4 (0.9%) were Sjogren syndrome, 24 (5.6%) were undefined vasculitis, 67 (% 15,8) had the other group of autoimmune and inflammatory diseases (Fig. 2).

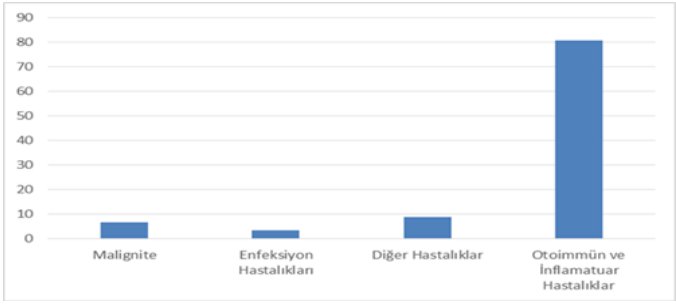

Fig. 1. Distribution of ANCA positive samples by patient groups

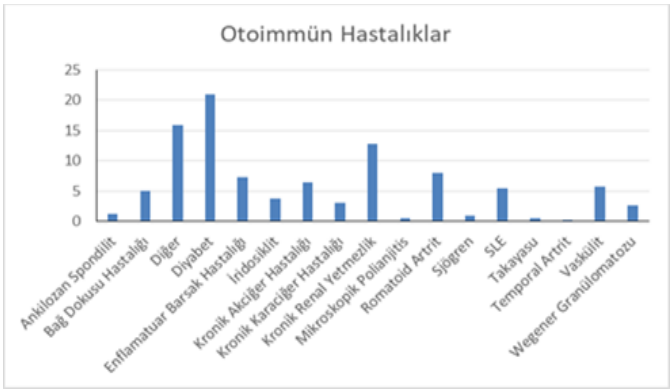

Fig. 2. Distribution of ANCA positive autoimmune and inflammatory diseases

4. Discussion

Antineutrophil cytoplasmic antibodies (ANCA) have been accepted as clinically relevant autoantibodies for more than 50 years. ANCA were originally detected by indirect immunofluorescence (IIF) on ethanol fixed neutrophils revealed as two major patterns; granular cytoplasmic staining (C-ANCA) or perinuclear staining (P-ANCA). Although it can be found in multiple autoimmune diseases, proteases 3 (PR3) and myeloperoxidase (MPO) are considered dominant autoantigens in small vascular vasculitis. However, less well-defined antigen specifities, also added value in the diagnosis of inflammatory bowel diseases and autoimmune liver diseases (6). Özdemir et al. obtained 11.4% ANCA positivity in patients by IIFA method in their study. Similarly, in our study, the positivity rate of ANCA by IIFA method was determined as 11.6%. When Özdemir et al. examined the diagnosis of patients who were positive for ANCA, they found that chronic lung diseases, connective tissue diseases, arthritis and systemic diseases were the most frequent (7). In our study, the most frequent diseases in the patients were diabetes mellitus, chronic kidney failure, rheumatoid arthritis and inflammatory bowel diseases. Polymorphonuclear neutrophils and inflammatory process play an important role in the development of late diabetic vascular complications. ANCA are considered important serological markers for vasculitis (8). In our study, diabetes was diagnosed in 20.9% of ANCA positive patients. In this respect, ANCA may be a predictor of vascular complications that may develop in diabetic patients. ANCA has been reported to be present in a wide variety of inflammatory conditions. In some diseases, ANCA positivity

has been shown to correlate with some features. A chronic and systemic inflammatory disease, rheumatoid arthritis (RA) is characterized by cartilage erosion, bone damage, and a chronic synovitis that can cause fibrous ankylosis of the joints. In patients with RA, ANCA has occurred against cytoplasmic antigens of neutrophils, especially to lactoferrin (LF), and not yet fully defined some polypeptides (9). In a study performed by Bandt et al. 32% of RA patients were found to be P-ANCA or atypical ANCA positive by IFA method (10). In the study of Özdemir et al., 4 of 44 patients who were positive for ANCA were found to be RA (7). In our study, the diagnosis of RA was 8% among all cases. Systemic lupus erythematosus (SLE) is a rheumatic disease that primarily affects young women. Inflammation and organ damage occurs when the immune complexes accumulate along the walls of the arteries (11). There are a number of antibodies in SLE, and some of them have been reported to show ANCA specificity with frequency of 25%. It has been shown that the ANCA positivity in SLE is correlated with both disease activity and severity (12). In our study, 3.7% of ANCA positive patients were being followed up with the diagnosis of SLE. Besides vasculitis, ANCA has been studied in inflammatory bowel disease (IBD). In addition to some other autoantibodies, ANCAs have been shown to be more common among IBD patients than healthy controls, but their benefits as a biomarker and their possible role in the pathogenesis are discussed. In the study performed by Kılıç et al., P-ANCA was found to be positive in 65% of UC and 2.5% of healthy persons (13). The diagnosis of inflammatory bowel disease was 7.1% in our study. ANCA is a prognostic marker which should be investigated in many diseases, especially vasculitis. It is concluded that ANCA is an indicator that should be routinely monitored in both the diagnosis and the follow-up of many autoimmune diseases. On the other hand, our data support the diagnosis of 0.8 % small vessel vasculitis as a result of the ANCA tests as a supportive laboratory examination of patients with a preliminary diagnosis of small vessel vasculitis. This situation reveals the necessity of reviewing the cost-effective usage policies of ANCA tests in our hospital.

Conflict of interest

The authors have no conflict of interest.

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Research Article

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Volume fraction of the cerebellum in Parkinson's patients

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Abstract

Most investigations on Parkinson's disease (PD) focus on the basal ganglia and brainstem, whereas the cerebellum has often been overlooked. The cerebellum is critical for motor control and increasing evidence suggests that it may be associated with the pathophysiology of PD. The aim of this study was to describe cerebral and cerebellar volumes in patients with PD and to compare results with healthy subjects. In the present study, 18 patients with PD (8 female, 10 male) and 19 controls (9 females, 10 males) were included. Structural magnetic resonance (MR) imaging was performed in both groups with a 1.5 Tesla scanner. The images were analyzed using ImageJ software. Volumes were estimated via planimetry and threshold stereological methods. The mean total cerebral volumes were 943.19 ± 91.67 cm^3 in control group and 909.83 ± 95.88 cm^3 in patients. The mean total cerebellar volumes and the volume fractions were found 140.44 ± 21.68 cm^3, 14.94 ± 2.17 % in control group and 140.52 ± 15.96 cm^3, 15.52 ± 1.73% in patients, respectively. There were no significant differences found in terms of cerebral and cerebellar parameters. Our knowledge about cerebellum and PD interaction remains limited, although, the cerebellum is a potential target for some parkinsonian symptoms. Further investigations are needed to understand the role of cerebellum in PD using newly developing imaging techniques.

Keywords: Parkinson's disease, cerebellum, volume fraction, planimetry, magnetic resonance

1. Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder, leads to resting tremor, stiffness, slowness and impaired balance. Loss of dopaminergic neurons in pars compacta of subtantia nigra is regarded as the main pathophysiologic mechanism (1). However, this classic model of the disease is not adequate in explaining of all the symptoms of PD, for example resting tremor (2). It is likely that basal ganglia is not the only responsible structure in disease development (1-3). New researches determine different connections besides the traditional assumption that, the cerebellum and basal ganglia are separate anatomic structures and have indirect connections at the cortical level (4-5). Results from recent anatomical studies indicates direct synaptic pathways between the cerebellum and the basal ganglia structures (5). Both the cerebellum and the basal ganglia have a role in motor and non-motor behaviours. Because of their dense and reciprocal interactions suggest the involvement of cerebellum in disease manifestations (3). Most investigations on PD focused on the basal ganglia and other cortical structures, whereas the cerebellum has often been overlooked (6). Cerebellum may contribute to the symptoms or may be influenced by the PD (7).

Although Parkinson's disease is diagnosed clinically, brain imaging methods are used excluding the alternative pathologies (8). Magnetic resonance (MR) imaging, because of allowing *in vivo* accurate measurements, is under consideration to be helpful in understanding the morphological changes in the brain during the disease. In recent years, numerous volumetric studies were conducted using different measurement techniques on MR images (9). Nevertheless, the results remain inconsistent and studies on cerebellum are few (10, 11).

Therefore, the aim of this study was determined to describe and compare the cerebral volume and the cerebellar volume and the volume fractions in Parkinson's patients comparing with controls using MR imaging-based analysis.

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2. Material and Methods

2.1. Ethical Statement

This study was carried out with the permission of the Medical Research Ethics Committee of Ondokuz Mayıs University. Written informed consent was obtained from all subjects before the procedures.

2.2. Participants

In the present study the total of 37 subjects, 19 control (9 females, 10 males) and 18 Parkinson's patients (8 females, 10 males) were participated. The mean ages of males and females in controls and patients were 54.89±6.82, 55.50±6.67 and 54.50±6.43, 59.20±4.54 years-old, respectively

2.3. Exclusion criteria

Patients with Parkinsonian/Parkinson plus syndromes and other neurodegenerative diseases, dementia and history of prior neurological disorder were excluded from the study. Patients with motion artifacts on their brain scans were excluded, although they had fulfilled the inclusion criteria.

2.4. Image processing and sampling

Structural magnetic resonance imaging was done the subjects using 1.5 Tesla (T) scanner (Philips, Achieva, The Netherlands). The image thickness was 1.1 mm. DICOM images were transferred to the ImageJ software and then converted into stack, the images were in coronal plane, which used for the measurements of the cerebral hemispheres. Second stack was obtained in sagittal plane with 1 mm in thickness for the measurement of the cerebellum. Systematic random sampling was done. The sampling fraction was 1/10 and 1/5 for the cerebrum and the cerebellum, respectively.

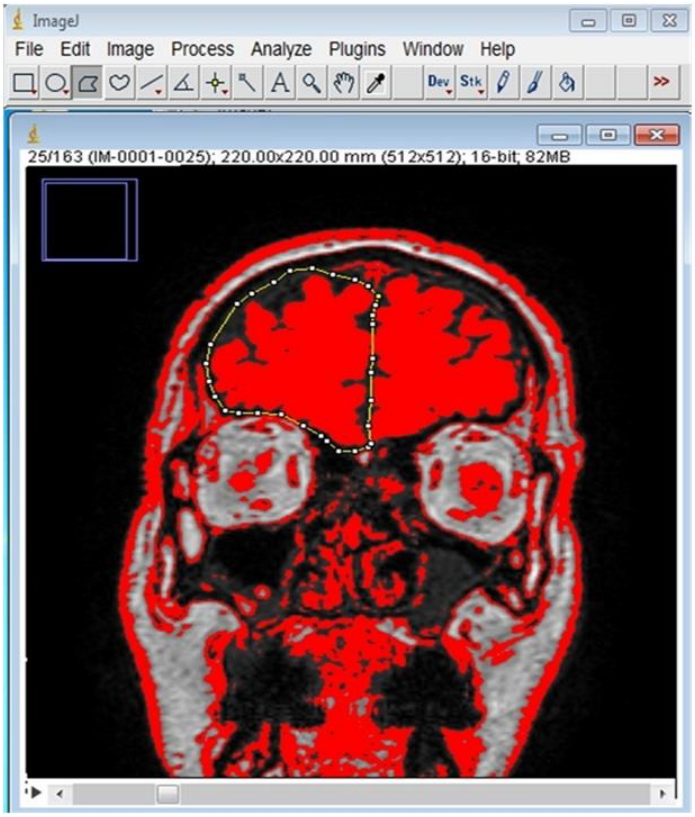

Fig. 1. Delineation of contour of the right cerebral hemisphere using the planimetry and the thresholding methods

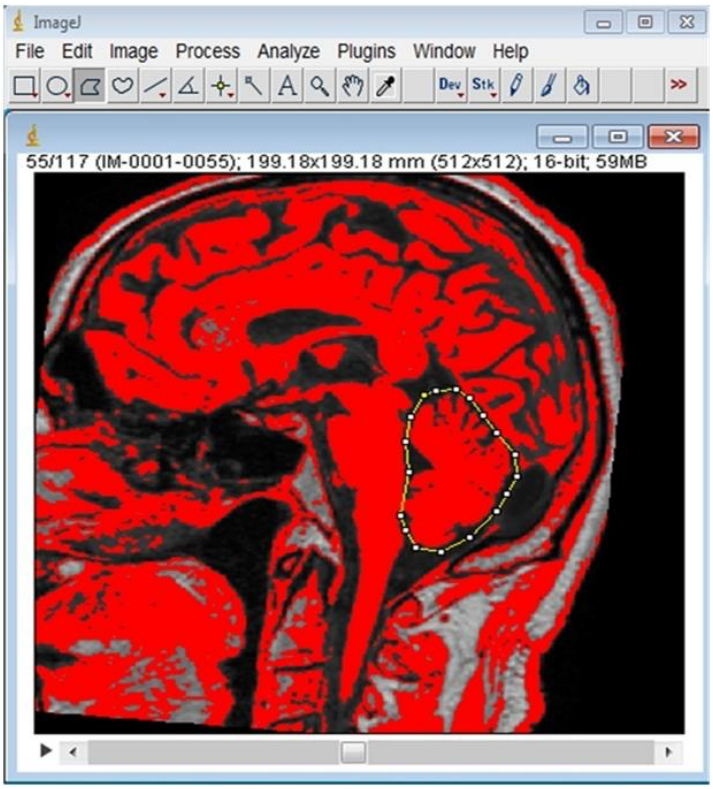

Fig. 2. Delineation of contour of the cerebellar hemisphere using the planimetry and the thresholding methods

Using thresholding, the cerebral and cerebellar hemispheres were determined using upper and lower limits of the structures. Delineations of the cerebral and the cerebellar hemispheres in coronal and sagittal sections on ImageJ software interface, respectively were given in Fig. 1 and 2. Planimetry method of the stereological techniques was done, the regions of interests were delineated (12). T1 weighted images were used for manual tracing of the borders of cerebrum and cerebellum. Finally, the delineated areas were measured and volume and volume fractions were calculated.

2.5. Statistical analysis

All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used for determining whether variables are normally distributed. Data are given as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables. Continuous variables were analysed with the two-way analysis of variances (ANOVA). Sex distribution between cases was evaluated with the Chi-square test. Two tailed p-values of less than 0.05 were considered statistically significant.

3. Results

We included 37 individuals (19 controls and 18 patients) into our study, mean age was 56.14 ± 6.20 (range 45 – 65). There was no significant difference between cases with regard to the age (p=0.421). There were 9 (47.37%) females and 10 (52.63%) males in the controls group while there were 8 (44.44%) females and 10 (55.56%) males in the patient's group. There was no significant difference between cases with regard to sex distribution (p=1.000). As a result of the analysis

of the cerebellar volumes, cerebral volumes and the volume fractions, we found no significant differences between the cases. Summary of the individuals' characteristics and measurements with regard to cases is given in Table 1.

Table 1. Summary of individuals' characteristics and measurements with regard to cases

	Cases			
	Control (n=19)	Patients (n=18)	Total	p
Age (year)	55.21 ± 6.56	57.11 ± 5.81	56.14 ± 6.20	0.421
Female	9 (47.37%)	8 (44.44%)	17 (45.95%)	1.000
Male	10 (52.63%)	10 (55.56%)	20 (54.05%)	
Right Hemisphere Cerebellar Volume (cm^3)	68.73 ± 10.67	68.50 ± 8.71	68.62 ± 9.63	0.910
Right Hemisphere Cerebral Volume (cm^3)	474.90 ± 45.65	455.65 ± 46.31	465.53 ± 46.36	0.111
Volume Fraction of the Right Cerebellum (%)	14.52 ± 2.17	15.09 ± 1.79	14.80 ± 1.98	0.375
Left Hemisphere Cerebellar Volume (cm^3)	71.72 ± 11.46	72.01 ± 7.82	71.86 ± 9.73	0.967
Left Hemisphere Cerebral Volume (cm^3)	468.29 ± 47.03	454.19 ± 51.28	461.43 ± 48.98	0.222
Volume Fraction of the Left Cerebellum (%)	15.37 ± 2.35	15.96 ± 1.85	15.66 ± 2.11	0.353
Total Cerebellar Volume (cm^3)	140.44 ± 21.68	140.52 ± 15.96	140.48 ± 18.85	0.968
Total Cerebral Volume (cm^3)	943.19 ± 91.67	909.83 ± 95.88	926.96 ± 93.96	0.153
Volume Fraction of the Cerebellum (%)	14.94 ± 2.17	15.52 ± 1.73	15.22 ± 1.97	0.345

Data are given as mean ± standard deviation and as frequency (percentage) for categorical variables; p values were obtained by two-way analysis of variances with cases and sex

Total cerebellar volume (mean ± standard deviation) with regard to the cases was given in Fig. 3. Volume fraction of the cerebellum (mean ± standard deviation) with regard to the cases were given in Fig. 4.

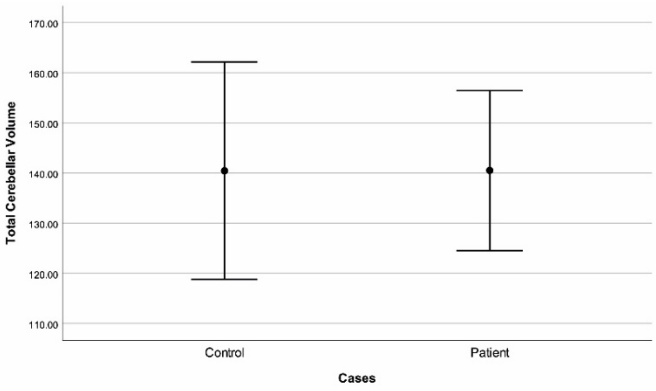

Fig. 3. Total Cerebellar Volume (mean ± standard deviation) with regard to the cases

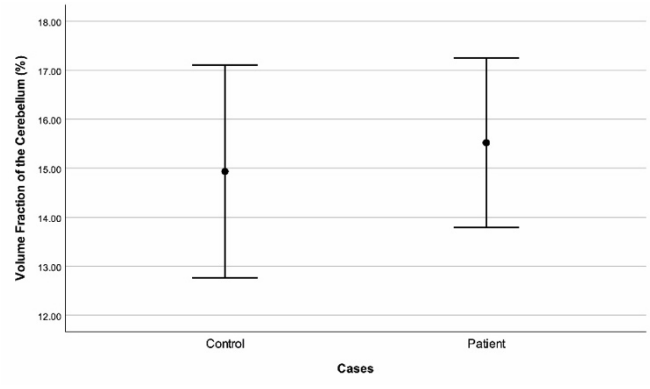

Fig. 4. Volume Fraction of the Cerebellum (mean ± standard deviation) with regard to the cases

The right hemisphere cerebral volume, left hemisphere cerebellar volume, left hemisphere cerebral volume, total cerebellar volume and the total cerebral volume were significantly higher in the males compared to females. On the other hand, there was no significant difference found between sexes with regard to age, right hemisphere cerebellar volume, volume fraction of the right cerebellum, volume fraction of the left cerebellum and volume fraction of the cerebellum.

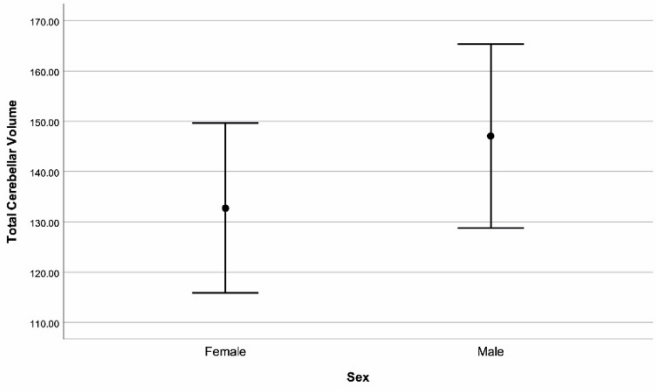

Fig. 5. Total Cerebellar Volume (mean ± standard deviation) with regard to sex

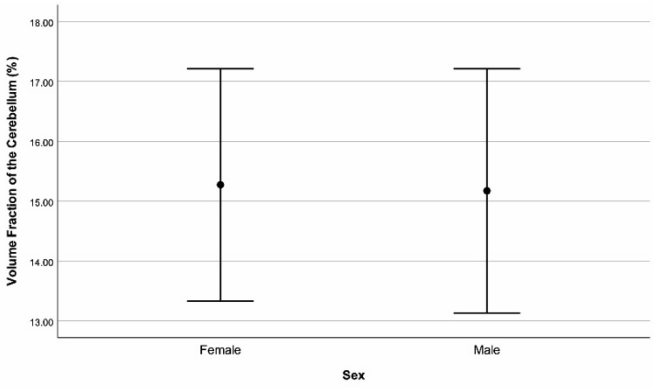

Fig. 6. Volume Fraction of the Cerebellum (mean ± standard deviation) with regard to sex

Also interactions between cases and sexes found as non-significant for all variables that means differences between sexes are independent from presence of Parkinson's disease (presence of Parkinson's disease has no effect on differences between sexes). Summary of individuals' characteristics and measurements with regard to sex is given in Table 2. Total

cerebellar volume (mean ± standard deviation) with regard to sex is given in Fig. 5. Volume fraction of the cerebellum (mean ± standard deviation) with regard to sex is given in Fig. 6

Table 2. Summary of individuals' characteristics and measurements with regard to sex

	Sex			
	Female (n=17)	Male (n=20)	p (sex)	p (cases*sex)
Age (year)	54.71 ± 6.44	57.35 ± 5.87	0.200	0.322
Right Hemisphere Cerebellar Volume (cm^3)	65.82 ± 9.15	70.99 ± 9.62	0.115	0.955
Right Hemisphere Cerebral Volume (cm^3)	438.68 ± 37.36	488.36 ± 41.28	<0.001	0.694
Volume Fraction of the Right Cerebellum (%)	15.04 ± 1.92	14.60 ± 2.07	0.496	0.757
Left Hemisphere Cerebellar Volume (cm^3)	66.90 ± 8.05	76.08 ± 9.15	0.004	0.700
Left Hemisphere Cerebral Volume (cm^3)	433.38 ± 40.74	485.27 ± 42.96	<0.001	0.225
Volume Fraction of the Left Cerebellum (%)	15.53 ± 2.11	15.77 ± 2.16	0.784	0.192
Total Cerebellar Volume (cm^3)	132.72 ± 16.89	147.07 ± 18.26	0.023	0.826
Total Cerebral Volume (cm^3)	872.06 ± 77.16	973.63 ± 82.01	<0.001	0.404
Volume Fraction of the Cerebellum (%)	15.27 ± 1.94	15.17 ± 2.04	0.839	0.401

Data are given as mean ± standard deviation and as frequency (percentage) for categorical variables
p values were obtained by two way analysis of variances with cases and sex

4. Discussion

Today, it is as of yet unknown whether cerebellar involvement is present in patients with PD (13). Conflicting results have been obtained in the few publications that have evaluated cerebellar volumes with volumetric MRI measurements (6). In this study, we aimed to address these controversial findings by comparing healthy subjects and patients with idiopathic PD in terms of volumetric MRI results. Our findings showed no significant differences between the two groups. Additionally, although we found that males had significantly larger right hemisphere cerebral volume, left hemisphere cerebellar volume, left hemisphere cerebral volume, total cerebellar volume and total cerebral volume when compared to females; detailed statistical analyses demonstrated that the presence of PD had no effect on these differences between the sexes. The study by Bharti et al., which was performed via voxel-based morphometry in 31 patients with PD, was in agreement with our results and showed no significant differences in the grey matter volume of cerebellar locomotor region, fastigial nucleus and dentate nucleus seed regions between Parkinson disease patients and healthy subjects. However, in the subgroup comparison of subjects with and without freezing of gait (FOG), the authors determined that PD patients had higher functional connectivity within these regions compared to healthy subjects (14). In another study, Ma et al. reported similar cerebellum volumes in patients with tremor-predominant PD and those with akinetic/rigidity-predominant PD (15).

There are also studies that report different results. For instance, in a voxel-based morphometry study, O'Callaghan et al. reported loss of grey matter throughout the cognitive and motor regions of the cerebellum in patients with PD, and more importantly, identified a significant inverse correlation between cerebellar connectivity and grey matter volume (16). Gao et al. also reported changes in volumetric measures in PD; their results showed that PD patients with normal cognition had loss in the posterior cerebellum, whereas those with mild cognitive impairment had loss in the anterior cerebellum (both comparisons relative to healthy subjects) (17). The cerebellar peduncle was also determined to demonstrate PD-related reduction in size when a subgroup of patients who had sleep disorder were compared with healthy subjects by Radziunas et al. (18).

We believe that the variations in previously reported results and the differences regarding our findings may be explained by several factors. The fact that the number of patients were higher in previous studies could have caused statistically-relevant differences; furthermore, in prior studies, the significant differences were mostly found in the comparison of healthy subjects with specific subgroups of patients with PD (such as those with FOG, mild cognitive impairment and sleep disorder). Today, it is well known that the cerebellum is not limited to the modulation of balance, with studies showing its relationships with cognition. For instance, several clinical/anatomical studies as well as functional MRI findings have shown that the posterior lobe of the cerebellum, particularly the crus I and crus II lobules, connect with the frontal cortex (19-21). Therefore, it is possible that more specific measurements of the effected regions could result in more accurate findings. Considering the limited number of patients and insufficient clinical data, we did not perform subgroup analyses in the present study. This characteristic may be identified as the primary limitation of our study; however, it must be noted that previous studies have not found any common results in terms of the change and localization of volumetric differences. Additionally, studies that determined significant alterations included considerably older PD patients, suggesting longer duration with disease; whereas, our results were performed in younger patients (average age: 57.1 years).

In this study, the cerebellum volumes were compared between Parkinson patients and healthy controls. No significant differences were found neither in the cerebrum volumes nor the cerebellum volumes between the groups as measured by a 1.5 Tesla MRI scanner. Lack of significance might be the result of relatively small sample size or limitations of the imaging method or volume estimations.

There are still controversial opinions about whether the

cerebellar volume is affected in PD. The literature data about the cerebellum and PD interaction remain limited, even though the cerebellum is potentially associated with the symptoms of PD. The further studies with higher number of subjects or more advanced imaging modalities are needed to clarify PD–related pathological alterations in the cerebellum and to determine the way in which cerebellar pathologic and compensatory effects change as the disorder progresses.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

None to declare.

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A morphometric evaluation of anterior fontanel and cranial sutures in infants using computed tomography

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Abstract

To retrospectively analyze anterior fontanel (AF) and the morphometric findings of cranial sutures in infants under two years of age who underwent cranial computed tomography (CT). A total of 227 cases, who had cranial CT examination, were studied retrospectively. Forty-five patients were excluded. The study was conducted with 182 patients who had adeqaute imaging with optimum quality. The diameter and area of AF and cranial sutures of the patients were measured using three-dimensional CT reformat and axial CT images. Male patients made up 53.8% of the total patients and the median age was 6 months. Normocephaly in 86.3%, plagiocephaly in 10.4%, scaphocephaly in 2.7% and trigonocephaly in 0.5% of the cases were present. The median AF transverse diameter was 29.75 mm, the median anteriorposterior diameter was 27.25 mm, and the median fontanel area was 400 mm^2. AF was closed in 30.4% in 13-18 months old patiets and 85.7% in 19-24 months old patients. Metopic suture was closed 10% in the first 3 months of age / their lives, 74.3% in 7-9 months of age, and 100% in 19-24 months of age. There was a significant negative correlation between head circumference and suture diameters in infants with open and normosephalic AF, in the CT examination ($p < 0.05$. R = - 0.106 -0.271). In this study, it was observed that 14.3% of AF did not close radiologically in 19-24 months in the Turkish population living in the Europe - Balkan region. This suggests that AF closes in some patients after the age of two.

Keywords: infant, cranial fontanel, computed tomography, anterior fontanel

1. Introduction

At birth, a baby has six fontanelles as anterior, posterior, two mastoids and two sphenoids. It is known that mastoid, sphenoid, posterior fontanelles ossify at 6 months or earlier (1,2) and the anterior fontanel (AF) ossify at around 18 months old (1,3). AF is the largest and most important fontanel in the newborn, consisting of a rhomboid non-mineralized fibrous membrane located between the frontal and parietal bones (4-6). This fibrous area provides enough flexibility to allow the brain to grow and the head to pass through the birth canal during birth without putting pressure on the skull (7).

There is a variation in the basic characteristic of a normal AF and it may differ according to populations and races. AF is on average 2.1 cm (0.6 - 3.6 cm) on the first day of life, and black babies have larger fontanelles (1.4 - 4.7 cm). AF closure (AFC) usually occurs within the first two years of life, with some studies reporting average closure times of 13-16 months. It can close in the first few months of life and the median age of closure is 13.8 months. When babies are three months old, 1% AF closes; 38% by 12 months and 96% by 24 months. AF tends to close earlier in boys than in girls (3, 8, 9).

Cranial sutures are a type of hyaline cartilage joint with a fibrous structure that occurs only in the skull, and is called synchondrosis. In a study conducted by Caffey et al. with an X-ray in 1978, it was reported that the metopic suture usually closes at the age of six, but may not close in 10% of the patients until adulthood (10). Vu et al. conducted a three-dimensional cranial computed tomographic (CT) study in 2001. This study showed that metopic (or frontal) suture fusion can normally occur at 3 months of age, and complete fusion can occur at 9 months of age. This proved that 3D CT scans can be used at an early age (3-9 months). Complete closure of the suture cannot be considered as evidence of metopic synostosis (11).

The sagittal suture is typically the suture that closes at the age of about 22 years, the coronal suture at approximately 24 years and the lambdoid and squamous sutures at approximately 26 and 60 years, respectively (12).

It is recommended to evaluate the size of AF using the index finger in the physical examination proposed by Popich (1972). However, in recent years, cross-sectional imaging methods have been more useful to accurately evaluate morphometric properties such as fontanel size and closure.

In this study, we aimed to examine the morphometric findings of AF and sutures in infants under two years of age with cranial CT.

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2. Materials and Methods

2.1. Ethical statement

The study was designed as a retrospective study which has been approved by local ethical committee of Tekirdag Namık Kemal University, Faculty of Medicine, Tekirdag, Turkey (Approval number: 2020.261.12.06). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's human research committee.

2.2. Patient population

A total of 227 patients, with cranial CT examination, were studied retrospectively between February 2019 and February 2021. Forty-five patients were excluded from the study due to the following reasons: fifteen hydrocepahy, two bilateral subdural effusion, one hydrocepahly and hemorrhage, twenty-two CT images with motion artifacts, two inadequate imaging, one anencepahy and one parenchymal hemorrhage. The remaining 182 patients with optimum imaging quality were included in the study (Fig. 1).

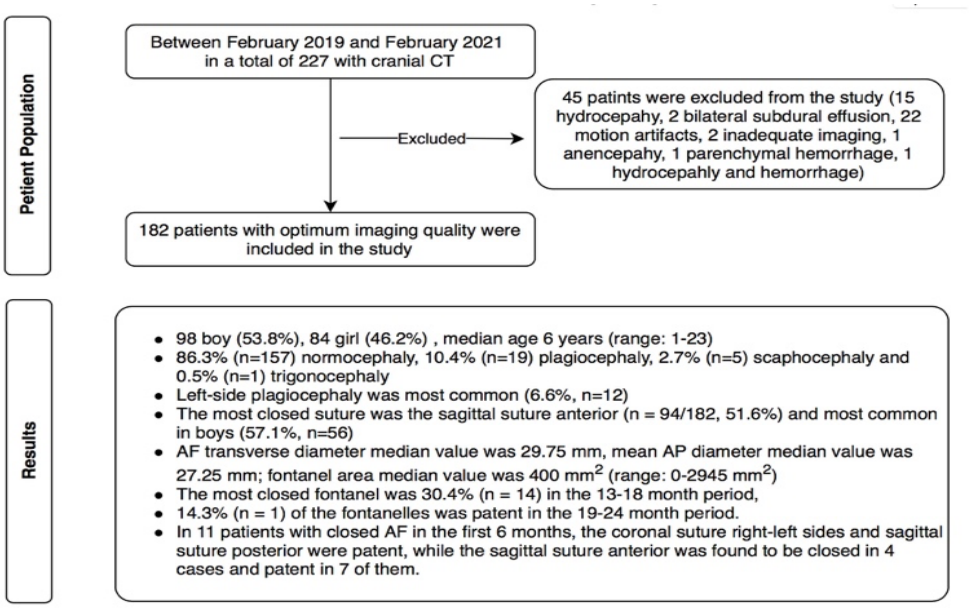

Fig. 1. Flow chart of the study

2.3. CT scanning and parameters

In the study, a 128-row multi-detector CT device (Aquilion™ Prime; Canon Medical Systems) was used for image acquisition. All scans were performed with the patient's supine, head first starting from below the base of skull to vertex, using the following parameters: tube voltage: 120 kV, 150 effective mAs; slice thickness: 1 mm.

2.4. CT image evaluation

CT images assessment was performed by a radiologist. The clinical and laboratory evaluation was done by a pediatrician. CT images with optimum imaging quality were included in the evaluation.

By using 3D reconstructions and a volume-rendering technique (VRT) methods in Sectra 7.0 workstation (Sectra AB, Linköping, Sweden), on 3D images the diameters (anterioposterior-AP and transvers) and area measurement of the AF, cranial shape and suture aperture status were evaluated (Fig. 2). On axial CT images, diameters of cranial sutures (metopic, sagital, coronal) were measured. On axial CT images of normocephalic groups, the head circumference measurements were calculated using formulas as following:

Head circumference = [(Cranial AP+Transvers diameters) /2] x 3.14

AFC Referring to the publications using our data on clinical evaluation, fontanel areas smaller than 114 mm^2 were considered as closed (13-16).

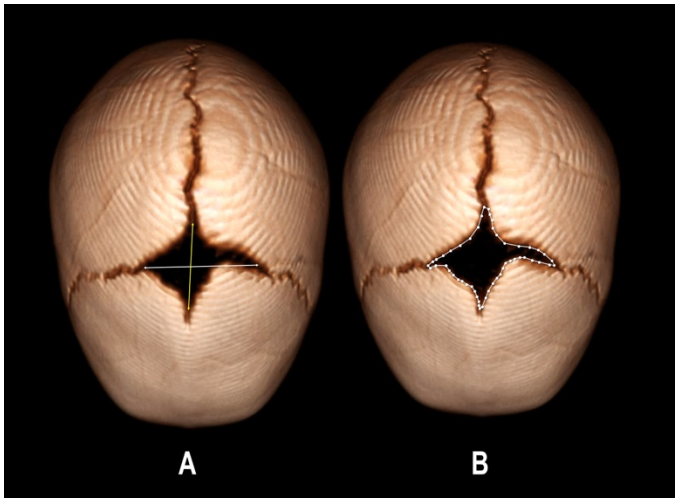

Fig. 2. AF diameters (AP and transverse) (A) and area measurement (B) in 3D reformatted images

2.5. Statistical analysis

Data analysis was performed using the statistical package program 22 (SPSS, Inc., Chicago IL, USA). Normality tests of the data showed an abnormal distribution. Descriptive analyses

of all data were performed and median (minimum- maximum) were given. In the evaluation of variance between age groups, Kruskal-Wallis test and in categorical data assessment Chi-square tests were used. The Spearman rho test was used to evaluate the correlation between groups. The statistical significance level was accepted as $p < 0.05$.

3. Results

3.1. Total patient population

The study population comprised of 98 boys (53.8%) and 84 girls (46.2%), and the median age was six months (range: 1-23). Normocephaly was found in 86.3% (n = 157) of the cases, plagiocephaly in 10.4% (n = 19), scaphocephaly in 2.7% (n = 5) and trigonocephaly in 0.5% (n = 1). Plagiocephaly was mostly observed on the left side (63%) and in the male gender (13.3% in boys, 7.1% in girls).

Metopic suture was the most closed suture (51.6%), followed by coronal suture right side (4.4%), coronal suture left side (3.8%) and sagittal suture. (2.2%). In our study, metopic suture closure was 57.1% (n = 56) in boys and 45.2% (n = 38) in girls. During the 19-24 months period, the sagittal suture was 100%, and 85.7% of the right and left coronal sutures were patent. In the 0-24 months period of the sutures, the median of metopic suture was 0 (0-11mm), sagittal suture median was 1.60 mm, coronal suture was 1.15 mm on the right, and the median of coronal suture was 1.30 mm on the left. In the first 6 months, the metopic suture was mostly closed at 23.7%.

AF median transverse diameter was 29.75 mm (range: 0 - 71.30), median AP diameter was 27.25 (range: 20-89.50) mm; median fontanel area was 400 mm^2 (range: 0-2945). In the first six months 11.3% of AF, in 7-12 months 28.3%, in 13-18 months 56% and in 19-24 months 85.7% of AF were closed (Fig. 3, 4; Table 1).

A statistically significant difference was found between age groups and fontanel area and diameter ($p<0.05$). A negative correlation was observed between age and fontanel diameters (transverse, AP) and area ($p<0.05$, r=-319, -538, -483, respectively). The Fontanel area and diameter decreased with increasing age.

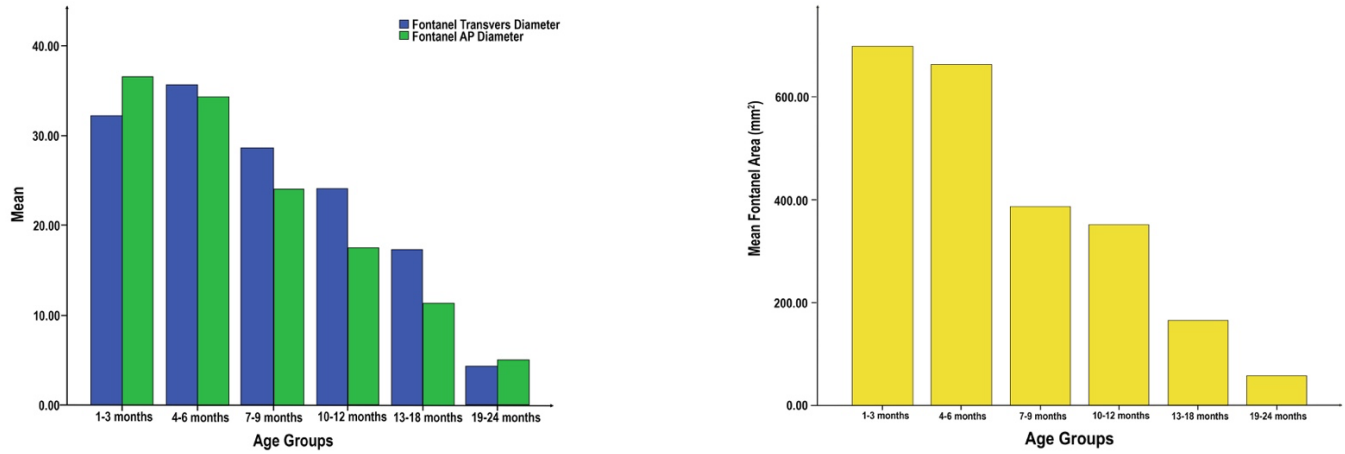

Fig. 3. Anterior fontanel AP diameter and area gradually decreasing according to age groups

Table 1. Patency of AF according to age groups (Field measurements are median values)

Anterior Fontanel Patency Status			
Age groups	**Closed (Below 114 mm^2)**	**Patent (Above 114 mm^2)**	**Total (n=182)**
1-3 months	10.0% (n=6) 58.34 ± 36.14 mm^2	90% (n=54) 709 ± 445.57 mm^2	n= 60
4-6 months	13.5% (n=5) 0 ± 26.31 mm^2	86.5% (n=32) 646.5 ± 556.63 mm^2	n= 37
7-9 months	25.7% (n=9) 17 ± 46.33 mm^2	74.3% (n=26) 433 ± 310.20 mm^2	n= 35
10-12 months	33.3% (n=6) 0 ± 42.85 mm^2	66.7% (n=12) 359 ± 371.07 mm^2	n= 18
13-18 months	56.0% (n=14) 0 ± 39.82 mm^2	44.0% (n=11) 220 ± 216.10 mm^2	n= 25
19-24 months	85.7% (n=6) 0 mm^2	14.3% (n=1) 397 mm^2	n= 7

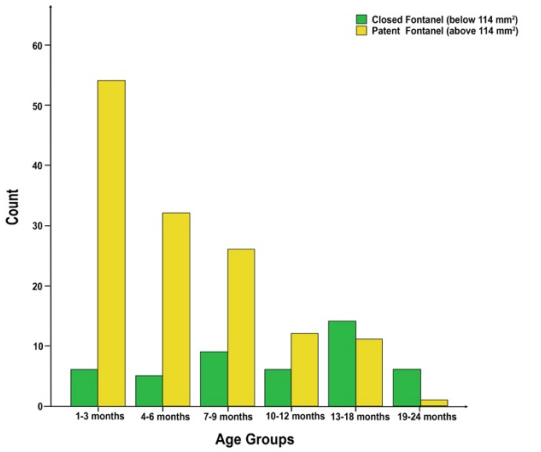

Fig. 4. Although it is shown that patent AF gradually decreases with age according to age groups, the presence of patent AF in the 19-24 months period (n = 1, 14.3%) has been shown and closed AF is mostly in 13-18 months

3.2. Normocephalic group

The measurements of AF and the sutures are given in Table 4. A statistically significant difference was observed between age groups in these defined parameters ($p<0.05$). A negative correlation was found between the fontanel area and the head circumference ($p<0.05$, $r=-0.393$). While age and head circumference were positively correlated, fontanel area, diameters and suture diameters showed a negative correlation ($p<0.05$) and decreased with increasing age. In the comparison between the head circumference according to gender, a statistically significant difference was observed in the head circumference ($p<0.05$) and the head size was more prominent in male gender. In the group with normocephalic and patent AF, the median head circumference was 391.56 mm (range: 300.18-458.44), and a negative significant correlation was found between the head circumference and the suture diameters ($p<0.05$, $r=-0.106$ -0.271).

4. Discussion

AFC requires investigation due to early, delayed, abnormal AF size and underlying mechanism of pathophysiology. Premature closure and reduced size of AF is thought to be syndromic craniosynostosis due to premature fusion of sagittal and coronal sutures (17, 18) Small size of AF or other etiologies of early AFC are thought to reflect the causes of microcephaly and may be due to fetal alcohol syndrome, hypoxic-ischemic damage or abnormal brain development due to congenital infections, malnutrition, chromosome abnormalities or dysmorphic syndromes (8).

In the literature, the AFC reported average closure times of 13-16 months (3, 9). Aisenson et al. showed that there was a normal fusion distribution between 4 and 26 months, and that AF closure occurred between 7 and 19 months in 90% (19). In studies using the CT modality (20, 21) in the first six months, the AFC rates in different populations were 30% in the Maori/Pasifika group, 38% in the New Zealand (NZ)-European group, 7-14% in the American group, and 25.7% in the current study had AFC in accordance with the literature (Table 2). This is due to the differences among races, but may be due to children living in countries with and without adequate sunlight or nutritional factors such as vitamin D (8, 9, 22).

The reported average AF area in the Maori/Pasifika group was initially 668 mm^2, this area had dropped to about 75% of its original size in 4-6 months, and it takes another 12 months for the next 25% to fully fuse, to about 25% in 10-12 months. Average area of AF in the NZ-Europe group in the 1-3 months period decreased to 854 mm^2, 650 mm^2 in 7-9 months and 45 mm^2 in 13-18 months (21). In our study, the median AF value was 599 mm^2, 47.07% was fused in 7-9 months, 60.1% was fused in 10-12 months and 85.30% in 13-18 months (Table 3)

Table 2. Comparison of the studies in the literature with the current study

Race	*n*	Modality	0-3 months, AFC %	4-6 months, AFC %	7-9 months, AFC %	10-12 months, AFC %	13-18 months, AFC %	19-24 months, AFC %
Maori/Pasifika (21)	116	CT, Clinical	0	25	30	47	80	100
NZ European (21)	47	CT, Clinical	0	11	38	60	100	50
Nigerian (4)	337	Clinical	4	11	35	54	ND	ND
American (20)	459	CT, Clinical	0	4	7	44	72	93
Iranian (30)	550	Clinical	0	0	11	50	94	100
Indian (36)	445	Clinical	0	2	4	23	64	87
Current Study (Turkish population, Balkan region)	182	CT	10	135	25.7	33.3	56	85.7

This indicates that there is a large amount of variation in fontanel size at birth and this variation continues throughout the AF closure process. In addition, in the present study, there is a case in which AF was still open during the 19-24 months period; it was similar to the case stated in the study in the Maori/Pasifika group (21). The average of the AF area in the first three months was 606 mm^2 (n = 32/116) in the Maori/Pasifika group, 854 mm^2 (n = 11/47) in the NZ / Europe group (21). The median of AF area in the first 3-4 months in the study by Pindrik et al. was found as 794.8 mm^2 (n = 37/459) (16). In our study, the median of AF area in the first three months was 599 ± 475.96 mm^2 and it was found to be lower than the other studies. This may be due to racial differences, geographic location, and nutritional status (8, 9, 22).

Table 3. AF area by age group

Age Groups	Anterior Fontanel Area (mm^2)	Total (n= 182)
1-3 months	599 (range: 0 - 2248)	n= 60
4-6 months	605 (range: 0 - 2945)	n= 37
7-9 months	317 (range: 0 - 1173)	n= 35
10-12 months	239.5 (range: 0 - 1360)	n= 18
13-18 months	88 (range: 0 - 691)	n= 25
19-24 months	0 (range: 0 - 397)	n= 7

Table 4. Measurements of the anterior fontanel and sutures in normocephalic group

	Anterior fontanel		Sutures	
Normocephalic group (n=157)	Transvers diameter	29.5 mm (range: 0-71.30)	Metopic	0 (0-11 mm)
	Anterioposterior diameter	27.2 mm (range: 0-89.50)	Sagittal	1.5 mm (range: 0-16.8)
	Area	403 mm^2 (range: 0-2945	Coronal right-side	1.2 mm (range: 0-15.6)
			Coronal left-side	1.3 mm (range: 0-14.2)

Median AF and sutures are given

The mean size of AF in the first six months in the Maori/Pasifika group was 580 mm^2 (21) and with an average value of 693 mm^2 was in the Australian study (25). In our study, the median of the AF area was 605 ± 514.30 mm^2 which was higher than the Maori/Pasifika study and lower than the Australian study, which indicates the variation of AF among populations. In a study conducted on 105 human fetuses in pregnant women, AF area increased with the increase in head circumference in the last trimester (26). In our study, unlike the antenatal study, a negative correlation ($p<0.05$) was found between the fontanel area and head circumference, and as the head circumference increased, the fontanel area decreased.

In the present study, in the normocephalic group the head circumference was statistically significantly larger in boys when compared to girls. In the total population of our study, no statistically significant difference was observed between the diameter and area of AF according to gender groups. While some studies reported significantly larger AF size in boys than girls (27) other studies reported no significant difference in AF size between genders (28-30). This suggests that structural and hormonal differences between the sexes may be related. The fontanel closure that occurs at the age of three months may be within normal limits, but the correlation of the head circumference should exclude the presence of a pathological condition. Craniosynostosis and abnormal brain development are associated with a small fontanel or early fontanelle closure. It is characterized by premature closure of one or more cranial sutures and an abnormal head shape (31). Although fusion of AF before six months or after 18 months is considered abnormal (23, 24, 32, 33) studies have shown that fusion can occur as early as 76 days or as late as 32 months in healthy individuals (7, 16). Early or delayed closure alone is not necessarily a pathological condition, but may represent a normal variant in a subset of healthy children. Therefore, these patients should be investigated in terms of various syndromes, diseases and toxic exposures that should be taken into account. Although a small AF or early closure may be idiopathic, conditions such as craniosynostosis, hyperthyroidism, abnormal cerebral development or fetal alcohol syndrome, hypoxic ischemic damage, congenital infections, malnutrition, chromosomal abnormality or Apert, Crouzon and Pfeiffer syndrome should be considered in the differential diagnosis (3, 7, 8, 31). In cases with delayed closure or increased AF size, congenital hypothyroidism, achondroplasia, chromosomal abnormalities, skeletal disorders (osteogenesis imperfecta, cleidocranial dysostosis or rickets), increased intracranial pressure (hydrocephalus, intracranial tumor, arteriovenous malformation) and dysmorphogenic syndromes should be considered (3, 16, 24).

In cranial CT study, approximately 30% of the metopic suture at 3-4 months of age, 50% at 5-6 months of age, 70% at 7-8 months of age, 100% in children 9 months and older has been found to be closed (11). In our study, 10% (n = 6/60) of the metopic suture was found to be closed in the first 3 months, 74.3% (n = 26/35) in 7-9 months and 100% (n = 7) closed in 19-24 months; the metopic suture was closing with increasing age. In the present study, metopic suture closure occurs at a later age according to the study data conducted by Vu et al (2001). There is a suggestion that racial, geographical and nutritional factors may play an important role in the American population.

The mean width of the sagittal suture at birth is 5.0 ± 0.2 mm, at one-month of age it is 2.4 ± 0.1 mm and gets narrower over time. In case of early closure of the sagittal suture, the skull becomes long, narrow and wedge-shaped and is called scaphocephalus. Sagittal suture is the most common suture in craniosynostosis (34, 35). In the current study, the median sagittal suture was 3.1 mm (1-16.80) at 1 month old, 2.5 mm (0-4.5) at 2 months old and 1.8 mm (0.80-5.0) at 3 months old, which was consistent with the literature. Similarly, the coronal suture narrows to 2.5 ± 0.1 mm at birth and to 1.3 mm ± 0.1 at 1 month of age. It remains without complete fusion throughout childhood and closes at 24 years old. In case of early closure, deformity such as brachiocephaly occurs (34). In the current study, the coronal suture narrowed from the median 1.7 mm to 1.4 mm on the right and the median from 2.15 mm to 1.70 mm on the left in the first three months. Trigonocephaly was detected in only one case (4%) morphologically on CT. The advantage of the study was quite adequate compared to the literature (in the Maori/Pasifika and NZ-European groups). The disadvantage was that the patients after 24 months were not included in the study. Due to the retrospective nature of the study, only patients with cranial CT examination under emergency conditions were included, and the lack of heterogeneity and standardization between age groups and genders may lead to differences in results between the groups.

The rate of non-AF closure in 19-24 months in the Turkish population living in the Europe-Balkan region was 14.3%, indicating that AF closure is at a later stage. Therefore, retrospective studies involving children over the age of two are needed.

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Prevalence of skin disorders among geriatric patients in the black sea region of Turkey

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Abstract

Aging is an unavoidable process affecting all organ systems including the skin. The elderly population is defined as people aged ≥65 years, and the elderly population is growing worldwide. The present study aims to determine the prevalence of dermatological diseases in the elderly patients aged ≥65 years and evaluate sociodemographic characteristics. The data of 300 geriatric patients aged ≥65 years who were admitted to our clinic between October 2013 and January 2014 were retrospectively reviewed. Of these patients, 130 (43.3%) were female and 170 (57.7%) were male. The mean age of the patients was 73.57 ±6.80 years. Eczematous dermatitis was detected in 77 of patients (25.7%). Of these patients, 135 (45%) had xerosis. The most common benign skin tumor was isolated seborrheic keratosis (n=82,58%). Actinic keratosis comprised the majority of malignant and premalignant lesions that occurred in 25 patients (8.3%). Cellulitis was the most common bacterial skin infection that occurred in 21 patients (7%). The rate of lichen planus was 0.6% in males and significantly more common in females with a rate of 3.1% ($p=0.09$; $p<0.05$). The rate of xerosis was 39.2% in patients aged 65-74 years, 53% in patients aged 75-84 years, and 54.2% in patients aged ≥85 years. The relationship between age and the rate of xerosis showed a borderline significance ($p=0.05$; $p<0.05$). Keeping in mind the most common dermatological problems in geriatric patients would enable early diagnosis of the conditions and selection of appropriate therapies.

Keywords: geriatric patients, prevalence, skin disorders, xerosis

1. Introduction

Geriatric patients are defined as people aged ≥65 years. Skin lesions are frequently encountered in the geriatric population (1). A decrease in the fertility rate due to challenges of modern life and an increase in the life expectancy have resulted in an increase in the ratio of the elderly people in the population. Scientific and technological advances in medicine, prevention of diseases and early diagnosis and treatment of the conditions, and the decrease in the infant mortality rate due to improvements in preventive healthcare services are other factors increasing the average life expectancy (2). According to the 2020 Turkish Statistical Institute (TÜİK) data in Turkey, the elderly population (aged ≥65 years) was 9.5% of the population in Turkey (3). According to the definition of the United Nations, countries with the proportion of older persons between 8% and 10 are considered to have moderate population aging, and countries with the proportion of older persons more than 10% are considered to have advanced population aging (4). It was reported in United Nations Development Programme that the proportion is projected to rise further to 16 per cent by 2050, so that one in six people in the world will be aged 65 years or over (4).

The skin functions impair with advancing age, such as cellular regeneration capacity, barrier functions, sensory perception, mechanical protection, wound healing, immune response, thermoregulation, sweat production, sebum production, vitamin D synthesis, and DNA repair capacity. As a result, skin changes such as coarsening, wrinkling and slack skin are common in the older patients (5). The mobility of patients decreases with increasing age, additional diseases occur, and the mobility of the older people reduces (6). An increase in the incidence of systemic conditions, skin damage caused by ultraviolet exposure, presence of xerosis, and peripheral vascular disorders also increase the incidence of skin disorders in geriatric patients (7, 8). It was reported that the prevalence of skin diseases in geriatric patients is 65%, and most elderly patients have more than one dermatological conditions (9). It is considered that epidemiological studies would lead the way for the planning of healthcare services delivered to the elderly patients and the development of preventive health services (2).

The present study evaluates the types of skin disorders observed in patients aged ≥65 years, and the distribution of these disorders by gender, age group and geographic characteristics.

2. Material and Methods

The present study was carried out after obtaining approval of the Düzce University Clinical Trials Ethics Committee with an approval number of 2014/31. The data of 300 geriatric patients aged ≥65 years who were admitted to the Dermatology Outpatient Clinics of Düzce University Faculty

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of Medicine between October 2013 and January 2014 were retrospectively reviewed. Age, gender and residence information were recorded. The patients were divided into two groups: patients residing in the town centers of the Düzce province and its districts and patients residing in the rural areas. Patients were also divided into age groups as 65-74 years, 75-84 years, and ≥85 years (2.5). The presenting symptoms and dermatological findings of the patients were recorded. Accordingly, the following disease groups were recorded: eczematous dermatitis, xerosis, pruritus, psoriasis, fungal infections, lichen planus, urticaria/angioedema, viral infections, bacterial infections, skin pigmentation disorders, benign and malign diseases of the skin, keratinization disorders, vesiculobullous diseases, mucous membrane disorders, infestations, rosacea, papulosquamous disorders, and others. These findings were compared according to age, age group and sociodemographic characteristics.

The study evaluated the relationship between the detailed prevalence of dermatological disorders in the elderly population aged ≥65 years and gender, sociodemographic and clinical characteristics of the patients. A histogram curve was used to evaluate whether a numerical variables was normally distributed. The categorical variables were expressed as number and percentage. Descriptive statistics (mean, standard deviation, median, minimum, maximum, percentage) were calculated for all study data. The categorical variables were compared using Pearson's chi-squared test, Fisher's exact test, and Fisher-Freeman-Halton test. The post-hoc Bonferroni test was used in categorical variables that showed significant difference in the initial tests. The statistical analysis was performed using PASW version 18 software. A p-value <0.05 was considered statistically significant.

3. Results

Of 300 patients included in the study, 130 (43.3%) were female and 170 were male, and the female-to-male ratio was 1.3:1. The mean age of the patients was 73.57 ± 6.80 years with a range of 65 to 99 years. The mean age was 73.49 ± 6.78 in females and 73.64 ± 6.84 years in males. There were 176 (58.7%) patients in the age group of 65-74 years, 100 patients (33.3%) in the age group 75-84 years, and 24 (8%) patients in the age group of ≥85 years.

Seventy-seven patients (25.7%) had eczematous dermatitis. The most common type of eczematous dermatitis was neurodermatitis that occurred in 18 patients. Patients with neurodermatitis accounted for 23.3% of all patients with eczematous dermatitis. This was followed asteatotic eczema in 10 patients (12%), irritant contact dermatitis in 9 patients (11.6%), nummular dermatitis in 8 patients (10.3%), and isolated stasis dermatitis in 7 patients (9.09%).

A total of 135 patients (45%) had isolated xerosis. Fifteen patients (5%) had psoriasis vulgaris, 73 patients (24.3%) had pruritus, and 5 patients (1.7%) had lichen planus. Fungal infections were observed in 89 patients (29.7%).

Benign skin tumors were observed in a total of 139 patients (46.3%). The most common benign skin tumors were isolated seborrheic keratosis (n=82, 58%) (27.3% of the entire study population) and isolated cherry angioma (n=22, 15.8%). There were two patients (1.4%) with isolated skin tag and 21 patients (15.1%) with cherry angioma coinciding with seborrheic keratosis.

Malignant and premalignant skin tumors were detected in a total of 54 patients (18%) in the present study. Of these patients, 25 (46%) had actinic keratosis, 15 (27.7%) had basosquamous carcinoma (BSC), 3 (5.5%) had squamous cell carcinoma (SCC), 7 (12%) had actinic keratosis and SCC, 1 (1.8%) had actinic keratosis and concurrent Bowen's disease, 1 (1.8%) had actinic keratosis and concurrent malignant melanoma, 1 (1.8%) had Kaposi's sarcoma, 1 (1.8%) had actinic keratosis and concurrent BSC. The bacterial infections of the skin were identified in 45 patients (15%). Of these patients, the majority had cellulitis (46.6%) and furuncles (31.1%). The viral infections of the skin were identified in 17 patients (3.7%). Of these patients, 10 (58.8%) had herpes zoster, 6 (35.2%) verruca vulgaris, and 1 (5.8%) had herpes simplex. Vesiculobullous diseases were identified in 8 patients (2.7%). Of these patients, 4 (50%) had pemphigus vulgaris, 2 (25%) had pemphigus foliaceus, 1 (12.5%) had bullous pemphigoid, and 1 (12.5%) had dermatitis herpetiformis. Urticarial skin rash was identified in 19 patients (7.3%). A callus was identified in 14 patients /4.7%) (Table 1). When gender distribution of the diseases was evaluated, 25.4% of females and 25.9% of males had eczematous dermatitis. The rate of eczematous dermatitis did not significantly differ between males and females (p=0.922; p>0.05). The rate of xerosis was 45.3% in males and 44.6% in females. The rate of xerosis did not significantly differ between males and females (p=0.907; p>0.05).

Table 1. Demografical features

	N*	(%)ᵝ
Patients aged 65-74 years	176	(58.7%)
Patients aged 75-84 years	100	33.3%)
Patients aged ≥85 years	24	(8%)
Mean Age£	73.57 ± 6.80	
Female	130	(43.3%)
Male	170	(56.7%)
Rural	150	(50%)
Urban	150	(50%)
Eczematous Dermatitis	77	(25.7%)
Xerosis	135	(45%)
Psoriasis Vulgaris	15	(5%)
Lichen Planus	5	(1.7%)
Benign Skin Tumors	139	(46.3%)
Premalign/ Malign Skin Tumors	54	(18%)
Bakteriyel Infections	45	(15%)
Viral Infections	17	(3.7%)
Vesiculobullous Diseases	8	(2.7%)
Urticarial Skin Rash	19	(7.3%)
Callus	14	(4.7%)

The rate of pruritus was 26.22% in females and 22.9% in males. The rate of pruritus did not significantly differ between males and females (p=0.520; p>0.05).

The rate of lichen planus was 0.6% in males and significantly more common in females with a rate of 3.1% (p=0.09; p<0.05). The rate of benign skin tumors was 41.5% in females and 50% in males. The rate of malignant and premalignant skin tumors was 13.8% in females and 21.2% in males. The rate of malignant and premalignant skin tumors did not significantly differ between males and females (p=0.101; p>0.05) (Table 2).

Table 2. Gender distribution of the diseases

	Female	Male 170 (66.7%)	P Value
Eczematous Dermatitis	25.4%	25.9%	0.922
Xerosis	44.6%	45.3%	0.907
Pruritus	26.22%	22.9%	0.520
Lichen Planus	3.1%	0.6%	0.09
Benign Skin Tumors	41.5%	50%	0.145
Premalign/ Malign Skin Tumors	13.8%	21.2%	0.101
Vesiculobullous Diseases	3.1%	2.4%	0.731
Bacterial Skin Infections	13.8%	15.9%	0.625

*P < 0.05 was considered statistically significant.

Of the study patients, 150 (50%) lived in the rural areas and 150 (50%) lived in the urban areas.The rate of callus was 7.3% in patients living in the rural areas and 2% in those living in the urban areas. The majority of individuals with callus (78.6%) lived in the rural areas (p=0.029; p<0.05).

In the present study, patients aged 65-74 years comprise 58.7%, patients aged 75-84 years comprise 33.3%, and patients aged ≥85 years comprise 8% of the entire study population (Table 3.).

The rate of eczematous dermatitis was 25.6% in patients aged 65-74 years, 22% in patients aged 75-84 years, and 41.7% in patients aged ≥85 years. There was a significant difference in the age distribution of eczematous dermatitis (p=0.140; p>0.05).

The rate of xerosis was 39.2% in patients aged 65-74 years, 53% in patients aged 75-84 years, and 54.2% in patients aged ≥85 years. The relationship between age and the rate of xerosis showed a borderline significance (p=0.05). Among patients aged 75-84 years, the number of patients with xerosis was marginally higher than the number of patients without xerosis (p=0.05). The distribution of xerosis in the other age groups was not statistically significant (Table 3).

The rate of pruritus was 20.5% in patients aged 65-74 years, 30% in patients aged 75-84 years, and 29.2% in patients aged ≥85 years. The rate of pruritus did not significantly differ across the age groups (p=0.175; p>0.05).

Table 3. Distribution of the diseases according to age groups

	65-74 years 176 (%58.7)	75-84 years 100 (%33.3)	≥85 years 24 (%8)	P value
Eczema tous Dermatitis	25.6%	22%	41.7%	0.140
Xerosis	39.2%	53%	54.2%	*0.05
Pruritus	20.5%	30%	29.2%	0.175
Benign Skin Tumors	43.8%	50%	50%	0.565
Premalign/ Malign Skin Tumors	13.1%	27%	16.7%	*0.015
Bakteriyel Infections	17.6%	11%	12.5%	0.314
Vesiculobullous Skin Diseases	1.7%	2%	12.5%	*0.025
Lichen Planus	2,3%	1%	0	0.777

*P < 0.05 was considered statistically significant.

The rate of benign skin tumors was 43.8% in patients aged 65-74 years, 50% in patients aged 75-84 years, and 50% in patients aged ≥85 years. Benign skin tumor that had the highest frequency in all age groups was seborrheic keratosis. Of patients with seborrheic keratosis, 52.4% were aged 65-74 years, 39% in patients aged 75-84 years, and 8.5% were aged ≥85 years. Skin tags were observed only int he 65-74 years age group. Of patients with a cherry angioma, 63.6% were aged 65-74 years, 27.3% were aged 75-84 years, and 9.1% were aged ≥85 years. The frequency of benign skin tumors did not significant change across the age groups (p=0.565; p>0.05).

The rate of bacterial skin infections was 17.6% in patients aged 65-74 years, 11% in patients aged 75-84 years, and 12.5% in patients aged ≥85 years. The most common bacterial skin infection in all age groups was cellulitis. The frequency of bacterial skin infections did not significantly change across the age groups (p=0.314; p>0.05).

The rate of malignant and premalignant skin diseases was 13.1% in patients aged 65-74 years, 27% in patients aged 75-84 years, and 16.7% in patients aged ≥85 years. The most common lesion was actinic keratosis in all age groups. The frequency of malignant and premalignant skin diseases significantly differ across the age groups. The rate of malignant and premalignant skin diseases was significantly lower in patients younger than 75 years than in patients aged 75-84 years (p=0.015; p<0.05) (Table 3.).

The rate of vesiculobullous skin diseases was 1.7% in patients aged 65-74 years, 2% in patients aged 75-84 years, and 12.5% in patients aged ≥85 years. The rate of vesiculobullous skin diseases was significantly higher in patients aged ≥85 years (12.5%) than in patients in the other age groups (1.7% and 2%, respectively) (p=0.025; p<0.05).

4. Discussion

The differentiation in the epidermis is impaired with aging, and focal tissue proliferations are often observed. Therefore, an increase in observed in the prevalence of various benign neoplasms with aging (8). The most common disease group in the present study was benign neoplasms of the skin (46%). Benign neoplasms of the skin were identified as one of the most common skin conditions in geriatric patients in similar studies (10-12). Darjani A et al. reported in 2021 that benign neoplasm was a common skin disease among patients with 68.3% (12). Also similar to our study the most frequently encoded individual diagnoses identified were “other and unspecified malignant neoplasm of skin” in a study performed in hospitalized geriatrics (13).

Seborrheic keratoses are very commonly encountered in the elderly population. Also in the present study, the most common skin condition among benign neoplasms of the skin was seborrheic keratosis, accounting for 27% of all benign skin tumors. In a study by Baykal et al., seborrheic keratosis was similarly identified as the most common benign neoplasm of the skin (14). The second most common benign neoplasm of the skin identified in the present study was cherry angioma with a rate of 7.3%. In an Indian study involving 320 geriatric patients, cherry angiomas were found to be one of the most common skin conditions, with a prevalence rate of 48.1% (15). Seborrheic keratosis was detected in of 42.6% patients in a recent study (16).

The skin becomes dry and itchy over years in the elderly patients. The stratum corneum is the skin layer functioning as the skin barrier that plays the most critical role in the regulation of water loss from the skin. Various factors such as the climate, drugs, malignant and endocrine disorders, infections and kidney diseases may induce dry skin (17). The increased incidence of xerosis with aging arises from the changes in the moisture of the skin and barrier functions (18). The second most common skin finding observed in geriatric patient population in the present study was xerosis with a rate of 45%. Various studies have reported rates ranging from 3.7% to 75% (2,8,19). This difference can be explained by the fact that xerosis is not only related to aging but other factors may also be involved. In a recent study xerosis was detected as 45.2% percentage in elderly patients (16).

There is an increased incidence of infectious diseases of the skin in the elderly population due to neurological deficits that are commonly observed in the elderly, impairment in immune functions, obesity, malnutrition, poor regeneration capacity in the epidermis, and particularly poor daily self care (2). The third most common disease group in the present study was fungal infections, which were detected in a total of 89 patients (29.7%). A study in Egypt found that skin infections were the most common skin condition in the elderly population (20). The prevalence of fungal skin infections was found to be 10.4% in a large-scale study involving 2,496 geriatric patients (21). Likely in a recent study showed that fungal infections are the must common skin infections (22). Viral infections were less frequent (3.7%) than the bacterial and fungal skin infections in the present study. Herpes zoster accounts for 37% of the viral infections. A study in Iran found a rate of as high as 8.2%, herpes zoster accounting for the majority of these cases (23). Herpes zoster is frequently encountered in the elderly population, particularly in parallel to a decline in cellular immunity with aging (24).

Pruritus is one of the most common skin conditions in the elderly, and it can be a part of the underlying skin disease or a manifesting symptom of systemic diseases such as endocrine, renal, hematological or rarely malignant diseases (25). Pruritus was found in 24.3% of the patients in the present study. A comprehensive study in Italy identified pruritus as the most common dermatological skin disorder (11). In a recent study senil pruritus wasdetected as 17% percentage (22). Since this study was conducted in the months between October 2013 and January 2014, when the air temperature in Düzce begins to decrease, probably makes the skin dry and, thus, prone to pruritus. Xerosis is an important etiological factor for pruritus.

The rate of eczematous dermatitis was 25.7% in the present study. Bilgili et al. identified eczematous dermatitis as the most common dermatological disorder in geriatric patient population, with a reported prevalence of 32.7% (21). Likely in a 455 patient study xerosis was detected 13.8% percentage (26). According to Liao et al., an increase in the incidence of inflammatory skin conditions is almost inevitable due to flattening in dermo-epidermal junction, dermal and epidermal atrophy, decrease in the number of melanocytes, Langerhans cells, and fibroblasts, and more importantly the decline in barrier functions of the skin (27).

Regarding malignancy incidence, Black Sea Region has remarkably higher rates than the rest of the country (28). Aging is a risk factor for most of cancers (29). The rate of malignant and premalignant skin diseases was 18% in the present study, and actinic keratoses accounted for 18% and BSC accounted for 27% of these patients. In another study in Turkey, BSC accounted for 83.3% of all malignant neoplasms (21). Nonmelanoma skin cancers are common in geriatric patients. Along with sun damage, the decline in cellular immunity and genetic factors also play a role in the development of these lesions (8,28). Relative difference in the rate of various tumor types may have been caused by the involvement of additional factors in the neoplastic process.

Furthermore, vesiculobullous diseases were identified in a total of 8 patients (2.7%). The rate of vesiculobullous diseases was reported to be 0.8% in a study involving 2,734 elderly patients (2). The finding of the present study may be caused by relatively small number of patients.

Various studies examining skin findings in the elderly have found variable female-to-male ratios. The rate of female-to-male ratio was 0.8 in the study by Baş et al., 0.8 in the study by Yalçın et al. and 1.1 in the study by Baykal et al (2,5,14). Of the patients in the present study, 130 (43.3%) were female and 170 were male, with a female-to-male ratio of 0.7. In a recent study it was found that female ratio is higher than male (30)

When the distribution of disease groups was examined according to gender in the elderly patients, common diseases and their frequency rates were similar between males and females. Xerosis was identified in 46% of females and noted as the most common dermatological disease in the present study. This was followed by eczemas (42.9%) and benign neoplasms of the skin (41.5%). In a study by Baş et al., eczemas were identified as the most common skin disease in females (2). The rate of only lichen planus was significantly higher in females than in males in the present study ($p=0.09$; $p<0.05$). Although the present study found no significant relationship between the prevalence of xerosis and gender, a study in the literature reported a high rate of xerosis in female elderly population (31). Another study in Turkey reported higher rate of pruritus in the elderly females than in males, while the present study found no significant difference between males and females in terms of the frequency of pruritus (32). The differences in the study findings may be caused by the differences in the number of studied patients.

Of the patients in the present study, 150 (50%) lived in the rural areas and 150 (50%) lived in the urban areas. When the distribution of disease groups was examined according to residence in the elderly patients, common diseases and their frequency rates were similar between patients living in the rural areas and those living in the urban areas. The rate of callus was 7.3% among patients living in the rural areas and 2% in those living in the urban areas. The majority of patients (78.6%) with callus lived in the rural areas ($p=0.029$; $p<0.05$). The risk factors for the development of corns and calluses on the feet are bumps over bony areas, abnormal biomechanical foot functions, ill-fitting shoes, and repeated trauma due to athletic activities (33). Significantly higher rate of calluses and corns in rural areas was attributed to the living conditions in these areas.

In our study, Most participants were in the age grouped between 65-74 years as the percentage of 58.7%, similar to our study conducted in Turkey, most of the participants' age were between 65-74 years (2). The most common skin conditions in patients aged 65-74 years were benign skin tumors (43.8%), xerosis (39.2%), and eczematous dermatitis (25.6%). Different from the present findings, a study in the literature reported eczematous dermatitis as the most common (21.6%) dermatological disorder in patients aged 65-74 years (6).

The most common skin conditions in patients aged 75-84 years were xerosis (53.0%) and benign skin tumors (50%), and pruritus. Likewise, the most common dermatosis in patients aged 75-84 years was eczematous dermatitis (2,6). Xerosis (54.2%), fungal skin infections (41.7%) and eczematous dermatoses (41.7%) were identified as the most common skin conditions in patients aged ≥85 years. Similarly, Yalçin et al. reported eczematous dermatoses as the second most common (14.1%) skin condition (5). Pruritus was reported as the most common skin condition in patients aged ≥85 years (6). In the study by Baş et al., the most common skin condition was pruritus (16.9%) and the second most common skin condition was fungal skin infections (15.4%) in patients aged ≥85 years (2).

The present study found no significant relationship between age and the prevalence of eczematous dermatitis, pruritus and bacterial skin infections, while the study by Baş et al. reported a tendency to increase in the prevalence of these skin conditions with aging (2). The present study found a marginally significant relationship between age and the occurrence of xerosis ($p=0.05$), the rate of which was found to be significantly increased in patients aged 75-84 years. One study in Turkey did not show an increased prevalence of xerosis with aging (2). Another study reported a significantly higher rate of xerosis in patients aged 65-74 years than in patients aged ≥75 years (21). The distribution of malignant and premalignant skin lesions showed a significant difference across the age groups. The rate of malignant and premalignant skin lesions was significantly lower in patients younger than ≤75 years than in patients aged 75-84 years ($p=0.015$; $p<0.05$). The study by Baş et al. demonstrated a tendency to increase in the incidence of precancerous lesions and malignant neoplasms with aging (2).

The rate of vesiculobullous diseases was significantly higher in patients aged ≥85 years than in the other age groups ($p=0.025$; $p<0.05$). However, the study by Baş et al. reported no significant difference (2). In another 150 cases of vesiculobullous lesions study showed that most patients belonged to the geriatric age group of more than 50 years (34). The most common disease group in the present study was benign neoplasms of the skin. Xerosis is another significant skin problem in the elderly and showed an increased prevalence in patients aged 74-85 years. Fungal infections that were the most common infectious dermatological problems in the elderly were found in different localizations in an individual patient, probably due to spread to other body parts or poor self-care practices. Zona zoster is common in the elderly due to a decline in cellular immunity (35). The presence of xerosis and an underlying medical condition makes pruritus an important complaint in the elderly population. In geriatric patients, the incidence of lichen planus is remarkably higher in females than in males. Callus is less frequently observed in the elderly with limited daily life activities in monotonous urban life. Advancing age

significantly increases the risk of developing malignant and premalignant skin tumors and vesiculobullous skin disorders in older people.

The limitation of this study is being based only on patients who come to the outpatient clinic. But it should be kept in mind that the awareness on the common dermatological problems in the older people would enable early diagnosis and selection of appropriate treatment of the diseases.

Conflict of Interest

None to declare.

Acknowledgments

None to declare.

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Clinical outcome of superior plate fixation for midshaft clavicular fractures

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Abstract

The middle clavicle fractures in both anatomy and position upon evaluation are considered displaced or unstable especially for those with high expectations for recreational activity. Although surgical treatment is recommended as the standard treatment modality for middle displaced fractures, there is no consensus about the type of operative treatment. 25 patients that diagnosed with middle clavicle fractures, who underwent surgery for displaced clavicle fractures. Surgical treatment was done with clavicle anatomic locked plate at all cases. The mean follow-up period was 24 months (range, 12–40 months). Bony union was achieved at a mean follow-up of 8 weeks (range 6-10 weeks). The mean Constant score was 97 (range, 92-100). There were no complications. The anatomical superior plate application were provides anatomical healing without shortening; allow the early movement by increasing the stability.

Keywords: middle clavicle, fracture, surgery, anatomic healing, early activity, sports medicine

1. Introduction

Clavicle fractures are most common in the middle 1/3 region (1). Middle age men are more affected and the most common mechanism of injury is a car accident or falling directly on it. Most of these fractures are displaced due to muscle action and weight of the arm (1).

Previously, conservative treatment with arm sling and figure-of-8 bandage was at the forefront; Recently, Surgery has become more popular due to the complications that occur due to conservative treatment as a painful nonunion, cosmetic reasons, scapulothoracic joint pain or disturbance and the patients' desire to return to work earlier.

In our study, we aimed to discuss the results of middle 1/3 fractures treated with a single anatomical locking plate screw system.

2. Materials and Methods

We prospectively reviewed 25 patients diagnosed with middle clavicle fractures who underwent surgery for displaced middle 1/3 fractures according to X-ray examination from March 2009 to May 2020 (Fig. 1). The average patient age was 38 years (range 24-52 years). 20 patients were male and rest of 5 patients were female; the right clavicle was injured in 19 patients whereas the left clavicle was injured in 6 cases. Only patients with acute surgical treatment (within 3 weeks of injury) with an anatomic clavicle locked plate and at least 1 year of follow-up were included in the study.

The average time from injury to surgery was 3 days (range, 1–7 days). The mean follow-up period was 24 months (range, 12–40 months). Eleven patients were injured in a cycling accident, four patients were injured in the ski, and five were injured falling off a horse, five were injured playing soccer. All participants were informed and informed consent form was obtained. Study was approved by our Institutional Review Board. Surgical procedures were performed under general anesthesia with the patient in the beach-chair position. A standard superior approach to the clavicle was used. After identification of the fracture site, all hematoma and debris were curetted and interposed soft tissue was removed. An anatomic clavicle plate was applied. The anatomical clavicle plate was fixed with at least 3 cortex on both sides of the fracture (Fig. 2).

Postoperatively, a sling was used for 10 days. Passive range of shoulder motion began at the second day. Elevation of the arm above the shoulder was prohibited for three weeks. Functional outcome of the shoulder was evaluated using a Constant scoring system (2). Union was evaluated radiologically.

3. Results

Bony union was achieved at a mean follow-up of 8 weeks (range 6-10 weeks) (Fig. 3). The mean Constant score was 97 (range, 92-100). There were no complications, such as deep infection, nonunion or malunion. All patients achieved satisfactory full range of shoulder motion. Implant loosening was not seen in the plate. Hardware removal was performed for prominence in ten case after the union was completed (Fig. 4).

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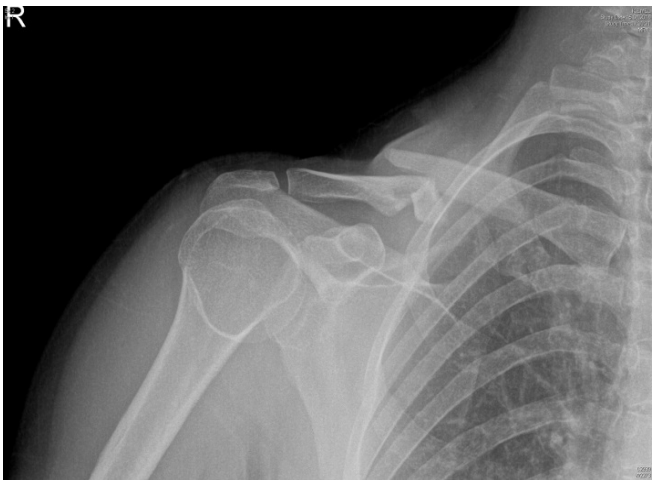

Fig. 1. 42 years woman's shoulder AP x-ray image showing that clavicle comminuted fracture

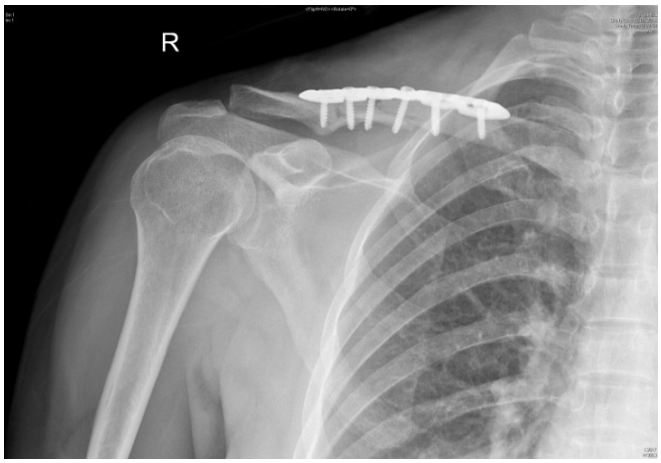

Fig. 2. 42 years woman's postoperative shoulder AP x-ray image showing that clavicle comminuted fracture that fixed anatomic plate

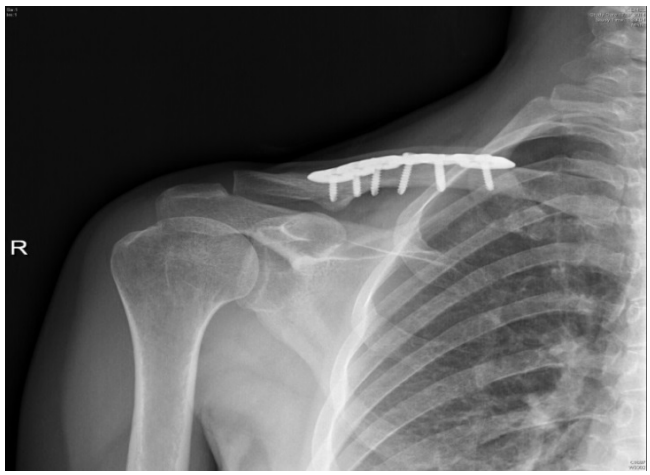

Fig. 3. 42 year's woman's follow-up shoulder AP x-ray image showing that achieved union clavicle comminuted fracture

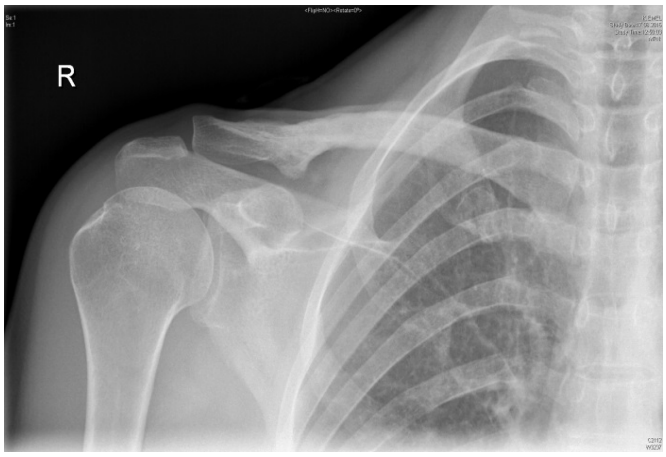

Fig. 4. 42 year's woman's follow-up shoulder AP x-ray image showing that achieved union clavicle comminuted fracture after the implant is removed

4. Discussion

Most of clavicle fractures are displaced due to muscular action and weight of the arm. Although many studies also suggest open reduction and fixation in the treatment of displaced mid-diaphyseal fractures, particularly those with 20 mm shortening, 100% displacement and bone defect (1). Conservative treatment of these displaced fractures may result in shortening, malunion, painfully nonunion, poor shoulder function, cosmetic problem. In a comparative study between surgically treated and conservatively treated displaced mid-diaphyseal fractures, high functional outcomes, low nonunion and malunion results were found in patients treated surgically (3). Thus, surgical treatment has been the first choice to avoid these problems and due to the high expectations of the patients; but ideal surgical treatment continues to be controversial (3-6). The main issue regarding surgical treatment of middle fractures is union and return to previous daily activities. Herein, we evaluated union, complications and results in a case series of patients treated with an anatomic plate.

The middle clavicle fractures in both anatomy and position upon evaluation; the distal fragment is located in the posterior-inferior position due to attachment of the deltoid and trapezius; the proximal fragment is both superior and anterior due to the sternocleidomastoid and pectoralis major muscles (2). Although this muscle is able to function, it is difficult to open between the fractured fragments and results in a gap, causing the union issue. In some fractures, the fracture line will have multi fragments. Based on the literature, there are many surgical options for treatment of displaced clavicle fractures due to the union problem, including anatomic locking plates, double plates, intramedullary nail (4, 7-10). Despite the numerous techniques available, none method has proven superior for the union rates; but reconstruction plates had very high implant failure rate compared the non-reconstruction plates (8, 11). In this reason, we only preferred the anatomical locking plate screw osteosynthesis option. Plates with different number of holes and different number of screws were used related the type of fracture and length of the clavicle.

Upon examination of the history of surgical treatments, nonlocking plate system were used. However, with technological developments, locking plate technology has proven beneficial in fracture treatment with poor bone quality, as well as for short segments and allowed the early movement (5, 6). This is especially important if the medial or

lateral fragment is small or osteopenia due to comminuted. Although, many authors reported that use of double plate provided sufficiently stable fixation for comminuted fracture or requesting early movement; Denise reported to return to professional athletic activity with treated anteroinferior plate at 2 weeks after surgery (7). As many authors have stated, we preferred a single plate application.

Despite the good stability, compression and mechanical fixation with plate fixation, complications such as infection and formation of scar tissue were found 6. Although the clavicle fixation as an intramedullary is cosmetically acceptable, complications rates of up to 75% were reported, namely lack of rotational control, the need for a second surgical procedure to remove the implant, skin problems, and implant migration and shortening due to comminuted (12). Therefore, plate fixation is the preferred treatment in our hospital. Optimal plate fixation for the treatment of mid-diaphyseal clavicle fracture is still controversial. Some studies suggest that anteroinferior plate fixation techniques are better, suggesting that plate prominence is felt less often. However, more soft tissue dissection is required for this plate fixation 4. Therefore, a high rate of wound infection or wound healing can be expected complications. The other point is the subclavian artery in the medial half of the clavicle was the closest to the posterior cortex (13). So that anteroinferior plate application can cause neurovascular injury in the medial clavicular area. In order to prevent this complication, we preferred superior plate application by taking the risk of skin irritation. Although clinically, plate prominence inferiority due to low profile of anatomically compatible plate in mid-diaphyseal clavicle fractures is low; all of our patients complained the plate prominence (12). We also think that the use of preformed anatomically compatible plates in our study reduces the duration of surgery and plate tiredness risk.

In a study conducted biomechanically, the anterior, antero-superior, and superior plating types were found to be the most important method for detecting axial fracture of superior plate in the detection of midshaft clavicle fractures. In the same study, no difference was found between torsional forces and resistance among all three types of plate fixation 5.

We believe we have achieved successful results on the fixation of the fracture with our superior plate fixation and with an early activity program applied to all patients

Complications such as shortening, painful nonunion, cosmetic disorder and excessive callus formation can be observed as a result of displaced or comminuted midshaft clavicle fractures. It is possible to obtain complete union with high patient satisfaction by avoiding the complications with anatomically compatible low profile locking plates.

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Conflicts of Interest
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COVID-19 exposure and health status of orthopedic residents: A survey study

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Abstract

Considering the increased patient burden and disruptions in the healthcare system, orthopedic residents are affected both psychologically and physically while working both in the management of trauma patients and caring for COVID-19 patients. Our objective was to investigate the virus exposure and health status of orthopedic residents during the pandemic and to review the measures that can be taken. A survey consisting of 15 questions was organized and circulated through e-mail groups and social media platforms in order to evaluate the health status of residents. Demographic data, co-morbidities, whether they had a COVID-19 infection, time they work in orthopedics-related and COVID-related units, whether there was infection among their colleagues or family members and the infected patient care were questioned. A total of 136 residents completed the survey, of which 41 (30.1%) were infected. A significant difference was found between COVID-infected and COVID-free residents in terms of comorbidities ($p=0.026$). Residents with infection among their colleagues had lower infection rates ($p<0.001$). No significant difference was found between groups in terms of the working periods in orthopedics-related or COVID-related units ($p>0.05$ for each). With this study, the infection rate among orthopedic residents were reported for the first time in the literature, considering the fact that a third of all the participants in our study were infected. The infection rate among the orthopaedics residents were reported for the first time in the literature with this study. The fact that residents with infected colleagues have lower infection rates, demonstrates the importance of self-awareness and protective behaviors. During the pandemic, all healthcare professionals should pay maximum attention for simple measures, like practicing protective behaviors and use of personal protective equipment.

Keywords: Covid-19 pandemic, orthopedics and traumatology, protective measures, resident, survey

1. Introduction

March 11, 2020 is the date when COVID-19 was declared as pandemic all over the world and the first case was detected in our country (1). Since that day, extraordinary measures have been taken against COVID-19 in our country, similar to those around the world, such as prohibitions of city entrances and exits, curfews, closure of social areas, turning regular hospitals into pandemic hospitals and continuously educating citizens and increasing perception about the importance of protective behaviors (2-4).

As part of these measures, all healthcare professionals have and continue to fight the COVID-19 infection alongside their primary duties, through regulations and decree laws. Although elective surgeries were stopped during the first and second waves, orthopedic residents continued to manage trauma patients while at the same time caring for COVID-19 patients and were inevitably affected both physically and psychologically during this process (5). Moreover, increasing patient burden and intense work pace also augmented these effects (6, 7).

Our objective was to investigate the virus exposure and health status of orthopedic residents during the pandemic and to review the measures that can be taken in order to reduce the residents' incidence of COVID-19 infection.

2. Material and Methods

Following the approval of the Scientific Research Platform of the Ministry of Health, a survey consisting of 15 questions was organized by two board-certified specialists of orthopedics and traumatology, in order to evaluate the health status of orthopedic residents (Table 1). According to the data from Turkish Association of Orthopedics and Traumatology (TOTBID), there are over 900 residents currently working in our country and we aimed to reach as many as possible to obtain a nation-wide conclusion. For this purpose, the 15-question survey was circulated in Turkish via the official e-mail group of TOTBID, and also through the social media platforms. In order to encourage the completion of the survey, questions were designed as the total filling time of all survey not to exceed three minutes. Participation in the survey was entirely voluntary, and participants who wished were given the right to leave blank questions they did not want to answer.

The survey was created using Google Forms (Mountain View, California, USA) and consisted of two parts. First part has designed to question the demographic data of the

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participants, such as age (older or younger than 30 years), gender, institution they work (university or training and research hospital), smoking, comorbidities and whether they had a COVID-19 infection or not in the last year. In terms of COVID-19 infection, participants only with a positive polymerase chain reaction (PCR) test were considered as "COVID-infected" whereas participants with compatible clinical or radiological findings with coronavirus infection but had a negative PCR result were considered as "COVID-free"; this classification was used in order to make an objective distinction between groups. The second part of the survey was designed to question the participants' working periods and virus exposure.

Table 1. A survey consisting of 15 questions

Your age?	
Your gender?	Male/Famale
Institution you work?	University Hospital/ Training and Research Hospital
Do you have any chronic diseases?	Yes/No
Do you smoke?	Yes/No
Did you have a PCR+COVID-19 infection in the last year?	Yes/No
How long have you worked in orthopedic emergency rooms during the last year?	Less than 4 days per month 4-8 days per month More than 8 days per month
How long have you worked in orthopedic inpatient services during the last year?	Less than 1 month 1-6 months More than 6 months
How long have you worked in orthopedic clinics during the last year?	Less than 1 month 1-6 months More than 6 months
How long have you worked in orthopedic operating rooms during the last year?	Less than 1 month 1-6 months More than 6 months
How long have you worked in COVID-related units (inpatient services, intensive care units, outpatient clinics, etc.) during the last year?	Less than 2 months 3-4 months 5-6 months More than 6 months
Have any of your colleagues in your clinic had a PCR+COVID-19 infection in the last year?	Yes/No
Have any of your family members who you live with had a PCR+COVID-19 infection in the last year?	Yes/No
Did you have any direct contact with a PCR+COVID-19 infected patient while wearing personal protective equipment?	Yes/No
Did you have any direct contact with a PCR+COVID-19 infected patient without wearing any personal protective equipment?	Yes/No

Participants were asked to specify their working periods in orthopedic emergency rooms, inpatient services, outpatient clinics, operating rooms and also in any COVID-related units (inpatient services, intensive care units, outpatient clinics). While determining the answer options, considering the working conditions of residents in daily practice, the working period in the orthopedic emergency room was determined as days/per month (less than 4 days, 4-8 days or more than 8 days) while the other periods were determined as months (less than 1 month, 1-6 months, more than 6 months). Participants were also questioned about whether they took part in treating a coronavirus-infected patient with or without personal protective equipment. They were also asked whether there were any infected healthcare professionals among their team or any infected family members staying in their house.

When evaluating the survey results, participants were divided into two groups based on whether they had a PCR-positive COVID infection or not: COVID-infected and COVID-free residents. Difference between groups in terms of demographic data, working periods and virus exposure were analyzed.

Statistical analysis was done with SPSS 26.0 version. Whether there was a difference between the groups in terms categorical data was compared with the Chi-square Test. When the observed values did not meet the Chi-square assumption, Fisher's Exact Test was used. The cases where the p value was less than 0.05 were considered significant.

3. Results

A total of 136 residents (approximately 15% of all residents in the country) completed the survey, of which 41 (30.1%) were infected. Among the participants, five residents chose not to fill in one question of the survey: three residents did not fill the "Working Period in COVID-related Units" question, one resident did not fill the "Working Period in Orthopedic Inpatient Services" question and another resident did not fill the "Working Period in Orthopedic Outpatient Clinics" question.

A significant difference was found between COVID-infected and COVID-free residents in terms of comorbidities ($p=0.026$). Detailed demographic data of the participants were shown in Table 2.

Residents with infected colleagues had lower infection rates ($p<0.001$). Detailed virus exposure of the residents can be seen in Table 3.

There was no significant difference between COVID-infected and COVID-free residents in terms of the working periods in orthopedics-related or COVID-related units ($p>0.05$ for each) (Table 4).

4. Discussion

Considering the high rate of infectiousness, lack of therapeutic treatment, continuing vaccine discussions and studies, and the prevalence of variants of the virus, the global pandemic of COVID-19 has affected all aspects of healthcare system (4). Residents have had their share of this

effect. There are several studies investigating the mental stress and educational defects of residents and other healthcare professionals from all branches in the literature, alas, studies evaluating the physical health status of them are quite limited (8-12).

Moreover, orthopedic residents were more worn out compared to other branches in this process, due to their active role in the care of both trauma patients and COVID-19 patients, although elective surgeries were suspended from time to time. To our knowledge, this study was the first to investigate the physical health status of orthopedic residents and this is the main strength of our study. Most important finding of our study was that approximately one third of orthopedic residents are infected during the pandemic in our country, with no significant difference between infection rates and working periods in orthopedics-related and COVID-related units. Furthermore, orthopedic residents who have COVID-infected colleagues in their team had lower infection rates.

Awareness, increased perception against COVID-19 and regular practice of protective behaviors such as washing hands regularly, covering mouth and nose when coughing, wearing masks and social distancing are known as the only effective ways in preventing the exposure of COVID-19 (13). Moreover, use of protective personal equipment is essential for healthcare workers (14).

Table 2. Demographic profile of the participants

Variables		Orthopedic Residents		P
		COVID-infected (n= 41)	COVID-free (n=95)	
Age	Under 30 years	25 (61%)	61 (64.2%)	0.720
	30 years and above	16 (39%)	34 (35.8%)	
Gender	Female	1 (2.4%)	1 (1.1%)	0.514
	Male	40 (97.6%)	94 (98.9%)	
Institution	Training and Research Hospitals	24 (58.5%)	67 (70.5%)	0.173
	University Hospitals	17 (41.5%)	28 (29.5%)	
Comorbidity	Yes	5 (12.2%)	2 (2.1%)	0.026
	None	36 (87.8%)	93 (97.9%)	
0.026	Yes	13 (31.7%)	43 (45.3%)	0.140
	None	28 (68.3%)	52 (54.7%)	

n: number of samples; P: statistical significance value

Table 3. History of infection among team members, family members and patients

Variables		Orthopedic Residents		P
		COVID-infected (n= 41)	COVID-free (n=95)	
Infection amongTeam Members	Yes	28 (68.3%)	92 (96.8%)	<0.001
	No	13 (31.7%)	3 (3.2%)	
Infection among Family Members	Yes	15 (36.6%)	22 (23.2%)	0.106
	No	26 (63.4%)	73 (76.8%)	
Contact with an Infected Patient with PPE*	Yes	35 (85.4%)	89 (93.7%)	0.184
	No	6 (14.6%)	6 (6.3%)	
Contact with an Infected Patient without PPE*	Yes	28 (68.3%)	74 (77.9%)	0.235
	No	13 (31.7%)	21 (22.1%)	

*PPE: Personal Protective Equipment; n: number of samples; P: statistical significance value

Table 4. Working periods of residents in orthopedics-related and COVID-related units

Variables		Orthopedic Residents		P
		COVID-infected (n= 41)	COVID-free (n=95)	
Working Period in Emergency Rooms (Per month)	0-4 days	10 (24.4%)	25 (26.3%)	0.956
	4-8 days	14 (34.1%)	33 (34.7%)	
	>8 days	17 (41.5%)	37 (38.9%)	
Working Period in Orthopedic Inpatient Services*	<1 month	11 (26.8%)	26 (27.7%)	0.955
	1 – 6 months	11 (26.8%)	27 (28.7%)	
	> 6 months	19 (46.3%)	41 (43.6%)	
Working Period in Orthopedic Outpatient Clinics*	<1 month	16 (39%)	29 (30.9%)	0.563
	1 – 6 months	12 (29.3%)	27 (28.7%)	
	> 6 months	13 (31.7%)	38 (40.4%)	
Working Period in Orthopedic Operating Rooms	<1 month	7 (17.1%)	14 (14.7%)	0.891
	1 – 6 months	15 (36.6%)	33 (34.7%)	
	> 6 months	19 (46.3%)	48 (50.5%)	
Working Period in COVID-related Units*	0 – 2 months	19 (46.3%)	40 (43.5%)	0.056
	3 – 4 months	18 (43.9%)	25 (27.2%)	
	5 – 6 months	3 (7.3%)	14 (15.2%)	
	> 6 months	1 (2.4%)	13 (14.1%)	

*Not all the participants have completed the survey. n: number of samples; P: statistical significance value.

Hirschmann et al. have stated the importance of using personal protective equipment and raising awareness for orthopedic surgeons (15). Our results are consistent with the literature. Although, nearly one third of all participants got infected during the pandemic, the fact that residents who have COVID-positive colleagues in their team had lower infection rates shows the importance of conscious and awareness in preventing contamination. Furthermore, the lack of difference in infection rates between orthopedic residents who treat COVID-infected patients with or without personal protective equipment supports our hypothesis that practicing protective behaviors and increasing awareness is crucial to prevent getting infected.

The fact that orthopedic residents working in training and research hospitals have significantly higher working periods in COVID-related units compared to residents working in university hospitals (p=0.002) can easily be explained by the administered regulations and decree laws, considering the transformation of large-scale training and research hospitals into pandemic hospitals. On the other hand, the similarity of infection rates among residents working in university or training and research hospitals and among orthopedics-related or COVID-related units indicates that, regardless of the institution and unit they work, orthopedic residents act consciously and well-informed against the pandemic and always pays attention to preventive behaviors and use of personal protective equipment, if necessary. During busy working hours, regardless of their duties of emergency nursing care or COVID-19 patient care, all residents must take care of themselves and pay attention to preventive measures.

A meta-analysis has stated that chronic respiratory diseases, diabetes, hypertension and cardiovascular disease are risk factors for COVID-19 infections (16). Abdulla et al. have found a correlation between the severity of COVID-19 and asthma and smoking (17). Algahtani et al. have stated that smoking and its underlying respiratory pathologies are known to be risk factors for severe COVID-19 infection (18). In our survey, 56 (41.2%) participants were smokers and 7 (5.1%) participants had chronic diseases; 4 (2.9%) participants had asthma whereas 3 (2.2%) participants had cardiovascular diseases. We have found a significant relationship between the presence of comorbidities and the occurrence of infection (p=0.026), similarly to the literature. On the other hand, the lack of a relationship between smoking and the infection rates in our study (p=0.140) can be explained by the relatively small sample size. Furthermore, there are many confounding factors related with infection rates, such as co-existing comorbidities, state of immune system, body resistance and having an active daily life.

There are many studies investigating the relationship between COVID-19 infection and age and gender. In their study of 8541 COVID-19 patients, Takeuchi et al. concluded that the incidence of the disease did not differ between genders (19). However, Martin et al. have stated that rate of infection is higher in women whereas complication rates and severity are higher in men (20). Many studies examining the relationship between age and COVID-19 infection have found a significant relationship between older age and severity and mortality of the disease (21, 22). However, most of these studies set the age of 60 as the limit. In our survey, with an age limit of 30 years, no significant difference was found between groups in terms of age and gender. Considering that the majority of orthopedic residents are male and younger adults, it was expected to find no relationship between the age and gender of the participants and the prevalence of the disease.

There are several limitations in our study. First and foremost, although our findings suggest a nation-wide idea about the health status and virus exposure of orthopedic residents across the country, a participation rate of 15% is an important limitation. Different results can be obtained with larger surveys, where the participation of more residents is encouraged. Moreover, by including other surgical and internal branches, better results can be obtained. Finally, the participants were divided into only two groups, as COVID-infected and COVID-free, according to the PCR results. Although this classification, as mentioned before, was chosen in order to make an objective distinction, the accuracy of the PCR test may affect the results of our study.

We have reached the conclusion that a third of all the participants in our study were infected with COVID-19, regardless of the clinics they work in. The infection rate among the orthopaedics residents were reported for the first time in the literature with this study. Residents with infected healthcare professionals in their team have lower infection rates, indicating the importance of self-awareness and protective behaviors. During the pandemic, all healthcare professionals should pay maximum attention for simple measures, like practicing protective behaviors and use of personal protective equipment.

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Conflicts of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Research Article

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The impact of corrective surgery for thoracolumbar kyphotic deformity on health-related quality of life in patients with ankylosing spondylitis

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Abstract

Ankylosing spondylitis is a chronic inflammatory disease. It might affect the facet, sacroiliac joint, and vertebra regions. It leads to thoracolumbar kyphotic deformity in the spine region. Both ankylosing spondylitis and kyphotic deformity impair the patients' quality of life. Our objective was to assess the impact of the correction of kyphotic deformity in ankylosing spondylitis on health-related quality of life. 11 thoracolumbar kyphosis patients diagnosed with ankylosing spondylitis were operated and their deformity was corrected. Medical Outcome Study Short Form-36 (SF-36), visual analog scale (VAS), and Oswestry disability index (ODI) studies were performed on patients before surgery and 1 month after surgery to assess their impact on health-related quality of life. In our study, postoperative changes in the sub-parameters of the SF-36 test, which was used to assess the health-related quality of life of patients, were determined to be statistically significant compared to post-surgery. Likewise, postoperative changes in VAS and ODI tests compared to pre-surgery were also statistically significant. Corrective surgery of thoracolumbar kyphosis in patients with ankylosing spondylitis has a positive impact on both better health-related quality of life and recovery of back and low back pain.

Keywords: ankylosing spondylitis, thoracolumbar kyphosis, visual analog scale, oswestry disability index, health-related quality of life

1. Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease. It primarily affects sacroiliac and facet joints as well as intervertebral disc structures. It causes thoracolumbar kyphotic deformity. This deformity causes cosmetic and functional impairments in patients and commonly ends up with a decrease in quality of life (1). The techniques of Multiple Smith-Petersen osteotomy (SPO), pedicle subtraction osteotomy (PSO), poly-segmental wedge osteotomy (PWO), and vertebral column resection (VCR) osteotomy are used in surgeries to correct thoracolumbar kyphotic deformity (2, 3).

AS has various effects on patients' health-related quality of life (HRQoL), including both physical and psychological domains (4). One of the most popular tools to study these effects is the 36-item Medical Outcome Study Short Form-36 (SF-36) test. SF-36 defines to what extent a health-related problem impacts an individual's functional ability, mental state, and perceived well-being in social and physical aspects (5). Moreover, patients with AS have common back pain. Visual analog scale (VAS) and Oswestry Disability Index (ODI) are frequently used methods in assessing these effects (6, 7).

The impact of AS disease on health-related quality of life has been revealed in the literature (8, 9). Furthermore, it is prevalently used by researchers for rheumatological and musculoskeletal disorders (10).

Our objective in the study was to assess the clinical well-being after corrective surgery of kyphotic deformity that occurs in AS disease, which is not adequate in the literature, using the VAS and ODI scales, and the impact on health-related quality of life using the 36-item Study Short Form-36 test.

2. Materials and Methods

Our study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before the tests. Ethics approval was obtained from Memorial Hospital ethics committee (Memorial Hospital ethics committee's decision dated 26.04.2021 and numbered 16). Between January 2017 and February 2021, 11 patients who met AS New York criteria and were operated with the diagnosis of thoracolumbar kyphosis were included in the study (11).

2.1. Inclusion criteria

1) Patients with a T1--12 angle of ≥60 °

2) Patients with a Global kyphosis (GK) angle of ≥70 ° (GK: Cobb angle between T1 and L5)

3) Patients with a coronal curve of <20 °

4) To not have a history of spine surgery

2.2. Exclusion criteria

Patients with severe systematic disease PSO was applied to 9 of 11 patients and multi-level SPO was applied to 2 of them. VAS, ODI, and SF-36 assessment studies were performed

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before the surgery and 1 month after surgery. SF-36 assessment scale consists of 8 sub-parameters. The assessment is performed with the sub-parameters including; physical function (10 items), social function (2 items), role physical (4 items), role emotional (3 items), mental health (5 items), vitality (4 items), bodily pain (2 items) and general health (5 items) (5). The sub-parameters are presented in Table I. In the ODI scale, the responses to the queries of pain severity, degree of pain change during personal care, lifting load, walking, standing, sitting, sleeping, social life, and travels are assessed. A score between 0 and 5 is given for each answered query. Queries, which have not been answered by the patient, are not taken into consideration. Assessment is calculated via the formula of the patient score= (the score obtained by the patient/the maximum possible score) X 100, considering the answered queries (12). VAS is used for digitizing some values that cannot be measured numerically. Two end definitions of the parameter to be assessed are written on both ends of a 100 mm line, and the assessment is made by asking the patient to indicate where his condition suits on this line by drawing a line or by placing a point or pointing (13).

Table I. Demographic characteristics of the patients

Number of patients	n: 11
Male	72% (n:8)
Female	28% (n:3)
Age	54.3 ±10.3

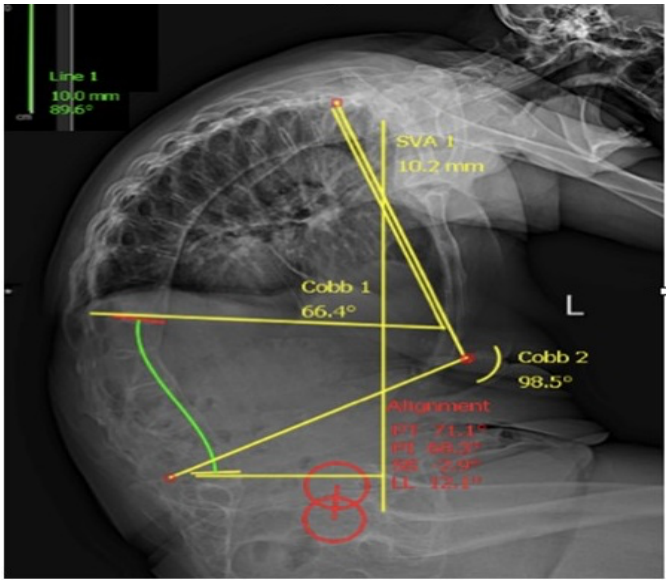

Fig. 1. Preoperative measurements of the patient with ankylosing spondylitis via the Surgimap. SVA: Sagittal Vertical Axis, PT: Pelvic Tilt, SS: Sacral Slopej Pl: Pelvic Insidence LL: Lumbar Lordosis

2.3. Surgery prodecure

Scheduling of the surgeries was made based on the scoliosis graphics taken from the patients before surgery. Measurements were made using the software of Surgimap (Neramis, Inc). The scoliosis radiograph of a measured patient is presented in Fig. 1. Under general anesthesia, the patient was placed on the operating table in a V-shaped prone position. Motor evoked potentials (MEP) and somatosensory evoked potentials (SSEP) of all patients were examined during surgery. The surgical area was determined via C-arm fluoroscopy. The subcutaneous was opened with a posterior midline approach. The fascia was opened bilaterally and the paravertebral muscles were dissected according to the procedure. Pedicle screws were placed. Osteotomy was applied to the vertebra or vertebrae according to the osteotomy technique, which was calculated on the Surgimap at the onset of the procedure. Correction maneuvers were performed with the help of the spinal surgery table under fluoroscopy and neuromonitoring. The layers were closed according to the procedure after the fusion process was performed and hemostasis was achieved, and then the procedure was completed. After surgery, follow-up scoliosis radiographs were taken on the second day, and the degree of correction of kyphotic deformity was measured (Fig. 2).

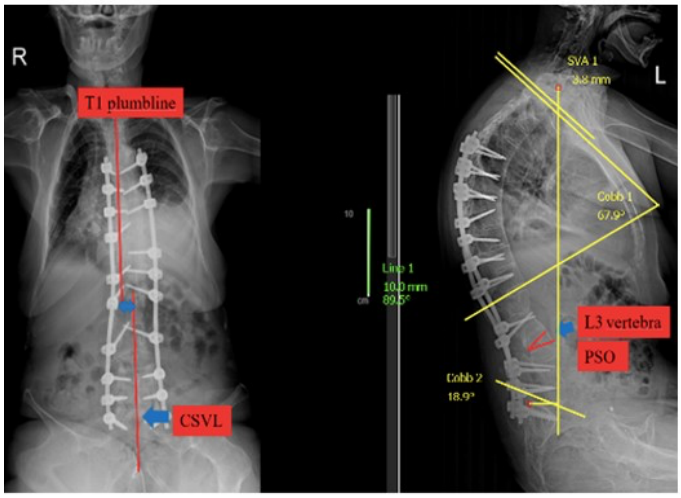

Fig. 2. Corrective surgery with L3 vertebra pedicle subtraction osteotomy. PSO: Pedicle Substraction Osteotomy, CSLV: Central Sacral Vertical Line

2.4. Statistical method

Statistical analysis was performed using Statistical Package for the Social Sciences programme (Version 22; SPSS, Chicago, IL). The Kolmogorov-Smirnov test was used to determine the normality of qualitative the data. Skewed data were analyzed with nonparametric tests. Baseline characteristics were given as mean (standard deviation). Wilcoxon test applied for dependent quantitative data (pre-post). Statistical significance was taken as $p<0.05$.

3. Results

11 patients who had been diagnosed with AS and underwent deformity surgery for thoracolumbar kyphosis were included in our study. Of the 11 patients, 72% (n=8) were male and 28% were female (n=3). The mean age was 54.3 ± 10.3 years. The demographic characteristics of the patients are presented in Table I. In our study, we assessed 8 sub-parameters of the SF-36 test during the preop period and at the 1th month during the postop period to examine health-related quality of life. In preoperative physical function assessment, the scoring was as

follows; minimum:5.0, maximum:30.0, mean:14.032±6.8823, while the postop scoring was as follows; minimum: 80.0, maximum: 100.0, mean: 91.452±6.4799. Regarding the statistical analysis of the physical function changes, the result has a p-value of<0.05 and the difference was significant. In the role physical assessment, preop scoring was as follows; minimum:0.0, maximum:50.0, mean 15.323±19.0147, while postop scoring was as follows; minimum:25.0, maximum:100.0, mean:75.806±22.8070. Regarding the statistical analysis of the role of physical changes, the difference was significant with p<0.05. In the role emotional assessment, preop scoring was as follows; minimum: 0.0, maximum: 66.6, mean: 9.668±17.6072, and postop scoring was as follows; minimum: 33.3, maximum: 100.0, mean: 88.155±20.2954. The difference was significant in the statistical analysis of the role physical changes with p<0.05. In the assessment of vitality, preop scoring was as follows; minimum: 0.0 maximum: 50.0 mean: 16.290±13.4144, and postop scoring was minimum: 50.0, maximum: 80.0, mean: 66.290±8.3634. The difference was significant in the statistical analysis of the vitality changes with p<0.05.

Regarding the assessment of mental health, preop scoring was as follows; minimum: 12.0, maximum: 72.0, mean: 45.290±18.1369, and postop scoring was minimum: 36.0, maximum: 80.0, mean: 65.290±11.5649. The difference was significant in the statistical analysis of the mental health changes with p<0.05. In the assessment of social function, preop scoring was as follows; minimum: 0.0, maximum: 50.0, mean: 14.516±16.1686, and postop scoring was minimum: 7.0, maximum: 100.0, mean: 75.629±19.9629. The difference was determined to be significant in the statistical analysis of the social function changes with p<0.05. In the assessment of bodily pain, preop scoring was as follows; minimum: 0.0, maximum: 67.5, mean: 13.500±15.1231, and postop scoring was minimum: 65.0, maximum: 100.0, mean: 89.032±9.8463. The difference was found to be significant in the statistical analysis of the bodily pain changes with p<0.05. In the general health assessment, preop scoring was as follows; minimum: 10.0, maximum: 50.0, mean: 33.387 ± 11.7748, and postop scoring was minimum: 50.0, maximum: 85.0, mean: 70.806±10.7313. The difference was significant in the statistical analysis of the general health changes with p<0.05. Statistical data are summarized in Table II and Table III. Moreover, we used VAS and ODI tests in our study to assess the pain. Preop VAS scoring was minimum: 5.0, maximum: 10.0, mean: 7.839±1.3928, and postop scoring was minimum: 1.0, maximum: 4.0, mean: 2.065±1.0935. The difference was significant in the statistical analysis of the changes in the VAS values with a p<0.05. Preop ODI scoring was minimum: 53.3, maximum: 90.0, mean: 77.765±11.5304, and postop scoring was minimum: 0.0, maximum: 8.5, mean: 5.042±2.0334. In the statistical evaluation of the changes in ODI data, the difference was significant with a p-value of<0.05. Statistical data are summarized in Table 4 and Table 5.

Table 2. The values of SF-36 sub-parameters of the patients

	Minimum	Maximum	Mean	Std.	Minimum
Physical function (preop)	5.0	30.0	14.032	6.8823	47.366
Role physical (preop)	.0	50.0	15.323	19.0147	361.559
Role emotional (preop)	.0	66.6	9.668	17.6072	310.012
Vitality (preop)	.0	50.0	16.290	13.4144	179.946
Mental health (preop)	12.0	72.0	45.290	18.1369	328.946
Social function (preop)	.0	50.0	14.516	16.1686	261.425
Bodily pain (preop)	.0	67.5	13.500	15.1231	228.707
General health (preop)	10.0	50.0	33.387	11.7748	138.645
Physical function (postop)	80.0	100.0	91.452	6.4799	41.989
Role physical (postop)	25.0	100.0	75.806	22.8070	520.161
Role emotional (postop)	33,3	100,0	88,155	20.2954	411.905
Vitality (postop)	50.0	80.0	66.290	8.3634	69.946
Mental health (postop)	36.0	80.0	65.290	11.5649	133.746
Social function (postop)	7.0	100.0	75.629	19.9629	398.516
Bodily pain (postop	65.0	100.0	89.032	9.8463	96.949
General health (postop)	50.0	85.0	70.806	10.7313	115.161

Table 3. Statistical analysis results of SF-36 parameters

	Z	Asymp. Sig. (2-tailed)
Physical Functions (postop)	-4.877[b]	0
Physical Functions (preop)	-4.828[b]	0
Role physical (postop)	-4.947[b]	0
Role physical (preop)	-4.871[b]	0
Role emotional (postop)	-4.869[b]	0
Role emotional (preop)	-4.858[b]	0
Vitality (postop)	-4.777[b]	0
Vitality (preop)	-4.868[b]	0

a. Wilcoxon Signed Ranks Test, b. Based on negative ranks.

Table 4. Results of patients' VAS and ODI values

	Minimum	Maximum	Mean	Std. Deviation	Variance
VAS (preop)	5.0	10.0	7.839	1.3928	1.940
VAS (postop)	1.0	4.0	2.065	1.0935	1.196
ODI (preop)	53.3	90.0	77.765	11.5304	132.951
ODI (postop)	.0	8.5	5.042	2.0334	4.135

VAS: Visual Analog Scale ODI:, Oswestry Disability Index

Table 5. VAS and ODI statistical values of the patients

Test Statistics		
	VAS (preop) VAS (postop)	ODI (preop) ODI (postop)
Z	-4.905b	-4.860b
Asymp. Sig.	.000	.000

4. Discussion

Ankylosing spondylitis is a chronic progressive inflammatory disease associated with HLA-B27, included in the group, namely spondyloarthritis (14). Back pain and hip pain due to involvement of the spine and sacroiliac joints are common in AS. It leads to fusion particularly in the anterior part of the vertebra and causes limitation of movement and related thoracolumbar kyphosis (15, 16).

Planning of kyphosis correction surgery and the osteotomy technique to be chosen in AS disease is effective on the amount of correction. SPO, PWO, PSO, and VCR are among the osteotomy techniques that are used in corrective surgery for deformity of AS patients (17, 18, 19). Deformity is progressive in AS disease. Thoracolumbar kyphosis in patients leads to sagittal imbalance. Due to this, the patient experiences restriction of forward gaze. It leads to impaired walking and problems in activities such as climbing up and down stairs as well as climbing ramps. Patients might experience frequent falls. Hence, it causes physical dysfunction and physical problems (20, 21). Likewise, the results of our study were in line with the literature. Before surgery, patients had functional restrictions due to their deformity. Following the deformity correction surgery, the restriction of forward gaze recovered in patients thanks to the correction of sagittal imbalance. Daily walks, climbing up and downstairs, climbing ramps, and routine activations of the patients improved. The restriction due to physical function and physical problems, which are among the SF-36 sub-parameters, differed significantly compared to preop.

Deterioration in bone structure, vertebral collapse fractures, inflammatory events in the joints, and flexion contracture deformities of the spine cause back and hip pain (22). Deformity in AS patients induces internal organ compression and rib pain due to advanced kyphosis (23). In our study, we used the VAS and ODI scale to assess pain. An improvement was detected in postop pain compared to preop. The changes in these values were statistically significant. Furthermore, the change in the pain sub-parameter of the SF-36 scale was statistically significant. The results related to pain experienced prior to correction surgery were similar to the findings in the literature (24).

Redesigning the sagittal balance in the spine, eliminating the need for compensatory mechanisms following correction surgery, and eliminating the compressive pain in the ribs or organs due to deformity by correction help to achieve these outcomes. Due to physical dysfunction and pain, the daily activities of AS patients fall behind compared to the normal population. This situation deteriorates social interactions. In our study, the change in the social function sub-parameter of the SF-36 scale displayed a statistically significant change after surgery compared to the preop period. In the postop period, a significant improvement was achieved in family relationships, time spent with the society, increase in job competencies, self-sufficiency and emotional well-being, and social function changes. Statistically, these sub-parameters changed significantly. There is considerably limited information in the literature about the basic mechanism of fatigue, which is clinically common in AS patients. However, it has been revealed in the previous studies that there are strong correlations between the patient's individual daily activity, physical capacity, back pain, spine flexibility, and quality of life (25). In our study, postop fatigue improved significantly compared to the preop period. The change after surgery was statistically significant. We consider that this result is due to the improvement of the physical functions of the patient, the ability to perform daily activities, no need for compensation mechanisms due to deformity correction, and the absence of pain. The changes in the general health perception in the SF-36 scale sub-parameter were statistically significant after surgery compared to the preop period. It is due to changes in physical and social functions, as well as a reduction in pain and fatigue. Our study has some limitations. Coronal imbalance in AS patients was not assessed in the study. The small number of patients and short follow-up periods are other limitations of our study.

AS is important for spine surgeons because of its progressive deformity, albeit it is a chronic inflammatory disease. The anormal balance in spinopelvic parameters impacts the quality of life directly. As back pain, progressive restriction of spine movements, and severe thoracolumbar kyphosis impair the quality of life in patients, well-planned surgery will be helpful in improving the quality of life by solving these problems.

Conflict of interest statement

The authors have no conflict of interest declaration.

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Anxiety, sleep quality and their relationship with inflammation in Takayasu's Arteritis

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Abstract

This study aimed to investigate anxiety, sleep quality, and their relationship with inflammation in patients with Takayasu's arteritis (TA). Twenty-four patients diagnosed with TA and sex and age matched healthy controls were enrolled in the study. The quality of sleep was evaluated by Pittsburgh sleep quality index (PSQI), and anxiety were assessed by The Spielberger State-Trait Anxiety Inventory and Hamilton Anxiety Rating Scale. The disease activity was evaluated with sedimentation and C-reactive protein (CRP). The levels of anxiety and overall PSQI scores were significantly higher in TA than in healthy controls. Sleep disturbance was identified in half of the TA patients. The presence of systemic findings, CRP, and all subscale items of the Hamilton Anxiety Rating Scale and Spielberger State-Trait Anxiety Inventory were found to be higher in TA patients with poor sleepers compared to good sleepers. There was a significant correlation between all components of PSQI and anxiety scores. The present study has demonstrated higher anxiety scores and poor sleep quality among patients in TA compared with healthy controls. TA patients with systemic findings and high inflammation should be evaluated for poor sleep quality. Also, remission in disease activity may be associated with better sleep and less anxiety scores.

Keywords: Takayasu's arteritis, anxiety, sleep quality, inflammation

1. Introduction

Takayasu's arteritis (TA) is a chronic granulomatous large-vessel arteritis predominantly affecting the aorta and its main branches (1). The inflammatory process of TA causes thickening, narrowing, occlusion of the affected vessels and finally results in various symptoms such as dizziness, upper limb intermittent claudication, aortic regurgitation, and retinopathy (1). Mortality and morbidity are generally related to ongoing inflammation and ischemia (1, 2).

Chronic vascular inflammation may cause morbidity as it affects the quality of life and functional status. In particular, in systemic vasculitis, health-related quality of life decreased at physical, social, and emotional levels and impaired compared to the general population (3, 4). Recent studies have suggested that quality of life parameters are impaired in small to medium vessel systemic vasculitides and also in TA (5). A study demonstrated that the quality of life including both physical and mental components was lower in TA patients than in healthy controls (6).

Depression and fatigue affect the quality of life with the social burden (7). Depressive disorders may be seen in many rheumatic diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), primary Sjogren's syndrome (SjS), and ankylosing spondylitis (8). The anxiety, depression, and fatigue scores were higher in SjS compared to healthy individuals (9, 10). Depression and high disease activity scores appear to be predictors of low sleep quality in RA patients (11). In patients with SLE, pain and fatigue are associated with sleep disorders (12). The psychosocial, psychological factors, and especially depression were reported as possible factors for sleep disorders in these patients (12). It has been reported that impaired quality of life, depression, and anxiety are more common in patients with TA (13).

To our knowledge, limited studies about anxiety, sleep quality, and their relationship with inflammation in patients with TA were presented. Our aim is to investigate the association between sleep quality and anxiety in the study. We also evaluated the relationship between inflammation markers with sleep quality and anxiety.

2. Materials and Methods

2.1. Patients enrollment

A total of 24 patients with TA and sex and age matched healthy subjects without any diseases were enrolled in this cross-sectional study in a single institution. All the patients

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fulfilled the 1990 American Society of Rheumatology classification criteria of TA (14). The study protocol was approved by the Faculty of Medicine Ethics Committee and designed consistent with the Declaration of Helsinki (approval number 2021/5). Written informed consent was obtained from all subjects. The clinical and laboratory characteristics such as age, sex, smoking, alcohol, medication, disease duration, presence of systemic findings, occupation, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) were evaluated. The disease activity of TA was evaluated with ESR and CRP.

2.2. Measurement of sleep quality: Pittsburgh sleep quality index

The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality over a 1-month time interval. Seven components including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction were evaluated. A global score (range: 0 to 21) was obtained from the components (15). Patients with a total score>5 are defined as poor sleepers.

2.3. Measurement of anxiety: The Hamilton Anxiety Rating Scale

It was used to measure the severity of perceived anxiety symptoms with 14 symptom-defined elements and caters to both psychological and somatic symptoms. Each item is scored on a basic numeric scoring of 0 (not present) to 4 (severe), and 0-7=no/minimal anxiety; 8-14=mild anxiety; 15-23=moderate anxiety; and 24 or greater=severe anxiety (16).

2.4. Measurement of anxiety: The Spielberger State-Trait Anxiety Inventory

The Spielberger State-Trait Anxiety Inventory (STAI) was used to assess the degree of anxiety with 2 subscales as state anxiety (STAI-S) and trait anxiety (STAI-T) (17). The statements in the inventory are rated from 1 to 4 according to how much of each item the individual is currently feeling (STAI-S) or how often each item is felt (STAI-T). The total scores range from 20, which reflects the lowest possible degree of anxiety (state or trait), to 80, the highest possible anxiety score (17).

2.5. Statistical analysis

Data statistics were analyzed with Statistical Package for Social Sciences (SPSS) for Windows (SPSS version 20.0, IBM, USA). The data were expressed as mean±standard deviation, median [25p-75p], frequency (n), and percentage (%). Kolmogorov-Smirnov test was used to determine the distribution of normality. The Student's t-test and Mann-Whitney U test were used to compare differences between two independent groups according to the distribution of normality. The chi-squared test and Fisher's exact test were used for the analysis of categorical data and independence between variables. Pearson/Spearman's correlation analyses were used to evaluate the relationship between two continuous variables. A p-value of less than 0.05 was considered statistically significant.

3. Results

A total of 24 patients with TA and age-sex matched healthy groups were included in the study. The mean age of patients with TA was 40.5±15.3 years, it was 39.2±12.4 years for the healthy group. The majority of the patients were female. The ratio of unemployed and employed patients was 6 (25.0%) and 18 (75.0%), respectively. 79.2% of the patients had systemic findings. There were no significant differences in age, gender, marital status, occupation, smoking, alcohol taking, and psychiatric medication between both groups. The mean ESR was 59.8±25.8 mm/h and the median CRP was 26.9 [6.5-35.8] mg/L, respectively. All patients were taking a corticosteroid, methotrexate, azathioprine, tocilizumab, or their combinations. Demographic, clinical, and laboratory characteristics of patients with TA are shown in Table 1.

Table 1. Demographic, clinical, and laboratory characteristics of patients with Takayasu arteritis

Demographic Parameters	Takayasu arteritis (n=24)	Healthy Group (n=24)	p
Age (years)*	40.5±15.3	39.2±12.4	NS
Gender n (%) Male Female	 2 (8.3%) 22 (91.7%)	 2 (8.3%) 22 (91.7%)	NS
Disease Duration (months)*	29.7±18.3	-	
Marital status n (%) Alone Marriage/family	 4 (16.7%) 20 (83.3%)	 8 (33.3%) 16 (66.7%)	NS
Occupation n (%) Employed Unemployed	 6 (25.0%) 18 (75.0%)	 10 (41.7%) 14 (58.3%)	NS
Smoking n (%) Yes No	 4 (16.7%) 20 (83.3%)	 7 (29.2%) 17 (70.8%)	NS
Alcohol n (%) Yes No	 1 (4.2%) 22 (95.8%)	 3 (12.5%) 21 (87.5%)	NS
Psychiatric Medication n (%)	6 (25.0%)	3 (12.5%)	NS
Presence of Systemic Findings n (%)	19 (79.2%)	-	
ESR (mm/h)*	59.8±25.8	17.2±14.7	**<0.001**
CRP (mg/L)**	26.9 [6.5-5.8]	2.0 [2.0-2.3]	**<0.001**

*mean± standard deviation; **median [25-75p]; ESR, erythrocyte sedimentation Rate; CRP, C-reactive protein; NS: not significant

The median psychological and somatic Hamilton Anxiety Rating Scale scores were 5.0 and 5.5 in patients with TA. 12.5% of the patients had moderate-severe anxiety and 4.2% of patients had severe anxiety. In the patient group, the mean state anxiety and trait anxiety scores were 43.9±6.9 and 45.7±8.6, respectively. When the patients and control groups were compared in terms of anxiety with STAI and Hamilton

Anxiety Rating Scale, the scores were significantly higher in patients with TA compared to healthy control (Table 2).

The PSQI scores for subjective sleep quality (p=0.01), sleep efficiency (p=0.002), sleep disturbance (p=0.003), daytime dysfunction (p=0.01), and overall score (p=0.003) were significantly higher in patients with Takayasu arteritis compared to the controls (Table 2). According to the PSQI, 12 (50.0%) of the patients with Takayasu arteritis and 3 (12.5%) of the healthy controls were classified as poor sleepers. There were significant differences in CRP, presence of systemic findings, Hamilton Anxiety Rating Scale score, STAI-S score, and STAI-T score. However, no significant differences were found in age, gender, marital status, occupation, smoking, alcohol, and ESR between poor and good sleepers in TA.

Table 2. The distribution of anxiety scales and Pittsburgh sleep quality index in patients with Takayasu arteritis and healthy controls

Variable	Takayasu arteritis (n=24)	Healthy Group (n=24)	p
Anxiety Status*			
Mild	12 (50.0%)	7 (29.2%)	
Moderate to severe	3 (12.5%)	-	**0.01**
Severe	1 (4.2%)	-	
Hamilton Anxiety Rating Scale Score**			
Psychological	5.0 [3.0-6.0]	2.0 [0-3.0]	**<0.001**
Somatic	5.5 [3.0-8.75]	1.0 [0-4.75]	**0.001**
Spielberger State-Trait Anxiety Inventory Score***			
State Anxiety	43.9±6.9	33.6±9.9	**<0.001**
Trait Anxiety	45.7±8.6	35.1±12.2	**0.001**
Pittsburgh sleep quality index			
Sleep latency	1.0 [0-2.0]	0 [0-1.0]	0.06
Sleep efficiency	0 [0-1.0]	0 [0-0]	**0.002**
Sleep duration	1.0 [0-1.0]	0 [0-1.0]	0.11
Sleep disturbance	1.0 [1,0-1.0]	1,0 [0-1.0]	**0.003**
Sleep medication	0 [0-0.75]	0 [0-0]	0.51
Daytime dysfunction	1.0 [0.25-2.0]	0 [0-1.0]	**0.01**
Subjective sleep quality	1.0 [0.25-1.0]	0 [0-1.0]	**0.01**
Overall score	5.5 [3.0-9.0]	0 [0-5.0]	**0.003**

*Hamilton Anxiety Rating Scale n (%); **median [25-75p]; ***mean±standard deviation

The PSQI scores for subjective sleep quality (p=0.002), sleep latency (p=0.004), sleep duration (p=0.02), sleep efficiency (p=0.02), sleep disturbance (p=0.03), daytime dysfunction (p=0.02), and total score (p<0.001) were significantly higher in poor sleepers than good sleepers. The comparison of patients' characteristics between good and poor sleepers are shown in Table 3.

Table 3. The comparison of patient characteristics between good and poor sleepers in patients with Takayasu Arteritis

	Poor sleeper (n=12)	Good sleeper (n=12)	p
Age (years)*	41.4±16.9	39.5±14.2	0.77
Gender (M: F)	1:11	1:11	1.00
Disease Duration (months)*	25.7±19.2	33.8±17.2	0.29
Presence of Systemic Findings n (%)	12 (100%)	7 (58.3%)	**0.03**
Education Status n (%)			
Less than high school	5 (41.7%)	6 (50.0%)	
High School	4 (33.3%)	6 (50.0%)	0.28
University	3 (25.0%)	-	
Marital status n (%)			
Alone	3 (25.0%)	1 (8.3%)	0.59
Marriage/family	9 (75.0%)	11 (91.7%)	
Occupation n (%)			
Employed	4 (33.3%)	2 (16.7%)	0.64
Unemployed	8 (66.7%)	10 (83.3%)	
Smoking n (%)			
Yes	3 (25.0%)	1 (8.3%)	0.59
No	9 (75.0%)	11 (91.7)	
Alcohol n (%)			
Yes	1 (8.3%)	-	1.00
No	11 (91.7%)	12 (100%)	
ESR (mm/h)*	61.2±26.8	51.5±24.3	0.36
CRP (mg/L)**	33,8 [21.5-39.1]	14,8 [4.4-30.1]	**0.01**
Anxiety Status***			
Mild	7 (58.3%)	5 (41.7%)	
Moderate to severe	3 (25.0%)	-	**0.02**
Severe	1 (8.3%)	-	
Hamilton Anxiety Rating Scale Score**			
Psychological	6.0 [4.2-8.0]	3.0 [1.2-5.0]	**0.02**
Somatic	8.0 [6.0-10.7]	3.5 [2.2-5.0]	**0.07**
Spielberger State-Trait Anxiety Inventory Score*			
State Anxiety	47.4±6.8	40.5±6.5	**0.01**
Trait Anxiety	52.0±5.6	34.9±6.0	**<0.001**

*mean± standard deviation; **median [25-75p]; ***Hamilton Anxiety Rating Scale n (%); ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

A significant correlation was found between CRP and overall score, sleep quality, with the correlation coefficient 0.429 and 0.111, respectively (p<0.05). The sleep latency, efficiency, duration, disturbance, medication, daytime dysfunction, and sleep quality were found to be correlated with Hamilton Anxiety Rating Scale Score, STAI-S, and STAI-T score. There was no significant correlation between STAI-T and sleep medication. Correlation coefficients between components of PSQI and clinical, laboratory, and anxiety scores in patients with TA are presented in Table 4.

Table 4. Correlation coefficients between components of Pittsburgh sleep quality index and clinical, laboratory and the anxiety scores in patients with Takayasu Arteritis

	Overall score	Sleep Latency	Sleep efficiency	Sleep duration	Sleep disturbance	Sleep medication	Daytime dysfunction	Sleep quality
Age (years)	0.079	0.028	0.183	0.085	0.009	0.220	0.078	0.211
Disease duration (months)	-0.233	-0.358	-0.044	-0.062	-0.107	-0.127	-0.168	-0.017
ESR (mm/h)	0.306	0.417	0.192	0.370	0.386	0.257	0.025	0.184
CRP (mg/L)	0.429*	0.273	0.214	0.183	0.170	0.270	0.111	0.440*
Hamilton Anxiety Rating Scale Score Psychological Somatic	0.652** 0.700**	0.516** 0.558**	0.404* 0.410*	0.635** 0.451*	0.566** 0.523**	0.474* 0.457*	0.438* 0.577**	0.415* 0.552**
Spielberger State-Trait Anxiety Inventory Score State Anxiety Trait Anxiety	0.667** 0.822**	0.583** 0.761**	0.560** 0.671**	0.521** 0.500*	0.484* 0.452*	0.407* 0.286	0.476* 0.663**	0.455* 0.528**

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; *p < 0.05; **p < 0.01

4. Discussion

In the present study, sleep quality and anxiety were investigated in patients with TA. In our results, we observed a correlation between anxiety scores and PSQI. ESR values were not different between the good sleeper and poor sleeper Takayasu patients. There was a correlation between CRP and overall and sleep quality scores of the PSQI, while a similar was not found for ESR. The presence of systemic symptoms was associated with poor sleep. Moreover, the anxiety scores were higher in poor sleepers compared to the good sleepers in TA patients.

Elevated acute phase reactants such as ESR and CRP indicate inflammation and active disease in TA. Although ESR and CRP are neither highly sensitive nor specific for disease activity in TA, they are still used in clinical practice to monitor disease activity and incorporated into the NIH disease activity score as well as the Indian Takayasu Clinical Activity Score disease activity measurement (18). The progressive inflammatory pattern and active disease have been reported to be associated with poor outcomes and postoperative complications in TA (19). Inflammation, increase in the permeability of the blood-brain barrier, structural and functional changes in the central nervous system play an important role in the development of depression and fatigue (7). The association between rheumatic disease activity with depressive symptoms and fatigue was found in chronic rheumatologic diseases (20). Improvement in fatigue by blocking inflammatory cytokines with biological agents supports this. (20).

In TA, the mood, happiness, energy levels, and thus daily life activities of the patients are affected (21). In fact, it was reported that there were changes in their working life and their job duties and they resigned from their jobs (21). In addition, quality of life is associated with disease activity and better quality of life with disease remission in TA (21). Nevertheless, chronic inflammation and disease activity have less effect on fatigue in TA than inflammatory diseases such as RA and SLE (22). Even so, supportive help is required in these areas due to the association of disease activity with anxiety and depression (13). In our study, we found the correlation of CRP with STAI-T (p=0.04, r=0.406), and ESR with psychological anxiety score (p=0.006, r=0.540) in TA. Also, ESR (63.6±26.6 vs 42.0±16.1; p=0.03) and CRP (31 vs 21.3; p=0.21) were high in TA with anxiety compared to TA without anxiety. Moreover, there was a significant difference for systemic symptoms in anxiety patients compared to the non-anxiety group (p=0.02).

In a study, it was reported that anxiety and depression were higher in TA compared to healthy controls (13). Similarly, our patients had higher anxiety scores than healthy controls. We found the median psychological anxiety score to be 5.0 and the somatic anxiety score to 5.5. In addition, the evaluations of the data obtained from STAI-S and STAI-T were similar to Hamilton Anxiety Rating Scale. It has been observed that both anxiety and depression are associated with the Study 36-Item Short-Form (SF-36) parameters in TA (13). Also; anxiety appears to be a permanent feature of mental health, due to the long-term consequences that impair the mental state.

Sleep is essential for learning, memory, and cognitive functions. So, sleep disorders and insufficient sleep may lead to many problems such as impaired quality of life, anxiety, depression, and poor physical status to death risk (23,24). Various studies have reported sleep disorders and poor sleep quality in ankylosing spondylitis, primary Sjogren's syndrome, Behçet's disease (BD), and RA (23-26). To our knowledge, there is no data on this issue in patients with TA. The studies mainly focused on comparing the sleep quality of BD patients with healthy volunteers (27-29). In overview59.8% of all BD patients have been reported to have

sleep problems (26). Higher scores for subjective sleep quality, sleep efficiency, sleep delay, and more sleep disturbance had been found in BD than healthy controls (27,28). In our study; sleep efficienty, sleep disturbance, daytime dysfunction, subjective sleep quality, and overall score were significantly higher in TA compared to healthy control. Lee et al. reported a positive correlation between disease activity and PSQI parameters such as subjective sleep quality, sleep duration, and sleep latency in patients with BD (29). When evaluated in terms of disease activity in our study, ESR and CRP levels were higher in patients with a diagnosis of TA compared to healthy controls and good sleepers. Moreover, there was a significant difference for CRP and the presence of systemic findings, but not for ESR were found between poor and good sleepers in TA. The study has a few limitations. Although the sample size is relatively small in our study, it is generally difficult to have a large number of samples in TA due to its rare presence. TA is a very rare disease and the number of cases was here in the single center. The sleep disturbance was only evaluated by a self-reported questionnaire and disease activity was only assessed with ESR and CRP. And, the information about the long-term results of the study is not known. To our knowledge, there have been no previous studies regarding sleep quality and its association with anxiety in patients with TA.

In conclusion, the present study has demonstrated higher anxiety scores and poor sleep quality among patients in TA compared with healthy controls. It seems that many PSQI parameters have significantly impaired in TA. Poor sleepers had higher disease activity, especially higher CRP, and also more anxiety. In particular, TA patients with systemic findings and high inflammation should be evaluated for poor sleep quality. Also, remission in disease activity may be associated with better sleep and less anxiety scores.

Conflict of interest

None to declare.

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None to declare.

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Lipid ratios improve early detection of atherosclerotic cardiovascular disease in women with hypertensive disorders in pregnancy

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Abstract

In a normal healthy pregnancy, increased lipid profiles help to encourage fetal development, but in hypertensive disorders in pregnancy, these changes in lipid profiles are amplified, which may predispose these women to atherosclerotic cardiovascular disease. The study's aim was to determine the alteration in lipid profile levels of women with hypertensive disorders in pregnancy and also calculate their atherogenic risk ratios, with the view to improving the predictive capacity of the lipid assay for the risk of arteriosclerosis and cardiovascular incidence. This study enlisted 190 participants, which included 124 pregnant women with preeclampsia, 30 pregnant women with pregnancy-induced hypertension, and 36 pregnant women with normal blood pressure who served as controls. Lipid profile was determined via the enzymatic method from blood samples obtained from the participants. When compared to normotensive control study participants, patients with hypertensive disorders in pregnancy had a slight increase in total cholesterol and LDL cholesterol, as well as a substantial difference in triglyceride levels. Despite minor increases in total and LDL cholesterol levels, the case group's mean atherogenic index plasma, atherogenic coefficient, and Castelli risk index I and II were all higher than the control group's. Individual lipid parameter measurements were found to be ineffective in evaluating the relative contribution of lipids to cardiovascular risk in pregnant patients with hypertensive disorders. Lipid ratios, also known as atherogenic indices, were found to be more effective in assessing the relative contribution of lipids to cardiovascular risk.

Keywords: dyslipidemia, atherogenic indices, hypertensive disorders in pregnancy, preeclampsia, lipid profile

1. Introduction

Hypertensive disorders in pregnancy (HDP) represent a group of conditions that are related to high blood pressure while pregnant. Preeclampsia/eclampsia, gestational hypertension without proteinuria, chronic hypertension, and preeclampsia superimposed on chronic hypertension all fall under the HDP umbrella (1). They are characterized by hypertension in pregnancy, regardless of gestational age, with or without proteinuria, and/or convulsions. It is a leading cause of maternal and feto-maternal morbidity and mortality, particularly in developing countries (1).

Globally, 2.73% of women suffer from HDP while the incidence of chronic hypertension, preeclampsia, and eclampsia are 0.29%, 2.16% and 0.28%, respectively (2). Hypertensive disorders in pregnancy are found to be more common in Africa, affecting one out of every ten women (3). In Nigeria, it is estimated that 5-10% of pregnancies are complicated by hypertensive disorders in pregnancy (HDP), which leads to more antenatal admissions than any other condition (4-6).

In healthy normotensive pregnancy, there is an increase in lipid production which helps to promote fetal growth. Studies have shown that these changes in lipid profile are amplified in hypertensive disorders in pregnancy and may predispose these women to atherosclerotic cardiovascular disease (7-9). The dyslipidemia trend seen in preeclampsia and gestational hypertension may also predispose these women to cardiovascular disease in the future (7, 10, 11).

The study's aim was to determine the alteration in lipid profile levels of women with hypertensive disorders in pregnancy and also calculate their atherogenic risk ratios, with the view to improving the predictive capacity of the lipid assay for the risk of arteriosclerosis and cardiovascular incidence.

2. Participants and Methods

A total of 190 people took part in this study. Participants' blood pressure was measured in the sitting position with a mercury

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sphygmomanometer after 10 minutes of rest.

2.1. Study Population

Pregnant normotensive women served as a control group in the study. The study also included women of reproductive age (18-45 years) who were currently pregnant and had been diagnosed with pregnancy-induced hypertension and preeclampsia. The last menstrual cycle, pregnancy test strip, and obstetrics scan results were used to determine pregnancy which was then divided into trimesters. The second trimester covered from fourteen to twenty-six weeks, and the third trimester from twenty-seven weeks and more. Preeclampsia was defined as having blood pressure of 140/90 mmHg or higher on at least two occasions separated by six hours and accompanied by significant proteinuria (300 mm/l or 500 mm/24 hrs) in the absence of a urinary tract infection in a previously normotensive woman, whereas pregnancy induced hypertension was defined as having blood pressure of 140/90 mmHg or higher on at least two occasions separated by six hours and in the absence of proteinuria (12).

Women below the ages of 18 and above the ages of 45 were excluded from the study. Women in the reproductive age group (18 to 45 years) who were not pregnant were also excluded. Also excluded from the study were women with a history of chronic hypertension, diabetes, chronic renal failure, or congestive heart failure, as well as those who met the inclusion criteria but declined to give consent.

2.2. Methodology

A venipuncture was used to collect approximately 2 mL of blood into a simple tube. Before being centrifuged for 15 minutes at 3000 rpm, the entire blood was able to clot and retract. The serum was extracted into 5ml plain tubes with a Pasteur pipette and stored at -20ºC before biochemical analysis. The lipid analysis was performed using an enzymatic method (13) with Randox Laboratory Limited reagents and the standard operating assay technique.

The blood lipid indexes were calculated using the following equations;

Friedewald equation for LDL Chol. = TC – (TG/5) – HDL Chol. (mg/dL)

Atherogenic index of plasma, AIP = Log TG / HDLChol.

Atherogenic coefficient, AC = Non HDL Chol / HDL Chol.

Non-HDL cholesterol, NHDL = Total Chol – HDL Chol

Very low-density lipoprotein, VLDL = trıglycerıdes / 5

Castelli Risk Index I, (CRI I) = TC / HDL Chol.

Castelli Risk Index II, (CRI II) = LDLC / HDLC

2.3. Ethical Clearance

This was obtained from Edo State Hospitals Management Board, Nigeria, with reference number A.723/56 dated September 16, 2014.

2.4. Statistical Analyses

The data obtained in the study were statistically analyzed using SPSS® version-21. The results were presented using percentages and the mean of repeated data. Correspondence studies were used to demonstrate a link between certain parameters and the participants' lipid status.

3. Results

Majority of the participants in the preeclampsia group was 31 – 35 yrs (44%), compared to 42% in the normotensive group and 20% in the negative control group (Figure 1). Demographic data of respondents as presented on Table 1 showed that majority of the participants were pre-eclamptic in their first marriage (74.2%). Similarly, in pregnancy-induced hypertension (PIH) (100%) and the normotensive group (91.7%), participants were majorly in their first marriage.

Table 2 shows results of lipid profiles of respondents presented on the basis of trimesters. Total cholesterol in the preeclamptic group was higher during the third trimester (211. 13 mg/dl) than in the second trimester (205.76 mg/dl). Similarly, triglyceride levels were lower during the second than at the 3rd trimester. Although significant differences in total cholesterol levels during the third trimester showed differences in concentration among the various study groups ($p>0.05$), no observable differences were recorded. Differences in HDL-cholesterol were minimal irrespective of trimester.

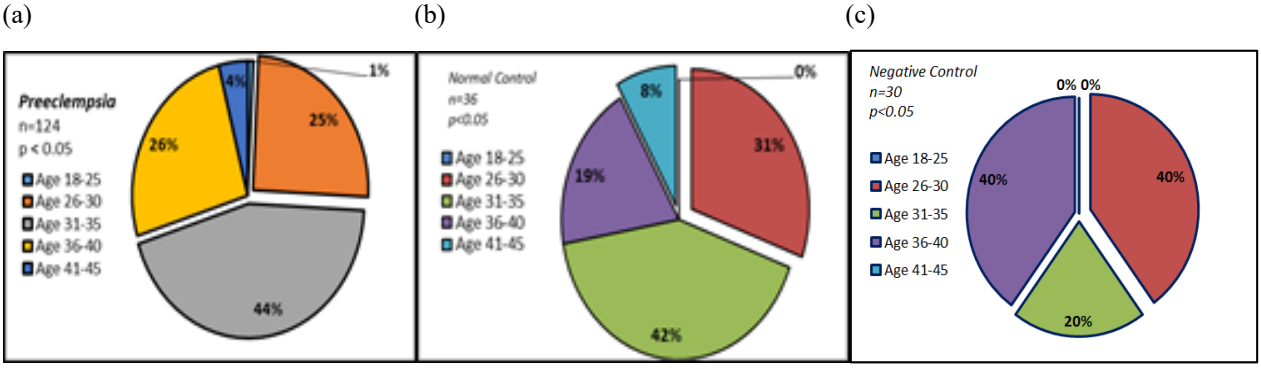

Fig. 1. Age groups of (a) pre-eclamptic and (b) control and (c) PIH respondents

Table 1. Demographic data of respondents

Queries	Preeclampsia cases (A) n (%) (N=124)	Control cases(B) n (%) (N=36)	PIH(C) n (%) (N=30)	(A+B)	(A+C)	(B+C)
				p-values		
Marital status						
Single	3 (2.4)	2 (5.6)	0	0.323	0.032*	0.041*
First Marriage	92 (74.2)	33 (91.7)	10 (100)	0.041	0.006*	0.032*
Remarried	29 (23.4)	1 (2.8)	0	0.013	0.027	0.072
Educational status						
None	4 (3.2)	0	0	0	0	0
Primary	17 (13.7)	3 (8.3)	3 (30)	0.442	0.441	0.989
Secondary	47 (37.9)	16 (44.5)	3 (30)	0.110	0028*	0.001*
Post-secondary	56 (45.2)	17 (47.2)	4 (40)	0.142	0.146	0.083
Job status						
Employed	102 (82.3)	27 (97.5)	8 (80)	0.192	0.892	0.173
Unemployed	22 (17.7)	9 (2.5)	2 (20)	0.014	0.070	0.009*

Table 2. Lipid profiles of respondents presented on the basis of trimesters. Only means of replicates have been presented

Queries	Trimester	Preeclampsia cases (A)	Control cases(B)	PIH(C)			
		(n=62)	(n=16)	(n=15)	(A+B)	(A+C)	(B+C)
					p-values		
Total Cholesterol	Second	205.76	195.435	196.574	0.364	0.626	0.734
	Third	211.131	202.815	213.22	0.354	0	0.012
Triglycerides	Second	156.029	113.631	135.648	0.002	0.369	0.326
	Third	153.431	130.352	200.942	0.015	0.01	0.006
HDL Cholesterol	Second	34.435	37.8	39.068	0.081	0.115	0.092
	Third	36.654	35.67	33.404	0.599	0	0
LDL Cholesterol	Second	145.86	135.735	130.376	0.244	0.26	0.261
	Third	145.56	141.085	128.98	0.607	0	0

Grouped data (totals) for Lipid profiles for assessment of dyslipidaemia in respondents, presented irrespective of trimester was determined (Table 3). Total cholesterol in the preeclamptic group was 208.44 mg/dl and 202.13 mg/dl in the PIH group ($p>0.05$). No significant differences in total cholesterol was reported between normotensive group (199.53 mg/dl) and the preeclamptoc group ($p>0.05$). triglycerides ranged from 122.92 – 154.73 mg/dl ($p<0.05$). The lowest triglyceride was reported in the Control group (122.92 mg/dl) ($p<0.05$). Based on severity of disease, only two categories of people were presented – mild and severe. No significant values in lipid profiles as separated by disease severity was reported (Table 4). No significant differences in lipid profiles was also reported on the basis of BMI (Table 5).

Lipid ratios of the study participants have been presented on Table 6. Generally, the preeclamptic group, antherogenic index plasma ratio (AIP) was highest (0.64) compared to that in the control (0.53) and PIH (0.60) groups respectively. During the second trimester, AIP was highest in preeclampsia. But during the third trimester, AIP was highest in PIH. The normotensive individuals had lowest AIP ratios at both trimesters. Similar ratios were reported in non-HDL, AC, and VLDL. While leveraging on lipid ratios separted on the basis of severity of preeclampsia, results showed AIP was highest in participants with severe preelclampsia (0.65) compared to mild preeclampsia (0.62). VLDL was also higher in severe preeclampsia. However, Non-HDL, AC, CRI-I and CRI-II respectively were higher in mild preeclampsia compared to severe preeclampsia (Table 6).

Table 3: Grouped data (totals) for Lipid profiles for assessment of dyslipidaemia respondents, presented irrespective of trimester

Queries	Preeclampsia cases (A)	Control cases(B)	PIH(C)			
	(µ±SEM)	(µ±SEM)	(µ±SEM)	p-value	p-value	p-value
	(mg/dl)	(mg/dl)	(mg/dl)	(A+B)	(A+C)	(B+C)
	(n=124)	(n=36)	(n=30)			
Total Cholesterol	208.44±3.39	199.53±5.97	202.13±21.21	0.21	0.307	0.209
Triglycerides	154.73±3.96	122.92±5.52	134.51±12.62	0	0.009	0.163
HDL Cholesterol	35.14±0.61	36.61±1.32	33.63	0.425	0.31	0.325
LDL Cholesterol	142.17±2.85	138.83±5.48	141.63	0.129	0.337	0.243

Table 4: Lipid profiles of preeclamptic subjects separated on the basis of severity of disease

Lipid profiles	Groups	N	Mean	Std. Error Mean	p-value
Total Cholesterol	Mild	39	209.94	5.02	0.718
	Severe	84	207.27	4.43	
Triglycerides	Mild	39	147.39	5.60	0.229
	Severe	84	157.72	5.20	
HDL Cholesterol	Mild	39	35.275	1.06	0.865
	Severe	84	35.498	0.74	
LDL Cholesterol	Mild	39	151.61	5.11	0.153
	Severe	84	145.83	6.22	

Table 5: Comparing Lipid profiles of preeclamptic subjects separated on the basis of BMI

	Group 1 – Normal vs Overweight						Group 2 – Normal vs Obese				
		N	Mean	SEM	p-value			N	Mean	SEM	p-value
Total Cholesterol	Normal	23	214.46	8.697	0.522		Normal	23	214.46	8.697	0.324
	Overweight	71	208.69	4.265			Obese	30	203.26	7.252	
Triglycerides	Normal	23	157.079	9.418	0.994		Normal	23	157.08	9.418	0.469
	Overweight	71	157.004	4.994			Obese	30	147.55	8.86	
HDL Cholesterol	Normal	23	33.8522	1.435	0.317		Normal	23	33.852	1.435	0.108
	Overweight	71	35.4573	0.78			Obese	30	37.051	1.31	
LDL Cholesterol	Normal	23	150.512	7.817	0.514		Normal	23	150.51	7.817	0.403
	Overweight	71	145.738	3.292			Obese	30	141.96	6.558	

Table 6: Lipid ratios of study participants

	AIP	NonHDL	AC	VLDL	CRI-I	CRI-II
General						
Preeclampsia	0.64	173	4.94	30.8	5.94	4.06
Control	0.53	163	4.53	24.4	5.53	3.85
PIH	0.6	168.37	5.01	26.8	6.01	4.21
At 2nd Trimester						
Preeclampsia	0.66	171.33	4.98	31.21	5.98	4.07
Control	0.48	157.64	4.17	22.73	5.17	3.57
PIH	0.54	157.51	4.03	27.13	5.03	3.34
At 3rd Trimester						
Preeclampsia	0.62	174.48	4.76	30.69	5.76	3.92
Control	0.56	167.15	4.69	26.07	5.69	3.96
PIH	0.78	179.82	5.38	40.19	6.38	4.18
Severity of Preeclampsia						
Mild preeclampsia	0.62	174.67	4.95	29.48	5.95	4.12
Severe preeclampsia	0.65	171.77	4.84	31.54	5.84	3.95

Note: AIP atherogenic index plasma, NonHDL non-HDL cholesterol, AC atherogenic coefficient, VLDL very low density lipoprotein, CRI-I Casterlly risk index-I, CRI-II Casterlly risk index-II

4. Discussion

In order to enhance the predictive ability of lipid profile assays for atherosclerotic cardiovascular disease, the current study used various lipid ratios or "atherogenic indices" to evaluate the risk of atherosclerosis and dyslipidemia in hypertensive disorders in pregnancy. When compared to normotensive control study participants, patients with hypertensive disorders in pregnancy had a slight increase in total cholesterol and LDL cholesterol, as well as a substantial difference in triglyceride levels. A substantial increase in serum triglyceride concentration in pre-eclampsia has been reported in previous research (14-16). A lipid profile that is abnormal is associated to atherosclerosis and has a direct effect on endothelial dysfunction (17).

This research aims to better understand the potential for early detection and prevention of cardiovascular disease in pregnant women with hypertension using lipid profile data. The researchers used lipid ratios, also known as atherogenic indices, to assess the risk of atherosclerotic cardiovascular disease in the case study because the lipid profile showed only minor changes. Despite the minor rise in total and LDL cholesterol levels, the case group's mean atherogenic index plasma (AIP) was higher than the control groups. AIP is a plasma atherogenicity marker that has been proposed. Higher AIP levels have been linked to an increased risk of cardiovascular disease (18). For its high correlation with apolipoprotein B levels, non-HDL cholesterol is believed to be a good surrogate marker for total apolipoprotein B. (19). On the other hand, standardized apolipoprotein B measurements are not always available in routine clinical procedures. As a result, the atherogenic coefficient, which is a simple ratio of non-HDL and HDL cholesterol, may be useful in determining whether a person is at risk of cardiovascular disease. In our current study, the atherogenic coefficient was also higher in the case study than in the control group, implying that pregnant women with hypertensive disorders face a higher cardiovascular risk.

Previous study has found that the cardiac risk ratio (TC/HDL), also known as the Castelli Risk Index I (CRI I), is significantly elevated in preeclamptic women (20-22). In the current study, we found an increase in Castelli risk index I and II in patients with hypertensive disease during pregnancy, despite minor changes in their lipid profile.

In pregnant patients with hypertension, lipid ratios, also known as atherogenic indices, were found to be more effective than individual lipid parameter measurements in determining the relative contribution of lipids to cardiovascular risk. Lipid ratios may aid in the early detection and prevention of atherosclerotic cardiovascular disease in women with hypertensive disorders during pregnancy, despite minor changes in their lipid profile levels.

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Conflict of interest

The authors declare no conflict of interest

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Investigation of the clinical course of Covid-19 patients according to blood groups

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Abstract

The aim of this study is to evaluate the effect of blood groups (BGs) on Covid-19 contraction and prognosis and to reveal the coefficients. Patients who referred to Covid-19 outpatient clinics and had an established diagnosis of Covid-19 were included in the study. Their BGs, previous diagnoses and blood examination findings were retrospectively analyzed. Duration of hospitalization, clinical course and survival were recorded. The mean age of 365 subjects, 210 female and 155 male, was 45,5 years. Subjects with BG A developed Covid-19 at significantly higher rates ($p = 0.001$), while BG O was found associated with lower rates ($p = 0.005$). Lymphocyte count was found lower ($p = 0.035$) and rate of lung parenchymal involvement was higher ($p = 0.003$) in patients with Rh antigen. It was found that a higher percentage of patients with B BG required treatment in the intensive care unit (ICU) compared to other ABO BGs ($p = 0.015$). These results suggest a higher risk of Covid-19 contraction in the population with BG A and lower risk for BG O population while indicating poorer prognosis for patients with BG B.

Keywords: covid-19, ABO BGs, Rh antigen, prognosis

1. Introduction

The new type of coronavirus which was emerged in China's Wuhan city in 2019 was named Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), and the disease it caused was called Coronavirus Disease 2019 (Covid-19) (1, 2). It shows a wide spectrum of clinical manifestations from asymptomatic to severe acute respiratory failure and death (3). A definitive treatment is yet to come.

One of the issues investigated regarding Covid-19 disease is its relationship with blood groups (BGs). Evidence exists that BGs play a key role in infectious diseases. In studies to date, the O allele was thought to act as a potential selective factor, affecting susceptibility to various pathogens of diseases such as malaria, Helicobacter pylori and cholera infections. A and B antigens are purportedly can be used as receptors by microorganisms (4). Rotavirus positive cases were found more common in cases with BG A while less common in cases with BG B (5,6). A study of animals with SARS-CoV infection revealed that when ACE2 expressing cells in the Chinese hamster ovary are transfected with the S protein, the S protein / ACE 2-

dependent adhesion of these cells to an ACE 2 expressing cell line is specifically inhibited by monoclonal or human native anti-A antibodies (7).

The observed relation of BG antigens to infections provoked interest regarding their probable role in rapidly spreading Covid-19. Despite many studies conducted on the prognosis, mortality and risk factors, there are limited data regarding the relationship of BGs and Covid-19. In this study, we aimed to compare the risk of contraction and prognostic features of the disease between different BGs.

2. Materials and Method

This was a retrospective cross-sectional study carried out in patients who referred to Umraniye Training and Research Hospital Covid-19 outpatient clinics. Inclusion criteria of the patients in the study were referral to Covid-19 outpatient clinics from April 15, 2020 to May 15, 2020, being 18 years or older, having BG information on hospital's records and having a definite diagnosis with a positive Covid-19 RT-PCR Test.

In this context, 365 patients were included in the study as the "Covid-19 Patient" group. In a study conducted in 2019, the frequency and distribution of BGs of patients thought to represent the Istanbul population was determined (8). These patients were included in our study as a control group and served as the basis for comparison of ABO and Rh rates. (8). History of the patients was analyzed retrospectively, as well as hematological" parameters like complete blood and Cero Reactive Protein (CRP) and thoracic tomography (TT). Intensive care admissions and survival of the patients were looked for. Based on these data, the prevalence and prognosis of the disease in each BG were evaluated. In 22 of 365 subjects,

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only Covid-19 RT-PCR test was performed without further examination. TT could not be performed in 3 patients due to pregnancy.

2.1. Statistical analysis of data

The data were analyzed by SPSS 25.0 software (SPSS, Inc, Chicago, IL, USA). Distribution of the data was tested using Kolmogorov Smirnov test. Besides descriptive statistical methods; t-test for parametric data, One Way Anova Test, Mann Whitney U test and Kruskal Wallis H test for non-parametric data were used. Chi-Square test was used to evaluate categorical data. Correlation analysis was used while analyzing quantitative data and significance was assumed as $p<0.05$ for all tests.

Table 1. Risk of disease acquisition in COVID-19 cases and controls

	Covid-19 N (%)	Control N (%)	P	Relative Risk	Odds ratio	Confidence Interval 95%
Group O	98 (26.8)	41878 (33.79)	**0.005**	0.720	0.719	0.570-0.906
Group A	191 (52.3)	54289 (43.81)	**0.001**	1.406	1.408	1.146-1.729
Group B	51 (14.0)	18854 (15.21)	0.509	0.905	0.905	0.673-1.217
Group AB	25 (6.8)	8879 (7.16)	0.815	0.953	0.953	0.634-1.431

3. Results

Three hundred sixty-five patients (210 female and 155 male) between the ages of 18-89 years (mean age= 45.5 ± 15.9 years) participated in the study. According to BGs, the mean ages of O, A, B, AB were 45 ± 15.6, 45 ± 15.7, 48 ± 16.9 y, 43 ± 15.9 years, respectively. While BG A predominated in the study group with 52.3%; 26.8% had BG O, 14.0% had BG B and 6.8% had BG AB. While 86.6% of the patients have the Rh antigen, 13.4% were in the Rh-negative. When we compared the BG rates of the Covid-19 patients with the control group; the rate of BG A in subjects was significantly higher compared to controls (52.3% versus 43.81%, p = 0.001), whereas BG O rate in subjects was significantly lower (26.8% vs 33.79%, p = 0.005) (Table 1). As for Rh antigen, cases and controls seemed similar (Table 1).

Values of CRP, White Blood Cells (WBC), Neutrophile (Nt), Lymphocyte (Ly) and Neutrophile to Lymphocyte Ratio (NLR) were separately compared between ABO and Rh BGs. No significant difference was found except Ly value, which was significantly lower in the Rh-positive group (p = 0.035) (Table 2).

Table 2. Comparison of hematological parameters in ABO and Rh blood groups

		Mean±SD	Median	Min-Max	P
CRP	**Group 0**	2.0±3.8	0.4	0.1-25.5	0.129**
	Group A	2.0±3.3	0.8	0.1-24.7	
	Group B	2.6±3.6	0.9	0.1-15.1	
	Group AB	1.7±3.0	0.3	0.1-13.1	
WBC (x1000/mm^3)	**Group 0**	6.18±2.55	5.63	2.06-19.29	0.671**
	Group A	6.37±2.63	5.91	3.05-25.64	
	Group B	6.44±2.22	6.10	2.96-13.68	
	Group AB	6.49±2.19	6.03	2.72-12.35	
NEU (x1000/mm^3)	**Group 0**	3.82±2.15	3.38	1.16-14.86	0.227**
	Group A	4.12±2.40	3.75	1.35-24.30	
	Group B	4.28±2.07	3.69	1.60-12.10	
	Group AB	4.22±1.95	3.92	1.01-10.50	
LY (x1000/mm^3)	**Group 0**	1.74±0.76	1.67	0.36-3.94	0.652*
	Group A	1.65±0.70	1.51	0.36-4.11	
	Group B	1.58±0.61	1.50	0.34-3.20	
	Group AB	1.77±0.74	1.49	0.64-3.43	
NLR	**Group 0**	2.61±1.87	2.04	0.60-11.88	0.351**
	Group A	3.08±3.11	2.36	0.51-35.22	
	Group B	3.42±3.58	2.37	0.90-24.00	
	Group AB	2.85±1.84	2.35	0.72-7.19	

*One Way ANOVA, ** Kruskall Wallis H Tes

Relationship between TT findings of patients with Covid-19 according to ABO and Rh BGs is shown in Table 3. No significant difference was found between ABO BGs in terms of lung involvement. However, Rh-positive patients had significantly higher lung involvement (Relative Risk = 1.408, Odds Ratio = 2.538, 95% Confidence Interval = 1.347-4.784, p = 0.003) (Table 3).

Relationship between intensive care admissions according to ABO BGs is shown in Table 4. The rate of admission to the intensive care unit was significantly higher in patients with BG B (Relative Risk = 3.078, Odds Ratio = 3.365, 95% Confidence Interval = 1.199-7.835, p = 0.015), while no significant difference was found according to Rh antigen. When we analyzed the relationship between the number of days of stay in the Intensive Care Unit (ICU) due to COVID 19 according to the ABO and Rh BGs, no significant difference was found (Table 4).

4. Discussion

In our study, we found that those with BG A are at higher risk for Covid-19 contraction, while this risk is lower for BG O. It was observed that higher percentage of patients with BG B required ICU.

Table 3: Relationship between ABO and Rh blood groups and Tomography findings

	CT Involvement							
	Yes		No					
	N	%	N	%	p	Relative Risk	Odds rario	Confidence interval 95%
Group O	63	26.3	28	28.0	0.658	1.031	1.110	0.658 – 1.874
Group A	126	52.5	50	50.0	0.674	0.970	0.905	0.567 – 1.443
Group B	33	13.8	15	15.0	0.763	1.030	1.107	0.572 – 2.143
Group AB	18	7.5	7	7.0	0.872	0.978	0.978	0375-2.297
Total	240	100.0	100	100.0				
Chi-Square								
Rh Negative	24	10.0	22	22.0				
Rh Positive	216	90.0	78	78.8	**0.003**	1.408	2.538	1.347 – 4.784
Total	240	100.0	100	100.0				
Chi-Square								

Table 4: Relationship between ABO and Rh blood groups and intensive care unit admissions

	Admission to Intensive Care Unit							
	Yes		No					
	N	%	N	%	p	Relative Risk	Odds rario	Confidence interval 95%
Group O	4	22.2	94	27.1	0.650	0.778	0.769	0.247-2.395
Group A	6	33.3	185	53.8	0.980	0.445	0.438	0.161-1.193
Group B	6	33.3	45	13.0	**0.015**	3.078	3.356	1.199-7.835
Group AB	2	11.1	23	6.6	0.463	1.700	1.761	0.381-8.129
Total	18	100.0	347	100.0				
Chi-Square								
Rh Negative	2	11.1	47	13.5				
Rh Positive	16	88.9	300	86.5	0.768	0.99	0.798	0.178-3.582
Total	18	100.0	347	100.0				
Chi-Square								

Table 5: Length of stay in ICU in terms of days according to ABO blood groups

		Length of stay, days				
		Mean±SD	Min	Max	Median	p
ICU stay*	**Group O**	11.50±5.26	4.00	16.00	13.00	0.941*
	Group A	12.00±6.96	6.00	25.00	10.00	
	Group B	11.83±10.63	3.00	29.00	7.00	
	Group AB	15.50±0.71	15.00	16.00	15.50	
ICU stay*	**Rh Negative**	10.00±5.66	6.00	14.00	10.00	0.621**
	Rh Positive	12.50±7.62	3.00	29.00	11.00	

***Kruskall Wallis H Test,**Man-Whitney U Test**

Other studies have yielded similar results to ours. Fan et al. reported that the rate of having Covid-19 infection among those with BG A was significantly higher (5). Li et al. found that the rate of BG A was significantly higher in patients infected with SARS-CoV-2 compared to healthy controls, while the rate of BG O was significantly lower (8). Another study reported that BG A was associated with a significantly higher risk for COVID-19, whereas BG O was associated with lower risk (9). Wu et al. have found that the proportion of patients with BG A in the COVID-19 group was significantly higher than that in the control group, whereas the proportion of patients with type O blood in COVID-19 was significantly lower (10). Our study supports other studies in the literature in terms of the rate of ABO BGs in patients with COVID-19 infection.

The intriguing relationship between ABO BGs and Covid-19 suggested whether the Rh antigen will also have an impact on the risk of Covid-19. Abdollahi et al. could not find a significant difference in terms of the presence of Rh antigen and having Covid-19 infection (11). Latz et al. found a rate of Covid-19 positivity significantly higher in people with Rh-positive BG (12). In a study including 227 patients with positive PCR test and 165 cases whose CT findings favored of Covid-19, it was found that Rh positivity was significantly higher in patients diagnosed with Covid-19 (13). In this study, we could not find a statistically significant relation between Rh antigen and Covid-19.

We also compared the CRP levels in ABO and Rh BGs in terms of prognosis. Patients with BG B had the highest mean CRP values while those with BG AB had the lowest, but no significant difference was found between ABO BGs. Besides, while the mean CRP values were increased in the Rh-positive group, the difference was not significant either. Similarly, Latz et al. found no significant difference in CRP values between ABO BGs (12).

Hematological parameters such as WBC, Nt, and Ly are also important markers showing the prognosis in Covid-19 disease. Fan et al. have conducted an analysis that included Covid-19 patients regardless of the severity of the disease and the control group and showed that the WBC values wasn't significantly different between the two groups, the rate of neutrophils was significantly higher in the Covid-19 group, and the lymphocyte count and lymphocyte ratio were significantly lower than the control group. In the same study, they compared ABO BGs with lymphocyte numbers of Covid-19 patients and showed that although the lymphocyte count was lower in individuals with A BG compared to other ABO BGs, the difference wasn't statistically significant (6). Latz et al. showed in their study that there was no statistically significant difference in WBC value between ABO BGs (13). In our study, when we compared ABO BGs regarding WBC and neutrophil counts, no statistically significant difference was found. When we compared the WBC and neutrophil counts regarding the Rh groups, there was no significant result here, either. When the ABO BGs were compared according to the lymphocyte count, there was no statistically significant difference, although the mean lymphocyte count was lower in individuals with B BG compared to other ABO BGs. On the other hand we found that the lymphocyte values were significantly lower in the Rh-positive group compared to the Rh-negative group.

One of the important prognostic markers of Covid-19 disease is NLR. In a study NLR was found to be significantly higher in patients with clinically severe disease compared to the non-severe group (14). In their retrospective cohort study involving 245 patients, Liu et al. have found that higher NLR was significantly associated with an increased risk of all-cause mortality during hospital stay (15). Nalbant et al. compared Covid-19 patients with a control group without Covid-19 and found that the NLR value was significantly higher in the

Covid-19 group compared to the control group (16). In our study, we compared NLR in BGs as a prognostic marker. Although B BG has the highest NLR among ABO BGs and O BG the lowest NLR, the difference between ABO BGs was not statistically significant. In Rh BGs, despite the NLR was higher in the Rh-positive group compared to the Rh-negative group, the difference was not statistically significant.

TT is an important imaging tool in Covid-19 disease. Although RT-PCR is the gold standard in diagnosis, the high rate of false negativity has increased the importance of TT which has a sensitivity of 98%. It is of great importance not only in diagnosis, but also in monitoring the progression of pneumonia and evaluating the effectiveness of treatment (17). Therefore, we have included TT in our study and compared TT involvement in different BGs. In ABO BGs, 52.5% of the patients with TT involvement had A BG and 7.5% of them had AB BG but no statistically significant difference was found between any ABO BGs in terms of TT involvement. When we examined the relationship between TT involvement and Rh antigen status, we found that the TT involvement of Rh-positive patients was statistically significantly higher than Rh-negative patients. In this case, the significantly higher TT involvement of Rh-positive patients compared to Rh-negative patients may indicate that the Rh antigen may be important in the course of the disease.

Clinical manifestations of patients infected with SARS-CoV-2 can range from mild, nonspecific symptoms to severe pneumonia with organ dysfunction (17). Therefore, the rate of admission to the intensive care unit is important in determining the severity of the disease and clinical course. In our study, when we compared the BGs and the rates of admission to the intensive care unit, we found that among ABO BGs, the rate of admission to the intensive care unit was significantly higher in patients with B BG. There was no statistically significant relationship between the presence of Rh antigen and admission to the intensive care unit. When we compared the days of stay in the intensive care unit, there was no statistically significant difference between both ABO BGs and the presence of Rh antigen and prolonged intensive care unit stay. May et al. have reported that 98 patients needed admission to intensive care unit in the follow-up of 165 patients admitted for inpatient care in their hospitals, and that there was no significant difference between ABO BGs of the patients getting inpatient care and patients admitted to the intensive care unit (18). In their study, Yaylacı et al. have reported that there was no statistically significant relationship between ABO BGs and admission to the intensive care unit, and that they found a statistically significant relationship between having Rh antigen and the rate of admission to the intensive care unit (19). In another study it was observed that there was no statistically significant difference between ABO BGs regarding the rate of patients admitted to the intensive care unit, but in the comparison between A or AB BGs (A + AB) and O or B BGs (O + B), it was observed that the A + AB group stayed longer in the intensive care unit and the difference was statistically significant (20). We think that different results between these studies may be related with the fact that there were no Rh-negative patients in the study of Yaylacı et al.

For mortality rates according to BGs, Latz et al. have reported that there was no significant relationship between ABO BGs and mortality rates in their study (12). Yaylacı et al. reported that there was no significant difference in the mortality rate between ABO BGs, but despite absence of mortality in the Rh-negative group patients mortality rate was significantly higher in Rh-positive group (19). Zietz et al. reported that they did not detect a significant relationship between BG and death due to Covid-19 in their study (20). Ray et al. have reported that O BG among ABO BGs and Rh-negative patients have a lower risk of mortality (21). In their study, Zhao et al. found that those with A BG had a higher risk of mortality compared to those other than A BG, while those with BG O had a lower risk of mortality than those other than BG O (9). In our study, 42.9% of the patients who died had B BG. Although we could not find a statistically significant difference in mortality between different ABO BGs, the mortality rate in group B patients was found to be very close to being statistically significantly higher. We think that we could not reach a statistically significant value due to the low number of patients included in our study and the low number of cases that resulted in mortality. Indeed, in our study, the rate of admission to intensive care, which is the main factor affecting mortality, was found to be significantly higher in group B patients. Again, although it did not reach a significant level, NLR, one of the important predictive markers of prognosis, was highest in group B patients. In the light of all these results, we can assume that in group B patients, Covid-19 infection has a more severe course and their prognosis is worse.

Covid-19 disease can progress with different clinical findings in people with similar backgrounds and descriptive features. The reasons for this difference have occupied the minds since the beginning of the epidemic. In this context, there are various hypotheses that many genetic and histopathological features, including HLA tissue antigens, may be the answer to different clinical course. The issue that blood groups may also be one of the reasons for the different clinical response of individuals to Covid-19 disease has been found in the literature for the last 1 year. However, the number of publications answering this question is limited in the literature and according to our search, there is only one publication in our country whose case number is limited (19). In this context, we think that our study contributes to the clarity of other studies that report limited and contradictory results examining the relationship between blood types and the prognosis of covid-19 disease. In addition, we think that the existence of only one publication from Turkey in this field increases the importance of our study.

Our study had some limitations. The relatively high false-

negative rate of the Covid-19 RT-PCR test and absences of BG information in hospital records limited the number of the study group. This situation restricted ability to attain statistically significant values, especially in mortality analyzes.

Results of our study are suggestive of the higher risk for BG A and lower risk for BG O of contracting Covid-19. The rate of admission to intensive care was significantly higher in BG B patients, indicative of a worse prognosis. Larger-scale clinical studies investigating the relationship between BGs and Covid-19 are needed to confirm these results.

Conflicts of Interest

There is no conflict of interest to declare.

Acknowledgments

None to declare.

Ethical Approval

This study was approved by the Ethics Committee of University of Health Sciences Turkey (date: 10.07.2020, No. 2020.07.10-39). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Effectiveness of ciprofloxacin in the treatment of Acute Otitis Media

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Abstract

Acute otitis externa is an infection of the outer ear canal that can occur at any age and is diagnosed by symptoms and examination findings. The aims of our study were to understand the seasonal frequency of acute otitis externa and to determine the susceptibility of causative bacteria to ciprofloxacin. Discharge samples were collected from the external ear canals of 76 patients diagnosed with acute otitis externa. The samples were evaluated and culture-antibiogram results were compiled. Routine microbiological methods were used for the reproduction of clinical material as bacterial and fungal cultures. The 76 enrolled patients were 18–80 years old (mean 41.6 years). Acute otitis externa occurred most frequently during summer, especially in July. Culture results revealed *Pseudomonas aeruginosa* growth in 30 cases (39.4%), *Staphylococcus aureus* in 18 cases (23.6%), and *Serratia* spp. in 5 cases (6.5%), while fungal growth was observed in 10 cases (13.1%). The antibiogram analyses determined ciprofloxacin resistance in *P. aeruginosa* in 13 patients (43.3%) and in *S. aureus* in 6 patients (33.3%). Acute otitis externa should be treated with antibiotics in accordance with culture antibiogram results, while keeping in mind that bacterial causes could be ciprofloxacin resistant.

Keywords: Acute otitis externa, season, culture antibiogram, ciprofloxacin effectiveness

1. Introduction

Acute otitis externa (AOE) is an infection of the outer ear canal that is diagnosed based on symptoms and examination findings. It can occur in individuals of any age and can occasionally affect the tympanic membrane and the auricle. It is generally unilateral, but bilateral occurrences can account for 10% of the cases (1). The infection may develop in response to many factors, including local trauma, high humidity, use of swimming pools, excessive serumen cleansing, anatomical anomalies, and the use of hearing aids (2, 3). AOE generally responds to localized and topical treatments; however, the presence of immunodeficiency or chronic otitis media can lead to serious complications. Malignant otitis externa should be considered, especially in patients with diabetes mellitus with severe ear pain and granulation in the outer ear canal who do not respond to topical treatments.

AOE is usually seen during the summer, and it causes discharge, pain, swelling, decreased hearing capacity, and increased itching in the outer ear canal (1, 4). Bacteria are the most common causative agents of AOE infections, but viruses and fungi may sporadically play a role in the etiology (5). *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most frequently isolated bacteria from infection cultures, whereas fungal infections may occur as secondary or primary to antibiotic treatment. AOE is usually treated locally, with treatments typically effective against the most common agents, namely *P. aeruginosa* and *S. aureus*. When aminoglycoside antibiotics are used in local treatment, chronic suppurative otitis media should be excluded (2).

Ciprofloxacin is commonly used to treat AOE. It is a broad-spectrum antibiotic of the fluoroquinolone group that works as a bactericide against gram-negative bacteria, with moderate effects on gram-positive bacteria (6). However, antibiotic treatment of AOE without identification of the etiological pathogen can prolong the treatment period and increase economic losses, complication rates, mortality, and bacterial antibiotic resistance (7). The aim of our study was to determine the age and sex distributions of the patients with AOE, the season and month when most infections occur, the frequency of causative pathogens detected in culture, and the susceptibility of causative bacteria to ciprofloxacin.

2. Materials and Methods

The study was approved by the Ethics Committee of University of HealthSciences- Samsun Health Practices and Research Center. This was a retrospective study of patient files of 76 individuals diagnosed with acute otitis externa and sampled for culture from the outer ear canal discharge in the otolaryngology clinic at Research Center between January and December 2019. Pediatric patients, pregnant patients, patients

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undergoing chemotherapy due to malignancy, patients with immune deficiency, patients with chronic otitis media, and patients who were already on antibiotic treatment prior to culture tests were excluded from the study.

Samples taken from the discharge in the outer ear canal were sent to the microbiology laboratory within 30 minutes inside Amies transport medium with charcoal (swab RTA, Turkey). Bacteriological examinations were conducted by plating the outer ear canal samples onto blood agar, chocolate agar, and Eosin Methylene Blue (EMB) agar, whereas samples with suspected fungal growth were plated onto Sabouraud dextrose agar (SDA). A *VITEK 2 automatic bacterial identification system (bioMérieux, France) was used for isolates that could not be identified by conventional methods. The antimicrobial susceptibilities of the isolated strains were evaluated and reported according to the criteria of EUCAST (European Committee on Antimicrobial Susceptibility Testing)* in the microbiology laboratory of our hospital.

In the clinic, local ciprofloxacin (0.3%), rifampicin (1%), aminoglycoside, and antifungal drops were administered to the patients without waiting for culture results. The culture results were evaluated by the clinicians and the treatment given to the patient was reviewed accordingly. Recorded data included the age and sex of the patients, frequency of AOE according to season and month, type of pathogen isolated from culture samples, and ciprofloxacin susceptibility of bacteria grown in culture.

Table 1. Culture results and ciprofloxacin susceptibility of bacteria isolated from ear canal discharge with acute otitis externa

Culture results		Ciprofloxacin		
	Number (n=76) (%)	Susceptible (%)	Resistant (%)	No antibiogram
Pseudomonas aeruginosa	30 (39.4%)	17 (56.6%)	13 (43.3%)	-
Staphylococcus aureus	18 (23.6%)	12 (66.6%)	6 (33.3%)	-
Serratia spp.	5 (6.5%)	4 (80%)	1 (20%)	-
Escherichia coli	4 (5.2%)	2 (50%)	2 (50%)	-
Proteus mirabilis	3 (3.9%)	3 (100%)	0	-
Klebsiella spp.	2 (2.6%)	2 (100%)	0	-
Enterobacter cloacae	2 (2.6%)	2 (100%)	0	-
Enterococcus faecalis	1 (1.3%)	-	-	1 (100%)
Comamonas testosteroni	1 (1.3%)	1 (100%)	0	-
Fungi	10 (13.1%)	-	-	-

3. Results

The ages of patients with AOE included in the study ranged between 18 and 80 years, with an average age of 42.6 years. Overall, 41 (54%) of the patients were female and 35 (46%) were male.

The most frequent season for AOE occurrences was summer, with 38 (50%) cases; the least frequent season was spring, with 8 (10.5%) cases. The highest diagnosis rate during the year occurred in July, with 18 cases (23.6%), while only 1 case (1.3%) was observed in May, which was the month with the least number of diagnoses (Fig 1).

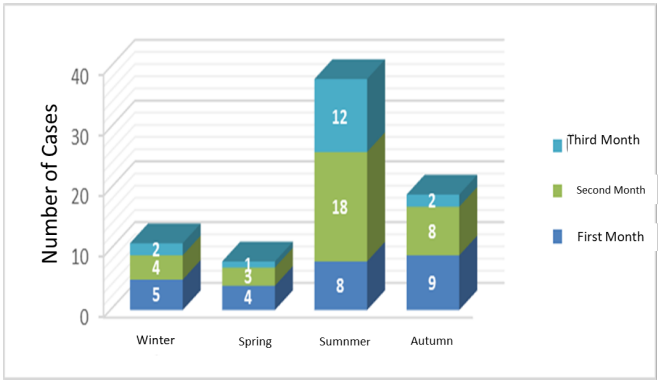

Fig. 1. Frequency of acute otitis externa by season and month.

The culture samples from the outer ear canal showed bacterial growth in 66 cases (86.8%), while fungal growth was observed in 10 cases (13.1%) (*Candida* spp. in 6 cases; *Aspergillus* spp. in 4 cases). Fifty-nine patients included in the study were given ciprofloxacin (77.6%), 6 patients were given rifampicin (7.9%), and 4 were given aminoglycoside (5.2%) as local antibiotics, while 7 were given antifungals. The results of culture-antibiogram tests demonstrated that the bacteria in 37 (62.7%) patients who were given ciprofloxacin were susceptible to that drug, while the bacteria in 22 (37.2%) patients were resistant to ciprofloxacin.

The bacteria cultured from patient samples were identified as *P. aeruginosa* in 30 cases (39.4%), *S. aureus* in 18 cases (23.6%), and *Serratia* spp. in 5 cases (6.5%). The antibiogram test revealed that *P. aeruginosa* was resistant to ciprofloxacin in 13 patients (43.3%), while *S. aureus* was resistant in 6 patients (33.3%) (Table 1).

4. Discussion

Acute otitis externa is an infection of the skin and subcutaneous tissue of the outer ear canal. It is an otology emergency that affects one in every 10 individuals. Most symptoms are mild, but they can cause necrosis, osteomyelitis, and facial nerve paralysis, and even death on rare occasions (8). Treatment of uncomplicated cases of AOE consists of cleaning the ear canal and administering analgesia, topical antiseptics, and antibiotics. The chosen topical antibiotics generally target the most common pathogens, namely *P. aeruginosa,* and *S. aureus*. The usual topical antibiotics are quinolones (ciprofloxacin), aminoglycosides (neomycin), and polymyxins (polymyxin B). Oral antibiotics should be administered to patients with diabetes, immunosuppression, or no response to local treatment (9).

The development of AOE infection is correlated with an alkaline shift of the normal acidic pH of the outer ear canal (10). The incidence of AOE also increases significantly during the summer, due to high temperatures and humidity (11). For example, Villedieu et al., in their study of 7770 patients with

otitis externa, reported that infection was seen most frequently in August and September and least frequently in April and May (12). In our study, our cases of AOE occurred most frequently during the summer and least frequently during the spring, with July being the month with the highest number of AOE diagnoses (18 cases; 23.6%) and May being the month with the fewest (1 case; 1.3%).

In addition to these seasonal differences in AOE occurrence, the bacterial pathogens associated with acute otitis externa can also show geographic variations. Overall, *P. aeruginosa* is generally considered responsible for 20–71.3% of cases, while *S. aureus* accounts for about 40% of cases (8, 13). Bacterial pathogens cause 98% of the AOE cases in North America, fungi such as *Aspergillus* and *Candida* are frequently causes of AOE in tropical or subtropical environments and in patients previously treated with antibiotics (13, 14). For example, Heward et al. reported *P. aeruginosa* growth in 31.1%, *Candida* growth in 22.9%, and *S. aureus* growth in 11.7% of the cultures produced from ear discharge samples of 217 patients (15). By contrast, Pino Rivero et al. found *P. aeruginosa* in 46.83% of the cultures from their patient samples, *S. aureus* in 18.98%, and fungal growth in 25% (16). Borsa et al. isolated *P. aeruginosa* in 59%, *S. aureus* in 14%, and fungal strains in 19% of their 76 individuals with otitis externa (17). In the current study, we detected *P aeruginosa* growth in 39.4%, *S. aureus* growth in 23.6%, fungal growth in 13.1%, and *Serratia* spp. growth in 5.6% of the cultures from the ear discharge samples of our patients.

Ear infections like AOE are also among the most common diseases associated with the excessive antibiotic use that generates antibiotic-resistant bacteria (18). In several studies, quinolone group ear drops were more effective at bacterial eradication and ear discharge reduction when compared to non-quinolone medications (19). In addition, no quinolone toxicity was encountered in human and animal studies (20). Pane et al. presented culture antibiograms of patients with otitis externa showing that *P. aeruginosa* is 100% and *S. aureus* is 66.6% sensitive to ciprofloxacin (21). Duarte et al. isolated *S. aureus* from 30.6% of their 173 patients with AOE and found 38.8% ciprofloxacin resistance in the antibiogram tests (22). Berenholz et al. studied culture antibiogram of 28 patients with malignant otitis externa and detected ciprofloxacin-resistant *Pseudomonas* in seven of those patients, suggesting that *Pseudomonas* could develop antibiotic resistance over time (23). Conversely, El-Nasr et al. detected *P. aeruginosa* growth in 65% of the culture samples from 60 patients with malignant otitis externa and found 77% antibiotic resistance in the antibiogram (24). The antibiogram analyses in the current study revealed that 43.3% of the *P. aeruginosa* and 33.3% of the *S. aureus* were ciprofloxacin resistant. In addition, evaluation of the culture antibiogram results of patients with empirical use of local ciprofloxacin revealed that the pathogens in 37.2% of the patients were resistant to ciprofloxacin.

Ciprofloxacin is frequently used locally or systemically to treat acute cases of otitis externa. However, the reported rate of occurrence of ciprofloxacin-resistant bacteria commonly isolated from patient cultures is concerning. This issue should be taken into consideration when treatments are administered prior to culturing patient samples. Treatment of AOE must be planned according to culture antibiogram results to decrease the treatment duration, to reduce morbidity, to prevent economic losses, and, most importantly, to diminish the generation of antibiotic-resistant bacteria. The retrospective nature and the low number of cases are limitations of our study; therefore, we suggest that large-scale prospective randomized studies are needed.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

Ethical Approval

The study was approved by the Ethics Committee of University of HealthSciences- Samsun Health Practices and Research Center. The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Risk factors affecting mortality and patient survival in patients above 60 years undergoing hemiarthroplasty due to hip fracture

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Abstract

The aim of this study was to retrospectively determine the risk factors affecting mortality and survival after partial prosthesis treatment of proximal femoral fractures in elderly patients. In this study, patients aged 60 years and over who underwent hemiarthroplasty with the diagnosis of proximal fracture of the femur between 2013 and 2016 were evaluated retrospectively. 94 patients (58 females and 36 males) were included in the study. Age, gender, fracture type and side, Garden and Evans Scores, Singh Index, ASA values, additional diseases, when they were operated after falling, stem type used, anesthesia methods, hospitalization periods, survivors Harris hip scores, UCLA scores, Barthel Index and VAS scores a total of 17 parameters were evaluated. When the fracture types of the cases were examined, it was seen that 58 patients had intertrochanteric and 36 patients had collum femoris fracture. The mean time from the day of fracture to operation was calculated as 5.61. Hypertension, diabetes, and coronary artery diseases were the most common diseases. Sixty-four out of 94 patients died, and 30 were still alive during our study. It was seen that 11 of the patients died in the first month, 11 of them died between 1-6 months postoperatively and 93% (n = 28) of the patients still alive were operated on in the first 5 days after fracture. Hip fractures are a serious cause of mortality and morbidity in the elderly. Physical and mental capacity of the patients before fracture is one of the most important predictors of postoperative mortality and morbidity. The main goal is to return patients to their daily lives in the shortest possible time. ASA values and comorbidities were found to be important in postoperative mortality.

Keywords: aged, comorbidity, hip fractures, mortality, osteoporosis, complications, prognosis, quality of life, risk factors

1. Introduction

Nowadays, hip fractures are frequently seen especially in the elderly patient group as a result of the increase in life expectancy and the increasing population. Hip fractures are an important orthopedic problem that may vary depending on the age of the patient, the severity of the trauma, and the displacement degree of the fracture, especially for the elderly population (1).

Conservative treatment is not preferred in the elderly population due to complications. Thanks to changes in the field of anesthesia and reanimation and new surgical techniques, hip fractures are treated surgically. The aim of surgical treatment is early movement. Surgical treatment options are internal fixation and arthroplasty. It has been reported that arthroplasty results after internal fixation are less successful than primary arthroplasty. Arthroplasty is preferred to reduce the possibility of reoperation and to return the patient to his pre-fracture condition early (2, 3).

The aim of this study is to examine the relationship between mortality, preoperative and postoperative medical conditions and vital factors in patients over 60 years of age who underwent hemiarthroplasty for hip fracture.

2. Materials and Methods

2.1. Patients

Patients aged 60 and over who were surgically treated at the Orthopedics and Traumatology Clinic of Süleyman Demirel University Medical Faculty Research and Practice Hospital between 2013 and 2016 with a diagnosis of hip fracture were screened through the hospital information system. A total of 173 patients were identified. 79 patients who did not have radiological imaging in the system and who could not be reached by phone were excluded from the study. Patients who had imaging and epicrisis information in the system but could not be reached by phone were scanned through the MERNIS (Central Population Management System) system and those whose date of death was determined were included in the study. 94 patients included in the study or their relatives were called by phone and information about the patients' preoperative and postoperative conditions was obtained. When evaluating 94 patients, age, gender, fracture type and side, Garden and Evans Scores, Singh indexes, ASA (American Society of Anesthesiologists) values, additional diseases, when they were operated after the fall, type of stem used, anesthesia methods, hospitalization times, survivors' Harris hip scores,

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UCLA (University of California at Los Angeles) scores, Barthel Index for daily activity evaluation and VAS (Visual Analog Scale for pain) scores, a total of 17 objective parameters were evaluated.

All of the survivors who were called by phone applied to our hospital voluntarily and were examined and scored. All of the patients were operated in the lateral decubitus position with a modified Gibson incision.

2.2. Statistical analysis

IBM SPSS Statistic 22.00 statistics program was used for statistical analysis. The compatibility of the quantitative data to normal distribution was examined with the Kolmogorov Smirnov test. T test and One Way ANOVA test were used for variables suitable for normal distribution. Mann Whitney U and Krusskal Walls tests were used for variables not suitable for normal distribution. Chi-square analysis was used for statistical comparisons for categorical variables, and descriptive statistics were shown as frequency (%). Linear regression analysis was used for correlation analysis and partial correlation test was used for correlation analysis.

3. Results

In our study, 58 of 94 patients were female (61.7%) and 36 were male (38.3%). The average age of the patients was 80.5 (± 6.85); the mean age of male patients was 78.6 (± 7.51) and the average age of the female was 81.7 (± 6.16). When the mean ages of both genders were compared, it was seen that the mean age of female patients was statistically significantly higher (p = 0.029) (Table 1).

Table 1. Demographic characteristics of the patients

	Male (n=36) (%38.3)	Female (n=58) (%61.7)	Total	P value
Mean Age	78.6 (±7.51)	81.7 (±6.16)	80.5 (±6.85)	0.029*
Fracture type/side	**Right**	**Left**	**Total**	**P value**
Collum femoris	23	13	36	0.248
Intertrochanteric	30	28	58	
Total	53	41	94	
Sex/Fracture type	**Intertrochanteric**	**Collum Femoris**	**Total**	**P value**
Male	23	13	36	0.731
Female	35	23	58	
Mean age	82.29 (±5.74)	77.69 (±7.58)	80.5 (±6.85)	0.003**

Evans Classification						
Intertrochanteric	**1**	**2**	**3**	**4**	**5**	**Total**
	6	13	6	15	18	**58**

Garden Classification					
Collum Femoris	**1**	**2**	**3**	**4**	**Total**
	-	3	11	22	**36**

Singh İndex							
	1	**2**	**3**	**4**	**5**	**P value**	**Total**
Intertrochanteric	8	22	21	7	0	0.220	58
Collum femoris	6	10	12	5	3		36

ASA Scores			
2	**3**	**4**	**Total**
52	30	12	94

Type of Anesthesia	
General	47
Spinal	47

Stem Type	
Straight	53
Calcar	41

* Mean age by sex Student T test (p=0.029)

** Relationship between fracture type and age Student's T test (p=0.003)

The average time elapsed from the day of the fracture to the operation day was calculated as 5.61 days (± 11.00). When the preoperative days and postoperative survival of the patients were examined, 93% (n = 28) of the patients who were still alive were operated in the first 5 days; when this situation was evaluated with the Chi-square test, it was found to be statistically significant (p = 0.018).

When the ASA scores of the patients were examined, it was seen that 52 patients (55.3%) had ASA 2, 30 patients (31.9%) had ASA 3, and 12 patients (12.8%) had ASA 4. When the mortality and survival times of the patients were examined with the ASA score, it was seen that both parameters had a statistically significant inverse correlation (p = 0.000).

When the anesthesia types of the patients in our study were examined, it was seen that 50% (n = 47) of them were operated under general anesthesia and 50% (n = 47) under spinal anesthesia. It was observed that the type of anesthesia administered did not have a statistically significant effect on survival time and mortality (p = 0.663).

Straight stem was used in 56.4% (n = 53) of the patients in our study, and calcar type stem was used in 43.6% (n = 41) of them. Cementless surgery was performed in 5 (5.3%) of the patients, and cemented technique was used in other patients. There was no statistically significant effect of stem type and cement status on mortality and morbidity of patients. (p = 0.212; p = 0.925)

When the comorbidities of the patients in our study were examined, when the presence of comorbidity and the postoperative and total hospitalization times of the patients were compared, the total length of stay and postoperative hospitalization time of the patients with comorbidities were significantly higher than those without any comorbidity. (p = 0.046; p = 0.030). Among the patients with comorbid diseases, 22 patients had 3 or more comorbidities, 18 patients had 2 different comorbidities, and 22 patients had one known comorbidity. As the number of comorbid diseases of the patients increased, a statistically significant decrease was observed in the survival time (p = 0.000) (Table 2).

Table 2. Comorbid diseases

Hypertension	37 (39.4%)
Diabetes	23 (24.5%)
Coronary Artery Disease	21 (22.3%)
Osteoporosis	2 (2.1%)
Chronic Kidney Disease	6 (6.4%)
Asthma & COPD	7 (7.4%)
Alzheimer	7 (7.4%)
Thyroid Disease	5 (5.3%)
Arrhythmia	4 (4.3%)
Cerebrovascular Disease	4 (4.3%)
Malignancy	6 (6.4%)
Hematological Diseases	3 (3.2%)

COPD: Chronic obstructive pulmonary disease

Coronary artery diseases (p = 0.001) and Alzheimer's disease (0.007) were found to have a statistically significant effect on the duration of survival in the regression analysis examining the relationship between the survival times and comorbidities.

Among the cases, in the postoperative period, infection occurred in 1 patient, periprosthetic fracture in 1 patient, and dislocation in 3 patients. When the effects of these three parameters on mortality and survival were examined, it was seen that there was no significant effect.

It was observed that 64 of 94 patients examined in our study died and 30 patients were still alive. It was observed that 11 of the patients who died in the first postoperative month, and 1 of these patients died at home after discharge, and 10 died at the hospital without being discharged. It was also seen that 11 patients who died between 1-6 months postoperatively. 5 of these patients are in the hospital after 1 month of hospitalization; It was seen that 6 of them died outside the hospital. 4 patients between 6-12 months; 15 patients between 12-24 months; It was observed that 23 patients died between 24-60 months (Table 3).

Table 3. Death time and survival of patients

	Number of patients
Death In the 1st Month Postoperatively	11 (11.7%)
Death between 1-6 Months	11 (11.7%)
Death between 6-12 Months	4 (4.3%)
Death between 12-24 Months	15 (16%)
Death between 24-60 Months	23 (24.5%)
Survivors	30 (31.9%)
Total	94

Comparing the average age of the patients who died and those who are still alive in our study, the average age of the patients who died was found to be statistically significantly higher. (p = 0.004) (Table 4).

Table 4. Relation of mean ages with mortality

	Number of Patients	Mean Age	Standard Deviation
Deceased Patients	64	81.91	6.361
Alive	30	77.60	7.040

The results of daily quality of life and activity scores applied on patients who are still alive during our study are given below as a table (Table 5).

Table 5. Activity and quality of life scores of surviving patients

	Poor	Fair	Good	Excellent	Total
UCLA	0	4	4	22	30
HARRIS	0	5	3	22	30

BARTHEL INDEX		
Very Dependent	**Partially Dependent**	**Minimally Dependent**
1	5	24

VISUAL PAIN SCALE (VPS)										
0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
0	19	7	4	0	0	0	0	0	0	0

The effects of comorbid diseases on postoperative daily life quality and activity scores were examined. It was observed that coronary artery diseases (p = 0.000) and respiratory system diseases had the most statistically significant effect on UCLA (p=0.018). Coronary artery diseases (p=0.000), diabetes (p=0.032) and respiratory system diseases (p=0.034) also had the most statistically significant effect on Harris scoring. It was observed that coronary artery diseases (p = 0.001) and diabetes had the most statistically significant effect on Visual Pain Scoring (VAS) (p=0.034). It was observed that coronary artery diseases (p=0.000), diabetes (p=0.012) and respiratory system diseases (p=0.014) negatively affected the statistically most significant effect on the Barthel index. As can be seen from these data, it is striking that coronary artery diseases, diabetes and chronic diseases of the respiratory system are the most common comorbid conditions that cause the most deterioration in the quality of life of patients in the postoperative period. It was also observed that as the comorbidity of comorbid diseases in the patients increased, the Barthel index scores decreased in a statistically significant way. (p=0.027)

4. Discussion

Hip fractures are a common health problem affecting especially the elderly population all over the world and become one of the leading causes of death in elderly people as the life expectancy increases. With advanced age, the risk of falling increases due to systemic diseases, decreased physical capacity, posture and gait disorders, and multiple and unbalanced fractures may occur in the upper end of the femur due to their osteoporosis (4).

The main finding of this study is that mortality is multifactorial rather than a single factor. When we classify these factors as changeable and unchangeable, we can say that age and comorbidities are patient-dependent and unchangeable factors, and the time until the operation and postoperative rehabilitation are changeable risk factors.

Of the 94 patients in our study, 58 were female (61.7%) and 36 were male (38.3%). Among the reasons for this high rate in women, they are less active, lack of estrogen after menopause, and the inability to replace them, and related to these, osteoporosis is more effective. Another reason for the increase in this ratio may be the dominance of women in the elderly population (5, 6). In a study conducted by NN Wazir et al. In 2006, the rate of women was 62.4% (7); In the study conducted by Anderson, 83% (8); in Seçkin's study, it was found to be 68% (9). The findings of our study were found to be in line with the literature. The average age of the patients was 80.5 (± 6.85); The mean age of the male patients was 78.6 (± 7.51) and the average age of the female gender was calculated as 81.7 (± 6.16). When the mean ages of both sexes were compared, it was observed that the mean age of female patients was statistically significantly higher and that female patients were numerically higher. In the study conducted by Bekerom et al. In 2010, the mean age of 115 patients who underwent THA (total hip arthroplasty) was found to be 82 years, and the average age of patients who underwent BHA (bipoplar hip arthroplasty) was 80 years (10). Somashekar et al. compared the UHA (unipolar hip arthroplasty) and BHA, and the mean age of the patients who underwent UHA was 75.7 years, and the patients who underwent BHA were found to be 67.3 years (11).

In the literature, there are studies reporting different opinions on whether the time until surgery increases mortality. Zuckerman et al. and Sexson and Lehner reported that mortality increased when the time between fracture and surgery increased, while Kenzora et al reported that the mortality rates in patients operated on the first day were significantly higher than those operated between the 2nd and 5th days in their studies (12-14).

In order to prevent this, they recommended taking precautions against the general condition disorder at the first admission of the patients and performing a surgical intervention with the necessary support. On the other hand, Şener et al. found that high comorbidities, prolonged fracture time and the time to surgery, worsening postoperative walking capacity and advanced age significantly increased mortality (15). As a result, they emphasized that accompanying comorbid factors, walking capacity and operative time should be considered in the treatment and rehabilitation planning of such patients. Doruk et al. it was emphasized that the mortality of patients who were not operated in the first 5 days was higher (16). Öztürk et al. in their study, it was shown that the operation time was not related to mortality (17). In the cases in our study, the mean time from the day of fracture to the operation day was calculated as 5.61 (±11.00). When the number of preoperative days and postoperative survival of the patients were examined, 93% of the patients who were still alive were operated in the first 5 days; When this situation was evaluated with the Chi-square test, it was found to be statistically significant. ($p=0.018$) It can be said that the operation of patients within the first 5 days after fracture has a positive effect on survival.

The ASA physical condition scale is often used to classify the preoperative general condition of patients with hip fractures. ASA I defines patients who do not have systemic disease other than surgical pathology, while ASA V defines patients who do not have a life expectancy of more than 24 hours regardless of the operation. Studies have shown that the higher the ASA class, the higher the risk of death in the long term. Hamlet et al. Found that the 3-year mortality rate (23%) of ASA I and II patients was significantly lower than the ASA III, IV, and V patients (39%) (18). Studies were examined in terms of ASA class distribution of patients who underwent arthroplasty. Nelson et al. reported that 47% of the patients were in ASA II and 50% were in ASA III in their partial arthroplasty series including 70 patients (19). In the study conducted by Hedbeck et al, in which UHA and BHA applications were compared, it was stated that the majority of patients in both the UHA (48%) and the BHA (50%) groups were ASA class II (20). Atay et al. reported that the preparation period for the operation was prolonged in patients with a high ASA score in their study on patients over the age of 60 who underwent arthroplasty due to hip fracture. After a 1-year follow-up, they found that the mortality rate was higher in patients with a high ASA score at the time of fracture and a long time until the operation (1). When the ASA scores of the patients in our study were examined, it was seen that 52 patients (55.3%) were ASA II, 30 patients (31.9%) were ASA III, and 12 (12.8%) were ASA IV. When the mortality and survival times of the patients were examined with the ASA score, it was seen that both parameters had a statistically significant inverse correlation.

The high average age of the patients who were operated on for femoral neck fractures causes the frequent occurrence of accompanying chronic diseases. In the study of Salvakçı, 14.4% of patients with femoral neck fracture who underwent hip arthroplasty had diabetes, 16.9% had coronary artery disease, 20.3% had hypertension, 1.7% had arrhythmia, and 2.4% had atrial fibrillation. reported that 10% had COPD,

3.38% had chronic renal failure and 3.38% had chronic hepatitis (21). In the study of Şener et al., which included 280 patients, hypertension (n: 48) and diabetes (n: 20) were found to be the most common accompanying chronic diseases (22). In the study of Çopuroğlu et al., which included 180 patients with femoral neck fracture, 22 (12.2%) patients had hypertension, 10 (5.5%) cancer, 7 (3.9%) heart disease, 6 (3.5%) patients have identified diabetes (23). When the additional diseases of the patients in our study were examined, 39.4% patients had hypertension, 24.5% patients had diabetes, 22.3% patients had coronary artery disease, 6.4% patients had chronic kidney failure, 7.4% patients had chronic lung diseases, 7.4% patient's Alzheimer's, 5.3% patient's thyroid disease, 4.3% patient's rhythm disorders, 4.3% patient's cerebrovascular disease, 6.4% patient's history of malignancy, 3.2% patient's history of hematological disease, 2.1% patient's known He had a history of osteoporosis and vitamin D deficiency. 34% of the patients did not have a history of any disease. Among the patients with comorbidity, 22 patients had 3 or more comorbidities, 18 patients had 2 different comorbidities and 22 patients had only one known comorbidity. When the presence of comorbidity and the postoperative and total hospitalization times of the patients were compared, the total length of hospital stay and the postoperative length of stay in patients with comorbidity were significantly higher than those without comorbidity (p=0.046; p=0.030). As the number of additional diseases of the patients increased, a statistically significant decrease was observed in the survival time (p=0.000). When we examined the relationship between the survival time of the patients and their comorbidities, it was seen that the most effective factors were coronary artery diseases (p=0.001) and Alzheimer's disease (p=0.007).

Many factors play a role in the success of the functional outcome of patients after surgery. Patients with hip fractures should be mobilized as soon as possible and returned to their daily activities as soon as possible. During our study, questionnaires evaluating quality of daily life and activity scoring were applied to patients who were still alive. It was examined how much the comorbidities of the patients could affect the postoperative quality of life and activity scoring. Coronary artery diseases (p=0.000) and respiratory system diseases (p=0.018) had the most statistically significant effects on the UCLA score; Coronary artery diseases (p=0.000), diabetes (p=0.032) and respiratory system diseases (p=0.034) had the most statistically significant effects on Harris scoring; Coronary artery diseases (p=0.001) and diabetes(p=0.034) had the most statistically significant effect on Visual Pain Scoring (VPS); It was observed that coronary artery diseases (p=0.000), diabetes (p=0.012) and respiratory system diseases (p=0.014) had the most statistically significant effect on the Barthel index. As it can be understood from these data, it is observed that the comorbid conditions that most cause deterioration in the quality of life of patients in the postoperative period are coronary artery diseases, diabetes and chronic diseases of the respiratory system, respectively. As the comorbidities of the patients increased, it was observed that the Barthel index scores decreased statistically significantly (p=0.027). When we look at the literature, it has been shown in many studies in parallel with our study that the presence of additional diseases before the fracture and the ambulatory status before the fracture cause postoperative morbidity and negatively affect rehabilitation (23-26).

Multiple chronic diseases that occur in advanced ages can lead to deterioration of general health status. Therefore, patients with hip fractures are more likely to die in the first year after fracture than their peers. In studies, the 1-year mortality rate of patients with femoral neck fractures varies between 14% and 36% (14, 24, 27). Death is basically; it may depend on many factors such as age, gender, chronic diseases, waiting time for surgery, type of anesthesia, and type of treatment (13, 24, 28, 29). This high rate of mortality is related to the preoperative general condition of the patient rather than the surgical intervention (30). It was observed that 64 of the 94 patients examined in our study died and 30 patients were still alive. It was observed that 11 of these patients died in the first month postoperatively, 1 of these patients died at home after discharge, and 10 of them died in the hospital before being discharged. It was reported that 11 patients died between 1-6 months postoperatively. 5 of these patients are in the hospital after a 1-month hospitalization period; It was seen that 6 of them died outside the hospital. It was observed that 4 patients died between 6-12 months; 15 patients died between 12-24 months; 23 patients died between 24-60 months. When the characteristics of the patients who died in the first month were examined; the mean age was calculated as 83.36 (±7.18) and no significant difference was observed between the other groups in terms of mean age (p=0.079). When the mean age of the patients who died and those who are still alive in our study were compared, the mean age of the patients who died was found to be statistically significantly higher (p=0.004). When examined in terms of ASA scores, a significant difference was observed between the patients who died in the first month and the patients in the other group (p=0.001). This was caused by the statistical difference between the ASA scores of patients who died between 24-60 months of age and are still alive and those who died in the first 1 month. Patients who died in this first month were more likely to have comorbidities than patients who lived longer (p=0.000). When the coronary artery disease (CAD) of deceased patients and surviving patients was compared, the frequency of CAD was found to be significantly higher in deceased patients (p=0.006). There was no significant difference between the groups in terms of other additional diseases of the patients in our study. There was no significant difference between the other groups in terms of fracture types of patients who died in the first month (p=0.788). When the number of preoperative days and postoperative survival were examined, 93% of the patients who were still alive were

operated in the first 5 days; when this situation was evaluated with the Chi-square test, it was found to be statistically significant (p=0.018). However, no statistically significant difference was found between the duration of the operation and mortality of the patients who died in the first month.

Fractures of the upper end of the femur are a serious trauma with mortal and morbid consequences for elderly patients. The prolongation of life expectancy has led to an increase in the number of geriatric patients, and accordingly, the incidence of femoral neck fracture has increased. The incidence of hip fractures due to osteoporosis increases with advancing age. Femoral neck fractures are more common in the elderly and women.

Waiting time for surgery negatively affects survival and functional results. Hemorrhage at the fracture line and metabolic effects of secreted cytokines should be eliminated. For this reason, surgery should be rushed and medical preparations should be completed as soon as possible.

The higher the preoperative ASA scores of the patients, the higher the risk of postoperative death.

Partial hip prosthesis is an appropriate treatment for patients with a low life expectancy, who have already received various treatments due to comorbidities, and whose general condition is very poor, who are admitted to the hospital due to femoral upper end fracture, in order to be able to stand up in a short time and to minimize the failure rate.

In the light of all this information, mortality after hip fractures is multifactorial and some of these are risk factors that cannot be changed. At this point, the surgeon should know the modifiable risk factors well and manage the process accordingly. Informing the patients and their relatives about the possible results of the operation in the preoperative period in line with this information and obtaining written consent is important in order to prevent the medicolegal problems that the physicians have been exposed to recently.

Conflict of interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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None to declare.

Ethical Approval

This study is approved by Süleyman Demirel Medical Faculty Local Ethics Committee on 21.05.2019 with the approval number of 175.

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Protective effects of tropisetron on diabetes-induced cardiomyopathy and apoptosis in the left ventricle of rats

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Abstract

Tropisetron, an antagonist of 5-HT3 receptor (5-HT3R), has exhibited a number of beneficial effects on the treatment of several diseases; however, its effect on diabetic cardiomyopathy, which is an important causal factor in morbidity and mortality among diabetic patients, remains to be fully elucidated. Therefore, this study was designed to investigate the effect of tropisetron on diabetes-induced cardiomyopathy and the molecular mediators possibly involved. Twenty-four male wistar rats were assigned into three groups, control, diabetic, and tropisetron–treated diabetic groups. After 14 days of treatment, the results revealed a significant increase in calcium/calmodulin-dependent protein kinaseIIδ (CaMKIIδ) total and isoforms δ2 and δ3 of CaMKIIδ, as well as myosin heavy chain (MHC)-β. Furthermore, it decreased MHC-α gene expression among the diabetic group compared to the control group. Western blot analysis showed a significant increase in Bax and cleaved caspase 3 protein levels and a significant decrease in Bcl-2 contents in heart tissue of diabetic rats in comparison to the control rats. Moreover, the levels of Tumor necrosis factor alpha (TNF-α), ICAM-1, and CaMKII in heart tissue of diabetic rats were significantly higher than those in the control rats. Significant amelioration of alteration in the genes expression and protein changes along with restoration of the elevated levels of TNF-α, ICAM-1, and CaMKII were found in the tropisetron–treated diabetic group compared to the diabetic group. Collectively, our study provided strong evidence that 5-HT3 antagonist tropisetron was capable of attenuating the development of experimental diabetic cardiomyopathy associated with the reduction of intramyocardial MHCs and CaMKIIδ gene expression, inflammation and cardiac hypertrophy.

Keywords: diabetes, apoptosis, MHCs, CaMKIIδ, tropisetron

1. Introduction

Diabetes Mellitus is a complex endocrine disorder resulting from a combination of genetic, environmental and immunological factors. Diabetic cardiomyopathy is the main type of cardiovascular disease that is manifested as a structural and functional alteration, and it is considered to be independent of macrovascular / microvascular disorders, including coronary artery disease and hypertension (1, 2). Abnormal cellular changes, such as cardiac hypertrophy, inflammation, fibrosis, and apoptosis are presented as important features of diabetic cardiomyopathy leading to diastolic and systolic dysfunction, and finally resulting in heart failure (3). The pathophysiology of diabetic cardiomyopathy is complex and multifunctional, and little is known about the mechanism of cardiac damage associated with diabetic situation (4). However, the role of hyperglycemia, hyperlipidemia, oxidative stress and inflammation in diabetes has been proven and reported as pathogenic parameters in various cardiovascular anomalies including cardiomyopathy (5, 6). Considering the above mentioned issue, lowering blood sugar and blood lipids, antioxidant and anti-inflammatory drugs, and appropriate physical activity can be useful in preventing and reducing diabetic complications including cardiomyopathy (7, 8). Although, according to previous studies, different components have been used to reduce the complications of diabetes, researchers are looking for new pharmaceutical and non-pharmaceutical substances in this case. The activation of the sympathetic nerve of the heart is a very important factor in the development of cardiac hypertrophy and ultimately heart failure, and it induces apoptosis, increases oxidative stress, and so on, through the activation of renin-angiotensin system (9-11). Therefore, the use of sympathetic nervous system antagonists is a valuable treatment for hypertrophy and cardiac failure. Serotonin is a neurohormone that has many physiological and pathophysiologic effects. It contains seven receptors including 5HT1-7, all of which are G-Protein receptors except for the 5-HT3, which is a ligand-gated ion channel. This receptor plays an important role in activating

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the sympathetic nervous system (12, 13). Cardiovascular responses enhanced by activation of the sympathetic nervous system reflex led to cardiac hypertrophy and ultimately cardiac failure (14). Activation of 5-HT3 receptors stimulates the reflexes of the sympathetic nerves, and also, it releases noradrenaline from the adrenal gland and the sympathetic nerve end, which in turn causes heart damages (15, 16).

In the current study, the fundamental role of CaMKIIδ, MHCs and inflammation in initiation and development of cardiomyopathy and heart failure tempted us to examine the following issues: we examined the effect of tropisetron on diabetic heart hypertrophic indexes including left ventricular weight, L.V.W / B.W and L.V.W / H.W. The second aim was to find out whether tropisetron mitigated the gene expression alteration of CaMKIIδ isoforms and MHCs in the diabetic heart. Investigating the effects of tropisetron on pro and anti-aopototic protein expression were our third aim in the current study. Finally, alleviating effects of tropisetron on heart tissue TNF-α, ICAM-1 and CaMK amounts were also investigated in the current study.

2. Materials and Methods

All procedures followed during this examination conformed to the ‹National Health and Medical research Care published by the National Institutes of Health (NIH publication, no.85–23, revised 1985), and the experimental protocol approved by the Animal Care Committee of Urmia University of Medical Sciences. Twenty-four male wistar rats (body weight: 240 ± 20 g) were maintained under standard laboratory conditions, having ad libitum access to standard laboratory chow and water. After one-week of acclimatization, rats were randomly divided into three experimental groups (n = 8 in each group): control, diabetic, and tropisetron–treated diabetic groups. Diabetes was induced by intraperitoneal injection of 55 mg/kg B.W, streptozotocin (STZ; Sigma, St Louis, Mo, USA) diluted in 0.1 mol/citrate buffer pH 4.5. The control rats received an equal volume of citrate buffer. The diabetic condition was determined 72 h later by measuring tail vein blood glucose using glocometer (Boehringer Mannheim Indianapolis); rats with a blood glucose concentration higher than 300 mg/dl were considered diabetic. Rats in the tropisetron–treated diabetic group received tropisetron with a dose of 3mg/kg body weight (Cayman Chemical Co, USA) saluted in normal saline (20% W/V) intraperitoneally once a day, for 14 days. The control rats received an equal volume of normal saline. After 14 days of treatment, the rats were anesthetized by ketamine (10%, 80 mg/kg B.W, IP) and xylazine (2%, 10 mg/kg B.W IP).

Following test termination, the animals were weighted out and anesthetized by ketamine (60 mg/kg) and xylazine (6mg/kg). The hearts were dissected out and freed from adipose and connective tissues for later measurements. Then we excised left ventricular wall (with septum) from the heart and weighed. Due to total RNA isolation, 100 mg of ventricular tissue was homogenized and immersed in one ml RiboxEX (GeneALL, Seoul, Korea) and kept at -80°C, up to the time of RNA isolation. The other parts of the tissues were rinsed and dried for biochemical analysis. In continue, we added the extraction buffer (10% wt / vol) containing a 50 mM phosphate buffer (pH 7.4) and subsequently homogenized in homogenizer namely Ultra Turrax (T10B, IKA, Germany). Next, the products were centrifuged at 10,000 × g at 4°C for 20 minutes. The collecting supernatant was stored at -80°C, up to the time of measurment. The other part of each left ventricular tissue was kept in the deep freeze for apoptotic protein detection by western blotting method.

2.1. Biochemical examinations

The TNF-α, ICAM-1, and CaMKII contents in the heart tissue were measured conducting the quantitative sandwich enzyme immunoassay method using a commercial rat TNF-α, ICAM-1(Shanghaicrystal Day, Biotech, China), and CaMKII (ZellBio, Germany) kit, following the protocol provided by the manufacturer.

Table 1. Sequences of primers used to evaluate expression of GAPDH, CaMKIIδtotal, and CaMKIIδ1, CaMKIIδ2, as well as MHC ispforms

Target Gene	Primer sequence	Product size
$CaMKII\delta_{total}$(forward)	5′-TGG CAA ACT AAA GAG GGA GC-3′	**199**
$CaMKII\delta_{total}$(reverse)	5′-CCA AAA TCC CAA TGA GAA GCC C-3′	
$CaMKII\delta_2$(forward)	5′-AAC CGG ATG GGG TAA AGG AG-3′	**230**
$CaMKII\delta_2$(reverse)	5′-CAA TGC TTC GGG TTC AAA GG-3′	
$CaMKII\delta_3$(forward)	5′-CGG ATG GGG TAA AGA AAA GG-3′	**164**
$CaMKII\delta_3$(reverse)	5′-CTC GAA GTC CCC ATT GTT GA-3′	
MHC-α(forward)	5'-AGA GTG ACA GGA TGA CGG CG-3'	**213**
MHC-α(reverse)	5'- TCT TGC CGT TTT CAG TTT CG-3'	
MHC-β(forward)	5'- CCA GAC AGA GGA AGA CAG GAA-3'	**280**
MHC-β(reversed)	5'- CAT CCT TAG GGT TGG GTA GCA-3'	
GAPDH (forward)	5′-AGA CAG CCG CAT CTT CTT GT-3′	**207**
GAPDH (reverse)	5′-CTT GCC GTG GGT AGA GTC AT-3′	

2.2. Quantitative real time PCR and RT-PCR

Total RNA was extracted using an extraction kit (Gene All, South Korea), according to the manufacturer's protocol. The real-time quantification of the target genes was carried out as described previously in our earlier study (17, 18). Reverse transcriptase (RT) was presented using Hyperscript™ Reverse Transcriptase (Gene All, South Korea). RT-PCR was performed with cDNA synthesis using an amplification reagent kit (Ampliqon, Denmark) by the XP-Cycler instrument (TCXPD, Bioer, and USA). The relative expression of CaMKIIδtotal and isoforms δ2 and δ3 of CaMKIIδ, as well as MHC-β and α isoforms mRNA were normalized to the amount of GAPDH in the same cDNA sample using the standard curve method. Gene Bank (http://blast.ncbi.nlm.gov/Blast.cgi) was used for planning the primer sequences (forward and reverse) of the target genes confirming with the Gene Runner software (Table 1). The amount of PCR yields was normalized to GAPDH as a housekeeping gene. We used the $2^{-(\Delta\Delta Ct)}$. Results were presented as the fold-difference to the relevant controls.

2.3. Western blotting

Bax, Bcl2, and cleaved caspase-3 proteins levels in the left ventricular tissue were determined by Western immunoblotting. Briefly, the tissue was washed once with phosphate buffer and lysed with lysis buffer containing 500 µL Tris-Hcl, 0.003gr EDTA, 0.08gr NaCl, 0.025gr Sodium Deoxycholate, 0.01gr SDS, 1 tablet Protease inhibitor cocktail, and 10 µl Triton (Np40) 1%. After a 30 min incubation on ice, the total cell lysates was centrifuged at 15,000 g for 20 min at 4º C, and the supernatant was collected and stored at 80º C until analysis. The protein concentration of the supernatant was measured by the Bradford assay kit (Bradford 1976). Equal amounts of proteins were loaded in each well after being mixed with a 2X sample loading buffer. The proteins were separated in 10% SDS-gels and then transferred to polyvinylidene fluride (PVDF) membrane. The membrane was incubated with a primary and an HRD-labled secondary antibody. After one hour of incubation in the shaker, the membranes were bathed in wash buffer and were washed for at least 3×5 min. Then, the membranes were incubated with the enhanced chemiluminescence (ECL, Amersham) reagents in a dark room. This was followed by exposure of the membrane to an X-ray film and visualization of the chemiluminescence of the binding by means of a visualizing machine. The intensity of the bands was determined using the Image J software (IJ 1.46r version, NIH, USA) and normalized to the bands of the internal control (beta-actin).

2.4. Statistical analysis

Normal distribution of data within each group was examined conducting the Kolmogorov–Smirnov test. The statistical differences between the groups were tested conducting a one-way ANOVA and then the Tukey's post hoc test. The data obtained from each test are presented as the mean ± S.E.M, and $p < 0.05$ is set as statistically significant.

3. Results

3.1. Effects of tropisetron on diabetes-induced cardiac hypertrophy

There was no difference found between heart weights of animals in the control, diabetic and tropisetron–treated diabetic groups when the hearts were harvested fourteen days after the treatment (table-2). Compared with the animals in the control group, the left ventricular weight (L.V.W), L.V.W / body weight (B.W) and L.V.W / heart weight(H.W) of animals in diabetic group were significantly higher ($p < 0.05$). In tropisetron–treated diabetic group, L.V.W, L.V.W / B.W and L.V.W / H.W were significantly lower than those in the diabetic group ($p < 0.05$). (Table-2).

Table 2. Left ventricular hypertrophic indexes, ICAM-1, CaMK, and TNF-α amounts in left ventricular tissue of the control, diabetes and diabetes+tropisetron groups

	Control	Diabetes	Diab+Tropisetron
L.V.W/B.W	1.51±0.06	2.55±0.25*	**2.14±0.07***
L.V.W/H.W	0.549±0.012	0.8±0.026*	**0.66±0.02*†**
H.W(gr)	0.8±0.017	0.68±0.12	**0.68±0.08**
L.V.W(gr)	0.43±0.018	0.57±0.05*	**0.46±0.025†**
ICAM-1(pg/ml)	0.99±0.144	1.55±0.11*	**0.77±0.11†**
CaMK(pg/ml)	95.23±4.6	177.17±2.89*	**151.7±3.97*†**
TNF-α(pg/ml)	38.47±2.59	72.87±3.2*	**53.69±4.45*†**

Values expressed as mean± S.E.M. *p<0.05, Significant difference versus the control group. †p< 0.05, Significant difference versus the diabetes group. Left ventricular weight (L.V.W), Body weight (B.W), heart weight (H.W)

3.2. Effect of diabetes and tropisetron treatment on left ventricular TNF-α, ICAM-1, and CaMKII

Results of the current study showed that STZ-induced diabetes resulted in a significant increase in left ventricular content of TNF-α, ICAM-1, and CaMKII in the diabetic group compared to the normal control group (table-2) ($p < 0.05$). Moreover, Ttropisetron treatment significantly attenuated the increased heart tissue level of these enzymes in tropisetron –treated diabetic group compared to the diabetic group ($p < 0.05$).

3.3. Effect of diabetes and tropisetron treatment on the left ventricular genes expression

STZ-induced diabetes significantly increased the expression of CaMKIIδtotal and isoforms δ2 and δ3 of CaMKIIδ related genes (mRNA) in the left ventricular of the diabetic group, when compared with the control group ($p < 0.004$). Tropisetron treatment in diabetic animals reduced the CaMKIIδ isoform related genes expressions markedly, compared to the diabetic group ($p < 0.004$). Furthermore, there were no significant differences between the tropisetron–

treated diabetic and the control rats. The MHC-α mRNA gene expression showed a significant decrease in the diabetic group compared to the control group. There were no significant differences found between the tropisetron-treated diabetic group and the control group in terms of MHC–α mRNA expression. In the diabetic group, a significant increase in the expression of MHC-β mRNA in the left ventricular of the rats was found when compared with the control group ($p < 0.05$).

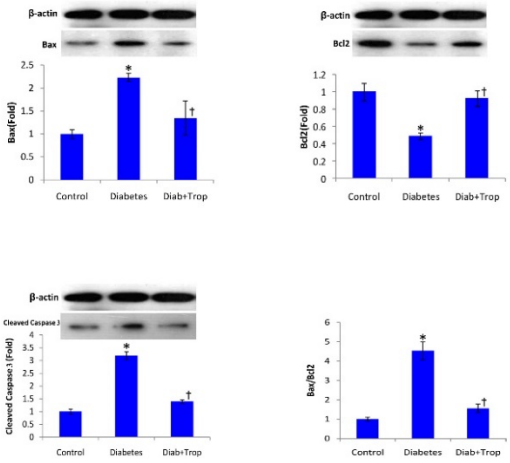

Fig. 1. Effect of tropisetron administered daily to diabetic rats for 14 days on bax, Bcl-2 and caspase-3 proteins expression in myocardium. The upper panel shows protein bands from a typical record and β-actin as housekeeping controls. Data are mean ±S.E.M. of 8 rats per group. *p< 0.05 vs. control group. †p < 0.05 vs. diabetic group

MHC-β mRNA expression had no significant differences between the tropisetron–treated diabetic group and the control. Interestingly, the ratio of MHC-β mRNA/ MHC-α mRNA expression demonstrated a significant increase in the diabetic group compared to the control group ($p < 0.05$). Tropisetron decreased the ratio of MHC-β mRNA/ MHC-α mRNA expression in diabetic animals in comparison with diabetic group ($p < 0.05$). Finally, no significant differences have been established between the tropisetron–treated diabetic group and the control group in terms of MHC-β mRNA/ MHC-α mRNA ratio.

3.4. Effect of diabetes and tropisetron treatment on left ventricular bax, Bcl-2 and caspase-3 activation

To estimate the effect of diabetes and tropisetron treatment on bax, Bcl-2, Bax/Bcl2 ratio, and caspase-3 activation, western blot analysis was performed in left ventricular tissue obtained from different groups of study after 14 days of treatment. As shown in figure 1, Bax protein expression increased significantly and Bcl-2 expression decreased in heart tissue of diabetic rats compared to the control rats ($p < 0.05$). The ratio of Bax / Bcl-2 also showed a significant increase among diabetic rats compared to the control rats ($p < 0.05$). Tropisetron administration to diabetic rats significantly reduced diabetes-induced, increased Bax and Bax/Bcl-2 ratio, and significantly increased diabetes-induced decreased Bcl-2 compared to the diabetic group. As an important mediator of apoptosis, in the current study, we examined the enzymatic activity of the caspase-3 with respect to protein cleaved caspase-3 conducting a western blot analysis. As shown in fig.1, the results revealed that diabetes led to a significant increase in cleaved caspase-3 expression in the heart tissue compared to the control group ($p < 0.05$). Tropisetron treatment significantly decreased cleaved caspase-3 expression in heart tissue of tropisetron–treated diabetic group compared to the diabetic group.

Table 3. Effect of diabetes and tropisetron +diabetes on changes of heart tissue gene expression of CaMKIIδ, β -MHC and α -MHC after 14 days treatment

	Control	Diabetes	Diab+Trop
CaMKIIδ$_{total}$ (fold)	1.49±0.26	5.88±0.53*	1.11±0.13†
CaMKIIδ$_2$ (fold)	1.68±0.23	7.35±0.47*	1.72±0.19†
CaMKIIδ$_3$ (fold)	2.15±0.1	8.45±0.74*	1.83±0.12†
MHC-α(fold)	1.27±0.15	0.54±0.3*	1.36±0.49†
MHC-β(fold)	3.73±0.34	7.59±0.6*	3.55±0.08†
β -MHC/ α -MHC	2.95±0.18	14.05±0.4*	2.61±0.7†

Values expressed as mean± S.E.M. *p<0.05, Significant difference versus the control group. †p< 0.05, Significant difference versus the diabetes group

4. Discussion

Our recent works and several others indicated that the overexpression of the predominant cardiac isoforms of CaMK including CaMKIIδ1 and CaMKIIδ2 is one of the hallmarks of molecular alteration that induces myocardial hypertrophy and heart failure (18-21). In addition, the association between CaMKIIδ isoforms expression alteration and shifts in cardiac function has been reported in pathologic conditions such as dilated cardiomyopathy, myocardial infarction, arrhythmia, and heart failure upon injuries such as pressure overload and ischemia-reperfusion (22-24). Furthermore, studies have also demonstrated that CaMKIIδ-knockout preserved the heart in several situation including ischemia-reperfusion damage, interstitial fibrosis after pressure overload and β-adrenergic stimulation, indicating strong documents for CaMKIIδ maladaptive functions in cardiac pathogenesis (25, 26). Some recent reports are in line with our study indicating a direct relationship between CaMKIIδ, hyperglycemia and type 1 diabetes-induced cardiomyopathy (4, 27). Another important achievement gained by enhancing CaMKIIδ activities in type 2 diabetes and its induced consequent alteration of contraction and relaxation prior to the development of heart failure have been yielded by Daniels et al (28). Based on their findings, Daniels et al., concluded that metabolism alteration in diabetic heart activated CaMKIIδ and altered heart function at the myocytes level, leading to the development of cardiac

dysfunction (28). In the present study, we confirmed that the expression of total and isoforms of CaMKIIδ, as well as the amount of CaMKIIδ in the heart tissue increased, following STZ-induced diabetes along high left ventricular weight, and increased L.V.W / B.W, and L.V.W / H.W ratio. Furthermore, tropisetron administration to diabetic rats restored CaMKIIδtotal and isoforms gene expression and decreased left ventricular weight, L.V.W / B.W, and L.V.W / H.W ratio. It has been recently reported that 5-HT3 receptor antagonists, such as tropisetron, protected against cardiac hypertrophy and restored the desensitization of cardiac adrenergic sensitivity in overload–induced cardiac hypertrophy in murine (29). It is well known that cardiac failure resulting from cardiac hypertrophy is a deadly condition and that sympathetic activation is an important pathological factor in promoting heart hypertrophy to heart failure (29). Put together, diabetes induced cardiomyopathy may be mediated at least in part by activation of CaMKIIδ pathway and blocking of this route by tropisetron protected against diabetes-induced cardiac hypertrophy.

In agreement with earlier studies (30, 31) in the present study, we found that STZ-induced diabetes caused an increase in expression of ventricular MHC-β and a reduction in expression of ventricular MHC-α. It has been previously reported that diabetes reduces cardiac and myocytes contractile kinetics (30). It is well established that daily ATP consumption by heart is five-fold greater than its own mass for maintenance of cellular ionic homeoatasis and rhythmic contraction (32). MHCs' consume a great part of this ATP to form strong cross-bridges with actin for production of the power stroke (32). Although, more than 93% amino acid sequence homology is between two isoforms of MHCs isoforms, the ATPase activities and actin filament rapid contractile velocity of MHC-α is two to three times more than MHC-β (33). In contrast to MHC-α, the MHC-β has a lower ATPase activity with a lower actin filament contractile velocity, and allows for a greater economy with a cross-bridge force generation (34). Due to the difference between physiologic function of α and MHC-β isoforms in stressful conditions such as diabetes and pressure-overload cardiac hypertrophy, the tendency is always to shift towards the lower activity of MHC-β for enhancing the efficiency and economy of force generation (34). Accordingly, gene expression transition from α to MHC-β isoform motivates compensatory/adaptive changes when sufficient amounts of ATP are not available, and this is because the β isoform is associated with a greater economic force generation compared to α isoforms. Here we found that compared with the control group, 5HT3 receptor antagonist restored cardiac fatal genes expression alteration to a favorite direct. Although pharmacologic strategies such as insulin therapy and lifestyle management are two factors that improve the ability of individuals to cope with diabetes and to maintain near normal glycemia, diabetes-induced cardiomyopathy and heart failure continue to be the main causes of morbidity and mortality in individuals with diabetes mellitus. Due to the basic pathological role of sympathetic activation in promoting heart hypertrophy to heart failure, current study results and those of previous studies provide evidence that antagonism of sympathetic nervous system is a valuable therapeutic method for diabetes-induced cardiac hypertrophy and heart failure (29, 35). In the current study, cardiac Bax and cleaved caspase-3 expression and Bax / Bcl-2 ratio in STZ-induced diabetes were significantly increased compared to the non-diabetic and the decreased pro-survival BCL-2 was improved by tropisetron administration. These finding are in agreement with those of a previous study showing similar alteration in pro-apoptotic and pro-survival members in rat pheochromocytoma cells exposed to high glucose and cardiac of STZ-induced diabetic rats (35, 36). As a pro-apoptotic protein Bax plays a fundamental role in the induction of apoptosis. Bcl-2, however, is known as an anti-apoptotic protein having protective properties against apoptosis pathways (37). Previous studies showed that suppression of Bax gene improved myocardial ischemia-reperfusion injury including amelioration of necrosis and apoptotic cell death in heart of the mice (38). The results of another study revealed that diabetes led to cardiac structural abnormality along decreased cardiac Bcl-2 and increased Bax, and that exercise restored cardiac structural alteration to normal conditions by improving Bcl-2 and Bax pathways (36). In the current study, tropisetron administration improved Bax, Bcl-2 and cleaved caspase-3 expression was parallel with improvement of MHCs isoforms and CaMKIIδ genes expression alteration, as well as amelioration of left ventricular weight, L.V.W / B.W, L.V.W / H.W. Our previous works and several other studies have indicated that oxidative stress plays an important role in diabetes-induced cardiomyopathy (6, 37-39). Oxidative stress-induced diabetic cardiomyopathy results from enhancement of reactive oxygen species and a decreased endogenous antioxidant capacity in myocardium (40, 41). Moreover, another important early and notable effect of oxidative stress on the heart is cardiac inflammation that is actively involved in the development of heart failure during diabetic cardiomyopathy (42). From among the various inflammatory cytokines involved in diabetic cardiomyopathy, TNF-α plays a crucial role in developing cardiac hypertrophy and heart failure through several ways including activation of mitogen-activated protein kinases (MAPK) and the extracellular signal-regulated kinase (ERK)(43). In addition, TNF-α is able to promote reactive oxygen species generation and modulate an inflammatory response by inducing production of pro-inflammatory cytokines such as interleukin (IL)-1β and its own production (44). Moreover, it has been reported that TNF-α induces myocardial hypertrophy and fibrosis by an increase in TGF-β1 signaling activation of nuclear factor –κB (NF-κB) (44, 45). Furthermore, the study by Westermann et al. pointed out that TNF- α antagonism improved the experimental cardiomyopathy corresponding to

a reduction of intra-myocardial inflammation and cardiac fibrosis (46). In the current study, TNF- α and ICAM-1 levels showed an increase, and administration of tropisetron improved left ventricular hypertrophy cardiac fatal gene expression. Previous studies investigating diabetic cardiomyopathy reported an association between diabetic cardiomyopathy and cellular adhesive molecules such as ICAM-1 and vascular adhesive molecule (VCAM)-1 (46).

In conclusion, with acknowledging the results obtained by previous studies showing the structural and functional demonstration of diabetic cardiomyopathy with details; our study presents several notable findings. First, in non-treated diabetic rats, heart hypertrophy indexes including left ventricular weight, L.V.W / B.W and L.V.W / H.W were significantly higher than those in control rats. Second, we demonstrated that STZ-induced diabetes causes a higher expression of fatal gene compared to that manifested by overexpression of CaMKIIδtotal, CaMKIIδ2, and CaMKIIδ3 mRNA and a shift in the MHC isoforms expression manifested by elevation of MHC-β mRNA and the ratio of MHC-β mRNA/ MHC-α mRNA expression in the heart tissue of rats. The third point is that STZ-induced diabetes leads to an increase in TNF-α, ICAM-1, and CaMK amounts in heart tissue of diabetic animals, compared to the control ones. All these processes are known as molecular mechanisms underlying cardiomyopathy and heart failure. The fourth point which in our view is the golden point is that treatment with tropisetron decreases left ventricular weight, L.V.W / B.W and L.V.W / H.W, improves gene expression alterations and restores TNF-α, ICAM-1, and CaMK amounts compared to those in the diabetic group. Taken together, current study results indicate that tropisetron has potential therapeutic efficacy in preventing the progression of diabetic cardiomyopathic, and further experimental and / or clinical studies, including therapeutic window studies, need to be performed to reveal such effects.

Conflict of interest

The authors declare that they have no conflict of interest.

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The place of smartphone applications ın emergency medicine

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Abstract

Medical mobile applications help improve patient care quality, reduce medical errors, and help physicians make faster, evidence-based decisions in patient care, follow-up and rehabilitation. In this study, it was aimed to determine the usage level of smart phone applications among emergency physicians, to investigate the effects of these applications on diagnosis and treatment, to examine their benefits, to determine the expectations regarding these applications, and to raise awareness on ethical issues. Between 02/25/2018 and 03/25/2018 emergency medicine residents in many provinces of Turkey, emergency medicine specialists, were investigated smartphone app to be used in practice with academics. A statistically significant difference was found between emergency medicine experience and mobile application use (p: 0.020). Most of the physicians surveyed had started using their first mobile apps 4 years ago. It was determined that most of the participants using mobile applications in the medical field were using them as a clinical decision tool. It was observed that those with visual expressions were mostly preferred in the use of mobile applications in the medical field (63.1%). It was determined that 75% of the participants found instant messaging applications useful in the professional field. The biggest problem identified in terms of medical ethics of mobile medical applications; was the thought of a violation of patient privacy. Although technological devices make our lives easier in many ways, examination is of great importance in the patient-physician relationship. Medical mobile applications should be prepared professionally and the content quality should be checked by experts. Due to the nature of current research, it is inevitable that technologies become outdated. There is a need for more comprehensive and up-to-date studies on this subject that appeal to large audiences.

Keywords: emergency medicine, mobile phones, mobile apps, technology

1. Introduction

Smartphones and tablet PCs are popular devices that have been integrated into the daily life of many people (1). Smartphones have become increasingly valuable in the healthcare industry and medical research due to the increasing number of smartphone users and functionality. Mobile technologies provide essential advantages for doctors in easy communication, data downloading, and accessing evidence (2). Clinicians, healthcare companies, and patients are closely interested in smartphone technologies. Smartphone technologies developed in the medicine category offer an opportunity in improving patient care and decreasing medical malpractice by promoting rapid access to evidence-based medical knowledge (3, 4). “ Mobile Health Applications User Trends Research in Turkey” was announced for the first time in Digital Health Summit Turkey 2013. It was reported by Georgetown Medical School that medical students have augmented their diagnostic capabilities by using smartphones and that mobile technologies contribute to the education of the students (5). Despite all advantages, there are many problems in this regard. Smartphones may have small display screens and hardware limitations, causing connection problems. The reliability of medical applications is controversial (6).

The present study evaluates the most widely used mobile applications developed for healthcare professionals by emergency physicians. The study aims to determine the scope of smartphone applications in the emergency medicine field, investigate their effects on diagnosis and treatment, and raise awareness about medical ethics.

2. Material and Method

A survey was conducted on the use of smartphone applications in emergency medicine practice among emergency medicine residents, emergency medicine physicians, and faculty members working in different provinces of Turkey between February 25, 2018, and March 25, 2018. The participation of volunteers was enabled by face-to-face communications or phone and e-mail contact. Before starting the data collection phase of the study, approval was granted by the Yüzüncü Yıl University Faculty

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of Medicine Clinical Trials Ethics Committee with a decision number of 16 dated February 16, 2018. Three hundred and twenty respondents were taken into consideration. General practitioners working in the emergency departments and physicians who do not use smartphones were not included in the survey.

Descriptive statistics for the studied variables included mean, standard deviation, minimum and maximum values, and categorical variables were expressed as number and percentage. The mean values for continuous variables were compared between the groups using a one-way analysis of variance. Following the analysis of variance, Duncan's multiple range test was used to determine significantly different values. A chi-square test was used to compare categorical variables between the groups. The level of statistical significance was set at an alpha of 5% in the calculations, and the SPSS version 21 software package was used in the analysis.

3. Results

Of the respondents, 70% were aged 26–35 years, 60.3% were males, 61.6% had an experience of more than six years, and 40% worked in the emergency department for more than six years (Table 1).

A statistically significant relationship was found between emergency medicine experience and the intended purpose of using mobile applications (P=0.020). When comparing age and intended purpose of use, the most common purpose of using smartphones was communication among respondents aged less than 45 years. In comparison, 58.3% of the respondents aged more than 45 years (n=7) used smartphones for academic-professional purposes, and 25% (n=5) use them for communication purposes (Fig. 1).

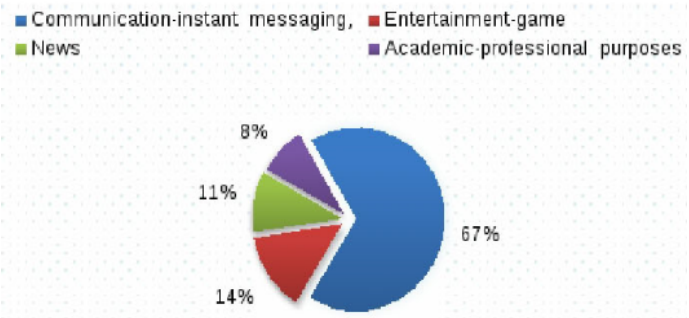

Fig 1. Mobile health applications user trends of the participant

Of the respondents, 45% (n=144) started using mobile applications four years ago while 61.5% of the specialists (n=88) and 52.9% of the faculty members (n=18) started using mobile applications four years ago (P=0.00).

It was found that the majority of participants using mobile applications in the field of medicine used these applications as a clinical decision-making tool during patient care (Fig. 2). Faculty members (70.6, n=24) were ahead of residents (39%, n=55) and specialists (38.2%, n=55) in terms of using the applications for literature search purposes (P=0.02).

Table 1. Sociodemographic data of the respondents participating in the survey titled "The place of smartphone applications in emergency medicine

Variable	n	%
Age		
Less than 25 years	4	1.3%
26-35 years	224	70%
36-45 years	80	25%
More than 45 years	12	3.8%
Gender		
Male	193	60.3%
Female	127	39.7%
Profession		
Specialist	145	45.3%
Research Associate	141	44.1%
Faculty Member	34	10.6%
Geographic Region		
Central Anatolia	76	23.8%
Marmara	68	21.3%
Eastern Anatolia	47	14.7%
Southeastern Anatolia	37	11.6%
Mediterranean	42	13.1%
Aegean	32	10%
Black Sea	18	5.6%
Years in Medicine		
1-3 years	53	16.6%
4-6 years	70	21.9%
7-10 years	101	31.6%
More than 10 years	96	30%
Years in Emergency		
1-3 years	94	29.4%
4-6 years	98	30.6%
7-10 years	74	23.1%
More than 10 years	54	16.9%

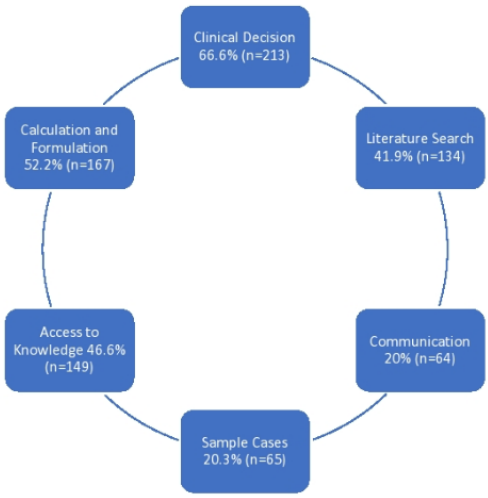

Fig 2. Professional uses of mobile health applications

Concerning the effect of mobile applications 'style of presenting the knowledge on the preference, applications with the visual presentation were the most liked and preferred among mobile applications in medicine (63.1%).

The applications teaching the content with a clinical basis,

such as differential diagnosis for a symptom, were rated as beneficial by 52.9% (n=18) of the faculty members, 49.6% (n=70) of the research associates, and 35% (n=51) of the specialists (P= 0.024). No significant difference was found among the occupational groups and the experience groups in emergency medicine regarding the use of calculation applications (P=0.876, P=0.993).

The most common expectations of the participants from mobile applications were being free of charge or cheap (Fig. 3) whereas 66.9% (n=97) of the specialists and 64.7% (n=22) of the faculty members attached importance to mobile applications being ad-free (P=0.007).

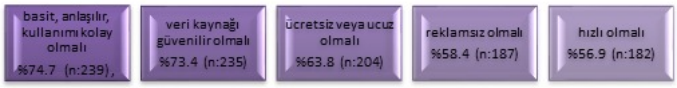

Fig 3. Expectations of the participants from mobile health applications

The most commonly used applications by the participants were Medscape, UpToDate, Calculate by Qx MD, TATD, PubMed mobile, MDCalc, and CepİlaÇ (Table 2). The UpToDate application was more commonly preferred by the faculty members than the specialists and residents (p=0.02).

Table 2. Variety of mobile health applications commonly used by the participants

	Very good (n)	Good (n)	Moderate (n)	Poor (n)	Total (n)	Rate (%)
Medscape	**92**	**107**	**22**	**.**	**221**	**70%**
UpToDate	82	81	29	1	193	61%
Calculate by QxMD	70	63	29	.	162	51%
TATD	48	71	33	7	159	50%
PubMed	40	69	23	.	132	42%
MDCalc Medical Calculator	41	40	27	.	108	34%
Cep İlaç	16	45	36	11	108	34%
WikEm	24	37	23	5	89	28%
ACLS	20	34	19	5	78	24%
5-Minute Emergency Consult	18	26	22	6	72	23%
Read by QxMD	23	28	17	2	70	22%
Annals of Emergency Medicine	15	29	20	2	66	21%
Micromedex Drug Reference	12	28	19	3	62	20%
Resuscitation	12	33	12	3	60	19%
EM Reference	9	24	13	3	59	18%
QuickEM	13	21	16	3	53	17%
SonoSchool	8	26	16	3	53	17%

The use of Pubmed applications was related to the occupational group and emergency experience (P=0.013). This application was rated as very good (29.4, n=10) and good (26.5%, n=9) by the faculty members and as good by the specialists (25%, n=36) and the residents (17.1%, n=24) (P=0.018) (Table 2).

The MDCalc use rate increased with increasing years worked in the emergency department, and faculty members participating in the survey reported more frequent use than the emergency medicine residents and specialists (P=0.00).

The most common problems that the participants face while using mobile health applications were over-detailed application content and the difficulty of reading the content on the smartphone (Fig. 4).

Emergency physicians used instant messaging applications, most commonly with cardiologists and orthopedists (Fig. 5).

ECG recordings and radiographic images were most commonly shared materials by the users of instant messaging applications (Fig. 6).

Fig 4. Problems encountered by the participants while using mobile health applications

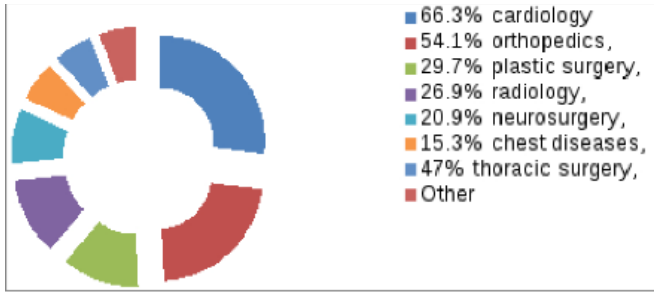

Fig 5. Departments with which emergency physicians use instant messaging the most

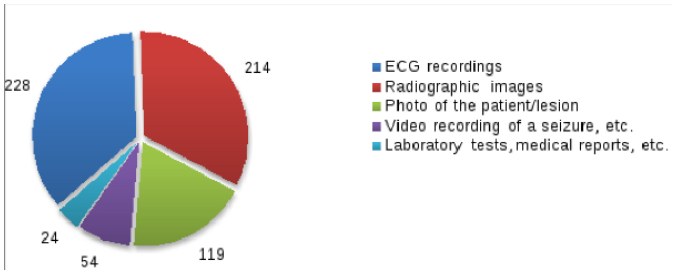

Fig 6. The most commonly shared materials by the participants in instant messaging applications

There was a significant difference in the use of paid applications among emergency physicians, faculty members, and residents (P=0.004). Of the respondents, 30.3% (n=97) reported institutional funding support for the use of these applications.

It was found that 11.3% of the participating physicians have taken part in the mobile application development process. Of physicians participating in the medical application development process, 52.8% were specialists, 36.1% were research associates, and 11.1% were faculty members. There was no significant difference among the occupation groups concerning participation in the mobile application development process (P=0.543). Of the participants, 28.8% have considered developing a mobile health application, and faculty members were more willing to develop a mobile health application than the other groups (P=0.013).

Of the participants, 75% found instant messaging applications helpful in their profession.

Privacy violations and a lack of control were regarded as the most significant problems of mobile health applications in terms of medical ethics. Also, incomplete or incorrect information and misguidance due to commercial purposes were the prominent concerns among the participants.

4. Discussion

There has been an increase in the volume of patients presenting to the emergency departments in recent years. The increase in emergency admissions causes delays in the examination and treatment of emergency patients, affecting patient satisfaction and healthcare quality unfavorably (7).

The role of smartphones in medicine and education appears promising and exciting, and a study reviewing all uses of smartphones in medicine and medical education has reported many uses of smartphones in medicine (8). The present study found that mobile phones are used for professional purposes at a rate of 92.8%.

A study examining the use of smartphones and mobile applications among emergency physicians and medical students has found that most participants possessed applications related to medicine and often preferred applications related to disease diagnosis and management, drug reference applications, and clinical scoring systems and calculators (9). Similar to their study, the present study found that emergency physicians used mobile applications for clinical decision making, calculation and formulation, accessing the knowledge, literature search, sample cases, and consultation purposes.

In Heidelberg University Hospital, the physicians designed a smartphone application to simplify procedures and existing paper-based guidelines for use by the physicians and nurses in the pediatric emergency clinic (10). The present study also found that 11.3% of the participants were actively involved in the development phase of any medical application, and 28.8% made designs to improve a medical application.

In 2011, Mohan et al. evaluated mobile health applications on PubMed, Google, and Apple Store platforms and reported more than 10,000 downloads related to medicine and healthcare, one-third of which were free of charge (11). The present study found that most participants preferred free-of-charge applications and paid and unpaid applications did not differ in quality and efficiency. It was also found that approximately one-third of the participants received institutional support for access to paid applications.

The studies evaluating teleconsultation and teleconference systems suggest that burn lesions can be examined for their sizes and depths as in bedside examination and that image quality of portable devices allows such examination. The studies in the literature have demonstrated the applicability of smartphone-based consultation systems in evaluating burn injuries (12). Similarly, 75% of the participants in the present study reported professional benefits of instant messaging applications. Emergency physicians often preferred these applications to communicate with cardiologists and orthopedists, and the most commonly shared materials were ECG recordings, radiographic images, and photos of skin lesions.

In a study by Xu and Zang, the main problems of mobile health applications are listed as the following: the complexity of classification, low accessibility, lack of control mechanisms, privacy concerns and user confidence (most mobile health applications do not warrant user privacy) (13). The present study also observed that privacy violation and lack of control mechanisms were the most significant problems for mobile applications in terms of medical ethics. At the same time, incomplete and incorrect knowledge and misguidance due to commercial purposes are prominent ethical concerns.

Recent mobile device-based observational studies are regarded as promising sources of information for researchers. In light of the present research, mobile applications published in the medicine category are considerably popular among emergency physicians and provide professional convenience.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

Before starting the data collection phase of the study, approval was granted by the Yüzüncü Yıl University Faculty of Medicine Clinical Trials Ethics Committee with a decision number of 16 dated February 16, 2018.

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The effects of the relationship between psychological status and nutritional status on success in adolescent students wih canonical correlation analysis

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Abstract

The primary aim of this study is to determine statistically significant relationship between nutrition and psychological status in adolescent students with the help of canonical correlation analysis, and then to reveal whether nutritional and psychological status of adolescents with gender has an effect on their educational success by using logistic regression analysis. Nutritional status and psychological status variable sets were created by using the Demographic Information Form, Beck Depression Inventory, Beck Anxiety Inventory, Conners-Wells Adolescent Self-Report Scale and Food Frequency Questinaire (FFQ), and antropometric measeruments. These assesments were applied face-to-face to the students with their consent and the scales were filled in by themselves. In the canonical correlation analysis, the variable set for Nutritional Status (U), were represented with body mass index (BMI) and also energy, iron, folic acid and calcium that were obtained by entering the FFQ into the Nutrition Information Systems (BeBiS Program). On the other hand the Psychological Status (V) variable set consisted of Beck depression scale, Beck anxiety scale and Conners-Wells scale scores. Finally, students' success levels were determined by taking their grade point averages over the e-school system of the Ministry of National Education for educational success. According to the canonical correlation analysis; the variable that contributed the most to the Nutritional Status (U) variable set was Body Mass Index while the variable that contributed the most to the V variable set was the Beck Depression Scale Score. The canonical correlation coefficient between the U and V variable sets was 22.4% and it was found statistically significant ($p<0.05$). In the logistic regression analysis, the dependent variable was educational success, which was categorized the grade point average as successful or unsuccessful with cutt-off points 60, then gender, U and V were taken as the independent variables. The result of the logistic regression analysis was determined as that gender and V had significant effects on the educational success in adolescents ($p<0.05$).

Keywords: adolescent, nutritional status, psychological status, canonical correlation analysis, educational success

1. Introduction

Adolescence is defined as the age range of 10-19 by the World Health Organization (WHO). It is a special period that covers the transition from childhood to adolescence and in terms of biological change and development, it has significant potential (1). Current epidemiological findings predict that one in five children is expected to develop some type of mental health problem when they reach adulthood, and that 50% of all adult mental health problems occur during adolescence (2). In this period, adolescents continue to develop not only in physically, but also cognitively and psychosocially (3).

Adolescence generally begins at the age of 12-13 in girls and 14-15 in boys (4). Since girls enter the adolescence period on average 2 years before than boys and complete the adolescence period 2 years earlier than boys on average, therefore physical and mental changes in this period also differ according to gender (5). In this period, it is known that the nutritional status of adolescents changes according to their psychological status, or similarly, their nutritional status affects their psychological status (6).

The main statistical analyzes used in our study are canonical correlation analysis and logistic regression analysis. Canonical correlation analysis is one of the multivariate statistical methods that aims to maximize the relationship between variable sets, each of which has more than one variable (7). Logistic regression analysis is used modelling discrete and continuous independent variables when the dependent variable is categorical (8).

In this context, the aim of our study is to determine statistically significant relationship of the nutritional status

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and the psychological status variables of adolescent students by using canonical correlation analysis and to reveal whether nutritional and psychological status with gender have an effect on on their educational success.

2. Materials and Methods

This study, is a cross-sectional study, which was conducted in the 2018-2019 academic year. It was carried out in 4 randomly selected state high schools in Istanbul, two of them were on the European side and the others were on the Anatolian side. 451 adolescent students participated to this study, the students filled the Demographic Information Form, Beck Depression Scale, Beck Anxiety Scale, Conners-Wells Adolescent Self-Report Scale and FFQ by themselves in the hours recommended by the school administration. This study is approved by local ethical commtite with the approval number 09.2019.938.

The variables as energy, iron, folic acid and calcium obtained from the entry of the FFQ into Nutrition Information Systems (the BeBiS program). This nutrient which was considered deficient and necessary in the nutrition status of adolescents in the Turkey Dietary Guidelines 2016 (9) and National Turkey Nutrition and Health Survey (TNHS) 2010 reports (9) with BMI, were selected for the Nutritional Status (X) variable set. Daily energy recommendation is an average of 2500 calories for adelescent girls and 3000 calories for adolescent boys. Daily recommendation is 330 mg for folic acid and 1150 mg for calcium. Daily iron recommendation is an average of 11 mg for girls and 13 mg for boys (10).

Beck depression scores, Beck anxiety scores, and Conners-Wells scores were considered as the variables, which expressed the Psychological Status (Y) variable set.

The success of the students was determined by taking their grade point averages over the e-school system of the Ministry of National Education and the grade was categorized as successful or unsuccessful with cutt-off points 60. Adolescent students with a score of 60 and above were considered successful and those with less than 60 points as unsuccessful.

2.1. Scales Used in the Study

Food Frequency Questionnaire: It is a questionnaire used to categorize certain foods consumed and the frequency of consumption of these foods such as fruit, vegetables, milk and dairy products, etc. Food consumption frequency questionnaire contains also questions about portion size and cooking methods (11).

Nutrition Information System (BeBiS Program): It is a program where all foods consumed including beverages were entered according the consumption amount and frequency, then daily energy, macro and micro nutrient etc. amounts can be determined (12). In our study, the foods that adolescent students reported in the FFQ questionnaire what they consume according to the meal information with their consumption frequency and amount were entered into the BeBiS (v8.2) software, then daily energy, water, carbohydrate, protein, fat, etc. quantities have been obtained.

Beck Depression Scale: This scale is developed by Beck et al. in 1961 and used to measure the emotional, somatic, cognitive and motivational symptoms of depression. It is a scale that shows the level or severity of depression by choosing the sentences that best express oneself in the last week, including the day of the application. A high score indicates the severity of depression. Turkish validity and reliability studies of the scale were performed by Hisli et al. in 1988 (13).

Beck Anxiety Inventory: This scale is developed by Beck et al. in 1988 and used to measure the frequency of anxiety symptoms. It is a self-assessment scale within the last week, including the day of application. A high score on the scale indicates the level of anxiety experienced by the person. The validity and reliability studies of the Turkish version of the scale were performed by Ulusoy et al. in 1993 (13).

Conners-Wells Adolescent Self-Report Scale: This scale was developed by Conners et al. in 1997. It consists of Conduct Disorder, Cognitive Problems and Hyperactivity subscales which aims to evaluate behavioral disorders, attention deficit and hyperactivity problems in adolescents. It is based on the self-evaluation of individuals aged 12-17 according to the last month. A high score from the Conners-Wells Adolescent Self-Report Scale indicates that the adolescent has the same level of problems as described in this scale. The validity and reliability studies of the Turkish version of the scale were performed by Kaner et al. in 2012 (14).

2.2. Canonical Correlation Analysis

Canonical correlation analysis is a reducing dimension method. It is a method based on the aim of maximizing the correlation between canonical variable pairs (U, V) formed by linear combinations of variable sets with more than one variable, in other words, examining the relationship between two variable sets consisting of more than one variable (15). Some assumptions are needed to be provided for the implementation of this analysis (16). These assumptions have to be multivariate normal distribution of the data, minimum error in terms of the relevant variables, no multicollinearity between the variables, and a fairly large sample size (20 times the number of variables) for reliability of the analysis results.

The mathematical representation of canonical correlation analysis can be expressed as follows:

Let there be two sets of independent variables X with p observations and Y with q observations,

$$X = X1 + X2 + \ldots + Xp ,$$

$$Y = Y1 + Y2 + \ldots + Yq$$

$$ai1.Xi1 + ai2.Xi2 + \ldots + aip.Xip = Ui \rightarrow \rho i \leftarrow Vi = bi1.Yi1 + bi2.Yi2 + \ldots + biq.Yiq$$

The equation giving the correlation between the U and V canonical variables can be expressed as follows;

$$\rho_{u,v} = \frac{Kov(U,V)}{\sqrt{Var(U)Var(V)}}$$

2.3. Logistic regression analysis

Logistic regression analysis is an analysis based on the logarithm of probability, odds and odds ratio where the independent variables are continuous or discrete when the dependent variable is a categorical variable (17).

The logistic regression model can be written as follows for p independent variables (18).

$$L = \ln\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1.X_1 + \ldots + \beta_p.Xp$$

In logistic regression analysis, the significance of the model is tested with the Omnibus chi-square test and the model is expected to be statistically significant ($p<0.05$). Nagelkerke R^2 is expressed as the percentage of independent variables explaining the dependent variable, and if it is close to 1, it means that the model is well determined (18). The efficiency of the best model created to explain the dependent variable gives the goodness of fit (19). In other words, it is the harmony between the observed value and the expected value in the dependent variable, and the Hosmer-Lemeshow statistics are used for this pupose (20). The fact that the result of this test was not found to be statistically significant ($p>0.05$) indicating that the model and data fit well (17). The percentage of correct classification shows how accurately the model classifies the dependent variable.

3. Results

451 adolescent students between the ages of 16-20 participated in the study. The descriptive characteristics of these students, defined as the "adolescent period", are given in Table 1.

It was determined that 53.2% (n=240) of the 451 adolescents participating in the study were girls. There was a significant difference between boys and girls for the average height and body weight, respectively ($p<0.0001$, $p< 0.0001$). In nutritional status variables; there was no significant difference between boys and girls for BMI and for the percentage amount of energy and iron that meet the known requirement ($p>0.05$), on the other hand; significant differences were observed between boys and girls for the percentage of meeting daily folic acid and calcium recommendations ($p<0.0001$) (Table 1).

In the psychological state variables; while there were statistically significant differences between boys and girls for Beck depression and Beck anxiety ($p<0.0001$), but there was no significant difference between boys and girls for Conners-Wells ($p>0.05$).

Table 1. Descriptive statistics

	Total (n=451)	***Girls (n=240)***	***Boys (n=211)***	
Variables	**Mean ± SD**	**Mean ± SD**	**Mean ± SD**	**p***
Characteristic Features				
Height (cm)	166.5 ± 8.6	160.8 ± 5.9	173.0 ± 6.3	
Body weight (kg)	62.5 ± 13.2	57.8 ± 11.0	67.8 ± 13.5	
Age (year)	16.8 ± 0.7	16.7 ± 0.6	16.9 ± 0.8	
Nutritional Status Variables (X_1)				
BMI (kg/m^2)	22.5 ± 4.1	22.4 ± 4.1	22.6 ± 4.1	0.586
Energy (kkal)	2998.0 ± 917.8	2760.4 ± 913.0 (110.4%)**	3268.3 ± 847.5 (108.9%)**	0.630
Folic acid (g)	379.3 ± 140.9	337.6 ± 124.0 (102.3%)**	426.7 ± 144.2 (129.3%)**	**<0.0001**
Calcium (g)	1152.8 ± 426.2	1061.7 ± 426.4 (92.3%)**	1256.3 ± 402.6 (109.2%)**	**<0.0001**
Iron (g)	15.3 ± 5.8	13.6 ± 5.4 (124.1%)**	17.1 ± 5.8 (131.9%)**	0.080
Psychological Status Variables (X_2)				
Beck Depression	13.6 ± 9.8	15.6 ± 10.2	11.2 ± 8.7	**<0.0001**
Beck Anxiety	14.3 ± 10.7	17.0 ± 11.0	11.2 ± 9.5	**<0.0001**
Conners-Wells	12.1 ± 6.0	12.1 ± 5.4	12.1 ± 6.6	0.990

*p values express the statistical significance of the difference between the means according to the characteristics of interest among the gender.
**Values shown in parentheses are the percentage of adolescents' meeting recommendation.

According to the results of canonical correlation analysis, the 1st canonical correlation coefficient was found as 0.224 and statistically significant with $p=0.022$. This means that there was a 22.4% relationship between nutritional status canonical variable set (U) and psychological status canonical variable set (V).

The linear canonical variable sets of nutritional status and psychological status were as follows.

The equation of the first canonical variable of the Nutritional Status variable set;

U= (-0.124)*BMI + (-0.001)*Energy + (0.011)*Folic Acid + (0.001)*Calcium + (-0.075)*Iron.

The variable that contributes the most to the canonical variable of nutritional status was body mass index and contributes approximately 12%. This negative contribution indicates that the nutritional status of adolescents with an increased body mass index was adversely affected.

The equation of the first canonical variable of the Psychological Status variable set;

V= (-0.095)*Beck Depression Scale + (0.009)*Beck Anxiety Scale + (-0.036)*Conners-Wells Scale.

The variable that contributes the most to the canonical variable of psychological status is the Beck depression score with a 10% contribution.

In the logistic regression analysis, the effects of nutritional status canonical variable (U) and psychological status canonical variable (V) with gender were examined on educational success of the adolescents. While the nutritional status canonical variable (U) was not statistically significant on the educational success of adelescents (p>0.05), but gender (OR= 3,309; %95 C.I.: 2,044 – 5,358) and psychological status canonical variable (OR= 1,389; %95 C.I.: 1,137 – 1,696) were found as significant variables respectively (p<0.0001, p<0.0001) Table 2.

Table 2. Logistic regression analysis output

	β Coefficient	Standard Error	Wald Statistics	p value	Odds Ratio	%95 C.I. Exp(B)	
						Lower	Upper
Gender	1.197	0.246	23.683	0.0001	3.309	2.044	5.358
Psychological Status (V)	0.328	0.102	10.372	0.001	1.389	1.137	1.696
Constant	1.081	0.228	58.069	0.0001	2.948		

According to the omnibus test result, this regression model was found to be statistically significant (p<0.001). The Nagelkerke R^2 value, which is expressed as the percentage of independent variables explaining the dependent variable, was found to be approximately 10% (0.103). Hosmer-Lemeshow test, which expresses the goodness of fit of the model, was p=0,704 then it can be said that the model-data fit at a sufficient level. Finally, the percentage of correct classification was found to be 74.5%.

4. Discussion

The significant relationship between nutritional status canonical and psychological status canonical variables of adolescents was found as 22.4% where the 1st canonical correlation coefficient was taken into account, according to the result of the canonical correlation analysis.

When it was taken into account of the nutritional problems and nutritional needs of adolescents; the variables as folic acid, calcium and iron which were taken for nutritional status canonical variable (U), were not found deficient in our study sample, contrary in TBSA 2010-2019 report. Besides, in all scales, the psychological status of adolescent students was not at alert level, generally. In a study, the adolescence period has positive effects on the mental health of boys, while depression and anxiety disorders are higher in girls (21). At the same time, in another study when the psychological status of adolescents compared between gender, it was observed that the mean score of psychological symptoms was higher in girls than in boys (22). In our study, the fact that adolescent girls were more depressive and anxious compared to boys, therefore it was consistent with the results of the studies mentioned.

The strenght of this study was to use logistic regression analysis, combining with the canonical correlation analysis. Once the significant relationship between nutritional status canonical variable (U), psychological status canonical variable (V) was determined, then to perform logistic regression these canonical varibales were used with gender on educational success. If educational success were analyzed separetley for indivudual nutrition and psychological variables; some variables might had been found statistically insignificant in univariate analyzes and thus these insignifant variables can not take place in multiple logistic regression analysis. However, the canonical correlation analysis creates the canonical variables, by using every variable in nutrition and psychological variable set even they have small contribution by assigning with a certain weigt. In other words, by this way, all variables considered were included in the logistic regression analysis with some weight (23).

Although Nagelkerke R^2 value, which is the percentage value of gender and psychological status canonical variable (V) explaining the educational success of adolescents, was low - about 10%- but it could be cited as the weakneses of this study. One reason might be that this study was a screening study and the other reason might be that the adolescent students have been filled all the forms and scales based on their own declaration. It can be said that gender is more effective on educational success than psychological status canonical variable and girls were 3,309 times more successful than boys. In addition, there is a statistically significant difference in terms of gender for Beck depression and Beck anxiety levels. Valid and reliable enough sample size is one of the assumptions of the canonical correlation analysis, 451 adolescents participated in this study that the results of the study findings could be considered reliable and valid. By this way the condition, that the sample size should be at least 20 times of the variable number, was satisfied (24).

Although canonical correlation analysis was used rarely in health sciences but it is also happened across in some studies. Erkorkmaz et al. (2013) titled “Examination of the Relationship Between Children's Eating Behaviors and Parents' Nutrition Styles Using Canonical Correlation Analysis”, were used canonical correlation analysis in their article. In another study, Çetin et al. (2015), titled “The Role of Five Factor Personality Traits in Explaining Psychological

Resilience: A Canonical Relationship Analysis" reported that the use of multivariate statistical methods, such as canonical correlation analysis which explains the relationship patterns of the variables in the selected variable sets, is highly considerable method in health sciences.

As a result, instead of comparing educational success status with the variables in the nutritional status and psychological status variable sets separately, it would be better to use canonical correlation analysis, which is the main analysis of our study. Because it is not correct to have an idea about the nutritional status of an adolescent by looking at only for a significant variable such as calcium or iron etc. Likewise, the same for the psychological status; if the Beck depression scale was not found statistically significant between successful and unsuccesful adelescent students but the two other scores as Beck Anxiety Scale and Conners-Wells Scale were found significant. Thus, it will not be easy to deduce a definite idea about psychological status.

For this reason, instead of comparing the variables in the sets of nutrition and psychological status with educational success one by one, it will be more reliable and valid to compare the new canonical variables obtained by the canonical correlation analysis with educational success. These new canonical variables are a linear combination of variables nutritional status and psychological status variable sets and the canonical variables are linearly formed with the contribution of each variable in the variable set. This analysis also increases the importance of the estimation results obtained by logistic regression analysis.

Conflict of interest

None to declare.

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Attitudes towards the COVID-19 vaccine: What do healthcare students think about the COVID-19 vaccine?

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Abstract

Vaccination is the most effective method in preventing infections and decreasing infection-related morbidity and mortality. In this study, health students' attitudes and thoughts about COVID-19 vaccines were evaluated. The study was conducted between January 18 and February 1, 2021. Ethics committee approval was obtained before starting study. Students who accepted to participate in study were asked to fill in the interview form via google questionnaire. Data were analyzed in SPSS 21 program, $p < 0.05$ was considered significant. 637 of participants were women and mean age was 20.74±7.32 years. 13.78% of students reported that they had disease and 34.02% of them had a family history of the disease. 71.83% of students had confusion about vaccine, 37.44% stated that they trusted vaccine, and 48.29% reported that they thought it was effective. If vaccine will protect themselves, their family, and friends (86.70%); if vaccine will protect community (86.95%), and stated that they would be vaccinated if vaccine would bring the people back to normalization (88.90%). There were 346 (42.20%) students who wanted to be vaccinated against COVID-19. In the study, although students reported that they want to be vaccinated if COVID-19 vaccine will protect themselves, their family, friends and society, and return public to normalization; It was concluded that level of confidence in the vaccine and desire to be vaccinated were low. Multidisciplinary studies are needed to increase COVID-19 vaccination rates.

Keywords: vaccination, COVID-19 vaccine, knowledge and attitude, health students

1. Introduction

In the last days of 2019, cases of pneumonia of unknown etiology were reported in Wuhan, the capital of the Chinese Hubei region (1). The rapidly spreading coronavirus disease was declared as a pandemic and emergency by the World Health Organization (WHO) on March 11, 2020, and recommendations were made to the world community to control the epidemic (2). Despite the quarantine measures taken, the disease spread rapidly outside the country and as of 16 May 2020, new coronavirus cases were recorded in 213 countries globally (3).

As well as the common cold, coronaviruses were caused various diseases known as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS). Although it is claimed that the new type of coronavirus is similar to SARS, it has been determined that it is largely different from SARS-CoV as a result of genetic analyzes (4). This virus was named 2019-nCoV when it first appeared and was named SARS-CoV-2 in the later stages of the epidemic, and the clinical disease caused by the virus was named Coronavirus disease 2019 (COVID-19) (5).

Coronaviruses are transmitted from person to person by droplets, as well as by contact of other individuals with the droplets shed by sick people through sneezing and coughing, and then by taking their hands to the mouth, nose and eye mucosa. The easy transmission of the disease in this way causes its rapid spread in a short time (6). For this reason, individual and social measures to prevent disease transmission all over the world and in our country come to the fore. Control of foodstuffs, disinfection processes, early diagnosis and reporting, isolation of sick individuals, travel restriction, health education, healthy nutrition, exercise, use of individual protective equipment and vaccination are among the practices that should be done to prevent contamination (7). In particular, vaccines, which are among the preventive measures, have proven to be the most effective and economical way to prevent and control infectious diseases (8).

Today, although the treatment protocols with proven effectiveness for coronavirus infections are limited, vaccine development studies continue. The aim of vaccination is to protect human health through the prevention of death, permanent disability, severe illness and disease. Vaccination is an extremely safe, effective and inexpensive method of preventing infectious diseases (9,10). One of the most important components in controlling the COVID-19 pandemic is to provide the highest level of immunity of the

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population with an effective and safe vaccine. However, the ongoing discussions about the pandemic and vaccines all over the world have increased the hesitations against vaccines. In order for vaccination campaigns to be successful, in addition to providing the public with access to the vaccine, it is necessary to inform the public about the effectiveness and safety of the vaccine in a transparent manner, and to carry out convincing studies on education, media and Internet platforms (9). Especially in a crisis environment such as an epidemic, people who use the media more believe that the information given by the media about taking conscious measures against infection is up-to-date and accurate. In this context, it is thought that if accurate information about the pandemic and vaccines is effectively communicated to the public through the media, people's risk perceptions about the issue will be healthier (11). Determining the attitudes of future healthcare professionals about vaccines and adding this to the literature will guide future studies. This study was conducted to evaluate the thoughts and attitudes of health students about the COVID-19 vaccine.

2. Materials and Methods

2.1. Study design

This study is a descriptive cross-sectional study

2.2. Place and time of the study

The study was carried out at Sakarya University (SAU) Vocational School of Health Services (SYHMYO) between 18 January-1 February 2021. There are a total of 8 different programs that provide associate degree education at SAU SHMYO.

2.3. Data collection tools

Demographic data and descriptive features form consists of 39 questions including demographic data of students, information about COVID-19 disease and vaccines.

2.4. Data collection

There were 1118 female and 510 male students in total studying at SAU SHMYO. The interview form was delivered to 1628 students. 820 students participated in the survey. Students who accepted to participate in the study and met the inclusion criteria were asked to fill in the interview form via google survey after obtaining the necessary ethical and institutional permissions. The School Interview form consists of “Demographic data and descriptive characteristics Form” and “Information on COVID-19 disease and vaccines”. Before starting data collection, consent was obtained from the participants and they were informed that the data obtained would not be shared anywhere else and that they could leave the study at any time. Data collection took approximately 8 minutes for each participant

2.5. Evaluation of data

Data were analyzed using the IBM SPSS 22 (Armonk, NY: IBM Corp) package program (12). Categorical variables were expressed as frequency and percentage values, discrete variables as arithmetic mean and standard deviation. Statistical significance level was taken as $p<0.05$.

3. Results

Of the students participating in the study, 637 (77.69%) were female and the mean age was 20.31±2.41 (18.00-36.00) years. When the distribution of students according to the program they are studying is examined; 41 (5.00%) anesthesia programs, 46 (5.61%) child development programs, 145 (17.68%) physiotherapy programs, 188 (22.93%) first and emergency aid programs, 60 (7.32%) optics program, 92 (11.22%) medical documentation and secretarial program, 92 (11.22%) medical laboratory technician program and 156 (19.02%) elderly care program students. Of the students, 450 (54.88%) were in the first year, 370 (45.12%) were in the second year; 451 (55.00%) were graduated from general high school and 369 (45.00%) were graduated from health vocational high school.

While 785 (95.73%) of the students lived with their families, 21 (2.57%) stayed with their friends and 14 (1.70%) were alone. 368 (44.88%) of the students lived in the city center, 322 (39.27%) lived in the district and 130 (15.85%) lived in the village.

Table 1. The answers given by the students to the questions about the COVID-19 vaccine

Information on the COVID-19 vaccine	n %
COVID-19 vaccine is effective	396 (48.29)
COVID-19 vaccine is safe	307 (37.44)
I reviewed the results of the COVID-19 vaccine study	382 (46.85)
I find the COVID-19 vaccine studies sufficient	221 (26.95)
I find the explanations about COVID-19 vaccines sufficient	120 (14,63)
According to the information I got from the TV, I will be vaccinated for COVID-19	123 (15.00)
According to the information I got from the internet, I will be vaccinated for COVID-19	138 (16.83)
I will be vaccinated because my family thinks I should be vaccinated.	116 (14.15)
I will be vaccinated because my friends asked me to vaccinate	42 (5.12)
If the COVID-19 vaccine will protect me, my family and friends, I will get vaccinated.	711 (86.70)
If the COVID-19 vaccine is going to protect society, I will be vaccinated.	713 (86.95)
If the COVID-19 vaccine will bring the public back to normalcy, I will be vaccinated.	729 (88.90)
I'm afraid of vaccines or injections.	197 (20.02)
I believe in natural and traditional solutions to prevent infections.	291 (35.49)
I will not be vaccinated because of my religious beliefs.	12 (1.46)
I will be vaccinated in case there is a travel restriction for those who are not vaccinated for COVID-19.	112 (13.66)

When their income status is evaluated, 509 (62.07%) students stated that their income is equal to their expenses, 204 (24.88%) their income is less than their expenses, and 107 (13.05%) their income is more than their expenses. While 732 (89.27%) of the students did not have any chronic disease, 88 (10.73%) had at least one chronic disease. The sociodemographic information of the students and their attitudes towards the acceptance of COVID-19 vaccines are shown in Table 1.

When the students' status of having COVID-19 disease is questioned; 113 (13.78%) reported that they had COVID-19 disease, 279 (34.02%) had a family history of the disease, and 465 (56.70%) had lost their lives in their immediate surroundings due to this disease. 279 (34.02%) of the students were taking medication/vitamin supplements to prevent COVID-19 disease. While 35.61% of the students who received vitamin/drug supplementation took vitamin C, 27.12% vitamin D and 6.83% zinc; 29.20% of the students were taking herbal tea and 1.24% were taking omega-3 and propolis.

331 (40.37%) of the students thought that they were exposed to questions about COVID-19 disease and 719 (87.69%) thought that there was information pollution about COVID-19 disease. When the sources of information about the COVID-19 disease were questioned, 441 (53.78%) of the students were from the statements of the ministry of health, 511 (62.31%) from the internet, 484 (59.02%) from television programs/news, 447 (54.51%)' of them were getting information from social media (facebook, instagram, twitter, linkedin etc.) and 180 (21.95%) from the statements of infection specialist doctors/microbiologists. Of the students, 598 (71.83%) had confusion about the COVID-19 vaccine, and 252 (30.73%) believed in conspiracy theories. There were 346 (42.20%) students who wanted to be vaccinated against COVID-19 and the answers given by the students to the information about the COVID-19 vaccine according to the acceptance of the COVID-19 vaccines are presented in Table 2. The students were asked “Which vaccine would you like to get from the COVID-19 vaccines?” their answers to the question are shown in Fig. 1.

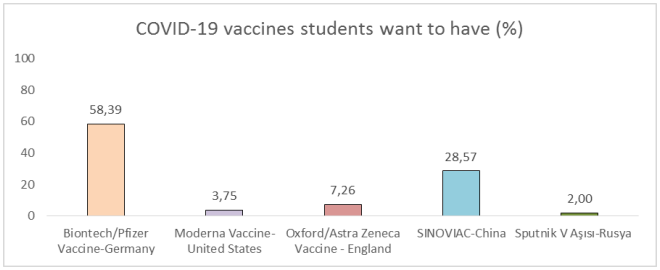

Fig. 1. Distribution of COVID-19 vaccines that students want to receive

4. Discussion

In this study, health students' attitudes towards COVID-19 vaccines and their willingness to be vaccinated were examined. The findings showed that approximately 42.20% of healthcare students wanted to be vaccinated against COVID-19. It has been reported that the immunization rate among individuals can be between 55% and 82%, depending on the prevention and mitigation strategies of COVID-19 disease in a population (13). This rate may vary between regions and even countries depending on the socioeconomic status, regional differences and the sensitivity of the society. In a study whose data were collected in September 2020 in our country, 68.6% of healthcare professionals stated that they could be vaccinated against COVID-19, and it was stated that students were eager for the vaccine (14). Again, in a study conducted in our country and the data were collected in December 2020, it was reported that 84.6% of healthcare professionals were willing to accept the COVID-19 vaccine (15). In a study conducted with 2678 healthcare workers in France, Belgium, and Canada, it was stated that 48.6% had high acceptance, 23.0% moderate acceptance, and 28.4% hesitation/reluctance (16). In the study conducted by Lucia et al. in the USA, it was stated that 23% of health students were reluctant to receive the COVID-19 vaccine, even if FDA approved it (17). In a study conducted with university students in Italy, which was heavily affected by the pandemic, it was reported that the rate of students who wanted to be vaccinated was 86.1% (18). The World Health Organization states that COVID-19 vaccines are still very effective in preventing serious illness and death against all current alarming variants (19). At the time of the study, it was thought that students' willingness to be vaccinated was low because the effect of vaccines in practice against COVID-19 variants was unclear.

In a study of healthcare workers, it was reported that approximately two-fifths of healthcare workers (n=92, 39.3%) agreed to receive the COVID-19 vaccine (20). In the study conducted by Askarina et al., 64.3% of the participants reported that they wanted to accept any COVID-19 vaccine, while Ochollo et al. in their study, reported that 52.4% of the individuals were willing to have the COVID-19 vaccine (21,22). Roy et al. (23), in their study on healthcare workers, reported that only 63% of healthcare workers would receive a COVID-19 vaccine. In our study, the willingness of health students to be vaccinated against COVID-19 was found to be 42.20%. The results of our study were found to be partially low in the desire to be vaccinated compared to the literature. This result was thought to be due to the fact that the COVID-19 vaccine application had just started in our country at the time of the study and the students' lack of knowledge about COVID-19 vaccines.

As information sharing regarding the spread of COVID-19 disease and control measures is updated, there is still uncertainty about the safety of vaccines. Roy et al. in their study; stated that the vast majority of healthcare workers were willing to be vaccinated against COVID-19 in the first wave of the COVID-19 pandemic, but 1 out of 6 healthcare

professionals stated that they were reluctant to be vaccinated due to concerns about the lack of information about the efficacy and safety of the vaccine. In the same study, healthcare workers reported very strong negative feelings about post-vaccine allergies, indicating their distrust of the vaccine (23). Agyekum et al. reported in their study that the majority of healthcare professionals (64.5%) were reluctant to accept COVID-19 vaccines due to their concerns about the safety of vaccines (20). Ochollo et al. stated in their study that the majority of those who did not want to be vaccinated were worried about the side effects of the vaccine, so they did not want to be vaccinated (22). In our study, the rate of confidence against COVID-19 vaccines was 37.44% and the rate of finding the vaccine effective was 48.29%. It was thought that these low rates might be due to the fact that health students did not find the explanations of the COVID-19 vaccine (14.63%) and the vaccine studies (26.95%) sufficient. In order to reverse the perception of insecurity towards the COVID-19 vaccine, programs should be organized through television programs and social media, especially the ministry of health, and the society should be informed about the importance of immunization in protection from COVID-19 infection. The society should be sensitized to vaccines and the community should be encouraged by training on vaccines.

Understanding the underlying causes of community vaccine reluctance is important for successful immunization intervention. Studies have shown that healthcare professionals are hesitant about or delaying the COVID-19 vaccine (23,24). Askarian et al. (21), explained that the main reasons for vaccine rejection were due to misunderstandings about vaccine efficacy and vaccine-related side effects. Roy et al. (23) explained the most important reasons for the reluctance of healthcare workers to be vaccinated as long and medium-term safety concerns, but in the study, healthcare workers stated that nothing would make them comfortable. In addition, healthcare workers with underlying health problems and religious concerns reported very strong negative feelings about being forced to get vaccinated. Ochollo et al. (22) reported in their study that the majority of those who did not want to be vaccinated were worried about the side effects of the vaccine, so they did not want to be vaccinated. In our study, students stated that they would like to be vaccinated if the COVID-19 vaccine would return the public to normalization (88.90%), if the vaccine would protect the society (86.95%), and if the vaccine would protect themselves, their family and friends (86.70%). In line with these results, education and information campaigns about COVID-19 vaccines should be organized, and the public should be informed about the importance of vaccines in protecting against COVID-19 infection and preventing disease-related deaths. The trust of the society should be gained by carrying out multidisciplinary studies on the protection of individual and public health and the acceleration of the return of the people to normalization with vaccination.

In a study conducted with nursing students, three-quarters of the students stated that the university provided information about COVID-19, and in the same study, it was stated that 95% of Indian students used social media as a source of information (25). In another study conducted with university students, it was reported that the most common source of information for COVID-19 was social media (77.1%), and that 24.2% of students used scientific articles as a source of information (26).

In the study conducted in Kenya, it was reported that most Kenyans received basic and important information about SARS-CoV-2 from television or social media (22). In our study, the information of health students about COVID-19 disease and vaccines, respectively; Internet (62.32%), television programs/news (59.02%), social media (54.51%), ministry of health (53.78%) and infectious diseases and microbiology experts (21.95%) In line with these results, effective use of television, internet and social media should be used effectively in vaccine acceptance. The society should be informed about COVID-19 vaccines (safety, effectiveness, side effects, etc.) by organizing programs about COVID-19 disease and vaccines on the internet, social media and television programs with the participation of infectious diseases, public health and microbiology specialists and other relevant sciences. Thus, it can be ensured that misunderstandings are eliminated and society's incentives for vaccination are increased. In addition, organizing vaccination campaigns on social media and television can be effective in the acceptance of the COVID-19 vaccine in the society.

As a result of, ın order to protect against the COVID-19 epidemic, vaccination with a vaccine will undoubtedly be the best cost-effective way and will ensure the control of the disease. However, today, when there is confusion about vaccines, it is of great importance to use the right information sources in order to successfully combat the epidemic (27). The concerns of both health students and the society about the safety and side effects of COVID-19 vaccines should be taken into account as early as possible and multidisciplinary education and information programs should be developed to address these concerns. Thus, it is thought that the vaccination rates in the society will increase even more.

Conflict of interest

No conflict of interest was declared by the authors

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Ethical Approval

The ethics committee of the research was obtained from the ethics committee of SAU Faculty of Medicine (the number E-71522473-050.01.04-608765).

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The effect of the COVID-19 pandemic on acute appendicitis cases

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Abstract

The COVID-19 outbreak has affected healthcare systems around the world, and has led to changes in the clinical and treatment approaches to all diseases. To reveal the reflection and negative effects of the psychological trauma associated with the COVID-19 pandemic among those with acute appendicitis. A retrospective analysis is made of the data of patients admitted to the emergency departments in our city (Trabzon, Turkey) and taken into operation. Comparative analysis of two patient groups diagnosed with acute appendicitis in our region was included in our study: In the COVID-19 pandemic period (Group 2); and on the same dates a year ago (Group 1). Groups 1 and 2 comprised 231 and 144 patients, respectively ($p<0.001$). There was no statistically significant difference in the type of anesthesia between the groups ($p=0.280$). There was no statistically significant difference between the groups in terms of median duration of surgery ($p=0.239$). There was a statistically significant difference in the pathological diagnoses of Groups 1 and 2 ($p<0.001$). Considering the pathological diagnoses, a significant difference was established in the duration of hospital stay of the cases, which was longer in patients diagnosed with perforated appendicitis ($p<0.001$). It is apparent that during the COVID-19 outbreak, hospitals are associated with increased transmission risk, causing people to delay their referral to the emergency department, and leading to an increase in irreversible complications and mortality rates.

Keywords: COVID-19 pandemic, emergency general surgery, appendicitis, acute appendicitis complications

1. Introduction

In December 2019, cases of pneumonia of unknown origin were identified in the city of Wuhan in the Hubei province of China. Chinese scientists revealed that the agent behind the pneumonia in these patients was “severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, known previously as 2019-nCoV)”. In February 2020, the disease was given the title Coronavirus Disease 2019 (COVID-19) in literature. The disease spread rapidly, and the World Health Organization (WHO) declared a pandemic on March 11, 2020, and COVID-19 spread rapidly, jeopardizing the health of the whole world, and especially healthcare workers (1). The health ministries of many countries decided to halt elective procedures to make room in hospitals and intensive care units for those infected with COVID-19, while delaying emergency procedures and interventions was not possible. It is known that those with somatic symptoms are associated with more frequent hospital admissions. According to literature, hospital admission is a significant safety-seeking behavior among patients with a fear of death, related to anxiety and panic disorders (2, 3). While hospital admissions play an important role in coping with a fear of death in those with Somatic Symptom Disorders, Panic Disorder and Anxiety Disorders, the fear of death from COVID-19 infection has led to hospitals being associated with a significantly increased risk of transmission, and consequently, as a trigger of fear. When it comes to the possibility of Coronavirus transmission, it can be said that symptoms that may indicate a serious health problem are often ignored, and patients with significant medical problems may exhibit avoidant behaviors related to hospital admissions to counter their fear of death. We believe that fears of COVID infection and death are likely to reduce the frequency of hospital admissions. Accordingly, the aim in the present study is to discuss the effect of the COVID-19 pandemic on patients with acute appendicitis (AA), as a cause of acute abdomen requiring general surgery, in the light of data garnered from the hospitals in our city.

2. Material and Methods

The present study included patients who were referred to general surgery consultation by emergency departments and diagnosed with AA during the COVID-19 pandemic in our city, as well as patients who were consulted for general surgery by the emergency department and diagnosed with AA in the same period one year ago.

The patients were divided into two groups. Group 1 included patients who presented from March 15, 2019 to May

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15, 2019; while Group 2 included patients who presented from March 15, 2020 to May 15, 2020, during the COVID-19 pandemic. The patients' age, gender, American Society of Anesthesiologists (ASA) score, type of anesthesia, duration of surgery, pathological diagnosis and duration of hospital stay were accessed retrospectively for Groups 1 and 2, and the differences between groups were investigated.

The data were analyzed using PASW Statistics (Version 18.0. Chicago: SPSS Inc.). The data were analyzed with descriptive statistics, and Chi-square and Mann-Whitney U tests. The statistical significance was set at $p < 0.05$.

3. Results

A retrospective analysis was made of 375 consecutive cases diagnosed with AA, including 231 (62%) female and 144 (38%) male patients with a median age of 26 (min 4–max 90) years. Groups 1 and 2 included 231 and 144 patients, respectively ($p < 0.001$, Table 1). There were 136 (59%) male and 95 (41%) female patients in Group 1, and 95 (66%) male and 49 (34%) female patients in Group 2, with no significant difference between the groups ($p = 0.169$, Table 1). There was no difference in the median age between the groups [26 (4–90) years, and 26.5 (5–82) years, respectively; $p = 0.531$, Table 1].

As can be seen in Table 1, there were 284 (75.5%) cases with an ASA score of 1, 78 (21%) with an ASA score of 2 and 13 (3.5%) cases with an ASA score 3. Table 1 reveals that the ASA scores were similar in Groups 1 and 2, and there was no statistically significant difference in the ASA scores of the two groups ($p = 0.827$). Among the operated patients, 329 (88%) were administered general anesthesia and 46 (12%) were administered spinal anesthesia. The number of patients administered general anesthesia was 206 (89%) in Group 1, compared to 123 (85%) in Group 2. The number of patients administered spinal anesthesia, in turn, was 25 (11%) and 21 (15%) in Groups 1 and 2, respectively. There was no statistically significant difference in the type of anesthesia between the groups ($p = 0.280$, Table 1).

The median duration of surgery was 50 (min 15–max 180) minutes for all cases. The median duration of surgery was 50 (min 15–max 180) minutes in Group 1, and 50 (min 30- max 150) minutes in Group 2, with no statistically significant difference between the groups ($p = 0.239$, Table 1).

Among all cases, the pathological result was reported to be acute appendicitis in 211 (56%), acute phlegmonous appendicitis in 93 (25%), acute perforated appendicitis in 40 (11%) and Non-Appendicitis (NA) in 31 (8%). The number of patients diagnosed with a pathology of acute appendicitis was 146 (63%) in Group 1 and 65 (45%) in Group 2. The number of patients diagnosed with a pathology of acute phlegmonous appendicitis was 51 (22%) and 42 (29%) in Groups 1 and 2, respectively. The number of patients diagnosed with a pathology of acute perforated appendicitis was 12 (5%) in Group 1 and 28 (19%) in Group 2. The number of patients diagnosed with NA was 22 (10%) in Group 1, and nine (7%) in Group 2. There was a statistically significant difference in the pathological diagnoses recorded in Groups 1 and 2 ($p < 0.001$, Table 1).

The median duration of hospital stay was similar in both groups, and no significant difference was established between the groups [2 (min 1–max 9), 2 (min 1–max 17), respectively; $p = 0.550$, Table 1].

Table 1. Demographics and perioperative findings of patients who underwent surgery

	Group 1	Group 2	Total	p value
Total number of patients	231	144	375	**p<0.001**
Gender, n (%)				
Male	136 (59)	95 (66)	231(62)	0.169
Female	95 (41)	49 (34)	144(38)	
Age, median (min-max), years	26 (4–90)	26.5 (5–82)	26 (4-90)	0.531
ASA*, n (%)				
• **A1**	175 (76)	109 (76)	284 (75.5)	
• **A2**	47 (20)	31 (21)	78 (21)	0.827
• **A3**	9 (4)	4 (3)	13 (3.5)	
Type of anesthesia, n (%)				
• **Spinal anesthesia**	25 (11)	21 (15)	46 (12%)	0.280
• **General anesthesia**	206 (89)	123 (85)	329 (88%)	
Duration of surgery (Min)				
• **Minimum**	15	30	15	
• **Maximum**	180	150	180	0.239
• **Median**	50	50	50	
Types of pathology n (%)				
• **Acute appendicitis**	146 (63)	65 (45)	211(56)	
• **Phlegmonous**	51 (22)	42 (29)	93 (25)	**p<0.001**
• **Perforated**	12 (5)	28 (19)	40 (11)	
• **NA****	22 (10)	9(7)	31 (8)	
Duration of hospital stay (days)				
• **Minimum**	1	1	1	
• **Maximum**	9	17	17	0.550
• **Median**	2	2	2	

*American Society of Anesthesiologists (ASA) classification; A1, A normal healthy patient; A2, A patient with mild systemic disease; A3, A patient with severe systemic disease that does not affect daily activities. **NA: Non-Appendicitis.

When the length of hospital stay was compared, the median duration was 2 (min 1–max 6) days for AA, 2 (min 1–max 9) days for phlegmonous appendicitis, 3 (min 1–max 17) days for perforated appendicitis and 2 (min 1–max 5) days for NA. Considering the pathological diagnoses, a significant difference was established in the duration of hospital stay of the cases, being longer in patients diagnosed with perforated appendicitis [3 (min 1–max 17) days; $p < 0.001$, Table 2].

Table 2. Duration of hospital stay according to pathological diagnosis

Duration of hospital stay	Minimum (days)	Maximum (days)	Median	p value
Acute appendicitis	1	6	2	p<0.001
Phlegmonous A	1	9	2	
Perforated A	1	17	3	
NA*	1	5	2	

*NA: Non-Appendicitis.

4. Discussion

The COVID-19 pandemic has come to affect the entire world, and continues to spread day by day. The virus and the pandemic conditions that have come to threaten our lives first emerged in March 2020 in our country, bringing about several changes that have transformed our entire lives. It is inevitable that this situation, in which vital routines are disrupted, people experience intense anxiety and significant restrictions are placed on their social lives, affecting also psychological health.

In these days, as the virus continues its spread in a second wave, the outbreak is seeming to cause great anxiety in those who have quarantined themselves at home, as well as those who have to go to work. New attitudes and behaviors are being observed, with many people tending to go out less or not to go out at all, increased frequencies of hand washing, and washing food when it enters the home.

This period can be perceived as an extraordinary situation in which many people experience intense anxiety, fear and stress, and there is a considerable likelihood that a picture will emerge in which psychological well-being is affected. Increased fears of contracting the virus can generate anxious moods and repetitive behaviors and a sense of inadequacy even in matters of hygiene. Adequate and controlled stress can benefit the person in any event, but too much can turn into a phobia. Obsessive-compulsive disorder can manifest in such symptoms such as excessive anxiety and anxiety disorder, or excessive cleaning in the belief that excessive contamination may occur, especially in those who are more negatively affected by the current situation. Typically, excessive anxiety is accompanied by disaster scenarios that trigger anxiety in the mind, and consequently such physical symptoms as palpitations, hyperventilation and sweating. This period, which it is believed will be better explained in mental health studies in the future, is believed to be characterized by increased anxiety, and obsessive, depressive, and phobic attitudes and behaviors.

Within this period, which has changed our habits at home, at work and on the street, and has led to the emergence of the several psychological attitudes mentioned above, a situation has arisen in which patient anxiety leads them to avoid going to healthcare institutions and getting help. In such situations, people delay accessing needed healthcare, ignore their symptoms, and avoid or fear attending hospitals due to the COVID-19 pandemic, leading to discontinuations of treatment for chronic diseases or hesitancy in going to the hospital and getting help, even in cases of pain.

The present study has sought answers to the following questions: Are patients delaying visits to emergency departments due to the COVID-19 pandemic? Does this cause us to encounter more complicated and difficult cases as surgeons? Have the mortality and morbidity levels associated with emergency surgical operations increased?

The COVID-19 pandemic caught us all off-guard, and has led us to a situation in which people worldwide are being adversely affected. This led to an increase in irreversible complications and mortality rates due people delaying referral to the emergency department. The diagnosis and treatment of conditions that would not be a threat to life and that would affect only quality of life if not treated urgently are postponed to a more appropriate time to reduce the hospital density. There have been several articles published emphasizing the effects of the COVID-19 pandemic on different surgical procedures performed under emergency conditions, and the precautions to be taken (4-6). However, there has yet been no study examining the extent to which delays in surgery affect human life in cases of AA, as the cause of acute abdomen requiring emergency surgery. In the present study, we discuss this issue through the cases of appendicitis, as the most common cause of acute abdomen.

AA is the most common cause of acute abdomen and surgical intervention in the world (7). It is more common in men than in women (8). The lifetime risk of developing AA has been reported to be 8.6% in men and 6.7% in women (9, 10). Although it develops most commonly between the ages of 10 and 19, it can occur in all age groups. In the present study, a retrospective analysis was made of 375 consecutive cases operated with a diagnosis of AA. The patients included 231 (61.6%) female and 144 (38.4%) male patients, with a median age of 26.0 (min 4–max 90) years. The findings of the present study were consistent with those literature in general and in terms of between-group comparisons (Table 1).

The reason for referral to the emergency department was predominantly abdominal pain, starting in the epigastrium or near the navel, following a loss of appetite and nausea, and localized towards the right lower quadrant in the following hours. In approximately 60% of patients, the localization of the pain shifts towards the right lower quadrant eight hours after the onset of symptoms. Vomiting typically occurs after the pain. In acute appendicitis, a physical examination reveals sensitivity, defense and rebound tenderness in the right lower quadrant, depending on the time of admission. Typical presentations of appendicitis may not develop in the elderly and in children. In general, mild leukocytosis of 10,000 to 18,000/mm^3 is identified in non-complicated appendicitis cases, and moderate polymorphonuclear dominance may sometimes be seen. A physical examination is essential in cases

of acute appendicitis. In radiological examinations, the sensitivity of ultrasonography is between 78% and 96%, and the specificity is between 85% and 98% (11). Although computed tomography is just as accurate as ultrasonography, or even more so, in establishing diagnosis, it has a harmful effect on patients and it is expensive in practice, but may be used when it is difficult to establish a diagnosis, and for the exclusion of differential diagnoses.

In cases of delays in referral to hospital, delays in diagnosis, and accordingly, delays in intervention, simple appendicitis may become complicated, resulting in abscesses and perforations. Delays in admission to surgery increases morbidity and mortality, with the mortality rate in particular due to appendicitis being < 0.07–0.7%. There were no mortalities in the present study (12).

The present study revealed a significant decrease in cases who presented to the emergency department and who were diagnosed with AA during the pandemic, as expected (231 vs. 144 patients, $p < 0.001$, Table 1).

There was no difference in the ASA scores of the groups (Table 1). When the type of anesthesia was examined, no significant difference was established between the groups. However, as in all operations performed during the pandemic, there was an increase in preference for spinal anesthesia, as a means of reducing the risk of transmission (Group 1, 11%; Group 2, 15%, Table 1). The absence of any significant difference in the present study resulted from our inexperience in the transmission routes of the virus and our preference for general anesthesia, in the thought that surgery would be challenging due to the potentially complicated patients.

Although the number of complicated patients seems high, there was no difference in the duration of surgery between the groups [50 minutes (min 15–max 180), 50 minutes (min 30–max 150) respectively; $p = 0.239$, Table 1], which we attribute to the experience and harmonized working of the surgical team.

In the present study, the NA rate was 8% (31 patients), compared to 2–40% in literature (13, 14). When the groups were compared, the number of patients diagnosed with NA was 22 (10%) in Group 1 and nine (6%) in Group 2. There was a statistically significant difference in the pathological diagnosis between Groups 1 Group 2 ($p < 0.001$, Table 1), which made it difficult to establish a diagnosis due to delayed admission. This complicated the cases, resulting in a decrease in the number of negative laparotomies. There is a reciprocal relationship between perforation rate and negative appendectomy, the perforation rate being 3.6% in young men, but higher in children and the elderly (15).

When age distribution was examined in the histopathological diagnosis subgroups, no statistically significant difference was noted between the groups ($p = 0.062$). The number of patients diagnosed with a pathology of acute phlegmonous appendicitis was 51 (22%) and 42 (29%) in Groups 1 and 2, respectively. The number of patients diagnosed with a pathology of acute perforated appendicitis was 12 (5%) in Group 1, and 28 (19%) in Group 2 ($p < 0.001$, Table 1). We believe that patients presented to the emergency department late, and so the appendicitis had sufficient time to become complicated. Accordingly, an increase in morbidity rates occurred.

The median duration of hospital stay was longer in complicated patients, being 2 (min 1–max 6) days for acute appendicitis, 2 (min 1–max 9) days for phlegmonous appendicitis, 3 (min 1–max 17) days for perforated appendicitis, and 2 (min 1–max 5) days for lymphoid hyperplasia. There was a significant difference in the median duration of hospital stay ($p < 0.001$, Table 2). Increased durations of hospital stays are detrimental to the national economy, and delay the return of patients to socioeconomic life.

Wound infections are the most common morbidity in complicated appendicitis. Unnecessary surgeries, perforation rates and hospital stay for patients without acute appendicitis can be reduced through the use of auxiliary diagnostic methods (16), including laparoscopy, scoring systems, ultrasonography, computed tomography and magnetic resonance (17). Today, the need for appendectomy in both complicated and uncomplicated appendicitis is a topic of frequent discussion, with medical treatment attracting more attention, with a growing level of support (18, 19). Appendectomy, however, preserves its value for final diagnosis, especially in the middle- and advanced-age groups, since primary and secondary tumors may be detected incidentally in appendectomy specimens (20).

The conservative follow-up of cases with AA during the COVID-19 pandemic may be applied with the surgeon's decision, considering the general condition of the patient. It should be remembered that a laparoscopic appendectomy will probably shorten the duration of hospital stay (21). On the other hand, whether the surgical procedure to be performed during the pandemic should be performed through laparoscopic or conventional methods remains controversial. While the contact of the surgical team with the fluid and tissues of the patient increases with conventional methods, the risk of viral contamination through the aerosol effect of the gas used in laparoscopic surgeries or surgical smoke should be taken into account. Percutaneous drainage should be performed in patients with peri-appendicular abscesses. Patients with evidence of perforation can be managed with percutaneous drainage or operation, depending on the patient's condition. Patients who do not respond to non-surgical treatment should undergo immediate surgery (22).

This period has witnessed an increase in irreversible complications and mortality rates due to people delaying their referral to the emergency department. Until vaccination studies have been completed, we, as healthcare professionals, will continue to make sacrifices for the maintenance of the physical,

psychological and social well-being of society.

Conflict of interest

None to declare.

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None to declare.

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Pediatric intensive care unit tracheostomy experiences in Ondokuz Mayıs University Faculty of Medicine

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Abstract

In this study; patients who underwent conventional tracheostomy while being followed up on a mechanical ventilator with endotracheal intubation in their pediatric intensive care unit were evaluated retrospectively. It was aimed to share the positive changes observed in clinical-mechanical ventilator parameters with the literature. Study data were obtained from the hospital information management system and recorded in the "Child Patient Evaluation Form with Tracheostomy" as follows: Demographic data, diagnosis of admission to pediatric intensive care unit, indications for mechanical ventilation and tracheostomy, changes in post-procedure mechanical ventilation parameters, tracheostomy complications, decannulation, survival and death rates etc. Post-discharge medical records were created by telephone interviews with parents. IBM SPSS 21 (Statistical Package for Social Sciences) program was used for statistical analysis. In our study; the most common indication (67.0%) for tracheostomy was the need for prolonged mechanical ventilation. Peak inspiratory pressure requirement on mechanical ventilator decreased statistically and tidal volume increased significantly in those who underwent tracheostomy due to prolonged mechanical ventilation requirement (both $p<0.001$). On the other hand, the mean length of stay in the pediatric intensive care unit after the procedure was statistically significantly shorter ($p<0.001$). Decannulation success was statistically significantly higher in those who underwent tracheostomy due to upper airway obstruction ($p<0.02$). In our study; only four (6.2%) patients died due to tracheotomy (cannula occlusion, unplanned decannulation, etc.). Clinicians should consider tracheostomy if extubation cannot be achieved in children and adolescents who have been given mechanical ventilation for a long time (>2-4 weeks) due to progressive primary disease. Tracheotomy should definitely be performed within appropriate medical indications in order to shorten the length of stay in the hospital/Pediatric intensive care unit and to provide medical care outside the hospital (e.g.; a suitable home environment) in order to create general psychosocial-physical well-being in the patients.

Keywords: pediatric intensive care unit, prolonged mechanical ventilation, tracheostomy, decannulation

1. Introduction

Tracheostomy is a procedure that creates a surgical airway in the cervical trachea in order to facilitate the passage of air or evacuation of secretions. It is relatively common in the pediatric age group today (1). The most common indications of tracheostomy are life-threatening upper airway obstruction, need for prolonged mechanical ventilation, and provision of an efficient pulmonary toilet (2-4). In the last 40 years, pediatric tracheostomy indications have shown a considerable change from upper airway obstruction to prolonged mechanical ventilation need (1, 5). Today, the need for prolonged mechanical ventilation is the most common indication in the Pediatric Intensive Care Unit (PICU) setting (2, 6, 7). About half of the airway resistance is caused by the upper airway. Tracheostomy has reduced the work of breathing via bypassing the upper airway and facilitating the pulmonary toilet (8). When compared to endotracheal intubation, laryngeal injury risk is lower with a tracheostomy. Other advantages of tracheostomy include decreased need for sedoanalgesia, increase patient mobilization and facilitate care and transport of patients (9-11). Finally, tracheostomy can provide to shortening of mechanical ventilation duration, reducing stay in hospital and intensive care unit (8, 12).

This procedure is technically more difficult and morbidity and mortality are higher in pediatric patients than adults (12). Complication rate after tracheostomy has been reported to be 10-20% with a death rate of 0.5-5% (13). There is no consensus on the timing of decannulation, decannulation procedure, and affecting factors of decannulation success rate in pediatric patients (1).

There are limited studies in the literature investigating the long-term outcome of pediatric tracheostomy and its effects on respiratory dynamics. In this study, the results of tracheostomy including decannulation were mainly investigated in addition to the demographic clinical characteristics of the patients who underwent surgical tracheostomy when they were followed up in PICU. In addition, the early effects of tracheostomy on ventilator parameters were also investigated in patients

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undergoing mechanical ventilation. A true emergency tracheostomy is relatively uncommon and the most likely cause is upper airway obstruction, where the patient cannot be intubated (14).

2. Material and Methods

Patients who underwent tracheostomy with the conventional surgical method in the operating room for 3 (three) main indications while receiving respiratory support on a mechanical ventilator in the PICU between January 2006 and May 2013 were included in this study. The decision for tracheostomy is given by an intensive care specialist and an otolaryngologist in our unit. The procedure is performed by an otolaryngologist who is experienced in pediatric tracheostomy.

The clinical and demographic characteristics of the patients, indication for mechanical ventilation and tracheostomy, early and late complications of tracheostomy, the effect of tracheostomy on mechanical ventilator parameters in ventilated patients, attempts of decannulation, and outcomes were recorded. Medical records; demographic characteristics (age, gender, chronic disease, etc.), indication for PICU admission, indication for mechanical ventilation and surgical tracheostomy, clinical and laboratory data before and after the procedure, and changes in mechanical ventilator follow-up parameters after the procedure [Positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), expiratory tidal volume (TV) and a fraction of inspired oxygen (FiO_2) needs before and 24 hours after tracheostomy], complications of tracheostomy, length of stay in the PICU before and after the procedure, analyzes of discharged patients, how decannulation was performed, duration and results of decannulation, survival and death rates of patients, etc. form were created. Post-discharge medical information was added to the patient evaluation form by making phone calls to the parents.

Prolonged mechanical ventilation (PMV) is defined as greater than 21 consecutive days of mechanical ventilation requirement for at least six hours per day. (15, 16) Pulmonary lung hygiene, formerly known as a pulmonary toilet; refers to exercises (cough or chest physiotherapy) and other procedures that help clear the respiratory tract from mucus and other secretions. PEEP, PIP, (TV), and FiO_2 needs before and 24 hours after tracheostomy were recorded in patients under mechanical ventilation. Complications within the first 7 days of tracheostomy were defined as early complications, complications after 7 days were defined as late complications.

Local ethical committee approval was obtained. Statistical analysis was done with Statistical Package for the Social Sciences software version 21.0 (IBM SPSS Statistics; New York, USA). The normal distribution of values was tested with the Kolmogorov-Smirnov test. Other tests used for statistical analysis were; the Kruskal-Wallis test, Mann-Whitney U test with Bonferroni correction, Chi-Square test, Wilcoxon test, and Two Proportion Z test. Numerical values were calculated as number (%), median (minimum-maximum), mean ± standard deviation. Statistical significance was accepted as $p<0.05$ for all tests.

3. Results

Surgical tracheostomy was performed in 104 (4.3%) of 2406 patients who were hospitalized in the Pediatric Intensive Care Unit (PICU) at the time of this study. At the beginning of the study, the medical data of a total of 104 patients were included in the retrospective evaluation, but four patients were excluded due to incomplete medical records. The most common reason for admission to the PICU was Acute Respiratory Failure. Only 13.0% of the patients had no known chronic disease. The most common accompanying chronic diseases were neurological-neuromuscular diseases. In our study, the average number of patients who underwent surgical tracheostomy per year among the patients followed in the PICU was 14.2 (4.3%) and 62 (62.0%) men. The median tracheostomy age was 13.5 (2-215) months.

Forty-eight (48.0%) patients were younger than one year of age when the surgical procedure was performed; the proportion of male patients was higher in females in both age groups (61.0% and 59.0% respectively). The demographic and clinical characteristics of the patients are shown below in Table 1.

Table 1. Clinical and demographic characteristics of study patients

Age (month) [median (minimum-maximum)]	**13.5 (2-215)**
• <1 years	48 (48.0%)
Male gender [n (%)]	**62 (62.0%)**
Comorbidity [n (%)]	**87 (87.0%)**
• Chronic neurological or neuromuscular disorders	45 (45.0%)
• Inherited metabolic disorders	11 (11.0%)
• Chromosomal abnormalities	8 (8.0%)
• Malignancy	8 (8.0%)
• Others	15 (15.0%)
Cause of PICU admission [n (%)]	
• Respiratory failure	48 (48.0%)
• Systemic infections, sepsis or septic shock	19 (19.0%)
• Neurological or neuromuscular disorders	13 (13.0%)
• Poisoning, trauma, near-drowning	9 (9.0%)
• Heart failure, cardiac arrhythmias	4 (4.0%)
• Metabolic disorders attack	4 (4.0%)
• Others	3 (3.0%)

In our study, surgical tracheostomy was performed in 67.0% of patients due to the need for prolonged mechanical ventilation 21.0% of patients due to upper airway obstruction, and 12.0% of patients due to the need for pulmonary care. In the patient group requiring prolonged mechanical ventilation, those with primary neurological/neuromuscular diseases (cerebral palsy, spinal muscular atrophy type-1, subacute sclerosing panencephalitis, metabolic-infectious encephalopathy, central hypoventilation syndrome, Duchenne muscular dystrophy, etc.) were in the majority 56.0%. Conditions that cause upper airway obstruction; craniofacial dysmorphism (Pierre Robin sequence, hypoplastic mandible-retrognathia, etc.), head and neck tumors (juvenile papilloma,

subglottic hemangioma, etc.), laryngeal web-trauma, subglottic stenosis-vocal cord hypertrophy due to endotracheal intubation, vocal cord hypertrophy (Fabry disease) and laryngomalacia (congenital). Frequent endotracheal aspiration and inadequate airway protective reflexes (e.g.; cough) were the main indications in a small number of patients who underwent tracheostomy due to the need for pulmonary lung hygiene.

The time from the date of hospitalization to the opening of a tracheostomy was longer than two weeks in 80.0% of patients. This period was shorter than 7 days in only 5.0% of patients; tracheostomy indication in these patients was acute upper airway obstruction. Emergency tracheostomy was performed in only five patients due to acute upper airway obstruction within the first 24 hours of admission to the PICU; all other patients were treated in an elective condition. In this study, no patient underwent emergency tracheostomy due to acute upper respiratory tract infection (e.g.; epiglottitis). Except for one patient with an emergency tracheostomy, the other patients received respiratory support with a mechanical ventilator before the tracheostomy was applied during their follow-up in the PICU.

Tracheostomy indications in our study; the need for prolonged mechanical ventilation, upper airway obstruction, and pulmonary lung hygiene. Five patients underwent emergency tracheostomy within their first 24 hours in the PICU, other patients had the procedure done under the elective situation. Barring one, all patients had received mechanical ventilation prior to tracheostomy. None of our patients underwent tracheostomy due to acute airway obstruction resulting from upper airway infection. The elapsed time from admission to tracheostomy was longer than two weeks in 80 patients. This is timeless than 7 days in only five patients. All of these five patients have upper airway obstruction. Length of stay in PICU before tracheostomy was shorter in patients who had upper airway obstruction than other indications. Indications for tracheostomy and elapsed time for tracheostomy are shown in Table 2.

Surgery-related pneumothorax developed in two patients; both cases were successfully treated with tube thoracotomy. One patient experienced accidental decannulation in the first 24 hours after surgery. A total of 12.0% of patients received erythrocyte transfusion in the first 24 hours after the procedure. The early (<7 days) complication rate of tracheostomy in this study was 20.0% and the late period (≥7 days) complication rate was 38.0%. While the most common early complications were minor (leakage) bleeding at the incision site and cannula obstruction, the most common late complication was granulation tissue formation at the wound site. Surgical tracheostomy-related complications are shown in Table 3.

The most interesting feature of this study; positive changes in mechanical ventilator follow-up parameters occurred quickly in the post-tracheostomy period in these patients who underwent conventional mechanical ventilation.

Table 2. Indications and timing of tracheostomy

Tracheostomy indications [n (%)]				
Prolonged mechanical ventilation	67 (67.0%)			
Upper air way obstruction	21 (21.0%)			
Pulmonary toilet	12 (12.0%)			
Time (form) of tracheostomy [n (%)]				
Emergency tracheostomy	5 (5.0%)			
Elective tracheostomy	95 (95.0%)			
Elapsed time from admission to tracheostomy (day) [median (minimum-maximum)]	**27.5 (1-132)**			
Upper airway obstruction	12.0 (1-56)			
Prolonged mechanical ventilation	28.0 (1-132)			
Pulmonary toilet	36 (9-60)			
Timing of tracheostomy	**Prolonged mechanical ventilation (n=67)**	**Upper airway obstruction (n=21)**	**Pulmonary toilet (n=12)**	**N (%)**
First week	0	5	0	5 (5%)
Second week	7	7	1	15 (15%)
Third week	7	4	2	13 (13%)
Fourth week	32	-	1	33 (33%)
>fourth week	21	5	8	34 (34%)

Table 3. Early and late complications associated with tracheostomy

Complication	**Early**	**Late**
Minor bleeding from incision area	12 (12.0%)	1 (1.0%)
Obstruction	5 (5.0%)	4 (4.0%)
Granulation formation	-	14 (14.0%)
Pneumothorax, subcutaneous emphysema	2 (2.0%)	-
Accidental decannulation	1 (1.0%)	9 (9.0%)
Soft tissue infection	-	6 (6.0%)
Total	**20 (20.0%)**	**38 (38.0%)**

Compared to pre-tracheostomy, it was noteworthy that the mean PIP requirement on a mechanical ventilator was statistically significantly decreased and mean TV significantly increased after 24 hours in the procedure (both $p<0.001$). Differences in other conventional mechanical ventilation monitoring parameters were not statistically significant. Changes in mechanical ventilator parameters with tracheostomy are shown in Table 4.

Tracheotomy was performed in 86.0% of patients, excluding 12.0% of patients who died in pre-discharge follow-up after tracheostomy during hospitalization in the PICU and 2.0% of patients transferred to other Healthcare Institutions for the effective treatment of their severe chronic disease. The patient was discharged from our unit. There were 1.2% patients who were discharged with planned decannulation at first discharge 36 (41.8%) patients with tracheostomy discharged

with free-flow oxygen support and 49 (57.0%) patients with tracheostomy discharged with a home mechanical ventilator. In 12.0% of patients who died during pre-discharge follow-up after tracheostomy deaths were due to progressive primary disease and septic shock; none of them were tracheostomy related (e.g.; accidental decannulation, cannula obstruction, pneumothorax hypovolemic shock) deaths.

Table 4. Tracheostomy related changes in mechanical ventilator parameters

Mechanical ventilation parameters		Before tracheostomy	24 hours after the tracheostomy	p
PIP (cmH_2O) (mean ± SD)		18.8 ± 3.5	16.7 ± 3.7	**<0.001**
PEEP (cmH_2O) (mean ± SD)		5.0 ± 0.4	4.9 ± 0.3	>0.05
Respiratory rate (breaths/minute) [median (minimum-maximum)]		22.0 (14-40)	21.0 (13-40)	>0.05
Expiratory TV (ml/kg) (mean ± SD)		77.5 ± 107.6	108.1 ± 109.3	**<0.001**
FiO_2 (%) [median (minimum-maximum)]		50.0 (35-80)	50.0 (30-70)	>0.05
Duration of mechanical ventilation	**Upper air way obstruction**	15.00 (1-66)		**<0.05**
	Prolonged mechanical ventilation	28.00 (7-126)		
	Pulmonary lung hygiene	34.50 (9-59)		

PIP: Peak inspiratory pressure, **PEEP:** Positive end expiratory pressure, **TV:** Tidal volume, **FiO_2:** Fraction of inspired oxygen

In our study; 73 (83.9%) of the patients with tracheostomy (with free-flow oxygen support and home-type mechanical ventilator) at discharge were admitted to the hospital again for various reasons. Airway-related causes were found in 56.6% of repeated hospitalizations (treatment of primary chronic disease, bacteremia-sepsis, etc.), and in 43.4% there were airway-related causes pneumonia 50.8% and elective planned decannulation 27.0% were the most common causes of airway-related hospitalization. In this study; 17.0% of the patients who underwent surgical tracheostomy underwent planned decannulation. The median follow-up period with a tracheostomy was 3.8 (2-9) months in patients who underwent planned decannulation. During follow-up, accidental decannulation was observed in nine patients. In our study, tracheostomy decannulation success was 10/26(38.5%). Decannulation success was undoubtedly higher in those that were planned; this situation was statistically significant ($p<0.05$). Decannulation attempts and success rate according to indications are shown in Table 5.

Decannulation success was also statistically significantly different according to tracheostomy indications ($p<0.02$). The decannulation success rate was 6/8 (75.0%) in patients with tracheostomy due to upper airway obstruction while this rate was 1/2 (50.0%) in patients with tracheostomy due to pulmonary care. The decannulation success rate was at least 2/7 (28.6%) in patients with tracheostomy due to the need for prolonged mechanical ventilation.

Table 5. Results of decannulation attempts

	Follow-up period with tracheostomy (month) [median (minimum-maximum)]	Planned decannulation	Accidental decannulation
		Successful [n (%)]	**Successful [n (%)]**
Upper air way obstruction (n:67)	2.5 (0 - 9)	7/9 (77.8%)	1/2 (50.0%)
Prolonged mechanical ventilation (n:21)	4.0 (2 - 6)	1/2 (50.0%)	0/7 (0.0%)
Pulmonary toilet (n:12)	4.0 (4 - 4)	2/7 (28.6%)	-
Total (n:100)	3.8 (2 - 9)	10/18 (55.6%)	1/9 (11.1%)

In our study, the median follow-up time on a mechanical ventilator during hospitalization in the PICU of the cases with successful decannulation was statistically significantly shorter after tracheostomy when compared to before tracheostomy ($p<0.01$). The overall survival analyses of the patients after the first discharge were evaluated with the "Log-Rank Test". In our study, the median survival time of patients with a tracheostomy was 7 months (according to gender; it was 8 months for boys and 5 months for girls).

4. Discussion

Tracheostomy is a procedure that is being used increasingly in pediatric intensive care units. Patients subject to tracheostomy in various centers are reported to be 0.1-5.7% of total patients (10, 16). In our study this percentage was 4.3%. Indications for pediatric tracheostomy have changed drastically in time (2, 3). Tracheostomy due to upper airway infections such as epiglottitis and diphtheria, which cause airway obstruction, has decreased while tracheostomy due to craniofacial anomalies has increased. Today, the leading reason for tracheostomy is the need for prolonged mechanical ventilation (2, 6, 7, 16). None of the patients in our study underwent tracheostomy due to airway obstruction resulting from acute upper airway infection.

Although different clinical studies provide different reports, the most common indication for tracheostomy in the childhood age group is the need for prolonged mechanical ventilation. If endotracheal extubation cannot be achieved in ≥2 weeks of follow-up in children and adolescents who require respiratory support on mechanical ventilation due to progressive primary disease, the application of tracheostomy

should be evaluated by clinicians. Prolonged endotracheal intubation increases the risk for complication; however, there is a lack of consensus on optimal tracheostomy timing in children (10, 17, 18). When extubation time cannot be immediately foreseen, early tracheostomy (within the first 7-10 days) is preferred for older children and adolescents (17, 19). There are some studies that support early tracheostomy for children in selected indications (17, 20-23). Although many studies have been published in the literature supporting early tracheostomy application in patients with endotracheal intubation and respiratory support in mechanical ventilators in PICU, our recommendation will be for focused (individually) decision making.

Various studies have shown the positive effect tracheostomy has on pulmonary functions (24-26). When compared to endotracheal intubation, tracheostomy has been shown to reduce work of breathing thus easing transition to spontaneous breathing. In turn, this could shorten mechanical ventilation duration and length of stay (LOS) in the Intensive Care Unit. Namdar et al. have reported a significant reduction in 8th hour PIP, PEEP, and FiO2 values post-tracheostomy for adult burn patients. They also report a significant decrease in pulmonary resistance and a significant increase in arterial partial oxygen pressure/FiO2 ratio (25). Sofi et al. report that compared to pre-tracheostomy, 24th hour PIP demand was reduced, dynamic compliance and oxygenation were increased after tracheostomy. However, they did not find a significant change in plateau pressure, static compliance, or PaCO2. One of the important results of this study that will contribute to the literature was the demonstration that tracheostomy in pediatric patients positively changed respiratory parameters in mechanical ventilators (26). In our study; compared with before tracheostomy, we found that the PIP value decreased statistically from the first 24 hours after the procedure and the expiratory TV increased statistically significantly. However, we could not find any statistically significant difference in other mechanical ventilator parameters.

Complication rates related to tracheostomy are reported in a wide range in the literature (3, 4, 7, 10, 13-18). We did not observe death due to tracheostomy in our study. Prolonged tracheostomy may increase the risk of complications, while early or accidental decannulation may increase the potential for unsuccessful decannulation (27). Therefore, the primary goal in patients undergoing tracheostomy due to treatable conditions should be decannulation at the most appropriate time. The literature on pediatric tracheotomy currently contains limited objective data on decannulation outcomes. Various studies report successful decannulation rates between 14.8% and 85.0% (21, 28-30). In our study, the planned decannulation success rate was found to be 55.6%, but the random decannulation success rate was found to be very low. We could not find any study in the literature comparing the success rates of planned decannulation and accidental decannulation in our study. Previous studies show that decannulation time is shorter and decannulation success is higher in upper airway obstructions compared to other indications (10, 29, 30). Our findings were consistent with the literature. In our study; the success rate was found to be higher in tracheostomies and planned decannulations performed due to upper airway obstruction.

The results of this study show tracheostomy can improve pulmonary mechanics in ventilated pediatric patients. Accidental decannulation should be avoided because of life-threatening complications and high failure rates. Further prospective studies are needed to evaluate the early and late effects of tracheostomy on pulmonary mechanics. This study is one of the few studies evaluating the effect of tracheostomy on pulmonary mechanics in pediatric patients. Limitations of the study include the retrospective nature of the study and the lack of evaluation for the late-stage effects tracheostomy has on pulmonary dynamics.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Effect of complete blood count parameters on the clinical course of COVID-19 in pregnant women

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Abstract

Coronavirus Disease-19 (COVID-19) pandemic, affected pregnant women as well as many people. Aim of this study is to compare complete blood count (CBC) parameters of pregnant women infected with COVID-19 to that of healthy pregnant women and determine their prognostic features. 142 pregnant women infected with COVID-19 and 46 healthy pregnant women, included in this retrospective case-control study. Patients infected with COVID-19 were grouped as mild, moderate and severe, according to the findings of oxygen saturation and lung involvement. Age, gestational age, gravida, hospitalization length and CBC parameters of the participants were compared, according to the groups. CBC test revealed that uninfected pregnant women had statistically lower level of white blood cell count (WBC, p=0.001), platelet count (p=0,024), neutrophil count (p=0,001), lymphocytes (p=0,005), monocytes (p=0,001) and platelecrit (p=0.007) than from infected pregnant women. Evaluation of pregnant women with COVID-19 grouped into 3 categories as mild, moderate and severe showed that age, gravida and hospitalization length were comparable between groups, WBC (p=0.012) and neutrophile (p=0.001) counts of mild group were significantly lower than moderate group and there was no significant difference between moderate and severe groups regarding WBC and neutrophile counts (respectively p=0,281, p=0.542). CBC analysis is simple, applicable, widely used and cheap laboratory method. CBC parameters seem as a candidate for predicting COVID-19 clinical course. However, larger sample sized prospective studies supporting this idea are required.

Keywords: COVID-19, pregnancy, complete blood count, disease severity

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes acute respiratory distress syndrome, defined in December 2019 in Wuhan city of China and caused a rapidly emerging endemic disease. Disease caused by this newly emerged virus is named coronavirus disease by World Health Organization at 11.02.2020 and announced as pandemic one month later (1). Diagnosis is usually based on identifying SARS-CoV-2 from respiratory tract secretions with real time polymerase chain reaction (rt-PCR) (2).

Physiological and anatomical changes, including suppression of cellular immunity which occurs to prevent fetal rejection during pregnancy, increased oxygen consumption, heart rate, stroke volume, and decreased lung capacity, may increase the likelihood for severe maternal disease (3). It has been suggested that the course and symptoms of COVID-19 in pregnancy do not differ from the normal population, in some studies (4, 5). In a systematic review performed by Zaigham (6), it is noted that most of the pregnant women with Covid-19 discharged without any major complication, but there are serious maternal morbidity and perinatal mortality in some cases.

Inflammation develops due to infectious diseases, and there are evidences suggests that it has an important role in the development of viral pneumonias, like COVID-19 (7). Heavy inflammation suppresses adoptive immunity, whereas causes imbalance on immune response (8). In these circumstances, circulating biological markers reflecting inflammation and immune system may also be candidates to be indicators for COVID-19 prognosis. Lymphopenia and neutrophilia have been identified as prognostic factors for severe cases of COVID-19, according to Australian and New Zealand guidelines (9). According to the study of Huang et al. (10), white blood cell count (WBC), neutrophil and lymphocyte count were determined as risk factors for intensive care needs of COVID-19 patients. Neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR) are also useful indicators in the prognosis of patients with viral pneumonia and an indicator of the systemic inflammatory response (11).

Complete blood count (CBC) examination is an inexpensive method that is widely available in many countries of the world. The aim of this study is to determine how CBC

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parameters change in pregnant women with covid 19 and their prognostic features.

2. Materials and Methods

This study designed in retrospective case control settings. 200 consecutive pregnant women admitted to Samsun Education and Research hospital with headache, cough, dyspnea diarrhea, diminished taste and smell perception, fever, myalgia included to the study. Presence of SARS-CoV-2 was investigated with rt-PCR method from nasopharyngeal and oropharyngeal swab samples and pregnant patients were hospitalized. All patients who had positive rt-PCR result included study group otherwise who had negative rt-PCR results included control group. Patient who had any known hematological disorders (n=5) or infected with other pathogens (n=7) were excluded from study. The patient who had negative test results discharged if their complaints did not worsen follow up continued in outpatient settings. SARS-CoV-2 patient classified with pulse oximetry and chest X-Ray findings as follow; oxygen saturation 94% and above without lung involvement cases were mild, oxygen saturation below 94% and involved lung areas lower than 50% were moderate, oxygen saturation lower than 94% and involved lung areas bigger than 50% were severe.

Gestational age was determined based on first day of last menstrual period or ultrasonographic findings at the first trimester. Venous blood samples analyzed with Coulter 180 hematology analyzer (Beckman Coulter Ireland Inc, Galway, Ireland). Following parameters were calculated, NLR, PLR and platelet to neutrophil ratio (platelet/neutrophil, PNR). Gestational age, gravida, length of hospital stays, oxygen saturation, chest X-ray and CBC parameters data of participants was obtained from hospital records.

Study performed with approval of Samsun training and research hospital noninvasive clinical research ethic committee (27.01.2021, 2021/2/2) and guidance of Helsinky declaration criteria.

2.1. Statistics

SPSS 25 (Statistical Package for Social Sciences) package program is used to analyze data. Descriptive statistics were presented as mean ± standard deviation and median (minimum-maximum) for continuous-measure variables, and number of observations and (%) for nominal variables. Whether the distribution of continuous-measure variables was normal or not was investigated by Kolmogorov Smirnov test and Shapiro-Wilks test. Mann-Whitney U test and Kruskal-Wallis test were used to determine whether there was a statistically significant difference between the groups in terms of continuous measurement variables that were not normally distributed; Whether there was a statistically significant difference in terms of normally distributed continuous measurement variables was evaluated with the independent samples T test and One-Way ANOVA. Nominal variables were evaluated with Chi-Square test, Fisher's Exact test and Fisher-Freeman Halton Exact test. In order for the differences to be considered statistically significant, the p value set to be less than 0.05. Bonferroni correction was performed to find out the source of significance for nominal variables found to be significant and for variables found to be significant by Kruskal-Wallis test, and those with p <0.017 were considered significant.

3. Results

Totally 188 pregnant women included to the study. The ages of 46 pregnant women with negative rt-PCR test were between 19 and 40, and the ages of 142 pregnant women with positive rt-PCR test were between 18 and 44 (p=0.002) (Table 1). While there was no difference between the groups in terms of gestational age (p=0.618) and gravida (p=0.552), hospitalization lengths of pregnant women with positive rt-PCR test were significantly longer (p<0.001). WBC (p<0.001), platelet count (p=0.024), neutrophil count (p<0.001), lymphocyte count (p=0.005), monocyte count (p=0.001), eosinophil count (p<0.001) and platelecrit (PCT) (p=0.007) levels of rt-PCR negative pregnant women were significantly higher than from rt-PCR positive group (Table 2).

Table 1. Comparison of variables according to rt-PCR results

Variables	rt-PCR (-) (n=46)	rt-PCR (+) (n=142)	p
Age (years)	26 (19-40)	30.50 (18-44)	**0.002**
Gestational age (weeks)	30.5 (5-41)	32 (5-41)	0.618
Gravida	2 (1-5)	2 (1-5)	0.552
Hospitalization length (days)	2 (1-9)	6 (1-16)	**<0.001**

Values are given as minimum-maximum median. Kruskal-Wallis test was applied.

Table 2. Comparison of complete blood count parameters of groups according to rt-PCR results

Variables	rt-PCR (-) (n=46)	rt-PCR (+) (n=142)	p
NLR	5.1 (0.53-17.80)	4.59 (0.82-25.33)	0.516*
PLR	163.22 (25.54-378.89)	176.08 (52.81-846.67)	0.201*
PNR	30.83 (9.86-76.67)	34.55 (9.19-209.52)	0.100*
WBC ($x10^3/\mu L$)	10.19 (6.70-17.80)	8.35 (2.66-22.30)	**<0.001$^{\delta}$**
RBC ($x10^6/\mu L$)	3.95 (2.92-5.66)	3.97 (2.22-5.24)	0.718*
Hemoglobin (g/dL)	11.7 (6.90-16.70)	11.55 (6.60-15)	0.382*
Platelet count ($x10^3/\mu L$)	257 (125-477)	215.50 (109-880)	**0.024***
Neutrophil count ($x10^3/\mu L$)	7.95 (4-15.40)	6.23 (1.80-17.50)	**<0.001***
Lymphocyte count ($x10^3/\mu L$)	1.60 (0.50-13.90)	1.20 (0.20-3.60)	**0.005***
Monocyte count ($x10^3/\mu L$)	0.60 (0.20-7.30)	0.40 (0.10-4)	**0.001***
Eosinophil count ($x10^3/\mu L$)	0.10 (0-1.10)	0 (0-0.30)	**<0.001***

Basophil count (x10^3/µL)	0 (0-0.70)	0 (0-0.60)	0.117*
MCV (fL)	85.20 (65-94.50)	85.05 (57.80-109)	0.508*
MCH (pg)	29.60 (21.20-33.70)	29.80 (6.70-38)	0.953*
MCHC (g/dL)	34.79 (5.29-35.90)	34.90 (28.40-38)	0.212*
RDW (%)	13,95 (12-33,2)	14.30 (11.80-22.30)	0.410*
MPV (fL)	8,90 (7-15)	8.80 (7-13.80)	0.421*
PCT (%)	0.21 (0.11-0.39)	0.19 (0.06-0.50)	**0.007***
PDW (%)	17.10 (15.50-19.50)	17.05 (15.60-19.99)	0.706*

($^\delta$ One-Way ANOVA test was applied) (* Kruskal-Wallis test was applied) Values are given as minimum-maximum median. Abbreviations: NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, PNR: platelet to neutrophil ratio, WBC: White blood cell count, RBC: Red blood cell count, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red cell distribution width, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width

When the group of rt-PCR positive pregnant women classified in their clinical status as mild, moderate and severe; age, gravida and length of hospital stay did not differ significantly between the groups, although the length of hospital stays, was significantly shorter in the mild group compared to the moderate group, there was no significant difference between the moderate and severe groups (p=0.099) (Table 3). Considering the hematological parameters; although the WBC (p=0.012) and neutrophil (p=0.001) values of mild clinical course group were significantly lower than from the moderate group, there was no significant difference between moderate and severe groups (p=0.281, p=0.542) (Table 4).

Table 3. Comparison of variables according to severity of the disease

Variables	Mild (n=82)	Moderate (n=44)	Severe (n=16)	p
Age (years)	31 (18-44)	28 (18-40)	31.50 (26-40)	0.061
Gestational age (weeks)	26 (5-40)	37 (11-40)	32.50 (8-41)	**0.001**
Gravida	2 (1-4)	2 (1-5)	2 (1-3)	0.464
Hospitalization length (days)	6 (1-13)	7 (1-16)	5 (1-13)	0.271

Values are given as minimum-maximum median. Kruskal-Wallis test was applied.

Table 4. Comparison of complete blood count parameters according to severity of the disease

Variables	Mild (n=82)	Moderate (n=44)	Severe (n=16)	p
NLR	4.26 (0.82-25.33)	5.45 (1.74-18.6)	5 (2.34-13.87)	0.054*
PLR	157.25 (52.81-846.67)	180.71 (60.95-397.50)	186.97 (69.40-744.4)	0.554*
PNR	37.99 (9.19-159.44)	33.25 (14.38-113.19)	32.01 (15.06-209.52)	0.205*
WBC (x10^3/µL)	7.15 (2.66-2.90)	9.30 (3.40-22.30)	8.59 (3.90-12.10)	**0.011**$^\delta$
RBC (x10^6/µL)	3.89 (2.22-5.01)	4.02 (3.20-5.24)	3.78 (2.42-4.55)	0.150$^\delta$
Hemoglobin (g/dL)	11.70 (7.70-14.10)	11.50 (9.30-14)	11.25 (6.60-15)	0.187$^\delta$
Platelet count (x10^3/µL)	211 (111-421)	222.50 (124-532)	217.50 (109-880)	0.484*
Neutrophil count (x10^3/µL)	5 (1.80-16.10)	7 (2.60-17.50)	6.28 (3.40-11.10)	**0.003***
Lymphocyte count (x10^3/µL)	1.20 (0.20-3.40)	1.25 (0.40-3.60)	1.20 (0.40-2.68)	0.494*
Monocyte count (x10^3/µL)	0.40 (0.10-4)	0.50 (0.10-1.30)	0.40 (0.10-0.70)	0.078*
Eosinophil count (x10^3/µL)	0 (0-0.30)	0 (0-0.30)	0 (0-0.20)	0.762*
Basophil count (x10^3/µL)	0 (0-0.20)	0 (0-0.60)	0 (0-0.50)	0.077*
MCV (fL)	85.10 (60.80-101)	84.40 (64.40-92.20)	87.90 (57.80-109)	0.339*
MCH (pg)	29.90 (6.70-36.50)	29.50 (21.40-33)	30 (17.70-38)	0.196*
MCHC (g/dL)	35.05 (28.40-36.29)	34.74 (31.80-37)	34.55 (30.70-38)	0.295*
RDW (%)	14.05 (11.80-22.30)	14.45 (12.40-21.90)	14.33 (12-20.70)	0.412*
MPV (fL)	8.80 (7-13.80)	8.80 (7.10-11)	8.64 (7-11.50)	0.616*
PCT (%)	0.18 (0.09-0.44)	0.20 (0.11-0.50)	0.19 (0.06-0.42)	0.465*
PDW (%)	17.10 (15.60-19.20)	17 (15.90-19)	16.89 (16-19.99)	0.777*

4. Discussion

Pregnant women who admitted Covid-19 related symptoms and underwent rt-PCR test, studied in this paper. WBC, platelet, neutrophil, lymphocyte, monocyte, eosinophil count results was significantly higher in rt-PCR negative patients than from positives. Another finding in this study is that WBC and neutrophil counts were higher in moderate cases than from mild cases.

Seyit et al. (12) evaluated 233 patients who admitted to the emergency department with COVID-19 related symptoms in a retrospective study. While PLR and NLR values were found significantly higher in SARS-CoV-2 positive patients, eosinophil, lymphocyte and platelet counts were found higher in SARS-CoV-2 negative patients, as in our study.

In a retrospective study which 443 patients diagnosed with COVID-19 were evaluated, it was found that NLR was significantly higher and platelet level lower in patients with severe clinical course than in non-severe patients. It has been

suggested that NLR is the most important factor determining the severity of COVID-19 and platelets are protective from severe course, with these findings (13). Presented study could not demonstrate any relation between severity of Covid-19 and NLR or platelet level, but platelet counts of SARS-CoV2 positive pregnant women found significantly lower than negatives. Although it is claimed that pregnancy has no effect on the course of COVID-19 (5), this difference may be due to the differences in the clinical classification of the severity criteria and the characteristics of the population included to the study. A retrospective study published by Yang et al. (14) which 93 patients diagnosed with COVID-19 were evaluated, has similar to our results. WBC and neutrophil counts were significantly higher in the group with severe clinical condition compared to those with non-severe, while NLR and PLR values were higher in severe COVID-19 patients' group, which differs from our results.

In the review of 18 studies conducted by Zaigham et al. (6), it was revealed that 59% of pregnant women with COVID-19 presented with lymphocytopenia. This finding supports the significantly low lymphocyte value of SARS-CoV-2 positive pregnant women in presented study. In a study conducted by Koç et al. (15) on 108 pregnant women, 39 of whom had COVID-19 and 69 of whom were healthy, and compared the hematological parameters. Unlike our results, RDW and NLO values were higher in pregnant women with COVID-19, while PCT levels were low. However, patients did not classified according disease severity in this study.

In a systematic review by Khartabil et al. (16), it was reported that while the WBC count was within normal limits or low in COVID-19 patients, it is increased in cases with a severe clinical course.

Hemogram parameters in pregnancy vary according to trimester (17). Because of this, hematological parameters of pregnant women in different trimesters and non-pregnant women with COVID-19 might have differences. For this reason, different results may have been obtained in different studies in the literature. Another issue is that although the rt-PCR test is the gold standard in the diagnosis of COVID-19, it cannot detect all cases (18). This mean that there are some COVID-19 patients who have negative rt-PCR tests.

The limitation of this paper is that it is not studied in a sufficiently large sample group because it was retrospective and single-centered. These must be considered when interpreting results and generalizing to the population. In addition, because of pregnant women in different trimesters were included to the study, our results were different from the literature.

However, as we know, there is no similar study in the literature that clinically classifies pregnant women with COVID-19 and compares hematological parameters. We think that we will first contribute to the literature on this subject.

As a result, although almost 2 years passed since the onset of the COVID-19 pandemic, there are still inadequate studies on the course of COVID-19, prognostic and diagnostic parameters in pregnant women. According to our results, WBC, platelet, neutrophil, lymphocyte, monocyte, eosinophil counts and PCT values were higher in SARS-CoV-2 negative patients, while WBC and neutrophil values were higher in moderately severe COVID-19 cases than in mild ones. CBC is an easily applicable, widely used and inexpensive laboratory method. CBC parameters appear to be candidates for predicting the course of COVID-19. However, prospective studies with larger samples are needed to support this idea.

Conflict of interest

None to declare.

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None to declare.

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Modified use of team-based learning in a general surgery course for fourth-year medical students

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Abstract

Team Based Learning (TBL) is a form of education based on student-centered learning in a crowded community consisting of small groups under the guidance of an expert trainer. Acute pancreatitis and fluid electrolyte disorders are important and difficult subjects of general surgery. This study was conducted in order to evaluate the success rates of team-based learning in undergraduate general surgery education. This prospective study study was performed in Kocaeli University School of Medicine, General Surgery courses. TBL study was applied for acute pancreatitis and fluid&electrolyte balance lessons. Readiness assurance and application oriented activities were done in each lesson. Readiness assurance quesitons were prepared for discussing and understanding the pathophysiology. After discussing tthe questions, each group tried to solve a patient oriented case. At the end of the course, a two-part questionnaire were applied to all students in order to take the feedbacksTotal 150 students from three courses included to the study. The vast majority of the students (130 people 86.6%) thought that the TBL study was better than the didactic lecture. And student wanted to Average score in all groups in TBL exam was 84.8. TBL study achieved high acceptance by the students. Although a new method, they adopted easily. General surgery subjects are suitable for this type of education model.

Keywords: general surgery, medical education, student-centered, team-based learning

1. Introduction

Medical education whose main purpose is to train "good physicians", is a lifelong education. Following classical lecture-based education, new education models have come to the fore in the 21st century. The tools that are used in new educational models are community-based practices, teamwork, and communication skills. Medicine is not only the knowledge but also, decision, evaluation, communication, discussion and collaboration. The strategies of the new programs are student-centered, problem-based, integrated, and systematic. The need for new learning methods has emerged because of the increasing number of students every year, the increase in the channels of access to information, technological developments, the need to analyze the lessons in which how much information should be given, the need for discussion opportunities to support communication skills among students

Team Based Learning (TBL) is a form of education based on student-centered learning in a crowded community consisting of small groups under the guidance of an expert trainer (1). In this method, in order to realize individual and team level learning, in-class and out-of-class activities and special tasks must be fulfilled by students (1,2). TBL provided the opportunity to continue teaching in a manner that was engaging, catered for larger number of students in decision making, and promoted active small group and class discussions (1). This method envisions a medical education where students had prepared for the lesson, actively participated in the exercises, defend their decisions passionately and frankly, and leave the session with information they can use in their professional life (3).

This study was conducted in order to evaluate the applicability of teamwork-based learning in undergraduate general surgery education in reaching the learning objectives and search the the students' perception of the model.

2. Materials and Methods

In our study, the Team-Based Learning (TBL) method was applied in the fluid& electrolyte balance and acute pancreatitis lessons during the theoretical practices of the Kocaeli University Faculty of Medicine Grade 4 General Surgery practice. The contribution of these two courses to the general surgery examination passing grade was 2%. Total 150 fourth-year medical students from three practice groups in acute pancreatitis and fluid&electrolyte balance modules were included in the study.

The stages of classical team-based learning are selfstudy reading, individual readiness assurance test (IRAT), team

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readiness assurance test (TRAT), immediate feedback, and clinical problem-solving activities respectively. Self-reading is study period out of school for IRAT and TRAT. In our study, pre-TBL learning goals were determined in the preparation phase. Teams were grouped by the trainer according to modular arithmetic Mode 7 within the order in the student's name list. Students in each group were about 6 or 7.

Table 1. Individual Readiness Assurance Test (IRAT) for Fluid&Electrolyte balance

1.Which of the followings are mostly found intracellular electrolyte ?
a. Cation: potassium, calcium, sodium Anion: Chlorine, Protien, Bicarbonate b. Cation: Sodium, manganese, protein Anion: Phosphate, Organic acid, Chlorine c. Cation: Potassium, Magnesium, Sodium Anion: Phosphate, Bicarbonate, Protein d. Cation: Sodium, Calcium, UreaAnion: Chlorine, Phosphorus, Sulphate e. Cation: Potassium, Protein, Calcium Anion: Protien, Glucose, Phosphorus
2. Which of the following is wrong about the changes that can be seen in the body as a result of excessive sweating in summer?
a. ADH is secreted from the posterior pituitary when plasma osmolarity rises above 295 mOsm / kg with dehydration. b. With dehydration, there is a drop in blood pressure. ANP release decreases due to the decrease in pressure in the atrium. Low ANP activates the sympathetic system and increases Renin release. Increased Renin release stimulates aldosterone. c. The electrolyte responsible for plasma osmolarity is sodium. We do not expect a decrease in osmolarity due to sodium loss with sweating. d. Tachycardia, tachypnea, muscle cramps and nausea are observed in the patient's clinic. Central nervous system findings occur due to sodium loss. e. Aldosterone stimulation due to dehydration occurs with the renin angiotensin system.
3.Which of the following is wrong about the causes of hypokalemia?
a. It is seen in patients with prolonged nasogastric tube drainage because of greater potassium loss from the stomach b. Since there is no sodium reabsorption in patients with ileocutaneous fistula, potassium loss is also accompanied. c. In the presence of giant villous adenoma in the colon, excessive potassium loss is observed due to diarrhea. d. Potassium reabsorption from the kidneys does not occur in renal failure. e. In high-dose insulin therapy, hypocalcemia is seen as potassium enters the cell.
4.Which of the following is true about the calcium mechanism?
a. Hypocalcemia is seen in patients with pancreatitis due to the precipitation of calcium in the pancreas. b. In hypocalcemia, twitching around the mouth and spasms in the fingertips are seen. c. We expect hypocalcemia due to hungry bone syndrome in patients with parathyroid hormone over 300pg/mL. d. Peptic ulcer, lethargy, weakness, constipation are the signs of hypocalcemia. e. In the presence of hypercalcemia, if there are ECG findings, the primary treatment is to protect the heart with calcium gluconate.
5.Which of the following metabolic conditions is not seen in hypokalemia?
a. Increase in plasma bicarbonate level b. Variable urinary potassium excretion c. Urine pH below 7.35 d. Increased urinary acid excretion e. Increase in pCO2 level in the compensated period
6.Which is the most reliable way to follow intravenous fluid therapy?
a. Blood pressure b. Respiratory rate c. Skin turgor-tonus d. Pulse e. Urine output
7.Which of the following is not one of the factors leading to Magnesium deficiency?
a. Starving b. Furosemide use c. Acute pancreatitis d. Hyperladosteronism e. Chronic alcoholis

As a result, students were prevented from forming groups with people whom they feel close to. Students were asked to prepare for fluid& electrolyte balance and acute pancreatitis courses. Resources to be used for course topics were presented to students. These were textbooks and lecture notes prepared in our department (Temel cerrahi Ed. İskender Sayek, Gunes Kitabevi, 2009; Schwartz's Principles of Surgery, Ed. F. Charles Brunicardi 10th edition, McGraw-Hill Education).

At the stage of Readiness Assurance, students were first given IRAT, which consists of multiple-choice questions (Table 1, Table 2). Total duration of IRAT was 7 minutes. The effect of this exam on the TBL score was 25%.

Afterwards, the predetermined teams came together. Team representatives were selected by the trainer from among the students with the least participation in the classes. Thus, these students was also provided to contribute at the highest level. Team Readiness Assurance Test was given to the teams, consisting of the same questions. Meanwhile, the instructor walked around with the students during the team discussions. He encouraged them to research and discuss. Total duration of

TRAT was 15 minutes. Questions were answered at the end of the exam. But answers of some questions were deliberately given wrong.

After the exam, the teams objected to the answers in writing and verbally with the help of the training materials. The teams whose objection was justified got points for that question. Those who did not object could not get any points for that question, even if their answers were correct. Scores were given the each member of the teams. The effect of this exam on the TBL score was 50%. The aim was to encourage students to object to what they thought was correct and to encourage them to make adequate preparation before coming to class.

Afterwards, the instructor gave lesson about the missing part of that subject. During the application phase, the same teams were asked open-ended questions to solve problems over case reports or lecture topics. These questions were answered by the team representative. Case questions were:

1. The patient with gastric outlet obstruction due to gastric ulcer has a nasogastric tube. Daily output from this nasogastric tube is 1000cc. He has no additional chronic diseases. Plan the fluid treatment of this patient.

2. How do you examine the patient who comes to the emergency room with signs of acute pancreatitis for local and systemic complications?

Diagnosis and treatment steps were discussed. Students in each group gave a score between 1 and 10 to the students in their group. Thus, giving feedback to students with inadequate participation by their peers was more effective for these students to question this situation and criticize themselves. Peer assessment also had a 25% effect on the TBL score. In this course, students were informed about scoring at the beginning of the TBL exercise.

At the end of the course, a questionnaire consisting of five-point Likert-scale (scored from 1 to 5) questions were applied to the students about the TBL session (Table 3). And also another quesitonnaire about TBL and traditional lectures were applied. The answers were strongly agree, agree, neutral, disagree and strongly disagree.

2.1. Statistical Analysis

At the end of the General Surgery Practice, the students were applied final general surgery examination in which 2 multi-choice questions about fluid&electrolyte balance and acute pancreatitis were exist.

The correct answer rate of students who entered TBL education were compared with the correct answer rates of previous year when traditional methods had been performed. The mean IRAT and TRAT scores were given as mean ± SEM. Data were analyzed by SPSS 20.0 (Chicago, IL, USA). Student t-test was used for comparision. A p-value less than 0.05 was considered statistically significant.

3. Results

The mean IRAT scores of the students in fluid&electrolyte and acute pancreatitis lessons were 3.1±0.8 and 4.2±1.2 respectively. The mean TRAT scores of the students in fluid&electrolyte and acute pancreatitis lessons were 5.6±1.8 and 6.1±0.8 respectively. The difference between IRAT and TRAT scores in fluid&electrolyte and acute pancreatitis lessons were significant (p=0.001 and p=0.01 respectively).

In the questionnaire questions, which are scored according to the Likert scale and the average of the results are taken, most of the students agreed that the TBL approach was very successful in terms of achieving the learning objectives and student participation. Again, the students thought that the course content of this study was well understood (Table 3).

Fig. 1. Students discussing during Team Readiness Assurance Test

The vast majority of the students (130 people 86.6% and 122 people 81.3%) thought that the student effort in the TBL study was higher than the traditional lecture method and the TBL study was better than the didactic lecture (Fig. 1).

While 132 (88%) of the students were willing to increase studies, 18 students (12%) did not want to increase it (Figure 2). Average score in all groups in TBL exam was 84.8. As a result of the peer assessment within the group, everyone in the group gave full points to each other. Although TBL was applied to the students in our study for the first time, it was observed that the students quickly adapted to this method.

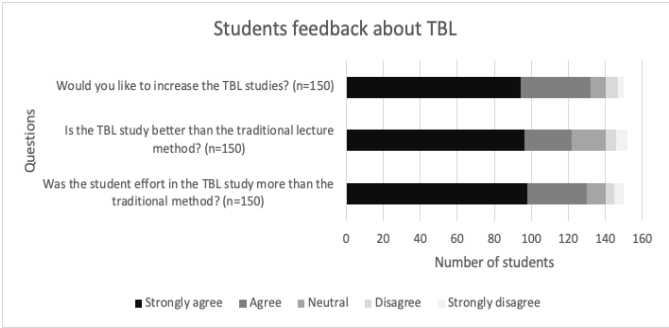

Fig. 2. Feedback evaluation of TBL among students

The succes of students after TBL method in fluid&electrolyte balance questions in final general surgery examination was higher than the students after lecture based method (Table 4). This difference was not significant in acute pancreatitis answers.

Table 2. Individual Readiness Assurance Test (IRAT) for acute pancreatitis

1.Which of the following is wrong about the mechanism of acute pancreatitis?

a. Inflammation due to oxidation of increased fatty acids is seen in acute pancreatitis caused by hyperlipidemia. Amylase may not increase in these cases.
b. Trypsin activation is seen due to increased trypsinogen production in hypercalcemia.
c. SPINK gene mutation is seen in idiopathic pancreatitis
d. Alcohol consumption acts by increasing the sensitivity of cholecystokinin in pancreatic cells.
e. Carsinoma of the head of the pancreas, Stones in ampulla vater, sphinchter of Oddi dysfunction act by increasing pancreatic duct pressure.

2.Which of the following clinical signs is not one of the local complications of acute pancreatitis?

a. Peptic ulcer
b. Pancreatic abscess
c. Pancreatic pseudocyst
d. Portal vein thrombosis
e. Obstructive jaundice

3.Abdominal pain like a belt around the trunk, nausea and vomiting begin in the patient after ERCP. The patient has obvious tenderness and defense in the epigastric region. Acute pancreatitis is considered in the patient. Which of the following tests is not needed in regarding the diagnosis and treatment of the patient?

f. Abdominal computed tomography
g. WBC
h. Glucose
i. LDH
j. Amylase

4.In the treatment of acute pancreatitis, make the treatment matching according to the following purposes. Multiple matches can be made.

Suppression of pancreatic exocrine function ...
Supporting lung functions ..
Supporting kidney functions ...
Suppression of cholinergic response ...
Elimination of etiology in biliary pancreatitis ...
Suppression of inflammation ...
* NG insertion
* Somatostatin administration
* Application of analgesia
* Discontinuation of oral intake
* Plasma transfusion
* Antibiotic treatment
* Hydration according to urine output
* Providing fluid balance from 40cc / kg
* ERCP
* Cholecystectomy
* N-acetylcysteine
* Calcium treatment
* Insulin therapy
* Pulmonary respiratory physiotherapy
* Dialysis
* Red blood cell transfusion
* TPN

5.Which of the systemic complications of acute pancreatitis is wrong?

a. Sudden blindness
b. Hypoglycemia
c. Hypocalcemia
d. Shock
e. Myocardial infarction

6.Which of the following is not one of the causes of acute pancreatitis?

a. Alcohol
b. Hydatid cyst
c. Gallstone
d. Exogenous estrogen
e. Mumps

7.What is the most common type of shock due to acute pancreatitis?

f. Hypovolemic shock
g. Septic shock
h. Obstructive shock
i. Cardiogenic shock
j. Neurological shock

Table 3. Evaluation of the success of TBL study among student

Questions	Mean±SD
How successful is the TBL study in achieving the learning objectives?	4.24±0.3
How well understood the content of the TBL study?	4.10±0.2
How successful is the TBL study in terms of student participation?	4.20±0.3

Likert-scale (scored from 1 to 5) was used

Table 4. Comparison of rate of the correct answers of the student in TBL and previous lecture based method

	TBL	Lecture	p
Fluid&Electrolyte Balance	80%	50%	P=0.02
Acute Pancreatitis	70%	60%	P=0.1

Student T test used

4. Discussion

In this study, we presented the application of the team-based learning method in the acute pancreatitis and fluid&electrolyte balance modules in the period 4 general surgery practice. The results of the feedback received from the students. TBL has been a good method that have been successfully applied in preclinical courses such as anatomy, pharmacology, pathology, physiology as well as clinical courses such as ophthalmology and endocrinology (4-7). Studies have shown that the short and long term learning goals are achieved at a high rate with TBL (4-7). In the TBL method, it was observed that the active participation and continuity of the students was higher (2,4). In our study, the learning objectives were achieved at a high rate.

In TBL study desing, the students who came without preparing for the TBL study are noticed in the İndividual Readiness Assurance Test (IRAT) and these students are not attended to the lesson (8). There was no such thing in our study. It is observed that students who come prepared to the lessons (high IRAT scores) are more involved in the TBL process. In our study the mean TRAT scores were significantly higher than IRAT. This shows us that team work, colaboration is very important for learning. A clear strength of TBL is having multiple, small groups of students in each teams, promoting inter and intra team discussion and peer learning (9,10). It was determined that students who came unprepared to the sessions generally did not like the peer assessment phase and these students generally made bad evaluations about their peers (8). In our study, it was observed that students gave full points to each other in peer assessment. This situation can be associated with the first time that students encounter the TBL method. If this method is applied more frequently, it is thought that this situation will change, it will cause students to feel responsible for each other and come prepared for the lesson, and it will increase active participation.

In a study comparing TBL and traditional learning method, no difference was found in the ratio of students paying attention to the lesson, while satisfaction and active participation of students in the lesson were higher in TBL. At the end of the study, the students stated that they preferred this method to the traditional method (9). In our study, a comparison was made by assessing the correct answere rates in final examination. Correct answer succes rate in fluid&electrolyte balance is higher in TBL method. This looks like a success but outcomes of learning is not only the correct answers. Medical education is not only the achieving the correct answers of the tests. That's the reason why new methods are needed in medical education. Previous studies comparing TBL, conventional and peer-asisted learning has showed better learning outcomes in TBL method (11). The comparsion of outcomes were evaluated by Objective Structured Clinical Examination (OSCE) in that study (11). The diffifulty in performing outcome measurement in general surgery phase 4 students is difficult especially special topics like fluid&electrolyte balance and acute pancreattitis. For this reason we presented our study with test documents for future studies. Outcome measurements for TBL and traditional methods in these special topics of General Surgery haven't been evaluated before. Better way obtaining is the feedback of students. There are several studies that measure the succes of TBL by students' feedback (12,13). Most of the students thought that the student effort in TBL was more than the traditional method and that TBL was a better and more successful method than the traditional method. It has been observed that students who have low success in traditional methods have more learning success in TBL method (10).

TBL is very different from problem-based learning (PBL) and other small group approaches because there is no need for more than one faculty or room in this method. Students should come prepared for the sessions. Each student is individually responsible for contributing to team productivity. The trainer must be an expert, but does not require any prior experience to run a successful TBL session. Students do not need any specific instructions from the stage they learn how to be collaborative and productive. In the previous studies favorable results about TBL were obtained when TBL was compared with other active learning methods like problem based learning or case based learning (10,14,15). TBL can replace the traditional lecture method or can be used as a complement to this method.

TBL is an education model with active participation of students, improving communication skills, increasing personal motivation, and achieving high success and satisfaction with a single instructor in classes with more students (1). With this method, students' attention can be kept alive and students gain experience in problem solving. It becomes more interesting because it goes through case reports and problem solutions, and enables students to develop problem-solving strategies. However, the time allocated is insufficient due to the fact that such education models are not widespread enough. It can be applied in limited internship groups in certain classes yet. The adaptation process to these new methods can be difficult for students who have grown up with classical learning methods from an early age. Questions in readiness test are important for the quality of TBL session. These questions must include arguable topics and also contain the basic pathophysiology of the lesson. Here in our study, as seen in the questions, the students can discuss the pathophsiology of acute pancreatitis, electrolyte disturbances. Questions determines the how students think and discuss the lessons. Because of the difficulty in preparation of questions, here we presented our questions. It's seen that these questions are well enough for discussion of the acute pancreatitis and fluid&electrolyte balance. In general

surgery education, fluid&electrolyte is a difficult subject for the mentors to teach and fort he students to learn. Because, there are so many biochemical reactions in it and also so many clinical scenario in it. When compared with the lesson acute pancreatitis, correct answer rate in the fluid&electrolyte lesson is less. These kind of questions can be collected and TBL question banks can be formed in future.

Nowadays, students prefer traditional methods rather than such active participation methods because there are factors that can put pressure on students such as medical specialty exams and these are mostly theoretical knowledge-based exams. They may think that such new learning models are a waste of time. For this reason, while such methods which are more catchy and have more contribution to professional life are encouraged to be preferred in medical education. It should also be considered to revise the specialty exams and medical education exams in line with these methods. In this way, students will be able to look at these methods from a more objective perspective. More studies should be done on student-centered learning methods and these methods should be made widespread in this way.

As a results, TBL study achieved high acceptance by the students. Although a new method, they adopted easily. General surgery subjects are suitable for this type of education model. Preperation of questions are the most important part of TBL session.

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Effect of inadequate antenatal care during the pandemic on maternal and fetal outcomes

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Abstract

To evaluate the effects of inadequate antenatal care (ANC) caused by the COVID-19 pandemic on pregnant women. In this retrospective study, pregnant women were divided into two groups as those presenting during the pandemic and non-pandemic periods. The pandemic period was selected as March 11, 2020- December 10, 2020 and the pre-pandemic period as March 11, 2019- December 10, 2019 corresponding to the same period a year earlier. Pregnant women receiving ANC three times or less was defined as inadequate ANC. The pregnant women were evaluated in terms of obstetric complications, including premature rupture of membranes, premature birth, placental abruption. gestational diabetes mellitus (GDM), preeclampsia, fetal or neonatal death, and maternal death. The study included 276 patients presenting during the pandemic period and 229 patients presenting during the non-pandemic period. When the pandemic and non-pandemic periods were compared, it was determined that the rates of fetal death, preeclampsia and GDM statistically significantly increased in the former. The rate of adequate ANC was 72.5% (n=166) in the non-pandemic period and 58.3% (n=161) in the pandemic period. When pregnancy complications were compared according to ANC during the pandemic, it was observed that the rates of fetal death, preeclampsia and GDM were higher among the pregnant women with inadequate ANC. Complications due to inadequate ANC may have more significant consequences than complications caused by a possible COVID-19 infection. During the pandemic period, healthcare professionals should ensure that women receive safe and effective care during both pregnancy and childbirth.

Keywords: antenatal care, pandemic period, complications, pregnancy

1. Introduction

Various measures have been taken all over the world including our country to prevent the spread of coronavirus disease (COVID-19), which has led to inadequate provision of many services, especially healthcare services. However, with the onset of the COVID-19 pandemic, presentation of pregnant women to obstetrics outpatient clinics has decreased due to the fear of contracting the virus and lack of information.

Health risks faced by women during pregnancy and childbirth need to be minimized, and it is known that these risks can be prevented with high-quality antenatal care (ANC) (1). ANC should be started from the first trimester and continued at regular intervals until the end of pregnancy. Receiving ANC at least four times increases the likelihood of receiving effective maternal health interventions during the antenatal period (2). In addition, ANC is important in reducing perinatal and maternal mortality and morbidity (3). Most risk factors can be detected in the follow-up sessions undertaken in the first trimester, and complications can be prevented with ANC provided in the early period (4-6). Complications due to inadequate ANC may have more significant consequences than those caused by a possible COVID-19 infection. Therefore, in this study, we aimed to evaluate the effects of inadequate ANC caused by the pandemic on pregnant women.Case Presentation

2. Material and Methods

2.1. Study design and participants

This retrospective study was conducted in the Obstetrics and Gynecology Clinic of a university training hospital. Study parameters were evaluated in two periods: pandemic and non-pandemic. The pandemic period was selected as March 11, 2020- December 10, 2020 and the non-pandemic period as March 11, 2019- December 10, 2019 corresponding to the same period a year earlier. Pregnant women at 24 and 40 weeks of gestation were included in the study. This study followed the principles of the Declaration of Helsinki and was approved by Clinical Research Ethical Committee of Aksaray University Faculty of Medicine with a protocol number of 2020/13-42. Pregnant patients under 18 or above 45 years, those with a history of recurrent miscarriage, diabetes, teratogenic drug use or trauma, pregnant women with a previous history of COVID-19 and those with known fetal chromosomal and/or structural anomalies were excluded from the study.

2.2. Data collection

Clinical data were obtained by reviewing the electronic database of the hospital. Age, gestational week, gravida, parity, single or multiple pregnancy history, vital findings at the time of presentation, maternal diseases, mode of delivery, risk

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factors during pregnancy, pregnancy outcomes and complications, obstetric ultrasonography results (presence of retroplacental bleeding, location of the placenta, fetal position, and fetal viability), cardiofetal findings, and the number of ANC visits during pregnancy were recorded.

2.3. Definitions

Stillbirth was defined as babies born without a heartbeat after 24 weeks of gestation, premature birth as delivery before 37 weeks of gestation, premature rupture of membranes (PROM) as the rupture of the membrane before regular contractions occurred, placental abruption as the partial or complete separation of the placenta during the prenatal period. Inadequate ANC visits was defined as the number of visits being less than four or/ and the first ANC visit was delayed (> 3 months) (7).

Table 1. Distribution of demographic characteristics and outcomes of pregnant women according to the evaluated periods

Variables	Non-pandemic period (n = 229)	Pandemic period (n = 276)	P value
Maternal age (years)	27.2 ± 3.6	26.7 ± 4.8	0.561
Parity			
Nulliparous	64 (27.9%)	81 (29.3%)	0.729
Multiparous	165 (72.1%)	196 (71.0%)	0.797
History of stillbirth	19 (8.3%)	28 (10.1%)	0.477
Adequate prenatal care	166 (72.5%)	161 (58.3%)	<0.001
Gestational age at delivery	38.3 ± 2.4	38.1 ± 2.2	0.893
Mode of delivery			
C/S (n = 1069)	442 (41.3%)	627 (58.7%)	<0.001
NSD (n = 1501)	820 (54.6%)	681 (45.4%)	<0.001
Preterm labor	56 (24.5%)	66 (23.9%)	0.889
Placental abruption	9 (3.9%)	10 (3.6%)	0.857
PROM	83 (36.8%)	103 (37.3%)	0.796
Fetal death	5 (2.2%)	16 (5.8%)	0.043
Neonatal death	1 (0.4%)	2 (0.7%)	0.570
Maternal death	0	1 (0.4%)	0.547
Preeclampsia	12 (5.2%)	29 (10.5%)	0.031
GDM	6 (2.6%)	19 (6.9%)	0.028
SGA (<10th percentile)	14 (6.1%)	20 (7.2%)	0.613

Data are presented as mean ± standard deviation, **C/S:** cesarean delivery, **NSD:** normal spontaneous delivery, **PROM:** premature rupture of membranes, **GDM:** gestational diabetes mellitus, **SGA:** small for gestational age

2.4. Outcome measures

The primary outcome of the study was the presence of obstetric complications, including spontaneous abortion, PROM, premature birth, placental abruption, gestational diabetes mellitus (GDM), preeclampsia, fetal or neonatal death, and maternal death. The secondary outcome was the association between inadequate ANC and obstetric complications.

2.5. Statistical methods

All statistical data were analyzed using SPSS for Windows, version 15.0 (SPSS Inc.; Chicago, IL, USA). First, the descriptive statistics [number (n), frequency (%), mean and standard deviation] of the variables in the study group were calculated. Pearson's chi-square or Fisher's test was used to compare categorical data.

The normality of data distribution tested with the Kolmogorov-Smirnov test. Student's t-test was used to compare normally distributed data and the Mann-Whitney U test to compare non-normally distributed data. A value of $p < 0.05$ was considered statistically significant.

3. Result

The study included 276 patients presenting during the pandemic and 229 patients presenting during the non-pandemic period. The mean age was 27.2±3.6 years for the non-pandemic period and 26.7±4.8 years for the pandemic period. The number of pregnancies, parity, maternal age, and gestational age at delivery did not statistically significantly differ between the two groups ($p>0.05$) (Table 1). We determined that the rate of cesarean delivery increased in the pandemic period compared to the non-pandemic period ($p< 0.001$).

When the non-pandemic and pandemic periods were compared, it was observed that the rates of fetal death, preeclampsia and GDM were statistically significantly increased in the latter ($p=0.043$, $p=0.031$, and $p=0.028$, respectively). However, there was no statistically significant difference in relation to the rates of PROM, preterm delivery and placental abruption. The rate of inadequate ANC was found to be 27.5% (n=63) in the non-pandemic period and 41.7% (n=115) in the pandemic period (Table 2).

When pregnancy complications were compared according to the number of ANC sessions attended, it was found that the rates of fetal death, preeclampsia and GDM were higher among the pregnant women with inadequate ANC (Table 3).

Table 2. Number of ANC sessions attended by pregnant women according to the evaluated periods

Number of ANC	Non-pandemic period (n = 229)	Pandemic period (n = 276)	P value
None	11 (4.8%)	23 (8.3%)	
1-3	52 (22.7%)	92 (33.3%)	0.004
≥4	166 (72.5%)	161 (58.3%)	

Table 3. Comparison of pregnancy complications and ANC rates during the pandemic period

Variables	Pandemic period		
	Adequate ANC (n = 161)	Inadequate ANC (n = 115)	P value
Preterm labor	37 (23.0%)	29 (25.2%)	0.668
Placental abruption	6 (5.2%)	4 (2.5%)	0.328
PROM	56 (34.8%)	47 (40.9%)	0.303
Fetal death	5 (3.1%)	11 (9.6%)	0.024
Neonatal death	1 (0.6%)	1 (0.9%)	0.810
Maternal death	0	1 (0.9%)	0.417
Preeclampsia	9 (5.6%)	20 (17.4%)	0.002
GDM	5 (3.1%)	14 (12.2%)	0.003
SGA (<10th percentile)	11 (9.6%)	9 (5.6%)	0.209

ANC: Antenatal care, **PROM:** Premature rupture of membranes, **GDM:** Gestational diabetes mellitus, **SGA:** Small for gestational age

4. Discussion

According to the guidelines published by the World Health Organization (WHO), there is no significant difference in the prevalence and clinical manifestations of the COVID-19 infection between pregnant and non-pregnant women or women of reproductive age (8). In the literature, although no correlation has been found between the COVID-19 infection and adverse maternal and fetal complications, it has been suggested that inadequate ANC during the pandemic period may be indirectly associated with adverse pregnancy outcomes (9). In the current study, we determined that inadequate ANC was associated with increased fetal death, PROM, preeclampsia and GDM during the pandemic.

Every woman should receive ANC at least four times during her pregnancy, and those with risky pregnancies should attend more ANC sessions. Inadequate ANC due to the pandemic may cause high risk factors (advanced age, hypertension, diabetes, bleeding diathesis, etc.) to be overlooked in pregnant women. Adequate ANC is important for reducing maternal and fetal complications. Previous studies have shown a significant decrease in gynecology and obstetrics outpatient and emergency presentations during the pandemic compared to the pre-pandemic period (10,11). In our study, we found that the rate of ANC decreased during the pandemic. The reasons for inadequate ANC may be due to the restrictions in transportation, inability to make an outpatient clinic appointment, fear of infection of contracting the virus at a healthcare institution, or failure to provide necessary pregnant training due to the pandemic.

GDM screening should be performed at the time of presentation for pregnant women with risk factors (obesity, history of GDM in previous pregnancy, polycystic ovary syndrome, etc.) and at weeks 24-28 for those without such risk factors (12). Failure to detect pregnant women with GDM in the early period may cause maternal and fetal complications. In the current study, we found that the frequency of GDM increased during the pandemic. Fewer visits to the hospital during the quarantine period, sedentary lifestyle, and inappropriate weight gain may have increased the rate of GDM. Dell'Utri et al., who compared the pandemic and non-pandemic periods, reported that the rate of fetal death increased during the pandemic (10). In our study, we determined that the rate of fetal death increased among the patients that received inadequate ANC during the pandemic. Dell'Utri et al. did not evaluate ANC during the pandemic. The reason for the increased fetal death rate during the pandemic may be due to inadequate ANC and pregnant women delaying their hospital visits due to the pandemic. In addition, in the absence of serious complaints, such as bleeding and pain, a symptom such as decreased fetal movement may have been overlooked despite its importance.

Manu Goyal et al. reported that the rate of preeclampsia increased during the pandemic compared to the pre-pandemic period (11). Similarly, in our study, we found that the rate of preeclampsia increased during the pandemic period. Increased stress and anxiety in pregnant women due to the risk of contracting COVID-19 may have indirectly caused an increase in the number of patients developing preeclampsia (13). Pregnancy-related hypertension may not be detected because blood pressure monitoring is not regularly undertaken in pregnant women receiving inadequate ANC. Blood pressure measurement is crucial in every follow-up of pregnant women. In addition, urinary protein measurement during the follow-up

allows for the diagnosis of hypertensive diseases, such as preeclampsia in pregnancy. Early detection and treatment of life-threatening conditions, such as preeclampsia are important to prevent maternal and fetal complications.

This study has certain limitations. First, the retrospective nature of the study limited data to those routinely collected. An important limitation was the exclusion of patients with missing data concerning obstetric outcomes among the women who developed complications. Second, this was a single-center study. Further studies involving multiple centers are needed to confirm our results.

In this study, we found that the rates of preeclampsia, fetal death and GDM increased in pregnant women who received inadequate ANC during the pandemic. Inadequate ANC may present with increased complication rates in pregnancy. During the pandemic, healthcare professionals should ensure that women receive safe and effective care during both pregnancy and childbirth.

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Conflict of Interest Statement
All authors report no conflict of interest.

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Research Article

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Bascom cleft lift technique in sacrococcygeal pilonidal disease: Results of tezel 4 and 5 cases

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Abstract

According to the Tezel classification, the surgical method to be applied for type 4 and type 5 sacrococcygeal pilonidal disease (SPD) patients is controversial. Our aim is to discuss the success of the Bascom Cleft Lift (BCL) technique in treating these patients. In the present study, patients who were operated on for primary or recurrent pilonidal sinus disease by the same surgeon (IAT) in a tertiary medical faculty hospital between January 2018 and January 2020 were retrospectively analyzed. Complication and recurrence rates after BCL were compared with the available literature. There were 10 patients who underwent BCL for SPD Tezel type 4 and type 5. The average age of the patients was 21 (16-29) years and 9 (90%) of them were male. The mean follow-up time was 22 (11-26) months. The mean operation time was 42 (35-58) minutes. The duration of hospitalization was 2.4 (1-5) days. Although the first patients stayed in the hospital for a long time, the last three patients stayed for a day each. Seroma developed in 2 (20%) patients, superficial infection in 1 (10%) and recurrence in 1 (10%) patient. Recurrence developed only in the patient who was operated in the eigth row. No patient was reoperated. BCL is a successful technique for treating Tezel type 4 and type 5 SPD patients.

Keywords: Bascom cleft lift, recurrence, sacrococcygeal pilonidal disease, pilonidal sinus

1. Introduction

Sacrococcygeal pilonidal disease (SPD) is a common disease that mostly affects young men (1). Damage to the epidermis in the deep natal cleft (intergluteal sulcus) due to moisture, hypoxia, bacteria, and hair(s) are blamed factors in the etiology of SPD (2). The disease sometimes persists for years without symptoms or it sometimes manifests with an acute abscess. The first abscess sometimes opens to the skin and drains spontaneously, and sometimes the abscess is treated by incision and drainage. However, most of them develop into chronic inflammatory lesions with discharge. There are many surgical methods recommended for both primary and recurrent cases. However, there is no consensus on which surgical method is most suitable to treat this disease.

SPD may present as asymptomatic sinus orifices, large abscesses, multiple sinuses, and patients who have undergone more than one surgical technique. Due to the differences in the manifestation of the SPD and the variation in the severity of the symptoms, it is illogical to apply the same surgical method to SPD cases. There are various classifications such as the Modified Cruse and Foord categorization (3), which are used to plan SPD treatment. However, we prefer the Tezel classification shown in Table 1 (4).

Table 1. Tezel classification for pilonidal disease.

Type	Definition
1	Asymptomatic
2	Acute pilonidal abscess
3	Symptomatic disease limited to navicular area
4	Extensive disease which extents outside the navicular area
5	Recurrent disease after any kind of definitive pilonidal surgery

Many methods such as rhomboid excision have been described, eliminating the natal cleft. Limberg flap or elliptical excision, Karydakis or V-Y advancement flap; and the Bascom Cleft Lift (BCL) technique is one of them (5). We prefer this technique in cases where one or more sinus mouths are outside the navicular region (Tezel type 4) and cases with recurrence (Tezel type 5).

Our aim in this study is to discuss the success of the

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BCL technique in treating Tezel type 4 and 5 SPD those through using patient data collected over a 2 year period.

2. Materials and Methods

In the present study, patients who were operated on for primary or recurrent pilonidal sinus disease by the same surgeon in a tertiary medical faculty hospital between January 2018 and January 2020 were retrospectively analyzed. Patients data were collected from the automation system of the hospital and by phone calling the patients for one on one interviews. Cases to whom BCL were applied that type 4 (Fig. 1) and type 5 according to the Tezel classification were included in the study (4). Cases that manifested as Tezel type 1, 2, 3 and those in which other techniques were applied were excluded from the study.

Patients' data on age, gender, body mass index (BMI), history of diabetes mellitus (DM), active smoking, type of Tezel classification and previous surgical treatments were recorded. In addition, information on the duration of the surgery, drain application, hospitalization time, complications, postoperative follow-up period, recovery, and whether a repeat surgery was needed were also recorded.

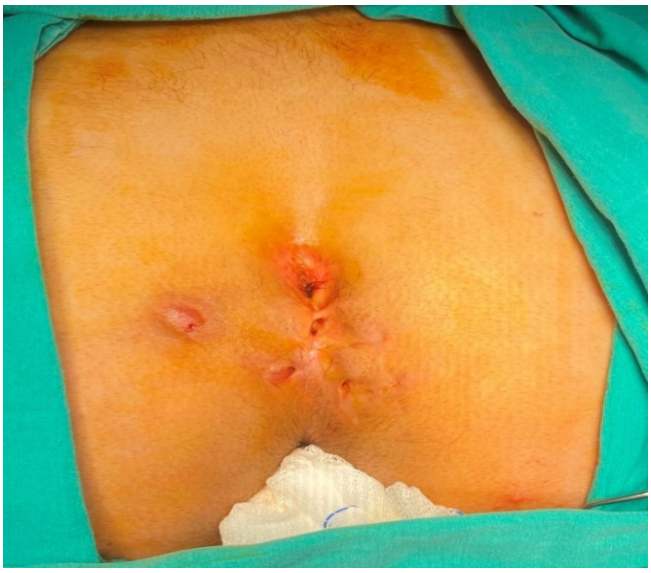

Fig. 1. Type 4 SPD photo according to Tezel classification

2.1. Surgical technique

A single dose of prophylactic antibiotic (1 gram Cefazolin) was administered 30 minutes before starting the operation. Spinal anesthesia was applied to all patients. The patients were placed on the operating table in the prone jackknife position and the operation area shaved. The navicular region was drawn first. Both gluteal areas were opened to both sides with sticking plasters. The surgery area was widely prepared with Betadine and draped in a sterile fashion. The planned flap was drawn with a sterile pen (Fig. 2). Only the skin containing the pits was removed by making an asymmetric elliptical incision in the navicular region. The sinuses were opened using a cautery by advancing the excised subcutaneous area through the sinus mouths to the stylet. The hairs were cleaned and all foreign bodies were removed from the environment by the curetted sinuses. Making sure that the granulation tissue does not contain hair, it was left in place. Subsequently, the flap was prepared, paying attention not to cross the border of the contralateral navicular region. When preparing the opposite flap a scalpel was used instead of a cautery in order not to damage the flap. Following hemostasis, the sticking plasters were opened and the gluteal regions were liberated. If a drain was to be placed, it was placed in the lowest plan. Deep subcutaneous tissues were sutured with 1/0 vicyrl, superficial subcutaneous tissues were sutured with 3/0 vicryl. The skin was closed primarily using the matress technique using 2/0 prolene.

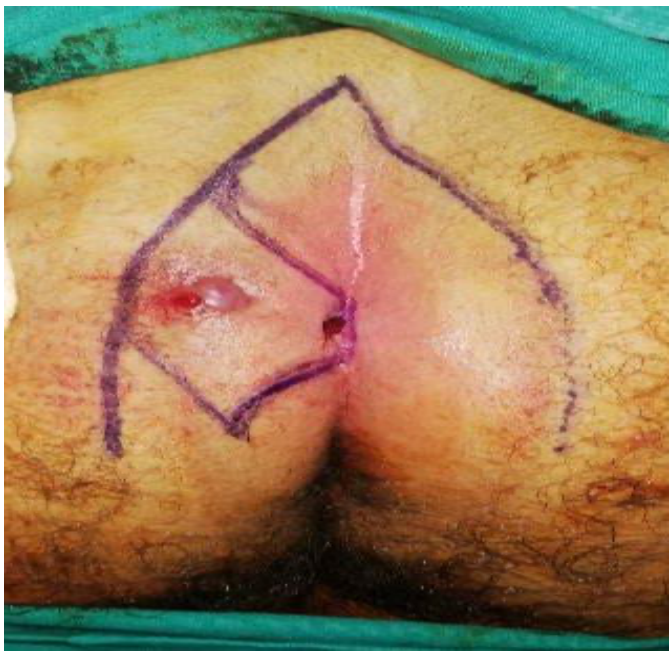

Fig. 2. The planned flap was drawn with a sterile pen

2.2. Statistical analysis

Data were entered into the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0. Complete descriptive statistics were used for all the nominal variables, and the data were presented as mean, frequency and percentage values.

3. Results

The specified period, 20 patients were operated by the same surgeon for SPD. Ten patients who During had Tezel type 4 and type 5 and underwent the BCL procedure were included in the study. Others were excluded from the study.

Table 2 shows that the median age of the patients was 21 years (range 16-29 years) and most of the patients were male (90%). The mean BMI was 25 kg/m^2 (range 20–30.5; Table 1). None of the patients had DM and one third of them were active smokers (3, 30%). Half of the patients had previously undergone surgery for SPD (5, 50%). Abscess drainage had previously performed in 2 (20%) patients before while closed-suction drain was applied to 8 (80%)

patients. The mean operation time was 42 (35-58) minutes, closed-suction drain was applied to 8 (80%) patients. The duration of hospital stay was 2.4 (1-5) days and the follow-up period was 22 (11-26) months. No complications were seen except seroma in 2 (20%) patients and superficial infection in 1 (10%) patient. While only 1 (10%) patient had recurrence, there was no patient who was reoperated (Table 2).

Table 2. Demographics, surgical history, operative details

Variable	Bascom cleft lift (n=10)
Age (years, range	21 (16-29)
Sex (n, %)	
Male	9 (%90)
Female	1 (%10)
BMI (kg/m2, range)	25 (20-30.5)
Obese (BMI>30) (n, %)	1 (%10)
Diabetes Mellitus, (n)	0
Active Smoker, (n, %)	3 (%30)
Presentation, (n, %)	
Primary	5 (%50)
Recurrence	5 (%50)
Previous drainage, (n, %)	2 (%20)
Operation duration (min, range)	42 (35–58)
Closed-suction Drain, (n, %)	8 (%80)
Hospital Duration (day, range)	2.4 (1-5)
Surgical area-related complications, (n,%)	
Wound Separation	0
Hematoma	0

The patients are listed in Table 3 according to the order of surgery. According to the classification 5 (50%) patients were Tezel type 4 while the other 5 (50%) were Tezel type 5. Three patients had no previous surgical intervention, including abscess drainage. Although the first patient stayed in the hospital for a long time, the last three patients stayed for a day each. Closed-suction drain was applied to two patients who developed seroma, and these two patients were hospitalized for four days. Superficial wound infection developed in the last operated patient. Recurrence developed only in the patient who was operated in the eighth row.

4. Discussion

Surgical procedures with flap preparation are not preferred for asymptomatic SPD and symptomatic SPD limited in the navicular area (Tezel type 1,2,3). Many methods are applied to such cases, from suggestions such as hygiene, clean cotton underwear and wide pants to simple procedures such as drainage and cleaning. With the advancement in technology, new methods such as laser destruction of the pilonidal sinus have been developed (6,7). We encounter many patients with Tezel type 1, type 2 and type 3 who do not benefit from the interventions and surgical methods performed. These patients tend to develop recurrence (Tezel type 5) and sometimes have one or more sinus orifices (Tezel type 4) that exceeded the navicular area when first diagnosed. However, simple methods are insufficient for Tezel type 4 and type 5 patients, thus, midline shift and flap methods come to the front. Yet, till today, the most suitable method for treating Tezel type 4 and type 5 SPD is disputable (8-10).

In our opinion, the ideal treatment for relapsed or widespread SPD should be a simple method that does requires a short or no hospitalization, less painful, cost-free and presents minimal chances of recurrence. In our clinic, BCL technique has been preferred for Tezel type 4 and type 5 cases. The BCL technique has undergone some modifications since it was first described, and its effectiveness is still debated (2, 11-13). Most of the people we applied BCL to, for Tezel type 4 and type 5 were men. In our study of the 10 cases, the median follow-up period of the patients was 22 (11-26) months and the median duration of operation was 42 (35-58) minutes. There are studies reporting operation time between 25-54 minutes (12-15). We think that our experience will improve as the number of patients we apply BCL increases and our operation time will shorten a little. In literature, there were reported values between 1.28 days and 2.95 days for hospital stay after BCL (12-16). In our results, the duration of hospital stay was found to be 2.4 (1-5) days. At this value, the recommended value was in the range but slightly higher. Looking at Table 3, it can be seen that the first BCL cases we performed were hospitalized for up to five days, but the last three cases were discharged one day later. This supports the idea that as our experience increases, the duration of hospital stay will decrease.

Dutkiewicz et al. (2019) performed BCL in 50 patients diagnosed with primary pilonidal sinus and reported the rate of major complications as 0% (16). Hatch et al. (2020) evaluated the postoperative outcomes of patients who

Table 3. Patient characteristics and results

Patient no.	Sex	Age (years)	Tezel Type	BMI (kg/m2)	Previous treatment	Hospital Stay (day)	Follow-up (month)	Morbidity
1	M	16	5	28	Primary closure Limberg flap	5	26	None
2	M	23	5	25	Marsupialization	2	25	None
3	M	29	4	25	Incision/drainage	1	25	None
4	M	21	5	28	Marsupialization	3	24	None
5	M	20	4	20	None	4	24	Seroma
6	F	18	4	23.5	Incision/drainage	2	23	None
7	M	17	5	30.5	Primary closure	4	23	Seroma
8	M	18	4	26	None	1	22	Rekurrens
9	M	18	5	19.5	Primary closure	1	16	None
10	M	26	4	25	None	1	11	Superficial Infection

underwent BCL in a retrospective study of 235 patients and reported a major complication rate of 19.4% (2). However, in recent studies, major complications after BCL have been reported with a rate of 1% to 14.5% (9, 12,14). When we look at Table 2, it is seen that we do not have major complications such as wound dehiscence, flap necrosis that would require re-operation. On the other hand, it is seen in Table 2 that while there is no hematoma in our results, seroma developed in two cases (20%) and superficial infection developed in one case (10%). Although Ortega et al. (2014) reported the rate of seroma as 15% in their study on 74 patients who underwent BCL (12), this rate was between 5.1% and 6.5% in other studies (2, 13, 14). In our study, rate of seroma is very high. The low number cases studied makes this rate seem high. Dutkiewicz et al. reported the superficial infection rates as 0% (16), but in literature, this rate ranges from 1% to 10% (2, 9, 12-15). Our superficial infection rate is at the upper limit of this average and it is high in our opinion.

At the same time, there are many different values reported for the recurrence rates of BCL applied cases. Umesh et al. reported the long-term results of 22 patients who underwent BCL, and reported the recurrence rate as high as 9% (17). On the contrary, in a prospective randomized study by (14), none of the 61 patients who underwent BCL developed recurrence (14). In literature, this rate is seen to be between 1.3% and 6% (9, 12-16). In our results, it is seen that recurrence developed in one case (10%). In Table 3, where the cases are listed chronologically from the first to the last, it is seen that the patient who developed recurrence was operated on in the 8th order. It is seen in Table 3 that half of the cases either had no surgery or only incision and drainage were applied, and the other half had at least one operation. Although it is conceivable that the performing BCL on patients who have undergone previous surgery and recurrence poses higher risks of developing, our only case of recurrence was primary pilonidal sinus case.

Although our complication and recurrence rates are a bit high, in our opinion, the BCL method is a flap method with very high success rates. We hope that our complication and recurrence rates will decrease once our number of patients increases and our learning curve process is completed. There are many studies in literature evaluating the results of the BCL method and reporting success results (9, 12-16). Despite these studies, the BCL technique has not yet become a standard technique by surgeons. The difficult in the application of the technique may be the reason why surgeons do not prefer this technique. In our opinion, for Tezel type 4 and type 5 cases, BCL is a very successful method with short hospitalization, low cost and low recurrence rate after a difficult learning process.

The weaknesses of our study are that our study is retrospective, the number of patients is very small and the surgeon performing the procedure has not yet completed the learning curve.

The BCL method is a successful method that should be preferred by a surgeon who has completed the learning process in Tezel type 4 and type 5 cases.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Investigation of plasmid-mediated quinolone resistance genes in carbapenem resistant Enterobacterales

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Abstract

Fluoroquinolones, are effective agents both against gram-positive and gram-negative bacteria. Quinolones show bactericidal effect as a result of inhibition of DNA gyrase and topoisomerase IV enzymes. Main quinolo resistance mechanisms are chromosomal mutations in these enzymes and decreased intracellular accumulation due to efflux pumps or decreased membrane uptake. Recently a new quinolone resistance mechanism mediated by plasmids has been defined. These plasmids carry genes called as qnr. Qnr genes do not cause quinolone resistance but they cause decreased quinolone susceptibility and lead to higher minimum inhibitory concentrations. Currently there are qnrA, qnrB, qnrC, qnrD and qnrS genes. This study was aimed to investigate the presence of plasmid-mediated quinolone resistance determinants in carbapenem resistant Enterobacterales isolates. A total 154 carbapenem resistant Enterobacterales isolates were included in the study. Presence of qnrA, qnrB, qnrC, qnrD and qnrS genes were investigated by multiplex polymerase chain reaction (PCR) method. The results of the PCR amplification revealed that qnrA was detected in two isolates (E6, E85) (1.29%), qnrB was detected in 12 isolates (8.4%) (E32, E43, E46, E61, E62, E84, E94, E149, E 166, E167, E177, E179) and qnrS was detected in six isolates (E15, E25, E57, E63, E70, E80) (4.54%). And one isolate (E9) was both positive for qnrB and qnrS. QnrC and qnrD were not detected in any isolates. Transferable quinolone resistance due to the dissemination of qnr genes may have important impacts in terms of infection control and treatment problems. Survey of plasmid mediated quinolone resistance will help to determine the size of the issue and guide the measures that should be taken to avoid escalation of resistance and dissemination problem.

Keywords: Qnr, Enterobacterales, quinolone, carbapenem

1. Introduction

Enterobacteriaceae are inhabitants of the intestinal flora and are among the most common human pathogens, causing infections such as cystitis and pyelonephritis with fever, septicemia, pneumonia, peritonitis, meningitis, and device-associated infections (1). Multidrug-resistant organisms are a major public health concern worldwide; of particular concern has been the emergence of resistance to carbapenem antimicrobial drugs among Enterobacteriaceae and quinolones are one of the options for treatment of carbapenem resistant enterobactericeae (CRE) infections (2, 3).

Quinolones are synthetic agents that are opponent to betalactames in clinical usage. They have been using in the treatment of both gram positive, gram negative and anaerobic bacterial infections (4). Quinolones show their bactericidal activity by inhibitng DNA gyrase and topoisomerase IV (5). The resistance development has been inevitable result of the widespread use of quinolones. The main resistance mechanism to quinolones are chromosomal mutations in

DNA gyrase (gyrA and gyr B) and topoisomerase IV (parC and par E). And other resistance mechanims are reduced accumulation of drug in the cell by hiperactivation of efflux pumps and decreased permeability of cell wall and plasmid mediated qnr (A, B, C, D, S), qepA and aac (6')- Ib- cr genes (6).

Plasmid mediated quinolone resistance was first reported in Klebsiella pneumoniae in 1998 and this resistance determinate called 'qnr' (7). Different qnr genes have been identified in time and first determinant named as qnrA. The primary structures of qnrA, qnrB, and qnrS are similar, with nine pentapeptide repeat units connected by a single glycine, followed by a cysteine, with variable numbers of units (8). He proteins that encoded by qnr genes are thought to protect DNA gyrase and topoisomerase IV by binding them from influence of quinolones (6).

The clinical importance of plasmid-mediated quinolone resistance is uncertain, although it is postulated that it may help to stabilize or select for mutations in the quinolone resistance-determining region (QRDR) of DNA gyrase and topoisomerase, which then confers high-level quinolone resistance (9).

In this study we aimed to investigate then prevelance of plasmid-mediated quinolone resistance determinants in carbapenem resistant Enterobactericeae.

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2. Materials and Methods

2.1. Bacterial isolates

Carbapenem resistant Enterobactarales clinical isolates (n=154, K. pneumoniae n=120, E. coli n=14, Klebsiella oxytoca n=10, Enterobacter cloacae n=4, Enterobacter aerogenes n=2, Proteus mirabilis n=2, Proteus vulgaris n=1, Providencia rettgeri n= 1) that isolated from clinical specimens in Microbiology laboratory of Ondokuz Mayıs University Faculty Medicine Hospital was tested in the study. Identification of the isolates was performed on Vitek MS (Biomeriux, France) and antimicrobial susceptibility was studied in Vitek2 Compact (Biomeriux, France) automated systems.

2.2. Polimerase chain reaction

DNA preperation was performed by a boiling technique that includes a heating step at 100˚C of colonies from Mueller-Hinton agar in a 500µl sterile distilled water for 20 min. followed by a centrifugation step of the cell suspension at 15000g for 20min, supernatant was used as template DNA in PCR. For optimisation of multiplex PCR well-characterized qnr-positive strains were used as positive controls. These strains were provided by: Prof. GA Jacoby (Lahey Clinic, Burlington, Massachusetts, USA), Prof. P Nordmann (Service de Bactériologie-Virologie, INSERM U914 "Emerging Resistance to Antibiotics", Hôpital de Bicêtre, Assistance Publique/Hôpitaux de Paris, Faculté de Médecine et Université Paris-Sud, K.-Bicêtre, France) and qnrC plasmid was provided by Prof. M Wang (Institute of Antibiotics, Huashan Hospital, Fudan University, 12 M. Wulumuqi Rd., Shanghai 200040, People's Republic of China).

Qnr A, qnrB, qnrC, qnrD and qnrS determinants were studied in multiplex PCR and primer pairs were used as identified by Kim et al. and Cavaco et al. (Table 1) (10, 11). Amplification was carried out with the following thermal cycling profile: 1 min at 95˚C and 35 cycles of amplification consisting of 1 min at 95˚C, 1 min at 60˚C and 1 min at 72˚C and 10 min at 72˚C for the final extension.

Ethical approve was taken from Ondokuz Mayıs University Clinical Research Ethics committe (B.30.2.ODM.0.20.08/364).

Table 1. Sequence of primers

Gene	Primer	Sequence	Bp	Ref
*qnr*A	Qnra-F QnrA-R	ATTTCTCACGCCAGGATTTG GATCGGCAAAGGTTAGGTCA	516	1017
*qnr*B	QnrB-F QnrB-R	GATCGTGAAAGCCAGAAAGG ATGAGCAACGATGCCTGGTA	476	10
*qnr*C	QnrC-F QnrC-R	GGGTTGTACATTTATTGAATCG CACCTACCCATTTATTTTC	307	10
*qnr*S	QnrS-F QnrS-R	GCAAGTTCATTGAACAGGGT TCTAAACCGTCGAGTTCGGCG	428	10
*qnr*D	QnrD-F QnrD-R	CGAGATCAATTTACGGGGAATA AACAAGCTGAAGCGCCTG	565	11

3. Results

3.1. Bacterial isolates

The distribution of specimens that CRE isolated were presented in Table 2. The most common specimen that CRE isolates were identified was urine (50.0%) and it was followed by blood (22,0%) and respiratory tract (13.6%) samples. Materials were sent from different clinics to the laboratory. Internal medicine clinic was the most frequent clinic (23.37%) that CRE isolates were isolated (Table 3).

Ciprofloxacin resistance was detected in 119 (77.27%) isolates. And 8 (1.29%) isolate were intermediate to ciprofloxacin.

3.2. Polimerase chain reaction

Positive control strains yielded expected bands (Fig. 1). QnrA was detected in two isolates (E6, E85) (1.29%), qnrB was detected in 12 isolates (8.4%) (E32, E43, E46, E61, E62, E84, E94, E149, E 166, E167, E177, E179) and qnrS was detected in six isolates (E15, E25, E57, E63, E70, E80) (4.54%). And one isolate (E9) was both positive for qnrB and qnrS. QnrC and qnrD were not detected in any isolates (Table 4).

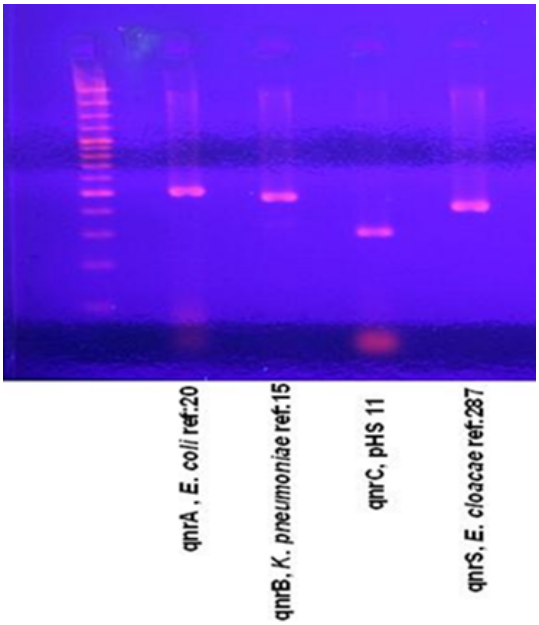

Fig. 1. Gel electrophoresis of positive qnrA, qnrB, qnrS and qnrC

Seventeen of the qnr determinant positive isolates found to be resistant to ciprofloxacin, four of them were intermediate and one of the isolate was susceptible to ciprofloxacin.

Table 2. Distribution of qnr positive isolates

	Isolate	Specimen type	Ciprofloxacin resistance
qnrA positive			
E6	*K.pneumoniae*	Urine	R
E5	*K.oxytoca*	Urine	R
qnrB positive			
E32	*K.pneumoniae*	Urine	I
E43	*K.pneumoniae*	Blood	R
E46	*K.pneumoniae*	Sterile body fluid	R
E61	*K.pneumoniae*	Sterile body fluid	R
E84	*K.pneumoniae*	Urine	R
E94	*E.cloacae*	Blood	S
E149	*K.pneumoniae*	Wound	R
E166	*K.pneumoniae*	Urine	I
E167	*E.aerogenes*	Tracheal aspirate	I
E177	*K.pneumoniae*	Wound	R
E179	*K.pneumoniae*	Urine	R
qnrS positive			
E15	*K. oxytoca*	Urine	R
E25	*E. coli*	Wound	I
E57	*E. cloacae*	Blood	R
E63	*K. oxytoca*	Urine	R
E70	*K. oxytoca*	Urine	R
E80	*K. oxytoca*	Urine	R
qnrB+qnrS positive			
E9	*E. coli*	Wound	R

Table 3. Distribution of clinical wards that samples sent

Clinical wards	N (%)
Internal Medicine	36(23.37%)
Pediatrics	22(14.28%)
Intensive care unit	21 (13.63%)
Neurology	17(11.03%)
Urology	11(7.14%)
Cardiology	10(6.50%)
Infectious Diseaes	8(5.20%)
Emercency	7(4.54%)
Surgery	7(4.54%)
Pulmonology	5(3.24%)
Other*	10(6.50%)

Table 4. Distribution of qnr positive isolates

	Isolate	Specimen type	Ciprofloxacin resistance
qnrA positive			
E6	*K.pneumoniae*	Urine	R
E5	*K.oxytoca*	Urine	R
qnrB positive			
E32	*K.pneumoniae*	Urine	I
E43	*K.pneumoniae*	Blood	R
E46	*K.pneumoniae*	Sterile body fluid	R
E61	*K.pneumoniae*	Sterile body fluid	R
E84	*K.pneumoniae*	Urine	R
E94	*E.cloacae*	Blood	S
E149	*K.pneumoniae*	Wound	R
E166	*K.pneumoniae*	Urine	I
E167	*E.aerogenes*	Tracheal aspirate	I
E177	*K.pneumoniae*	Wound	R
E179	*K.pneumoniae*	Urine	R
qnrS positive			
E15	*K. oxytoca*	Urine	R
E25	*E. coli*	Wound	I
E57	*E. cloacae*	Blood	R
E63	*K. oxytoca*	Urine	R
E70	*K. oxytoca*	Urine	R
E80	*K. oxytoca*	Urine	R
qnrB+qnrS positive			
E9	*E. coli*	Wound	R

4. Discussion

Quinolones are synthetic chemotherapeutic agents that have a bactericidal effect. Nalidixic acid, which was used in the 1960s, has expanded its antimicrobial effect spectrum and changed its pharmacodynamic properties with the changes made in its chemical structures. Today, they are effective on both gram-positive, gram-negative and anaerobes. The use of quinolones has become widespread with these changes over time (12). Widespread use has brought along the problem of resistance. The main development of resistance to quinolone antibiotics occurs through two mechanisms: a change in the target of quinolones and a decrease in membrane permeability or a decrease in drug accumulation within the cell due to the presence of pulse pumps (13). Both of these resistance mechanisms are of chromosomal origin. However, they first identified a new gene region that belongs to the repeating

pentapeptide family consisting of 218 aa from 1998 K. pneumoniae isolates and transferred by the plasmid called qnr (14). Later, this gene region was named qnrA. These qnr genes generally differ in sequence by 35% or more from qnrA and from each other. Furthermore, most of them contain allelic variants differing by 10% or less (qnrA: 8, qnrS: 9, qnrB: 88, qnrC: 1, qnrD: 2, and qnrVC: 7) in which qnrB constitutes the most heterogeneous cluster of the qnr gene family (15).

Qnr genes in the Enterobactericeae family have been previously investigated in different centers in Turkey. In a study conducted in our country in 2005, the qnr A gene region was investigated in 49 isolates and one E. cloacae and one C. freundii qnrA gene were detected14 (16). Later, Öktem et al. qnrA, qnrB and qnrS genes were investigated in 356 Enterobacteriaceae members isolated from blood cultures, and qnrA was detected in 61 isolates and qnrS in 3 isolates. It was observed that two of the isolates with qnrA and one of the isolates with qnrS formed ESBL (17).

In another study conducted in our country, qnrA, qnrB, qnrS genes were investigated in a total of 460 gram negative bacteria isolated from intensive care patients, and 1 qnrB1 and 2 qnrS1 genes were found in three (0.65%) E. cloacae isolates. They investigated the frequency of qnrA, qnrB, qnrS, aac (6 ') - Ib-cr genes in a total of 248 E. coli and K. pneumoniae isolates isolated from different hospitals in Turkey, qnrB1 on different plasmids in 1 K. pneumoniae isolates. and detected the aac (6 ') - Ib-cr genes (18). Coban et al. İnvestigated the qnr genes in total of 647 Enterobactericeae isolate and determined qnrA in two isolates, qnrB in six isolates and qnrS in two isolates (19).

In a multicenter study conducted in Spain, 19010 isolates (18624 Salmonella spp., 285 E. coli, 68 Shigella spp., 29 K. pneumoniae, 2 C. freundii and 2 P. mirabilis) were investigated for quinolone resistance and decreased ciprofloxacin susceptibility (Qnr genes were investigated in 123 isolates showing MIC 0.12-0.5 mg / L) but sensitive to nalidixic acid and 2 Salmonella spp. isolate qnrB, 25 Salmonella spp. and qnrA in 1 E. coli isolate, 4 Salmonella spp. The qnrS gene was detected in the isolate (20). Again, 485 Salmonella spp. isolated from human, animal, food and environment collected from 13 European countries. and in 133 E. coli isolates, the presence of quinolone resistance genes transferred by plasmid was investigated and in 59% of Salmonella spp. isolates (288/485); positivity was detected in 15% (20/133) of E. coli isolates, qnrA 3 Salmonella spp. isolate, qnrB 138 Salmonella spp. and in 1 E. coli isolate, qnrS 125 Salmonella spp. and in 19 E. coli isolates (21).

Majlesi et al. tested total of 100 fluoroquinolone-resistant Enterobacteriaceae and determined two (2%) were positive for qnrS, seventeen (17%) isolates were positive for qnrB (22). In a study total of 155 bacterial strains tested were found harboring at least one qnr gene consisting of 74 (47.74%) qnrB, 73 (47.10%) qnrS and 4 (2.58%) qnrA (23). Amin et al. investigated the presence of qnrA, qnrB and class I integron in Enterobacter spp. isolates and they found that 29% of the isolates were positive for qnrB and none of them positive for qnrA, and 22.4% of the isolates were positive for both qnrB and int1 (24).

Antibiotic resistance is an emerging problem in Enterobactericeae, carbapenem resistance is increasing and other antimicrobials like quinolones are drug of choice. But sometimes resistance to more than one group of antimicrobials can be seen. Therefore identifying ways of resistance development and increasing the number of studies related to them and identifying the worldwide spread can help develop treatment strategies will be.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Laparoscopic gastric cancer surgery for 65 age and elderly patients: A single center experience

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Abstract

Therapeutic modalities for elderly gastric cancer (GC) patients have enlarged with extended life expectancy. The aim of this study was to investigate the outcomes of surgical therapies for GC patients of age 65 and older with a single center experience. Eighty-eight patients who underwent laparoscopic surgery for GC were included in the study. The relationships between surgical methods and clinicopathological or prognostic features were analyzed. The median age of the patients was 72 (65-91) years. Sixty patients (75%) were male. The median BMI was 25 kg/m2 (17.5-42). The most common ASA score was 2 (n=58, 72.5%) and tumors were mostly localized in the distal 1/3 of the stomach (n=39, 48.7%). The median CEA and CA19-9 levels were 1.94 ng/ml(0.07-93.8)and 10IU/ml (0.05-449.3), respectively. Eleven patients (13.8%) hadprevious abdominal surgery history. The most common operation type was subtotal gastrectomy (n=33, 41.3%). The median operation time was 300 min (45-720) and the median intraoperative blood loss was 100 ml (0-800). There were eleven conversion (13.8%). The median first time to oral intake was 2 days (1-10) and length of hospital stay was 7 days (1-48). Postoperative serious complications occurred in fourteen (17.5%) patients. The mean of retrieved lymph node was 30.27 ± 17.08. The most common pathological T stage was T4 (53.75%). The mediantime to chemotherapy was 41 days (6-220). Laparoscopic gastric surgery is a safe and feasible method that can be performed in elderly patients with appropriate oncological principles. The risk of surgery is substantially higher in elderly patients. Therefore, maximal attention should be paid to perioperative care for the prevention and treatment of perioperative complications.

Keywords: minimal invasive, elderly patient, geriatric, complication, conversion, mortality

1. Introduction

The proportion of the elderly with malignancy and comorbid diseases in the general population has increased with the increase in life expectancy (1). Approximately 60% of all cancers and 70% of cancer-related deaths occur in individuals over the age of 65 (2). Gastric cancer is one of the most common cancers in the world and surgery is the unique curative option for this problem, but surgery poses a problem for elderly patients (3). Minimally invasive surgical procedures should be considered in the first place for these patients(4).

The use of laparoscopy for gastric cancer surgery in elderly patients is gradually increasing (3). Elderly patients have severe comorbidities and poor functional capacities that do not allow them to withstand serious surgical trauma, unlike non-elderly patients (5). Prolonged operative time, prolonged exposure to anesthesia, the possibility that pneumoperitoneum (due to carbon dioxide) may adversely affect cardiovascular and pulmonary systems are major concerns of laparoscopic gastrectomy for elderly patients (6). It has been reported in many studies that laparoscopic gastric cancer surgery (LGCS) is not a contraindication and can be performed safely in elderly patients (7). In this study, we aimed to present our experiences and results of LGCS in elderly (aged 65 and over) patients.

2. Materials and Methods

This study was approved by the local ethical committee (2021/1395). One-hundred and eighty-five patients underwent LGC between November 2014 and December 2020. The inclusion criteria were the age ≥65 years and had adenocarcinoma pathological results. One-hundred and five patients were excluded due to their age were<65 and had another pathological results except adenocarcinoma. Finally, eighty patients were included in the study. There was no special preoperative nutritional support for malnourished patients. Written informed consent was obtained from patients before surgery. The operations were performed by the senior surgeon or training surgeons under the supervision of the senior surgeon. The details of the surgical procedures have

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been reported in previous studies (8-11).

Appropriate postoperative chemotherapy regimen was decided by medical oncologists. Postoperative complications were defined as any complication that occurred during the hospital stay or in the first 30 days after surgery and were classified as Clavien-Dindo classification (12). Any complication grade 3 or higher was accepted as a serious complication. Age, gender, The American Society of Anesthesiologists classification (ASA), body mass index (BMI), previous abdominal surgery, tumor location, carcinoembryonic antigen (CEA) (normal value between 0-5.5 ng/ml) and carbohydrate antigen 19.9 (CA 19-9) (normal value between 0-35 IU/ml) levels, operative time, intraoperative blood loss, type of gastrectomy, specimen extraction technique, conversion rate, time to oral intake, length of hospital stays, pathological T stage and tumor size, number of retrieved and positive lymph nodes, postoperative complications, reoperation rates, 30-day and 90-day mortality, and time to adjuvant chemotherapy were analyzed.

We used the Shapiro-Wilk test to assess the normality of the distribution of continuous variables. Continuous variables were defined as mean ± standard deviation or median (minimum-maximum) as appropriate. Categorical variables were defined as frequency (percentage). We used the IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, N.Y., USA) for statistical analyses.

Table 1. Preoperative findings and demographic data of the patients

	Study group (n= 80)
Age (year)	72 (65-91)
Gender (male)	60 (75%)
BMI (kg/m^2)	25 (17.5-42)
ASA	
1	3 (3.8%)
2	58 (72.5%)
3	19 (23.8%)
Previous abdominal surgery (yes)	11 (13.8%)
Distal subtotal gastrectomy	1
Gastroenterostomy	1
Laparoscopic gastric wedge resection	1
Cholecystectomy	1
Cholecystectomy and total abdominal hysterectomy	2
Total abdominal hysterectomy	1
Segmenter colectomy	2
Laparoscopic appendectomy	1
Appendectomy	
Location	
Proximal	33 (41.3%)
Middle	4 (5%)
Distal	39 (48.7%)
Linitis plastica	4 (5%)
CEA (ng/ml)	1.94 (0.07-93.8)
Ca 19-9 (IU/ml)	10 (0.05-449.3)

BMI: Body mass index, ASA: The American Society of Anesthesiologists classification, CEA: Carcinoembryonic antigen, Ca 19-9: Carbohydrate antigen 19.9

3. Results

3.1. Patient characteristics

Table 1 shows the preoperative findings and demographic data of the patients. The median age of the patients was 72(65-91) years. Sixty patients (75%) were male. The median BMI was 25kg/m^2 (17.5-42). The most common ASA score was 2 (n=58, 72.5%) and tumors were mostly localized in the distal 1/3 of the stomach (n=39, 48.7%). The median CEA and CA19-9 levels were 1.94 ng/ml (0.07-93.8) and 10 IU/ml (0.05-449.3), respectively. Eleven patients (13.8%) had previous abdominal surgery history.

3.2. Intraoperative outcomes

Intraoperative variables are summarized in Table 2. The most common operation type was subtotal gastrectomy (n=33, 41.3%). The median operation time was 300 min (45-720) and the median intraoperative blood loss was 100 ml (0-800). There were eleven conversion (13.8%). The reasons for conversion were the difficulty to get the tumor-free proximal margin laparoscopically in two patients and locally advanced gastric cancer for three patients. One patient with mesenteric injury and one patient with right iliac artery injury due to trocar access, the difficulty of performing the esophagojejunostomy due to adhesions in one patient, esophagojejunostomy leakage detected intraoperatively in one patient, suspicion of hepatoduodenal ligament invasion in one patient, and deep bradycardia for one patient were the other reasons. The specimen extraction techniques were transvaginal (n=3), transanal (n=1), and transabdominal (trocar site (n=2), suprapubic (n=54), upper midline laparotomy (n=11), upper midline minilaparotomy (n=3)). Since resection was not done, specimen extraction was not performed in six patients.

Table 2. Intraoperative variables.

	Study group (n= 80)
Operation type	
Proximal gastrectomy+esophagogastrostomy	3 (3.8%)
Subtotal gastrectomy+gastroenterostomy	33 (41.3%)
Total gastrectomy+ esophagoenterostomy	26 (32.5%)
Gastroenterostomy	4 (5%)
Peritoneal biopsy	5 (6.3%)
Feeding jejunostomy	1 (1.3%)
Peritoneal biopsy+Feeding jejunostomy	1 (1.3%)
Complementary gastrectomy	2 (2.5%)
Wedge resection	1 (1.3%)
Subtotal gastrectomy+jejunal interposition	3 (3.8%)
Diagnostic laparoscopy	1 (1.3%)
Operative time (min)	300 (45-720)
Intraoperative blood loss (ml)	100 (0-800)
Conversion	11 (13.8%)
Specimen extraction	
Transvaginal	3 (3.7%)
Transanal	1 (1.3%)
Trocar site	2 (2.5%)
Suprapubic	54 (67.5%)
Laparotomy	11 (13.8%)
Minilaparotomy	3 (3.7%)
No resection	6 (7.5%)

3.3. Postoperative outcomes

Postoperative variables are summarized in Table 3. The median

first time to oral intake was 2 days (1-10) and length of hospital stay was 7 days (1-48). Postoperative serious complications occurred in fourteen (17.5%) patients. The patients with leakages (Two with duodenal stump leakage, one with both esophagojejunostomy and enteroenterostomy leakage, one with jejunogastrostomy leakage, one with gastroenterostomy leakage and evisceration), the patient with splenic artery bleeding, and the patient with stenosis in enteroenterostomy anastomosis were managed surgically. One patient with intraabdominal hemorrhage was taken operation again but no focus was detected in relaparotomy. A patient developed fascial dehiscence on the postoperative 9th day and was treated surgically. Mortality was observed in two patients during the hospital stays. One patient with enteroenterostomy leakage and brid ileus died due to sepsis. Another patient underwent repeated laparotomies due to intraabdominal hemorrhage. The bleeding focus could not be detected, multiple organ resections were performed due to intestinal ischemia. All efforts failed, and the patient died. Three patients were treated with interventional procedures (biloma was drained percutaneously in one patient, hydronephrosis was treated with double j catheter in one patient, and bladder injury due to cystofix placement was treated interventionally in one patient). One patient died due to unstable condition with advanced cancer and, one patient died due to with liver failure within postoperative 30-day. The mean of retrieved lymph node was 30.27 ± 17.08. The most common pathological T stage was T4 (53.75%). The median time to chemotherapy was 41 days (6-220).

Table 3. Postoperative variables

	Study group (n= 80)
Time to oral intake (day)	2 (1-10)
Length of hospital stay (day)	7 (1-48)
Postoperative serious complication (Clavien-Dindo classification)	14 (17.5%)
3a	3 (3.8%)
3b	9 (11.3%)
5	1 (1.3%)
Reoperation	10 (12,5%)
30-day-mortality	4 (5%)
90-day-mortality	8 (10%)
Tumor size (cm)	5.5 (0.6-20)
Retrieved lymph nodes	30.27 ± 17.08
Positive lymph nodes	5 (0-59)
T stage	
Tinstu	1 (1.25%)
T1	10 (12.5%)
T2	2 (2.5 %)
T3	24 (30%)
T4	43 (53.75%)
Time to adjuvant chemotherapy (day)	41 (6-220)

4. Discussion

Laparoscopic gastrectomy has advantages such as less intraoperative bleeding, shorter hospital stay, early return of bowel functions, and better cosmetic appearance compared to open gastrectomy (13). It is known that laparoscopic gastrectomy is not a risk factor for postoperative complications (6).However, elderly patients have a higher rate of comorbidities compared to non-elderly patients (14). Previous studies have emphasized that comorbidities are important risk factors for postoperative complications in laparoscopic gastrectomy (4). Also, some studies stated that prolonged operation time and increased blood loss increase surgical stress and postoperative complications and are important risk factors for 30-day mortality (15-16). Huang et al. (14) reported that blood loss of more than 75 cc during laparoscopic gastrectomy was an independent risk factor for major complications. Therefore, more care should be taken in the decision of surgery for elderly patients.

In a meta-analysis, it was stated that the postoperative complication rate in elderly patients who underwent laparoscopic gastrectomy for gastric cancer was higher than in non-elderly patients. In the same study, it was also emphasized that surgical complications were similar, but the main difference was in non-surgical complications (5).In another study, no difference was found in terms of postoperative complications in elderly and non-elderly patients who underwent laparoscopic and open gastrectomy (17). Similarly, Sheng et al. (3) found a similar rate of major complications after laparoscopic total gastrectomy between patients younger than 70 years of age and older. In a study conducted on 2014 patients, the postoperative complication rate was 13.6% after laparoscopic gastrectomy (18). In our study, the rate of postoperative complications was 17.5% and was a little higher than the literature.

In a study investigating the safety of laparoscopic gastrectomy in elderly patients, it was concluded that the postoperative mortality rate, time to oral intake, and length of hospital stay were not affected by age (2). In another study, elderly patients were found to have a shorter operative time, similar intraoperative blood loss, and a longer hospital stay compared to non-elderly patients (5).

Some surgeons are reluctant to perform D2 lymph node dissection because they think it increases morbidity (6). Liang et al. (19) compared D1 and D2 lymph node dissections in patients over 70 years of age and found no significant survival difference. In a systematic review and meta-analysis by Yu Pan et al. (5), it was concluded that fewer lymph nodes were dissected in elderly patients in laparoscopic gastrectomy surgery.Shimada et al. (2) reported that the short-term effects of laparoscopic gastrectomy were the similar in elderly and non-elderly patients. In another study, no difference was found in terms of tumor recurrence, 5-year disease-free survival, and overall survival (3). We have achieved approximately 30 lymph nodes dissection and this was compatible to oncological principles.

The conversion rate in laparoscopic gastrectomy was reported from 0% to 20% in the literature which shows differences according to the patient's condition and surgical experience (20). In the study of Suematsu et al. (4) in which they examined the results of laparoscopic surgery in elderly

gastric cancer patients, the conversion rate (9%) was found to be higher in elderly patients than in non-elderly patients. All patients with conversion had a history of the previous laparotomy. The conversions were due to adhesions in two patients and major bleeding in one patient.We found a conversion rate of 13.8%. The most common cause of conversion was locally advanced gastric cancer.

The limitations of this study were that it was a retrospective, single arm study. No control group was included and the number of patients was limited.

Laparoscopic gastric cancer surgery is a safe and feasible method that can be performed in elderly patients with appropriate oncological principles. It is clear that the operative and postoperative risks are generally higher in elderly patients due to comorbidities. Therefore, maximal attention should be paid to perioperative care for the prevention and treatment of perioperative complications.

Conflict of interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Acknowledgments

This study was approved by the local ethical committee (2021/1395). All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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The role of paraaortic lymphadenectomy along with sentinel mapping in clinically uterine confined intermediate-high risk endometrial cancer

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Abstract

This study aimed to find out whether sentinel algorithm can be sufficient in clinically uterine confined intermediate-high risk endometrial cancer. Detailed pathology characteristics and follow-up records of the 70 intermediate-high risk endometrial cancer patients were identified. Outcomes of patients who are performed sentinel algorithm and sentinel mapping followed by systematic pelvic and paraaortic lymph node dissection were compared. All patients who had obvious extrauterine disease in preoperative and intraoperative evaluation were excluded. Sentinel mapping is performed with methilene blue and cervical injection. 66 patients were identified (sentinel algorithm group, 25; Paraaortic lymph node dissection group, 45). Paraaortic lymph node dissection group had more high grade patients (p=0.02). The mean number of lymph nodes harvested was 11.3 and 36.9, respectively, in sentinel algorithm group and paraaortic lymph node dissection group(p<0.001) and there was more lymph node metastasis in paraaortic lymph node dissection group (12% and 31,7%; p=0.07). 84% in the sentinel algorithm group and 92.7% in the paraaortic lymph node dissection group, respectively, received adjuvant therapy (p=0.02). Overall, four patients recurred within the first three year following surgery, two patients had systematic multiple metastasis and both of them died due to disease. There was no significant difference between the two groups in terms of overall survival (p = 0.252), disease specific survival (p = 0.10) and disease-free survival (p = 0.577). The mean follow-up period was calculated as 29.33 months. To date, there is no prospective study focused on whether sentinel lymphadenectomy in endometrial cancer is sufficient for management of moderate high-risk endometrial cancer and to establish the necessity of paraaortic lymphadenectomy in this patient group. Our study indicates that for clinically uterine confined intermediate-high risk endometrial cancer patients sentinel lymph node algorithm can be sufficient. Further studies are needed to confirm this finding.

Keywords: endometrial cancer, sentinel lymph node, paraaortic lymph node dissection, sentinel algorithm

1. Introduction

Although the role of lymphadenectomy in the management of EC is controversial, the role of paraaortic lymphadenectomy which is more difficult to perform with higher complication rates and requires advanced surgical ability and experience is considered more controversial (1, 2).

In recent years, the role of sentinel lymphadenectomy in gynecological malignancies has been investigated widely and is gradually taking place in the guidelines (3, 4). The main reason for this is the therapeutic effect of lymphadenectomy has not been proven in randomized controlled studies in endometrial cancer. Currently, lymphadenectomy only plays a role in tailoring the accurate adjuvant therapy (2, 5).

Patients with no or less than a half of myometrial invasion and low grade endometrial cancer have negligible risk of lymph node metastasis, however, precise definition of this group of patients is not possible preoperatively (6, 7). In the setting of systematic pelvic and paraaortic lymphadenectomy to all patients with endometrial cancer, a significant number of patients face the potential short and long term morbidities of lymphadenectomy without any survival benefit. In addition, whether this full systematic lymphadenectomy has a survival benefit in patients considered high risk for lymphatic metastasis (i.e., deep myometrial invasion, high grade lesions) is not clear. In a study comparing sentinel lymphadenectomy and systematic lymphadenectomy in the management of endometrial cancer; it was reported that the rate of metastasis detection was higher with sentinel lymphadenectomy and there was no overall survival difference between the two groups (8).

In our study, we evaluated the outcomes of patients with intermediate-high risk endometrial cancer who underwent sentinel algorithm and sentinel lymphadenectomy followed by systematic pelvic and paraaortic lymphadenectomy.

2. Materials and Methods

After approval of the Ethics Committee, the data of 179 endometrial cancer patients operated in Istanbul Prof Dr Cemil Tascioglu City Hospital and Bahcesehir University Hospital between May 2016 and November 2019 were retrospectively analyzed. The cases who had FIGO stage IIIA-IIIB-IV disease, in whom sentinel mapping had not been

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performed and those with myometrial invasion less than ½ and grade 1-2 with no lymphovascular space invasion were excluded. Additionally, the cases who had obvious lymph node metastasis in imaging were excluded. Detailed pathology characteristics and follow-up records of the 66 intermediate-high risk endometrial cancer cases were recorded. Intermediate-high risk defined as: 1) Low grade patients with myometrial invasion <1/2 and no lymphovascular space invasion, 2) High grade patients (grade 3 and non-endometrioid types) with any myometrial invasion, 3) All patients with >1/2 myometrial invasion with any grade (4).

In our clinic, management of all endometrial cancer cases was performed according to the algorithm in Fig. 1. For sentinel lymphatic mapping, 4 cc of methylene blue was injected into the cervix on 3-9 o'clock before the operation. Sentinel node dissection was performed first than followed by systematic pelvic lymphadenectomy with or without paraaortic lymphadenectomy according to the preoperative condition of the patients. All operations were performed by the same surgical team.

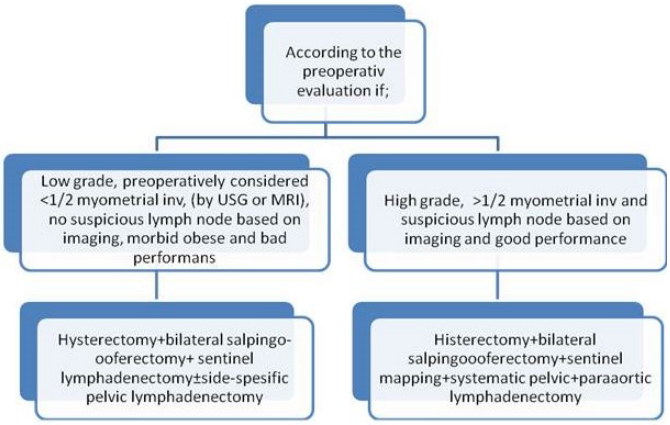

Fig. 1. Management of endometrial cancer in our clinic

All sentinel nodes are assessed by trained gynecologic pathologists. Pathologic ultra-staging includes standard lymph node assessment, which involves sectioning the SLN once along the longitudinal axis and staining it with hematoxylin and eosin to determine if it contains metastatic tumor cells. If tumor cells are identified, the lymph node is considered positive and no additional sectioning or staining is performed. However, if the initial hematoxylin and eosin is negative, further pathologic assessment—which include additional sectioning and staining of the SLN with hematoxylin and eosin and immunohistochemistry (cytokeratin stains AE1:AE3)—is performed to examine the SLN for low-volume metastatic disease. Micrometastasis is defined as a focus of metastatic tumor cells measuring >0.2 mm and ≤2 mm, whereas isolated tumor cells are defined as microscopic clusters and single cells measuring ≤0.2 mm. For the purposes of this analysis, isolated tumor cells, micrometastases, and macrometastasis were all considered node-positive.

Demographic data, pathology findings and follow-up findings were recorded. Staging was adapted according to FIGO 2009 system. Clinical, pathological and surgical features were recorded for all patients. Lymphovascular space invasion has been identified by pathologists as tumor cells on or into the wall of a capillary-like area. The presence of artificial tumor displacement is excluded. The last follow-up date, the recurrence date and the disease follow-up were recorded at the last follow-up visit. Overall survival was defined as the time from the operation dates until the death of the patient for any reason after the operation. Disease free survival was defined as the period from the operation date of the patient to the date when the recurrence was proved with pathology reports.

2.1. Statistics

Survival curves plotted by Kaplan-Meier methods and comparisons were made using log-rank Scale. Cox proportional hazards regression multivariate analysis (after univariate meanings, the relationship between survival of variables). Qualitative parameters were compared by Pearson's or Fisher's exact test. Continuous parameters compared by Student's t-test or Mann-Whitney U test. All statistical tests were two-sided and statistical significance levelis set at 0.05. Data analysis done by Versions for Windows using IBM SPSS Statistics 20.0, Armonk, NY

3. Results

Hystopathologic characteristics of 66 patients who were defined as intermediate-high risk for recurrence are detailed in Table 1. Sentinel node was detected in at least one side in 57 cases (86.4%), and bilateral sentinel nodes were found in 45 cases (68.2%). Lymphatic metastasis was detected in 16 (24.2%) cases, 10 of these cases were isolated tumor cell metastasis (15.1%), 2 of cases were micrometastasis (3%) and 4 were macrometastasis (6%). Seven (10.6%) patients did not receive adjuvant therapy after the operation or received only Intracavitary Radiotherapy, 35 (53%) patients received external beam radiotherapy and Intracavitary Radiotherapy, 24 (36.4%) patients received chemotherapy and radiotherapy combined. The mean follow-up period was calculated as 29.33 months. 41 patient underwent sentinel lymphadenectomy followed by pelvic and paraaortic lymphadenectomy, while 25 patients underwent only pelvic lymphadenectomy according to sentinel algorithm. The clinicopathologic characteristics of the patients between two groups were compared in Table 2. There was no statistically significant difference between two groups for mean age, body mass index, FIGO stage, tumor size, depth of myometrial invasion, lymphovascular space invasion, cervical stromal invasion, the detection rate of sentinel node and follow-up time. However, patient with high grade tumor were higher in paraaortic lymph node dissection group (p=0.02). Additionally, patients in paraaortic lymph node dissection group received more adjuvant therapy (92.7% vs. 84%, p=0.02).

Table 1. Clinicopathologic characteristics of the all cases

Charachteristics	n=66
age (median)	61 (40-87)
Bmi(median)	30.09 (19.53- 50.67)
hystologic type	
Endometrioid	53 (80.3%)
Non-endometrioid	5 (7.6%)
Carcinosarcom	8 (12.1%)
Mean lymph node count	27.2 (17.4%)
Mean pelvic lymph node count	17.3 (±8.2)
Mean paraaortic lymph node count	15.8 (±10.1)
Grade	
1	13 (%20)
2	27 (%41.5)
3	25 (%38.5)
FIGO Stage	
IA	9 (%13.6)
IB	36 (%54.5)
II	5 (%7.6)
IIIC1	11 (%16.7)
IIIC2	5 (%7.6)
myometrial invazion	
<1/2	11 (%16.7)
>1/2	55 (%83.3)
LVSI	
Negative	51 (%77.3)
Positive	15 (%22.7)
Cervical stromal inv	
Negative	59 (%89.4)
Positive	7 (%10.6)
Sentinel mapping	
None	9 (%13.6)
Unilateral	12 (%18.2)
Bilateral	45 (%68.2)
Lymph node metastasis	16 (%24.2)
Isolated Tumor Cell	10 (%15.1)
Micrometastasis	2 (%3)
Macrometastasis	4 (%6)
Isolated paraaortic metastasis (n=45)	2 (%4.4)
Adjuvant Treatment	
none or ICRT	7 (%10.6)
EBRT+ICRT	35 (%53)
RT+Chemotherapy	24 (%36.4)
Follow-up time (Month)	25.35 (5-47)

The average number of lymph nodes removed in the paraaortic lymph node dissection group was significantly higher than that of sentinel algorithm group (36.9 and 11.3 respectively; p = 0.001) and patients in paraaortic lymph node dissection group had more lymphatic metastasis. However the difference was not statistically significant (31.7% vs. 12%, p = 0.07) (Table 3). In patients in whom paraaortic lymph node dissection performed, 12 had pelvic lymph node metastasis. Among 12 patients, 3 (25%) had also paraaortic lymph node metastasis. In addition, 2 (4.9%) cases had isolated paraaortic metastasis.

Overall, four patients recurred within the first three year following surgery, two patients had systematic multiple metastasis and both of them died due to disease. One of the other two patients had a pelvic nodal recurrence and second patient had a vaginal cuff recurrence. Both patients are treated with chemotherapy following secondary surgery.

Table 2. Clinicopathologic characteristics of the both groups

Charachteristics	Pelvic only (n=25)	palnd+pelvic (n=41)	p value
Age (y)	62.08	60.8	0.62
BMI	33.5	30.4	0.06
FIGO Stage			0.15
IA	4 (16%)	5 (12.2%)	
IB	16 (64%)	20 (48.8%)	
II	3 (12%)	2 (4.9%)	
IIIC1	2 (8%)	9 (22%)	
IIIC2	-	5 (12.2%)	
Tumor Grade			**0.02**
1	7 (29.2%)	6 (14.6%)	
2	13 (54.2%)	14 (34,1%)	
3	4 (16.7%)	21 (51.2%)	
Tumor Size(mm)	43.4	44.1	0.87
MyometrialInvazion			
<1/2	4 (16)	7 (17,1)	0.91
>1/2	21 (84)	34 (82.9)	
LVSI			0.30
Neg	21 (%84)	30 (%73.2)	
Poz	4 (%16)	11 (%26.8)	
CervicalStromalInv			0.59
Neg	23 (92%)	36 (87.8)	
Poz	2(8%)	5 (12.2)	
Sentinel Mapping			0.06
None	6 (24)	3 (7.3)	
Unilateral	6 (24)	6 (14.6)	
Bilateral	13 (52)	32 (78)	
AdjuvantTherapy			0.02
None	4 (16)	3 (7.3)	
RT	17 (68)	18 (43.9)	
RT+Chemo	4 (16)	20 (48.8)	
Follow-upTime	26.28	24.68	0.58

Table 3. Nodal assesment paterns of both groups

	Sentinel algorthim (n=25)	pelvic+paraaortic lymphadenectomy (n=41)	p value
Number of pelvic node retrieved	11.3	36.9	**0.001**
Presence of lymph node metastasis			0.07
Neg	22 (88)	28 (68.3)	
Poz	3 (12)	13 (31.7)	
Location of Metastatic Lymph Node			0.17
pln-/paln-	22 (88)	27 (65.9)	
pln+/paln-	3 (12)	9 (22)	
pln+/paln+	0	3 (7.3)	
pln-/paln+	0	2 (4.9)	

In univariate analysis, none of the risk factors was related to recurrence and death. Additionally, paraaortic lymph node dissection was not related to recurrence or death.

Table 4. Univariate analysis of factors associated with overall survival based on all 66 patients

Characteristics	Univariate analysis	
	HR (%95 CI)	P
Age	1.10 (1.01-1.19)	0.801
BMI	0.83 (0.68-1.00)	0.544
FIGO Grade		0.261
1	Reference	
2	0.41 (0.02-6.66)	
3	1.03 (0.1-10.19)	
FIGO Stage		0.64
I	Reference	
II	3,34 (0.34-32.44)	
III	1.09 (0.11-10.62)	
Cerical Stromal Invasion		0.33
no	Reference	
yes	2.04 (0.22-18.33)	
LVSI		0.077
no	Reference	
yes	1.26 (0.13-11.53)	
Presence of Paraaortic lymphadenectomy		0.252
No or Paraaortic LND not performed	Reference	
Yes	0.94 (0.15-5.65)	
Adjuvant therapy		0.649
None or only ICRT	Reference	
EBRT+ICRT		
Chemotherapy+EBRT+ICRT		

In Kaplan Meier analysis, there was no significant difference between the two groups in terms of overall survival (p = 0.252), disease specific survival (p = 0.10) and disease-free survival (p = 0.577) (Fig. 2).

4. Discussion

Lymphadenectomy remains a controversial issue in the surgical management of endometrial cancer. The risk of lymph node involvement in high risk endometrial cancer is between the ranges of 16-37.8 %, (8, 9, and 10). At least 62, 2 % of patients with the high risk uterine factors underwent unnecessary lymphatic dissection. Two randomized controlled studies on this subject report that lymphadenectomy has no therapeutic effect in endometrial cancer. However, the most criticized parts of the studies were that omission of paraaortic lymph node dissection and the low number of removed lymph nodes. On the other hand, sentinel lymphadenectomy has been introduced recently in the management of endometrial cancer in order to detect metastatic lymph nodes with the highest accuracy and to decide the most appropriate adjuvant therapy and it is recommended in NCCN guidelines (3). Although it is thought that lymphadenectomy has no therapeutic effect in the low-risk endometrium cancer group, the role of lymphadenectomy in patients with intermediate-high risk endometrial cancer has not been clarified yet (8).

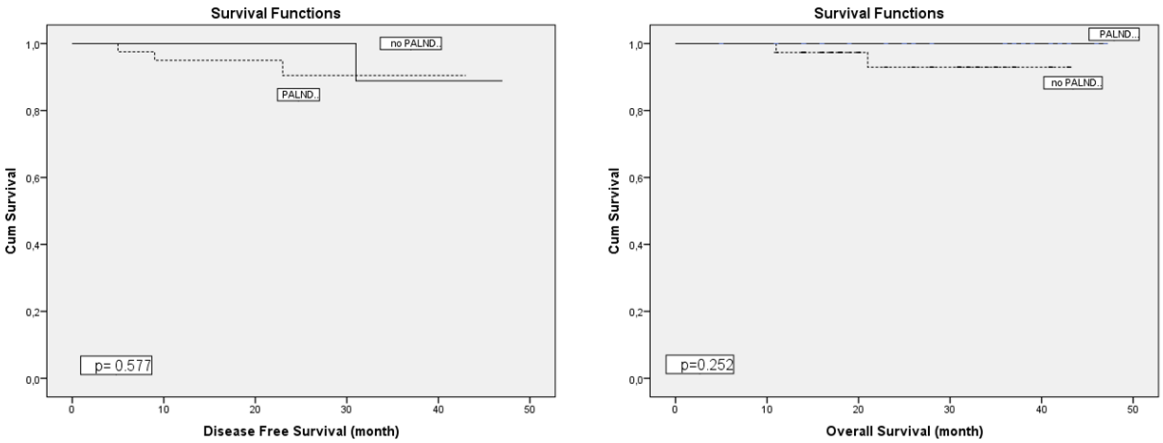

Fig. 2. The comparison of overall survival, disease specific survival and disease free survival between group

Previously published data supports the efficacy and oncologic safety of sentinel lymphadenectomy algorithm in endometrioid endometrial cancer with limited myometrial invasion, but few reports have evaluated its efficacy and safety in the setting of deeply invasive endometrioid histology, (6, and 7).

In the SEPAL study, one of the most comprehensive studies investigating the role of efficacy of paraaortic lymphadenectomy in the management of intermediate-high risk endometrial cancer, it was reported that paraaortic lymphadenectomy had a positive effect on survey, (1). Furthermore, Mariani et al. evaluated patients who had pelvic lymphatic metastasis with or without paraaortic lymph node dissection and revealed that paraaortic lymphadenectomy improved 5-year progression free survival and overall survival suggesting a therapeutic benefit of paraaortic lymph node dissection (11).On the contrary, Schlappea et al.; compared the outcomes of the sentinel algoritm versus systematic pelvic + paraaortic lymph node dissection approaches in the management of high-intermediate risk endometrial cancer and found no difference between the two groups in terms of overall and disease free survival,(8).

The findings in our study indicate that paraaortic lymph node dissection does not contribute to mean overall survival and disease free survival in patients with intermediate-high risk endometrial cancer and clinically uterine confined. We performed systematic lymphadenectomy after sentinel lymphadenectomy and we added paraaortic lymph node dissection in 64.2% of the cases. The number of patients with lymphatic metastasis was 16 (24%) and among these patients

only 4 patients had macrometastasis. We excluded all patients with suspicious node in preoperative imaging and intraoperative evaluation. This low rate of macrometastasis and inefficiency of systematic lymph node dissection may be due to this selection of patients.

The rate of isolated paraaortic lymph node metastasis in endometrial cancer has been reported as 2-5% in the studies conducted in the literature bears the concern that these cases can be skipped with the sentinel algorithm, (9, 12,13). In our study, isolated paraaortic metastasis was detected in 2 (4.9%) cases. Both metastasis were low volume and were in the sentinel nods. In literature there are some studies conducted to resolve this concern by detecting paraaortic sentinel node with fundal injection in addition to cervical injection, (14).

Concern about the sentinel algorithm, 35% of cases having pelvic metastasis have also paraaortic metastasis and these metastatic nodes are missed, (15). In our study, paraaortic metastasis was detected in 25% of cases with pelvic lymphatic metastasis. However, the clinical significance of metastatic paraaortic nodes that are not excised is unknown, when these cases receive adjuvant therapy.

The limitations of our study are that it's retrospective nature and that the group undergoing paraortic lymphadenectomy received statistically significantly more adjuvant therapy. Eighty four percent of the patients in sentinel algorithm group and 92.7% of the patients who underwent systematic lymphadenectomy received adjuvant therapy and 48% of the patients in this latter group received chemotherapy in addition to radiotherapy.

To date, there is no prospective study focused on whether sentinel lymphadenectomy in endometrial cancer is sufficient for management of moderate high-risk endometrium cancer and the necessity of paraaortic lymphadenectomy in this patient group. Our study indicates that for clinically uterine confined intermediate-high risk endometrial cancer patients sentinel lymph node algorithm can be sufficient. Further studies are needed to confirm this finding.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Research Article

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Determination of the healthcare satisfaction of the parents staying in the hospital with their children diagnosed COVID-19 towards family-centered care

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Abstract

To determine the healthcare satisfaction of the parents staying in the hospital with their children diagnosed Covid-19 towards family-centered care and to determine the relationship between them. This was a descriptive, correlational and cross-sectional type study. Data were collected in a pediatric outpatient clinic of a university hospital between March-June 2021. The universe of the study consisted of 141 parents, and the calculated sample size was 59. The study was completed with 64 parents. Data of the study were collected in the light of literature by using Sociodemographic Information Form, The Family-Centered Care Scale and The Pediatric Quality of Life Healthcare Satisfaction Inventory. Data were analyzed by SPSS 21 statistical package program. The ethics approval was taken from the clinical research ethics committee of the relevant university. The mean score of the parents from the Family-Centered Care Scale was 60.58±8.77, the mean PedsQL Healthcare Satisfaction Inventory score of the parents was found to be 71.75±24.21. A positive and moderate level of correlation was found between the Family-Centered Care Scale and PedsQL Healthcare Satisfaction Inventory and their subscales. It was found that nurses helped families and children to feel well cared for; however, they did not get the opinions of the family at a sufficient level while planning care. In the study, the healthcare satisfaction of the parents was at an adequate level. Besides, it was determined that the opinions of parents regarding family-centered care positively affected their satisfaction.

Keywords: Covid-19, family-centered care, healthcare satisfaction, nursing

1. Introduction

Coronavirus disease (COVID-19), that was detected in December 2019, was announced as a pandemic by World Health Organization (WHO). This global epidemic has influenced whole world in a short time (1-3, 4). While the symptoms of Covid-19 infection, which is also seen in children, have been reported as fever and dry cough, the disease was reported to progress to ARDS or multiorgan failure in pediatric cases in a recent study (5). It was also reported that clinical symptoms were more severe among children under six years old compared to older ones and this situation led to the extension of the treatment process and made the process more difficult (6).

Supporting the parents of hospitalized children is an important aspect of nursing care. Supportive care behaviors of the nurses can be accounted as listening and empathy, informing and making explanations, encouraging the family about the child's care and giving trust, confirming, providing attention and value, maintaining integrity, making suggestions, and guiding in solving existing problems (7). Therefore, providing nursing care to the child and his/her family as a whole including physical, emotional, social, and spiritual aspects is the essence of philosophy under family-centered care (8, 9). Besides experiencing intense stress and fear about the health conditions of their children, parents also expect their needs such as taking good care of their children, being in a safe environment, trusting healthcare professionals, and getting informed to be met (9-11).

Opinions of the parents are crucial for the evaluation of the outcomes of healthcare services given to pediatric patients (8, 9, 12,13). Family-centered care has been indicated to affect the efficient use of healthcare services provided, the health conditions of the individuals, and access to care in a positive way (14-16). Moreover, family support is important in the health services given in the field of pediatrics in terms of shortening the hospitalization time which is one of the significant quality indicators and ensuring patient safety (17). In this context, this study was carried out to determine the healthcare satisfaction of the parents staying in the hospital besides their children diagnosed with Covid-19 towards family-centered care and to determine the relationship between them. Answers were sought for the following questions:

- What is the level of attitudes among the parents towards family-centered care?
- What is the level of healthcare satisfaction among the parents?
- Is there a relationship between the attitudes of parents

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towards family-centered care and their healthcare satisfaction?

2. Materials and Methods

2.1. Type of the study

This was a descriptive, correlational and cross-sectional type study.

2.2. The sample and universe of the study

Data were collected in a pediatric outpatient clinic of a university hospital between March-June 2021. The inclusion criteria of the study were hospitalization and discharge of the child from the hospital due to Covid-19 or MIS-C diagnosis and the parent taking care of the child should be literate and open to communication. The universe of the study was composed of parents of the children who were hospitalized due to Covid-19 or Multisystem Inflammatory Syndrome associated with Covid-19 (MIS-C) and came to the outpatient clinic one week after their discharge from the hospital between the indicated dates. The incidence of Covid-19 was determined as 4% among the children in the study by Karacan et al. (2020) in Turkey (18). Considering the incidence of Covid-19 among children, the sample size was calculated. The universe of the study consisted of 141 parents whose children were hospitalized and treated in the pediatric infection service of a university hospital between indicated dates, and the calculated sample size was 59. The study was completed with 64 parents.2.2.1. The Chronic Venous Insufficiency Quality of Life Questionnaire (CIVIQ)

CIVIQ was used to assess quality of life in chronic venous insufficiency which consists of 20 items.It has been established that this disease-specific questionnaire is valid and highly reproducible with great internal coordination and high responsiveness rate. It has also been established that it is a precious tool in both clinical practice and trials for evaluating improvement in patients' HRQoL. It includes subsections fields about pain, physical, physiological and social. The score for each item was in between 1–5 (18).

2.3. Data collection instruments

Data of the study were collected in the light of literature by using Sociodemographic Information Form which was prepared by the researcher, The Family-Centered Care Scale (FCCS) and The Pediatric Quality of Life (PEDSQL) Healthcare Satisfaction Inventory.

Sociodemographic information form

This form was generated by the researchers and composed of 10 questions including sociodemographic characteristics of the children and parents (age and sex of the child, age and sex of the parent, education status, income status, family type), previous hospitalization experience of the child, presence of any chronic disease and hospitalization time.

The family-centered care scale

This scale was developed by Curley et al. (2013) to determine parents' experiences regarding family-centered nursing care and the validity and reliability study of its Turkish version was conducted by Altiparmak and Arslan (2016). The scale is composed of two parts including "importance" and "consistency" and 7 items. The total score of this 5-point Likert-type scale is between 7-35. Parents assess how important the care given by nurses in the important part and how much interest nurses show in the child's care is assessed in the consistency part. The scores of importance and consistency are combined under a single score and this score is expressed as a percentage of the match. A high percentage of matches indicates that nurses take care of parents and good care is given to the child. On the other hand, a low score means that nurses do not take care of the parents adequately and they do not allocate sufficient time for the child's care. Cronbach alpha reliability coefficient of the scale is 0.79 (8). In this study, it was found as 0.91.

The pediatric quality of life (pedsql)

Healthcare Satisfaction Inventory: This inventory was developed by Varni (2000) to determine the healthcare satisfaction of parents and the validity and reliability study of its Turkish version was conducted by Ulus and Kublay (2012). The questions included in the scale measure satisfaction from medical care services and psychosocial satisfaction. The scale includes 6 subscales (information, inclusion of family, communication, technical skills, emotional needs, and overall satisfaction) and 25 items. The questions of this 5-point Likert type scale are graded as "0: never, 1:sometimes, 2:often, 3:almost always, 4: always". The score that can be taken from the scale varies between 0-100. Healthcare satisfaction increases as the scores are increased. Cronbach Alpha coefficient of the scale, which is calculated by Ulus and Kublay (2012), is 0.96 (9). Cronbach Alpha coefficient was determined as 0.97 in this study.

2.4. Data collection

Parents were informed before starting to collect data, and their consent was taken. Data were collected from the individuals who came for control examination one week after discharge through face-to-face interview technique as compliant with pandemic conditions.

2.5. Assessment of data

Data were analyzed by SPSS 21 (Statistical Package for Social Science for Windows) statistical package program. Kolmogorov-Smirnov test was used to test the normality assumption of data. Descriptive statistics and correlation analysis (Pearson correlation analysis) were used to analyze data. The results were analyzed within a confidence interval of 95% and a significance level of $p<0.05$.

2.6. Ethical aspect of the study

An ethics approval was taken from the clinical research ethics committee of the relevant university (OMÜ/KAEK NO:2021/120, application date:03.16.2021) and institutional permission was obtained from the university hospital where the study would be conducted to collect data. Written permissions were taken from the authors to use the scales. Parents were

informed about the purpose of the study, their questions were answered and their verbal consents were taken. The study was carried out in compliance with the principles of the Helsinki Declaration.

3. Results

The mean age of the parents included in the study was 37.14±7.47 years old; 92.2% were females and 87.5% were mothers. It was determined that 28.1% of the parents were elementary/secondary school graduates and 67.2% were unemployed. Moreover, 71.9% of the families had a core family, 37.5% were living in the county and 53.1% had income equal to the expenses.

The mean age of the children was found to be 8.42±5.89 years old, and 51.6% were females. It was also determined that 57.8% of the children had a history of previous hospitalization, 12.5% had a chronic disease, 85.9% were hospitalized due to Covid-19, and hospitalization time was 7.28±2.64 days (Table 1).

Table 1. Descriptive characteristics of the parents and their children (n:64)

X̄±Sd (Min-Max)			
Parental age: 37.14±7.47 (21-59) **Child's age: 8.42±5.89 (1-17)** **Hospitalization time (days): 7.28±2.64 (4-20)**			
		Number (n)	**Percentage (%)**
Sex of the parent	Female	59	92.2
	Male	5	7.8
Parental trait	Mother	56	87.5
	Father	5	7.8
	Other	3	4.7
Education status	Elementary school	18	28.1
	Secondary school	18	28.1
	High school	14	21.9
	University	14	21.9
Employment status of the parent	Unemployed	43	67.2
	Employed	21	32.8
Family type	Core	46	71.9
	Patriarchal	18	28.1
Living place	City	22	34.4
	County	24	37.5
	Village	18	28.1
Income status	Income less than expenses	13	20.3
	Income equal to the expenses	34	53.1
	Income more than expenses	17	26.6
Sex of the child	Female	33	51.6
	Male	31	48.4
Diagnosis of the child	Covid-19	55	85.9
	Covid-19+MIS-C	9	14.1
Child's experience of the previous hospitalization	Yes	37	57.8
	No	27	42.2
Presence of any chronic disease	Yes	8	12.5
	No	56	87.5

Descriptive statistics and matching rates of the scores given to the family-centered care scale were given in Table 2. While item 7 had the highest matching rate (56.3%), item 3 was found to have the lowest matching rate (48.4%) (Table 2).

Table 2. Descriptive statistics and matching rates of the family-centered care scale

Family-Centered Care Scale Items	Importance Level		Consistency Level		Match	
	Min-Max	X̄±Sd	Min-Max	X̄±Sd	n	%
Nurses help me to feel welcomed.	3-5	4.78±0.51	1-5	4.05±0.93	33	51.6
Nurses help me to feel important in my child's care.	3-5	4.88±0.37	1-5	4.05±0.98	32	51.6
Nurses treat me as a valued team member when planning my child's nursing care.	1-5	4.56±0.88	1-5	3.84±1.11	33	48.4
Nurses give explanations about the nursing care they provide.	2-5	4.61±0.80	1-5	3.81±1.12	33	50.0
Nurses explain about changes I could expect in my child's condition.	1-5	4.67±0.81	1-5	3.83±1.14	34	53.1
Nurses help my child to feel well cared for.	2-5	4.78±0.60	1-5	3.94±1.11	34	54.7
Nurses help me to feel well cared for.	2-5	4.80±0.56	1-5	3.98±1.10	35	56.3

The mean score of the parents from the Family-Centered Care Scale (FCCS) was 60.58±8.77, and their mean scores were 33.08±3.49 in importance and 27.50 ±7.03 in the consistency subscales. In the study, the mean PedsQL Healthcare Satisfaction Inventory score of the parents was found to be 71.75±24.21; and their mean scores were 14.40±4.88 in information, 11.20±4.14 in the inclusion of family, 14.15±5.14 in communication, 11.42±4.36 in technical skills, 11.14±4.39 in emotional needs, and 9.42±2.92 in overall satisfaction subscales (Table 3). A positive and moderate level of correlation was found between the Family-Centered Care Scale and PedsQL Healthcare Satisfaction Inventory and their subscales (Table 4).

Table 3. Descriptive statistics of the scores given to the Family-Centered Care Scale and PedsQL Healthcare Satisfaction Inventory

Total Scores of the Scales and subscales	X̄±Sd	Min-Max
Family-Centered Care Scale Matching Rates	60.58±8.77	34-70
Family-Centered Care Importance	33.08±3.49	19-35
Family-Centered Care Consistency	27.50±7.03	7-35
PedsQL Healthcare Satisfaction Inventory Total	71.75±24.21	23-100
Information subscale	14.40±4.88	3-20
Inclusion of family subscale	11.20±4.14	2-16
Communication subscale	14.15±5.14	4-20
Technical skills subscale	11.42±4.36	3-16
Emotional needs subscale	11.14±4.39	2-16
Overall satisfaction subscale	9.42±2.92	1-12

X̄: Mean; Sd: Standard deviation; Min.: Minimum; Max.: Maximum

Table 4. The Correlations Between Family-Centered Care Scale (FCCS) and PedsQL Healthcare Satisfaction Inventory

	r	p
FCCS Total- PedsQL HCSI Total	0.606	0.000
FCCS Total- PedsQL HCSI- Information	0.457	0.000
FCCS Total- PedsQL HCSI- Inclusion of Family	0.535	0.000
FCCS Total- PedsQL HCSI- Communication	0.627	0.000
FCCS Total- PedsQL HCSI- Technical Skills	0.630	0.000
FCCS Total- PedsQL HCSI- Emotional Needs	0.574	0.000
FCCS Total- PedsQL HCSI- Overall Satisfaction	0.591	0.000

r: Pearson correlation test; r=0,00-0,25 very weak, r=0,26-0,49 weak, r=0,50-0,69 moderate, r=0,70-0,89 high, r=0,90-1,00 very high; p<0.001)

4. Discussion

In the study, it was determined that importance and consistency matching rates in the family-centered care scale ranged between 48.4% and 56.3%. It was also seen that the item as 'Nurses help me to feel well cared for' had the highest and the item as 'Nurses treat me as a valued team member when planning my child's nursing care' had the lowest matching rates (Table 2). Among the previous studies, Arabiat et al. (2018) found the highest matching rate in the item as 'Nurses help me to feel well cared for' as similar to this study (19). In the study by Garli and Cinar (2020), it was determined that nurses helped the child and the family to feel well cared for, but they did not explain the changes that might be expected in the child's condition at an adequate level (20). Moreover, Gunay et al. (2017) found that parents mostly had expectations such as having training about the disease of their children, its treatment, the procedures performed, and care at home at the end of discussions made for family-centered care in the pediatric oncology clinic (21). Accordingly, it may be concluded that nurses do not get the opinions of parents at a sufficient level while planning care although care given to the pediatric patients by the nurses are evaluated positively by the parents. This suggests that nurses might not prefer to include parents in the care process due to the strict isolation measures during the pandemic, their excess workload, and the intense stress they experienced during this period.

Healthcare satisfaction levels of the parents were found to be high in the study (Table 3). Similarly, the healthcare satisfaction of the parents was found to be at a high level in some previous studies (9, 22, 23). Uysal and Cirlak (2014) carried out a study with parents of children with an acute health problem and found expectation and satisfaction levels of the families for nursing care at a high level (24). In the study by Ghadery-Sefat et al. (2016), it was found that supportive nursing care given to the mothers in the neonatal intensive care unit positively affected their care satisfaction through mother-infant bonding (25). Parents' satisfaction with the care services provided by nurses during the Covid-19 pandemic points out the effect of family-centered care they provide. Moreover, the importance given to the safety of patients and employees by the hospital management during the pandemic might have been effective.

When the relationship between family-centered care and healthcare satisfaction was examined in the study, a positive and moderate level correlation was found (Table 4). In the performed studies, family-centered care was determined to affect parent satisfaction positively (14-16, 26, 27). In the experimental study by Rostami et al. (2015), family-centered care practice was found to enhance parent satisfaction (28). In a study carried out with mothers of premature infants, positive effects of family-centered care were observed on the mother's satisfaction and readmission of the newborn (16). Furthermore,

the study by Crespo et al. (2016) which was conducted with the parents of children with the oncological disease showed that parents experienced less care burden when they perceived the health service provided as family-centered; and this affected life quality and life satisfaction of the parents more positively (29). This circumstance suggests that family-centered care, which nurses provide to parents in the context of their educative roles (information, inclusion in the care and giving a say, etc.), is effective in meeting the requirements of the parents and thus, parents' satisfaction is positively influenced by the care service they are provided.

The limitations of the study were its conduction in a single university hospital, having access only to the parents who came back for control after discharge from the hospital, and interpretation of the results based on parents' statements.

In conclusion, this study which was carried out to determine the relationship between family-centered care given to Covid-19 positive pediatric patients and healthcare satisfaction of their parents, it was found that nurses helped families and children to feel well cared for; however, they did not get the opinions of the family at a sufficient level while planning care. It was concluded in the study that the healthcare satisfaction of the parents was at an adequate level. Besides, it was determined that the opinions of parents regarding family-centered care positively affected their satisfaction.

Since family-centered care is important under the strict isolation conditions taken during the pandemic, nurses are recommended to maintain continuity of family-centered care services in the hospitals and to give more importance to the inclusion of parents in the care. Also, it is suggested to emphasize the subjects such as providing emotional support, healthy communication, empathy, and stress management during in-service training organized for the nurses in the hospitals to pursue continuity of communication and trust-based cooperation between the nurses and parents. Moreover, it is recommended to evaluate satisfaction levels of nurses and parents at regular intervals for the assessment of healthcare satisfaction and care given and to take measures for this in line with hospital quality standards during this period.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Treatment and outcomes of upper extremity metastases

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Abstract

The incidence of bone metastases increases in direct proportion to the incidence of cancer. Upper extremity metastases are also a serious surgical problem. It is very important to publish experiences on this subject. Treatment results of 80 patients with upper extremity metastases were collected retrospectively. 47 (58.75%) of the patients were male and 33 (41.25%) were female. The most common location for metastasis was the humerus and the most common surgical treatment was intramedullary nailing. Non-surgical treatments were used in 24 (30%) patients. Considering the severity of functional losses and the difficulty of surgical options, it is important to collect and evaluate the treatment approaches of upper extremity metastases.

Keywords: bone metastasis, upper extremity, humerus, intramedullary nailing

1. Introduction

Bone metastases are the third most common site in all metastases (1). Cancer metastasizes in 60-70% of patients (2). 1.2 million new metastasis cases are seen in America every year (3, 4). Although there is no definitive data about our country, it is estimated that there are about 300 thousand metastasis cases. Breast, kidney, lung, prostate, and thyroid metastases are malignancies with a high frequency in the first diagnosis. Clinically, 3-15% of cases have metastasis at first diagnosis (5-7). Therefore, the treatment of metastatic cancer disease is crucial.

Upper extremity metastases are seen less common compared to lower extremities and spine metastasis. Therefore, there are few studies in the literature for the upper extremity metastasis and there is no consensus about the optimal treatment for these conditions.

This article has aimed to evaluate different treatment methods and results in rare upper extremity metastasis sites.

2. Material and Methods

Data of 80 patients with radiologically, histopathologically, and scinthigraphically proven upper extremity metastases treated in our institution between 1999 and 2005 were analyzed. Data were evaluated according to patients, age, gender, primary malignancy, bone localization, operation, operation localization choice, and operations distribution in localizations. Direct radiographic methods were used in the initial admission, follow-up of all patients. In the postoperative follow-ups, our cases were followed up at six weeks, 3-, 5-, 7-, 9-, 11 months respectively, and at 3-month intervals in the following year.

Whole Body Bone Scintigraphy was performed with Sophy Camera DSX rectangular (single-headed) for preoperative diagnosis and staging in all cases. Microsoft Excel 2002 were used in the graphical and statistical analysis of the data.

3. Results

Between September 1999 and December 2005, 80 upper extremity metastases of 80 patients were included in the study. 47 (58.75%) of our patients were male, and 33 (41.25%) were female. The mean age of the cases in the series was 54.8. The distribution of our cases according to the diseases was as in Fig. 1. Lung carcinoma was the most common primary of the cases (19 cases, 23.75%). Breast carcinoma was the second most frequent, with 13 cases (16.25%). The most common location in the upper extremity was the humerus (80% of 80 cases). The diaphysis was the most common site in the humerus (44 cases, 55% in the upper extremity bones, 68.75% in the humerus). 70% of the patients have undergone surgery. 30% of the patients were managed with non-operative

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treatment methods and follow-up and/or radiotherapy. The most common operation was intramedullary nailing in 34 cases (62.97%). Tumor resection prostheses were the second common operation. (13 cases, 24.07%).

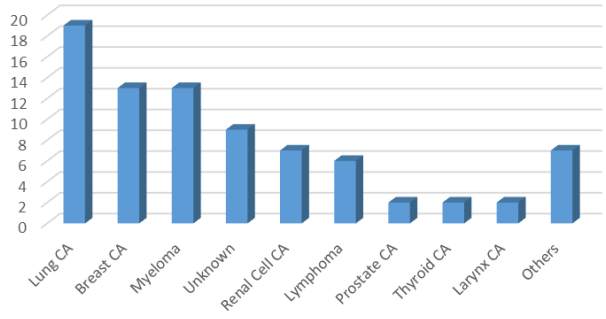

Fig. 1. Distribution of primary malignancy

The distribution of tumors in the clavicle was 2 (40%) lung carcinoma, 2 (40%) multiple myeloma, and 1 (20%) thyroid carcinoma. All metastases in the clavicle were followed up conservatively. Tumors in the scapula were seen as lymphoma in 2 (33.33%), multiple myeloma in 2 (33.33%), endometrial carcinoma in 1 (16.67%), and primary unknown in 1 (16.67%) patient. No operative approach was performed for any of the scapula tumors. 2 (50%) lung carcinomas, 1 (25%) myeloma, and 1 (25%) lymphoma of the metastases seen in the radius were found as primer tumors. The distribution of primary bone tumors in the humeral diaphysis was ranked as breast carcinoma (27.5%), lung carcinoma (20%), and multiple myeloma (17.5%) in the third place (Table 1). Eleven of our patients with involvement of the humeral diaphysis were breast carcinoma (25%). The frequencies are listed as lung carcinoma, multiple myeloma, and renal carcinoma.

Table 1. Distribution of metastases in the humeral diaphysis according to primary malignancies

Primary origin	Cases	%
Lung CA	8	18.2
Myeloma	7	15.9
Breast CA	11	25
Renal Cell CA	5	11.4
Prostate CA	2	4.5
Larynx CA	1	2.3
Lymphoma	2	4.5
Melanoma	1	2.37
Nasopharynx CA	1	2.37
Thyroid CA	1	2.37
Synovial Sarcoma	1	2.37
Unknown	4	9.1

Intramedullary nailing was chosen as the treatment method for 34 (72.27%) of these diaphyseal metastatic patients. Flexible rods in 5 (11.36%), radiotherapy and follow-up in 3 (6.8%) patients, hindquarter amputation in 1 case (2.23%), and total modular tumor resection humerus endoprosthesis in 1 case (2.23%) (Fig. 2. & 3.). The mean age of the cases proximal to the humerus was 58.25 years. Of 16 patients, 12 male and 6 female, 4 lung carcinoma, 4 primary site could not be found, 2 patients had breast carcinoma. others were cervical carcinoma, clear cell carcinoma, larynx carcinoma, lymphoma, multiple myeloma, and esophageal carcinoma. Modular tumor resection shoulder endoprosthesis was applied to 12 of them. 4 of them underwent radiotherapy and were kept under follow-up. Of the four male cases with a mean age of 65.25 years in the distal humerus, two had lung carcinoma and two had renal carcinoma. An above-elbow amputation was performed on one lung carcinoma patient. Elbow resection prosthesis was applied to one patient with renal carcinoma. 2 patients received radiotherapy and were only followed up.

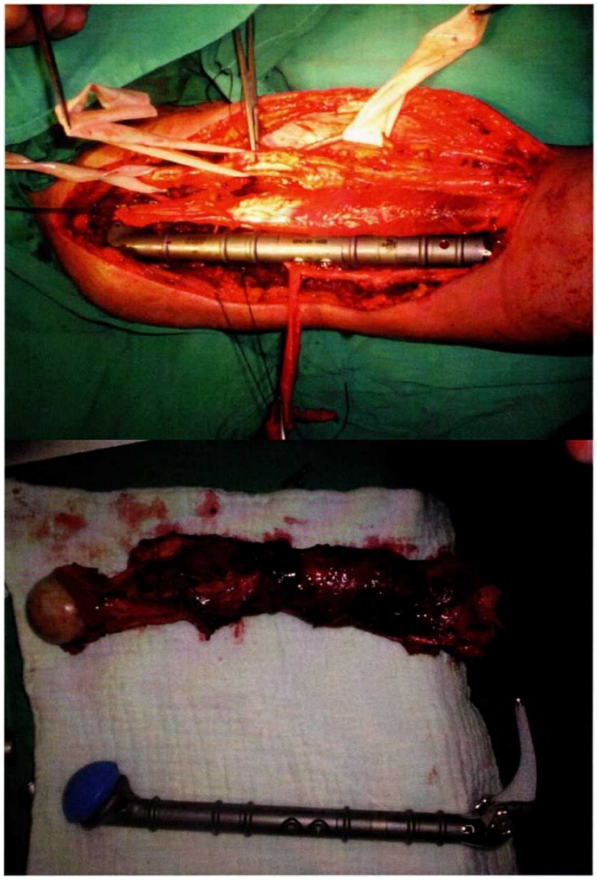

Fig. 2. Total humerus replacement

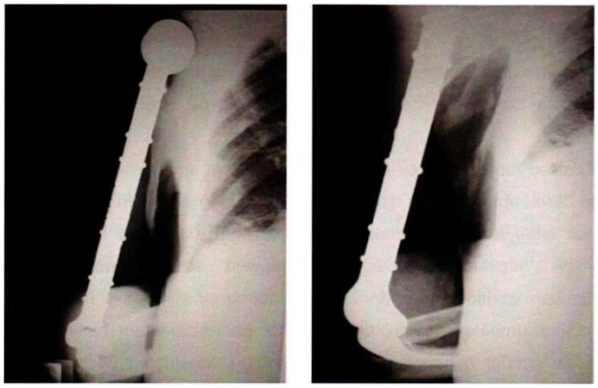

Fig. 3. Total humerus replacement (radiogram)

In terms of treatment methods, one of the two amputated cases was lung carcinoma and lymphoma. They were both male and their mean age was 67.5. The patient with lymphoma

had received radiotherapy before amputation.

The patient who underwent modular tumor resection elbow endoprosthesis was a 68-year-old male patient with renal carcinoma at a 7-year follow-up. Flexible rod and PMMA were applied 14 months before our operation. Modular resection elbow endoprosthesis was applied to the patient due to implant failure and implant migration to the elbow joint. The patient survived for 19 months without pain and with limited elbow movements.

The mean age of 12 patients who underwent shoulder endoprosthesis application was 55.5, and 8 were male and 4 were female. Of these patients, 4 (33.33%) were lung carcinoma, 2 (16.67%) breast carcinoma, and 2 (16.67%) were primary unknown. Others were clear cell carcinoma, carcinoma of the larynx, carcinoma of the cervix, and esophagus.

Of 5 patients (2 females, 3 males), a flexible rod (with Rush pin) was applied, all in the humeral diaphysis, 2 had breast carcinoma, 1 had larynx carcinoma, and 1 had renal carcinoma. No complications were encountered in our patients who remained in our follow-up period.

Lesions of all 34 patients who underwent intramedullary nailing were in the humeral diaphysis. The mean age of the patients was 57.85, and they had a distribution of 18 females and 16 males. Their distribution for the primer was as in Table 2.

Table 2. Distribution of primary malignancies of intramedullary nailing surgery cases

Primary	IMN cases	%
Breast CA	9	26
Lung CA	7	21
Multiple Myeloma	5	15
Renal Cell CA	3	9
Prostate CA	2	6
Nasophx CA	1	3
Malign Melanoma	1	3
Lymphoma	1	3
Synovial Sarcoma	1	3
Thyroid CA	1	3
Unknown	3	9

Only 2 (2.5%) patients were followed up without radiotherapy. Twenty-two (27.5%) of the patients were followed up after radiotherapy application. The mean age of these patients was 63.46 years, and they constituted a series of 24 cases consisting of 16 women and 8 men. The most common was multiple myeloma with 7 (29.17%). Lung carcinoma was the second with 6 (25%) cases. In order of frequency, 4 (16.67%) lymphomas, 4 (16.67%) were of unknown origin, 1 (4.12%) were renal carcinoma, endometrial carcinoma, and thyroid carcinoma. The bone distribution of this series was as in Table 3.

Table 3. Distribution of localizations of non-surgical cases

Bone	Number of cases	%
Clavicula	5	21
Humerus Diaphysis	4	17
Humerus Distalis	2	8
Humerus Proksimalis	4	17
Radius	3	13
Scapula	5	21
Ulna	1	4

4. Discussion

Despite surgical techniques and technological advances, metastatic bone tumors still represent great challenges for orthopedic oncologists (8). Upper and lower extremity bone metastases show serious differences in terms of tumor biology and functional expectations. In his study, Fidler showed no difference between the upper and lower extremities in terms of impending fracture.

We have limited information about fracture risk in metastases of the upper extremity since studies mainly focus on the lower extremity and peritrochanteric fractures. Mirels achieved important results in a scoring study to predict fracture risk in the light of these findings (2, 9). We did not use this scoring system in our series, but when the literature is reviewed, it is seen that this scoring has obvious advantages and is recommended.

There are several differences between upper extremity pathological fractures and lower extremity fractures. There are adhesion places of important soft tissue structures in the proximal humerus for shoulder functions, especially the rotator cuff. Therefore, the expected functional results in involvement close to the shoulder are quite limited. The intramedullary canal of the humerus is quite narrow, especially in women. This is one of the technical difficulties (5, 10). Intramedullary application in our series was preferred in diaphyseal involvement. It constituted an important group with a rate of 72.27%, and since breast carcinoma is the most common, this medullary canal stenosis was also observed by us. With adequate preoperative planning and examination of intact upper extremity radiographs, this problem has been eliminated. Breast, lung, and renal cell carcinoma often metastasize to the upper extremity, and myeloma and lymphoma can also metastasize. Of the patients in our study, 23.75% had lung carcinoma and 16.25% had breast carcinoma. Male patient dominance was 1/1.42.

The life of the cancer patient is limited. Fracture risk should be carefully evaluated in plain radiographs. Rigid fixation or arthroplasty should be chosen. Surgery should have minimal morbidity. These should be taken into account and planning should be done carefully. It is generally accepted that if the survival of more than 6 months is expected, surgery can be planned for metastases. After the detection of metastasis in breast cancer and lymphoma, the average survival rate is 28 months, in prostate and renal cancers it is 20 months, and in lung cancer, it is 6 months. However, the mean survival after

surgery for humeral metastases was found to be 8-10 months. Our series found the survival rates to be 26 months in breast carcinoma, 29 months in myeloma, and 9 months in lung carcinoma. While the best bone healing is expected in myeloma and renal cell carcinoma, bone healing cannot be seen in lung carcinomas. Regardless of the fixation technique in pathological fractures, bone healing is expected around 6 months.

Better results were obtained in cases with arthroplasty surgery compared to osteosynthesis. Better results were obtained with nailing in the diaphysis of long bones. Cementing can be added to procedures to increase the stability (11).

However, in our clinical observations, it should not be the first choice for being a major surgical procedure and yield approximately the same results as endoprosthesis and intramedullary nailing in terms of stability. Küntscher, Gama and Russell-Taylor nails can be used for this purpose (8).

Endoprostheses were used more frequently, especially in the lower extremities, and good results were obtained. Modular tumor prostheses became available in the late 1980s. For metastases, the combination of plate and rod with PMMA was the most common method. Endoprostheses may be the first choice in the failure of these reconstructions and extensive bone loss (12, 13).

Surgery is not the only option in the treatment of upper extremity metastases. Considering that the majority of those who underwent surgery were fractured or at risk of fracture. We did not perform surgery on all clavicle and scapula metastases, and we provided them with a painless extremity only with follow-up and radiotherapy. Radiotherapy was applied as 3000 cGy in ten sessions. In the literature, it was observed that 90% of the patients had a significant reduction in pain, and 50% of the patients were completely relieved of the pain. However, the results of radiotherapy in our study are not within the scope of the study (5).

The humerus was the only bone to be operated on and the approach varied according to the localization in the humerus. Curettage and PMMA can be used in the treatment of small and painful lesions, even without fixation.

However, none of the proximal humerus lesions among our patients were small enough to allow this. We decided to operate in 75% of these cases and applied tumor resection endoprosthesis in all of them. We observed a satisfactory functional and almost complete recovery in terms of pain.

In terms of pain, 58.82% of 34 intramedullary applications consisting of humeral diaphysis cases were completely healed and 29.41% were healed almost completely. Functionally, the shoulder joint range of motions were comfortable enough to allow daily activities. Although adequate results were published with flexible rods, especially in the 1980s, they are recommended with an undisputed superiority in the current approach, especially when cementing is added to intramedullary nailing.

Intramedullary nailing is the gold standard if Mirels scoring is used primarily for diaphyseal involvement.

Due to the low number of distal humerus cases (4 cases), we did not have the chance to try the recommended treatment protocols in sufficient numbers. We do not have enough data to contribute to the scientific discussion, with one case going to amputation due to severe soft tissue involvement and vascular nerve invasions. The other two cases were followed up with radiotherapy and tumor resection elbow prosthesis is applied only in one case. Osteosynthesis, PMMA application, and retrograde flexible rods are recommended for this region in the literature. Tumor resection elbow prosthesis is another recommended alternative in advanced cases.

Function after resection in humeral metastases remains a critical problem. Early range of motion exercises to be given after the treatment allow us to reach the maximum limits that can be reached in shoulder and elbow endoprosthesis (14).

The metastatic problems in the upper extremity region in orthopedic surgery are a very problematic issue regarding treatment outcome expectations and patient satisfaction.

However, when the upper extremity is examined alone, it is clear that significant gains can be achieved in cases that have not progressed compared to the lower extremities and that the pathological involvement does not tend to progress, as long as the results are better, especially if the functional expectations are not high.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Research Article

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Neuroprotective effect of carvacrol in an experimental cerebral ischemia and reperfusion rat model

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Abstract

The Neuroprotective effect of carvacrol, which has anti-inflammatory and antioxidant effects, on infarcted cerebral tissue is present in literature, but this contribution was not sufficiently clarified in terms of biochemistry. It is aimed to investigate the effect of orally administered carvacrol on plasma and intraparenchymal levels of TBARS, GSH, SOD, CAT, GSH-Px, IL-1β, IL-4, and TNF-α after the formation of global ischemia in cerebral tissue. Four groups were formed, each containing ten Wistar albino rats. After anesthesia and analgesia, bilateral carotid communis arteries of rats in the first two groups were clamped for 15 minutes with aneurysm clips. Oral 50 mg/kg/day carvacrol was administered for 15 days to the first group (I/R+CRV) of these two groups in which cerebral ischemia-reperfusion (I/R) was established. On the other hand, %0,01 carboxymethylcellulose (CMC), which is a solvent of carvacrol, at a same volume of first group was administered orally for the same duration to the other group in which also I/R was established (I/R+CMC). In the other two groups in which ischemia was not induced, only carotid artery dissections were made and sutured again. In these two groups, 50 mg/kg/day of carvacrol was administered to the first group (CRV). The Same dose of CMC was administered to the second group (control group). After all these treatments, plasma was collected, and brain tissue was dissected from all groups at the end of the 15th day. Carvacrol can be included in the possible treatment regimen of cerebral stroke with the help of other studies that can be supported on this topic.

Keywords: ischemia reperfusion, carvacrol, CMC, CAT, GSH-Px, GSH, IL-1β, IL-4, SOD, TBARS, TNF-α.

1. Introduction

Cerebrovascular accident (CVA) is a disease that is characterized by temporary or permanent occlusion of any of the vessels feeding the cerebral tissue or the disruption of the blood supply to the brain tissue due to extravasation of blood, which can cause serious neurological findings. The incidence of this pathology, which can cause mortality and morbidity, is expected to increase because of an elevated number of elderly populations in the future. Despite the increased diversity of treatment modalities and medical treatments, ideal treatment is still not present and a sufficient level of knowledge and experience has not been developed from the studies carried out (1, 2).

In recent years, the use of plant-derived drugs, which have attracted attention due to their antitumor and antioxidant effects, are becoming widespread in most diseases (2). Of these, carvacrol (CRV), which is obtained from thyme extract, is a popular research topic and there are studies in the literature showing that it may have a significant benefit in many diseases (3, 4). Phenolic compounds, present in the structure of CRV, are responsible from the antioxidant activity and they are strong neutralizing molecules against metabolites of oxidative stress (5, 6). Biochemical analysis in studies that were conducted to show the neuroprotective effect of CRV, which can be a glimmer of hope for CVA treatment, is not comprehensive enough. Our aim in this research is to investigate the effect of CRV, a powerful antioxidant, on an experimental I/R rat model.

2. Material and Methods

This study was planned in accordance with the Guide for the Care and Use of Laboratory Animals. This study was investigated by Malatya İnonu University Experimental Animals Ethics Committee and Ethics committee approval was obtained on 03.06.2016 with the decision number 2016/A-79. Wistar–albino rats were obtained from the University's Experimental Animal Production and Research Centre. Experimental procedure was conducted at the laboratory of the same center. A total number of 40 male Wistar Albino rats weighing approximately between 250-300 g were used in this

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study. Rats were randomly divided into 4 groups. Groups are as follows,

1st Group: Control group (n=10). In this group cerebral ischemia will not be induced, only 50/mg/kg/day carboxymethylcellulose (CMC), which is the solvent, will be administered for 15 days. 2nd Group: Ischemia-reperfusion (I/R) group (n=10). In this group, cerebral ischemia will be induced and only CMC will be administered for 15 days at a dose of 50mg/kg/day. Cerebral ischemia was induced in this group and only CMC was administered at a dose of 50mg/kg/day for 15 days. 3rd Group: I/R + CRV group (n=10). In this group, cerebral ischemia will be induced, and 50 mg/kg/day CRV was administered for 15 days. 4th Group: CRV group (n=10). 50 mg/kg/day CRV was administered for 15 days without inducing cerebral ischemia.

CMC, which was used as a solvent of CRV, was administered via gavage for 15 days to rats in control group (1st group). An ischemia model was created, as previously practiced in the literature (2), in rats in the I/R group (group 2). The muscle, ligament, and adventitia tissue around both common carotid arteries (CCA) were carefully stripped with the microsurgery method for ischemia induced groups (Fig. 1). Before starting drug therapies, the rats in the ischemia groups were exposed to ischemia for 15 minutes by clamping the bilateral common carotid arteries with Sugita® clips. Then reperfusion was applied for 24 hours. After 24 hours, same dose of CMC was given for the same duration (2). In the third group (I/R+CRV), CRV was administered via gavage for 15 days starting one day after I/R with a dose of 50 mg/kg/day. Finally in the 4th group (CRV); CRV dissolved in CMC at the same dose was administered via gavage for 15 days.

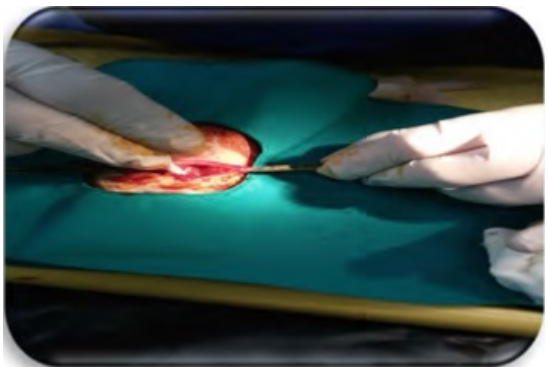

Fig. 1. Dissection of rat carotid arter

At the end of 15 days, brain tissue resection was performed under appropriate anesthesia (ketamine (60 mg/day) + xylazine (10 mg/kg)) and 4-6 cc of blood was collected from the left cardiac ventricle. After collection of blood, a craniectomy was performed to completely remove all components of the neuronal tissue, including the cerebrum, cerebellum, and brain stem. The collected tissue samples at the end of scarification were stored at -80°C until examination of TBARS levels and SOD, CAT, GSH-Pc, GSH and protein measurements. Tissue sampling and homogenate preparation were performed as stated in the literature (2). Cytokine levels in plasma were determined by the ELISA method using commercial kits in accordance with the procedures included in the kits. For TNF-a (cat#EK0526) and IL-1β (cat#EK0393), Boster® brand commercial kit was used and for IL-4 (lot#20161209) Relassay diagnostics® commercial kit was used. Results were read on a 450 nm microplate (CIOM Medical Co. Ltd, Changchun, China) reader.

2.1. Statistical Analysis

While evaluating the findings obtained in the study, SPSS (Statistical Package for Social Sciences) for Windows 11.5 program was used for statistical analysis. Study data were presented as mean±standard deviation and descriptive statistics were used. A Chi-square test was used to compare qualitative data. Kruskal Wallis test was used to compare the groups. Mann-Whitney U test was used for pairwise group comparisons for the parameters with a significant difference. A p-value of <0.05 was considered statistically significant.

3. Results

The values of TBARS, SOD, CAT, GSH, and GSH-Px levels taken from the brain tissue sample are given in Table 1. As a result of the evaluation, TBARS level, which is an indicator of oxidative damage, increased statistically significantly in I/R-induced rat brain tissue (IR group) compared to the control and all other groups. At the same time, it has been determined that CRV administration statistically significantly reduces the increase in TBARS caused by I/R and the level of TBARS in I/R+CRV group approached the values of the control group.

It was observed that no statistically significant changes are present between the group to which only CRV was administered and the control group. However, it was observed that I/R+CRV administration causes a statistically significant decrease in the levels of GSH, SOD, GSH-Px, and CAT, which are antioxidant defense system elements compare to the I/R+CMC group. However, it was observed that administration of CRV eliminated the changes in GSH, GSH-Px, CAT, and SOD levels due to I/R and a statistical difference was present when compared with I/R group. As shown in Table 2 and 3 of this experimental study in rats, the levels of TNF-α and IL-1β, which are proinflammatory parameters and important mediators of acute inflammation, in the blood and brain tissue supernatant were statistically significantly lower in I/R and I/R + CRV groups when compared with control and CRV groups. However, it has been determined that there was a significant difference between the I/R and I/R + CRV groups. In conclusion, it has been determined that the increase in both cytokine levels due to ischemia was partially eliminated by CRV as seen in figure 2, 3, 4, and 5. On the other hand, the level of IL-4, an anti-inflammatory cytokine, was significantly decreased in I/R group both in serum and brain supernatant, and this decrease was significantly improved with CRV treatment as shown in figure 6 and 7.

Table 1. The level of TBARS, GSH, CAT, SOD and GSH-Px in ischemia-induced (I/R) and CRV administered (with therapeutic purpose) rats (mean±SD n=10)

	TBARS nmol/gr	GSH µmol/gr	SOD U/mg	CAT µmol/gr	GSH-Px µmol/gr
Control	14.28±1.27[a]	255.8±28.1[a]	14.97±1.56[a]	0.014±0.0002[a]	231.4±21.1[a]
CRV	13.37±1.16[a]	280.1±32.5[a]	15.31±1.70[a]	0.013±0.0004[a]	225.9±19.2[a]
I/R	19.10±2.03[b]	163.9±24.6[b]	9.57±0.95[b]	0.006±0.0003[b]	152.1±14.2[b]
I/R+CRV	15.19±2.91[a]	215.7±28.9[c]	12.98±1.25[c]	0.010±0.0005[c]	198.7±18.7[c]

The letters a, b and c in the same column indicate the statistical difference (p≤0.05) between the groups.

Table 2. IL-1β, TNF- α and IL-4 levels in rat serum

Serum	IL-1β pg/ml	TNF- α pg/ml	IL-4 ng/L
Control	360.9±50.6[c]	81.5±10.4[c]	43.75±1.01[c]
I/R	693.2±25.2[a]	167.8±23.2[a]	27.43±2.97[a]
CRV	391.5±46.6[c]	80.3±7.48[c]	43.18±1.14[bc]
I/R+CRV	482.9±60.2[b]	109.0±13.7[b]	40.65±2.76[b]

The letters a, b and c in the same column indicate the statistical difference (p≤0.05) between the groups

Table 3. IL-1β, TNF-α and IL-4 levels in rat brain supernatant

Serum	IL-1β pg/ml	TNF- α pg/ml	IL-4 ng/L
Control	44.4±5.08[d]	45.33±9.92[c]	19.98±1.85[c]
I/R	94.4±9.77[a]	102.4±7.35[a]	11.17±0.74[a]
CRV	35.0±7.73[c]	50.75±11.6[c]	21.86±2.56[c]
I/R+ CRV	63.9±4.56[b]	86.16±9.27[b]	15.61±1.70[b]

The letters a, b and c in the same column indicate the statistical difference (p≤0.05) between the groups

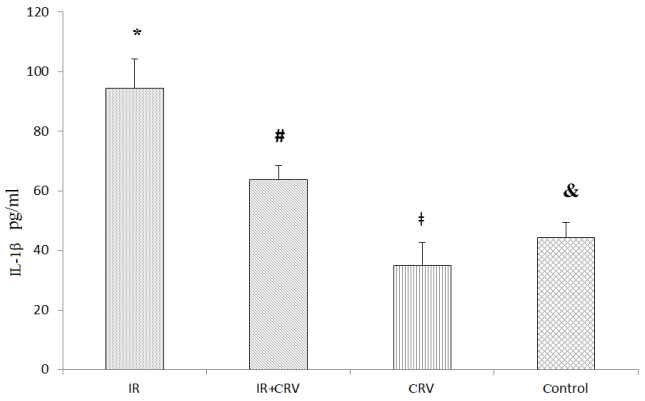

Fig. 2. Rat serum IL-1β levels (pg/ml±SD); * # ǂ and & show the difference between groups (p<0.05)

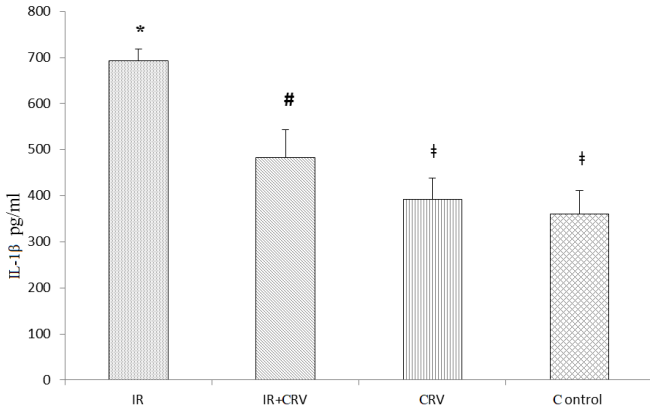

Fig. 3. Rat brain IL-1β levels (pg/ml ±SD); * # ǂ and & show the difference between groups (p<0.05)

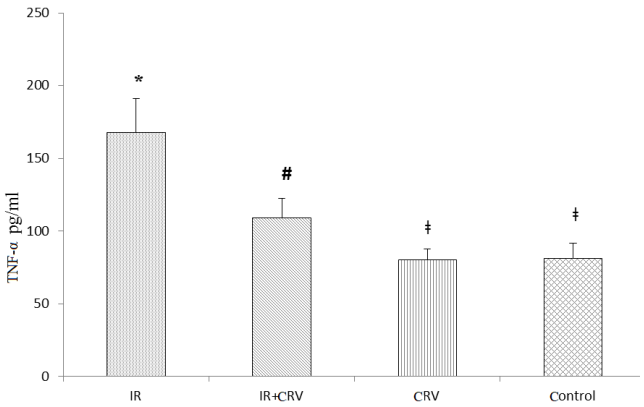

Fig. 4. Rat brain TNF-α levels (pg/ml ±SD); * # ǂ and & show the difference between groups (p<0.05)

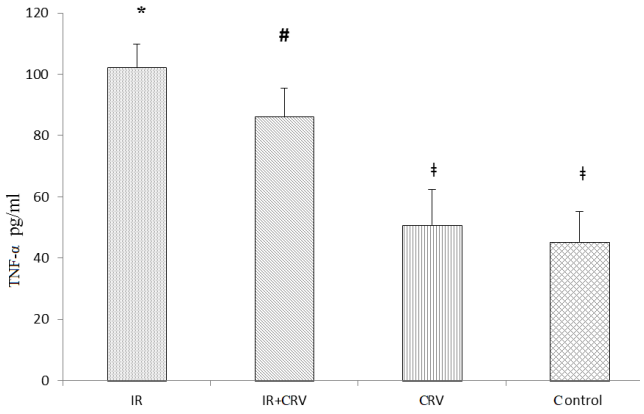

Fig. 5. Rat serum TNF-α levels (pg/ml ±SD); * # ǂ and & show the difference between groups (p<0.05)

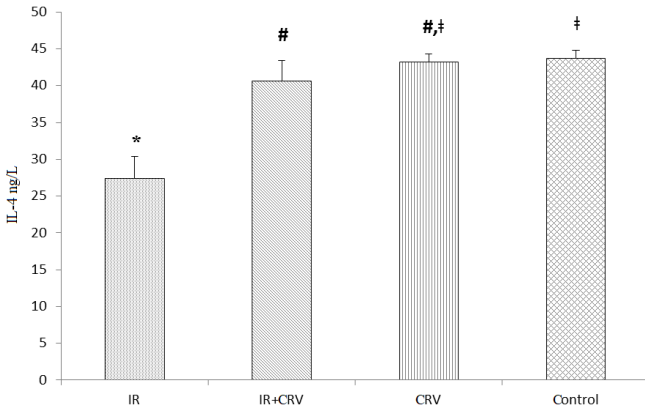

Fig. 6. Rat brain IL-4 levels (ng/L ±SD); * # ǂ and & show the difference between groups (p<0.05)

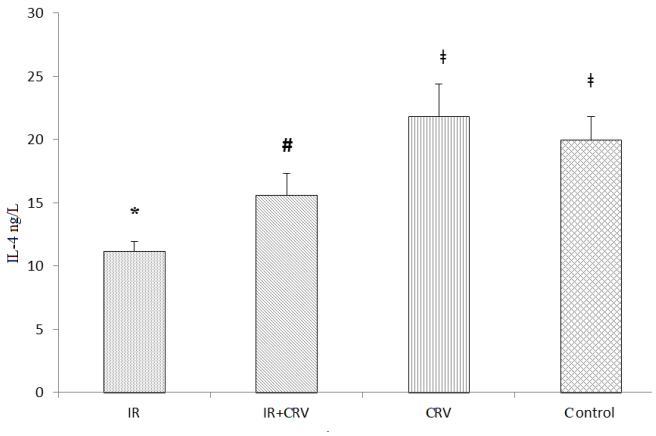

Fig. 7. Rat serum IL-4 levels (ng/L ±SD); * # ǂ and & show the difference between groups ($p<0.05$)

4. Discussion

I/R injury is one of the types of injuries that occurs in cerebral stroke. The most important mechanism for I/R injury is an accumulation of oxygen free radicals (OFR) and subsequent cell damage (2, 6). OFR have a feature that can disrupt the integrity of cell membrane by forming lipid peroxidation. The injury of the parenchyma might increase because of the increased release of OFR from leukocytes that migrate to the area during re-oxygenation. Leukocytes have an affinity to accumulate at reperfused tissues during I/R. Cell damage further increases with the presence and involvement of cytokines which were released afterwards. In order to prevent this, the main goal is to prevent the destructive effect of OFR in cerebral I/R injury (7, 8).

Experimental and clinical studies are present about reducing OFR in I/R injury (9, 10, 11). Antioxidants (vitamin E, ascorbic acid, glutathione etc.) and various enzymes (catalase, superoxide dismutase, glutathione peroxidase etc.) were tested in these studies (10, 11, 12). The results of the drugs, which stand out with their antioxidant properties, are promising especially in experimental studies. A drug with high therapeutic potential in this regard is CRV. Although there are various studies in the literature about the effect of CRV on the neural injury model (3, 4), we detect that this issue is not sufficiently analyzed. In our study, we aimed to demonstrate the effect of CRV on cerebral I/R injury, especially with biochemical analysis. Suo et al., showed in their experimental study that, CRV decreases I/R injury in liver tissue by regulating thePI3K-Akt pathway. As a result of that study, it has been reported that CRV significantly reduces ALT and AST serum levels, histological changes, and apoptosis of liver cells in rats after liver I/R. In addition to that, it has been stated that it protects against tissue damage due to I/R, significantly reduces SOD activity and increase MDA content. Also, CRV displays an antioxidant activity by restoring the CAT activity and GSH content (13). There are also other studies that demonstrate the anti-oxidative feature of CRV at the molecular level. There are several studies that showed that CRV decreases the expression of Bax and increases the expression of Bcl-2 (11, 14, 15). When our results were compared with the literature, it can be seen that similar results were obtained in terms of antioxidant parameters and CRV causes an improvement of ischemic parameters in I/R.

Wanget al., showed that CRV prevents ethanol-induced hippocampal neuron damage. They reported that the level of SOD, GSH, GSH-PX, and CAT were significantly changed with 50 and 100 mg/kg CRV treatment in rats exposed to ethanol. In addition to that, it was seen in the same study that the level of MDA, which is an important indicator of lipid peroxidation, was repressed (3). Our results about the activities of SOD, GSH, GSH-PX, and CAT enzymes between I/R and I/R + CRV groups were similar to the study of Wanget al.

Yuet al., also investigated the effect of CRV after I/R like our study. They reported that 50mg/kg CRV treatment given after 75 minutes of ischemia and 24 hours of reperfusion injury significantly reduced the infarct volume and improved neurological deficits. They showed that the neuroprotective characteristic of CRV is also dose-dependent (16). In our study, a similar experiment was conducted on I/R induced rats. It has been observed that CRV provides a decrease in mediators that can increase ischemia through oxidative damage, and an increase in protective enzymes. Both studies are similar in this manner, and the efficacy of CRV, which is a protective agent against ischemic injury, was reinforced both in our study and in this study.

Another study on the neuroprotective properties of CRV was conducted with a trauma model. It has been shown in mice given CRV after traumatic brain injury that brain injury was significantly recovered, and a marked improvement was observed (17). Additionally, it has been shown in the literature that the addition of TRPC1 elimination to CRV treatment causes a significant improvement (18). Jiang et al., also emphasized that CRV has a neuroprotective and therapeutic feature in traumatic spinal cord injury (14). Guan at al. reported that CRV protects hippocampal neurons against I/R in rats by inhibiting ferroptosis by increasing the glutathione peroxidase 4 expression (19). Also, CRV reduces neuronal damage after Cerebral I/R via attenuation of transient receptor potential melastatin (20). All these studies in the literature support the data in our study and show that CRV may be a potential treatment for cerebral I/R injury.

Our study showed that CRV significantly prevents I/R damage due to its antioxidant and anti-inflammatory properties. CRV is a promising molecule not only for I/R but also for many neurological diseases, and this effect should be demonstrated with similar studies.

Conflict of interest

The author(s) confirm that this article content has no conflicts of interest.

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Appendiceal stump closure with hem-o-lok clips in laparoscopic appendectomy

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Abstract

Various appendiceal stump closure techniques are used in laparoscopic appendectomy (LA). The purpose of this study was to investigate the safety and usefulness of the Hemolok clip for the closure of appendicular stumps in LA. From January 2015 to October 2018, a total of 87 consecutive patients underwent LA by three surgeons with planned use of Hemolok clips. In 9 (10.3%) patients, hemolok clips could not be used for the closure of the stump. The remaining 78 patients were included for analysis. The demographics, operation time, hospitalization time and complications were recorded. Of these 78 patients, 39 (50%) were male and 39 (50%) were female. The mean age was 28.55 ± 10.61 (18-73) years and median operation time was 51.3 (30-160) minutes. Twenty-two (28.2%) of the patients had complicated appendicitis (perforated, necrotic). The median time until oral diet allowance was 10.48 (4-36) hours after surgery and median hospitalization time was 22.92 (6-72) hours. Postoperative complications were seen in 4 (5.1%) patients; two had abdominal pain, one had abdominal distention and one had trocar site infection. None of the complications were associated with the use of hemolok clips. None of the patients required reoperation. The appendiceal diameter was found to be greater in patients without hemolok closure compared to patients with hemolok closure ($p = 0.003$). The closure of the appendix stump with hemolok in LA is an appropriate, safe, fast and cost-effective technique. It is important to note that the appendix stump should not be extremely edematous or necrotic in order to be able to apply hemolok clips. Ideally, the stump should have a diameter smaller than 1 cm.

Keywords: acute appendicitis, laparoscopic appendectomy, appendiceal stump, hem-o-lok clip

1. Introduction

The most common acute abdominal pathology requiring emergency surgery is acute appendicitis, with a lifetime risk of 8.6% for men and 6.7% for women (1,2). The curative treatment of acute appendicitis is appendectomy which may be done through an open incision in the abdomen or through laparoscopic techniques (3). Laparoscopic appendectomy (LA) was first described in 1983 by Semm as an alternative to open surgery (4). With this method and advances in techniques, beneficial outcomes such as shorter hospitalization, less postoperative pain, earlier return to work and better cosmetic results emerged as the advantages of LA compared to open appendectomy, indicating that this method was more than an alternative to classical surgery. As such, LA has gained significant popularity and is now recommended as the new 'gold standard' technique for appendectomy (5).

The main concern in LA is the matter of closure of the appendiceal stump because most complications develop as a result of leakage from the stump. Many methods are used to close the stump in LA. The methods of stump closure include intracorporeal knotting, endoloop, titanium clips, endostapler, and more recently, the use of nonabsorbable plastic polymer clips (6-9). Most of these techniques are either time consuming or expensive, or they are not commonly available as their production is often limited (10). Less expensive techniques, such as endoloops or intracorporeal knotting, are used as a standard method in many institutions to close the appendiceal stump in LA.

The aim of this retrospective clinical study was to evaluate the safety and efficacy of the universally available polymer locking ligation system (Hem-o-lok clip) for stump closure in L.

2. Materials and Methods

In this sudy, we retrospectively examined 87 consecutive patients that were successfully treated via laparoscopy after being diagnosed with acute appendicitis between January 2015 and October 2018. In 78 of them, hem-o-lok clips were used to close the appendix stump. The study was performed in accordance with the ethical standards specified in the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Ordu University (Date: 15.11.2018, No: 2018-226). Informed consent was obtained from all individual participants included in the study. All operations were done by two surgeons experienced in minimally invasive techniques who routinely perform a variety of laparoscopic general surgery procedures. In some cases, a surgical trainee (first to fifth year of surgical training) was also present and contributed to the surgery under the supervision of the two specialists. hem-o-lok clips were used

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for closure of the stump whenever possible.

Surgery was described briefly, as follows: pneumoperitoneum was obtained by the use of a Veress needle. Three laparoscopic ports were placed: A 10-mm at the umbilicus, a 5-mm at the midline just cephalic to the pubic bone, and a 10-mm trocar at the left iliac fossae. After the initial laparoscopic evaluation of the abdominal cavity, a Harmonic scalpel was used (Ultracision, Ethicon Endosurgery, Cincinnati, OH) for the sectioning and hemostasis of the appendicular mesentery. Occlusion of the appendicular base was performed by using two nonabsorbable hem-o-lok XL polymeric clips (Weck Closure Systems, Triangle Park, NC) (Image 1). The size of the XL clip was 17.33 mm in the outer arch and 13.58 mm in the inner arch. Results were analyzed statistically using the SPSS 15.0 program (SPSS Inc., Chicago, IL, USA). Variables expressed as mean, standard deviation, median, minimum and maximum values, and count and percentage. The Student's t-test was used for the comparison of quantitative values, and the chi-square test was used for the comparison of categorical values.

3. Results

Of the 78 patients who received hem-o-lok clips, 39 (50%) were male and 39 (50%) were female. The mean age of the patients was 28.55 ± 10.61 (18-73) years. Operation time was between 30 min and 160 min and the median time was 51.3 min. In one patient, the abscess around the cecum was drained. There were no complications such as bleeding and perforation. The median time until allowance of oral diet was 10.48 (4-36) hours and median hospital stay was 22.92 (6-72) hours. Twenty-two (28.2%) patients had complicated appendicitis (perforated/necrotic). Postoperatively, two of the patients had abdominal pain, one had abdominal distention and another had trocar site infection. The abdominal pain and distention resolved within 3-4 hours without any additional treatment. The patient who developed a trocar site infection completely recovered with dressing and antibiotics. In addition, no major complications, such as intraabdominal abscess, stump opening or gastrointestinal tract perforations, were observed in this study. We did not have any patients who required re-hospitalization or re-operation (Table 1).

During the study period, the appendix stump could not be closed with the hem-o-lok clip in 9 (10.3%) of the patients who underwent LA. The reasons were either necrotic appendix root or the size of the appendix (extremely large due to edema etc.). Four of these patients received endoscopic stapling and five underwent the endoloop closure. The median appendix diameter of the patients in which hem-o-lok clips could be applied was 9.35 (4-15) mm. The median appendix diameter in the 9 patients without hem-o-lok application was 13.33 (8-34) mm. There was a statistically significant difference between the two groups in terms of appendix diameter ($p = 0.003$). In patients who could not receive hem-o-lok clips, the operation time was between 45 min and 90 min, with a median of 51.6 min. There was no statistically significant difference between the hem-o-lok and non-hem-o-lok groupsin terms of operation time ($p > 0.05$).

Table 1. The data of patients whose appendiceal stumps were closed with Hem-o-lok clips during laparoscopic appendectomy

Gender	
Male	39 (50%)
Female	39 (50%)
Mean age (year)	28.55 ± 10.61 (18-73)
Mean operation time (min)	51.3 (30-160)
Mean diameter of the Appendix (mm)	9.35 (4-15)
Number of complicated appendix	22 (28.2%)
Mean time of oral diet (hrs)	10.48 (4-36)
Mean time of hospitalization (hrs)	22.92 (6-72)
Postoperative Complications	
Major Complication	0 (0.0%)
Minor Complication	4 (5.1%)
Trocar site infection	1 (1.3%)
Postoperative abdominal distention	1 (1.3%)
Postoperative abdominal pain	2 (2.6%)

4. Discussion

LA is currently the preferred technique for the treatment of acute appendicitis. In recent studies, it has been estimated that >50% of appendectomies are performed by laparoscopic approach (11). The most important step in LA is the appropriate closure of the appendicular stump which enables avoidance of serious complications such as postoperative fistula, peritonitis, abscess and sepsis (12).

There is no unanimously accepted suggestion regarding the closure of the appendicular stump in LA. However, it is widely accepted that the ideal method for appendix stump closure should be safe, accessible, technically simple and cost effective. Various appendiceal stump closure techniques have been described in the literature, including endoloop, intracorporeal knotting, metal titanium clips, endostaplers and polymer plastic clips. Every technique has its own benefits and disadvantages (6-9).

The current literature most commonly describes using either a suture ligature 'endoloop' or an endoscopic stapler to close the appendix (13,14). Endoloops are one of the first methods used to close the appendiceal stump. Endoloop is a laparoscopic knot lasso made of silk or polyglactine. Closure of the appendix stump with endoloop is a common procedure and has lower cost compared to staplers (15,16). The main problem with this method is that the knot may be loose and this could lead to leaks from the appendiceal stump. The use of endoloop for the closure of appendiceal stump in some cases may prolong surgery time due to the need for experience in the application (15). On the other hand, the endoscopic stapler method is a safe and widely-accepted method, but at the same time it is the most expensive method when compared with other techniques (17). Staplers allow simultaneous sealing and division of both the mesentery of the appendix and the appendix base. One of the major

advantages is that it is safe even when the appendix base is inflamed and its diameter is too large (18).

In recent years, laparoscopic clips have been proposed as an alternative method for the closure of the appendiceal stump during laparoscopic appendectomy. Rickert et al. offered evidence that the use of titanium clips had significant success in the closure of appendiceal stumps. The most important feature of titanium clips in comparison to other commercially available clips is the size; appendiceal stumps up to 20 mm in diameter can be securely closed with these clips (19). The disadvantage of titanium clips is reported to be the risk of displacement during manipulations required for the laparoscopic procedure (20).

The safety of hem-o-lok clips has been demonstrated in various areas of surgery, including the in ligation procedures of the ureter, cystic duct or vessels up to 16 mm in diameter (21). In recent years, several articles have described the use of non absorbable hem-o-lok clips which agree that these are safe, easy-to-use and relatively inexpensive (8,15,22). Al-Temimi et al. found that hem-o-lok clips could be used safely with no increase in intraoperative bleeding, stump dehiscence or postoperative complications in comparison to endoscopic staplers (23). Parteke et al. found that there were no differences in postoperative complications between hem-o-lok clips (3.9%) and endoscopic stapling (5.4%) (8). In our study, the results are similar to the literature in terms of risks, as there were no major complications in the 78 hem-o-lok clip recipients.

Intra-abdominal abscess is the most common surgical complication following LA procedures (14,24). Studies on the endoloop procedure demonstrate a relatively high rate of intra-abdominal abscess (up to 5%) (25). In a large retrospective study, Soll et al. found that complications (including intraabdominal abscess) developed less frequently after the use of hem-o-lok clips compared to the endoloop method (1% vs. 4%, $p = 0.012$) (26). In our study, none of our patients developed intraabdominal abscess.

Hem-o-lok clips are available in a range of sizes including M (medium), ML (medium-large), L (large) to XL (extra-large) that are suggested to be able to ligate tissue bundle sizes up to 16 mm. Although their marketing statements suggest that hem-o-lok clips may be used for closures up to 16 mm diameter, the reliability is decreased in cases where the appendix base diameter is over 1 cm. For instance, Hue et al. suggested the use of hem-o-lok clips when the diameter of the appendiceal stump was less than 10 mm and only in the presence of mild inflammation (27). Our experience is also similar, and the fact that there was a significant difference in stump diameter between the two groups (with and without hem-o-lok) indicates that their use in the severely inflamed appendix may not be reliable, or even possible, in some situations. The main advantages of using of hem-o-lok clips for appendiceal stump closure are the lack of a learning curve for application, the ease of application, and low cost (28). In addition, Hem-o-lok clips are reported to cause a milder reaction from the host tissue compared to endoloops (29).

The Hem-o-lokclip offers significant reduction in costs when compared to endoscopic staplers, and provides a simpler application when compared to suture ligature techniques (30). However, in the presence of necrosis or severe edema, other methods should be considered for the closure of the appendiceal stump. The decision to apply Hem-o-lok on patients with thick appendiceal base and/or acute inflamed tissue should be made with respect to intraoperative status and surgical judgment on a patient-by-patient basis.

There are several limitations in this retrospective study. First of all, our study was not a prospective randomized study and, as mentioned before, the use of hem-o-lok clips was planned in all patients. Thus, comparisons could only be performed in a limited number of subjects in which hem-o-lok application was unfeasible. Secondly, the study population can be considered to be limited for the assessment of outcomes in a widely-used and popular technique such as LA.

In conclusion, the use of nonabsorbable polymeric hem-o-lok clips are feasible and cost-effective for the closure of appendiceal stumps of up to 10 mm in diameter. The results of our study have encouraged us to continue to use this technique. Further randomized controlled trials are needed to compare the hem-o-lok technique to different methods of appendiceal stump closure.

Conflict of interest

None to declare.

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The study was performed in accordance with the ethical standards specified in the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Ordu University (Date: 15.11.2018, No: 2018-226).

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Research Article

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Comparison of the interobserver reliability of ultrasonography and radiography in diagnosis of developmental dysplasia of the hip

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Abstract

We aimed to compare the interobserver reliability of ultrasonography (USG) and x-ray (XR) and to calculate the sensitivity and specificity of these tests in the diagnosis of developmental dysplasia of the hip (DDH). This retrospective study was conducted among 150 USG and 300 XR images of infants examined for DDH between January 2013 and June 2015. The sonographic angle measurements and hip classifications of each USG and XR were carried out by five orthopedic surgeons specialized in pediatric orthopedics. Both USG and XR showed almost perfect agreement between five observers (κUSG=0.936, κXR=0.927, respectively, p<.0001). In patients under the age of 6 months, the interobserver reliability was almost perfect for USG and substantial for XR (κUSG=0.957, κXR=0.809, respectively, p<.0001). In patients older than 6 months, although interobserver agreement of both tests were almost perfect (κ>0.81), XR showed slightly higher agreement than USG (κXR=0.912, κUSG=0.885, respectively, p<.0001). In the diagnosis of DDH, both USG and plain x-rays are effective radiological tests because they offer high interobserver reliability. However, the surgeon's practical training and experience significantly affect the reliability in the evaluation of pediatric hip USG and XR.

Keywords: Developmental dysplasia of the hip, ultrasonography, plain x-ray, interobserver reliability

1. Introduction

Developmental dysplasia of the hip (DDH) contains a broad spectrum of aberrant development of the acetabulum and proximal femur (1, 2). The incidence of DDH in routine screening has been reported as 5-30/1000 (3). Treatment in the first months of the infant is simpler and has a better prognosis, hence early diagnosis and treatment is critical (4). As the infant gets older, the potential for harmonious development of the hip decreases and reduction becomes more challenging. Therefore, the assessment of plain X-ray (XR) and ultrasonography (USG) and the staging discrepancies depending on these assessments may cause critical varieties in diagnosis and treatment. High consistency is crucial among the surgeons amid the diagnosis.

In the sonographic examination defined by Graf, the relationship between the femoral head and the acetabulum is evaluated using angular measurements of pediatric hip (5). XR is also frequently used in diagnosis, however less preferred in patients younger than 6 months due to ionizing radiation and the difficulty of imaging the non-ossified cartilage structures of the hip (6). Since XR findings may be affected by the position of the pelvis, different measurements may occur among surgeons (7). Due to the varieties in evaluation encountered in both USG and XR, inconsistencies may occur between measurements, and standardization in staging and treatment may deteriorate. While many orthopedic disorders can be diagnosed using physical examinations rather than precise radiological measurements, the accuracy of the radiological assessment is much more decisive than the physical examination findings in DDH (8, 9).

Although there are studies evaluating the efficacy of USG in the diagnosis and treatment of DDH in the literature (10, 11, 12, 13), no study has been observed comparing the interobserver reliability between USG and XR in terms of measurement and DDH staging criteria. Therefore, we aimed to compare the interobserver reliability of USG and XR imaging techniques and to calculate sensitivity and specificity of these tests in the diagnosis of DDH.

2. Materials and methods

In this study, 150 USG and 300 XR images of infant patients (mean age; USG=4 months, XR=7 months) were evaluated for DDH screening between January 2013 and June 2015. The study was approved by the local university ethics committee for clinical trials and conducted in accordance with the principles of the Declaration of Helsinki. Printed copies of all 450 images were sent to five orthopedic surgeons who received specific training on pediatric hip evaluation and DDH. The measurements and classifications were carried out by the observers retrospectively. All observers were blinded to the

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evaluation results of the other.

All USG imaging were performed by the same surgeon who has a pediatric sonography practice certificate. XR imaging consisted of plain radiographs taken in the radiology department. Inclusion criteria were established according to the quality and suitability of the images for evaluation. Suitability for USG was determined according to standard plane criteria, which consisted of a straight iliac wing line, a clear visualization of the acetabular labrum and a complete visualization of the transition point from the ilium to the triradiate cartilage (14). For XR, these criteria were; entirety of the bony pelvis from superior of the iliac crest to the proximal shaft of the femur, symmetrical view of obturator foramen, equal concavity of the iliac wings and greater trochanters of the proximal femur (15).

Observers were asked to make the measurements in each XR and USG and to classify the hip according to the evaluation criteria. In XR, these criteria were; acetabular index measurement, continuity of Shenton-Menard line and the location of the hip in four quadrants formed according to Hilgenreiner's and Perkin's lines. In USG, alpha and beta angle measurements according to Graf method and determination of hip type according to Graf classification were requested from the observers. After the data were compiled, interobserver reliability analysis was performed for both USG and XR, regardless of age and age dependent groups among the patients. In addition, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of both USG and XR were calculated separately for each observer. Any superiority between the imaging tests among the groups in terms of interobserver reliability was addressed.

2.1 Statistical Analysis

Statistical analysis was performed using the SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA) Fleiss kappa test for interobserver reliability. Reliability and consistency evaluation was classified according to the widely used Landis and Koch interpretation of kappa's values ($\kappa \geq 0.81$ equals almost perfect, κ=0.61-0.8 as substantial, κ=0.41-0.6 as moderate, κ=0.21-0.4 as fair, and $\kappa \leq 0.2$ as slight correlation). Assessment of statistical differences between kappa values was calculated with 95% confidence interval (CI) and $p<0.05$ was accepted as statistically significant.

3. Results

Both USG and XR showed almost perfect agreement between five observers when the radiological tests were evaluated regardless of age (κUSG=0.936, κXR=0.927, respectively, $p<.0001$).

When patients were grouped as below and under the age of 6 months, it was observed that in patients under the age of 6 months, the interobserver reliability was almost perfect for USG and substantial for XR (κUSG=0.957, κXR=0.809, respectively, $p<.0001$). In patients older than 6 months, although interobserver agreement of both tests were almost perfect (κ>0.81), XR showed slightly higher agreement than USG (κXR=0.912, κUSG=0.885, respectively, $p<.0001$).

Table 1. Kappa coefficients for interobserver reliability of ultrasonography (USG) and plain X-ray (XR) between five observers

Kappa coefficients for interobserver reliability		
	USG	**XR**
< 6 months of age	0.957	0.809
> 6 months of age	0.885	0.912
All ages	0.936	0.927

Overall, although interobserver reliability of both USG and XR showed statistically significant reliability (Table 1), no statistically significant difference was found between USG and XR in terms of interobserver reliability, based on overlapping 95% confidence intervals.

Table 2. Ultrasonography (USG) consistency calculations between five observers

USG consistency tests for all patients				
	Sensitivity (%)	**Specificity (%)**	**Positive Predictive Value (%)**	**Negative Predictive Value (%)**
1. observer	66.6	53.3	63.1	57.1
2. observer	77.7	46.6	63.6	63.6
3. observer	76	50	82.6	40
4. observer	82.6	60	82.6	60
5. observer	79.1	55.5	82.6	50

According to the calculations made for each observer separately, the sensitivity range of USG between observers was 66.6%-82.6%, the specificity range was between 46.6%-60%, the PPV range was between 63.1%-82.6%, and finally the NPV range was between 40%- 60% (Table 2). On the other hand, the sensitivity of XR among observers was between 71.2%-82.9%, specificity was between 43.7%-66.6%, PPV range was between 78%-88.8%, and NPV range was between 33.3%-70.8% (Table 3).

Table 3. Plain X-ray (XR) consistency calculations between five observers

XR consistency tests for all patients				
	Sensitivity (%)	**Specificity (%)**	**Positive Predictive Value (%)**	**Negative Predictive Value (%)**
1. observer	69.8	56.7	73.3	52.7
2. observer	81.3	58.5	70.5	68.5
3. observer	73.6	45.8	81.1	35.4
4. observer	81.1	64.5	83.5	60.6
5. observer	76.6	60.8	86.7	40

4. Discussion

While many orthopedic disorders are commonly diagnosed based on physical examination findings, radiological evaluation and measurements are more decisive in diagnosis of DDH (8, 9). The reduction of the femoral head in acetabulum

is ascertained according to the USG and XR findings and the treatment strategy is determined accordingly. There are a few studies reporting the reliability of USG for the diagnosis of DDH in the literature (5, 16-19) yet sonographic assessments are well-known to be operator-dependent. This means that the quality of the obtained images and their accurate interpretation depend on the experience and knowledge of the sonographer (21). Therefore, the subjective nature of this test may cause different measurements among the surgeons during both sonographic assessment and evaluation (21) and may lead to divergent classifications for diagnosis and treatment of DDH which may raise questions about standardization (10, 22-25). The fact that the sonographies we used in our study were applied by a single person, significantly reduces the possibility of this subjective application. Kolb et al. stated that the reliability of hip sonography with the Graf method is increasing gradually, but different measurements originating from the transducer cannot be avoided, and they reported that transducer inclination creates measurement differences that affect clinical results (28). These studies led to the questioning of the reliability of USG in the diagnosis DDH and the necessity for interobserver reliability studies. Dias et al. investigated the reliability of 62 USG sections among five observers and reported that they observed moderate agreement on alpha angle measurement and poor agreement on beta angle measurement. In their study, the authors generally reported poor interobserver reliability of USG in the diagnosis of DDH (10). When the studies conducted after the 2000s were investigated, it is noticed that the interobserver reliability has begun to increase parallel to the improving experience on USG over the years. Çopuroğlu et al. investigated the reliability of USG among seven observers of 33 pediatric patients and reported high interobserver reliability of alpha angle measurement (22). The authors stated that different classifications can be made from the same USG sections due to different alpha angle measurements, and they also observed many different measurements of the same USG in their very own study. They also claimed that the best results were obtained when USG and plain radiography were evaluated together (22).

In the study of Orak et al. interobserver reliability was investigated among four different observers on 50 infants and meaningful differences were reported between the observers. In this study, the authors reported quite wide range in terms of reliability; 3.6%-44.5% agreement range in alpha angle measurement and 0.9%- 45.3% agreement range in beta angle measurement were reported (23). Likewise, it has also been reported that the variations of positioning the infant and the XR device may cause diversity especially among the distinct experience levels of physicians evaluating the x-rays (26). Ismiarto et al. analyzed the interobserver reliability between junior and senior orthopedic residents for XR using Fleiss kappa test. The kappa value of Tönnis classification among seniors and juniors were 0.715 and 0.577, respectively. The authors claimed that the difference was due to the fact that juniors have less experience than seniors (24). Compared to this study, our study showed higher reliability for XR (κXR=0.927) which was probably due to specific training and over 10 years of experience of our observers in pediatric hip ultrasonography. Singh et al. studied the interobserver reliability of XR and reported a very high reliability with a 0.935 kappa value. In our study, we also obtained high kappa value for XR (κXR=0.927) (27).

Although limited number of studies investigating interobserver reliability for both USG and XR are observed in the literature, there is only one study comparing the reliability of these tests in the diagnosis of DDH. This study was conducted in 1990, in which Terjesen et al. examined 312 pediatric hips with USG and XR, it was stated that the authors could make the same diagnosis in 303 of 312 pediatric hips examined. In this study, the authors made a general comparison of the adequacy of diagnosis rather than investigating the reliability of specific measurements (20). In our study, we compared the reliability of USG and XR between five observers using a large series of USG and XR with a total number of 150 USG and 300 XR images, and the observer results were classified as normal, acetabular dysplasia, subluxation and dislocation according to the measurements and the consistency of the diagnosis of DDH was investigated. The interobserver reliability in our study was higher compared to the literature. The possible reasons of this superiority were that all our observers were active performers of pediatric orthopedics and had been performing and evaluating hip sonography according to the Graf method over 10 years. In addition, it is likely that all sonographs were performed by a single surgeon which improves the standardization of the imaging.

In our study, it was observed that the interobserver reliability of USG and XR was high in both infants younger than 6 months and older than 6 months. Although there was no statistically significant difference, we observed that the interobserver reliability of USG was higher in infants younger than 6 months according to Fleiss kappa values, and the interobserver reliability of XR was slightly higher in children older than 6 months. This may be based on that the bony structures become more prominent on direct radiographs around 6 months depending on the ossification mechanism. X-ray assessments may be more consistent after 6 months due to the ossified structures. In our daily routine practices in our clinic, we effectively diagnose and treat developmental hip dysplasia by using both USG and XR examinations together in infants. We prefer USG more frequently, especially in children younger than 6 months, which offers high interobserver reliability.

In the diagnosis of DDH, both USG and plain X-ray imaging techniques are effective methods because they offer high interobserver reliability. However, the surgeon's

experience significantly affects the reliability in the evaluation of pediatric hip USG and XR.

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None

Declaration of conflicting interests

The author declares that there is no conflict of interest.

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Predictors of adverse outcomes in pregnant women with intrauterine hematoma

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Abstract

To investigate the relationship between clinical features evaluated at presentation and the presence of adverse maternal or perinatal outcomes in pregnant women with intrauterine hematoma (IUH). Pregnant women aged 18 years and over who were diagnosed with IUH and had a single live fetus of six to 12 weeks at that time were retrospectively reviewed for the period from January 1, 2019 to July 30, 2021. The patients were divided into two groups according to the presence or absence of adverse pregnancy outcomes after IUH. The clinical features of the patients were evaluated. The effect of clinical factors on adverse pregnancy outcomes was determined using the logistic regression analysis. We found adverse pregnancy outcomes in 31.6% (n=42) of 133 patients included in the study. According to the multiple logistic regression analysis, age≥35 years [odds ratio (OR): 2.62, 95% confidence interval (CI): 1.16-4.37, p<0.001], presence of vaginal bleeding (OR: 2.53, 95% CI: 1.34-3.89, p=0.001), hematoma size≥4 cm (OR: 2.38, 95% CI: 1.08-4.15, p=0.023) and presence of retroplacental hematoma (OR: 2.44, 95% CI: 1.68-3.56, p<0.001) were risk factors for adverse pregnancy outcomes. In the presence of IUH, pregnant women aged ≥35 years and those with vaginal bleeding, hematoma size of ≥4 cm, and retroplacental hematoma are at risk of adverse pregnancy outcomes. These factors can help identify pregnant women who require close monitoring.

Keywords: adverse outcome, intrauterine hematoma, pregnancy, predictors

1. Introduction

Intrauterine hematoma (IUH), which is usually detected on routine obstetric ultrasonography, is a common complication in early pregnancy (1). The incidence of IUH varies according to populations, ranging from 0.5% to 39.5% (2). Multiple hematomas may develop in the maternal-placental-fetal unit. IUHs are generally seen as subchorionic (between the chorion and uterine wall) and retroplacental (between the placenta and myometrium) (3). More than half of hematomas occur in the first trimester and typically disappear within the first three months after diagnosis.

In the literature, different results have been reported from studies investigating the effect of IUH on pregnancy outcomes. Some studies have shown that IUH may be associated with complications such as miscarriage, premature rupture of membranes, (PROM) preterm birth, small for gestational age (SGA), gestational hypertension, preeclampsia, neonatal asphyxia, and fetal death (4, 5). However, there are also studies suggesting that IUH is not associated with adverse pregnancy outcomes (6, 7). The aim of the current study was to define the population of pregnant women followed up with IUH in our clinic and determine the risk factors of IUH that can predict adverse maternal or perinatal outcomes in these patients.

2. Materials and methods

2.1. Patient selection

This retrospective study was carried out in the Gynecology and Obstetrics Clinic of our hospital between January 1, 2019 and July 30, 2021, and ethical approval was obtained from the local ethics committee (number: 2021/11-05). The study population consisted of pregnant women who had a single live fetus of six to 12 week according to the crown-rump length measurements performed on transvaginal ultrasound (TVUSG) imaging. Pregnant women (age ≥ 18 years) diagnosed with IUH by TVUSG and gave birth in our hospital were included in the study group. Patients whose records could not be reached, cases in which TVUSG did not show fetal heartbeat, and women with multiple pregnancies and fetal congenital malformations were excluded from the study.

2.2. Data collection and processing

Cases were identified using the electronic medical database of the obstetric department of the hospital. The patients' age, parity, gestational week when IUH was detected, gestational week at delivery, mode of delivery, pregnancy outcomes and complications, fetal birth weight, APGAR score, and obstetric ultrasonography results were recorded. The patients were divided into two groups according to the presence or absence of adverse maternal or perinatal outcomes after IUH. The

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maternal and perinatal outcomes of IUH were compared between the two groups.

2.3. Definitions

SGA was defined as birth weight below the 10th percentile at a given gestational age (2), preterm birth as delivery before 37 weeks of gestation, miscarriage as the termination of pregnancy before 24 weeks or when the fetus weighed less than 500 grams, and stillbirth as a baby being born without a heartbeat after the 24th gestational week (8). The patients' hematoma size was categorized as small (<4 cm) and large (>4 cm) (9).

Table 1. Demographic and obstetric characteristics of the study population

Variables	Total (n = 133)	Presence of adverse outcomes		P-value
		Yes (n = 42)	No (n = 91)	
Maternal age (years)	28.7±2.8	28.2±2.6	28.9±2.6	0.160
Age > 35 years	26 (19.5%)	18 (42.9%)	8 (8.8%)	<0.001
Systolic blood pressure (mmHg)	125±9	122±7	126±10	0.102
Diastolic blood pressure (mmHg)	87±3	88±4	87±3	0.101
Heart rate (per minute)	93±8	95±8	92±8	0.094
Body mass index (kg/cm^2)	25 (23-26)	24 (23-25)	25 (23-26)	0.316
Parity				
Nulliparous	22 (16.5%)	4 (9.5%)	18 (19.8%)	0.436
1	62 (46.6%)	23 (54.8%)	39 (42.9%)	
2	33 (24.8%)	10 (23.8%)	23 (25.3%)	
3+	16 (12.0%)	5 (11.9%)	11 (12.1%)	
Complaints				
Vaginal bleeding	53 (51.1%)	31 (73.8%)	22 (24.2%)	<0.001
Pelvic pain	77 (57.9%)	23 (54.8%)	54 (59.3%)	0.619
Presence of risk factors				
Previous miscarriages	25 (18.8%)	12 (28.6%)	13 (14.3%)	0.045
Hypertension	3 (2.3%)	1 (2.3%)	2 (2.2%)	0.947
Smoking	5 (3.8%)	2 (4.8%)	3 (3.3%)	0.680
Diabetes (pregestational and gestational)	8 (6.0%)	3 (7.1%)	5 (5.5%)	0.710
Artificial pregnancy	1 (0.8%)	1 (2.4%)	0	0.140
Size of hematoma				
<4 cm	73 (54.9%)	14 (33.3%)	59 (64.8%)	0.001
≥4 cm	60 (45.1%)	28 (66.7%)	32 (35.2%)	
Localization of hematoma				
Anterior	81 (60.9%)	32 (76.2%)	49 (53.8%)	0.014
Posterior	52 (39.1%)	10 (23.8%)	42 (46.2%)	
Position of hematoma				
Retroplacental	42 (31.6%)	28 (66.7%)	14 (15.4%)	<0.001
Subchorionic	91 (68.4%)	14 (33.3%)	77 (84.6%)	
Gestational age at first visit				
6 0/7-6 6/7	13 (9.8%)	5 (11.9%)	8 (8.8%)	0.985
7 0/7-7 6/7	27 (20.3%)	9 (21.4%)	18 (19.8%)	
8 0/7-8 6/7	42 (31.6%)	13 (31.0%)	29 (31.9%)	
9 0/7-9 6/7	16 (12.0%)	5 (11.9%)	11 (12.1%)	
10 0/7–10 6/7	19 (14.3%)	6 (14.3%)	13 (14.3%)	
11 0/7–11 6/7	16 (12.0%)	4 (9.5%)	12 (13.2%)	
Mode of delivery				
C/S	37 (27.8%)	13 (31.0%)	24 (26.4%)	0.584
NSD	96 (72.2%)	29 (69.0%)	67 (73.6%)	
Gestational age at delivery	38.0 (36.7-39.0)	38.2 (37.7-39.5)	38.0 (36.0-38.9)	0.117
Birth weight (g)	3433±810	3171±786	3554±796	<0.001
Admission to NICU	3 (2.3%)	2 (4.8%)	1 (1.1%)	0.186

Data are presented as mean ± standard deviation, median (25%–75% quartiles) or n (%), C/S: Cesarean delivery, NSD: Normal spontaneous delivery, NICU: Neonatal intensive care unit

2.4. Outcome measures

The primary outcome was the presence of adverse maternal or perinatal outcomes after IUH development during pregnancy. Adverse maternal or perinatal outcomes were defined as spontaneous abortion, PROM, placental abruption, delivery before 37 weeks of gestation, SGA, fetal distress, low fifth-minute APGAR score, fetal or neonatal death, and maternal death. The secondary outcome was the relationship between adverse pregnancy outcomes and demographic data, clinical features, and obstetric ultrasonography results.

2.5. Statistical methods

All statistical data were analyzed using SPSS for Windows, version 22.0 (SPSS Inc.; Chicago, IL, USA). First, the descriptive statistics [number (n), frequencies (%), mean and standard deviation] of the variables were calculated. Pearson's chi-square or Fisher's test was used to compare categorical data. The normality of data distribution was tested with the Kolmogorov-Smirnov test. Student's t-test was used to compare normally distributed data, and the Mann-Whitney U test was used to compare non-normally distributed data. Univariate and multivariate logistic regression analyses were performed to determine the relationship between the presence of adverse maternal or perinatal outcomes after IUH development during pregnancy and clinical risk factors. Variables with a p value of <0.05 in the univariate logistic regression analysis were included in the multivariate logistic regression analysis. The statistical significance limit was taken as $p < 0.05$.

3. Results

The study included 133 patients who met the criteria. The rate of adverse pregnancy outcomes after IUH was 31.6% (42/133). The mean (±standard deviation) maternal age was 28.2 ± 2.6 years in the group with adverse pregnancy outcomes and 28.9 ± 2.6 years in the group without adverse pregnancy outcomes. In both groups, IUH was most detected at gestational weeks 8 0/7–8 6/7. The demographic and clinical characteristics of the cases are shown in Table 1. Vaginal bleeding was found at a higher rate (73.8%) in the group with adverse pregnancy outcomes. The most common adverse pregnancy outcome was abortion at 26.2% (n = 11). Table 2 presents the distribution of adverse pregnancy outcomes due to IUH.

Table 2. Type and rate of adverse outcomes following intrauterine hematoma in the study population

Adverse pregnancy outcomes	Number of cases* n (%)
Spontaneous abortion	12 (28.6%)
Placental abruption	4 (9.5%)
Delivery <37 weeks	9 (21.4%)
Small for gestational age (<10th percentile)	7 (16.7%)
Premature rupture of membrane	4 (9.5%)
Apgar score < 7 at 5 min	5 (11.9%)
Fetal distress	7 (16.7%)
Fetal or neonatal death	1 (2.4%)
Maternal death	0

* Some women had more than one adverse outcome; therefore, the total of all adverse outcomes exceeded the number of women with adverse outcomes (n = 42).

The effect of clinical factors on adverse pregnancy outcomes was determined using the logistic regression analysis and are listed in Table 3. In the regression analysis, age ≥ 35 years [odds ratio (OR): 2.62, 95% confidence interval (CI): 1.16-4.37, p < 0.001], presence of vaginal bleeding (OR: 2.53, 95% CI: 1.34-3.89, p = 0.001), hematoma size ≥ 4 cm (OR: 2.38, 95% CI: 1.08-4.15, p = 0.023), retroplacental hematoma (OR: 2.44, 95% CI: 1.68-3.56, p < 0.001) were determined to increase the likelihood of developing adverse pregnancy outcomes among the women with IUH. Table 4 shows the distribution of the number of risk factors according to the study groups.

Table 3. Univariate and multivariate analyses of predictive factors for adverse pregnancy outcomes

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	P value	OR	95% CI	P value
Age ≥ 35 years	3.29	1.48-8.64	<0.001	2.62	1.16-4.37	<0.001
Vaginal bleeding	2.94	1.57-5.46	<0.001	2.53	1.34-3.89	0.001
Previous miscarriages	1.14	1.03–2.57	0.045	1.04	0.95-3.76	0.214
Size of hematoma ≥ 4 cm	2.71	1.21-4.85	0.001	2.38	1.08-4.15	0.023
Anterior localization	2.12	1.64-4.76	0.014	1.65	0.85–5.94	0.117
Retroplacental hematoma	2.87	1.54-3.88	<0.001	2.44	1.68-3.56	<0.001

OR: odds ratio; CI: confidence interval

Table 4. Number of risk factors present in patients

Number of risk factors	Total (n=133)	Presence of adverse outcomes	
		Yes (n = 42)	No (n = 91)
No risk factor	38 (100%)	2 (5.3%)	36 (94.7%)
One risk factor	49 (100%)	6 (12.2%)	43 (87.8%)
Two risk factors	20 (100%)	12 (60.0%)	8 (40.0%)
Three risk factors	16 (100%)	13 (81.3%)	3 (18.8%)
Four risk factors	10 (100%)	9 (90.0%)	1 (10.0%)

4. Discussion

IUHs are common findings in routine obstetric ultrasonography, especially in the first trimester of pregnancy. It has been shown that there may be a significant association between IUH and adverse pregnancy outcomes (5, 8). Although IUHs often spontaneously disappear without causing any problems, the main challenge for clinicians is to identify patients at high risk of adverse pregnancy outcomes. Therefore, the identification of reliable positive or negative predictors of

adverse pregnancy outcomes in patients who have developed IUH is necessary to prevent possible complications. In this study, we found adverse pregnancy outcomes in 31.6% (n = 42) of the pregnant women that developed IUH. We observed that in the presence of IUH, maternal age, hematoma size, hematoma position, and vaginal bleeding were associated with adverse pregnancy outcomes in the later weeks of gestation.

The mechanism of the relationship between IUH and adverse perinatal outcomes had not yet been clearly elucidated (2). The development of placental vascular structures starts from the fifth gestational week. A large hematoma formed in the early weeks may disrupt the invasion of the extravillous trophoblast, leading to the loss of placental function by affecting the physiology of spiral arteries in later weeks. Studies evaluating the size of the hematoma have reported that the presence of large hematoma is associated with adverse pregnancy outcomes (10-12). It has been reported that the probability of abortion was higher in large hematomas (13). It has also been shown that maternal age, presence of vaginal bleeding and gestational week at which hematoma is observed are associated with adverse pregnancy outcomes in early pregnancy (14). However, discussions continue concerning the prognostic value of hematoma size, gestational week at which bleeding is observed, and presence of concurrent vaginal bleeding (15). The literature also contains studies reporting that adverse pregnancy outcomes, such as abortion, preterm labor, and PROM have no significant relationship with hematoma size, gestational week, and bleeding time (9, 16). In the current study, we compared the baseline clinical data of patients with and without adverse pregnancy outcomes and determined that age, presence of vaginal bleeding, and hematoma position and size might be good predictive parameters for adverse pregnancy outcomes. The presence of these risk factors can help identify pregnant women who require close monitoring.

Some studies have shown that the presence of IUH in pregnancies is associated with increased adverse pregnancy outcomes, such as preeclampsia, miscarriage, preterm delivery, intrauterine growth restriction, abruption, SGA, cesarean section, and low one-minute and five-minute APGAR scores (13, 14). The early perfusion of the intervillous space, impaired trophoblast invasion, impaired angiogenesis, and weakness of the retroplacental space may be possible mechanisms for adverse perinatal outcomes (5, 17). The main effect of IUH on early pregnancy is pregnancy loss (18). On the other hand, there are also researchers suggesting that there is no significant relationship between IUH and adverse pregnancy outcomes (18, 19). The location of IUH within the placenta or the uterine wall is another prognostic factor associated with obstetric complications. Al-Memar et al. showed that the size of IUH did not affect pregnancy outcomes, but the presence of retroplacental IUH was associated with an increased risk of antenatal complications (8). Similarly, Nagy et al. reported that retroplacental hematomas were significantly associated with an increased risk of adverse maternal and neonatal complications (10). Our results confirm that the presence of retroplacental hematoma is associated with adverse pregnancy outcomes.

This study has certain limitations. First concerns the limited number of patients who met the inclusion criteria. The sample comprised a relatively small study population since we only included pregnant women had a live fetus of six to 12 weeks of age at the time of IUH development. Second, the study was conducted in a single center. Third, the retrospective nature of the study limited data to those routinely collected. Finally, sonographic evaluations were undertaken by different physicians, which may have cause variability in measurements.

We determined that 31.6% of the pregnant women who developed IUH had adverse pregnancy outcomes. In most cases, IUH spontaneously disappears without causing any problems, but obstetric complications related to the mother and fetus are not uncommon in these patients. In the presence of IUH, pregnancy age ≥ 35 years, vaginal bleeding, hematoma size ≥ 4 cm, and retroplacental hematoma constitute a higher risk for adverse pregnancy outcomes. The presence of these risk factors can help identify pregnant women who require close monitoring

Conflict of interest

All authors report no conflict of interest.

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Relationship between index of cardio-electrophysiological balance and hydroxychloroquine in patients with COVID-19

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Abstract

Hydroxychloroquine (HCQ) treatment is frequently prescribed for coronavirus disease 2019 (COVID-19). Electrocardiographic (ECG) monitorization is recommended because HCQ causes QT interval prolongation. The index of cardioelectrophysiological balance (iCEB), calculated as the ratio of QT interval / QRS duration. In recent years, iCEB has been described as an important marker for dysrhthmias. Decreased or increased iCEB is related with lethal ventricular arrhythmias. In our research, we purposed to investigate the relationship between iCEB and HCQ in patients with COVID-19. 200 patients (males, 84; females, 116; 60.4 ± 13.8 years) with PCR positive and chest tomography findings compatible with COVID-19 pneumonia were registered in the research. Demographic, clinical, and laboratory data for all patients were collected. ECG was recorded from all patients on admission to COVID-19 clinic, in oral treatment with HCQ (200 mg, twice daily) for at least 5 days. iCEB (QT/QRS) was calculated from the 12-lead electrocardiogram.The mean age of the patients was 60.4 ± 13.8 years. Compared to admission ECG, ECG on day 5 showed significant increases in heart rate, QT interval, corrected QT (QTc) interval, and iCEB. Our results suggested that iCEB is related with HCQ treatment in patients with COVID-19. Previous studies stated that high iCEB is related with torsade de Pointes (TdP), ventricular tachycardia.

Keywords: electrocardiography, hydroxychloroquine, arrhythmia, COVID-19

1. Introduction

Coronavirus disease-2019 (COVID-19) is the important reason of the pandemic disease. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is cause of COVID-19. COVID-19 is an important cause of disability and fatality. The clinical manifestation of COVID-19 is various, from myalgia to severe acute respiratory distress syndrome (1). To date, there are no efficacious COVID-19 treatment. Patients are treated with several nonspecific drugs. Gautret et al. shows that HCQ is now one of the most used therapies for COVID-19 patients (2). However, HCQ can cause QT prolongation. Drug related QT-interval prolongation is important risk of fatal ventricular dysrhythmias and mortality. Therefore, ECG records of COVID-19 patients treated with HCQ treatment is important to recognize QT prolongation (3).

QT dispersion (QTd) is an indirect ECG measures of the ventricular repolarization (4). There are different results of the prognostic value of QTd in COVID-19 patients. For this reason, its prognostic value in COVID-19 remain contradictory. Recently a new noninvasive marker iCEB among the repolarization and the depolarization of the action potential was developed as an important risk parameter of dysrhythmia. iCEB was measured as the proportion of QT interval / QRS duration, which plays a significant role in dysrhythmia (5).

In this study, we researched the relation between iCEB and HCQ treatment in COVID-19 patients.

2. Materials and Methods

2.1. Study participants and design

A total of 282 patients with PCR positive and chest tomography results appropriate with COVID-19 pneumonia admitted to the COVID-19 clinics were enrolled in this study between 1 April 2020 and 1 September 2020. COVID-19 patients with ECGs that could not be calculated (n = 8), patients with right and left bundle branch block in ECG (n = 12), and those without control ECG (n = 29) were excepted. Furthermore, patients with a hospitalization duration < 5 days (n = 33) were excluded from the study. Therefore, 200 COVID-19 patients (males, 84; females, 116; mean age, 60.4 ± 13.8 years) were included in the research. Clinical characteristics of patients were recorded. The patients were treated with HCQ (400 mg/d for 5 days). Twelve-lead ECGs were analysed in each patient before HCQ treatment, 3 and 5 days after HCQ treatment. The HCQ treatment was not started in patients with contraindications, including hypopotasemia, or when the QTc interval was greater than 500 ms, according to the Bazett formula. The HCQ treatment was stopped if there was a QTc greater than 60 ms compared with a baseline or when the QTc interval was more than 500

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ms. We also paid important attention to possible drug interactions. Particularly, medications that could prolong the QTc interval. Our research was accepted by the Ethics Committee of Health Sciences University of Turkey, Diyarbakir Gazi Yasargil Education and Research Hospital (Reference Number of Ethic Committee: 499, Date:03 / 07 / 2020), and informed assent was obtained. The study was performed with respect to the Helsinki Declaration of ethical guidelines revised in 2013.

Table 1. Demographic features of patients on admission

Baseline characteristics	N (%)
Sex	
Female	116 (58%)
Male	84 (42%)
Age (years)	60.4 ± 13.8
Smoking	46 (23%)
Heart failure	8 (4%)
Hypertension	24 (12%)
Coronary artery disease	14 (7%)
Cerebrovascular disease	6 (3%)
Diabetes mellitus	38 (19%)
Chronic kidney disease	12 (6%)

2.2. Analysis of QT, iCEB

12-lead ECGs were saved at 10 mm/mv gain and 25 mm/s speed with ECG-9132K Nihon Kohden ECG (Nihon Kohden Corporation, Tokyo, Japan). ECG was saved at hospitalization in the COVID-19 clinic for patients with a COVID-19. Thereafter ECG parameters were manually calculated. All ECG parameters were calculated by skilled cardiolog who was oblivious of the clinical parameters. The QT interval was calculated from the onset of the QRS to the termination of the T-wave. The termination of the T-wave was described as the dot of go back to the isoelectric line. In patients where the T-wave was interrupted by a U-wave, the end of the T-wave was described as the lowest point between the T- and U-waves. For example, the T-wave could not be dependable described owing to especially low voltage (< 0.1 mV), calculation of QT interval was not performed. As a result, these leads were excepted from the ECG analysis. So that, except the efficacy of the heart rate (HR), the QT interval was calculated with respect to the Bazett formula (QTc=QT/square root of RR interval). QTd was described as the maximum QT minus minimum QT intervals. T peak to T end (Tpe) was calculated with a scale from the peak of the T-wave to its end. The QRS duration was calculated from the inception of the Q wave, or the R wave if Q wave was not observable, to the J point. iCEB was measured by both the ratio of QT/QRS, calculated from the ECG recordings (6).

2.3. PCR Analyses for COVID-19

Nasopharyngeal swab technique (nose or throat) for specimen collecting for COVID-19 based upon the disease control guidelines for COVID-19 (7). Nasopharyngeal and oropharyngeal specimens were gathered from the cases by synthetic fiber swabs (Citotest Scientific Co, Haimen City, PR China). The swab materials were put into 3 ml sterile viral transport material (Citotest Scientific Co) in the course of the gathering and carried with biohazard sample bag. Thereafter the specimen was received, they were carried to the PCR analyses laboratory and tested about a few hours. Specimens were swirled for 3–5 s previous to testing and a adjusted pipette was utilized to carry the specimen volume defined in producer's directives for utilization. The molecular identification methods include the analysis of nucleic acids present in the sample to detection the virus. The identification of COVID-19 was done by reverse transcription-polymerase chain reaction (RT-PCR) testing utilizing the CFX96 Real-Time System (Bio-Rad, USA) (8). Identification was made with the RT-PCR kits, the Bio-Speddy (Bioeksen R&D Technologies Inc. COVID-19 RT-qPCR Detection Kit v2.0, Istanbul, Turkey). Viral RNA subtraction from specimen were carried to with respect to the producer's directives. In order to automated viral nucleic acid subtraction process CFX96 Real-Time System (Bio-Rad, USA) was utilized. A negative (human specimen control) was contained in each RNA subtraction process, and a non-formwork (water) control was contained in each RT-PCR actuate. An internal control amplification was carried out to observe RNA subtraction and RT-PCR quality.

Table 2. Laboratory findings of patients on admission to hospital

Parameters	Values
Hemoglobin, g/dL	11.7 ± 2.1
Platelet count, ($\times 10^3/\mu L$)	274 ± 156
White blood cell count, ($\times 10^3/\mu L$)	8.6 ±3.5
Neutrophil cell count, ($\times 10^3/\mu L$)	5.7 ± 2.9
Lymphocyte cell count, ($\times 10^3/\mu L$)	1.4 ± 0.8
Serum creatinine, mg/dL	1.13 ± 0.89
Alanine aminotransferase, U/L	36 ± 14
Serum potassium, mEq/L	4.1 ± 0.7
Serum sodium, mEq/L	135.7 ± 2.9
Albumin , g/L	39 ± 11
Calcium , mg/dL	8.56 ± 0.9
C-reactive protein, mg/dL	37.8 ± 24.2
Ferritin, ng/mL	118 (52 - 220)
D-dimer, ng / mL	357 ± 223
Systolic BP, mm Hg	125.7 ± 18.6
Diastolic BP, mm Hg	75 ± 12.3

*BP.Blood pressure

2.4. Statistical analysis

Statistical analysis was execute with the SPSS statistical program (Version 12.0; SPSS Inc., Chicago, IL,USA). All baseline parameters were analyzed. Continuous variables are stated as mean±SD and categorical parameters are defined as percentages. Continuous variables were compared utilizing the paired t-test if the data were normally deployed and Wilcoxon's rank sum test if the data were not normally deployed. p values < 0.05 were contemplated statistically important. Correlation analyses were utilized to identify the relationship between iCEB and clinical parameters.

3. Results

3.1. Patient characteristics

Baseline clinical parameters of the 200 study cases are listed in Table 1. Mean patient age was 60.4 ± 13.8 years, and 116

of the patients (58%) were female. Cardiovascular comorbidities contained arterial hypertension (n = 24 [12%]), systolic heart failure (n = 8 [4%]), coronary artery disease (n = 44 [7%]), and diabetes mellitus (n = 38 [19%]). A total of 12 patients (6%) had renal failure. A whole of 12 patients (6%) had cerebrovascular disease (Table 1). The laboratory parameters of the cases at the time of presentation are demonstrated in Table 2.

3.2. ECG characteristics during HCQ treatment

A 12-lead ECG was saved at admission before starting HCQ therapy and fifth day after HCQ treatment in whole study cases. ECG parameters in the course of HCQ treatment are listed in Table 3. Heart rate, QT interval, QTc interval, iCEB, Tp-e and Tp-e/QT were importantly higher after HCQ therapy than before HCQ treatment. There are no significant changes in QRS duration.

Table 3. Electrocardiographic parameters of the patients

Variables	1. Day	5.day	p Value
Heart rate (beats/min)	83 (76-91)	96 (81-106)	< 0.001
QT interval (ms)	363.6 ± 35	379 ± 30	< 0.001
QTc interval (ms)	418 ± 36.5	455.6 ± 29.4	0.005
QRS (ms)	84.8 ± 6.8	89.3 ± 11.8	0.899
Tp-e interval (ms)	58.2±5.4	66.4±7.1	<0.001
Tp-e / QT ratio	0.15±0.04	0.17±0.06	0.02
iCEB	4.57 ± 0.27	5.11 ± 0.51	< 0.001

* iCEB: İndex of cardioelectrophysiological balance

Correlation analysis performed to research the association between iCEB and clinical parameters showed a positive correlation between the iCEB and HCQ and age and negative correlation between iCEB and potassium level (Table 4).

Table 4. Correlation between 5. day iCEB score and clinical parameters in patients with COVID-19

Parameters	Correlation coefficient (r value)	p Value
Age	0.571	0.032
Coronary artery disease	0.314	0.567
Hypertension	0.213	0.574
Diabetes mellitus	0.287	0.615
Cr Cl level at initiation	0.419	0.714
Potassium level at initiation	-0.374	0.040
Calcium level at initiation	0.325	0.591
HCQ treatment	0.618	0.032
CRP	0.028	0.756

*CrCl: Creatinin Clirence, † iCEB: İndex of cardioelectrophysiological balance, ‡ HCQ: Hydroxychloroquine

4. Discussion

Previous clinical studies show that prolonged QT interval is associated with arrhythmia risk (6,9). Drug-related QT interval prolongation is a significant cause for TdP. Also, it is significant to contemplate that already attentive monitoring of the QT interval may solely reduce the risk of TdP. Lethal arrhythmias frequently become in the setting of unexpected episodic alteration in the R-R interval, such as when APCs, VPCs, or pauses consist. In these patients, TdP can occur although the QTc interval in merely slightly extended at baseline (10).

HCQ activates calcium and sodium channel blockades. These channels have got membrane-stabilizing effects. Calcium and sodium channel blockades might conclusion in conduction disturbances with a QRS interval widening, QT prolongation, and atrioventricular block (11). This side effect might be also increased in the COVID-19 disease. Other causes of arrythmias are drug-to-drug interplay (clarithromycin, azithromycin, antivirals, etc) and acute infection related fever, dehydration and electrolyte abnormalities (12). COVID-19 is especially responsible for an acute respiratory disease. In addition, COVID-19 can cause acute coronary syndrome and myocarditis (13,14).

Previous study stated that, addition of azithromycin to chloroquine can cause prolongation of about 15 ms in the QTc interval (15,16). Nevertheless, drug related lethal arrythmia risk is significantly higher in hospitalized patients. Lethal arrythmia risk is significantly higher in cases who have another risk factors for arrythmia. Arrythmia risk factors are genetic factors (17), advanced age, existence of underlying cardiovascular disease, electrolyte disturbances, and combination thearpy with other QT-prolonging drugs (18-20). In the present study, we found that heart rate, Tp-e, Tp-e/QT, QT, QTc were importantly higher after HCQ treatment in COVID-19 patients.

Nevertheless, there is some drawbacks the usage of QT prolongation as the unique risk sign for dysrhythmias. The normal QT interval is no guarantee for absence of proarrhythmia. For this reason, an investigation is in progress for better evaluation of arrhythmia risk markers. In recent years, iCEB was recommended as a novel and noninvasive biomarker to estimate the risk for both TdP and non-TdP VT/VF. It was proposed that an optimum equilibrium between repolarization (QT interval), and depolarization (QRS duration) are very important to protect the electrical steadiness of the ventricles: diverging too much from this sensitive equilibrium may actually be proarrhythmic (21).

iCEB (QT/QRS) is an easy but efficacious ECG substitute of the cardiac wavelength. Robyns et al. found that the correlation between the effective refracter period calculated during electrophysiologic study and the uncorrected QT interval, so ancillary the notion of this novel parameter as an ECG substitute for cardiac wavelength (6). Only limited data are present on cardiac wavelength as a risk determinative, primarily owing to the invasive character to calculate it. They found that iCEB is a readily measurable local estimate of the cardiac wavelength. iCEB is increased in circumstances that make susceptible predispose to TdP. iCEB calculated from the ECG, could serve as a significant, novel and non-invasive parameter for potential risks of cardiac dysrhythmias beyond long QTs and TdP. Causes of prolonged QT-interval (inherited long QTs) are significantly increasing iCEB. Increasing iCEB is associated with TdPs (6). For this reason, iCEB might use as a noninvasive and easily quantifiable marker to determine increased arrhythmic risk (6). Nevertheless, to our knowledge, no studies in the literature have researched the association between the iCEB and HCQ treatment in COVID-19 patients.

In this research, we found that iCEB score was importantly higher after HCQ treatment in COVID-19 patients. For this reason, we propose that individual risk/benefit evaluating should be carried out before treatment with HCQ. We suggested that daily ECG monitoring, with reappraisel of treatment if high-risk parameters seem (iCEB, QTc interval).

Conflict of interest

The authors report no conflicts of interest.

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The optimal surgical approach for solid pseudopapillary neoplasm of the pancreas: A retrospective study

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Abstract

The most effective surgical approach for solid pseudopapillary neoplasms (SPNs) remains unclear. We conducted a retrospective study of 14 patients diagnosed with SPN between September 2013 and October 2021. Thirteen patients were female, and the median age was 39.5 (18–63) years. The mean tumour diameter was 5.2 ± 2.2 (range, 2–10) cm. The type of surgery was decided based on the tumour location and the extrapancreatic invasion status. The conservative (organ-preserving) surgical procedure was spleen-preserving distal pancreatectomy (n=3). The radical surgical procedures included pancreaticoduodenectomy, with either venous reconstruction (n=2) or without (n=4), and distal pancreatectomy + splenectomy (n=5); similar to performed for pancreatic cancer regional lymphadenectomy was not performed. Tumour resection margins were free in all patients. There were no cases of lymph node metastasis, but the number of examined lymph nodes was significantly higher in the radical surgery group (p=0.03). A female patient developed multiple liver metastases one year after distal pancreatectomy + splenectomy. Her number of examined lymph nodes was the highest of the cohort (n=24). The mean follow-up time was 40 ± 23.5 months. All patients were alive at the end of the study. In conclusıon; necessity for radical surgery may be associated with malignant behaviour. Therefore, the extent of the surgical operation may be expanded during radical procedures for SPNs.

Keywords: conservative surgery, optimal surgical approach, radical surgery, solid pseudopapillary neoplasm

1. Introduction

Solid pseudopapillary neoplasms (SPNs) are rare, cystic exocrine tumours that account for 1–2% of all pancreatic neoplasms (1). SPNs occur most often in young women and with no notable symptoms (2, 3). These tumours are generally large, well-circumscribed, and consist of solid and cystic components (4). Although most SPNs have stable characteristics, malignant behaviour has been identified in 10–15% of patients (5-7). Surgical resection is the mainstay and only curative treatment strategy whether the disease shows a malignant behaviour or not (1-13). Many authors recommend conservative surgery because of the low malignancy potency of these tumours (1-6, 8-10, 13). However, in the case of pancreatic parenchymal infiltration and involvement of adjacent structures, radical surgical approaches are required (7). In this study, we aimed to present the outcomes of our cohort of 14 patients with SPN in whom 11 radical surgical procedures were performed.

2. Materials and Methods

The study was approved by the ethics committee (2021/462). We searched our database and found records of 14 patients with a confirmed pathological diagnosis of SPN from September 2013 to October 2021. We conducted a retrospective study to analyse the patient variables, such as their demographics, clinical presentation, radiological findings, tumour size and location, strategy of the surgery, pathological and immunohistochemical analyses, as well as short and long-term outcomes. Informed consent was obtained from all the study participants.

The radical surgical procedures included pancreaticoduodenectomy (with or without venous reconstruction) and distal pancreatectomy + splenectomy, and the conservative surgical procedure was spleen-preserving distal pancreatectomy (7). Whenever feasible, we performed conservative surgery. Regional lymphadenectomy recommended by The International Study Group on Pancreatic Surgery for pancreatic adenocarcinoma was not routinely performed (14). Postoperative pancreatic fistulas were evaluated considering The International Study Group of Pancreatic Surgery consensus recommendations (15). Postoperative complications were evaluated according to Clavien-Dindo classifications (16), and those ≥ 3A were defined as severe. R0 resection was considered tumour-free surgical margin whereas R1 was considered the microscopic presence of tumour cells at the surgical margin. Univariate analyses of clinicopathological features were performed to compare the conservative and radical procedures. All statistical analyses were performed using IBM SPSS 26.0 (IBM Corp., Armonk, New York, USA).

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3. Results

3.1. Clinical features

The clinicopathological features are listed in Table 1. Thirteen of the 14 patients were female, and the median age was 39.5 (18–63) years. The most common clinical presentation was abdominal pain: it was found in half of the patients. One patient was referred with jaundice. No patient had weight loss, a history of trauma, or pancreatitis. The tumours were located on the head/neck in six and body/tail in eight patients. The mean tumour diameter was 5.2 ± 2.2 (range, 2–10) cm.

Table 1. Clinicopathological features of 14 patients with SPNs

	Patients (n=14)	%
Age years, mean (range)	39.5 (18-63)	
Gender		
Female	13	92.9
Symptoms		
Abdominal pain	5	35.7
Abdominal pain and jaundice	1	7.1
Abdominal pain and diarrhea	1	7.1
Nausea and vomiting	1	7.1
Radiographic appearence		
Solid-cystic	8	57.1
Solid	4	28.6
Cystic	2	14.3
Calcification on imaging, yes	8	57.1
Location		
Head or neck	6	42.9
Body or tail	8	57.1
Radical surgery		
Pancreaticoduodenectomy	6	42.9
Distal pancreatectomy + splenectomy	5	35.7
Conservative surgery		
Splen preserving distal pancreatectomy	3	21.4
Size cm, mean (range)	5.2 (2-10)	
Resection margin status		
R0	14	100
Lenf node status		
Number of metastasis	0	0
Follow-up months, mean±sd	40.0 ± 23.5	
Recurrence		
Hepatic metastasis	1	7.1
Outcome		
Alive	14	100

3.2. Preoperative investigations

Preoperative tumour markers (carbohydrate antigen 19-9 [CA 19-9] and carcinoembryonic antigen [CEA]) were tested in eight cases, and they were within normal limits.

Radiological scans were performed preoperatively, including computed tomography (CT) in 11 patients and magnetic resonance imaging (MRI) in 5 patients. On imaging, the tumours were described as well-encapsulated in all cases, solid and cystic in eight cases, and solid in four cases. Eight patients had calcifications, while seven had haemorrhage and necrosis. SPN was being referred in the imaging reports of eight patients.

Endoscopic ultrasonography (EUS) with fine-needle aspiration biopsy (FNA) was performed in five patients. A definitive preoperative pathological diagnosis was obtained in only one patient whose tumour was at the pancreatic head. Two patients were misdiagnosed with pancreatic neuroendocrine tumours and two others with unidentified benign lesions.

3.3. Surgical management and postoperative outcomes

In Table 2, we evaluate the clinicopathological features according to surgical approach. The type of surgery was decided based on the tumour location and involvement of adjacent structures, such as the portal and splenic veins. Eleven patients underwent radical surgery, including pancreaticoduodenectomy in six (concomitant end-to-end portal vein reconstruction in one and primary venorraphy in one) and distal pancreatectomy + splenectomy in five. The remaining three patients underwent spleen-preserving distal pancreatectomy. The total mean operation time was 3.9 hours; it ranged from 1.8 to 6.8 hours. Intraoperative blood transfusion was required in eight patients. The length of stay, intraoperative blood transfusion, and operation time were significantly higher in the radical surgery group ($p<0.05$).

Table 2. Comparison of surgical approaches

Clinicopathologic factors	Radical (n = 11)	Conservative (n = 3)	p value
Gender, famele	11 (100)	2 (66.7)	0.21
Age, years (mean± SD)	41 ± 14.7	34 ± 6.2	0.44
Symptoms, yes, n (%)	8 (72.7)	1 (33.3)	0.50
Tumor location, n (%)			0.20
Head or neck	6 (54.5)	0	
Body or tail	5 (45.5)	3 (100)	
Tumor size, cm (%)			1.0
<5	5 (45.5)	1 (33.3)	
>5	6 (54.5)	2 (66.7)	
Intraoperative blood transfusion, unit (median, range)	2 (0-3)	1 (0-1)	0.03+
Operation time, hour (mean ± SD)	4.2± 1.8	2.6 ± 0.3	0.01+
Postoperative complications, yes, n (%)	6 (54.5)	0	0.20
Lengt of stay, day (median, range)	9 (5-21)	5 (4-5)	0.02+
Hemorrhage or necrosis, n (%)			1.0
No	1 (9.1)	0	
Hemorrhage	2 (18.2)	1(33.3)	
Hemorrhage + necrosis	8 (72.7)	2(66.7)	
Tumor capsul formation, n (%)			1.0
Intact	4 (36.4)	1 (33.3)	
Perforation	3 (27.3)	1 (33.3)	
Invasion	4 (36.4)	1 (33.3)	
Evaluated lymph node number (median, range)	12 (0-24)	0 (0-6)	0.03+
Recurrence, yes, n (%)	1 (9.1)	0	0.58
Tumor feature, n (%)			1.0
Solid and cystic	7 (63.6)	3 (100)	
Solid	2 (14.3)	0	
Cystic	2 (14.3)	0	
Follow-up time month (mean ± SD)	39.2 ± 7.3	43 ± 14.7	0.81

+: statistically significant

No patient in the cohort had any severe postoperative complications. Nine patients developed postoperative

complications, including pancreatic fistula (n=2), wound infection (n=3), both of these (n=2), and delayed gastric emptying (n=2).

3.4. Pathological findings

All tumour specimens had a fibrous pseudocapsule, multiple solid and cystic components, and areas of haemorrhage and necrosis, and the observed fibrous capsule was thin, the tumours pseudopapillary, and there were uniform, poorly cohesive neoplastic cells. There was capsule perforation and capsule involvement in four and five patients, respectively. There was infiltration of the splenic veins, portal veins, and pancreatic parenchyma in four, two, and eight patients, respectively. There were no lymph node metastases, but the examined lymph node number was significantly higher in the radical surgery group (p=0.03). The resection margins were free in all patients. There was no lymphovascular or perineural invasion. The mitotic activity was low or undetectable in all patients. Immunohistochemical examinations included ß-catenin, vimentin, CD-10, CD-56, alfa-1-antitrypsin, neuroendocrine markers (chromogranin A, synaptophysin), progesterone receptors, cytokeratin (AE1/AE3), and Ki-67. The immunohistochemical features of the cohort are listed in Table 3.

Table 3. Immunohistochemical features of 14 patients with SPNs

Antigen	Test number n,(%)	Positive (%)
Beta-catenin	13 (92.9)	13 (100)
CD-10	13 (92.9)	12 (92.3)
CD-56	7 (50)	6 (85.7)
Alfa-1-antitripsin	6 (42.8)	5 (83.3)
Vimentine	11(78.6)	11 (100)
Progesteron receptor	8 (57.1)	8 (100)
Neuroendocrine markers		
Chromogranin A	11 (78.6)	3 (27.3)
Synaptophysin	12 (85.7)	5 (41.7)
Ki-67 (≤ 3 %)	7 (50)	7 (100)
Cytokeratin (AE1/AE3)	2 (14.3)	1 (50)

3.5. Follow-up and survival

After discharge, the patients were followed up every 3 or 6 months by cross-sectional imaging (CT or MRI) and routine laboratory investigations. The mean follow-up time was 40.0 ± 23.5 months.

A 46-year-old female patient developed multiple liver metastases at the end of the first year. She had undergone distal pancreatectomy + splenectomy because of a solid, calcified lesion on preoperative imaging, and splenic vein invasion was observed intraoperatively. On pathological investigation, the tumour was 8.5 cm, had areas of haemorrhage and necrosis, was solid, and had an intact capsule but was invaded by tumour cells, and splenic vein involvement was observed. Twenty-four non-metastatic lymph nodes were detected, and this was the highest number in the cohort.

4. Discussion

The current cohort included 14 patients with SPN who underwent radical or conservative surgery (n=11 and 3, respectively). The length of stay, intraoperative blood transfusion, operation time, and examined lymph node number were found to be significantly higher in the radical surgery group, as expected.

Surgical resection is a unique treatment for SPNs. The surgical strategy should be decided based on the tumour location and involvement of adjacent structures (11). Complete resection should be the primary strategy irrespective of whether the adjacent structures are involved or not (10). Although SPNs have a low malignant potential (17), the association between pancreatic parenchymal infiltration , extrapancreatic invasion , R1 resection , lymph node metastasis , and likely recurrence is known (2, 13). Although regional lymphadenectomy was not recommended in most studies, because lymph node metastasis is rare (1, 9, 10, 12), there may be recurrence in lymph nodes (8) or locally (7, 12, 13). The number of the lymph nodes that are surgically removed is essential for staging of pancreatic ductal adenocarcinoma: patients with higher than 12 lymph nodes have been found to have longer survival (18). The evaluated highest number of lymph nodes (n=24) in this series was in a patient with liver metastasis, and invasion of the splenic vein was observed both in the intraoperative and pathological examination. For these reasons, regional lymphadenectomy and confirmation of R0 resection margin may be necessary during radical surgery. On the other hand, we think that conservative surgery should be performed both when there is no suspicion of structure involvement on imaging and when the diagnosis of SPN is confirmed pathologically before surgery.

Unfortunately, serum tumour markers are not helpful in preoperative diagnosis (4, 9, 10, 12, 19). In a multicenter study (9) in which 97 cases were examined, the CEA levels were elevated in two patients and the CA19-9 levels in three patients. Similarly, Goh et al. found elevated levels only in 2 of 23 patients (19). Reddy et al. (4), Butte et al. (12), and Bostancı et al. (10) did not observe any elevated tumour marker levels in their cohorts. In this study, we examined eight cases preoperatively, and there were no elevated tumour marker levels.

There has been an increase in the diagnosis of SPNs in the last decade with more using in the use of abdominal imaging techniques (2). Although different imaging methods have been used to diagnose SPNs (1), CT is the most commonly used abdominal imaging technique (2, 9, 12). On CT, these tumours typically appear as well-circumscribed masses with varying degrees of solid components, haemorrhage in cystic degeneration, and sometimes calcification (2, 12). Solid components frequently get contrasted in a similar way to the pancreatic parenchyma on arterial and venous phases, which is unlike the case in adenocarcinomas and neuroendocrine tumours (4). MRI can detect cystic degeneration, haemorrhage, and the integrity of the tumour capsule better than CT (3, 10). Eleven of the patients in our series were assessed with CT and 5 with MRI, and 8 of the 14 were diagnosed or suspected of

having SPN. From our experience, evaluation with MRI is required when CT provides insufficient results.

Notably, some studies have recently reported the EUS-FNA findings for the preoperative diagnosis of SPN (2, 4, 12, 20). However, these reports differ in the rate of using EUS-FNA and its diagnostic accuracy. As per the meta-analysis of Law et al, the diagnostic rate was 69.5% (2). According to a multicenter study (20), the diagnosis of SPN was made in 21 of 28 patients. In the study by Butte et al., 40% of the patients underwent FNA, and the diagnostic rate was 56% (12). A definitive diagnosis was obtained in one of five patients before surgery in the current study. In our opinion, the differential diagnosis of SPN affects the choice of surgical procedure. If there is no suspicion of parenchymal or extrapancreatic invasion on preoperative imaging, EUS-FNA and standardised pathological examination are required.

In some studies, malignant behaviour was associated with male sex (7), younger age (4), tumours larger than 5 cm (8, 11, 12), and capsular invasion on pathological assessment (13). Lubezky et al. detected liver recurrence in 4 out of 32 patients, and they presented tumour diameter as the only significant factor for recurrence (mean 8 vs. 5.2 cm) (8). Butte et al. also underlined the prognostic importance of tumour diameter (mean 7.8 vs. 4.2 cm) with regard to recurrence (12). Similar to the literature, our patient with recurrence had a tumour larger than 5 cm in diameter and pathological capsular invasion. Remarkably, her age (46 years) and sex were not risk factors for recurrence in the current literature.

Recent studies highlight beta-catenin, e-cadherin, and CD10 as important in the diagnosis of SPN (13, 17). However, immunohistochemical studies are not sufficient to determine the prognosis of these tumours (13). In contrast, advanced nuclear grade, perineural-lymphovascular invasion, high mitotic activity, and extensive necrosis may be related to poor prognosis (11, 13). There is promising research on the prognostic significance of the Ki-67 immunoreactivity ratio (3, 9, 13). In a study by Yepuri et al., more than 4% Ki-67 immunoreactivity was associated with early recurrence, but the results were not significant (13). In the current study, we did not observe perineural-lymphovascular invasion, and mitotic activity was low; additionally, Ki-67 immunoreactivity was lower than 4%.

SPNs show 2–15% malignant behaviour following surgery (2, 5, 6, 8). The most common recurrence areas of SPNs are the liver and the peritoneum (5, 8, 13), and the median recurrence times were 41 (13) and 50.5 months (2) in recent meta-analyses. Metastasis may be present at the time of diagnosis or develop in the years following surgery (8). Fortunately, patients have been reported to have a long life expectancy despite having developed recurrence (5). Surgery has not been determined to be of value in metastatic disease (8). However, some authors (5, 9) recommend surgery in case of resectable metastasis, whether determined perioperatively or during follow-up. Adjuvant treatment with 5-FU or gemcitabine and/or radiotherapy may be helpful for the treatment of unresectable metastatic SPNs (2). One of our patients developed multiple metastases in the liver one year after surgery, and adjuvant chemotherapy was planned followıng a decision by a multidisciplinary team.

Some meta-analyses (2, 13) have recommended a follow-up time of at least 5 years. However, long-term follow-up (up to 15 years) is essential for those with poor prognostic factors (13). The mean follow-up time in the current cohort was 40 ± 23.5 months; it was similar to those of the previous series (49.2 (8), 44 (12), and 36.1 (2) months). A critical question for follow-up is which imaging method to use. The contribution of positron emission tomography in determining recurrence remains undefined, but some SPNs markedly uptake 2-deoxy-2-fluoro-D-glucose during preoperative diagnosis (21). We think that, in addition to CT and/or MRI, positron emission tomography should be utilised in patients with potentially poor prognostic factors. The main limitations of this study were its retrospective nature and the small number of patients.

In conclusion, necessity for radical surgery may be associated with malignant behaviour. Therefore, the extent of the surgical operation and lymphadenectomy may be expanded during radical procedures for SPNs. In contrast, whenever feasible, conservative surgical procedures should be performed.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Can you count on willing to respond (WTR) results? In a pandemic, you may be alone

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Abstract

Willingness to Respond (WTR) is the measurement of employees' preferences to come to work during off-hours when needed. Are these answers given before a disaster realistic? Another question of the study was, "Can we speed up the required staff to reach the hospital?" WTR survey has applied to emergency service staff. After that, the off-duty staff was called to work at a time they did not know beforehand. The study tried to identify how much WTR reflected the reality. Ninety of 98 (91.8%) participants whose surveys were evaluated answered "Yes" to "If you are called in case of disaster, would you come to duty?" question. When asked whether they will come to work according to disaster types, this rate was measured as 36.7% in "In the case of an infectious disease of which treatment is not clear". WTR surveys can be used to predict the level of participation of staff on off-hours in meeting the need for additional labor. These surveys' results can be expected to be similar to the labor participation rates in case of a real disaster and the arrival time of the staff at the hospital can be improved with new communication methods.

Keywords: disaster medicine, hospital communication systems, disaster planning, hospital incident command system

1. Introduction

The loss of regional function that affects the people, goods, economy, and the environment that the region cannot overcome by using its means is called a disaster. Regions or organizations experiencing disasters need to increase their functional capacity at the level required by the disaster (1).

The Hospital Incident Command System (HICS) is based on the principle of increasing the functional capacity of hospitals and managing their existing facilities at the highest level. The capacity increase is directly related to the material and labor needed (2). One of the most important capacity increase elements is to call all the staff needed by the emergency plan and ensure the use of labor with appropriate timelines. However, due to the disaster's communication disorders, it may be challenging to communicate with staff who are out of working hours. Due to these difficulties in communication, time may be lost in recruiting labor (3).

This study's primary purpose is to announce the resulting labor need to the staff without losing time and design a system where the future staff information can be followed simultaneously and measuring its benefits. Another aim of the study is to determine whether the staff will participate in off-hours in disaster situations by using a survey method and to test the verisimilitudinous of this prediction in the actual drill.

2. Materials and Methods

2.1. Study design

Our study was designed as a prospective cross-sectional-descriptive study. Also, a survey was applied to investigate the reasons for the behavioral characteristics of the participants. Our study was conducted in November and December 2013 in the Emergency Medicine Department Adult Emergency Service of Gazi University Faculty of Medicine Hospital, an 1150-bed tertiary hospital in Ankara. The annual number of adult patient admissions to the emergency department is 58.000.

The ethics committee approval for the study was obtained from the Gazi University Clinical Research Ethics Committee. The study was conducted under the principles of the "World Medical Association Declaration of Helsinki."

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2.1.1. Establishing a new communication system

It was aimed to develop a system that is less likely to be affected by excessive use intensity in disaster situations, resistant to the physical effects of the disaster, and able to communicate quickly with the staff who are not on duty. Accordingly, it was concluded that satellite communication is suitable as a communication method by examining the existing literature. To transfer information quickly to the off-duty staff and to invite them to their duties, a satellite-mediated computer-aided system was established together with Globalstar Avrasya Satellite Voice and Data İletişim AŞ ®, one of the satellite communication service providers serving our region. In this system, after the decision to invite off-duty staff to the hospital, the phone number determined for the system is called; a message is left that includes the type of disaster, the number of victims affected, the location of the disaster, and the estimated arrival time of the victims to the hospital. This voicemail left is delivered to all registered participants who are designated as off-duty personnel. After the message is delivered, they are asked with the voice response system, whether they will come to the hospital to start their duty. Disaster managers over the internet can monitor this whole process; thus, it provides an idea about the quality and quantity of the staff reached and who declared that they would come and enables the logistics problems to be calculated rapidly.

2.1.2. Pre-drill survey application

With this study, we aimed to investigate the participants' willingness to come for duty in case of disaster and the behavioral characteristics that will occur if they need to stay overtime. The questions were asked about the obstacles to work out of office hours with the survey applied to the participants.

2.1.3. Disaster drill

In previous applications in our hospital, the staff to be called in case of a need were informed one by one by phone. With this study, the time measurements of the existing and new systems were performed, and it was investigated whether there was a significant difference between them.

Participants were randomly divided into two groups based on their duties and distance of their homes to the hospital. One group was called one by one by phone, the other group was called through the newly established system, and the following message was delivered: I am Dr FB, we have been notified that an explosion occurred in Kırıkkale weapon factory. It was told that there were more than 100 wounded and that the victims would reach us approximately 45 minutes later. Come to the hospital immediately to start working."

Call hours of the users were recorded. The total time spent by the caller was measured. When the called people came to the hospital, the arrival times were recorded by a member who did not know how they were called until that time. The duration between the time when the participants in both groups were called, and when they reached the hospital were recorded.

2.1.4. Post-drill survey application

Another survey was applied to those who came to the hospital to start their duty after being called, including their perceptions about the location and call at the time of application.

2.2. Statistical method

All data were recorded in SPSS 20.0 (SPSS Inc.®, Chicago, USA) program, and statistical analysis was performed. Descriptive statistics were made as arithmetic mean±standard deviation, median (minimum, maximum, frequency, and percentage).

First, the data were evaluated for the normal distribution in comparison of time measurements with the help of the Kolmogorov-Smirnov test, histogram, and P-P graphics; the comparison was made with the Mann-Whitney U Test because the measured values did not fit the normal distribution. The statistical significance level was accepted as $p<0.05$ in all analyzes.

2.3. Inclusion and exclusion criteria of participants

At the time of the study, all research assistants, intern doctors, nurses, emergency medical technicians, laboratory staff, and allied health staff working in the Emergency Department of the Emergency Medicine Department of Gazi University Faculty of Medicine were enrolled in the study. The study executor and people who did not want to participate in the study were not included in the study.

3. Results

Assistant doctor (n = 30), intern doctor (n = 26), nurse (n = 22), emergency medical technician (n = 12), laboratory technician (n = 12), warehouse supervisor (n = 5) and patient care staff (n = 18) who were on the list of emergency service staff between November and December 2013 were determined. 29 (96.7%) assistant doctors, 26 (100%) intern doctors, 16 (72.7%) nurses, 10 (83.3%) emergency medical technicians, 8 (66.7%) laboratory staff, 4 warehouse supervisors (80%) and 9 (50%) nursing staff were included in the study.

3.1. Results of the pre-drill survey

Survey No:1 was applied to a total of 103 people enrolled in the study. Five of these surveys were not considered severe due to conflicting answers and excluded. The remaining 98 surveys were taken into evaluation (Table 1). The average age of the participants was 28.1±5.5 years (median: 27, min: 19, max: 51). The average term of duty is 45.03 months when the periods of duty are evaluated (average: 45.03±52.9; median:24 (min:1, max:300)).

To the question "Would you come to work if you are called to work due to a disaster during off-hours?" directed to the participants, 90 (91.8%) of the 98 participants gave a

positive answer. In another question, they were asked whether they would go to work to start working if they accidentally receive disaster news during off-hours. 59 of 96 people (61.5% among respondents) answered the question that two people (2%) did not answer stated that they would go, while 37 (38.5%) stated that they would not.

Table 1. Demographic characteristics of the survey participants

	#	*Percentage (%)**
Gender		
Female	50	51
Male	48	49
Duty		
Researcher Physician	29	29.6
Intern Doctor	24	24.5
Nurse	17	17.3
Patient Care Staff	10	10.2
Emergency Medical Technician	9	9.2
Lab technician	9	9.2
Transportation Choice		
By foot	25	25.5
Minibus	25	25.5
Private Vehicle	22	22.4
Bus	16	16.3
Subway	8	8.2
Taxi	1	1
Unanswered	1	1
Marital Status		
Single	57	58.2
Married	41	41.8
People and Pets they take care of		
Child	20	20.4
Elders	8	8.2
Pet	8	8.2
Patient	7	7.1

****: In-title column percentage***
Total number of participants whose survey was accepted=98

Participants were asked about the factors that push them to work in case of disaster. The sense of responsibility (55%) was the answer mostly given, the second most frequent answer (39%) was the desire to help the victims, and the least common answer was avoiding problems with the employer (6%). Participants were asked that under what conditions the probability of working in case of a disaster increases? The answers to this question, to which 96 people answered, and their percentages among all the answers are shown in Table 2.

Participants were asked whether they would come to work if they received a disaster call outside of working hours by specifying the disaster type. This question was answered by 98 participants, going to work status of the staff, if called, out of office hours by disaster types is shown in Figure 1.

The relationship of the answers given whether they would come to work if they are called in case of disaster to the participants with gender, duty (clinical or allied health staff), marital status, presence of children, presence of a patient at home, presence of elderly at home and having pets were investigated. Staff is grouped under two main headings: "Clinic (assistant doctor, intern doctor, nurse, and emergency medical technicians)" and "Allied Health Staff (laboratory technicians and patient care staff)." In this study, the only factor affecting coming to work has created a statistically significant difference as "Duty" (by sing Fisher's precision test, p = 0.043). There is no significant difference in other groups.

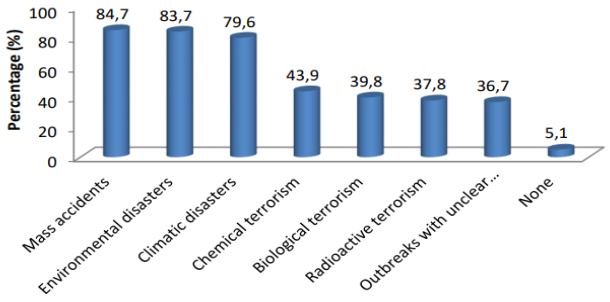

Fig.1. Going to work status of the personnel, if called, out of office hours by disaster types

3.2. Drill results

In the second part of the study, a drill including calling of off-duty personnel and time measurements was applied. The distribution of the two groups in this drill in terms of duties is shown in Table 3.

10 (12.7%) of the 79 people called due to the drill did not come to the hospital, although they were called. Sixty-nine people (87.3%) came to the hospital after being called. The method by which those who came to the drill were called, as shown in Table 3. According to the search method, when the coming rates were compared, there was no statistically significant difference (p = 0.737 was calculated using Fisher's precision test).

The duration between the beginning of the drill and the arrival of the staff (disaster-call duration) and the duration between reaching the staff and the staff's arrival to the hospital (call-hospital duration) were measured. These two measurements were collected, and the duration between the beginning of the drill and the arrival of the staff to the hospital (disaster-hospital) was calculated. The averages of these periods in both groups are shown in Table 3. When the durations occurred during the call with the two methods were compared, the "HICS activation-call" durations (p = 0.0001) and the "HICS activation-hospital" durations (p = 0.006) were statistically significant in the two groups, but there was no statistically significant difference between the call-hospital durations (p = 0.556). When the relationship between coming or not coming for duty as a result of a call and the task of the participant was investigated, it was not found statistically significant (87.9% of the clinical staff who came after the call; 84.6% of the allied health staff) (by Pearson chi-square method, p = 0.248). When the relationship between coming or not coming as a result of a call and the gender of the participant was investigated, it was not found statistically significant (using Fisher's precision test, p = 1.000).

Table 2. Factors thought to increase the probability of working in case of disaster*

What factors increase your probability of working in case of a disaster?	Answers	
	Number (n)	%
If precautions are taken against the dangers caused by disasters (such as security and vaccination)	58	20.1
If my family's safety is ensured	58	20.1
If my communication needs with my relatives are met	38	13.1
If my transportation needs are met	34	11.8
If my family's care needs (nursery, patient/elderly care) are met	32	11.1
If my duty in case of a disaster is predetermined	29	10.0
If employees working due to the disaster are appreciated	23	8.0
If employees are paid additional wages due to disaster	14	4.8
None	3	1.0
Total number of options checked	289	100.0
*: Multiple options can be marked in this question.		

Table 3. Call methods and distribution of duties

	Call Method					Total
	Manual		Automated			
	N	%*	N	*	N	%*
Clinic	34	51.5	32	48.5	66	100
Allied Health Staff	6	46.2	7	53.8	13	100
Total	40	50.6	39	49.4	79	100

Table 4. Distribution of the response to the call according to the call method

		Response to the call			
		Came		Did not come	
		N	%	N	%
Call method	Manual	34	85.0	6	15.0
	Automated	35	89.7	4	10.3

Table 5. Comparison of "Call by HICS (Hospital Incident Command System) activation", "coming to hospital by call" and "coming to hospital by HICS activation" as per the method of call

	Call method		P*
	Manual	Automated	
	Mean ± SD	Mean ± SD	
Duration between HICS activation and call (min)	18.26 ± 13.24	2.0 ± 0.00	.0001
Duration between the call and the staff's arrival at the hospital (min)	33.65 ± 23.30	31.23 ± 20.20	.556
Duration between the HICS activation and the staff's arrival at the hospital (min)	51.91 ± 33.00	33.23 ± 20.20	.006

4. Discussion

In this study, the possibility of coming to work in case of a disaster, the possibility of working overtime, the obstacles in front of both, and solution suggestions were investigated to meet the staff need, which is one of the logistics needs in disaster situations. There are a limited number of publications in the literature investigating the probability of coming to work in the event of a disaster. Among these publications, the ones that were designed similar to this study were examined in terms of the participant cluster, the types of disasters questioned, obstacles, and suggestions.

Although the desire to come to work in the event of a disaster, which is defined as "WTR - Willing to Respond" in the literature, varies from publishing to publishing, it was observed that generally close results were achieved. In this study, 91.8% (90/98) of the participants stated that they would come to work in disasters. Ogedegbe et al., who conducted a similar study, found this rate as 93% (4).

When the relationship of the probability of coming to work in case of disaster with age, gender, duty, duty term, marital status, presence of children, elderly care, patient care, and pet care was examined, a significant direct relationship was found only in the type of duty, but not in others. However, it is not statistically significant the difference between those who have. In a study conducted by Qureshi et al. in 2005, it was concluded that female gender, elderly care, and patient care affect working in disasters (5). The reason for this difference may be that other family members in our country are more likely to reduce the care burden of people in special circumstances.

In another study published by Steffen et al. in 2004, no significant difference was found between age groups and disaster participation, as in this study (6). In the article of Masterson et al., published in 2009, it was stated that they could not find any significance between coming to work due to a call and duty, age, having children; however, they explained that there is a difference in the gender that is applicable only in case of biological terror (7).

In this study, the connection between disaster types and the desire to work in disasters was also investigated. 84.7% of the participants stated that they would come to work in mass accidents and provided the highest participation. Qureshi et al. calculated this rate as 85.7% (5). In the study of Steffen et al., the willingness to come to work in a plane crash, which was presented as an example of mass accidents, was found to be 98% (6). Masterson et al. found the participation rate for plane crashes to be 98% (7).

While the rate of those who stated that they would not work even if they were called during off-duty hours in any of

the disaster types is 5.1%, only 36.7% of the participants stated that they would come to work if they were called in an epidemic with an unclear treatment. This rate was shown as the lowest participated disaster, with 48% in the study of Qureshi et al. (5).

When the factors that could cause the participants not to come in disasters were evaluated, it was measured that 32.8% of the answers could be health problems, and 30.5% could be transportation problems. In Qureshi's study, while transportation problems were first with 33.4%, health problems were reported as 14.9% (5). In the article published by Ogedegbe et al. in 2012, it was shown that child care is the biggest obstacle to coming to work in case of disaster. An important reason for this difference between the studies is thought to be due to the demographic characteristics of the participants; as a matter of fact, in the study conducted in our hospital, it was concluded that only 20.4% of the participants had children and therefore child care did not rank first as an obstacle (4).

When the factors that can increase the probability of working in case of a disaster are examined, 20.1% of the responders (60.4% of all participants) stated that they would consider working if the safety of their families is ensured, and 20.1% (60.4% of all participants) stated that they think that the probability of coming to work in disasters will increase if precautions are taken against the dangers caused by the disaster. In parallel with the results, another publication showing that taking personal security measures against the risks created by the disaster will increase participation in disasters is the study of Kruus et al. (8). In this study, Kruus et al. pointed out that the probability of working in case of a disaster will increase by ensuring the participants' family's safety. In a similar study, Mackler et al. stated that when personal protective measures are taken, the desire to participate increases (9).

The ratio of the participants who said that they would work overtime in case of a disaster is 94.7%. In total, 66.3% of the participants stated that they could work 8 hours or more, 27.4% of them up to 8 hours. In the study of Steffen et al., while the duration of overtime for the male gender was calculated approximately 7 hours more, no significant difference was found between the genders in this study conducted in our hospital (Fisher's precision test, $p = 1.000$) (6).

77% of the participants defined the willingness to work in the event of a disaster as a sense of responsibility (since it is a question with more than one answer marked, 55% of the total answers, 77% of all participants marked this answer). In a similar study, DiMaggio et al. stated that 83% of the participants had the highest rate and wanted to work in disasters because of their sense of responsibility (10).

When the disaster drill, which is the second part of the study, and the results of the survey applied after it was evaluated, it was seen that the automatic call system significantly changed the notification time, and accordingly, the duration between the disaster and the arrival of the staff to the hospital significantly decreased. Since there is no similar study in the literature, the data could not be compared with other studies. This study's distinctive feature is that it is the only study that measures the duration of coming to the hospital of the staff out of working hours if needed.

Although it is seen that calling the staff one by one in the traditional method used to reach the staff is time-consuming, it has been concluded that the computer-aided automatic call system does not contribute to the number of coming staff. It was concluded that the proportion of participants who came to those who did not come in both systems was independent of duty and gender.

The rate of coming to work in case of disaster, which appeared in the first survey and referred to as "WTR - Willingness to Respond" in the literature, was calculated as 91.8% in this study; however, no study measuring how much this ratio would be in real life could not be found in the literature. Participation in the study as a result of the drill was calculated as 87.3%. Unlike other studies in the literature, not only through a survey but also with a real drill, the rate of employees who are out of working hours to work in disasters was measured. This case, which is described as "WTR (Willingness to Respond)" in the literature, has been tested with a drill, and it was found that there is a statistically insignificant difference between the survey results and reality. Although the benefit measured in this study is time-oriented, it is thought that satellite communication will be useful in providing an uninterrupted communication channel in a real disaster.

The study was conducted in a single center. Changes in the perception of the staff in other centers may affect the outcomes. Besides, participants in the study were only emergency room workers. Hospital Incident Command System concerns all hospital staff. In multi-center studies applied to all hospital clinics, these problems will decrease, and the reliability will increase with the increase in the number of participants. The fact that the study has more than one step (application of the survey no.1, conducting a drill, and application of the survey no.2) indisposed the participants' volunteering will and made them reluctant to answer the survey questions may have affected the results. Studies conducted with shorter surveys and longer intervals between steps may be less affected by this negative effect.

The study was produced using the emergency medicine graduation thesis made in 2013. For this reason, in the course of time, serious developments have been experienced in communication systems and many applications have been developed that can be used in disaster communication other than voice calls. Due to the date of the study, these

applications could not be mentioned.

The sample size was not calculated in the study, as every person working in the emergency department was planned to be included in the study.

A computer-aided satellite communication system was investigated in this study to meet the logistics needs. In the measurements made with the new system designed to reach the staff out of working hours, it has been seen that this system, which can make mass calls compared to the existing communication system using mobile phones and fixed phones, can benefit greatly in terms of time. By developing disaster communication systems, the functions of Hospital Incident Command System can be improved by saving time in reaching logistics needs such as labor.

In order to provide labor in disasters, it will be beneficial to take precautions that protect the staff and their family from the damage caused by the disaster and improve the staff's transportation services. The reasons underlying the change in the desire to work in disasters should be investigated, and solution plans should be created.

While creating Hospital Incident Command System, WTR surveys can be used to predict the level of participation of staff on off-hours in meeting the need for additional labor. These surveys' results can be expected to be similar to the labor participation rates in case of a real disaster.

Conflict of interest

The authors have no potential conflicts to interest to declare.

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Comparison of autogenous basilic vein, polytetrafluoroethylene and polycarbonate grafts for haemodialysis access

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Abstract

This study aims to present data obtained by comparing the results of three different kinds of arterio-venous fistula (AVF) in hemodialysis patients. One hundred twenty (120) patients were operated with autogenous brachiobasilic (BBF) AVF, upper arm polytetrafluoroethylene (PTFE) or polycarbonate-urethane (PCU) graft AVF in our centre between January 2015 and January 2018. They were enrolled for a retrospective study into three groups; BBF Group (n=54), PTFE Graft Group (n=36), PCU Graft Group (n=30). Their data was analyzed, primary and secondary patency rates, complications and cannulation time were calculated. Primary patency rates of the 1st, 2nd and 3rd years were recorded to be respectively 81.4%, 72.2% and 59.2% in the Autogenous Arteriovenous Fistula (BBF) Group; 61.1%, 55.5% and 44.4% in the PTFE Group and 63.3%, 60% and 46.6% in the PCU Group. Infections occurred in 3.7% of BBF patients, in 8.3% of PTFE patients and 10% of PCU patients. First cannulation times were: 69± 17 (day) in BBF Group, 20 ± 5 (day) in PTFE Group and 10± 3(day) in PCU Group. BBF was observed to perform better than AVG in terms of primary and secondary patency and to result in low infection rates. On the other hand, first cannulation was performed earlier in both graft AVFs. There was no significant difference between PTFE and PCU in terms of our outcomes.

Keywords: arterio-venous fistula (AVF), basilic vein graft, PTFE dialysis graft, polycarbonate dialysis graft

1. Introduction

Vascular access is of extreme importance in dialysis dependent chronic renal insufficiency patients. Autogenous arteriovenous fistula (aAVF) is the most frequently used and desired access due to high patency rates and low morbidity (1). However, maturation of aAVF requires several weeks to months and it is not always feasible to obtain a healthy aAVF because of previously damaged superficial veins. Distal forearm aAVFs are the first choice and as they become unavailable, they are followed by brachio-cephalic aAVFs, while superficialised brachio-basilic aAVFs, graft AVFs and permanent catheters are later options.

Superficialised brachio-basilic fistula is an aAVF that requires a double staged surgical procedure (4). First the brachio-basilic fistula is created, then it is superficialised to make it accessible for cannulation. Despite the complicity of the procedure, basilic vein offers an adequate diameter for aAVF and thanks to the depth of the location, previous damage due to intravenous injection is less expected.

Arteriovenous fistulas constructed with a synthetic graft anastomosed between a native artery and veins provide an alternative solution when a functional aAVF cannot be obtained (1-3). Easy cannulation and early maturation are some of the advantages of graft AVFs. However, they demonstrate lower patency rates and require more re-interventions compared to aAVFs. Polytetrafluorethylene (PTFE) grafts are the most commonly used option and polycarbonate-urethane (PCU) grafts are another valid choice.

There are high number of studies comparing the results and longevity of aAVF, prosthetic grafts (5, 6), and/or autogenous brachiobasilic aAVF (4, 7). Most of them are retrospective studies conducted on different patient populations. However, no literature study has been found to compare autogenous brachiobasilic aAVFs (BBF), Politetra plouro etilen (PTFEgraft AVFs) and Polycorbonate (PCU graft AVFs.) In this parallel, the main aim of this study was to make a retrospective comparison of the use of these three kinds of AVFs in similar patients.

2. Materials and Method

2.1. Ethical Board Approval

Approval was obtained from the Ethical Board of Human Researches of İstinye University on 10.04.2021 (Protocol No 21-81).

2.2. Patient population

One hundred twenty (120) patients who were operated in our centre, Medical Park Samsun Hospital, between January 2015 and January 2018 had been enrolled for a retrospective study. Study participants were chosen from a pool of patients who had previous non-functioning lower arm aAVFs or brachiocephalic

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aAVFs, or who lacked suitable veins for aAVF.

Other inclusion criteria were brachial or basilic vein diameter ≥ 2.5mm and lack of proximal vein thrombosis/constriction. Study patients were randomized into three groups; BBF Group (n=54), PTFE Graft Group (n=36), PCU graft group (n=30). Written consent was duly obtained, and patients' demographic data and past medical history were recorded.

2.3. Preoperative assessment

All study patients were performed detailed vascular examination, including arterial and venous doppler ultrasonography. Venography was avoided to minimalize the risk of phlebitis. MR angiography was performed in 28 patients with previous catheter history to diagnose subclavian vein thromboses or striction.

Table 1. Patients characteristics

	AVF (n=54)	PTFE (n=36)	PCU (n=30)
Age	56.3 ± 8.5	54.2 ± 10.3	57.1 ± 9.8
Male	36 67%	26 72%	21 70%
Female	18 33%	10 28%	9 30%
Primary disease			
DM	31 (57.4%)	19 (52.7%)	15 (50%)
GN	12 (22.2%)	9 (25%)	8(26.6%)
Other	11 (20.37%)	8 (22.2%)	7 (23.3%)
Comorbidity			
HT	33 (61.1%)	23 (63.8%)	20 (66.6%)
IHD	6 (11.1%)	6 (16.6%)	4 (13.3%)
PAD	4 (7.4%)	2 (5.5%)	2 (6.6%)
Smoking history	34 (62.9%)	23 (63.8%)	20 (66.6%)

2.4. Surgical technique

All operations were performed under supraclavicular block anaesthesia. In BBF Group (n=54), a two-stage surgery was performed. At first stage, aAVF was created between the brachial artery and basilic vein at antecubital fossa. End-to-side anastomoses was performed using 6/0 polypropylene. The second stage of the operation was completed 30±2 days later and included basilic vein mobilization and superficialisation from the deep fascia. Skin was incised longitudinally from antecubital fossa till axilla, just above the basilic vein. The basilic vein was gently separated from the cutaneous antebrachial nerve to avoid injury, and branches were ligated.

In PTFE Group (n=36), a 6mm PTFE graft (WL Gore and Associates Inc, Phoenix, Arizona, USA and Bard Inc, Tempe, Arizona, USA) was anastomosed between the brachial artery and axillary vein, in a straight configuration. Two different skin incision were made, arterial one being at the antecubital fossa and venous one at the axilla. Graft was tunnelled under the skin. End-to-side anastomoses were performed using 6/0 polypropylene. The same technique was applied also to the PCU Group (n=30) with the one single difference of the graft material used *AVflo™ graft (NICAST,* Lod, Israel). Distal limb perfusion was monitored by pulse oximeter in all procedures.

3. Results

Statistical analysis was performed using the Statistical Analysis System (SAS Institute Inc., Cary, NC). Results were presented as mean ± standard deviation for continuous and as frequency (percent) for categorical variables.

Major outcomes of the present study are related to the primary patency (time period from the access placement until the first thrombosis or reintervention to maintain patency) and secondary patency (time period from placement until abandonment of access due to permanent occlusion).

Primary patency rates of the 1st, 2nd and 3rd years were recorded to be respectively 81.4%, 72.2% and 59.2% in the autogenous arteriovenous fistula (BBF) Group; 61.1%, 55.5% and 44.4% in the PTFE Group and 63.3%, 60% and 46.6% in the PCU Group (Table 2). This finding demonstrates that BBF has a significantly higher primary patency rate than both PTFE and PCU (Table 2) while no significant difference was noticed between the PTFE and PCU grafts.

Table 2. Patency rates and other outcomes

Primary patency			
1 year	44 (81.4%)	22 (61.1%)	19 (63.3%)
2 year	39 (72.2%)	20 (55.5%)	18 (60%)
3 year	32 (59.2%)	16 (44.4%)	14 (46.6%)
Secondary patency			
1 year	50 (92.5%)	29 (80.5%)	25 (83.3%)
2 year	47 (87%)	27 (75%)	23 (76.6%)
3 year	40 (74%)	19 (52.7%)	16 (53.3%)
Other outcomes			
Haemorrhage	2 (3.7%)	2 (5.5%)	1 (3.3%)
Infection	2 (3.7%)	3 (8.3%)	3 (10%)
Seroma	0	0	0
Surgical banding	3	0	0
Surgical plication	0	1	1
1st cannulation	69 ± 17 days	20 ± 5 days	10± 3 days

The average primary patency duration was 881.7±593.2 days for autogenous arteriovenous fistula, 473.5±393.2 days for PTFE graft and 481.5±432.7 days for polycarbonate graft (p=0.0000), which points a significant difference. BBF graft produced better results than the synthetic grafts due to its high both primary and secondary patency rates as well as reduced complications such as infection. However, no significant difference was found between the PTFE and PCU grafts.

4. Discussion

It is not easy to establish and maintain an adequate permanent haemodialysis access. Autogenous AVFs, grafts and permanent catheters have been valid options applied in this scope. Autogenous AVFs have been used widely for years due to their simplicity and low morbidity. Lower arm aAVFs and brachiocephalic aAVFs are excellent examples. However, lack of suitable veins or failure of present access force the surgeon

to seek alternative solutions accompanied by higher complexity and morbidity rates. Permanent catheters are generally used as a last resort because of their high risk for infective endocarditis and venous thromboses.

Superficialised BBF is an aAVF created by a double-staged procedure. It was first reported by Dagher (8) in 1976 and has regained popularity lately with the widely spread of autologous grafts. After a short superficial segment, the basilic vein dives deep under the fascia, which protects it from injections and injuries, making it a preferable graft for aAVF (9). It also has a sufficient diameter for a good run-off (10) and is durable to infection as an autogenous graft (9,11).

While the autogenous grafts are more advantageous in general, graft usage is a helpful tool and more advantageous in patients in urgent need of vascular access as they enable immediate use.

While the most common cause of AVF failure is venous stenosis, it may rarely result from arterial stenosis. In such cases, reduced thrill or replacement of thrill by pulsation, edema in the arm, clogged dialysis needle and post-dialysis prolonged bleeding from the dialysis needle point are recorded. Graft thrombosis is the most important reason of graft failure and occurs due to stenosis related to intimal hyperplasia. Treatment consists in surgical or endovascular intervention. According to the results of a study published in 2009, there is no difference between the early-stage results of thrombectomy with surgical intervention and endovascular intervention (12). Success of the procedure depends on its capacity to target the stenosis that may develop during the procedure. Intervening particularly in the stenosis in the venous anastomosis segment of the graft increases the patency chance of the graft by preventing repeated thromboses. To ensure secondary patency, the grafts were performed thrombectomy using fogarty catheter under local anaesthesia. In cases of suspected post-thrombectomy stenosis; 0.035-inch hydrophilic wire was passed for venous lesions and 0.025-inch hydrophilic wire for arteriyel lesions under fluoroscopy and, angioplasty was performed during the same session. The key point in preventing recurrent thrombosis and increasing patency rate is removal of stenosis.

In graft infections, generally local temperature increase and tenderness are experienced at the needle access site on the graft. Sometimes such systemic symptoms as fever and bacteraemia. Graft infection is mainly related to gram (+) bacteria and, staphylococcus aureus is the most frequent pathogen (50-90%). (13) Empiric broad spectrum antibiotic therapy is started without waiting for blood culture results. Low virulence infections generally occur in punction sites and are cured with antibiotherapy and local resection. In the present study, local infection developed in the needle access points of 2 cases (3.7½ %) in the autogenous graft group; of 3 cases (8.3%) in the PTFE group; and of 3 cases (10%) in the polycarbonate group. The infections were contained using antibiotics. Minor outcomes are related to the acute haemorrhage in early postoperative period leading to surgical revision, infection (requiring removal of the access) and first cannulation time (decided by the nephrologist after judging maturation of access). In rare conditions, infection occurs near anastomotic site and can lead to life threatening haemorrhage. Graft removal should be considered in these cases. We did not experience any potential threatening graft infection during this study. No significant difference was noted between the study groups regarding early haemorrhage.

BBF group showed significantly lower infection rates than both grafts while the comparison between the PTFE and PCU groups produced similar infection rates. On the other hand, first cannulation time was significantly lower in both graft groups compared to BBF, but no such difference was recorded between the PTFE and PCU groups.

Perigraft seroma is a rare complication of PTFE grafts. It consists in a fibrotic pseudo-capsule created by sterile serum extravasation from graft and can lead to graft resection. No such complication was encountered during this study; thus, it is not included in Table 2.

Dialysis grafts may be in positioned in a straight or loop configuration. We applied a straight configuration in all our patients. Artery was explored right above antecubital fossa and vein was explored in axillar fossa. Graft was passed under the skin and heparin was administered. Arterial anastomose was performed followed by venous anastomose.

Synthetic grafts are suitable to be used after 2-4 weeks. Although early cannulation grafts (including first 24 hours) are available, their usage is limited only in emergent situations due to high risk of haemorrhage or thrombosis.

Distal hand ischemia may develop in extremities with AV graft. Generally, hand pain and coldness occur 1 hour after starting dialysis and, tissue loss can happen in serious ischemia, especially in diabetic patients with poor vascular bed. (14) Proximal arterial stenosis, if exists, can be treated with endovascular procedures, while surgical banding or plication can be performed in high flow conditions. We performed surgical banding with 6mm PTFE in three patients in BBF group, and plication in one patient in PTFE and one patient in PCU group (Table 2).

When applied, neural blockade leads to venous dilation, which itself results in high quality anastomose and increased early patency rate. Prophylactic broad-spectrum antibiotics decreases (15) graft infection, and all our patients received prophylactic antibiotics before surgery.

Study patients had their first follow-up by the vascular surgeon at the end of the 1st month of placement of the access and subsequent check-ups annually.

In conclusion, the present study demonstrates superiority of BBF compared to AVG in terms of primary and secondary

patency, and low infection rates. On the other hand, AVG leads to notable early first cannulation. Comparison of PTFE and PCU grafts points out no significant difference in any of the study outcomes. In this framework, this study suggests that vascular access in complicated patients should be planned on individual basis, taking into consideration condition of the proximal arm veins, urgency of haemodialysis and general state of patient.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

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Ethical Approval

The study was approved by the Ethics Committee for Research on Human Sciences of İstinye University (date: 04.10.2021, No. 21-81).

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Comparison of endoloop and Hem-o-lok clip for stump closure in laparoscopic appendectomy: which one is more cost-effective. A retrospective study

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Abstract

We aimed to show the effect of closure of the appendix stump with different methods during laparoscopic appendectomy (LA), on postoperative complications, healing process and costs. Patients who underwent LA due to acute appendicitis in the last 5 years in Rize were retrospectively analyzed. Our study includes comparative analysis on two patient groups in which we carried LA. We used endoloop (EL) in Group 1 and hem-o-lok polymeric clip (HC) in Group 2 to close the appendix stump. Patients were compared in terms of demographic characteristics, American Society of Anesthesiologists (ASA) score, preoperative white blood cell and C-reactive protein (CRP) elevation, whether a drain was used, appendix diameter, pathological diagnosis, postoperative complications, duration of surgery and length of stay, and cost. Of 209 patients, 111 (51.2%) were male and 98 (48.8%) were female. The frequency of drain placement was higher in Group 2 (P = 0.005). No stump leakage was observed in either group, but the incidence of other postoperative complications was significantly higher in the EL group (P=0.041). The use of HC is cheaper than the use of EL. There was no significant difference in other parameters. Both EL and HC are used safely in LA. Although both methods do not have obvious advantages over each other, HC stands out one step further due to its more affordable cost and less possibility of postoperative complications.

Keywords: appendectomy, complications, stump, laparoscopy

1. Introduction

Acute appendicitis (AA) is the most common cause of emergency surgery worldwide. The standard technique is open appendectomy using the Mc-Burney incision. Laparoscopic appendectomy (LA) was first performed in 1983 as an alternative to open appendectomy (1). With advances in laparoscopy and surgical instruments, the laparoscopic approach to appendectomy has gained wide acceptance over the years.

LA is a safe procedure that provides shorter hospital stay, less wound infection, and faster postoperative recovery (2). LA is recommended as the first choice, especially in the elderly, obese patients and women (3, 4). The most important step in avoiding complications such as appendiceal stump leakage, peritonitis, sepsis, and fistula that may develop in the postoperative period during appendectomy is the safe closure of the stump (5). Many different methods have been used to close the stump in LA. Endoloop, non-absorbable polymeric clips, titanium clips, extracorporeal knots, intracorporeal ligatures, staples and ligasure are among these stump closure methods (3). There is no consensus on which of these methods is the gold Standard (6).

The ideal method for appendiceal stump closure should be safe, accessible, simple to use, and cost-effective (7-10). Stapler use is the safest and most expensive closure method, especially in inflamed, enlarged and wide-based stumps (7). The use of the Endoloop (EL) is technically complex and may require short training, but it is less costly than staples (11). Hem-o-lok polymeric clip (HC), stands out in terms of ease of use, reduction in operation time and cost (12).

2. Materials and Methods

Our study was carried out retrospectively with the approval of the ethics committee of Recep Tayyip Erdogan University, Faculty of Medicine (approval date:25/11/2021, number: 2021/205). Two hundred and nine patients who underwent LA between January 2018 and September 2021 at Rize Recep Tayyip Erdoğan University Training and Research Hospital were included in the study. The appendix stump was closed with EL (CovidienTM, SurgitieTM, Ligating Loop with Delivery System, United States) or HC (Hem-o-lok ligation system, Teleflex Medical, North Carolina, United States). Patients whose appendix stump was closed using a single EL were included in Group 1, and patients whose appendiceal

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stump was closed using a single HC were included in Group 2.

Patients who used different stump closure techniques, had two or more ligatures, and were converted to open appendectomy for any reason were not included in the study. Patients' age, gender, American Society of Anesthesiologists (ASA) score, preoperative white blood cell and C-reactive protein (CRP) elevation, whether a drain was used, appendix diameter, pathological diagnosis, postoperative complications, duration of surgery and hospitalization, cost were recorded separately for Group 1 and Group 2. Differences between groups were compared.

2.1 Surgical technique

All operations were performed by the same surgical team and a standard protocol was followed in the surgical procedure.In general anesthesia induction, two grams of intravenous cefazolin was administered as antibiotic prophylaxis.A 10 mm trocar was placed above the umbilicus, followed by a 30° scope and examination of the peritoneal cavity. A 5 mm trocar was placed 4-5 cm above the pubis in the midline, and the second trocar (5 mm in Group 1, 10 mm in Group 2) was placed in the left lower quadrant. (Fig. 1).

The mesoappendix was resected with a 5 mm vessel closure device ligasure (CovidienTM LigaSureTM Maryland Jaw Laparoscopic Sealer/Divider, Unites States). In Group 1, a single EL was placed on the base of the appendix, and in Group 2, a single HC was placed on the base of the appendix and cut using a ligasure (Fig. 2). Different methods were used when the stump of the appendix could not be closed safely using a single EL or a single HC. Laparoscopic stapler, double EL or double HC were used in these cases, but these cases were excluded from the study. The use of a drain was not standard, this was decided during the procedure. A sampling bag was used for perforated appendicitis.

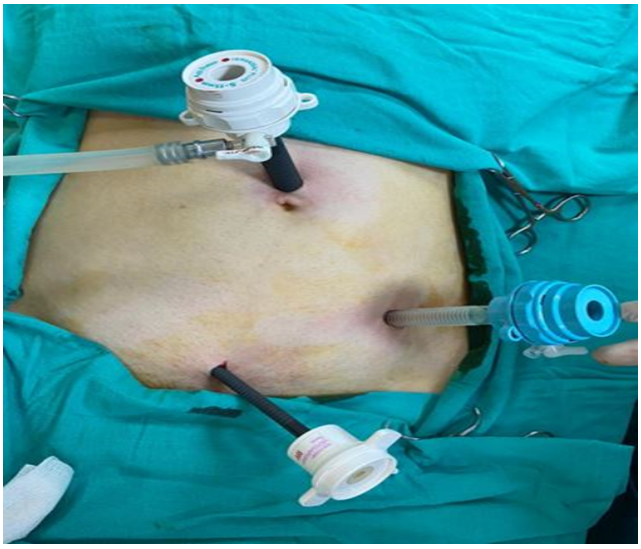

Fig. 1. Locations of the trocars

2.2 Statistical analysis

Statistical analyzes were performed with IBM SPSS V22 (Chicago, Unites States). Categorical data were presented with numbers and percentages, and continuous variables with mean and standard deviation. The distribution properties of continuous variables were evaluated with the Kolmogorov-Smirnov test and the Shapiro-Wilk test. Chi-square test was used to evaluate the relationship between stump closure technique and categorical variables, and Mann Whitney-U test was used to evaluate its relationship with continuous variables. The statistical significance level was accepted as P <0.05 in all statistical analyses.

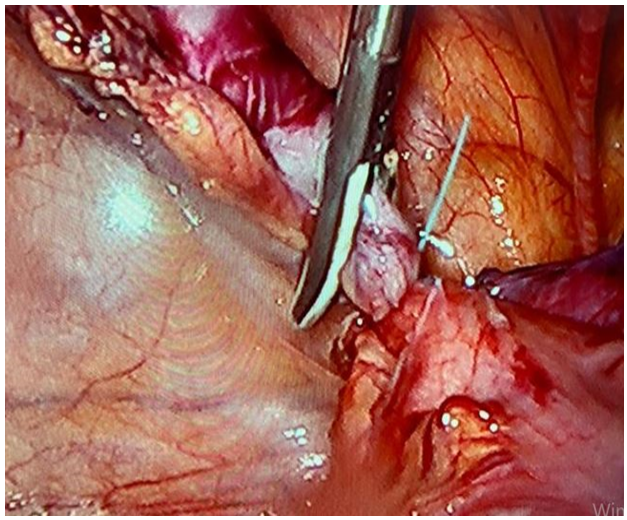

Fig. 2. Closing of the appendicular stump with application of one endoloop and cut off with ligasure

3. Results

There were 107 (51.2%) patients in Group 1 and 102 (48.8%) patients in Group 2. Of 209 patients, 111 (53.1%) were male and 98 (46.9%) were female. The mean age was 39.8 (minimum 18, maximum 90 years). Demographic data of the patients are defined in Table 1. There was no difference in terms of comorbid diseases in both groups according to ASA scores (P =0.659, Table 1). There was no difference between the groups in terms of preoperative white blood cell and CRP elevation (P =0.842, P =0.498, respectively Table 1). Mean operative times were 54 and 55 minutes for Group 1 and Group 2, respectively (P =0.321, Table 2).

The use of drains was significantly higher in Group 2 (P =0.005, Table 2). On macroscopic examination, appendix diameter was similar between both groups (P =0.865, Table 2). There was no difference between the two groups in terms of pathological diagnosis (P =0.830, Table 2). No stump leakage was observed in any patient in either group. Other postoperative complications were significantly higher in Group 1 (P =0.041, Table 2). Mean length of hospital stay was similar in both groups (P =0.436, Table 2). While the cost of one EL used in Group 1 is approximately $43, the cost of one HC used in Group 2 is approximately $6. The cost of EL associated with cost effectiveness is approximately 7 times higher (Table 2).

Table 1. Demographic characteristics of patients and preoperative findings

	Group 1 (Endoloop) n:107	Group 2 (Hem-o-lok) n:102	P
Gender,n(%)			
Male	57(53.3)	54(52.9)	0.962
Female	50(46.7)	48(47.1)	0.450
Age,years (min-max),(SD)	40.4 (18-81) (±15.94)	39.2	0.450
A1	30	34	0.659
A2	62	53	
A3	15	15	
WBC height,n(%)			
Yes	81(75.7)	76(14.5)	
No	26(24.3)	26(25.5)	0.842
CRP Height,n(%)			
Yes	79(73.8)	71(69.6)	
No	28(26.2)	31.(30.3)	0,498

min = minimum, max = maximum;SD = standard deviation;ASA= American society of anesthesiologists;WBC = white blood cell;CRP= C-reactive protein.

Table 2. Peroperative and postoperative findings

	Group 1 (Endoloop) n:107	Group 2 (Hem-o-lok) n:102	P
Operation time, minutes (min-max),(SD)	54.1 (25-120)(±25.3)	55.5 (20-120)(±22.6)	0.321
Drain use,n(%)			
Yes	23(21.5)	40(39.2)	**0.005**
No	84(78.5)	62(60.8)	
Appendix diameter,mm (min-max), (SD)	11.07 (4-28)(±4.65)	11.58 (5-40)(±5.98)	0.865
Pathology,n(%)			
Kataral	79(73.8)	69(67.6)	
Perforated	6(5.6)	5(4.9)	0.830
Gangrenous/phlegmon	14(13.1)	18(17.6)	
Lymphoid hyperplasia	5(4.7)	7(6.9)	
Incidental tumor	3(2.8)	3(2.9)	
Postoperative complication,n(%)			
Yes	17(15.9)	7(6.9)	**0.041**
No	90(84.1)	95(93.1)	
Postoperative complications,n(%)			
Wound infection	3(2.8)	1(0.9)	
Intra-abdominal abscess	3(2.8)	2(1.9)	
Hematoma/bleeding	3(2.8)	1(0.9)	
Brid	4(3.7)	4(3.9)	
Other (pulmonary, cardiac etc.)	5(4.7)	3(2.9)	
Length of stay, days (min-max), (SD)	2.82 (1-13)(±2.69)	2.29 (1-13)(±1.86)	0.436
Cost,Turkish Liras($)	395(43)	58(6)	

min = minimum; max = maximum; SD = standard deviation.

4. Discussion

Today, with the widespread use of laparoscopy in every field and the development of technological surgical instruments, LA has become a preferred method by many surgeons in the treatment of acute appendicitis.LA has advantages such as shorter hospital stay, less wound infection, shorter return to daily life, less postoperative ileus, less postoperative pain, and better cosmetic results (13,14). In addition, it is one of the advantages of the laparoscopic approach to distinguish other gastrointestinal pathologies or gynecological pathologies that can mimic appendicitis clinically, and to evaluate the abdomen completely (15,16). The most important step to avoid serious complications such as stump leakage, peritonitis, and sepsis after appendectomy is the safe closure of the appendix stump. Stump leakage may occur when unsafe techniques are used (17,18). No technique has yet been shown to be superior to the other in closure of the appendix stump (19). The ideal method should be safe, accessible, simple to use, cost-effective, and have acceptable complication rates.Intracorporeal or extracorporeal simple ligation, EL, metal or polymeric clips, and endostaps have been described for safe stump closure in LA (20). Bali et al. compared EL and intracorporeal knotting in their study, and they found no difference between the groups, except that the operation time was shorter in patients using EL (21). In a study comparing HC and metal clips, metal clips were found to be more cost-effective (22). Arer et al. reported in their study that extracorporeal knotting is an effective, safe and cost-effective alternative to HCs (23). There are multiple studies comparing HC and EL. In all of these studies, it was reported that HC can be applied more easily, in a short time, and is cheaper (24,25). In our study, no significant difference

was observed in terms of operation times in both groups. This does not mean that HC is not feasible in a shorter time.In our study, more drains were used in the HC group. Patients in the HC group were more complicated cases, and therefore, the operation time may have been prolonged, making them similar to the EL group (Table 2). Knight et al. He evaluated 10 studies involving 7 prospective and 1 randomized controlled 702 patients on appendiceal stump closure methods between 2000 and 2017 (26). As a result of this study, it was determined that the HC method had the lowest complication rate compared to other techniques.In our study, various complications were experienced in 26 patients, and postoperative complications were significantly less common in the HC group, consistent with the literature (Table 2). HCs are used safely in cystic duct ligation, ureter ligation and vessel ligation (27). HC may have caused fewer complications due to its robust structure and secure locking mechanism. It has been reported that the safest method is endoscopic stapler in cases where the appendix stump cannot be closed safely with other techniques (28). However, this method has disadvantages such as long working time, high cost and trocar site hernia.In our study, a 10 mm trocar was used in the left lower quadrant of the HC group, and the risk for trocar site hernia may have increased, but we could not have detected it correctly due to the short postoperative follow-up period.In terms of cost, the use of HC in our study is approximately 7 times cheaper than the use of EL and is compatible with the literature.

This study has several limitations. Our study is a retrospective study and it is impossible to randomize patients.Most of the patients who underwent LA are discharged within a day or two.Complications following supportive treatment may not have been detected in some of the patients included in the study due to the short follow-up period.

Both EL and HC are suitable surgical options for safe closure of the appendix stump in LA. HC appears to be slightly superior to EL due to its ease of administration, fewer postoperative complications, and lower costs.

Conflict of interest

The authors declared no conflict of interest.

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Association of CYP24A1 gene, Vitamin D deficiency and heart diseases in Pakistani patients

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Abstract

To analyze the association of CYP24A1 gene polymorphism with vitamin D deficiency and its related cardiovascular disorders in the Pakistani population. The present prospective cohort study was carried out at KRL and Rawalpindi General Hospital from January 2017 to December 2018. A total of 110 subjects suffering from heart diseases like hypertension, myocardial infarction, or congestive cardiac failure (age range 12-90 years) were enrolled in this study with informed consent. Sampling was done by non-probability convenience sampling. Blood 24Hydroxyvitmin D levels were assessed in the participants by using an electrochemiluminescence system. Genetic polymorphism in the CYP24A1 gene was screened in selected patients (n=15) through PCR-RFLP, after genomic DNA extraction from the whole blood. Data were analyzed using SPSS version 24 for Mac. Fisher's exact test and chi-square tests were applied for qualitative variables. The risk of polymorphism in CYP24A1(SNP rs6013897) genotypes TT, AT, and AA was determined by calculating the odds ratio and confidence interval. P-value <0.05 was considered statistically significant. We observed the highest level of vitamin D deficiency in patients of age group 18-45 years and insufficiency in age group 50-60years. A greater percentage of female patients (34.19%) were deficient in Vitamin D as compared to males (25.72%). Vitamin D deficiency was found to be associated with cardiovascular diseases like hypertension (P=0.000*), myocardial infarction (P=0.334), and heart failure (0.001*). CYP24A1 (SNP rs6013897) was significantly associated (P=0.000*) with vitamin D deficiency and heart diseases (P=0.004*). Moreover, significant polymorphism of genotype AT was observed in our subjects. {P=0.007*, Cramer's V =.003 and 95% CI (0.44-17.27)}. There is an association of CYP24A1 gene polymorphism with vitamin D deficiency and heart diseases. Prevention of low vitamin D levels in individuals with this known genetic marker may help to avert the development of heart diseases in Pakistan.

Keywords: vit D deficiency, cardiovascular diseases, CYP24A1 gene, polymorphism

1. Introduction

The steroid hormone Vitamin D is found to have a variety of functions in humans. The receptor (VDR) of an active form of Vitamin D is also present in vascular smooth muscle cells and cardiomyocytes (1). In recent research, the deficiency of Vitamin D is found to be associated with cardiovascular diseases. Recently vitamin D metabolism has been found to modulate many cardiovascular functions. The low serum levels of vitamin D are associated with hypertension, coronary artery disease (CAD), and heart failure (HF) (2).

This is very strange that despite high levels of sunshine, in Pakistan high levels of deficiency are found among all age groups, genders, income levels, and locations. There is a need for public health strategies to decrease the deficiency rate by food fortification and increasing exposure to sunlight (3).

According to American guidelines serum 25-hydroxyvitamin D levels are labeled a) deficient, when below or equal to 20 ng/mL, b) insufficient, when between 20 and 30 ng/mL, and c) normal when greater than 30 ng/mL (4).

The cause of vitamin D deficiency may be related to sun exposure, diet, and its absorption from the intestines. In Pakistan, this may be due to an indoor lifestyle (sun deprivation) especially in females, use of sunscreens, advanced age, air pollution, smoking, poor food absorption (malabsorption syndromes), Kidney or liver diseases, and drugs like anticonvulsants or glucocorticoids (3). Vitamin D deficiency is associated with hypertension. Its mechanism of action is by renin gene expression which increases the synthesis of renin leading to hypertension (5).

CAD has been associated with vitamin D deficiency its cause may be due to the presence of VDR in both the myocardium and vascular cells. In cases of Myocardial infarction, Vitamin D deficiency is found to be very common and the prognosis of the disease depends on the level of its deficiency (5).

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HF has been associated with vitamin D deficiency. A high prevalence of vitamin D deficiency is found in patients with HF, and it was inversely correlated with left ventricular function and severity of disease (5).

The gene CYP24A1encodes is a member of the cytochrome P450 superfamily of enzymes. The cytochrome P450 proteins are monooxygenase which is responsible for catalyzing several reactions in the synthesis of cholesterol, steroids, lipids, drug metabolism, and it is found to regulate the level of vitamin D3. The genetic polymorphism of CYP24A1, hydroxylase-enzyme is suspected to be responsible for the inactivation of vitamin D (6).

Alternatively, spliced transcript variants encoding different isoforms have been found for this gene. 1,25-dihydroxyvitamin D3 is the physiologically most active form of vitaminD3 which binds to the vitamin D receptor. Inactivation of Vitamin D: Several hydroxylation steps occur in the catabolism of 1,25-dihydroxyvitamin D3 to calcitroic acid. The first of these steps are catalyzed by the enzyme 1,25-hydroxyvitamin-D3-24-hydroxylase, which is encoded by the CYP24A1 gene (7).

Our objective was to identify genetic variants responsible for the variation in serum 25(OH)D levels The inactivation of vitamin D metabolites relies upon two pathways which both include steps catalyzed by 1,25-hydroxyvitamin-D3-24-hydroxylase; CYP24A1 encodes this mitochondrial enzyme which is part of the cytochrome P450 system. We hypothesized that candidate gene CYP24A1, functionally important for vitamin D metabolism and pathways, must be responsible for variation in serum 25(OH)D levels.

2. Materials and Methods

In the present prospective cohort study, a total of 110 male and female subjects from the age range (12-90 years) were included. This was conducted from January 2017 to December 2018. 110 patients, male (40) and female (70) age range 20–60 years were recruited from KRL hospital and Rawalpindi General hospital. we randomly sampled patients. Of the 150 participants selected for this study, 30 (20%) were excluded because the serum 25(OH)D level could not be measured or was below the lower detection limit, and 10 (6.6%) were excluded because less than 95% of the markers were successfully genotyped across all the SNPs. This exclusion process left 110 participants (70 women and 40 men) for analysis. The clinical characteristics and mean laboratory values of the 70 women and 40 men are shown in Table 1, Fig 1. Vitamin D (deficient) are patients with vitamin D levels<25 ng/ml. Vitamin D (insufficient) with vitamin D levels from 25-32ng/ml and vitamin D normal with levels between 32-80 ng/ml

All the subjects included in the present study had been admitted to the hospital for cardiovascular diseases like hypertension, Myocardial infarction, or congestive heart failure. The subjects were excluded from the study if they had diseases deemed to affect vitamin D metabolisms, such as cancer, hyperthyroidism, diabetes mellitus, primary hyperparathyroidism, pituitary, or adrenal and rheumatic diseases. Participants who had taken vitamin D and/or calcium supplements within the past 3 months were also excluded. After these exclusions, 110 participants entered the study. The study was approved by the Ethics Committee of the KRL hospital. All the participants signed informed consent forms before entering the study. Vitamin D (deficient) are patients with vitamin D levels<25 ng/ml. Vitamin D (insufficient) with vitamin D levels from 25-32ng/ml and vitamin D normal with levels between 32-80 ng/ml.

2.1. Measuring serum 25(OH)D

The serum levels of 25(OH)D were determined using an automated Roche electrochemiluminescence system (E170; Roche Diagnostic GmbH, Mannheim, Germany). The intraassay coefficients of variation (CVs) for 25(OH)D were 5.7% at a level of 25.2 ng/mL, 5.7% at a level of 39.9 ng/ml, and 5.4% at a level of 65.6 ng/mL, respectively. The interassay CVs for 25(OH)D were 9.9% at a level of 25.2 ng/mL, 7.3% at a level of 39.9 ng/ml, and 6.9% at a level of 65.6 ng/mL, respectively. The lower detection limit of 25(OH)D was 4ng/mL. Blood 24Hydroxyvitmin D levels were assessed in the participants.

Genetic polymorphism in the CYP24A1 gene was screened in selected patients (5 male) and (10 female) through PCR-RFLP, after genomic DNA extraction from the whole blood. DNA was extracted from peripheral blood samples through QIAamp DNA mini kit (Qiagen) according to the manufacturer's protocol and was quantified using an ND-1000 spectrophotometer (NanoDrop; Thermo Fisher Scientific Inc). The polymorphism in CYP24A1(rs6013897) was amplified using the primer's 5'-CTTGATCCAATGTCCGCAC-3' (forward) and 5'-CTTTGGGTAGGTTACTTCGC-3' (reverse). The amplicons were electrophoresed on 2% agarose gel stained with ethidium bromide and were visualized under UV light. The PCR products were purified using FastAP Thermosensitive Alkaline Phosphatase (Thermo Fisher Scientific Inc.) and exonuclease 1(Fermantas). The samples were placed in a 96-well optical plate and sequenced using a BigDye Terminator v3.1 Cycle Sequencing Kit and Big Dye Xterminator Purification kit. The plate was then placed in a 3500xL Genetic Analyzer (Applied Biosystems Inc.) for electrophoresis. The products of sequencing were visualized, and results were interpreted using the Sequence Scanner Software v1 (Applied Biosystems). `Cytogenetic Location: 20q13.2, which is the long (q) arm of chromosome 20 at position 13.2 and Molecular Location: base pairs 54,145,731 to 54,174,032 on chromosome 20.

Data were analyzed using SPSS version 24 for Mac. Pearson's coefficient for correlation was calculated for 25(OH)D levels with age and gender. Fisher's exact test and

chi-square test were applied for qualitative variables. The risk of polymorphism in CYP24A1(SNP rs6013897) genotypes TT, AT and AA was determined by calculating the odds ratio at the 95%confidence interval. A P value <0.05 was considered statistically significant.

3. Results

The study included 110 participants (70 women and 40 men) for analysis. The clinical characteristics and mean laboratory values of the 70 women and 40 men are shown in Table 1, Fig 1. Vitamin D (deficient) are patients with vitamin D levels<25 ng/ml. Vitamin D (insufficient) with vitamin D levels from 25-32ng/ml and vitamin D normal with levels between 32-80 ng/ml.

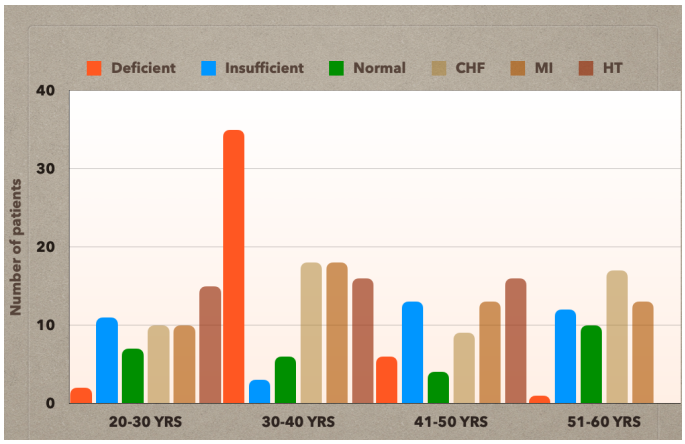

Fig. 1. Distribution of patients of different age groups with congestive heart failure (CHF), myocardial infarction (MI), hypertension (HT), Vit D deficiency, insufficiency, and normal levels.

Generally, the men had higher serum 25(OH)D levels than the women, and old age was significantly associated with its deficiency. By Pearson correlation analysis, 25(OH)D levels showed a significant correlation with age (r = -0.206*; p < 0.05) and gender (r=-0.579*; P<0.001). We observed the highest level of vitamin D deficiency in patients of age group 18-45 years and insufficiency in age group 50-60 years as shown in Fig 1.

A greater percentage of female patients (34.19%) were deficient in Vitamin D as compared to males (25.72%) shown in Fig 2. Vitamin D deficiency was found to be associated with cardiovascular diseases like hypertension (P=0.000*), myocardial infarction (P=0.334), and heart failure (0.001*). CYP24A1 (SNP rs6013897) was significantly associated (P=0.000*) with vitamin D deficiency and heart diseases (P=0.004*).

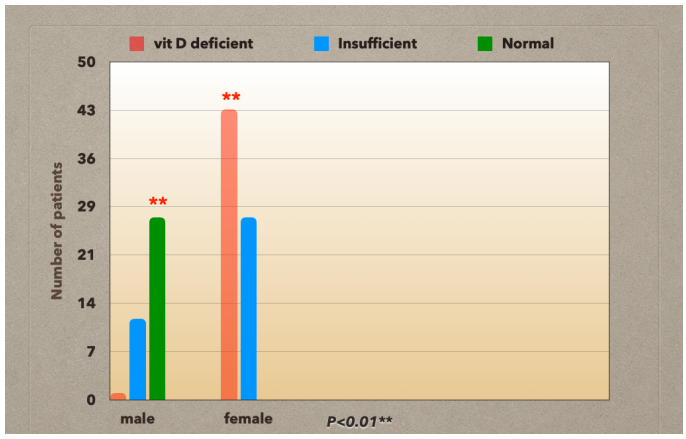

Fig. 2. Distribution of Vit D deficient, insufficient and normal males and females with heart diseases

Moreover, significant polymorphism of genotype AT was observed in our subjects. {P=0.007*, Cramer's V =.003 and 95% CI (0.44-17.27)} Table 1, 2 and 3.

Table 1. The polymorphism of CYP24A1(rs 6013897) genotypes TT, AT, and AA is associated with the risk of Vit D deficiency and heart diseases

CYP24A1	TT			AT			AA		
SNP(rs 6013897)	P	CV	95% CI	P	CV	95% CI	P	CV	95% CI
Vit D deficiency	0.667	0.189	0.904-1.366	0.007**	0.756	1.44-17.27	0.667	0.189	0.904-1.366
Heart diseases	0.73	0.53	0.913-1.32	0.026*	0.013	1.39-9.62	0.73	0.53	0.913-1.326

Fisher,s exact test P<0.001**, CV=Cramer's V, Odds ratio=OR, 95% CI= Confidence interval

Table 2. The risk of association of CYP24A1 gene and Vitamin D deficiency in patients of heart diseases like MI, HT, and CHF

Heart Diseases												
	MI				HT				CHF			
CYP24A1	P	CV	OR	95% CI	P	CV	OR	95% CI	P	CV	OR	95% CI
	0.58	0.264	4.0	0.323-49.5	**0.047***	0.57	16.0	1.09-234.2	0.667	0.464	1	0.904-1.366
Vit-D deficiency	0.294	0.264	4.0	0.323-49.5	**0.047***	0.025	16	1.093-234.2	0.667	0.464	1	0.904-1.366

Table 3. Correlation of Heart disease, CYP24A1 gene, and Vitamin D deficiency in patients

Correlations				
		Heart disease	CYP24A1	Vit D (deficient)<25 ng/ml
Heart disease	Pearson Correlation	1	.853**	.853**
	Sig. (2. tailed)		0.000	0.000
CYP24A1	Pearson Correlation	.853**	1	1.000**
	Sig. (2. tailed)	0.000		0.000
Vit D (deficient)<25 ng/ml	Pearson Correlation	.853**	1.000**	1
	Sig. (2. tailed)	0.000	0.000	

**Correlation is significant at the 0.01 level (2-tailed)

4. Discussion

There is an association between Vitamin D deficiency, cardiovascular diseases, and the CYP24A1 gene. The Vitamin D endocrine system is essential for calcium homeostasis, and low levels of vitamin D metabolites are associated with cardiovascular disease risk. CYP24A1 is an important gene which encodes 1, 25-dihydroxyvitamin D3 24-hydroxylase enzyme. This enzyme degrades the hormonally active form of vitamin D, Calcitriol, and its precursor Calcidiol. Calcitriol has anti-proliferative and pro-apoptotic functions. Genetic polymorphism at key positions in CYP24A1 has shown an association with deficient levels of vitamin D and related diseases. The study confirms the association of CYP24A1 gene polymorphism with vitamin D deficiency and its related cardiovascular disorders in the Pakistani population.

Different studies have implicated a deficient level of Vitamin D in cardiovascular diseases, including coronary artery disease. Currently, the metabolism and homeostasis of Vit D have garnered a lot of interest, and research is being carried out to observe the benefit of this vitamin in the cardiovascular system. Since the hydroxylase enzyme which causes the inactivation of Vit D is controlled by gene expression, so the effect of genetic polymorphism rs2762939 of CYP24A1 in modifying the inactivation of vitamin D, is under consideration (8). It has been reported that the loss of CYP24A1 function resulted in an increased serum concentration of 1,25-dihydroxyvitamin D (9).

For the control of Vit D level, the CYP24A1A gene is the third cytochrome P-450 gene. This gene, located on chromosome 20, at 20q13.2-q13.3, spanning 20.53 kb on the reverse strand, carries the code for the 1a,25(OH)2D inactivation protein (10).In a study conducted on a family using Terminal deoxynucleotidyl Transferase (TdT), an intronic SNP, rs17219315, was found to be associated with 25(OH)D levels (11). However, in another study, no significant association was observed between CYP24A1 and serum 25(OH)D concentration (12). In addition, CYP24A1 polymorphisms were associated with many diseases, such as stroke and hypertension. Wei Yang et al. reported that CYP24A1 rs1570669 was linked to a reduced risk of stroke, and rs6068816 could increase susceptibility to ischemic stroke indicating that in the Chinese population CYP24A1 gene polymorphism is associated with heart diseases (13).

In our study, we found an association of vitamin D deficiency with hypertension which is due to the involvement of the renin-angiotensin-aldosterone system (RAAS). The juxtaglomerular cells of the kidney produce and release renin, which then brings about the conversion of Angiotensin I to Angiotensin II, ultimately resulting in increased secretion of aldosterone. Angiotensin has a direct effect on increasing blood pressure by its vaso-constrictor activity. Its indirect effect in causing an increase in blood pressure is due to its salt and water retaining activity. Research using VDR and 1α-hydroxylase knockout mice have described abnormally increased activity of the renin-angiotensin-aldosterone system. Vitamin D has been reported to cause inhibition of the gene for renin production, thus resulting in reduced activity of this system (14).

Furthermore, an association of vitamin D deficiency with hypertension was also observed and an inverse association was observed between serum levels of 25-hydroxyvitamin D and Blood Pressure (15,16). Some prospective studies have also been conducted to assess the association of vitamin D with variations in BP as well as the development of hypertension. In Groningen, Holland, Van Ballegooijen et al. (2015), measured vitamin D levels of about five thousand normotensive people, who were then followed up for almost six and a half years. At the end of the study period, 20% of the participants with low levels of vitamin D developed hypertension, thereby indicating an increased risk of development of increased BP in individuals with low levels of this vitamin. (17)

In our study, we found an association of myocardial infarction with reduced vitamin D levels. This is understandable, considering the presence of vitamin D receptors in the heart muscle as well as vascular cells. Different epidemiological studies have reported increased occurrence of coronary artery disease and vitamin D deficiency in countries located away from the equatorial regions and in wintertime when exposure to sunlight is limited (18). Studies have also proposed a likely association of vitamin deficiency with the immediate and long-term prognosis of acute myocardial infarction (MI) as this deficiency was observed quite frequently in patients of acute myocardial infarction (AMI) (19). Additionally, an association of vitamin D levels with the number of coronary vessels affected is the reason claimed for observance of complications associated with MI as well as a repetition of unfavorable cardiac outcomes, etc., in people with low Vit D (18).

The Health Professionals Follow-up Study observed about eighteen thousand males for ten years and noted a positive correlation of reduced vitamin D levels with raised AMI risk, keeping in mind various risk factors (19) Furthermore, prospective studies have reported a high occurrence of vitamin D deficiency in individuals admitted to the hospital for acute MI. A multicenter study on two hundred and thirty-nine patients suffering from acute coronary syndrome indicated that 96% of them suffered reduced vitamin D levels at the time of admission to the medical care facility. (20). In patients hospitalized with Acute Coronary Syndrome (ACS), the intra-hospital death rate is seen to be associated with serious vitamin D deficiency. In a study (21) the patients of ACS observed a 24% rate of intra-hospital cardiovascular mortality when vitamin D levels fell to below 10 ng/mL. This mortality rate was appreciably greater than that observed in the remaining patients in whom it was only 4.9% (21).

Even though research has shown a link between vitamin D

and Heart Failure (HF), the precise mechanism using which, a deficient level of this vitamin results in poor clinical prognosis, is unsure. A likely mechanism suggested is the development of cardiorenal syndrome or deterioration in kidney function (22). The cardiovascular and renal systems being inextricably linked affect the activity of the other. Increased sympathetic stimulation, systemic inflammation, and up-regulated activity of the Renin-Angiotensin-Aldosterone System (RAAS) lead to worsening of the cardiorenal syndrome resulting in an imbalance of water and electrolytes, endothelial dysfunction, and possibly leading to left ventricular remodeling and myocardial fibrosis. The result is a positive feedback mechanism that leads to a further worsening in the functioning of these systems (23). The deficiency of vitamin D may result in amplification of the inflammatory response leading to increased cytokine production. This may exert a damaging effect on cardiac muscle by promoting cell hypertrophy, apoptosis, and replacement by fibrous tissue, a reduction in force of contraction of the heart, as well as causing fibrosis and failure of the kidneys (24).

There is an association between vitamin D deficiency, cardiovascular diseases, and the CYP24A1 gene. This finding may help to prevent and treat such cardiovascular disorders by identifying the high-risk individuals, with known genetic markers of vitamin D deficiency of the Pakistani population. As the incidence of cardiovascular diseases is increasing in the Pakistani population, a greater focus will be needed to better elucidate the role of vitamin D in the pathogenesis of symptoms. Cardiovascular diseases remain the main cause of mortality in several countries worldwide. An understanding of the pathophysiological mechanisms involved, as well as their risk factors, is essential for the planning of prevention and treatment strategies. A better understanding of the genetic involvement of VDR gene polymorphisms in the regulation of vitamin D metabolite concentrations from further studies may have important implications in the use of the genetic profile to identify individuals who may be at risk for deficiency of vitamin D.

Conflict of interest

None to declare.

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Clinical and surgical evaluation of cyst hydatid cases in a training and research hospital in Şanlıurfa province

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Abstract

Echinococcus, which is a zoonotic agent, is endemic in our country and causes hydatid disease by localizing in various organs in the human intermediate host. This study aims to present the demographic and clinical characteristics of patients treated for hydatid cysts in our hospital, determine the methods used for treatment, and review the complications in detail. Cases reported to have a hydatid cyst in the surgical material pathology result in Şanlıurfa Training and Research Hospital were evaluated between March 2017 and December 2019. All patients were living in Turkey, which is endemic for hydatid cysts. The records of the patients who were operated on with the pre-diagnosis of cyst hydatid after the examinations and whose pathology results were reported as hydatid cysts were reviewed retrospectively. During the study dates, a total of 84 patients, 55 (65.4%) female and 29 (34.5%) male, were operated on for cyst hydatid in our hospital. The mean age of the patients was 28.6 (min: 2-max: 67). Seventeen (20%) of the patients were in the pediatric age group. When the patients were examined in terms of the number of cysts, 65 (77.3%) patients had a single cyst, while 19 (22.6%) patients had more than one cyst. When evaluated in terms of cyst location, liver localization was observed in 35 (41.6%) patients, liver and lung co-location in 4 (4.7%) patients, lung location in 19 (22.6%) patients, spleen location in 2 (2.3%) patients, and brain location in 2 (2.3%) patients. localization, adnexal localization in 6 (7.1%) patients, renal localization in 2 (2.3%) patients, and soft tissue localization in 14 (16.6%) patients. In the pediatric age group, cyst localization was 4 in the liver, 10 in the lung, 2 in the brain, and 1 in soft tissue. Preoperative serology test results of 42 patients were reported as positive (+) (1/320-1/2560). The average duration of hospitalization was 1-27 days. When the postoperative complications of the patients were examined, the biliary fistula was found in 4 (4.7%) patients, prolonged air leak in 2 (2.3%) patients, pneumothorax in 1 (1.1%) patient, empyema in 1 (1.1%) patient, who was operated for liver cyst hydatid and postoperative seroma was observed in 5 (5.9%) patients. The mean specimen diameter in the pathology results was 2-20 cm. Cyst hydatid disease caused by echinococcus is endemic in our country and often requires surgical intervention. Imaging methods and serology are used in the diagnosis, but a negative serology does not rule out this disease. Patients should be followed up for possible complications after surgery.

Keywords: echinococcus granulosu, hydatid cysts, treatment, complication

1. Introduction

Hydatid cyst is a parasitic disease most commonly found in the liver and lung, caused by Echinococcus granulosus, which is more common, especially in livestock populations (1). The disease is more common in younger people. It has a global distribution, and Mediterranean, Middle East, Eastern Europe, Australia, South America, and African countries are considered endemic in terms of echinococcal infection (2). Although its prevalence in Turkey is lower than in previous years, it varies between 5-40 per 10,000 people and is higher in regions where animal husbandry is common such as rural areas of Eastern and Southeastern Anatolia (3).

Echinococcus granulosus is transmitted to the intermediate host, humans, by infected food. After the larvae are taken, they are absorbed from the duodenum, come to the liver via the venous route, attach to the sinusoids, and form the liver cyst hydatid. Larvae exceeding sinusoids cause disease in peripheral organs with systemic circulation (4). The liver and lungs act as a filter for the parasite. Hydatid cysts occur at a ratio of 50-70% in the liver and 20-30% in the lungs. Rarely, parasites that enter the systemic circulation cause disease in other organs and soft tissues (5). The most common involvement is in the spleen after the liver and lung, while cyst localization in the heart and brain are less common (6). Soft tissue and intramuscular hydatid cysts are rare (0.7-0.9%) even in endemic countries. The growth rate of the cyst may vary depending on the organ. Cases of pulmonary hydatid cysts allow the cysts to reach larger sizes than other organs due to the spongy structure of the lung and may manifest symptoms earlier (7). Slow-growing hydatid cysts remain asymptomatic for a long time. While the disease becomes symptomatic with compression on surrounding tissues and organs, rupture of the

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cyst may cause severe allergic reactions (8).

Ultrasonography is considered the most common imaging method in diagnosing liver cyst hydatids, with its easy application and evaluation of cyst sizes, localization, number, and viability (9). Cross-sectional imaging is preferred in pulmonary hydatid cysts. Immunological diagnostic methods for hydatid cyst are considered helpful in the primary evaluation, complementary to imaging methods, and useful in the follow-up after surgery and pharmacological treatment (10).

Hydatid cyst treatment is managed according to the patient, the stage of the disease, and the location. There are different options for treatment, including medical treatment, percutaneous and surgical interventions (11). Life-threatening complications such as cyst rupture and anaphylaxis may occur in the interventional period. Also, an intensive care unit may be required for complications occurring in the postoperative period.

This study aims to present the demographic and clinical characteristics of patients treated for hydatid cysts in our hospital, determine the methods used for treatment, and review the complications in detail.

2. Material and Methods

Cases that were reported to have a hydatid cyst in the surgical material pathology result in Şanlıurfa Training and Research Hospital were evaluated between March 2017 and December 2019. All patients were living in Turkey, which is endemic for hydatid cysts. The records of the patients who were operated on with the pre-diagnosis of cyst hydatid after the examinations and whose pathology results were reported as hydatid cysts were reviewed retrospectively. The study was conducted under the Helsinki Declaration. The study was approved by the Harran University Medical Faculty Hospital Local Ethics Committee. Since percutaneous treatment was not performed in our hospital, patients who required PAIR were transferred to another center and were not included in the study. Age, gender, nationality, serology results, preoperative abdominal and/or superficial ultrasonography (USG), tomography (CT) and magnetic resonance imaging (MRI) findings, number of cysts, pathology reports, surgery performed, duration of operation, anesthesia method applied, postoperative complications, duration of stay in intensive care unit and duration of hospital stay of the patients were recorded from the file records.

3. Results

Between March 2017 and December 2019, 84 patients were operated on for hydatid cyst in our hospital. 65 (77.3%) of the patients were Turkish, and 19 (22.6%) were Syrian. 55 (65.4%) of the patients were female, and 29 (34.5%) were male. The mean age of the patients was 28.6 (min: 2-max: 67). 17 (20%) of the patients were in the second decade, and 24 (28.5%) were in the third decade. Seventeen (20%) of the patients were in the pediatric age group. When the patients were examined in terms of the number of cysts, 65 (77.3%) patients had a single cyst, while 19 (22.6%) patients had more than one cyst. When evaluated in terms of cyst location, liver localization was observed in 35 (41.6%) patients, liver and lung co-location in 4 (4.7%) patients, lung location in 19 (22.6%) patients, spleen location in 2 (2.3%) patients, and brain location in 2 (2.3%) patients. localization, adnexal localization in 6 (7.1%) patients, renal localization in 2 (2.3%) patients, and soft tissue localization in 14 (16.6%) patients. In the pediatric age group, cyst localization was 4 in the liver, 10 in the lung, 2 in the brain, and 1 in soft tissue. Preoperative serology test results of 42 patients were reported as positive (+) (1/320-1/2560). While the most common complaint in liver localized cysts was abdominal pain, the most common complaint in lung localized hydatid cysts was cough and shortness of breath and a palpable mass in soft tissue hydatid cysts.

General anesthesia was applied to 74 (88%) patients during the operation, spinal anesthesia was applied to 4 (4.7%) patients, and local anesthesia was applied to 6 (7.1%) patients. Emergency surgery was performed in 12 (14.2%) patients due to spontaneous cyst rupture (7 liver hydatid cysts, five lung hydatid cysts). During the operation, laparoscopic surgery was performed in 14 (16.6%) patients, laparotomy in 33 (39.2%) patients, thoracotomy in 21 (25%) patients, craniotomy in 2 (2.3%) patients, and local excision in 14 (16.6%) patients. Simultaneous cholecystectomy was performed in 5 (5.9%) patients who were operated on for liver hydatid cysts. Splenectomy was performed in 2 patients, partial nephrectomy in 2 patients, and endoscopic surgery in 6 patients (one salpingectomy, four laparoscopic cystectomies, one transabdominal hysterectomy + unilateral salpingo-oophorectomy (TAH+USO)), and lobectomy in 2 patients. Operation times ranged from 20 to 200 minutes. 6 (7.1%) patients were followed up in the postoperative intensive care unit. The average duration of hospitalization was 1-27 days. When the postoperative complications of the patients were examined, the biliary fistula was found in 4 (4.7%) patients, prolonged air leak in 2 (2.3%) patients, pneumothorax in 1 (1.1%) patient, empyema in 1 (1.1%) patient, who was operated for liver cyst hydatid and postoperative seroma was observed in 5 (5.9%) patients. The mean specimen diameter in the pathology results was 2-20 cm.

4. Discussion

Hydatid cyst, which is the larval stage of Echinococcus granulosus, has been recognized since an-cient times. Hippocrates (460-377 BC) reported the presence of hydatid cysts in cattle and pigs and defined the hydatid cyst she detected in the human liver as "a sac filled with water (Jecur aqua re-pletum)".

The initial stage of primary EG infection is mostly asymptomatic. Many infections develop in childhood but do not show clinical signs until adulthood. Since approximately 50% of the cases can continue asymptomatically, they cannot

be diagnosed or detected incidentally during autopsy (12).

Symptoms and findings in patients depending on the location and size of the cyst. Small and/or calcified cysts may remain asymptomatic. However, complications such as symptoms due to mass compression in organs, obstruction of blood or lymphatic flow, rupture, and secondary bacterial infections may develop.

When making a diagnosis, it is important to know the occupation, hobbies, living conditions, educa-tion, socio-economic level, and other exposures of the patient. Although nonspecific leukopenia or thrombocytopenia, mild eosinophilia, and abnormalities in nonspecific liver function tests are ob-served, it has no diagnostic value. Eosinophilia is observed in 15% or less of cases and is usually detected when antigenic cyst fluid is exposed to the environment (13).

Infections caused by echinococcus, a zoonotic agent, have been on the list of diseases which has to be reported in our country since 2005. In the report published by the General Directorate of Public Health in Turkey in 2020, it was reported that the number of cases is increasing (14). In the report, which examines different pieces of literature from Turkey and the world, the female/male ratio of the disease varies between studies (15). In the European Centre for Disease Prevention and Control 2016 echinococcus annual epidemiologic report, the highest number of cases was reported in the age group of 25−44 years; the highest notification rate was reported in the age groups 25 years of age above. In our study, the female/male ratio was 1.8, and the age range was between 2 and 67 years. The mean age was found to be 28.6.

Hydatid cyst disease, which is endemic in our country, is transmitted to humans by consuming food contaminated with parasite eggs and sometimes by direct contact. Respiratory transmission is not observed. After the hatched embryos enter from the intestinal system, they come to the liver with portal circulation and locate here frequently (70-75%). The second organ in which the hydatid cyst is most commonly locate is the lung (20-30%). Lung localization is more common in the pediatric age group (16). In our study, 46.4% liver localization and 27.3% lung localization were seen in all patient groups. As per the literature, the most common location was lung (58.8%) in the pediatric age group. Compared to the literature, the lack of liver hydatid cyst and the proportional excess of lung hydatid cyst in our study can be attributed to the exclusion of patients who will be adminis-tered PAIR.

In order of frequency, spleen, soft tissue, intra-abdominal, kidney, brain, bone, pancreatic breast, pelvis, joint, bladder, heart, ovary, thyroid, retroperitoneum, incision scar, and common bile duct are among the localizations outside the liver and lungs (17). Intramuscular localization is rare due to muscle contraction and lactic acid. In our study, soft tissue localization was the most common location other than hepatopulmonary location.

Radiological imaging methods and serological tests are used in the diagnosis of hydatid cysts. The sensitivity and specificity of laboratory and serological tests in the diagnosis of hydatid cyst are limited. There are two major EG antigens. Antigen 5 is the major parasite antigen found on the inner surface of the germinal membrane, daughter vesicles, and protoscolices. Antigen B is a highly immunogenic polymeric lipoprotein and shows greater specificity than detection of antigen 5. When these antigens are examined by ELISA, the sensitivity is around 60-90%, and the specificity is approximately 90% (18,19). In another study conducted in our country, while the sensitivity of the UAV, ELISA, and WB tests were 96.7%, 87.1%, and 100%, respectively, the specificities of these tests were 82.2%, 89.2%, and 85.7% (20).

Serological and immunological tests may be negative in the early period; therefore, radiological imaging methods are more reliable (21). Serological tests are used in the diagnosis as well as in the post-treatment follow-up. Our study observed that a preoperative serology test was performed in 50% of the patients, and it was positive.

The most common clinical findings in patients diagnosed with hepatic hydatid cyst are abdominal pain and abdominal mass/hepatomegaly, and these rates are reported to be 56-84% and 31-86%, respectively, in the literature (22). Cysts located in the lung grow faster than cysts in the liver and give symptoms after compression or rupture of the surrounding tissues. The most common symptoms are shortness of breath and chest pain after coughing (23). The most common complaints in our patients were abdominal pain for liver cyst hydatid and cough for lung cyst hydatid. Medical treatment, open and laparoscopic surgical excision, and PAIR for type I-II hydatid cysts with appropriate localization are used in the treatment of hydatid cysts.

The most common complication of hepatic hydatid cyst is 5-25% intrabiliary rupture (23). After surgery in lung hydatid cysts, the most common complications are prolonged air leak, empyema, and pneumonia (23,24). In the study conducted by Tercan et al. (25), atelectasis (3.3%), biliary fistula (3.0%), and abscess (2.5%) were reported as the most common complications. In our study, the biliary fistula rate among hepatic hydatid cysts was 10.2%, and prolonged air leakage between pulmonary hydatid cysts was 4.3%.

Cyst hydatid disease caused by echinococcus is endemic in our country. Patients admitted with various symptoms depending on the location of the cyst. Some patients are diagnosed incidentally without any symptoms due to the elasticity of the tissue. Treatment of hydatid cyst is surgical. Imaging methods and serology are used in the diagnosis, but a negative serology does not rule out this disease. Patients should be followed up for possible complications after surgery.

Ethics Committee Approval

The study was approved by the Harran University Medical

Faculty Hospital Local Ethics Committee (approval no: HRU/21.15.14).

Conflict of Interest

No conflict of interest was declared by the authors.

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Association between non-alcoholic fatty liver disease and endometrial cancer

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Abstract

Metabolic syndrome (MetS) increase the risk of endometrial cancer (EC). Non-alcoholic fatty liver disease (NAFLD) is related with MetS and share many risk factors with EC that may have significant roles in its development; however, the relationship between NAFLD and EC remains unclear. 207 patients who were operated for endometrial cancer in our hospital between 2011 and 2015, and 243 gynecological patients without a history of malignancy who were randomly selected as the control group. NAFLD was diagnosed based on abdominal ultrasonography findings. There was no significant difference presence of diabetes mellitus and ALT, AST levels between EC group and control group. In EC group, age, body masss indeks (BMI), hypertension and NAFLD were significantly higher than those in control group ($P < 0.001$). Logistic regression analysis showed that age and NAFLD are independent risk factors for presence of EC. Age and NAFLD were a possible independent risk factor for EC in the present study. Therefore, a multi-center and large-population study will be needed to prove our conclusions.

Keywords: endometrial cancer, non-alcoholic fatty liver disease, obesity, metabolic syndrome

1. Introduction

Endometrial carcinoma (EC) is one of the most common gynecological malignancies and as the worldwide burden of EC continues to increase, interest is growing in the development of early preventive strategies for women at increased risk (1). Especially endometrial adenocarcinoma (type 1) is related to a series of endocrine and metabolic disorders which may influence estrogen/progesterone levels, which may increase the risk of malignant endometrial changes (1-4). According to the World Cancer Research Fund, being overweight or obese is related to an increased incidence of EC (5). For these people, the risk of EC is associated with their lifestyle, dietary factors and physical inactivity (6-8). Non-alcoholic fatty liver disease (NAFLD), defined as excess lipit accumulation in the liver, which has become the most common cause of chronic liver disease in children and adolescents, and a major cause of liver disease in adults (9). The incidence of NAFLD is dramatically increasing in parallel with an increasing prevalence of obesity due to diet and lifestyle changes worldwide. EC and NAFLD share common risk factors such as obesity, diabetes and the presence of metabolic syndrome (MetS) and its component disorders (10).

There is large body of literature linking the risk of EC with individual conditions associated with MetS, however association with NAFLD has not been established (10-14).

Therefore, the aim of the present study was to evaluate the relationship between NAFLD and clinicopathological features of patients with endometrial adenocarcinoma.

2. Participants and Methods

After Institutional Review Board approvals, patients with endometrioid EC who underwent primary surgical treatment between January 2011 and December 2015 at the Department of Gynecologic Oncology, Zekai Tahir Burak Education and Research Hospital were retrospectively reviewed. All patients provided informed consent for the surgical procedure and research use of their medical information at admission. Type 1 endometrial cancer patients with distant metastasis, type 2 endometrial cancer patients or additional malignancies were excluded from the study. A total of 207 EC patients met the criteria and were included in the study. A history of medical conditions, including type 2 diabetes, clinical obesity, drug treated hypertension, and drug-treated or clinical diagnosis of hyperlipidemia, was self-reported and included age at first diagnosis. Anthropometric data were collected, and biochemical analyses were performed in routine health examinations. We calculated body mass index (BMI) as weight/height^2 (kg/m^2). Serum biochemical test results taken from the patients and control group were recorded from the digital archives. Diabetes mellitus (DM) was defined by any or all of the following: exposure to any antidiabetic agents, hemoglobin A1c ≥6.5%, fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL) in two measurements 1 month apart. Blood pressure was measured in rest state with a standard mercury

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sphygmomanometer and hypertension was identified by a resting blood pressure of ≥140/90 mm Hg. All the participants routinely underwent hepatic ultrasonography (US) scanning (Siemens; Munich, Germany) by experienced radiologists. Exception of viral hepatitis, cirrhosis, liver cancer or other liver disease, and excess alcohol consumption, participants meeting specific ultrasonographic features including hepatomegaly, diffusely increased echogenicity of liver parenchyma, and blurring of vasculature were diagnosed as NAFLD (15). The values of CA125 were pre-surgery values. The control group comprised 243 individuals with no oncological or systemic disease and no history of diabetes mellitus, obesity or MetS. The statistical analysis was performed with the SPSS 19.0 (SPSS, Chicago, IL). The statistical results are presented as the mean± standard deviation or percentages. Independent sample Student t test was used for continues variables and Chi-squared for categorical variables. In addition, logistic regression analysis was also performed to estimate the probability of the presence of hypertension, hepatosteatosis, BMI and age and the 95% CI for each risk factor adjusting for EC.

3. Results

In our study, 207 patients who were operated for endometrial cancer in our hospital between 2011 and 2015, and 243 gynecological patients without a history of malignancy who were randomly selected as the control group. Baseline characteristics of the study participants with patient and control group were summarized in Table 1.

Table 1. Differences between patient and control group

	Control group (n: 243)	Patient (n:207)	P
Age (year, std)	49.9±10.3	58.1±10.7	<0.001
Hypertension (n, %)	8 (25.8 %)	23 (%74.2)	<0.001
Diabetes mellitus (n, %)	51 (49.5 %)	52 (50.5 %)	0.313
AST (IU/L, std)	20.2±9.98	21.9±9.90	0.066
ALT (IU/L)	20.2±16.9	22.4±13.4	0.122
NAFLD (n, %)	100 (40 %)	150 (60 %)	<0.001
BMI (kg/m^2).	23.82±3.49	25.96±3.32	0.035

Mean age of the patients was higher than control group (58.1±10.7 year vs 49.9±10.3 year p<0.001). Hypertension and NAFLD were observed more frequently in individuals with EC than in the control group (23 (74.2%) vs 8 (25.8 %) p<0.001 and 150 (60%) vs 100 (40%) p<0.001). Compared with normal subjects, the endometrial cancer group subjects had higher BMI (23.82±3.49 kg/m^2 vs 25.96±3.32 kg/m^2 p<0.001). There were no differences of AST, ALT levels and prevalence of diabetes mellitus in both group (Fig. 1).

Table 2. Logistic regression analysis

Risk factor	RR (%95 OR)	P
Hypertension	0.5 (0.2-1.2)	0.143
BMI (kg/m^2).	0.4 (0.32-1.05)	0.06
NAFLD	0.3 (0.19-0.45)	<0.001
Age	1.08 (1.06-1.1)	<0.001

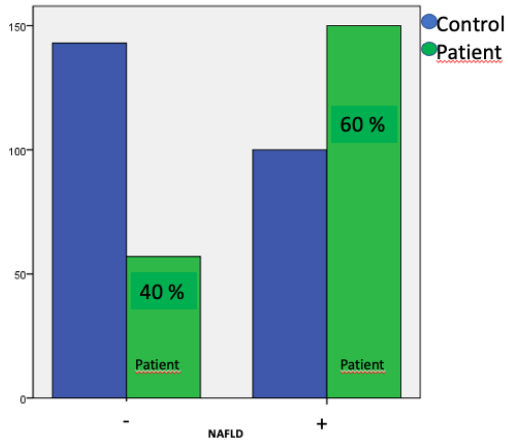

Fig. 1. NAFLD was more in patients

When logistic regression analysis was performed for age, hypertension, BMI and the presence of NAFLD, it was determined that age and the presence of NAFLD were independent risk factors for endometrial cancer (Table 2).

4. Discussion

In this retrospective study, we demonstrated that patients with EC had a higher incidence of NAFLD than the general population. To our best knowledge, this is the first cohort study investigating the presence of NAFLD in EC patients.

Recently, many risk factors have been linked to the occurrence of EC, such as obesity, diabetes and hyperinsulinemia. In addition, a sedentary lifestyle, Lynch syndrome, nulliparity, early menarche, and anovulatory conditions were also found to be potential risk factors for EC.

NAFLD is usually an outcome of ectopic fat storage due to chronic positive energy balance leading to obesity. It is characterized by excess deposition of triglycerides (TG) in the hepatocyte followed by development of inflammatory NAFLD and fibrogenic responses. Although there are some noninvasive diagnostic techniques to evaluate NAFLD, liver biopsy is the gold standard for diagnosis. Conventional US is often the first imaging modality used to evaluate fatty liver clinically, especially for screening of suspected NAFLD, due to its lack of invasiveness, wide availability, and relatively low cost (15,16).

NAFLD is the most common chronic liver disease worldwide and associated with visceral obesity, insulin resistance, type 2 diabetes (T2D) and has been often considered as the hepatic expression of the MetS. There are some potential biological mechanisms by which MetS modulates cancer risk. First, adipose tissue is an important source of estrogen and estrogen induces proliferation of endometrial cancer cells (1, 17, 18). Also, MetS is represented by insulin resistance and hyperinsulinemia, and hyperinsulinemia leads to decreased hepatic synthesis of insulin-like growth factor (IGF)-binding protein 1 (IGFBP-1) and protein 2 (IGFBP-2) and may result in increased bioactivity of IGF-I (19). IGF-1 promotes proliferation and is anti-apoptotic. In addition, some authors

believe that NAFLD directly leads to insulin resistance and hyperinsulinemia (20, 21). There are many studies continually confirming that NAFLD is closely related to the increased risk of various cancers, including oesophagus, stomach, pancreas, colorectal, breast and urinary system cancers (22, 23). But its relationship in endometrial cancer has not been investigated before.

Age is an important risk factor for EC. EC incidence and mortality are dramatically increased in people aged 50 years or older (24). In our study age of the patient group was significantly higher than the control group.

Some limitations exist in the present study. First of all, this is a single-center retrospective analysis and the number of the patients is relatively small. As in other observational studies, it is possible that confounding due to unmeasured confounders might have somewhat distorted the results obtained. Also, it was not practical to control for all possible risk factors, such as dietary factors and lifestyle.

In conclusion, this retrospective cohort study demonstrated that patients with EC had a higher incidence of NAFLD. These data suggest that further investigation of potential interactions between endogenous and exogenous factors involved in endometrial carcinogenesis may help to clarify the magnitude and extent of EC risk experienced by persons with NAFLD. Our findings will provide insights to health care providers about the risk for EC those women diagnosed with NAFLD and underscore the need for interventions to treat and prevent EC. Therefore, a multi-center and large-population study will be needed to prove our conclusions.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Research Article

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Investigation of poor prognostic markers in covid-19 patients hospitalized from emergency department

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Abstract

On March 11. 2020, the World Health Organization declared the coronavirus disease-2019 (COVID-19) outbreak a pandemic. The surge in the number of infected patients has strained healthcare systems globally. The insufficient number of hospital and intensive care unit (ICU) beds has caused a serious problem in patient care and follow-up worldwide. We determined patients who were admitted to the emergency department and hospitalized with a preliminary diagnosis of COVID-19 between March 11, 2020 and November 15, 2020. We recorded all subjects' admission vital signs, anamnesis, physical examination notes, laboratory tests and notes describing the hospital stay from the hospital information system. Patients discharged without requiring ICU admission were included in the good clinical prognosis (GCP) group. Patients who were admitted to the ICU or died in hospital were included in the poor clinical prognosis (PCP) group. When hematological and biochemical parameters were compared, white cell, neutrophil, platelet counts, glucose, urea, creatinine and bilirubin levels were significantly higher and lymphocyte count, hemoglobin, hematocrit, sodium and chlorine levels were lower in the PCP group. Moreover, sedimentation, C Reactive Protein (CRP), ferritin, High Sensitive Troponin I, D-dimer and lactate levels were significantly higher among patients with a poor prognosis. We assessed and identified the more important potential early indicators of prognosis mentioned in the literature that are applicable in the emergency setting. In light of this information, we aimed to establish a basis for the development of future scoring systems.

Keywords: Covid-19, intensive care unit, emergenct unit, poor prognostic markers

1. Introduction

On March 11, 2020, the World Health Organization declared the COVID-19 outbreak a pandemic. As of March 11, 2021, over 117 million cases of COVID-19 and over 2.6 million related deaths worldwide have been reported (1). The disease has caused significant concern among healthcare providers due to its being a previously unknown disease, rapid person-toperson transmission, a poor understanding of transmission routes, the unpredictable clinical course, lack of knowledge about treatment and management, and its life-threatening nature. The surge in the number of infected patients has strained healthcare systems globally. The insufficient number of hospital and ICU beds have caused a serious problem in patient care and follow-up worldwide. One lesson taught by the COVID-19 pandemic is the importance of early recognition and isolation. Uncertainties surrounding the spread and management of the disease mean diligent monitoring is required. Garcia-Castrilla et al. argue that “the most important actions should focus on limiting the spread of infection, identifying all cases and estimating disease severity” (2). Therefore, early indicators of prognosis will have a significant impact on patient management. Accordingly, we examined the parameters that have been potentially associated in the literature with a poor prognosis. We investigated the predictive value of laboratory parameters, demographic characteristics, and comorbidities deemed significant by previous research for prognosis. It is well established that even the smallest research can prove useful guidelines to the clinicians during epidemics.

2. Materials and Methods

2.1. Study desing and setting

The study was conducted in the İzmir Odemis State Hospital, which receives an average of 100,000 patients annually. We chose patients who were admitted to the emergency department and hospitalized with a preliminary diagnosis of COVID-19 between March 11, 2020 and November 15, 2020. The exclusion criteria were as follows: being aged below 18 years, being hospitalized for the purpose of isolation (no chance of isolation at home, living alone and thus having no caregivers, mentally unequipped to care for themselves, etc.), referral to a different department, and a negative PCR test.

2.2. Study population

We screened the files of 96760 patients admitted to the emergency department between March 11, 2020 and November 15, 2020. Among these, 4421 had been hospitalized, 650 of which had suspected or confirmed COVID-19. PCR tests confirmed the COVID-19 diagnosis in 170 patients. Twenty-nine patients were excluded due to meeting the

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exclusion criteria: being aged <18 years (n = 4), incomplete data (n = 1), and hospitalized for the purpose of isolation (n = 24). The remaining 141 patients were recruited.

2.3. Data source and variables

We recorded all subjects' admission vital signs, anamnesis, physical examination notes, laboratory tests, and notes describing the hospital stay from the hospital information system in case files. Patients discharged without requiring ICU admission were included in the good clinical prognosis (GCP) group. Patients who were admitted to the ICU or died in hospital were included in the poor clinical prognosis (PCP) group. We compared demographic characteristics, laboratory results, and comorbidities between the two groups. We prepared ROC curves for all parameters. According to the Republic of Turkey Ministry of Health adult COVID-19 treatment guidelines, ICU admission criteria are as follows: dyspnea, respiratory distress, respiratory rate ≥30/min, PaO_2/FiO_2 <300, increased oxygen requirement, SpO_2 <90% or PaO_2 <70 mmHg despite 5 L/min oxygen therapy, hypotension (systolic blood pressure <90 mmHg and >40 mmHg drop from baseline SBP and mean arterial pressure <65 mmHg), tachycardia (>100 bpm), acute kidney injury, acute liver dysfunction, confusion, immune suppression, acute organ dysfunction (such as acute bleeding or diathesis), elevated troponin and arrhythmia, lactate >2 mmol, and skin disorders such as abnormal capillary refill and cutis marmorata (3).

2.4. Statistical Analysis

Cochran's formula was used to calculate sample size. For this calculation, we used the COVID-19 ICU admission rate (9.1%) reported by the Ministry of Health on October 19, 2020. Accordingly (d=0.5), 125 subjects were required for a Type 1 error of 5%. After the sample size was calculated and power analysis was conducted, the data were analyzed using SPSS v25.5 (IBM, NY, USA). The Shapiro–Wilk and Kolmogorov–Smirnov normality tests were used to determine whether the variables were normally distributed. The Mann–Whitney U test and Student's t-test were used for the comparison of continuous variables, and the chi-square and Fisher's exact test were used for the comparison of categorical data. The results were presented as median (minimum-maximum), mean ± SD, and numbers and percentages (%). The optimal cut-off value, sensitivity, specificity, and odds ratios for the prediction of prognosis were calculated using ROC analysis, area under the curve, and the Youden index. The results were presented with 95% confidence intervals. In all analyses, a P value <0.05 was considered statistically significant.

2.5. Ethics statement

The study protocol was reviewed and approved by the Dr. Suat Seren Training and Research Hospital Izmir-Turkey (approval number and date; 25-17.12.2020), and the requirement for informed consent was waived due to the retrospective nature of this study.

3. Results

We screened the files of 96760 patients admitted to the emergency department between March 11, 2020 and November 15, 2020. Among these, 4421 had been hospitalized, 650 of which had suspected or confirmed COVID-19. PCR tests confirmed the COVID-19 diagnosis in 170 patients. Twenty-nine patients were excluded due to meeting the exclusion criteria: being aged <18 years (n = 4), incomplete data (n = 1), and hospitalized for the purpose of isolation (n = 24). The remaining 141 patients were recruited. The mean age of the participants was 63.3±15.00 ~~years~~ (range 18-94) and 67 (47.51%) were women. Admission complaints included respiratory distress (n = 78, 55.32%), cough (n = 53, 37.59%), and fever (n = 40, 28.37%) and 101 patients (71.63%) had a history of chronic illness. There were 95 patients (67.38%) in the GCP group and 46 patients (32.62%) in the PCP group. A poor clinical prognosis was significantly associated with the older age and male sex. In terms of admission complaints, respiratory distress was significantly more common in the PCP group. Among the comorbidities, hypertension (HT) and chronic obstructive pulmonary disease (COPD) were significantly more common in the PCP group. The demographic characteristics, comorbidities, admission complaints, and vital signs of the two groups are compared in Table 1.

Table 1. Demographic characteristics, additional diseases, complaints and vital signs at the time of application of the patients

	GCPG (n=95)	PCPG (n=46)	P
Demographics			
Age	59.50±14.29	71.10±13.6	**<0.001**
Sex Female Male	 53 (55.79%) 42 (44.22%)	 14 (30.43%) 32 (69.57%)	**0.005**
Comorbidity	58 (61.05%)	43 (93.48%)	**<0.001**
HT	35 (36.84%)	25 (54.35%)	**0.049**
DM	24 (25.26%)	19 (41.30%)	0.052
COPD	6 (6.31%)	10 (21.73%)	**0.007**
Asthma	11 (11.57%)	2 (4.34%)	0.164
CVD	6 (6.31%)	8 (17.39%)	0.067
Complaints			
Dispnea	42 (44.21%)	36 (78.26%)	**<0.001**
Fever	26 (27.36%)	14 (30.43%)	0.705
Cough	39 (41.05%)	14 (30.43%)	0.222
Weakness	38 (40.00%)	15 (32.60%)	0.396
Vital Signs			
Fever	36.60 (36.00-40.00)	36.80(36.00-40.00)	0.475
SBP DBP	124.00 (90.00-166.00) 77.00 (44.00-120.00)	130.00 (93.00-210.00) 75.00 (54.00-110.00)	0.099 0.664
HR	86.00 (56.00-124.00)	89.50 (58.00-166.00)	0.050
RR	20.00 (16.00-28.00)	21.00 (16.00-44.00)	**0.032**
Sat. O_2	96.00 (78.00-100.00)	88.00 (63.00-99.00)	**<0.001**

Abbreviations: HT, hypertension; DM, Diabetes Mellitus; COPD, Cronic Obstructive Pulmoner Disease; CVD, Cardiovasculer Disease; SBP, Sistolic Blood Pressure; DBP, Diastolic Blood Pressure; HR, Heart Rate; RR, Respiratory Rate; Sat O2, Pulse Oxygen Saturation Percent

When hematological parameters were compared, white cell, neutrophil, and platelet counts were significantly higher, and lymphocyte count and hemoglobin and hematocrit lower in the PCP group. In terms of biochemical parameters, glucose, urea, creatinine, AST, LDH and total and direct bilirubin levels were significantly higher and sodium and chlorine levels were significantly lower in the PCP group. Moreover, sedimentation, CRP, ferritin, HS troponin I, CK, CK-MB, D-dimer, PT, INR, and lactate levels were significantly higher among patients with a poor prognosis. The studied laboratory parameters of the PCP and GCP groups are presented and compared in Table 2. We evaluated the value of each parameter in predicting poor prognosis. The resulting ROC curves are plotted in Fig. 1. Sensitivity, specificity, and cut-off values are shown in Table 3.

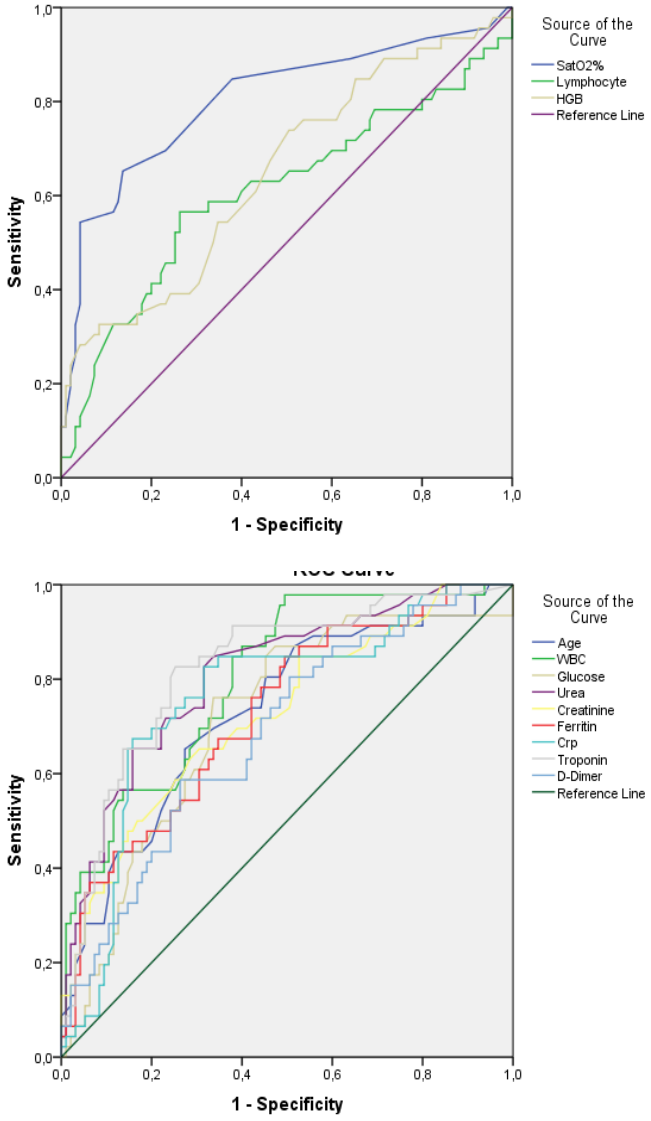

Fig. 1. ROC curves of decreasing and increasing parameters as indicators of poor prognosis

Table 2. The laboratory parameters; the averages and statistical meanings of these parameters in the GCPG and PCPG groups

Laboratory parameters	GCPG (n=95)	PCPG (n=46)	P
WBC (10^3/µL)	5.38 (2.32-14.22)	8.33 (3.08-17.56)	**<0.001**
Neutrophil (10^3/µL)	3.83 (0.87-11.77)	6.29 (1.98-15.25)	**<0.001**
Lymphocyte (10^3/µL)	1.14 (0.37-2.94)	0.84 (0.23-5.64)	**0.035**
Hmg (g/dL)	13.40±1.41	12.38±2.02	**0.003**
Hct (%)	39.17±3.85	36.69±5.28	**0.006**
MCV (fL)	84.21±4.67	85.22±11.02	0.565
MCH (pg)	28.90 (21.40-34.00)	29.70 (19.4-38.2)	0.487
MCHC (g/dL)	34.71±1.24	33.74±1.56	0.068
M (fL)	10.65 (9.0-13.90)	10.95 (9.1-13.6)	0.379
Platelet (10Λ3/µL)	184.00 (101-385)	221.0 (40-353)	**0.030**
Glukoz (mg/dL)	113.00 (82-596)	146.50 (56-486)	**<0.001**
Urea (mg/dL)	32.00 (12-121)	58.00 (22-187)	**<0.001**
Creatinin (mg/dL)	0.95 (0.45-1.71)	1.16 (0.73-3.24)	**<0.001**
AST (U/L)	29.00 (10.00-93.00)	44.50 (16-260)	**0.001**
ALT (U/L)	22.00 (6.00-82.00)	24.50 (8-95.)	0.587
ALP (U/L)	65.00 (24-174)	62.00 (20-175)	0.569
LDH (U/L)	314.00 (134-788)	411 (214-1207)	**<0.001**
Bilirubin totaly (mg/dL)	0.49 (0.14-1.73)	0.66 (0.20-2.00)	**<0.001**
Bilirubin direct (mg/dL)	0.12 (0.01-0.37)	0.18 (0.01-0.78)	**<0.001**
GGT (UL)	26.00 (6.00-233.00)	33.00 (8-255)	0.071
Sodium (mmol/L)	135.00 (124-143)	133.00 (124-158)	**0.049**
Clor (mmol/L)	101.00 (91-109)	99.00 (91-121)	**0.023**
Calcium (mmol/L)	1.11 (0.62-1.35)	1.12 (1.00-1.42)	0.393
Potassium (mmol/L)	4.10 (3.30-5.60)	4.20 (2.70-6.40)	0.886
Magnesium (mmol/L)	1.93 (1.30-3.20)	2.00 (1.52-2.69)	0.221
CRP (mg/L)	34.35 (0.20-159.30)	103.20 (2.7-160)	**<0.001**
CK (U/L)	94.50 (16-1246)	188.50 (20-5565)	**0.001**
CK-MB (U/L)	20.60 (9.00-126.90)	28.00 (11-168)	**0.010**
Hs Troponin I (ng/L)	5.20 (0.00-304.40)	25.40 (0.00-1419.60)	**<0.001**
D-dimer (ng/ml(FEU))	135.20 (3-3143)	258.3 (52-4765)	**<0.001**
Ferritin (ug/L)	128.00 (7-1437.1)	339.8 (50.6-1344.6)	**<0.001**
Sedimentation (mm/hour)	46.00 (10-105)	64.5 (9-133)	**0.004**
APTT (sn)	31.30 (23.70-46.20)	31.90 (20.20-76.20)	0.084
INR	1.04 (0.85-2.47)	1.11 (0.94-15.05)	**<0.001**
PT (sn)	12.05 (10.20-25.50)	13.00 (11-131.7)	**<0.001**
pH	7.42±0.05	7.40±0.07	0.144
pO_2 (mmHg)	35.00 (15-112)	31.50 (11-127)	0.992
pCO_2 (mmHg)	38.00 (27.00-58.00)	37.50 (23-66)	0.441
SO_2 (%)	70.60 (20.60-99.60)	62 (14.6-99.3)	0.751
Lactate (mmol/L)	1.50 (0.60-3.40)	2.10 (1.00-14.50)	**<0.001**

Abbreviations: WBC; White Blood Cell, Hmg; Hemoglobin, Hct; Hemotocrit, MCV; Mean Corpuscular Volume, MCH; mean corpusculer Hemoglobin, MCHC; mean corpusculer hemoglobin concentration, MPV; mean platelet volume, ALT; alanine aminotransferase, ALP; alkaline Phosphatase, APTT; activated partial thromboplastin time, AST; aspartate aminotransferase, LDH; Lactate Dehydrogenase, GGT; gamma-glutamyl transferase, CRP; c-reactive Protein, CK; creatine Kinase, CK-MB; creatine kinase isoenzymes, HS Troponin; High Sensitive Troponin, APTT; activated partial thromboplastin time, INR; international normalization ratio, PT; Prothrombin Time, sO2 (%); Oxygen Saturation percent

Table 3. Prediction and cut-off values of parameters for poor prognosis (ROC Analysis)

	AUC	95%CI	P value	Sensitivity	Specificity	Cut off Value
Age	0.731	0.641-0.820	<0.001	65.2%	72.6%	67.50
Sat.O_2	0.804	0.719-0.889	<0.001	65.2%	86.3%	92.50
WBC	0.801	0.727-0.876	<0.001	84.8%	62.1%	6.175
Lymphocyte	0.610	0.502-0.718	0.035	58.7%	67.4%	0.99
Hmg	0.649	0.551-0.748	0.004	54.3%	65.3%	12.85
Glucose	0.714	0.624-0.805	<0.001	76.1%	66.3%	126.5
Ürea	0.810	0.734-0.886	<0.001	82.6%	68.4%	35.50
Creatinin	0.724	0.634-0.814	<0.001	65.2%	69.5%	1.05
Ferritin	0.728	0.640-0.816	<0.001	67.4%	65.3%	246.85
CRP	0.762	0.675-0.848	<0.001	84.8%	65.3%	50.45
Troponin	0.823	0.749-0.898	<0.001	82.6%	74.7%	8.90
D-Dimer	0.685	0.593-0.777	<0.001	58.7%	73.7%	223.90

4. Discussion

We found that mean age was significantly higher in the PCP group. Duan et al. demonstrated a significant association between age and a severe prognosis during hospitalization for COVID-19 (4). Similarly, Moradi et al. found that increased age was associated with increased COVID-19-related mortality (5). Multivariate logistic regression analysis by Zang JJ et al. identified advanced age as an independent risk factor for death among severely ill patients (6). Our study is consistent with the literature in that advanced age is a significant risk factor for mortality and severe COVID-19 disease.

We also found that poor prognosis was significantly associated with the male sex. Similarly, Li et al. demonstrated that male sex was significantly (p=0.006) associated with a severe prognosis (7). In our study, comorbidities were significantly more common in the PCP group than in the GCP group (93.48% vs. 61.05%, p<0.001). In particular, the prevalence of HT and COPD was significantly different between the two groups. Pan et al. also showed that patients with HT had significantly poorer prognoses compared to those without it (8). A systematic review and meta-analysis by Zhao et al. suggested that concomitant COPD is associated with a 4-fold increase in the risk of developing severe COVID-19 disease (9).

Respiratory distress at admission was significantly associated with a poor prognosis (p=0.001). Consistently, Varol et al. emphasized dyspnea in their COVID-19 mortality index (CoLACD) (10). Admission oxygen saturation, as measured by pulse oximetry, was significantly lower in the PCP group compared to the GCP group (88.00% vs. 9600%, p <0.001).

Bahl et al. showed that admission oxygen saturation was significantly higher among patients who survived versus those who died (92% vs. 88%, p <0.001) (11). We found that the mean WBC count was significantly higher in the PCP group (8.33 vs. 5.38 × 10^3/μL, p<0.001). Huang et al. reported that the WBC count of patients admitted to the ICU was 11.30 × 10^3/μL compared to 5.70 × 10^3/μL in patients who did not require intensive care (p=0.011) (12). Peiró et al. reported that leukocyte count was higher in patients who survived versus those who died, albeit not significantly higher (p=0.065) (13). The discrepancy between our results and those reported by Peiró et al. may be because they included patients who were admitted to the ICU and survived in the good prognosis group. In our study, the mean neutrophil count was significantly higher in the PCP group (6.29 vs. 3.83 × 10^3/μL, p<0.001). Varol et al. compared the neutrophil counts of COVID-19 patients who recovered and those who died and reported a significantly higher neutrophil count in those who died (6.90 vs. 4.35 × 10^3/μL, p<0.001) (10). Numerous studies suggest an association between a low lymphocyte count and poor prognosis. Like our study, Wang et al. reported significantly reduced lymphocytes in patients with a poor prognosis (0.84 vs. 1.14× 10^3/μL, p=0.035) (14).

In a meta-analysis of 19 studies, Hariyanto et al. demonstrated a significant relationship between severe COVID-19 disease and CRP levels (15). We similarly found that CRP was significantly higher in the poor clinical prognosis group. Studies on cardiac markers report that troponin I and troponin T elevation in COVID-19 were associated with acute myocardial injury, ICU admission, hospital deaths, and severe inflammation (16-19). In our study, cardiac markers were significantly higher in the PCP group. CK-MB elevation in COVID-19 was associated with acute myocardial injury, ICU admission, and hospital deaths (14, 16, 20, 21). In our study, CK-MB was significantly higher in the PCP group. Huang C. et al. reported that D-dimer was higher in COVID-19 patients who required intensive care (12). We similarly found that D-dimer levels were higher among PCP patients. Zhou et al. reported that LDH and ferritin were significantly higher in patients who died (20). A meta-analysis of studies from December 25, 2019 and June 1, 2020 by Cheng et al. indicated that ferritin was significantly higher in severe COVID-19. These findings are consistent with our results (22).

Xiaochen Li et al. noted that approximately 50% of all COVID-19 patients were classified as severe and severe disease was associated with advanced age, HT, and elevated

cytokine and LDH levels. Again, that study associated male sex, advanced age, leukocytosis, elevated lactate dehydrogenase, cardiac injury, hyperglycemia, and high-dose corticosteroid use with death among severe COVID-19 patients (23). Eboni G et al. reported that hospital mortality was significantly associated with increased age; increased respiratory rate at admission; elevated lactate, creatinine, or procalcitonin; and low platelet or lymphocyte count (24). The major limitations of our study involved its retrospective nature. Our analysis relied on the accuracy of patient records. The retrospective nature of our study precluded us from making interim assessments during transfer to intensive care.

We assessed and identified the more important potential early indicators of prognosis mentioned in the literature that are applicable in the emergency setting. In light of this information, we aimed to establish a basis for the development of future scoring systems. Further studies are needed to overcome the problems faced by the health system and to improve patient management during the COVID-19 pandemic.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Iatrogenic leg length inequality may cause low back pain due to scoliosis

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Abstract

The aim of this manuscript is to discuss iatrogenic leg length inequality as an aetiologic factor of degenerative scoliosis and low back pain. Iatrogenic type leg length inequality prevalence is getting higher recently, because of increasing number of hip and knee surgery parallel to the increasing number of elder people in population. We presented four cases, who had low back pain due to degenerative scoliosis caused by leg length inequality. Case 1, 2 and 3 were elder people who had previous knee or hip surgery. Case 4 was a young lady who had low back pain due to degenerative scoliosis and leg length inequality and she had no previous surgery. In Case 1, 2 and 3, leg length inequality was iatrogenic type which was caused by hip or knee surgery. This iatrogenic leg length inequality caused degenerative scoliosis same as in case 4, who had anatomical leg length inequality. Iatrogenic leg length inequality may cause degenerative scoliosis, thus low back pain. Scoliosis caused by leg length inequality cannot be compensated by elder people or even young people whose abdominal muscles week.

Keywords: leg length inequality, leg length discrepancy, iatrogenic, degenerative scoliosis, low back pain

1. Introduction

Low back pain is one of the most important medical condition that causes disability. Up to 84% of population suffer from it during their life time (1). Its financial dimension is also big problem for governments (2-5). The causes of low back pain are mainly degenerative diseases of spine, musculoskeletal disorders, lower extremity joint diseases (hip-knee).

Several authors have suggested that leg length inequality also may cause low back pain and it may occur after hip or knee surgery (6-9). This iatrogenic type of leg length inequality prevalence is getting higher recently, because of increasing number of hip and knee surgery parallel to the increasing number of elder people in population.

Recently we also realized that more people, who had previous hip or knee surgery, have been admitting to our clinic with the complaint of low back pain. This was our starting point for this manuscript.

2. Material and Methods

We selected to present four cases among patients who had low back pain and had previous hip or knee surgery.

2.1. Case 1

Seventy-three years old female patient admitted to our department with the complaint of low back pain and weakness on her lower extremity. She had been suffering from low back pain for 15 years, but ten days ago it became unbearable, and her lower extremities lost their strength. In her neurological examination there was 80% loss on distal parts and 60% loss on proximal parts of lower extremity bilaterally. Laseque sign was negative. We noticed that her left leg was 4 cm shorter than the right leg probably due to right knee arthroplasty which was performed one year ago. In her radiological investigation there were severe degenerative changes and scoliosis concave to the right side (Fig. 1). We thought that it was a rigid deformity, so we performed only L3 and L4 laminectomy and foraminotomies. Her pain complaint resolved but weakness on her lower extremities did not improve so much.

2.2. Case 2

Sixty-four years old female patient who had left knee arthroplasty 17 years ago and right knee arthroplasty 5 years ago, admitted to our department with the complaint of low back pain and neurological claudication. Her low back pain was increasing while she was standing. She feels more comfortable while she was sitting or bending. In her examination there was no motor deficit or laseque sign, but her left leg was 2 cm shorter than the other. In her radiological examination there were severe degeneration and scoliosis concave to the right side (Fig. 2). We performed left L2, L4 hemilaminotomy, bilateral L3 hemilaminotomy and foraminotomies. We corrected her leg length inequality with a shoe insert. She had no more low back pain and claudication after surgery.

2.3. Case 3

Sixty-two years old female patient who had surgery two times for lumbar discectomy admitted to our department with the complaint of severe low back pain. She had no leg pain. She

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had also right knee arthroplasty. In her neurological examination there was no motor deficit. In her radiological examination there were L3 total laminectomy, L4 partial laminectomy from upper part and, scoliosis concave to the right side (Fig. 3). We noticed that her left leg was shorter than the right side probably due to previous knee arthroplasty. We corrected it with shoe insert. But her pain persisted. We performed L2, L3, L4 transpedicular fixation and decompression. After the surgery there was no low back pain and neurological defisit. She continued to use shoe insert after surgery.

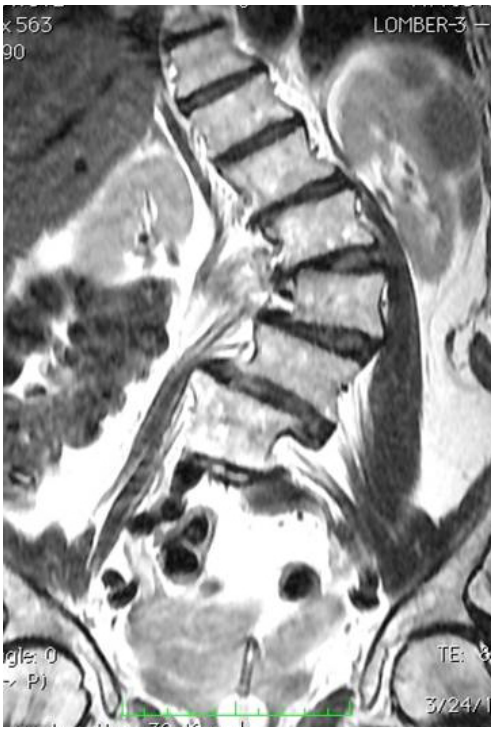

Fig. 1. Severe degenerative changes and scoliosis concave to the right side

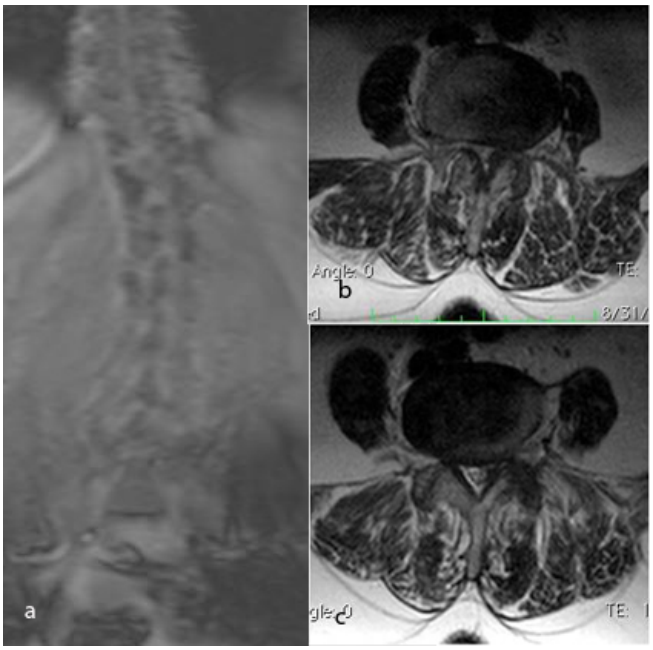

Fig. 2. a- Scoliosis, b- and c- lumbar stenosis

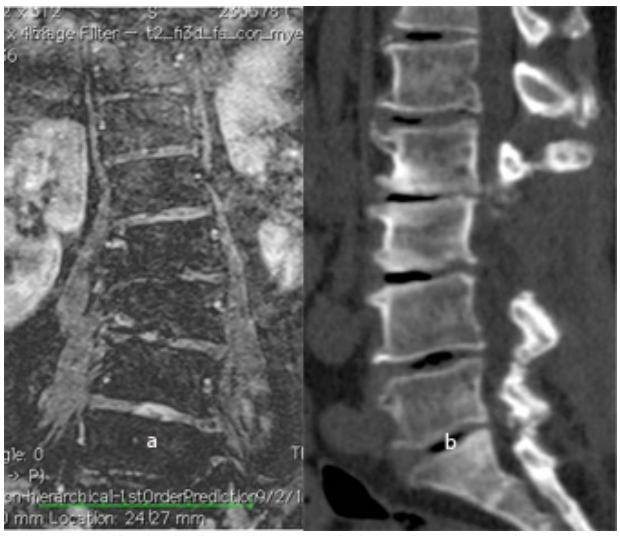

Fig. 3. a- Scoliosis, b- laminectomy defects due to previous surgery

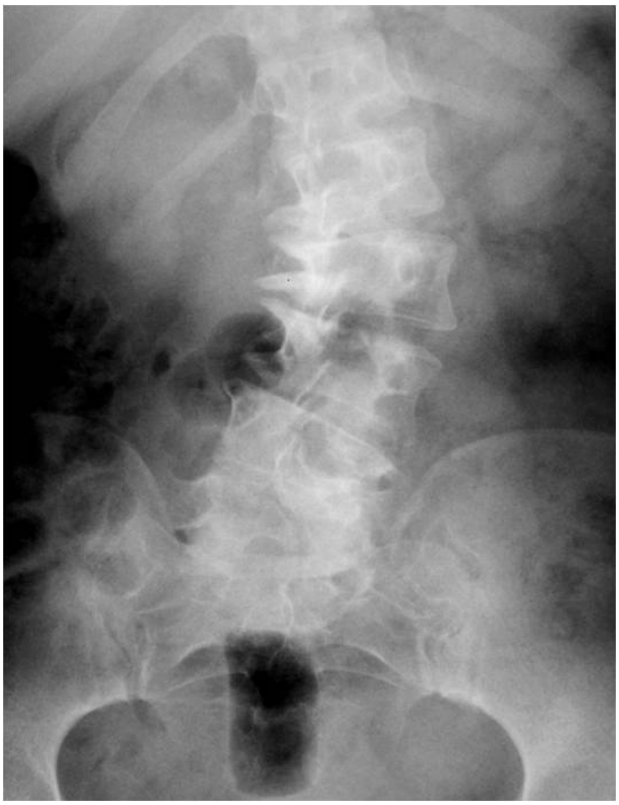

Fig. 4. Scoliosis concave to the right side

2.4. Case 4

Twenty-eight years old female patient had low back and left leg pain. Her complaint increased after her second birth. There was no motor deficit or root sign in her neurological examination. Her left leg was 6 cm shorter than right side. There was pain on her left hip with movement. In her radiological examination there was scoliosis concave to the right side (figure 4). We corrected her leg inequality with shoe insert and, we recommended her lumbar isometric exercises. After five months of exercise, she said her complaints remain same. We recommended her surgery and corrected her scoliosis with T12-L5 transpedicular instrumentation. After surgery there was no complaint of low back or leg pain and she continued to use shoe insert.

3. Discussion

Changes in lumbar lordosis and sacral inclination have been described in patients with mechanical low back pain, degenerative lumbar disc disease, scoliosis and lumbar surgery. Low back pain has close relationship with mechanical factors. It has been very well known that changes in lumbar lordosis and sacral inclination may cause low back pain (10). Increase in lumbar lordosis makes sacral inclination angle wider. It has been shown that lumbar lordosis and sacral inclination were also related to the hip extension. This is described as hip-spine syndrome by Offiersky et al. (11). In this situation if hip has flexion deformity, this will end up with loss of lumbar lordosis.

Similarly degenerative changes in knee often cause limitation of extension. Murata et al showed that there was a positive correlation between the knee angle and lumbar lordosis. Limitation of knee extension led to loss of lumbar lordosis. Murata et al called it "knee-spine syndrome" (12).

Skeletal system has to be in good balance. It always try to maintain the line of the center of gravity within the base of support. If the balance impairs in one part, it has to be compensated by another part. If the problem becomes chronic then the compensation mechanisms cause degeneration. Knee-spine syndrome or hip spine syndrome are the results of this rule in sagittal plane.

Either in hip-spine syndrome or in knee-spine syndrome intradiscal pressure is increased due to loss of lumbar lordosis. Increased intradiscal pressure may cause low back pain.

Leg length inequality also effects biomechanical characteristics of spine and pelvis in coronal plane. Leg length inequality or anisomelia is a bilateral asymmetry in lower limb lengths. There are two types of leg length inequality: anatomical and functional (13, 14).

In anatomical short leg, bony components of the lower limb are actually different in length. In this type of leg length inequality anterior and posterior iliac spines are lower on the side of the short leg (15). In functional short leg, main cause is pelvic rotation caused by scoliosis or joint contractures. In this type, posterior iliac spine higher on short leg side while anterior iliac spine is higher on the long leg side. Some writers describe a third type; environmental leg length inequality (16). This type mainly caused by drainage slopes built into roads and effect road runners.

Relationship between leg length inequality and low back pain is controversial. According to the some publications there are no relationship between low back pain and presence of leg length inequality (17, 18), while some others advocate that low back pain prevalence is higher among individuals who have leg length inequality (6, 7).

According to the advocators of leg length inequality-low back pain relationship, leg length inequality may cause scoliosis. Scoliosis is the lateral bending of spinal column. It can be classified as functional and structural (19). Functional scoliosis is a transient phenomenon which is related to the biomechanical changes in spinal column, pelvis and lower extremities. Pelvic tilt is the first step for leg length inequality induced scoliosis. Body try to maintain the line of the center of gravity within the base of support by pelvic tilting and related functional scoliosis. The degree of scoliosis depends on the magnitude of the leg length inequality (20). In a scoliotic patient, spinal column is concave to the longer leg side. This concavity causes a compression on the annulus of the intervertebral disc, thus patients suffer from low back pain and sciatica on concave side. Latz et al found alterations of glycosaminoglycan content in intervertebral discs of patients with leg length discrepancy (21). Balik et al suggest that abnormal loading due to leg length inequality may cause to lumbar disc herniation, so low back pain (22).

Although there is a relationship between the degree of scoliosis and leg length inequality, it has been reported that there is no close relation between the degree of the scoliosis and severity of the back pain (14). There are some interesting publications in the literature. For example, Nourbakhsh et al evaluated the relationship between low back pain and 17 different mechanical factor in 600 patient at the age of 43 ± 15 (23). According to their publication endurance of the back extensor muscles had the highest association with low back pain. Length of the back extensor muscles, and the strength of the hip flexor, hip adductor, and abdominal muscles also had a significant association with low back pain. They couldn't find any correlation with low back pain and degree of pelvic tilt and lumbar lordosis, leg length inequality, length of hamstrings, iliopsoas and abdominal muscles. There is a dilemma here. For low back pain, are these structural changes predictive factors or consequences?

This knowledge makes us think an alternative hypothesis. According to this hypothesis extremity inequality which has begun from the early time of life may not be the cause or the result of low back pain. Body can compensate these structural faults. But if structural changes occur at the elderly, it may cause low back pain. Studies have shown that fat mass increases and muscle mass decreases with age (24). Abdominal muscles are weaker in elder people. Because of this, they cannot compensate new structural changes.

When we look at the case 1-3 from this point of view, these elder people have not any complaint of low back pain until certain age. They have all knee or hip surgery and have leg length inequality. They have complaints related to the scoliosis. It is difficult to discriminate whether the scoliosis is structural or functional related to leg length inequality. How much does leg length inequality contribute on scoliosis formation? If they hadn't leg length inequality, would they have such a severe scoliosis or degeneration?

We can find our answers partly on case 4. She is a young person who have severe degenerative scoliosis. In a young

person, such a severe degeneration can only occur if there is a balance problem on spinal column. There is only leg length inequality in our hands for the explanation of scoliosis. This young woman couldn't compensate the scoliosis formation probably because of her abdominal muscle weakness due to two childbirth.

Another point for patients who have scoliosis is that leg length measurement must be routine in their physical examination. Sometimes a simple shoe insertion may be enough to relieve pain without surgery.

We can explain scoliosis formation on cases 1-3 with the leg length inequality due to knee or hip surgery. This means iatrogenic leg length inequality may cause degenerative scoliosis. Balik et al suggested the relation between leg length inequality and lumbar disc herniation. They did not give any information about the causes of leg length inequality of their patients (22). According to our knowledge there is no publication about degenerative scoliosis related to iatrogenic leg length inequality.

Iatrogenic leg length inequality may occur after hip or knee surgery. There are several publications which mention this problem (9, 25-30). As the expected lifetime gets higher in population, more people need hip or knee surgery and people who have leg length inequality due to hip or spine surgery have increased. This iatrogenic type of leg length inequality can be classified separately instead of inside the anatomical group.

Leg length inequality is also common problem among people who uses prosthesis due to lower limb amputation. According to Friberg's study only 15% of 113 Finnish war-disabled amputees have acceptable prosthesis and these people have chronic pain symptoms of low back, hip and knee correlated significantly with the lateral asymmetry caused by incorrect length of the prosthesis (31). Unilateral sciatica or chronic hip pain occurred mainly on the long leg side independently of the side of amputation. In these patients, leg length inequality causes pelvic tilt and functional scoliosis. According to Friberg these compensation mechanisms have predisposing role in the etiology of chronic low back and hip pain symptoms. If these veteran soldiers who must have had strong muscles cannot compensate scoliosis due to leg length inequality, this means it is more difficult for elder people whose muscles are weaker.

Another point is that leg length inequality can be seen in normal population too. According to the Gofton et al 7% of the asymptomatic adult population has a leg length inequality greater than 12 mm (32). If the difference is greater than 11 mm, symptoms usually begin (33). Some publications suggested that modified shoes or shoe inserts are useful in treatment of mild leg length inequality (34, 35). Sometimes attractive view of the scoliosis may mislead our attention to the spinal column in a patient who have scoliosis and leg length inequality at the same time. Such a misdiagnosis may lead doctor and patient easily to an unnecessary surgery instead of simple solution like prescribing a shoe insert. Measuring leg length must be routine in neurosurgical examination for the patients with low back pain.

Leg length inequality is one of the causes of low back pain and degenerative scoliosis. Iatrogenic leg length inequality due to hip or knee surgery also may cause low back pain and degenerative scoliosis or worsen existing complaints. According to best of our knowledge there is no publication in English literature suggesting relation between iatrogenic leg length inequality and degenerative scoliosis related low back pain. Young people can compensate it but elder people and women whose abdominal muscles are weak due to high number of births cannot compensate such an impairment because of muscle weakness. Evaluation of leg length must be a part of neurosurgical examination especially for patients who have scoliosis. Leg length inequality which become more prominent after scoliosis surgery can be corrected by using shoe inserts.

Conflict of interest

The authors declare that there is no conflict of interest.

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Research Article

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Retrospective analysis of the patients undergoing neuroanaesthesia between the years 2015-2019

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Abstract

This study aimed to retrospectively evaluate the patients who underwent neuroanesthesia at Ondokuz Mayıs University Faculty of Medicine Hospital between 2015 and 2019. We included all patients who underwent neuroanesthesia between 01.01.2015 and 31.12.2019 and recorded demographic characteristics, comorbidities, type of surgery performed, anesthesia management and complications. We included a total of 5172 patients in the study. 52.9% of the patients were male and the mean age was 43.2%. We observed that the patients were operated most frequently for herniopathy (21.3%), shunt/external ventricular drainage (19.7%) and cranial mass (18.7%), and 77.3% of the cases were elective surgery. The average duration of anesthesia was 145.9 minutes. Thiopental (46.7%) and propofol (45.6%) were used most frequently as induction agents, while rocuronium (93.7%) was preferred as the neuromuscular blocking agent in almost all patients. Remifentanil (81.4%) was the most commonly used intraoperative analgesic. While inhalation anesthesia was preferred for maintenance in 3077 (59.5%) patients, total intravenous anesthesia was used in 1811 (35.1%) patients. Complications developed in 24.1% of the patients, and cardiovascular complications were observed in 71.9%. The study evinced that 1282 patients (24.8%) needed postoperative intensive care. This study revealed that the repetition of retrospective studies at regular intervals would contribute to the development of anesthesiology by enabling both the evaluation of the practices in the same clinic and the comparison between clinics.

Keywords: neuroanesthesia, neurosurgery, perioperative period, retrospective

1. Introduction

Anesthesia can be defined as neuroanesthesia in interventions performed due to self-induced or neurological injuries of the central nervous system (CNS) or peripheral nervous system (PSS). A good understanding of neuroanatomy and physiology, being familiar with the effects of drugs used on the brain and spinal cord, and protecting the brain and spinal cord constitute the basis of neuroanesthesia (1). Intracranial mass surgeries, ischemic cerebrovascular and neurological diseases, aneurysms and arteriovenous malformations, functional neurosurgery, interventional neuroradiology, spinal cord surgery, neurotrauma, pediatric neurosurgical procedures all constitute neurosurgical operations, and therefore neuroanesthesia (1-3).

Neuroanesthesia covers anesthesia applications in neurosurgical surgery. The objectives of neuroanesthesia are to provide the most suitable operating conditions for a neurosurgical operation, to maintain oxygenation with cerebral perfusion while providing optimum conditions, and to protect cerebrovascular autoregulation. The technique to be applied for the operation should protect intraoperative and postoperative hemodynamic stability under surgical stress, should not delay recovery and awakening, and should allow early neurological evaluation. Preventing the increase in intracranial pressure (ICP), suppressing the hypertensive response due to surgical stress and not impairing venous return are indispensable parts of neuroanesthesia (1-3).

We performed in this study a retrospective analysis of patients who underwent neuroanesthesia in the last five years at Ondokuz Mayıs University Faculty of Medicine Hospital and discussed the results in light of the literature. We also aimed to evaluate and develop neuroanesthesia applications positively.

2. Materials and Methods

We retrospectively analyzed patients who underwent neuroanesthesia between 2015 and 2019 in the neurosurgery operating room of Ondokuz Mayıs University Faculty of Medicine Hospital. The study was approved by the Local Ethics Committee (Date: 08.10.2020 Decision no: 2020/542). We obtained the study data from the online hospital information system and preoperative and intraoperative registration forms in the patient files and excluded patients whose surgeries were canceled for any reason or whose records were missing.

We recorded the patients' gender, age, American Society of Anesthesiologists (ASA) scores, comorbidities, type of

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surgery, duration of anesthesia, methods used in monitoring, agents used in anesthesia induction and maintenance, intraoperative fluid and blood management, analgesia management, complications, and postoperative intensive care need. We analyzed the data with IBM SPSS V23, evaluated conformity to normal distribution with the Kolmogorov-Smirnov test and used Chi-square, Kruskal Wallis and Mann-Whitney U tests to compare the variables. We expressed the data as arithmetic mean±SD (standard deviation), number and percentage and considered $P<0.05$ significant.

3. Results

We included 5172 patients in the study. 52.9% were male, and the mean age was 43.2 ± 24 years. The most frequently performed operations were 21.3% herniopathy, 19.7% shunt/EVD (external ventricular drainage) and 18.7% intracranial mass. 63.7% of the patients had at least one concomitant systemic disease. 48.6% had cardiovascular, 27.4% endocrine, and 25.1% neurological system diseases. Anesthesia times averaged 145.9 ± 75.5 minutes. Table 1 shows the patients' demographic data.

Table 1. Demographic data of the patients

Frequency n (%)		
Gender	Woman/Man	2435 (47.1)/2737 (52.9)
Age		43.2 ± 24.0
ASA Score	I	1205 (23.3)
	II	2652 (51.3)
	III	1050 (20.3)
	IV	222 (4.3)
	V	43 (0.8)
Comorbidities	Cardiovascular	1607 (48.6)
	Endocrine	904 (27.4)
	Neurological	829 (25.1)
	Pulmonary	314 (9.5)
	Trauma	307 (9.3)
Surgery Type	Herniopathy	1100 (21.3)
	Shunt/EVD	1018 (19.7)
	Cranial mass	966 (18.7)
	Spinal mass	239 (4.6)
	Others	1849 (35.7)
Duration of Anesthesia		145.9 ± 75.5

Table 2. Agents used in anesthesia management

Frequency n (%)		
Hypnotics	Thiopental/Propofol	2413 (46.7)/ 2358 (45.6)
Neuromuscular Blocker	Rocuronium	4832 (93.4)
Inhalation Agents	Sevoflurane	1508 (29.2)
	Desflurane	1565 (30.3)
	Propofol	1874 (36.2)
Early Postoperative Analgesics	Pethidine	900 (46.7)
	Tramadol	1125 (58.4)
	NSAID	91 (4.7)
Fluid Therapy	Saline/Colloid	4263 (82.4)/ 777 (15.0)
Blood Products		342 (6.6)
Reverse NMB	Neostigmine	2233 (43.2)
	Sugammadex	1310 (25.3)
	Unused	1572 (30.4)

Table 3. Complications and need for ICU admission

Frequency n (%)		
Complications	Cardiovascular	897 (71.9)
	Metabolic	145 (11.6)
	Allergic	139 (11.1)
	Pulmonary	120 (9.6)
	Others	19 (1.5)
ICU Need		1282 (24.8)

Thiopental (46.7%) and propofol (45.6%) were preferred most frequently as induction agents, and rocuronium (93.7%) was preferred as the neuromuscular blocking agent in almost all patients. Remifentanil (81.4%) was the most commonly used intraoperative analgesic. In maintenance, inhalation anesthesia was preferred in 59.5% of patients, while total intravenous anesthesia was preferred in 35.1%. The most commonly used postoperative analgesic was tramadol (54.8%), while the most commonly used maintenance fluid was 0.9% NaCl (82,4%). The use of colloid and blood products were 15.0% and 6.6%, respectively. The agent used to reverse neuromuscular blockade (NMB) was neostigmine (43.2%). In the early postoperative period, the need for analgesics in the recovery unit was 37.3%. Tramadol (58.4%) was the most widely used postoperative analgesic. Table II details the agents used in anesthesia management.

The most frequent surgery types which difficult intubation was encountered were Spinal fracture surgery, herniopathy surgery, and cranial mass and instrumentation surgery. The difficult intubation incidences for these surgeries were 21%,20%,11% respectively.

Complications developed in 24.1% of the patients where 71.9% were cardiovascular complications. The need for postoperative intensive care unit (ICU) admission was 24.8%. The greatest need for postoperative intensive care unit was in intraparenchymal bleeding surgeries (96.2%), decompression surgeries (91.7%) and aneurysm surgeries (87.6%). Table III shows complications and ICU need details.

4. Discussion

We evaluated 5172 patients who underwent neuroanesthesia for neurosurgery between 01.01.2015 and 31.12.2019 in Ondokuz Mayıs University Faculty of Medicine, Department of Anesthesiology and Reanimation. Neuroanesthesia covers anesthesia applications in neurosurgical surgery. We aimed to provide the most suitable operating conditions for a neurosurgical operation, maintain oxygenation with cerebral perfusion while providing optimum conditions, and preserve cerebrovascular autoregulation. The technique to be applied for the operation should protect intraoperative and postoperative hemodynamic stability under surgical stress, should not delay recovery and awakening, and should allow early neurological evaluation. Preventing the increase in ICP, suppressing the hypertensive response due to surgical stress and not impairing venous return are indispensable parts of neuroanesthesia. With this study, we aimed to evaluate the neuroanesthesia process and effectiveness at Ondokuz Mayıs University Faculty of

Medicine Hospital clinic and prepare a data source to guide neuroanesthesia applications.

Gokduman et al. (4) found that 52% of the patients who were operated for an intracranial mass were male. In accordance with the literature, 52.9% of the patients in our study were male, and the mean age of the patients was 43.2 ± 24 years. A comparison between the mean age and the type of surgery revealed that the highest mean age was 64.2 ± 9.6 in narrow canal surgery type, and the lowest mean age was 3.3 ± 11.3 in operations related to congenital/genetic diseases. The patients' ASA scores showed that 51.3% were ASA 2. These rates were also consistent with the results of similar studies in the literature. As in the study by Bozkurt et al. (5), the reason for the high number of ASA 2 patients may be possibly due to the average age of the patients who underwent surgery being in the middle age group and above, the rate of at least one systemic disease getting higher with increasing age, and smoking and alcohol use, which increases the ASA score at a high rate in those who do not have co-morbid systemic diseases

Neurosurgical cases are quite diverse and differ by age group. Herniopathy in elderly patients and hydrocephalus surgery in pediatric patients have been reported commonly (10,11). In accordance with the literature data, herniopathies (25.6%) constituted the majority of patients over the age of 18 in our study, while shunt/EVD surgery (57.6%) was dominant in patients under 18 years of age. Emergency cases revealed that the most common indications in our patients over the age of 18 were shunt/EVD and subdural hematoma and emergency pediatric patients under the age of 18 were mostly operated for shunt/EVD and cranial fractures. Isık et al. reported in two studies that emergency indications were subdural and epidural hematoma for adults, and epidural hematoma and cranial fracture for pediatric patients (6,7).

The duration of anesthesia depends on many factors such as the type of operation to be performed, the surgical techniques to be applied, the physical condition of the patient, and the skill of the anesthesiologist and surgeon. The average duration of anesthesia was 145.9 ± 75.5 minutes in our study. We found anesthesia times to be 176.2 ± 55.8 minutes in cranial surgical procedures and 129.8 ± 40.1 minutes in spinal surgical procedures.

Although the rate of intubation difficulty varies in studies, the incidence is reported between 1.8-8.2% (8). Yegin et al. (9) found the rate of intubation difficulty to be 3.3%, while Sabanci et al. (10) found it as 4.1% in their study of 603 patients. We also found intubation difficulties in 236 (4.6%) patients in our study. We found the causes of difficulty in intubation as 41.1% neck motion restriction, 18.2% high larynx and 11.9% short-muscular neck. In their research, Dimitriou et al. (11) found intubation difficulty to be more common in men than in women. We also found the same in our study, and that it was statistically significant ($p<0.05$). Considering the surgeries with intubation difficulties, the most common was spinal fracture with 21%, herniopathy with 20%, and spinal instrumentation with 11%. This is possibly due to fractures, hernias and masses restricting neck movements, preventing positioning, making it difficult to reach the trachea and making suitable conditions for intubation difficult, especially in the cervical region.

Thiopental has neuroprotective effects, propofol has a rapid recovery profile, and both are widely used for induction in neuroanesthesia (10). We found in our study that 72.4% thiopental was preferred in cranial surgical procedures in induction, and 91.1% propofol was preferred in spinal surgery procedures. We also observed that thiopental was preferred for cranial surgical operations due to its neuroprotective effects, and propofol was preferred in cases where rapid awakening and early neurological evaluation was required after spinal surgical operations.

The minimal effect of rocuronium on brain metabolism, rapid onset, short half-life, and rapid reversal with sugammadex have increased the use of neuromuscular blocking agents (NMB) for neuroanesthesia (1).

The total intravenous anesthesia (TIVA) technique and its component, propofol, are common in anesthesia maintenance due to hemodynamic stability, rapid neurological recovery, minimal effect on neuromonitoring, and negative cerebral effects of inhalation agents (12). We found in our study that the most commonly used maintenance agent was propofol with 36.2% and that it was preferred especially in cranial space-occupying surgeries with high ICP and in selected spinal neurosurgical surgeries with neuromonitoring. We also found that desflurane with 30.3% and sevoflurane with 29.2% were used in the second and third frequencies, respectively. We determined that 58.3% propofol, 30.1% sevoflurane and 11.5% desflurane were used as agents in the maintenance of anesthesia in cranial surgical procedures; while 61.8% desflurane, 30.1% sevoflurane and 8.0% propofol were used in the maintenance of anesthesia in spinal surgical procedures.

The rapid onset and disappearance of remifentanil's effect, its immediate onset after administration, and easy dose adjustment without worrying about the delay in awakening with deep analgesia have increased its use in balanced inhalation anesthesia (3,13). In our study, the most commonly used opioid analgesic was remifentanil with 81.4%.

Although TIVA has some advantages over inhalation anesthesia in the intraoperative and early postoperative period, comparing the medium and long-term results, the difference between them is considered to be insignificant (14). We observed in our study that 59.5% inhalation and 35.1% TIVA were preferred as the maintenance method.

It is safe to assume that the possibility of complications increases with age, prolongation of anesthesia duration and presence of comorbidity (15). Although complications in the intraoperative period are various, the most common one is

cardiovascular complications. In their study, Gercek et al. (16) found the rate of intraoperative complications as 25.6%. In our study, we similarly found the complication rate as 24.1%. In the study by Minami et al. (17) 63.2% of intraoperative complications were cardiac and 21.8% pulmonary complications. In our study, 71.9% of intraoperative complications were cardiovascular, 11.6% metabolic, 11.1% allergic and 9.6% pulmonary complications. The most common intraoperative complications were subarachnoid hemorrhage (SAH) with 64.4%, decompression surgery with 58.3%, and intraparenchymal hemorrhage surgery with 57%. The incidence of intraoperative complications was significantly higher in patients who were admitted to surgery urgently than those admitted to surgery electively, and similarly, the rate of intraoperative complications was higher in patients with concomitant systemic disease ($p<0.005$).

The need for intensive care after neurosurgical operation may be considered for close neurological follow-up and treatment. Yeğin et al. found the need for postoperative intensive care as 21.7% in patients who underwent neuroanesthesia (9). We found it similarly as 24.8%. We also found that the need for postoperative intensive care increased significantly between years ($p<0.005$). The need for postoperative intensive care existed mostly in intraparenchymal bleeding surgery with 96.2%, decompression surgery with 91.7% and aneurysm surgery with 87.6%. Furthermore, our study evinced that the need for postoperative intensive care was higher in patients admitted to emergency surgery than those who received elective surgery, and the duration of anesthesia was longer in patients who needed postoperative intensive care compared to patients who did not need postoperative intensive care ($p<0.005$).

From the anesthesia records kept in a regular and systematic way, many studies covering large patient series can be carried out in a healthy way. We concluded that the repetition of retrospective studies at regular intervals could allow both the continuous evaluation of the practices in the same clinic and the comparison between the clinics and thus, contribute to the development of anesthesiology.

Conflict of interest

There is no conflict of interest to declare.

Acknowledgments

None to declare.

Ethical Approval

The study was approved by the Ethics Committee of Ondokuz Mayıs University (Date: 08.10.2020 Decision no: 2020/542). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Research Article

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Can serum SCUBE1 levels be useful in the diagnosis of bladder cancer?

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Abstract

Bladder cancer (BC) is the most common malignancy of the urinary system and the sixth most prevalent cancer in both men and women. There is currently no biomarker identified to facilitate the diagnosis of BC and which can be considered as the gold standard. The aim of this study was to determine the diagnostic significance of serum signal peptide-CUB-EGF domain-containing protein 1 (SCUBE1) levels in patients newly diagnosed with BC and to compare the sensitivity and specificity of SCUBE1 with those of carbonic anhydrases IX (CAIX), which has previously been shown to be positive in BC. SCUBE1 and CAIX levels were investigated using enzyme-linked immunosorbent assay (ELISA) in serum samples from 19 patients with bladder cancer and 25 healthy peers. Levels of both were significantly higher in the BC group compared with the control group (p=0.0001). Based on ROC analysis, SCUBE1 emerged as a sensitive test, similarly to CAIX, for identifying BC. These findings suggest that increased SCUBE1 levels may be a useful addition to clinical findings of disease in the diagnosis of BC patients.

Keywords: bladder cancer, carbonic anhydrase, SCUBE1, CAIX

1. Introduction

Cancer is a major public health problem worldwide and the second leading cause of death in the USA. Some 1.8 million new cancer cases and 606,500 cancer-related deaths are projected to occur in the USA in 2020 (1). Bladder cancer (BC) is the most common malignancy of the urinary system and the sixth most prevalent cancer in both men and women. More than half a million people were diagnosed with BC worldwide in 2018, and 200,000 died from the disease (2). It is estimated that approximately 81,400 new cases of BC will be diagnosed in adults in the USA in 2020, of which 17,980 will be fatal (1). BC generally arises from epithelial cells, and more rarely from mesenchymal cells. The best-established and most important risk factor for BC development is smoking. Chemicals in tobacco chemicals increase the expression of proteins involved in inflammation, and activate genetic and epigenetic pathways, thereby adversely affecting the cell cycle by inducing uncontrolled cell proliferation. BC is a complex disease involving various molecular and pathological pathways, and therefore exhibits different behaviors depending on the clinical staging of the tumor and the molecular type. The diagnosis and monitoring of BC largely involve invasive tests involving periodic cystoscopy. Although this is a reliable method, the procedure is highly uncomfortable for the patient and causes comorbidity. Due to this disadvantage of the method, studies on developing new biomarkers have been accelerated by taking into account the metabolic events that play a role in the pathogenesis of BC. Biomarkers associated with hypoxia, inflammation and oxidative stress have been shown to be capable of use in the diagnosis of BC (2-4). However, there is currently no biomarker identified to facilitate the diagnosis of BC and which can be considered as the gold standard (2).

Carbonic anhydrases (CAs) are mostly zinc-containing metalloenzymes which catalyze the reversible hydration of carbon dioxide. They also play a role in the development stages of various cancers. Carbonic anhydrase IX (CAIX), which can be induced by hypoxia and is one of the best cellular biomarkers of hypoxia, plays an important role in pH regulation in cancer cells. By regulating intracellular and extracellular pH, it helps these cells adapt to adverse conditions in the tumor microenvironment (5). Previous studies have shown that CAIX is a biomarker capable of use in the diagnosis of various cancers, including BC (6-10).

Signal peptide-CUB-EGF domain-containing protein 1 (SCUBE1) was discovered in the early 2000s. The production of this cell surface glycoprotein begins in early embryogenesis, and it is present in platelets and endothelial cells (11). SCUBE1 consists of nine consecutively edited EGF-like repeats following an N-terminal signal peptide sequence, an intermediate region, three cysteine-rich repeat motifs, and a

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CUB region at the C terminal (12). These secreted proteins exhibit confirmed interactions with the angiogenesis-related signal system. Like other proteins containing EGF and CUB domains, they are involved in stages, such as organogenesis and morphogenesis. As with cell surface and other secreted glycoproteins, they are expressed in tissues with rich blood supplies and primary osteoblasts and bones. SCUBE genes have been shown to be expressed from developing tissues, such as gonads, the central nervous system, dermomyotome, digital mesenchyme, and limb buds during mouse embryogenesis. In addition to embryonic expression, SCUBE1 has been found to be expressed in endothelium and platelets (13). SCUBE1 has recently been demonstrated in various carcinomas, such as gastric and renal cell carcinoma (9,12). However, there is no study examining SCUBE1 levels in BC patients. The aim of this study was to determine the diagnostic significance of serum SCUBE1 levels in patients newly diagnosed with BC and to compare the sensitivity and specificity of SCUBE1 with those of CAIX, previously shown to be positive in BC.

2. Materials and methods

2.1. Study group

Informed consent was obtained from all patients and controls. Approval for the study was granted by the local ethics committee. Nineteen patients newly diagnosed with BC with stage T2 were included as the study group and 25 healthy peers as the control group. Coronary or liver failure, chronic inflammatory diseases or anemia, receiving chemotherapy, or using oral contraceptives and anticoagulants were excluded from the study in the selection of control and patient groups. Control groups were randomly selected from among patients with no history of urothelial and other malignancy, after the detailed medical history, laboratory and radiology results were evaluated. Patients were selected from individuals presenting to the urology clinic. The urothelial cancer diagnose in patients was based on laboratory examinations, radiological imaging in line with their complaints and transurethral resection of bladder cancer. Tumor grade was determined using the 2016 World Health Organization classification of Tumours of the Urinary System and Male Genital Organs system (14) and the pathologic stage using the 2017 American Joint Committee on Cancer eighth edition cancer staging manual system (15). The tumour, node, metastasis classification (TNM) of the patients was Ta: Non-invasive papillary carcinoma, Tis: Carcinoma in situ: 'flat tumour' and T1: Tumour invades subepithelial connective tissue. All the patients present with papillary urothelial carcinoma. The urothelial tumors were noninvasive in all patients. The noninvasive urothelial tumors included low-grade papillary urothelial carcinomas in this study. In addition, by examining the patients' records, data on demographic information, smoking history, medical history, tumor recurrence, metastasis, treatment, and clinical outcome were collected. Five-milliliter blood samples from each individual were placed into vacutainer tubes without anticoagulant. These were then centrifuged at 1800xg for 10 minutes. Serum samples were stored at -80ºC until being used for measurements.

2.2. Determination of serum CAIX levels

Serum CAIX levels were determined using enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Catalog No: DCA900, Minneapolis, USA) according to the manufacturer's recommendations. The absorbance of the samples was measured at 450 nm wavelength on a microplate reader (Molecular Devices Versamax, California, USA). The results are given in pg/mL. The intra-assay CV reliability of this ELISA method was found to be <3% and the confidence of the inter-assay CV was <6%.

2.3. Determination of serum SCUBE1 levels

Serum SCUBE1 levels were determined using ELISA kits (Cusabio, Catalog No: CSB-E15005h, Wuhan, China) according to the manufacturer's recommendations. The absorbance of the samples was measured at 450 nm wavelength on a microplate reader (Molecular Devices Versamax, California, USA). The results are given in ng/mL. The confidence of the intra-assay CV of this ELISA method was <8% and the confidence of the inter-assay distribution was <10%.

2.4. Statistical analysis

The results were expressed as mean±standard deviation for normally distributed variables and as median (interquartile range [IQR]) values for non-normally distributed variables. Statistical analysis was performed on Statistical Package for the Social Sciences (Version 23.0, NY, USA) statistical software. Compatibility with normal distribution was determined using the Kolmogorov-Smirnov test. Differences between the two groups were analyzed using Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Chi square test was applied to evaluate the smokers' data among the groups. Receiver operating characteristic (ROC) curves were used to detect the discriminatory dominance of CAIX and SCUBE1 for the identification of BC. Sensitivity and specificity were determined from ROC graphs for CAIX and SCUBE1. $p<0.05$ was regarded as significant.

3. Results

Forty-four individuals were enrolled in the study. SCUBE1 and CAIX levels were determined in serum samples from 19 BC patients [9 male, 10 female; median age 56 (51.0-62.0) years] and 25 controls [12 male, 13 female; median age 53 (50.0-62.0) years]. No significant difference was observed between patients and controls in terms of age ($p>0.05$). The clinical and biochemical parameters of BC and control groups were given in Table 1 and Fig. 1. Mean SCUBE1 levels were 18.6±6.20 ng/mL in the BC patients and 8.61±5.22 ng/mL in the control group and were statistically significantly higher in the BC patients ($p=0.0001$). Median (IQR) CAIX values were 54.1 (40.5-114.6) pg/mL in the BC patients and 22.3 (10.6-36.1) pg/mL in the control group. CAIX levels were statistically

significantly higher compared to the control group (p=0.0001). ROC curve analysis was also used to quantify serum SCUBE1 and CAIX levels. Values for cut-off points, AUC, sensitivity and specificity for individual parameters are shown in Fig. 2. The significant power of SCUBE1 was similar to that observed in CAIX (p= 0.0001).

Table 1. Comparison of biochemical parameters in BC and control groups

Parameters	BC (n:19)	Control (n:25)	p
BMI (kg/m^2)	26.4±2.81	25.7±3.50	0.240
Smoker, n (%)	13 (68.4)	10 (40)	0.136*
SCUBE1 (ng/mL	18.6±6.20	8.61±5.22	0.0001**
CAIX (pg/mL)	82.8±65.4 54.1 (40.5-114.6)	27.1±19.3 22.3 (10.6-36.1)	0.0001***

Data were expressed as: mean±SD, median (inter quartile range for 25-75%). *p shows differences between control and cancer according to Chi square test, **p shows differences between control and cancer according to student t test, ***p shows differences between control and cancer according to Mann-Whitney U test.

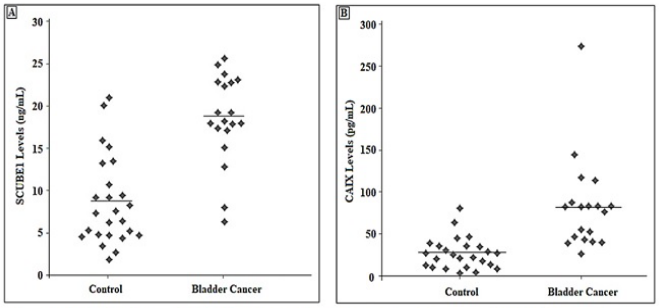

Fig. 1. SCUBE1 (A) and CAIX (B) levels in the bladder cancer and control groups

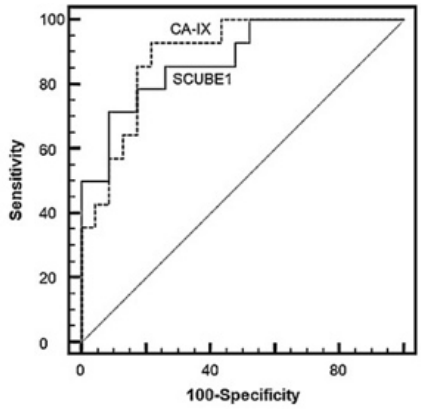

Fig. 2. ROC curve analysis of CA-IX and SCUBE1 levels in patients with bladder cancer and their AUC, p values, sensitivity and specificity

4. Discussion

Bladder cancer entails the highest costs per patient of all cancers, due to the diagnostic protocols currently in use and the fact that many patients live long after diagnosis. The gold standard for the diagnosis of BC remains direct visualization of the urothelium using conventional white light cystoscopy. Urine cytology continues to play an important role in the diagnosis and follow-up of BC. In addition, the US Food and Drug Administration (FDA)-approved UroVysion and nuclear matrix protein 22 (NMP22) are also used in the diagnosis and follow-up of BC in clinical applications (16). Despite the existing diagnostic markers used in BC diagnosis, there is still a need for non-invasive, simple, and inexpensive tests capable of use in the clinical setting.

Hypoxia is a consequence of the rapid growth of many tumors, including BC, and is an important regulator of gene expression. CAIX, a hypoxia-dependent member of the carbonic anhydrase family, plays a role in intracellular pH, cell proliferation, and cell content, and regulates tumor progression (17). Hypoxia leads to overexpression of some genes mediated by hypoxia-inducible factor 1. This overexpression also triggers CAIX expression. Although weak CAIX expression is observed in the normal gastric mucosa, small intestine, biliary tract, and seminal canals, its expression has not been observed in other organ systems, including the urinary tract. Surprisingly, CAIX is abundantly expressed as a direct result of hypoxia in a large number of cancers, but it is also affected by other means and by genetic disorders (18). CAIX levels in the circulation have been investigated in various cancers such as renal cell, gastric and breast cancer, and high levels have been determined (6-9). However, Hyrsl *et al*. determined that serum CAIX did not exceed normal levels in transitional cell carcinoma patients (10). In the present study, serum CAIX levels were higher in patients with BC than in the healthy controls. This finding supports the possibility of CAIX being used in the diagnosis of BC, in agreement with the previous literature.

SCUBE1, a cell surface glycoprotein belonging to the epidermal growth factor (EGF) superfamily, functions as a newly defined platelet-endothelial adhesion molecule (19). An immunohistochemically soluble adhesion molecule, SCUBE1 has been detected in the subendothelial matrix of advanced atherosclerotic lesions in humans. This protein is regarded as a novel biomarker of platelet activation in acute thrombotic diseases (20). For the first time in the literature, serum SCUBE1 values in BC patients were found to be statistically higher than in the healthy control group in this study. An AUC value of 0.879 for SCUBE1 was associated with 71% sensitivity and 92% specificity, while an AUC value of 0.891 for CAIX was associated with 93% sensitivity and 78% specificity. In previous studies evaluating potential biomarkers in bladder cancer, Sakinewicz *et al.* reported that podoplanin exhibits 72% sensitivity and 69% selectivity (21), while Tokarzewicz et al demonstrated that cystatin C shows 87% sensitivity and 92% selectivity in patients with BC (22). Wang *et al*. also reported that bladder cancer-specific antigen-1 exhibits 74% sensitivity and 69% selectivity (23). Interestingly, in a recently published study, Guszcz *et al.* showed that the plasma aromatase biomarker exhibited 100% sensitivity and 100% selectivity in their study of 78 patients with BC and 18 healthy controls (24). From this point of view, it is seen that the results obtained in the study are compatible

with the values obtained for other biomarkers in BC patients.

Based on these results, the sensitivity and specificity of SCUBE1 appear to be quite similar to those of CAIX. In addition to its embryonic expression, SCUBE1 has been found to be expressed in the endothelium and platelets (13). SCUBE1 is stored in inactive platelet α-granules. Thrombin is transported to the cell surface as a result of platelet stimulation and activation through various stimulants, such as inflammation and hypoxia. SCUBE1 is transported to the platelet surface under thrombotic conditions. It is then separated from the platelet surface and released into the circulation in the form of small, soluble particles and is included in the thrombus (25). There is a known association between thrombosis and cancer and the presence of tumor cells in the thrombus (26). Coagulation dysfunction can be considered primary evidence of malignancy (27). Many tumors stimulate the clotting cascade and trigger the production of procoagulants, resulting in an inflammatory response. This inflammatory response increases the release of more procoagulants from tumor cells (28). Circulating SCUBE1 levels have been found to increase in various diseases involving platelet activation, such as acute coronary syndrome, and acute ischemic stroke (19). An increase in plasma SCUBE1 levels has also been observed in patients with such pathological conditions as acute mesenteric ischemia (29), end stage renal failure (30), Crimean-Congo hemorrhagic fever (31), renal cell cancer (9), breast cancer (32) and stomach cancer (12).

The main limitation of this study is the low number of patients. Further studies are needed to examine SCUBE1 levels and relationship by increasing the number of patients and adding cases of low and high grade papillary urothelial carcinomas. The precise presentation of the findings can be better understood in the longitudinal follow-up of a larger group of patients.

The principle conclusions from the new findings from this study are that SCUBE1 is as sensitive and specific as CAIX in the circulation in the diagnosis of BC, and that the use of SCUBE1 together with CAIX can also help support clinical findings in the diagnosis of BC.

Conflict of interest

None to declare.

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Ethical approval

The study was approved by the Ethics Committee of Karadeniz Technical University (No: 2013/13). The study was conducted in accordance with the principles of the Declaration of Helsinki.

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Review Article

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A clinical review: Covid-19 and dermatology

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Abstract

On March 11, 2020, the World Health Organization (WHO) declared Corona Virus Disease-2019(COVID-19) as a pandemic disease caused by SARS-CoV-2. During the COVID-19 pandemic, the importance of dermatology practice in patient management has emerged. Skin involvement was rarely documented in the first reported case series. The reason for this has been shown to be that a complete dermatological examination can not be performed in cases. Over time, significantly higher rates of skin findings have been reported.The mechanism of skin lesions associated with COVID-19 is not yet clear. The most common view is that lymphocytic vasculitis caused by vascularly located viral particles and langerhans cell activation is caused by an immune response to infection leading to vasodilation and spongiosis.Keratinocytes are thought to be secondary targets.It has been emphasized that skin findings are encountered at rates varying between 2-20% in COVID-19 patients. Casas et al. performed the first prospective study to classify the skin manifestations of COVID-19 into five major groups, including pseudo-chilblains (19%), other vesicular eruptions (9%), maculopapuler eruption (47%), livedo or necrosis (6%) and urticarial lesions (19%).

Keywords: COVID-19, dermatology, cutaneous manifestations, histopatology

1. Introduction

Coronaviruses (CoV) are RNA viruses belonging to the Orthocoronavirinae subgroup of the Coronaviridae family. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is in the beta subclass of this enveloped, positive-polar, single-stranded virus family (1).

SARS-CoV-2 was reported as a newly identified viral pneumonia agent in Wuhan, China in December 2019. SARS-CoV-2 belongs to the coronavirus family and the clinical condition it causes has been named COVID-19 disease (2). On March 11, 2020, the World Health Organization (WHO) declared Corona Virus Disease-2019 (COVID-19) as a pandemic disease caused by SARS-CoV-2. The COVID-19 pandemic represents the most serious health crisis faced by the modern world and being able to control this pandemic and its consequences cause a great effort all over the world (3,4).

During the COVID-19 pandemic, the importance of dermatology practice in patient management has emerged. Skin involvement was rarely documented in the first reported case series. The reason for this has been shown to be that a complete dermatological examination can not be performed in cases. Over time, significantly higher rates of skin findings have been reported (5).

2. Cutaneous Manifestations of COVID-19

The mechanism of skin lesions associated with COVID-19 is not yet clear. The most common view is that lymphocytic vasculitis caused by vascularly located viral particles and langerhans cell activation is caused by an immune response to infection leading to vasodilation and spongiosis. Keratinocytes are thought to be secondary targets (6). It has been emphasized that skin findings are encountered at rates varying between 2-20% in COVID-19 patients (7). Casas et al. (5) performed the first prospective study to classify the skin manifestations of COVID-19 into five major groups, including pseudo-chilblains (19%), other vesicular eruptions (9%), maculopapuler eruption (47%), livedo or necrosis (6%) and urticarial lesions (19%). In the pediatric COVID-19 patient group, signs such as petechiae, ecchymosis and vasculitic skin symptoms were also observed. These vascular changes are thought to be related to COVID-19's retention of porphyrin by affecting the p chain of hemoglobin and blocking heme synthesis (8).

2.1. Pseudo-chilblains

Itchy or painful acral lesions that become evident with exposure to cold are defined as pernio. Pernio may be idiopathic (primary)or may develop secondary to some systemic diseases. Mostly can manifest as erythematous-to-violaceous papular, nodular, or vesiculobullous, ulcerating skin symptoms (9).

Pseudochilblains, known as COVID toes, are painful, pernio-like acral lesions that can be encountered in patients of all age groups (10,11). These lesions resembling chilblains can be in the appearance of purpura and affect the hands and feet (5). Foot involvement alone is present in most of the cases (85.7%). It has seen that the hands and feet were involved in a lower rate (7%) or only the hands (6%) (10,11). Magro et al.

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(12), reported that the lung and skin of 5 cases diagnosed with severe COVID-19 evaluated the tissues. In 3 cases, they described skin purpura and livedo racemosa, microvascular thrombotic disorder and D-dimer elevation. In the lung and skin tissues of the cases complement accumulation, complement activation and microvascular thrombosis has been detected. They stated that complement-mediated microvascular damage and thrombosis may be an important pathogenetic mechanism in COVID19. Therefore, it was stated that anticoagulant and anticomplement therapies were might be important in early intervention in severe cases. Freeman et al. (13) examined 505 cases of COVID19 with dermatological findings. In 318 (63%) of cases pernio-like lesions were present. Patients with pernio-like lesions had milder signs of COVID-19. They were also generally young and healthy. In this study, pernio-like lesions were the only symptom in 55% of the patients. Other COVID-19 symptoms were present in 45% of patients with pernio-like lesions. The most common symptoms were cough (21%), headache (15%), sore throat (12%) and fever (12%). In patients with other COVID-19 symptoms, pernio-like lesions appeared after other symptoms. Osorio et al. (14) studied 14 cases with pseudo-chilblain lesions. The mean age of the cases was 13.2 years. COVID19 was detected in 2 of the cases. It has been emphasized that pseudo-chilblain in lesions is a late manifestation of COVID-19, mostly observed in young patients with mild symptoms (5,13,14).

Histopathological Findings

In the pathology of a case with PCR positive for COVID 19 and pernio-like lesions, intense superficial and deep lymphocytic inflammation and mild vacuolar interface dermatitis consistent with pernio and connective tissue disease were observed. No thrombus was observed (13). Several other reported pathology reports showed findings consistent with pernio-like changes: Spongiosis, vacuolar interface change, apoptotic epidermal keratinocytes. Some cases showed superficial and deep perivascular lymphocytic or lymphohistiocytic infiltrate, without evidence of vasculitis. Small vessel lymphocytic vasculitis without microthrombus, a subepidermal bleb and rarely lymphocytic vasculitis with microthrombus and underlying epidermal necrosis have been reported in a smaller number of cases (13,14).

2.2. Vesicular Eruptions

Vesicular eruptions associated with COVID-19 occur in two forms as diffuse and localized forms. The diffuse type is polymorphic and has a widespread distribution, while the local type is monomorphic and localized only on the trunk. Although vesicular eruption often occurs after the onset of typical COVID-19 symptoms, it can sometimes occur before symptoms begin (15). Some authors have noted an increase in the frequency of herpesvirus in COVID-19 patients, with some of the vesicular lesions associated with it. In the presence of herpesvirus accompanying COVID-19 disease, the formation of hemorrhagic vesicles and bullae with sizes ranging from 2-3 mm to 1 cm has been demonstrated (16). In a multicenter study conducted in Italy, 18.2% of COVID-related skin manifestations were papulovesicular rash. In addition, although papulovesicular exanthema occurs more frequently in the adult population, In the study of Marzano et al. (17) the median age was 60 years.

Histopathological Findings

Significant acantholysis and dyskeratosis were observed in the histopathology of three cases with papulovesicular rash associated with COVID-19. Because of these histopathological findings, the authors do not use the term “chickenpox-like rash”. They used the term “COVID-19 associated acantholytic rash” to group these cases. In the report of another papulovesicular case there was extensive epidermal necrosis with bursting, ac antholysis and swelling of keratinocytes, ballooning of keratinocytes, and signs of endothelitis (18,19).

2.3. Maculopapuler Eruption

Maculopapular rash is a common skin finding. It occurs in bacterial and viral infections like scarlet fever, measles, rubella, erythrovirus (parvovirus B19, smallpox, varicella. It is also seen as heat rash and hypersensitivity reactions (exanthematous drug reactions) (20). The skin findings of 88 COVID-19 patients were examined in a study. Skin findings occurred in one-fifth of the patients. Skin findings were present in 8 patients at the time of admission. The majority of rashes that occurred during follow-up in 10 patients were erythematous maculopapular rash. There was no correlation between the severity of the disease and skin findings (21,22). Maculopapular rash, which is mostly located on the trunk, is reported as the most common dermatological finding associated with COVID-19. Extremities and face are often seen to be protected. The maculopapular rash associated with severe COVID-19 usually resolves within 10 days (23). Atypical maculopapular eruptions may occur in patients with COVID-19. In some patients, scaly rash with perifollicular location was observed. In addition, pityriasis rosacea-like lesions, purpuric lesions, erythema elevatum diutinum-like pseudovesicles and erythema multiforme were also observed (5). In some cases, symptoms of COVID-19 mimics the rash found in other viral infections. A case diagnosed as a Denga fever due to skin rash, petechiae on initial examination, low platelet count and fever. When respiratory problems begin within a few days definitive diagnosis of COVID-19 infection by excluding other common viral infections confirmed by RT-PCR (22) There is a suspicion that COVID19 may be a trigger for maculopapular rash. However, the role of SARS-CoV-2 in inducing skin lesions is unclear and needs to be clarified by further observations.

Histopathological Findings

Histologically, maculopapular lesions have different features. Maculopapular lesion biopsies mostly contains superficial perivascular dermatitis with lymphocytic infiltrate, neutrophils, eosinophils, nuclear debris, and dilated vessels in the papillary and middle dermis. Hydropic changes in the epidermis with minimal acanthosis, subcorneal pustules, mild

spongiosis, basal cell vacuolation and parakeratosis foci are found (24). Rosell-Diaz et al. (25) presented a lichenoid model with the presence of eosinophils in the biopsy of maculopapular lesions. In one study, the histopathology of maculopapular eruptions was classified according to lesion onset as follows: In early-onset lesions, perivascular lymphocytic infiltrate and spongiosis with moderate epidermal and dermal eosinophils were observed. However, in late-onset lesions, histiocytes were found in collagen fibers with perivascular lymphocyte infiltration. These late-onset lesions do not contain mucin deposits (26).

2.4. Livedo Reticularis/Racemosa-Like Skin Findings

Livedo reticularis (LR) is a cutaneous physical finding characterized by a transient or permanent, red-blue or purple, net-like cyanotic pattern. LR can occur in a variety of physiological and pathological conditions. It may indicate cutaneous blood flow disturbance (27). The pathophysiology of these lesions is unclear. Bouaziz et al (28) stated that immune dysregulation, vasculitis, vessel thrombosis, or neoangiogenesis may produce this clinical picture. In a study conducted in France with 277 patients with suspected COVID-19, livedo reticularis was found in 4 patients (1%) (29). In another study investigating vascular skin manifestations associated with COVID-19, livedo was observed in 1 out of 7 patients (28). These differences in rates may be due to cases with unclear diagnosis of COVID19 (29). Tusheva et al. (30) reported a case of unilateral LR in a patient, with a fatal outcome. They observed patchy bilateral lung opacities on the chest radiograph of a 59-year-old female patient with a history of dry cough, mild shortness of breath, and low-grade fever. The diagnosis of COVID-19 was confirmed by polymerase chain reaction. There was no whitening or tenderness in the dermatological examination. Red to purple reticular discoloration was present for 8 hours in the distal right lower extremity. Coagulation disorders may be seen in patients infected with COVID-19. In this case they detected thrombocytopenia, increased D-dimer level and prolongation of prothrombin time. Thus, they stated that macro and micro thrombosis attacks formed livedo reticularis. Various mechanisms exist to explain this clinical picture and livedo reticularis seen with COVID 19. Disseminated intravascular coagulation, antiphospholipid syndrome, features of COVID19, activation of complement cascade, and drug interactions may be responsible for the development of livedo and necrosis (31,32). Additional clinical trials may determine whether anticoagulants can improve overall outcomes in the treatment of such liveoid manifestations (33).

Histopathological Findings

The histopathology of LR varies according to the underlying cause. There are no histopathological changes in physiological forms. In secondary causes, a number of changes may occur, such as vasculitis, calcium deposition in vessel walls (calciphylaxis), intravascular eosinophilic occlusion (monoclonal cryoglobulinemia), intraluminal thrombosis (hypercoagulation states), cholesterol cleavage (cholesterol embolism), and crystal deposition (27). Khalil et al. (34) presented a 34-year-old female patient with livedo reticularis that developed with COVID19. Histopathologically, perivascular lymphocytic infiltration, superficial dermal mucin increase, and necrotic keratinocytes indicating viral exantemia were observed. The observation of mucin on this biopsy may be directly related to the exanthem or may indicate a subclinical condition masked by infection.

Table 1. Overview of clinical patterns in major studies on cutaneous manifestations associated with COVID-19

	Pseudo-chilblain	Vesicular	Urticarial	Maculopapuler	Livedo or necrosis
Galván Casas et al.(5)	19%	9%	19%	47%	6%
Nirenberg et al. (10)	Foot involvent				
Piccolo et al. (11)	Alone 85.7%				
Magro et al. (12)					Livedo racemosa(3cases)
Freeman et al. (13)	63%				
Marzano et al (17)		18.2% papulovesicular rash			
Recalcati et al. (21)				Maculopapuler rash(10 cases)	
de Masson etal.(29)					1%Livedo
reticularis(LR)					
Bouaziz et al. (28)				13%LR	
Tusheva et al. (30)					Unilateral LR
Damme et al. (37)			2 cases with acute urticaria		

2.5. Urticarial Lesions

Urticaria is characterized by itchy and edematous plaques called "urtica". Angioedema may develop along with urticaria when deep dermal and/or subcutaneous involvement occurs. Clinically, conditions lasting less than 6 weeks are classified as acute, and conditions lasting for 6 weeks or longer as chronic urticaria (35). There is limited data on the relationship between urticaria and COVID-19. It has been stated that there may be susceptibility to COVID-19 in patients with urticaria, and viral symptoms (cough, fever, shortness of breath, myalgia) should be questioned in cases with urticaria plaques (5). There are studies indicating that acute urticaria among dermatological

emergencies may be associated with COVID-19(36). Damme et al. (37). reported 2 cases, 71-year-old male and 39-year-old female, who were diagnosed with COVID-19. In both cases, weakness and fever were observed before the definitive diagnosis of COVID-19; In addition to these symptoms, they have been reported to have acute urticaria attacks. In a study conducted in Belgium, it was emphasized that there was a significant increase in the frequency of urticaria and urticarial vasculitis in patients presenting with dermatological complaints during the pandemic period. Despite this, no association was seen between COVID-19 and urticaria severity (38).

Histopathological Findings

The histopathological data available on urticaria cases associated with COVID19 are not sufficient (39). Amator et al (40) found in biopsy of a case of urticaria associated with COVID19 lichenoid and vacuolar interphase dermatitis, mild spongiosis, dyskeratotic basal keratinocytes and superficial perivascular lymphocytic infiltrate.

3. Dermatological findings associated with COVID19 prevention measures

The term "Maskne" was first defined during the (COVID-19) pandemic. It is a type of acne mechanic, previously described, associated with personal protective equipment. Maskne formation is caused by mechanical stress (pressure, congestion, friction), temperature increase, humidity and microbiome dysbiosis. Follicular occlusion triggers the picture. Mask wear time, tropical climatesand increased sweating are risk factors (41,42,43). However, the pathogenesis of mask-induced acne has not been fully clarified (44).

Suggested clinical criteria for maskne:

1.Acne formation or exacerbation of existing acne within the mask area within 6 weeks of the onset of regular surgical mask use

2. Involvement in a prominent pattern called the O-zone

3. Exclusion of differential diagnoses such as perioral dermatitis, seborrheic dermatitis, pityrosporum folliculitis and acne rosacea (41).

Maskne, can also increase the feeling of discomfort and itching on the face, increasing touching the face and thus the transmission of COVID19 (45). Some measures to prevent maskne are mentioned. In order to shorten the mask wearing time, it is necessary to take intermittent breaks and change the mask frequently (46). Han et al. (47) recommended changing the mask after 4 hours for the surgical mask and after 3 days for the N95 mask. Desai et al. (48) stated that after using the mask for 2 hours, a break of 15 minutes should be taken. There are also studies that recommend applying an oil-controlling moisturizer before wearing a mask to reduce sebum secretion (47,49,50). A literature series highlighted the importance of safety, tolerance and comfort in mask design. American Academy of Dermatology Association does not recommend the use of strong products such as retinoids, chemical peels, and exfoliants that can irritate the skin or increase maskne (51,52).

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Review Article

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The impact of COVID-19 on global health and other aspects of human life

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Abstract

COVID-19 has emerged as a serious public health problem in recent times. It is an infectious disease caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The place of origin of this virus is Wuhan city, China in late December 2019, has spread throughout the world rapidly. There are two important classes of the Coronavirus affecting human beings: Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS). Coronavirus is a positive-sense, single-stranded RNA (+ssRNA) virus. Diagnosis of the COVID-19 is done by taking a nasal swab, tracheal aspirate or bronchoalveolar samples and RT-PCR. COVID-19 treatment generally depends on the severity and/or the health status of the infected patient. The treatment strategy, so far, includes the use of antiviral drugs. Clinical trials of vaccines were started in early 2020 by different companies and some are released that are in use. Preventive measures are social/physical distancing, masking and isolation of infected individuals. Although educational systems have used various learning management systems there are concerns about the online teaching system in comparison to the traditional classroom teaching system. In this review, we have tried to analyze the impact of COVID-19 on the health systems worldwide and other aspects of human life

Keywords: COVID-19, educational systems, global health, real-time PCR, vaccine

1. Introduction

Coronaviruses are enveloped, positive sense, single stranded RNA viruses that are responsible for infectious diseases affecting the respiratory system. It is a common virus affecting members of the animal kingdom, including humans, birds and other mammals. Recently, the serovar of coronavirus i.e., (SARS-CoV-2) (Fig. 1) was discovered in Wuhan city, (Huanan Seafood Wholesale Market of Wuhan, through animal-to-human transmission), Hubei Province, China (1-3). There are many assumptions about the theory of natural host of this virus, which means is still unknown and is believed to have an animal origin e.g., pangolins, bats, etc. It is assumed human acquired infection from these animals, but research is still going on. The first case of COVID-19 was reported at the end of 2019.Since then, the occurrence and distribution of coronavirus, it has spread all over the world causing a pandemic situation and thus a healthcare emergency (4-5).

It may differ from country to country or content to other, but it is very clear that, most affected countries are USA, India, Brazil, Russia, Italy, China, Iran, Egypt, Israel, all gulf countries and other. It shows that the infection and outbreak of (SARS-CoV-2) are distributed throughout the world. In India, the first case of (SARS-CoV-2) was reported in Kerala. Most numbers of the positive case reported states till date in India are Maharashtra, Kerala, Uttar Pradesh and also spread almost of all states in India. The total confirmed Coronavirus Cases is 282 by 20th January 2020. It has been reported from four countries including China (278 cases), Thailand (2 cases), Japan (1 case) and the Republic of Korea (1 case). COVID-19 has resulted in a 'once-in-a-century pandemic' with about 198,910,438 Coronavirus cases, deaths 4,238,581, Recovered179,527,290 globally by First-August 2021 (6-12).

The Taxonomy, classification of a novel Coronavirus (SARS-CoV-2) showed as, Coronavirus Phylum is (Incertaesedis), Order (Nidovirales), Family (Coronaviridae), Subfamily (Orthocoronavirinae), and Genus (Betacoronavirus). The coronavirus subfamily is further classified into four genera: alpha, beta, gamma, and delta coronaviruses. (1) Alpha-coronavirus (alphaCoV), (2) Beta-coronavirus (betaCoV), (3) Delta-coronavirus (delta IV) and (4) Gamma-coronavirus (gammaCoV). Out of these the Alpha and Beta coronaviruses cause human infections. The Severe Acute Respiratory Syndrome Virus (SARS-CoV) virus, (SARS-CoV-2) virus and the Middle East Respiratory Syndrome (MERS-CoV) virus belong to the Beta coronavirus (betaCoV) genera. The Morphological characteristics of a novel coronavirus (SARS-CoV-2) demonstrated that, "Coronavirus" name is derived from the Latin word corona, meaning "crown" or "wreath" (13-15).

It has large fringe, bulbous surface projections and viral spike peplomers, which are proteins on the external of the virus. The outer viral envelope comprises of a lipid bilayer

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where the membrane, envelope and spike structural proteins are attached (7).

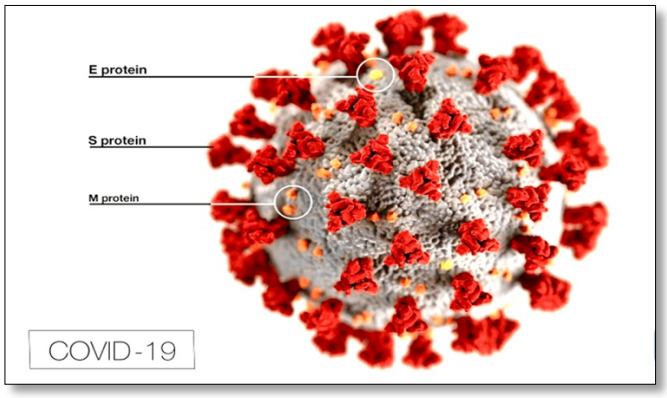

Fig. 1. Corona virus structure [7]

Problem of the research

This study focused on analyze and evaluate about the influence / impact of covid-19 on global health, education, economy, security, management and other aspects of human life. These aspects are the backbone of human being life. It is required best methods to minimize the negative impact on them by controlling the pandemic (taking care of/protecting methods). Clinical studies should continue in a bigger scale, to increase the availability of antiviral drugs and evaluate the level of toxicity of these medications (14). And also accelerate the study of vaccinations. All these processes will lead to a normal life before COVID-19 discovered.

Significance of the research

COVID-19 has disrupted many aspects of life and the lives of individuals around the world. The current investigation is basically aimed to understand most of the aspects of COVID-19 from day one till date. There are many aims and objectives which evaluated, for the examples history of pandemics, SARS-CoV2, Severe Acute Respiratory Syndrome (SARS), Middle Eastern Respiratory Virus (MERS), Evolutionary origin, Transmission of the virus, Pathophysiology, Clinical presentation, Testing, Treatment and Implications for research (16-19).

The study might have an impact on treatment COVID-19. This study focused and analyze about influence of covid-19 on health, education, economy, security, management and other aspects of human life, which is required to concentrate on minimizing the negative effects of this a pandemic by protecting our self from the virus by social distancing, masking and isolation of infected individuals as well as taking care of our immune system. Scientists should do more clinical studies, to increase the availability of antiviral drugs and evaluate the level of toxicity of these medications. This study tried to analyze the influence of COVID-19 on the health systems worldwide and other aspects of human life.

Scope of the research

Research scope of Infectious disease (SARS-CoV2) spread primarily from person-to-person. It has spread between people most often when they are physically close. It transmits very easily and sustainably through the air, primarily via droplets containing small particles of a disease, such as aerosols, produced after an infected person breathes, coughs, sneezes, talks or sings.

The current investigation is basically aimed to understand the effects of the COVID-19 on global health, education, economy, security, management and other aspects of human life by focus, analyze and evaluate minimize the negative impact on them by different methods or controlling the pandemic. Scientists should do more clinical studies, to increase the availability of antiviral drugs and evaluate the level of toxicity of these medications. And also accelerate the study of vaccinations and alto boost one's immune system along with preventive measures of social distancing, masking and isolation of infected individuals. All these processes will lead to a normal life before COVID-19 discovered.

Objectives of the research

This manuscript highlights potential areas like current health system challenges, education, security, management, global business, culture and other aspects of human life, which get influence/impact by COVID-19. The main objectives of this paper are to provide awareness and identify the research areas related to COVID-19 by identifying the best methods to minimize the negative impact on these aspects of controlling the pandemic COVID-19. (Taking care of/protecting methods). Clinical studies should continue in a bigger scale, to increase the availability of antiviral drugs and evaluate the level of toxicity of these medications. And also accelerate the study of vaccinations. It may help improve the understanding of this disease, which will have positive impacts of this pandemic scenario of change as the disease spreads. The study of the disease can also lead to the development of life-saving drugs or vaccines. Better health is central to human happiness and well-being.

Limitation of the research

The main drawback about the study of a pandemic of COVID-19 is zoonotic and originated in China. There are many theories about the originality of the virus means identifying the animal source of the infectious agent and have not determined whether a persistent animal reservoir of the infectious agent exists. If the disease is a seasonal disease that would have receded on its own. Scientists have not yet been able to answer some questions regarding COVID-19.

The other, the treatment, limited availability of antivirals at the beginning of the pandemic and no vaccine; a lot of medications were initially repurposed to treat COVID-19 but due to the acute side effects of these drugs treatment is unsuccessful story, that is why the entire world suffering. There are more clinical studies continue to be done to help for full control of this a pandemic.

Gaps in the knowledge of Coronavirus and its effects

It appears the Coronavirus is an infectious disease, zoonotic and originated in China. There are many theories about the

source of the infectious but not yet confirm the main. So many questions are still not answered by the Scientists. The answers to these questions would undoubtedly advance the world's ability to predict and prepare for a resurgence of COVID-19.

COVID-19 has had a huge impact on medical research, among other things. All organizations, including healthcare organizations, universities and research centers were influenced by COVID-19 and started bleeding cash. The SARS-CoV-2 virus has significantly affected the health, economy, and socio-economic fabric of the global society.

The study has been carried out the impact of covid-19 on global health and other aspects of human life. Coronavirus (COVID-19) pandemic is growing exponentially in the whole world (globally). It was first identified in December 2019 in Wuhan, Hubei, China, and has resulted in an ongoing pandemic. The total confirmed Coronavirus Cases is 282 by 20th January 2020. It has been reported from four countries including China (278 cases), Thailand (2 cases), Japan (1 case) and the Republic of Korea (1 case). COVID-19 has resulted in a 'once-in-a-century pandemic' with about 198,910,438 Coronavirus cases, deaths 4,238,581, Recovered179,527,290 globally by First-August 2021(20-25).

An overwhelming amount of literature started pouring out of countries, impacted the most at the onset of the pandemic. Almost every journal has provided free access to articles on COVID-19. Researchers, technologists, doctors and other health care workers are working day and night to bridge the gap from day one till today, for the development of vaccines and medicines (antiviral properties and immunomodulatory properties) with little known side effects can be used in the fight with COVID-19 (22).

Data collection

In order to achieve the goals of the study, it is very important to be extracted the information from best scientific resources on coronavirus-related research to complete the tasks of the research paper.

These are different classes of reliable sources for COVID-19,which implemented in this research paper such as research on COVID-19 , one of them, The World Health Organization, On the World Health Organization (WHO) website, experts provide a global perspective of the COVID-19 virus, while also sharing individual best practices on topics all information and updates about COVID-19, (Scientific / medical journals), best websites (Scientific / medical websites), such as the Clarivate Web of Science (WoS), Elsevier Scopus, and PMC-sourced materials drawn from CORD-19 (COVID-19 Open Research Dataset), Health and Medical News, Coronavirus and Higher Education like Search engines (e.g. Google), and Business and the Economy.

Comparative analysis

Any overlap between articles found across the different source materials were removed.

History of Pandemics

A pandemic has been historically described as "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries and usually affecting a large number of people". There are several types of secondary data are applied in the research paper.

I. Spanish flu (H1N1-influenza virus) in 1918-1919 causing about 20-50 million victims. And also, the virus infected 500 million people worldwide.

II. Asian flu (H2N2-influenza virus) that originated in Guizhou, China, in 1957-1958 causing about 1-4 million victims.

III. Hong Kong flu (H3N2-influenza virus) in 1968 causing about 1-4 million victims. It is suspected that this virus evolved from the strain of influenza (99).

Current pandemics

WHO uses the term "global epidemic" / other authors called as "pandemic"

A. HIV (Human Immunodeficiency Virus) /**AIDS** (Acquired Immunodeficiency Syndrome) as described by some as pandemic and by WHO as a global epidemic, HIV is believed to have originated in Africa and started with the first case in the Democratic Republic of Congo in 1976 and in 2006, the HIV prevalence rate among pregnant women in South Africa was 29%. Education in African content plays a very important role in decreasing the percentage of infection rates, by teaching them about safer sexual practices and Bloodborne infection precautions training. Since then, has affected more than 37.9 million people with about 770,000 deaths in 2018 from HIV related illnesses.

B. Swine flu started in 2009 is a respiratory disease caused by influenza (H1N1 viruses) pandemic. It is a relatively new strain of an influenza virus that causes symptoms similar to the regular flu. Swine flu originated in pigs but is spread/ transmission primarily from person to person. It is confirmed at laboratory that 18,500 victims; but researchers estimate that about 200,000 respiratory deaths and about 80,000 cardiovascular deaths were related to this pandemic.

C. COVID-19 (coronavirus disease), which covered by this research paper (23).

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2)

On its discovery, the scholars named it '2019 novel coronavirus (2019-nCoV)'. However, the World Health Organization renamed the virus as 'Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)'. The disease caused by (SARS-CoV-2) is called 'Coronavirus Disease 2019 (COVID-19) (6)'. Molecular and Genome information of coronavirus studies shows that after the genome analysis study of nCoV-2019 revealed that two viruses may have been combined (24).

It is an RNA molecule contains a positive-sense, single-stranded RNA genome with a genome size range for 30 to 34 kilobases (largest among RNA viruses). It contains at least 15 genes, including the S gene, which codes for surface proteins. Molecular phylogenetic analysis showed nCoV is 88% similar to bat derived SAR- like coronavirus 79% close to SAR-Cov and 50% similar to MERS-Cov (Middle East Respiratory Syndrome Coronavirus). The following sign and symptoms report from the person who has received the (SARS-CoV-2) infection. A Transmission electron micrograph of (SARS-CoV-2) virus particles is represented in (Fig. 2).

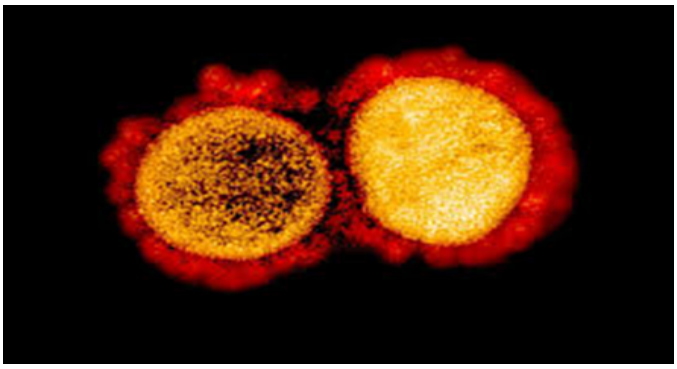

Fig. 2. Transmission electron micrograph of (SARS-CoV-2) virus particles, isolated from a patient (National Institutes of Allergy and Infectious Diseases) (7)

Severe Acute Respiratory Syndrome (SARS)

SARS (Severe Acute Respiratory Syndrome) is a viral respiratory disease of zoonotic origin caused by severe acute respiratory syndrome coronavirus (SARS-CoV or SARS-CoV-1). Coronaviruses commonly cause infections in both humans and animals. SARS originated in China in Nov 2002 with the outbreak rapidly spreading and resulting in about 8000 cases and an estimated 800 deaths.

Cases of SARS was reported in about 30 countries and the outbreak was controlled by epidemiological surveillance, identification, and isolation of patients, contact tracing and quarantining of contacts, thereby interrupting person-to-person transmission of the virus. Treatment involves supportive care. There are no specific antiviral treatments or vaccines available (24-26). There has been no known transmission of SARS anywhere in the world since 2004.

Testing /Diagnosis

The Laboratory Diagnosis, which detecting and testing of coronavirus (SARS-CoV-2) by different methods or techniques such as Polymerase chain reaction (PCR) tests, Rt polymerase chain reaction (RT-PCR), and Serological techniques. Real-time RT-PCR assays are recommended for diagnosis of COVID-19. The sampling is done by taking a nasopharyngeal swab from patients in order to detect (SARS-CoV-2) Positive results are indicated based on RT-PCR of above samples only. Few cases have reported a positive RT-PCR for nasopharyngeal swab, but a negative RT-PCR for urine and stool samples of patients. Since the respiratory system is affected in COVID-19, the results of nasopharyngeal swab are considered valid as against any other pathological samples. RT-PCR is an extremely sensitive technique and plays a very important role for a confirmed diagnosis of COVID-19 (7-9).

Middle Eastern Respiratory Virus

The Middle East Respiratory Syndrome (MERS) is another type of coronavirus. It enters its host cell by binding to the DPP4 receptor. Typically, the host of MERS coronavirus includes humans, bats, and camels. The first instance of this virus was recorded in Saudi Arabia in June 2012, when the patient died of pneumonia and renal failure. MERS was also responsible for a pandemic from spreading in over 27 countries. Statistically, WHO has estimated about 2500 cases with more than 800 deaths from MERS in 2020 (10-11).

Transmission of Coronavirus

The Mode of Transmission of coronavirus, it can be possible by these methods, like Human-to-human contact (personal contact), cough and sneeze through the air, and contaminated object.

Pathophysiology

Pathophysiology (consisting of the Greek origin words “pathos” = suffering; “physis” = nature, origin; and “logos” = “the study of”). The study of abnormal changes in body functions that are the causes, consequences, or concomitants of COVID-19 processes.

COVID-19 can affect the upper respiratory tract (sinuses, nose, and throat) and the lower respiratory tract (windpipe and lungs). SARS-CoV-2 enters host cells through interaction of its spike protein with the entry receptor the angiotensin-converting enzyme type 2 (ACE2) in the presence of Transmembrane protease, serine 2 (TMPRSS2). Proposed mechanisms for COVID-19 caused by infection with SARS-CoV-2 include (1) direct virus-mediated cell damage; (2) dysregulation of the renin–angiotensin–aldosterone system (RAAS) as a consequence of deregulation of ACE2 related to viral entry, which leads to decreased cleavage of angiotensin I and angiotensin II; (3) endothelial cell damage and thromboinflammation; And (4) dysregulation of the immune response and hyperinflammation caused by inhibition of interferon signaling by the virus, T cell lymphodepletion, and the production of proinflammatory cytokines, particularly IL-6 and TNFα (26).

Clinical Presentation

According to scientists, there are three classes of medical conditions when the virus infects the respiratory system. First is a mild, second moderate and lastly a severe condition is reported. Both first- and second-degree cases do not require special care since the immune system effectively helps in overcoming the symptoms of the disease. However, the third scenario requires special treatment, failing which full recovery of patients is not possible. The patients may require a respiratory support system, nursing support and heavy dose of

medicines (12-15). Table 1 represents the common symptoms associated with COVID-19.

Prevention

The coronavirus disease 2019 (COVID-19) global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major public health event. The government bodies and health officials in China have been working extremely hard to slow down the spread of COVID-19 (1-5). The purpose of 'social distancing' is to reduce the transmission of this disease. It is advised for people to maintain 2-meter distance from each other. This is considered as a safe distance by WHO. Other preventing ways, such as wash your hand regularly with Sanitizers or soap or 70% alcohol, Wear face mask and always cover your mouth while coughing or sneezing. The mortality rate is very low, i.e., 2% to 8% and the highest is observed in older persons. Other measures include curfews and lockdowns to discourage large gatherings. It is a very important step to minimize the spread of this disease.

Jordan was the first Arab country to implement these rules and regulations and excellent results of the above measures was observed. WHO classified the countries into Areawide basis on the severity of the diseases/ infection risks: (a) High-risk (so called "red zone" or level 1 risk zone; (b) mean risk (level 2 risk zone); (c) remaining area, which was considered at low risk (level 3 risk zone). In the subsequent phases, it makes the approaches for these areas easily by taken major protections and safety (27-36).

The Exponential Moving Average (EMA) has recommended that patients do not interrupt their treatment with Angiotensin Converting Enzyme (ACE) inhibitors or Angiotensin Receptor Blockers (ARBs). They further suggest that switching over to other medicines is not required in case of COVID-19 disease. According to the international scientists and epidemiologists, diseases like hypertension, heart failure or renal diseases could worsen the condition of patients suffering from COVID-19. This may occur due to decreased immunity. Hence it is recommended that in such cases patients continue to use prescribed medications. It is also supported by clinical evidence (26).

To ensure effective prevention and control should be implementing early of these processes (detection, reporting, diagnosis, isolation, and treatment) and also full supports of centralized responses for these processes such as (centralized coordination by experts, centralized allocation of resources, centralized placement of patients, and centralized provision of treatment) with all of these efforts which may leads to avoid the complication for (COVID-19) cases/patients. Incorporation of mobile technology, big data, and artificial intelligence into COVID-19 responding increased access to health services, reduced misinformation and minimize the impact of fake news. All of the previous steps, plays a very important rule to change the scenario of (COVID-19) by controlling outbreaks and contribution into the treatment of pandemic disease (37-43).

As a special population, children have special respiratory tract structure characteristics, immature immune system, and susceptibility to respiratory virus infections. Therefore, it is highly important for clinicians to treat the infected children cautiously despite most pediatric patients have milder symptoms and better prognosis compared with the adult patients. Very special care recommends for children during the process of prevention, diagnosis, and treatment of children with COVID-19 summarized epidemiology, clinical characteristics, diagnostic criteria, clinical classifications, differential diagnosis, and treatments (44-49).

The Sign and symptoms of coronavirus include Higher Fever, Dry Cough, Fatigue, Sore throat, Shortness of breath, and Sputum production. The incubation period for SARS-CoV-2 is normally 5 to 6 days but may range from 2 to 14 days. World Health Organization (WHO) declared coronavirus outbreak a pandemic and Public Health Emergency of International Concern (PHEIC).

Asymptomatic illness

When a patient is a carrier for a disease/ infection of (COVID-19) by having a positive test of molecular diagnostic (polymerase chain reaction) or antigen test for (SARS-CoV-2) but experiences no symptoms. There are reports of loss of sense of smell in people who otherwise have no symptoms, it considered under this case. The best method of treatment should have self-isolate at home. It does not require more testing or additional treatment and If they remain asymptomatic, they can discontinue isolation 10 days from the day of tested. It's important to follow physical distancing guidance to avoid spreading the virus since no indications having the virus. If the clinical condition deteriorates, they should check with doctors.

Mild illness

This group includes patients with various signs and symptoms of COVID 19 such as (fever, dry cough, tiredness, feeling slightly breathless, muscle pain, headache, sore throat, diarrhea). Patients with second level [pre-symptomatic (SARS-CoV-2) infection] should do self-isolate at home. No additional laboratory testing and no specific treatment.

Moderate illness

People who have evidence of lower respiratory disease by clinical assessment or Imaging or a saturation of oxygen (SpO_2) ≥94% on room air at sea level. Tend to have an increased heart rate, particularly if they're moving around and this is caused by inflammation further into the lungs, so symptoms like coughing and breathlessness may be worse. Patients should be monitored closely (hospital), isolation, limiting provider exposure; laboratory tests including complete blood counts, metabolic profile, renal and liver function studies; ECG, imaging. The treatment should refer to Antiviral Therapy, Immune-Based Therapy. otherwise, their condition may become worse.

Table 1. Comparison of common symptoms between common cold, hay fever and COVID-19 [1, 4-7,15]

Symptoms	Cold	Flu	Allergies	COVID-19
Fever	Rare	Common and high (above 100 degrees); lasts for 3 to 4 days.	No	Common, one of the first sign; start weak and become worse (above 100 degrees)
Headaches	Rare	Prominent	Common	Sometimes
Body Aches	Sometimes	Common and usually severe	Never	Sometimes
Fatigue	Very mild	Common, may last for 2 to 3 weeks	Common	Sometimes
Extra Exhaustion	No	Early Prominent	Unusual	Sometimes
Stuffy Nose	Common	Sometimes	Common	Sometimes
Sneezing	Unusual	Sometimes	Common	Rare
Sore throat	Common	Sometimes	Sometimes	Sometimes
Shortness of breath	No	No	No	Sometimes
Chest discomfort, cough	Mild to moderate, hacking cough	Common and can be severe	Sometimes	Usual, dry cough
Chills	Rarely	Common	No	Sometimes
Treatment	Pain relievers, cough syrup, decongestants	Annual vaccine, Antiviral drugs 1 to 2 days after symptoms start	Allergy Medications and controlling environment	No known vaccines or treatment

*This is not a complete list of symptoms and is only a guide, anyone who is concerned should contact a medical provider

Severe illness

Patients who have respiratory frequency >30 breaths per minute, SpO2 <94% on room People who have respiratory failure, septic shock, and/or multiple organ dysfunction. The difference between severe and critical illness is very small, only one a hospital healthcare professional will make. Both severity levels need to be in hospital urgently. Treatment of COVID-19 should apply Antiviral Therapy, Immune-Based Therapy.

Critical illness

People who have respiratory failure, septic shock, and/or multiple organ dysfunction. The difference between severe and critical illness is very small, only one a hospital healthcare professional will make. Both severity levels need to be in hospital urgently. Treatment of COVID-19 should apply Antiviral Therapy, Immune-Based Therapy.

Dedicated intensive care unit (ICU) plays a pivotal role in treatment COVID-19 especially for Severe illness and Critical illness. The ICU is divided into green, yellow, and red areas. Each ICU bed is equipped with a full monitoring of vital parameters and a mechanical ventilator. Each monitor is duplicated in the centralized control unit equipped with microphones and glasses to allow the communications between the staff. In the ICU, there is a laboratory section including two dedicated ultrasound machines, disposable fiberoptic bronchoscopes, video laryngoscope, point-of-care arterial blood gas and coagulation analyses, transport ventilator, and emergency cart with a defibrillator. Medical team (doctors and nurses) available 24 hours ×7 days for special COVID-19 patients. This is standard by WHO. Aerosol Box, An Operating Room Security Measure in COVID-19 Pandemic plays an effective role in preventing direct infections for medical staff by minimizing the risk and decreasing significantly the stress factor on them, which leads to Efficient job for treatment of COVID-19 patients (51-55).

Treatment For COVID-19

Immune-based therapy

This type of therapy describes as the treatment of disease by activating or suppressing the immune system. It's designed to elicit or amplify an immune response are called as activation immunotherapies whereas immunotherapies that reduce or suppress are called as suppression immunotherapies. These phenomena can be called as Immunotherapy or biological therapy.

This type used for treatment COVID-19. COVID-19 convalescent plasma or (SARS-CoV-2) immune globulins are obtained from individuals who have recovered from an infection and have generated an immune response against the infecting pathogen. Neutralizing antibodies are thought to be the main active component; other immune mediators may also contribute. It is strongly recommended to follow local/regional medical society guidelines for its use. National Institutes of Health (NIH) summarized that no complete data/research evidences are available to go with or against this type of treatment COVID-19.

Therapeutic options

In severe cases of COVID-19 infection, the virus can enter the bloodstream and infect endothelial and other target cells in the kidneys, esophagus, bladder, ileum, heart tissues, and central nervous system. And critically ill patients with COVID-19 infection often present signs of high oxidative stress and systemic inflammation the leading causes of mortality. Nuclear factor E2-related factor 2 (Nrf2) is a transcription factor that in humans is encoded by the NFE2L2 gene. (Nrf2) plays a very important role to reduce reactive oxygen species (ROS) together with glutathione biosynthesis precursors, e.g., N acetylcysteine. This treatment can be used to reduce damage to cells and tissues, to prevent respiratory failure, and acute respiratory distress syndrome (ARDS) for COVID-19 patients. (Nrf2) activity significantly decreases with age, elderly patients

due to susceptibility to oxidative stress-mediated diseases, which include type 2 diabetes, chronic inflammation, and viral infections (54).

Treatments of coronavirus are the main core of this epidemic/ problem, so far, no permanent treatment is available, however on a trial basis antiviral drugs have been used, such as Remdesivir, Chloroquine, Hydroxychloroquine, Favipiravir, Ritonavir/lopinavir. Moreover, various types of COVID-19. Vaccines are under development. However, suspected ADRs to these drugs, are being reported to Vigibase, the WHO global database of individual case safety reports (ICSRs) which is managed by the Uppsala Monitoring Centre in Sweden (18). A clinical trial of vaccine development has been started by different companies across the globe.

In the course of Coronavirus Disease 2019 (COVID- 19) - related acute hypoxemic respiratory failure (AHRF), which is severe arterial hypoxemia that is refractory to supplemental oxygen. Nasal high flow (NHF) represents a new method to support breathing. It is devices are able to produce a heated and humidified airflow applied by a large bore nasal prong [50]. The application of NHF as first-line ventilatory support during COVID-19-related AHRF may have obviated the need for intubation in up to a may have obviated the need for intubation in up to a third of cases. In this circumstance, the ROX index measured within the first 4h after NHF initiation could be an easy-to-use marker of early ventilatory response.

Drug–Drug Interactions and Side Effects

These medicines have, it is own limitations due to the toxicity of these drugs as well as is not particular or specific for (COVID-19). It may be playing a rule, but not very import one. In the USA, the treatment of COVID-19 patients, involved the use of drugs like chloroquine and hydroxychloroquine, which needs to be monitored carefully. This is due to the side effects associated with these medicines, indicated by the advisory of the USFDA. These drugs were used extensively either individually or in combination with other medicines (to improve their efficiency and minimize the harmful effects). The US Medical scholars monitored the general health of the COVID-19 patients during the treatment and evaluated the level of toxicity of these drugs. They reported toxic effects, in contrast to the expected benefits, with the use of these drugs [16]. The European Medicines Agency (EMA) has also stated a high risk associated with the use of chloroquine or hydroxychloroquine treatment of COVID-19. Further, they encourage close monitoring of patients. Moreover, Denmark had stopped trials immediately due to the negative impact of these drugs on COVID-19 patients (23-24).

A study reported the treatment of COVID-19 patients with Hydroxychloroquine, Azithromycin, Lopinavir/Ritonavir and Chloroquine. These patients were also receiving other drugs associated with QTc prolongation. The investigation, carried out in France, indicated the association of these drugs with cardiac Adverse Drug Reactions (ADRs). They showed the risk of cardiotoxicity can be avoided by analyzing the positive benefit to risk balance of any chosen drug (17). Another investigation further confirmed that a high-dose Chloroquine should not be recommended in patients with a severe COVID-19 condition since it leads to severe complications. These investigations, carried out by a randomized clinical trial. JAMA Network Open, further indicated that the light -doses should be monitored (33-34). Researchers from Ireland have also confirmed that the use of Hydroxychloroquine for treatment of COVID-19 patients may result in increasing the cardiotoxicity, which may be fatal (35). An investigation of benefit-risk assessment team (BRAT), for Remdesivir in COVID-19 (Mechanism of action, Pharmacokinetics uses, and Clinical toxicities), concluded that this drug is not effective at all for COVID-19 treatment (19).

The Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly available for the treatment of pain. In some countries they are also used for treatment of fever. The NSAID such as ibuprofen is available by prescription as well as over-the-counter. However, there has been awareness created through news reports (particularly of social media) mentioning that both WHO and BRAT have indicated worsening of COVID-19 symptoms with the use of NSAIDs (including ibuprofen) (20). A recent letter published in 'The Lancet' was reported by the USFDA. This study hypothesized an increase in the concentration of a specific enzyme (a molecule that aids the cellular biochemical reactions) with the use of NSAIDs.

The enzyme, in turn, may further aggravate the symptoms of COVID-19. A survey conducted by the 'French National Agency for Medicines and Health Products Safety (ANSM)' in May 2019, has also suggested the worsening of symptoms in the case of certain bacterial infections and chickenpox (varicella) with the use of NSAIDs like ibuprofen and ketoprofen (21-22). Despite the reports of harmful effects of NSAIDs in aggravating the symptoms of COVID-19, there has been no scientific evidence reported by US FDA and EMA to confirm the same (27-28). Hence, the patients should continue to use the NSAIDs as directed by their doctor or pharmacist, healthcare professional in accordance with labelling instructions (27-28).

Scientists in Italy indicated that the patients suffering from COVID-19 have an increased chance of acquiring the Guillain-Barré syndrome (GBS) (25). The findings of a prospective French study published in Circulation: Arrhythmia and Electrophysiology suggested the use of lopinavir/ritonavir (LPV/RTV; Kaletra) in elderly patients, with COVID-19 symptoms, may increase the risk of bradycardia (2)]. Similar studies have suggested that there are no implications of renin-angiotensin-aldosterone system medications with COVID-19 patients of all ages. Moreover, if any such implications are present, it may be non-significant (30-32).

Table 2. Development of various vaccines for the treatment of COVID-19 (37, 42, 50-53)

Name of the vaccine	Manufacturer	Properties	Clinical Trial stages
mRNA-1273	Moderna and NIAID	mRNA vaccine	Done & in use
BNT162	BioNTech and Pfizer	mRNA vaccine	Done & in use
INO-4800	Inovio Pharmaceuticals	DNA vaccine	Done & on hold from (U.S) FDA
AZD1222	University of Oxford and AstraZeneca	Adenovirus vaccine	Done & on hold from (U.S.) FDA
Ad5-nCoV	CanSino Biologics	Adenovirus vaccine	Phase-III
PiCoVacc	Sinovac	Inactivated virus, plus adjuvant	Phase-III done
NVX-CoV2373	Novavax	Protein subunit	Phase-III
mRNA-1273	Moderna	LNP-encapsulated mRNA vaccine encoding S protein	Done & in use
LV-SMENP-DC	Shenzhen Geno-Immune Medical Institute	DCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins; administered with antigen-specific CTLs	Phase-II
Pathogen-specific aAPC	Shenzhen Geno-Immune Medical Institute	aAPCs modified with lentiviral vector expressing synthetic minigene based on domains of selected viral proteins	Phase-I

Development of a vaccine(s) against COVID-19

A COVID-19 vaccine is a biotechnology product intended to provide acquired immunity against coronavirus disease 2019 (COVID-19). There were 321 vaccine candidates are in different stages of development or have been developed and in the clinical trial phase, a 2.5-fold increase since April. However, no candidate has completed clinical trials to prove its safety and efficacy yet (51). Some 42 vaccine candidates were in clinical research: namely 33 in Phase I–II trials and 9 in Phase II–III trials (51-54).

Impact Of COVID-19

Health Care System And Education

The COVID-19 pandemic has impacted the entire world. It has touched so many areas of individual lives, affecting the health of individuals and the scope of social activities. The capacity of health care systems is also challenged in the course of the current pandemic. It has also affected the education and working sectors (36).

According to the UNESCO (2020), nearly 90% of the world's student population had experienced disruption of their academic progress due to the precautions and policies implemented by the government to prevent the spread of COVID-19. This accounts for over 1.5 billion learners in 165 countries. The norms of an education system which includes face to face classroom experience has been replaced by online education systems (37).

This has been described as "largest simultaneous shock to all education systems in our lifetimes" by the Global Director of Education (38). The international health crisis faced due to COVID-19 has particularly affected the early childhood education systems. It has not only led to unprecedented and dramatic changes in the lives of children, but also their parents, teachers, tutors and other mentors involved in shaping the educational society. In addition, the fear of collapsing early childhood education system has called for policies like for COVID-19 financial packages to protect the same (39-40).

Hence COVID-19 has not only suspended the normal childhood activities including school attendance, family interactions and outdoor activities with friends, but also disrupted the social-emotional benefits that children derive from engaging in these experiences. Small children are increasingly affected by this experience because they are naturally vulnerable to the belief that the adults are capable of controlling the surrounding incidents. They are dependent on adults for their basic needs. Hence, a situation where the adults in the family cannot devise a coping mechanism to deal with the immediate and adaptive demand of the situation leaves a strong impact on the basic confidence and analysis potential of a toddler In this context, Xafis (2020) has noted that the individuals who have most commonly faced injustice created by the misdistribution of power, money and resources are the individuals most negatively affected. This is true, particularly for children who are living in poverty and experience insecurities related to food and shelter. Similarly, children residing in remote areas or sidelined by the mainstream society (e.g., indigenous people and migrant workers) are equally affected. In addition, these pandemics exacerbate the problems experienced by children who are chronically ill or have disabilities, and/or are suffering from neglect or abuse (41).

As concerning as these immediate and observable consequences of COVID-19 may seem, the truth is that the future holds several challenges in coping with the long-term effects of the pandemic. From a scholar's perspective, it can be said that we are now "participants in the biggest unplanned experiment that education has ever seen in our lifetimes" (42). On the positive side, a study has indicated improving hygiene practices among individuals during the COVID-19 pandemic. It has transformed the attitude of people towards viral infections and they are now more alert in taking preventive measures (43).

Global Economy

COVID-19 pandemic associated with illness and mortality are

lower than the indirect losses caused by the crisis. Many countries are experiencing a recession, even though COVID-19 has not had a serious effect on them in terms of health. In the present of COVID-19, the global economy changes to a sudden stop, causing shocks to supply and demand. Starting in January 2020, country after country suffered outbreaks of the new coronavirus, with each facing epidemiological shocks that led to economic and financial shocks as a consequence. The impact of coronavirus on the global economy will extend beyond 2020. According to forecasts from the International Monetary Fund and World Bank, GDP per capita at the end of 2021 is still expected to be lower than December 2019 in most countries (Fig. 3).

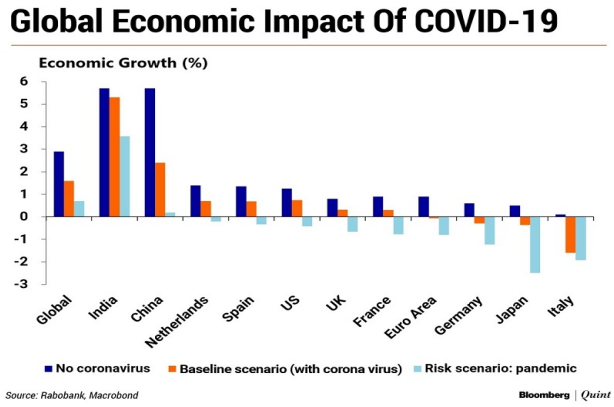

Fig. 3. Barograph representing the global impact of COVID-19 on economy [38]

The influence of the Corona pandemic on global financial markets / financial globalization, shows very clearly due to some factors, such as low oil prices, feelings of fear and panic which affected investors because of pandemic. Lack of control which significantly decreased global economy and also and what caused it to slow down the failure of the production machine, the best example of this scenario is China (38).

Artificial Intelligence Effects

The implementation of artificial intelligence has played a very important role during this pandemic, by helping scientists with information related to testing methods, machine learning and data mining tools. These tools have impacted the COVID-19 advance research in a way that it has led to an intellectually demanding society (36). COVID-19 pandemic has most intriguing challenged the theories and practices of infectious disease control and prediction.

Security

Interpol reported an increase in fake medical products to fight against COVID-19 pandemic, to get fast cash. The criminals are taking advantage of the high market demand for personal protection and hygiene products [44].

Management In Human Life

The alternative pricing models for COVID-19 treatment was released by the Institute for Clinical and Economic Review (ICER). According to ICER, the first course of normal treatment of COVID-19 treatment with Remdesivir was $US10 for a 10-day treatment course. The second model accounted for a threshold of $US50,000. This ICER-COVID model indicated mortality benefit of a 10-day treatment course from the ACCT. The approximate price of this treatment was suggested to be $4500. It is hence suggested by ICER that the clinical evidence, uncertainty and cost-effectiveness analysis should be viewed with caution. They further indicated that the policy makers should consider lower thresholds by weighing factors like uncertainty and affordability in order to promote immediate and broad use of such models (45). According to other studies, there exist six policy options for pricing of the novel COVID-19 vaccines and treatments. They offer different approaches depending on the role of government and the private market. American scientists have concluded that COVID-19 treatment is substantially higher than other common infectious diseases.

It has been observed that economically challenged groups are depending on older form of drugs for the treatment of COVID-19. However, several acute side effects of these drugs have been reported. Hence it is crucial to increase the access to safe and effective opioid agonist treatment (OAT) and prevent the consumption of harmful drugs during this pandemic. In this effect, Ireland opted for one of the best methods for overcoming the challenges of COVID-19 pandemic. They delivered telephonic and video consultation to save the time and energy of healthcare professionals as well as the patients (46).

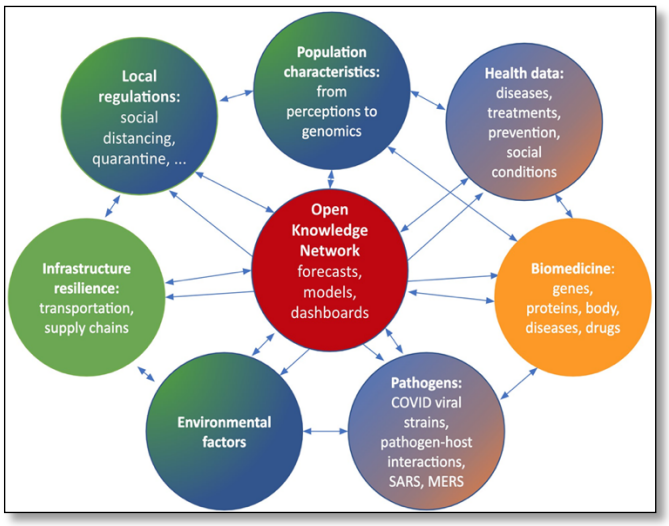

Fig. 4. Transmission and prevention of COVID-19 disease (53)

Implications On Research

COVID-19 is a serious health problem. Most patients of COVID-19 show positive results by RT-PCR assays. However, many patients show multiple negative tests of same assays. This may be because these patients are carriers of the virus, and the collected samples do not contain the required titre of these viruses that is necessary for detection. It is recommended to do the full medical checkup and know patient's exposure history, clinical manifestations, laboratory tests, and typical imaging findings like chest radiography and CT scan. These factors play a vital role in making preliminary diagnosis and guide early isolation and treatment. The RT-PCR is recommended for the

treatment for the patients and prevention of spreading of disease.

It can be summarized COVID-19 have an impact on current health system challenges, education, security, management, global business, culture and other aspects of human life. The main objectives of this paper are to provide awareness and identify the research areas related to COVID-19 by identifying the best methods to minimize the negative impact on these aspects of controlling the pandemic COVID-19. Clinical studies should continue for the antiviral drugs investigation and its limitations. And also accelerate the study of vaccinations.

2. Result and Disucssion

COVID-19 pandemic is a public health emergency of international concern. Our study emphasizes on global health, education system, economy, security, management and other aspects of human life which impact by COVID-19.

It is required to concentrate on minimizing the negative effects of this a pandemic by protecting our self from the virus by social distancing, masking and isolation of infected individuals as well as taking care of our immune system.

There are many aims and objectives which evaluated, for the examples history of pandemics, SARS-CoV2, Severe Acute Respiratory Syndrome (SARS), Middle Eastern Respiratory Virus (MERS), Evolutionary origin, Transmission of the virus, Pathophysiology, Clinical presentation, Testing, Treatment and Implications for research. Also mentioned about the toxic effects of the commonly used drugs for the treatment of COVID-19 and the suggestive models for minimizing these effects and further studies.

It is also important to note that the treatment of COVID-19 greatly depends on immunity system of the patients for asymptomatic, mild, moderate, severe, and critical cases. The advanced cases, however, need personal attention and medical care.

Due to socio-economic ramifications on society and also affect all aspects of life, the future research will be multi-disciplinary and trans-national.

These are a new wave of research in the biological and the medical sciences, to increase the availability of antiviral drugs and evaluate the level of toxicity of these medications. This is for the well-being of the civilization.

Future Perspective

The EU leaders have agreed on its reconstructing after COVID-19 plane on 21 July 2020. In this regard, they have announced a highly anticipated plan, the 'Next Generation EU', to jointly borrow €750 billion to respond to the coronavirus pandemic.

New several approaches are being studied to improve the activity and reduce the undesirable side effects of antiviral drugs implemented for the treatment of COVID-19 patients since. Scientists are looking for therapeutic regimens with proven efficacy and approval of vaccines. They are also searching for new drugs, combinations of drugs, and newer delivery techniques.

One such technique includes a novel approach to targeting drugs more specific at the cellular level to maximize the antibody response through nanoparticles to produce effective treatment measures with minimum side effects.

Also, there are many areas of research needed regarding COVID-19, especially undertake extensive clinical research area which will be significant impacted on this pandemic, which leads to a normalized life of the human being.

Appealing to WHO and government institutions to create a health system to protect human beings from viral infection by transmission and put the suitable treatment for all human beings in entering the world without exception.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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Case Report

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A mortal Covid-19 case with SARS-CoV-2 variant VOC-202012/01 after two doses of CoronaVac® vaccination, case report

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Abstract

Many countries have started their vaccination program against the ongoing COVID-19 pandemic. One of these countries, the Republic of Turkey began to use the CoronaVac® vaccine and a large number of people in the country have been vaccinated so far. The efficacy rate of CoronaVac® vaccine 14 days after two doses was reported as 83% for cases requiring medical treatment and 100% for hospitalization or severe-mortal cases. In addition, in a recent study, it was reported that Coronavac vaccine prevented 86.5% death due to covid-19 in the population over 60 years old, 14 days after receiving two doses of CoronaVac. The effectiveness of the vaccine in subgroups such as patients exposed to SARS-CoV-2 virus in less than 14 days, advanced age, comorbidity, and immunosuppression is not yet known. In addition, its effectiveness against different variants of the SARS-CoV-2 virus is not clear. An 85-year-old female patient with a positive SARS-CoV-2 Variant VOC-202012/01 Polymerase Chain Reaction test was admitted to the emergency department with dyspnea. The patient, whose tachycardia, tachypnea and auxiliary respiratory muscle use continued despite 60 L / min of 100% oxygen therapy with a high flow nasal cannula and whose PaO2 / fiO2 ratio was 63, was intubated. Bilateral widespread multifocal ground glass densities consistent with COVID-19 were observed in the thorax computed tomography. The patient, who was followed up in the intensive care unit, died on the 11th day of her follow-up. There are no cases of severe COVID-19 disease reported in the literature yet after the CoronaVac® vaccine. In this case report, we present a severe COVID-19 patient with a positive PCR test for SARS-CoV-2 Variant VOC-202012/01 11 days after the second dose of CoronaVac® administration.

Keywords: covid-19, covid 19 vaccine, coronavac, severe covid-19 disease, acute respiratory syndrome coronavirus 2

1. Introduction

While the COVID-19 pandemic continues, at least seven vaccines have been approved to date for emergency use in various countries and there are many vaccines that are candidates (1). One of these vaccines, CoronaVac® (Sinovac Biotech Ltd.Beijing, China), is an inactive vaccine and the Sinovac company unofficially announced the results of the phase 3 study (2, 3). According to these results, 13.718 patients were randomized to the study, and the vaccine's effectiveness in preventing severe disease was 100% since there was no patient requiring medical treatment or hospitalization in the vaccine group (3). These results are promising. However, large studies have not yet been carried out to investigate the negative effects of mutations on the effectiveness of vaccines.

In this manuscript, a case mortal of COVID-19 with a positive result for the Polymerase Chain Reaction (PCR) test for SARS-CoV-2 Variant VOC-202012/01, 11 days after receiving two doses of CoronaVac® vaccine is reported.

1. Case Report

An 85-year-old female patient staying in a nursing facility was brought to the emergency department with shortness of breath. Three days before the patient's arrival, it was learned that the SARS-CoV-2 PCR test was positive for “VOC-202012/01” (United Kingdom variant). It was learned that the first dose of CoronaVac® vaccine was administered 41 days, and the second dose 11 days before the positive PCR test. The patient's history included dementia and coronary artery disease and use of donepezil, memantine, quetiapine, sertraline and clopidogrel. Oxygen saturation of the patient under 10 L/min oxygen with a non-rebreather mask was 85%, arterial blood pressure 165/98 mmHg, pulse 120 beats/min, respiratory rate 32/min and body temperature 36.7C° and the electrocardiography was within normal limits. The patient, whose Glasgow coma scale was 15, had decreased respiratory sounds bilaterally. Thorax computed tomography of the patient showed bilateral diffuse ground glass densities compatible with COVID-19 (Fig. 1) and the blood tests are summarized in table 1. The patient, whose PaO2/FiO2 ratio was calculated as 63 under 100% oxygen at 60L/min with high flow nasal cannula therapy (HFNC), was intubated due to persistent tachypnea despite HFNC support. The treatment protocol applied in the intensive care unit(ICU) is summarized in table 2. The patient died on the 11th day of the ICU follow-up. Informed consent was obtained from the patient for the publication of her information and images during the emergency care follow-up.

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Table 1. Results of the laboratory tests of the patient in the emergency department

Test	Result
C-Reactive protein	87 (0-5 mg/dL)
White blood cells	7190 (4000-10000 10^3 u/L)
Lymphocyte	640 (800-4000 10^3 u/L)
Troponin	0.024 (0-0.014 µ/g/L)
Lactate dehydrogenase	459 (125-220 U/L)
Arterial blood gas analysis	
pH	7.41
$PaCO_2$	44 (35-48 mmHg)
PaO_2 (under 60L/min oxygen with HFNC)	62.4 (83-108 mmHg)
SpO_2 (under 60L/min oxygen with HFNC)	91.3 (95-99 %)
Lactate level	1.1 (0.5-1.6 mmol/L)
Aspartate aminotransferase	58 (5-34 U/L)
Alanine aminotransferase	32 (0-33 U/L)
Creatinine	0.69 (0.57-1.11 mg/dL)

* HFNC: high-flow nasal cannula

Table 2. Treatment the patient received in the intensive care unit

Drugs	Doses, routes	Time (days)
Meropenem	3x500 mg, IV*	10
Enoxaparin sodium	4000 anti-Xa lU, SC*	11
Favipiravir	2x600 mg, PO*	7
Prednisolone	1x250 mg, IV	3
	1x80 mg, IV	3
	1x40 mg, IV	5
Norepinephrine†	N/A	N/A
Dopamine†	N/A	N/A

* IV: intravenous, SC: subcutaneous PO: peroral
The inotropic drug dose and duration given to the patient was titrated to a mean arterial pressure> 65 mmHg.

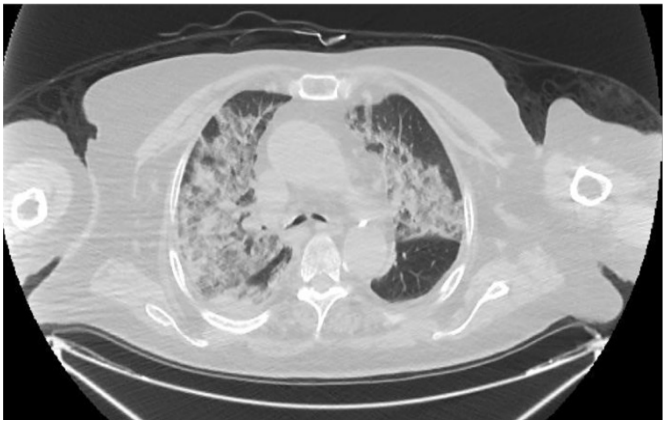

Fig. 1 Bilaterall diffuse ground glass densities are seen in the axial section of the patient's thoracic computed tomography

2. Discussion

In October 2020, a new mutation that occurred in the spike protein of the SARS-CoV-2 virus, known as VOC-202012/01 or "UK variant", was identified in the United Kingdom (4). The primary concern was whether the immunity against SARS-CoV-2 effective against the new mutation. It has been reported that neutralizing antibodies obtained from 12 patients with previously infected COVID-19 cases in Italy have the same neutralizing effect against the VOC-202012/01 variant in the laboratory (5). In addition, in a study conducted with 40 patients who received BNT162b2, an mRNA-based vaccine, showed sufficient neutralizing antibody titer against VOC-202012/01 mutation (6). Although it is predicted that vaccines will need to be updated due to multiple mutations in the future, there are opinions stating that a single mutation on the spike protein would not require such an update (4). However, there are no studies investigating the effectiveness of CoronaVac® vaccine in VOC-202012/01 mutation yet.

In the Republic of Turkey where our case is being reported, it's stated that there are 54 million people whose first dose and 47 million people whose second dose of CoronaVac® has been delivered, until the date of this report (7). Considering these numbers, it is noteworthy that no severe COVID-19 infection has been reported in the vaccinated population so far. This indicates that the cause of this severe COVID-19 may be related with patient-related factors. Our patient is likely to be immunosuppressive due to obesity, coronary artery disease, advanced age and staying in a nursing facility. Although there is no study on CoronaVac® vaccine yet, it has been reported that many vaccines have statistically significantly lower neutralizing antibody levels and low protective efficacy in immunosuppressive patients compared to the normal patient group (8). According to the results of the study investigating the safety, tolerability and immunogenicity of CoronaVac® in patients over 60 years old, the rate of seroconversion detection 28 days after the second dose vaccine was reported as 98% (9). Considering that sufficient neutralizing antibody generation efficiency of the vaccine is not 100%, our patient's positive COVID-19 PCR test 11 days after the second dose of vaccine may be related to the fact that she has not yet developed an adequate antibody response. However, the major limitation of this case report is that there was no antibody titer result after vaccination and before PCR positivity. In a recent study, it was reported that CoronaVac prevented 86.5% death due to covid-19 in the population over 60 years of age who had been vaccinated in two doses (10).

As with many other vaccines, the immune response that develops for CoronaVac® is multifactorial. The vaccine response may not be as effective in immunosuppressive patients as in the immunocompetent population. This article is the first reported case of mortal COVID-19 infection after the CoronaVac® vaccine in Turkey.

Conflict of interest

The authors declare no conflict of interest.

Acknowlenments

Informed consent was obtained from the patient for the publication of her information and images during the emergency care follow-up.

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Case Report

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The use of ezpap in patients with Covid-19 pneumonia and multiple sclerosis

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Abstract

In patients with multiple sclerosis (MS) respiratory muscle weakness and related development of respiratory failure are important causes of mortality. Complications such as atelectasis and susceptibility to respiratory infections are common in these patients. In cases of atelectasis and hypoxemia that develop due to the weakness of inspiratory muscles, the use of EzPAP® positive airway pressure therapy system should also be kept in mind, in addition to nasal oxygen and NIMV treatment options. In this case, we aimed to present our patient with the diagnosis of MS who was followed up for severe Covid 19 pneumonia and for whom EzPAP® positive airway pressure therapy system was used for treatment.

Keywords: multiple sclerosis, COVID-19, EzPAP®, pneumonia

1. Introduction

Since December 2019, the disease called "Novel Coronavirus Disease (COVID-19)" caused by a novel type of coronavirus has first spread from Wuhan Province of China to other provinces and then to the whole world rapidly (1). The clinic of Covid-19 has a wide spectrum from asymptomatic infection to systemic involvement, even “Acute Respiratory Distress Syndrome (ARDS)” and multi-organ failure (2). In most patients, oxygen therapy under close monitoring is sufficient. Oxygen therapy can be applied with conventional low-flow methods or with high-flow nasal oxygen (HFNO) cannula. If the patient does not require immediate intubation, a non-invasive mechanical ventilator (NIMV) can be tried (3). Multiple Sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system. In these patients, besides the musculoskeletal and neurological problems, swallowing disorders, respiratory muscle weakness, and related development of respiratory failure are important causes of mortality. The main respiratory problems seen in MS patients are, decreased ventilation due to inspiratory muscle weakness, deterioration of effective coughing, and increased risk of aspiration and pneumonia. Due to the breaths with low tidal volume, atelectasis may develop in patients, the rate of right-to-left shunt increases, and subsequent hypoxemia may be observed (4). We aimed to present a patient with MS diagnosis, who was followed up in our clinic for severe Covid-19 pneumonia and for whom EzPAP® positive airway pressure therapy system was used for the treatment.

2. Case Report

A 71-year-old female patient was admitted to the emergency department with a complaint of shortness of breath for three days. Upon admission, the vital signs were as follows: fever: 36.2 ℃, blood pressure: 120/80 mmHg, pulse: 79 bpm, and oxygen saturation: 85% at room air. It was learned that she had multiple sclerosis and hypertension diseases and she had been paraplegic for 25 years due to MS. Bilateral increased nonhomogeneous density areas were observed on chest radiography. In the laboratory findings, white blood cell count was 16100 / µl, lymphocyte count 1600/ µl, Na: 120 mEq / L, C-reactive protein (CRP): 166 mg / L, D-dimer: 0.45 mg / L, ferritin 300 ng / ml and cardiac troponin was normal. Concurrent Covid-19 Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) was positive. The patient was diagnosed with Covid-19 pneumonia, due to the presence of bilateral multilobar ground glass infiltration areas in thorax computed tomography (CT), and she was hospitalized in the Covid clinic. Favipiravir, methylprednisolone, low molecular weight heparin (LMWH) and nonspecific antibiotherapy treatments were initiated. Oxygen therapy of the patient, who was using an oxygen concentrator at home due to her current illness, was continued with nasal cannulae. On the sixth day of hospitalization, a control chest radiograph was obtained due to a decrease in the oxygen saturation of the patient. Because a progression was detected on the radiograph, HFNO and intermittent NIMV treatments were given. For the patient, whose oxygenation and control chest radiographs did not fully improve, EzPAP® positive airway pressure therapy system (Fig. 1) was used for the atelectasis. After EzPAP® treatment, the oxygen saturation of the patient was 90% and above, and a

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significant regression was observed in the control chest X-ray (Fig. 2).

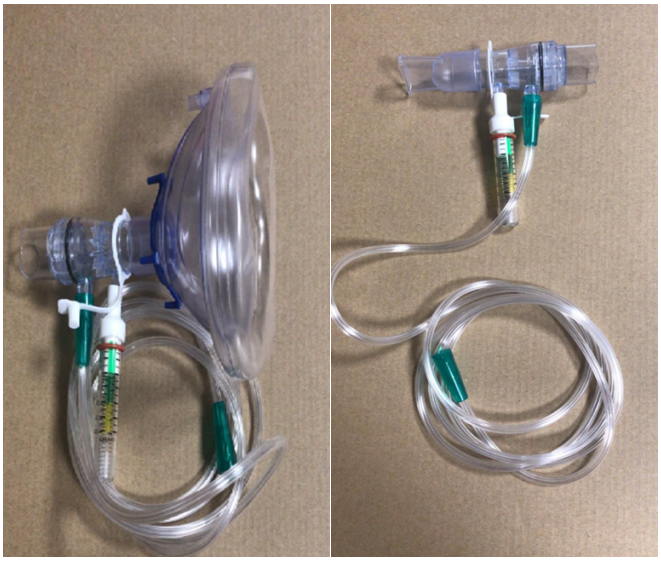

Fig. 1. EzPAP® positive airway pressure therapy system

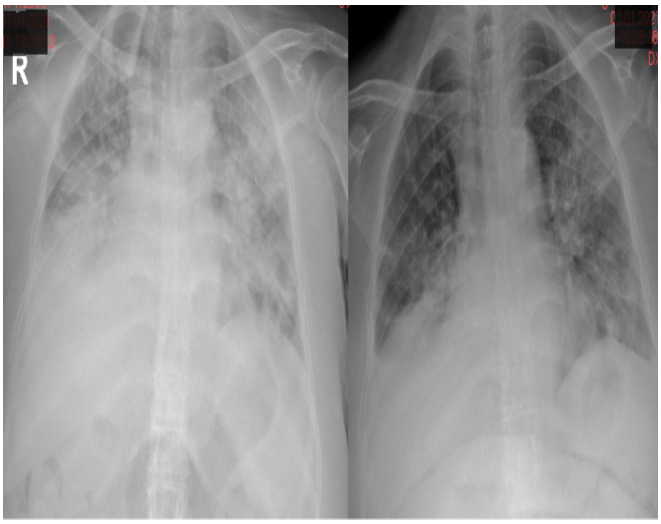

Fig. 2. Chest radiographs (before (left) and after (right) treatment of EzPAP®)

3. Discussion

The virus that spread from Wuhan, China to the whole world in December 2019 and caused Covid-19 was named SARS-CoV-2. The main cause of mortality and morbidity in this disease is acute viral pneumonia that causes ARDS. In the Covid-19 disease, the clinic of the patient may range from asymptomatic infection to severe pneumonia. In patients with severe pneumonia, respiratory failure, shock, or several organ failures develops, and follow-up and treatment in intensive care units are required (5). The World Health Organization (WHO) recommends maintaining oxygen saturation ≥ 90%. Oxygen therapy can be given with conventional low-flow (<15 L / min) or high-flow methods (3). In adults with acute hypoxemic respiratory failure despite the conventional oxygen therapy, the use of HFNO therapy instead of conventional oxygen therapy is recommended. EzPAP® positive airway pressure therapy system is a portable and disposable system that is developed as an alternative to the inspiratory positive pressure therapy (Intermittent positive pressure breathing; IPPB) used in patients with spontaneous breathing. During its use, inspiration is supported by the flow, and PEP is applied during expiration. It provides the expansion of the lungs by increasing the functional capacity. Preliminary studies have shown its effectiveness in the treatment of atelectasis in patients in intensive care units (6-7). In a study by Rieg et al., a probable more effective improvement in pulmonary oxygenation was detected with oxygen therapy using the EzPAP® system, in patients at high risk of postoperative hypoxemia. Therefore, the EzPAP® system was presented as a well-tolerated, effective, cost-effective, and easy-to-operate system to improve postoperative oxygenation (8).

MS is an autoimmune central nervous system disease that is characterized by inflammation, demyelination, and axon damage. Commonly observed symptoms are weakness in the extremities, sensory symptoms, ataxia, bladder problems, fatigue, diplopia, visual symptoms such as blurred vision, dysarthria, and cognitive symptoms such as memory-concentration-attention disorder (9). Since MS is a chronic and usually progressive disease, many signs and symptoms which do not cause any disability at the beginning of the disease may cause further disabilities that affect the patient's functional activities after a while. Especially in multiple sclerosis patients with attacks, many drugs are widely used with the latest developments in the treatment of MS (10). However, all patients do not get the expected response with these treatments and some of the patients turn into a progressive form. In both acute and chronic periods, the most important cause of mortality and morbidity is the respiratory system being affected by neuromuscular diseases. Progressive weakness and mechanical disadvantage of respiratory muscles are responsible for the rapid and superficial breathing, and alveolar hypoventilation causes chronic CO2 retention in these patients. Respiratory muscle weakness causes impaired ventilation and accumulation of pulmonary secretions due to ineffective coughing. This situation leads to complications such as atelectasis and susceptibility to respiratory infections.

In the literature, it is emphasized that respiratory muscle weakness develops in the advanced stages of MS (11). Atelectasis may develop due to inspiratory muscle weakness and may cause a right to left physiological shunt. Chronic atelectasis increases respiratory workload by decreasing the compliance of the inspiratory system, and a vicious circle develops by the increased respiratory muscle weakness. The respiratory muscles can be helped by applying force manually or mechanically to the body or by applying intermittent pressure to the airway. Some devices help inspiratory muscles, while others facilitate coughing by mainly helping expiratory muscles (12).

In observational studies conducted in patients with neuromuscular disease who have acute respiratory failure and who need short-term mechanical ventilation, NIV was found to

reduce the need for IMV, shorten the length of stay in the intensive care unit and reduce mortality (13). In a prospective cohort study in which 17 patients with neuromuscular diseases who received NIV for acute respiratory failure were involved, a requirement of IMV did not develop in 79% of the patients (14). NIV may prevent or delay the progression of chronic respiratory failure in intermittent long-term NIV use in patients with nocturnal hypoventilation or early chronic respiratory failure (15).

In our case, there was respiratory muscle weakness due to being paraplegic for approximately 25 years. There was a history of regular oxygen support with a nasal cannula and intermittent NIMV use before the hospitalization with Covid 19 pneumonia. Impairment in oxygenation and radiological progression was detected in the patient, who received favipiravir, methylprednisolone, LMWH and nonspecific antibiotherapy treatments for Covid 19 pneumonia and who did not meet the cytokine storm parameters during follow-up. Atelectasis due to respiratory muscle weakness caused by the underlying disease was thought when and effective improvement was not observed with HFNO and intermittent NIMV treatments, so treatment of EzPAP® positive airway pressure therapy system was given.

After EzPAP® treatment, an improvement in oxygenation was observed in the first hour and a significant regression was seen in the density of chest radiographs taken 1 day later. In cases of atelectasis and hypoxemia due to inspiratory muscle weakness, the use of EzPAP® positive airway pressure therapy system should be kept in mind besides the HFNO and NIMV treatment options. This treatment option can be tried in patient groups with neuromuscular diseases as a preventive method from the highly complicated invasive mechanical ventilator use.

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Acute fulminant liver failure, COVID -19 and 2-day intensive care unit follow-up period: A Case Report

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Abstract

We aimed to share our case who developed liver failure due to covid-19, which is more severe than we have ever encountered. A 67-year-old male patient was brought to our hospital by ambulance with complaints of weakness and eating and drinking disorder. In the first examination, the patient was conscious, oriented and cooperative. The liver and kidney function tests and whole blood parameters of the patient at the first admission were within normal limits. The patient was admitted to the intensive care unit because of comorbidities and oxygen support may be required. It was found that the patient's liver function tests were found to be elevated in the examinations on the first intensive care unit day. Transplantation and Plasmapheresis could not be performed due to the patient's general condition. In the follow-up, orotracheal intubation was performed for the patient whose general condition deteriorated, blood pressure decreasing and positive inotropic therapy was initiated on the second ICU day. The patient whose general condition deteriorated could not be saved despite all interventions. Although our knowledge about SARS-CoV-2 is not sufficient yet, we think that it should be kept in mind that it may also cause fulminant liver failure.

Keywords: SARS-CoV-2, fulminant liver failure, covid-19, intensive care unit

1. Introduction

A previously unidentified viral pneumonia was detected in Wuhan, China, from December 31, 2019, to January 7, 2020. After these dates, the virus spread all over the world and caused a pandemic. The first case of the pandemic was seen on March 11, 2020, in Turkey. COVID-19 ranging in severity from mild asymptomatic disease to severe acute respiratory distress syndrome and has become a central health problem worldwide. We aimed to share our case who developed liver failure due to covid-19, which is more severe than we have ever encountered. The SARS-CoV-2 virus typically presents with fever and upper respiratory tract symptoms. Non respiratory symptoms of SARS-CoV-2 infection include gastrointestinal symptoms such as diarrhea, vomiting and abdominal pain occurring in 17.6% of patients (1). It is observed in 18.2% of patients with non-severe disease and 39.4% of patients with severe disease (2). While research on the pathogenesis of the disease and its effects in different populations was ongoing, we aimed to report our health care worker who presented with SARS-CoV-2 infection and non-icteric hepatitis with fulminant course.

2. Case Report

A 67-year-old male patient was brought to our hospital by ambulance with complaints of weakness and eating and drinking disorder. It was learned from the patient that he had been hospitalized for 5 days due to COVID-19 and left the hospital, refusing the treatment of his own will. In the first examination, the patient was conscious, oriented and cooperative. He had no spontaneous breathing effort, no dyspnea, mild tachypnea (respiratory rate was 25/min), his oxygen saturation (SPO_2) was 98% with receiving 8 L/min oxygen support from reservoir mask. His heart rate was 74/min and his blood pressure was 100/70 mmHg. The patient with known congestive heart failure, pacemaker, ischemic heart disease, hypertension, diabetes mellitus, chronic renal failure without need of dialysis was hospitalized in the intensive care unit (ICU). When the drugs he used we requestioned, it was learned that he had been using metoprolol, carvedilol, clopidogrel and furosemide. Also, he was using favipiravir for 5 days for the treatment of COVID-19. The liver and kidney function tests and whole blood parameters of the patient at the first admission were within normal limits (Table 1). The patient was admitted to the intensive care unit because of comorbidities and oxygen support may be required. On the first day of the patient's stay in the intensive care unit, symptomatic treatment was arranged after consultations with gastroenterology, infectious diseases, cardiology and internal medicine departments. It

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was found that the patient's liver function tests were found to be elevated in the examinations on the first intensive care unit day at 12.00 a.m. (Table 1).

Table 1. Laboratory parameters of the patient on ward, on ICU first day and on ICU second day

	WARD	ICU 1.day	ICU 2.day
WBC (10^9/l)	10.40	18.04	17.06
Hb/Htc(g/dL/%)	11.8/37	13.3/41.8	13.1/40.3
Lymphocyte (10^9/L)	0.45	0.73	0.65
Platelet (10^9/L)	257	182	167
ALT (U/L)	25	1127	1712
AST (U/L)	41	1046	1647
Urea (mg/dL)	281.0	273.0	322.0
Creatinine (mg/dL)	3.33	2.93	3.36
D dimer (ng FEU/ml)		6412	6325
INR	1.38	6.02	
CRP (mg/L)	25	25	30
Procalcitonin (ng/ml)		0.55	
Albumin (g/L)		35.2	
Total Bilirubin/Direct Bilirubin (mg/dL)	0.61-0.39	1.87/0.82	2.23/1.31
pH		7.354	7.228
pO_2 (mmHg)		361.9	153.5
pCO_2 (mmHg)		26.9	20.1
Lactate (mmol/L)		5.09	10.81
HCO_3std (mmol/L)		17.2	11.7
K (mmol/L)		5.12	5.81
O_2% (est)		98.7	99.8

It was thought that there was moderate to severe lung involvement in the chest X-ray (Fig.1) There was no evidence of hypoxia, ischemia or hypotension that would cause liver failure. The viral hepatitis markers (anti-HAV IgM, HBsAg, anti-HBs, anti-HBc IgM and IgG, anti-HCV), autoimmune markers (ANA, ASMA, AMA, anti-LKM), ceruloplasmin, Fe, TIBC, % Fe saturation, ferritin investigated were negative. All causes of fulminant non-icteric hepatitis (medicines, infections) and acute liver failure were excluded. Transplantation was arranged after consultations with gastroenterology, infectious diseases, cardiology and internal medicine departments. Upon this, the situation was discussed with the transplantation center, but it was stated that transplantation could not be performed due to the current condition of the patient, his additional diseases and contagious disease. With the diagnosis of acute renal failure, hemodiafiltration was initiated in the patient who developed anuria during follow-up and whose renal function tests deteriorated on the first ICU day at 21.00 p.m. Plasmapheresis could not be performed due to the patient's general condition. In the follow-up, orotracheal intubation was performed for the patient whose general condition deteriorated, blood pressure decreasing and positive inotropic therapy was initiated on the second ICU day 08.00 a.m. The patient whose general condition deteriorated further on the second day of his intensive care hospitalization at 13.00 a.m. could not be saved despite all interventions. Written informed consent was obtained from the patient's family for this study.

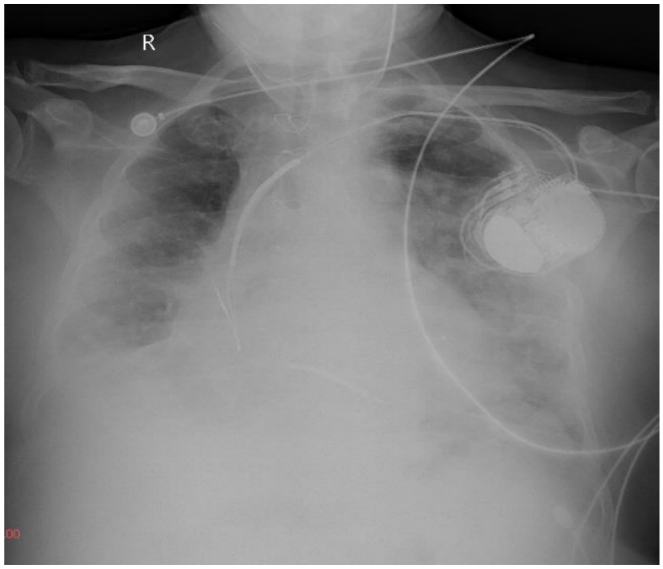

Fig. 1. Chest x-ray of the patient at ICU

3. Discussion

In our case report, we tried to explain the rapidly progressive liver failure, which we thought was caused by covid-19. Liver injury is more common among patients admitted to the intensive care unit, reaching up to 62% compared to 25% of patients who do not require intensive care. In most patients, liver damage is temporary and no intervention is required. The mechanism of liver damage in patients with COVID-19 may be due to the fact that SARS-CoV-2 directly infects liver cells (2). Similar to the respiratory viruses, SARS-CoV-2 can induce hepatic damage through an altered immune response involving cytotoxic T cells and Kupffer cells (3). Although other reasons other than COVID-19, especially liver failure secondary to multiple organ dysfunction syndrome, could not be completely excluded in our patient, hypotension was avoided in our patient whose EF was 20%, and in the follow-up, the patient did not develop hypotension, and because of the absence of hypoxia, the diagnosis of ischemic hepatitis was excluded. Viral markers and autoimmune markers were negative and there was no history of chronic liver disease. While high levels of liver aminotransferase have been observed in SARS-CoV-2 infection, severe liver failure has not been defined yet in similar situations (4). Favipiravir, which was also used in the treatment of our patient, was an RNA polymerase inhibitory antiviral agent (5). During Favipiravir treatment; diarrhea, increased transaminase levels, hyperuricemia and neutropenia may develop. The reported elevation in transaminase level secondary to the Favipiravir use was never as high as we encountered in our patient. Since it is not metabolized by the CYP450 system, it does not interact with drugs metabolized by this pathway. Wander et al. presented a case of acute hepatitis after covid-19 in a 59-year-old female patient with immunosuppression.

This patient presented with gastrointestinal symptoms such as vomiting and abdominal pain. Unlike our patient, hydroxychloroquine was used in the treatment of covid-19 in

the patient whose hepatitis markers were negative, as in our patient. The patient recovered completely with supportive treatment and the drugs she used herself (6).

In the case report of Melquist et al., a 36-year-old female patient who presented with gastrointestinal symptoms developed a sudden onset of clouding of consciousness on the 3rd day of follow-up. The patient, who was intubated on the fourth day and the diagnosis of liver failure was supported by transjugular biopsy, was successfully extubated 1 week after admission. Liver transplantation was also discussed in this patient, but it was observed that the patient recovered completely with supportive treatment (7).

Our patient had eating and drinking disorders and loss of appetite. Unlike the patients in the literature, our patient used favipiravir instead of hydroxychloroquine. Since we are in the discussing of the treatment (transplantation) of our patient and rapidly progress we could not have a radiological examination. The rapid progression and the need for dialysis after the sudden increase in liver enzymes have taken us away from liver disease due to drug interaction.

Although our knowledge about SARS-CoV-2 is not sufficient yet, we think that it should be kept in mind that it may also cause fulminant liver failure.

Conflict of interest

None.

Acknowledgments

None.

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Central venous catheter related Superior Vena Cava Syndrome after renal transplantation in two cases

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Abstract

Vena cava superior syndrome is a specific clinical disease; very important obstruction of the large central veins. Catheter-related deep vein thrombosis (DVT) and vena cava superior (VCS) syndrome are rare but serious complications that require specific care in these selected renal transplant recipient. Thrombosis formation, is a major complication of central venous catheter (CVC) attempts, however, arterial puncture, hematoma, and pneumothorax are more common complications**.** Mechanical complications of (CVC) have been reported in 5% to 19%. Incidences of CVC thrombosis have been reported in up to 66% of patients in venographic studies, however; VCS syndrome is a rare complication. After evaluating the catheter-related thrombosis risk, hemodialysis catheters were found to be the highest risk in comparison with other catheters. Catheter-related DVT and VCS syndrome are rare but serious complications require specific care in these renal transplant recipients. We report two cases of vena cava superior syndrome due to CVC thrombosis after kidney transplantation in two chronic renal disease patients with histories of previous catheter thrombosis.

Keywords: end stage renal disease, vena cava superior syndrome, central venous catheter, catheter related deep vein thrombosis

1. Introduction

Catheter-related deep vein thrombosis (DVT) and vena cava superior (VCS) syndrome are rare but serious complications that require specific care in these selected renal transplant recipients. Catheters with large diameters increase the risk of thrombosis because blood flow is obstructed. The coagulation pathway has started, and permanent inflammation due to the existence of a catheter can cause intimal hyperplasia**.** The catheter's tip being parallel to the longitudinal axis of the VCS' course, avoidance of the direct contact with the vessel's wall are major factors in preventing the development of thrombus. In addition, central venous catheter (CVC) complications are more frequent in cases of chronic kidney failure, multi-organ failure, and sepsis, which lead to a compromised immune system.

We report two cases of vena cava superior syndrome due to CVC thrombosis after kidney transplantation in two chronic renal disease patients with histories of previous catheter thrombosis.

2. Case Report

2.1. Case 1

A 41-year-old female patient diagnosed with end stage renal disease (ESRD) with an unknown etiology received a cadaveric kidney transplantation (KT). She had a history of thrombosis related with the hemodialysis (HD) access both in the left brachial arteriovenous fistula (AVF) and the HD catheter during an eight years chronic HD program. We performed right radial arterial cannulation and right internal jugular venous catheter placement intra-operatively. The patient received induction immune-suppressant treatment with anti-thymocyte globulin (ATG) Fresenius for three days. Swelling of the right arm developed on postoperative day four, and Doppler ultrasound (US) revealed thrombosis of the right axillary and distal brachial veins. Thrombi were detected by magnetic resonance angiography (MRA) in both the intersection of the right brachiocephalic vein and VCS and in the brain. A simultaneous ventilation/perfusion scintigraphy (V/Q Scan) revealed resorbing acute emboli in the lungs. Excluding the presence of Heterozygote MTHFR A1298C, Heterozygote F5 Leiden, and Heterozygote PAI-1 mutation, all other thrombus panel tests were normal. Anticoagulation was performed by low molecular weight heparin enoxaparin sodium. On postoperative day six, the patient's creatinine erose to 3.1 mg/dl, and urine output decreased. The renal Doppler US was consistent with acute rejection, and the allograft biopsy was postponed because the patient received anticoagulation and plasmapheresis treatment for presumed antibody rejection. On postoperative day thirteen, the Control Doppler US revealed no thrombi in the upper extremity and

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jugular veins. The delayed allograft biopsy showed healing acute antibody mediated rejection. On postoperative day thirty-two, the patient was discharged after normalization of the kidney functions.

2.2. Case 2

A 41-year-old male patient diagnosed with ESRD with an unknown etiology received a cadaveric kidney transplantation (KT). And he received HD treatment for twelve months. Intra-operatively right radial arterial cannulation and a right internal jugular venous catheter placement were performed. The patient received induction immunosuppressant treatment with ATG Fresenius for three days. The rest of his hospital stay was uneventful, and the patient was discharged on postoperative day six with three immunosuppressant medications, including tacrolimus (TRL), mycophenolate mofetil (MMF), and a steroid. He was readmitted to the ward for swelling and erythema of the neck on postoperative day ten. The right jugular vein was completely thrombosed, and it was accompanied by a widening of the superficial veins and the development of collateral veins. An upper extremity MR revealed similar results. Anticoagulant treatment with low molecular weight heparin (enoxaparin) was initiated. All blood tests regarding thrombi and the V/Q scan of the lungs were negative. The rest of his hospital stay was uneventful; he was discharged with a prescription for warfarin.

3. Discussion

Mechanical complications of CVC have been reported in 5% to 19% of patients who receive central venous catheters. Thrombosis formation is decidedly a major complication of CVC insertions; however, arterial puncture, hematoma, and pneumothorax are more common complications (1). Incidences of CVC thrombosis have been reported in up to 66% of patients in studies of venography however, VCS syndrome is a rare complication (2). It has also been reported that patients have tolerated subclavian catheters better than left internal jugular catheters. The risk of thrombi development is high in the left internal jugular vein than the right internal jugular vein, because it is related with two strong angulations of the catheter that are required to reach to right atrium. In addition, the risk of thrombus development is higher in the subclavian vein than the right internal jugular vein (42% vs 10%) (3). In a study reporting 2128 CVC days internal jugular vein catheterization was determined to carry the highest risk of thrombosis development, followed by the femoral (36%), upper limb (27%), and subclavian (9%) routes. After evaluating the catheter-related risk of developing thrombosis, hemodialysis catheters were found to present the highest risk in comparison with other catheters (4).

The physiological period of ESRD patients differ from the healthy population. Their serum creatinine level is generally higher and their hematocrit level, platelet production and properties (adhesion, aggregation are generally decreased), and life cycles are under the normal activity and because of the uremia (5,6). Therefore; the uremia, anemia, and thrombocytopenia in this group of patients prevent thrombus formation and increase bleeding risk compared with the healthy population.

Living-donor renal transplantation procedures are more successful than cadaveric kidney transplantation, because cadaveric kidney takes longer to reach a normal value of suitable renal function and serum creatinine level. This delay diminishes the risk of thrombus formation. Post-operative heparin administration should only be used in hypercoagulable manifestations suggested by some author, such as collagen vascular disease, deep venous thrombosis history, anti-thrombin 3 (AT3) deficit, diabetes, multiple miscarriages, protein S deficit, or protein C resistance (7,8). In thrombophilia cases, observe to clarify the anti-coagulant therapy is more beneficial than standard anti-coagulant therapy. One of the major complications resulting from graft loss is renal allograft vascular thrombosis. The rate of thrombosis varies between 0.5% and 6% (9). Researchers suggest the use of anti-coagulant therapies to reduce the risk of complication in all renal transplant recipients. Low molecular weight heparin (LMWH), per-oral anti-coagulants (aspirin, warfarin), heparin have been used together or separately in the anti-coagulant therapy. Some studies have suggested that LMWH reduces the possibility of post-operative thrombosis and does not raise the surgical bleeding risk (7,10). According to some author, prophylactic heparinization can cause increased morbidity in kidney transplant patients. Mohan et al proved that intra operative heparin administration increases the post-operative transplant demand and does not decrease the frequency of graft thrombosis. (11) Likewise, another study defined the increase the risk of bleeding caused by LMWH and aspirin in used together in the early post-op. period (12). Unlike; The risk of vascular thrombosis increased by heparin induced thrombocytopenia (HIT). HIT caused by an immunological reaction and the patients using heparin have an up to 5% increased risk of vascular thrombosis caused by HIT (13).

We do not administer heparin routinely after renal transplantation except for patients with risk factors. In patients diagnosed with the ESRD, fibrinogen and inflammatory markers were elevated and these are the risk factors for the development of thrombosis. In other epidemiologic studies, hemodialysis and kidney transplantation were suggested to increase the risk for thrombosis. Cessation of prophylactic anticoagulant treatment ten days prior to surgery to decrease peri- and post-operative bleeding might increase the risk of thrombosis beginning on the day of cessation of the treatment. Anticoagulation treatment should be initiated in the early postoperative period.

Development of VCS syndrome due to CVC placement is related to multiple factors. Recurrent catheter placement

attempts and leaving the catheter catheters remaining in the same site for long durations lead to the development of recurring endothelial injury and chronic inflammation, which result in the development of thrombus and injury to the vein wall.

VCS syndrome is rarely caused by CVC-related thrombosis. Malignant tumors are significant causes of VCS syndrome. Physical examinations are the simplest way to detect thrombus or VCS syndrome in patients with a history of VCS placement. The venous blood flow resistance rises as the SVC syndrome becomes compressed, and the symptoms and signs occur. The most common signs and symptoms are neck and facial swelling, hoarseness, headache, dyspnea, pain, and other symptoms (14).

Mean treatment options for VCS syndrome include treatment of the original malignancy, anti-coagulation, endovascular standing, and surgery in patients diagnosed with VCS syndrome (14). The first signs observed during physical examinations in our study were swelling and erythematic on the right side of the chest and face. Ultrasound (US) revealed increased vein diameter, cessation of the blood flow, and images compatible with thrombi. Computerized tomography (CT) is a valuable tool for the evaluation of the compressing masses on the central veins. Although Doppler US has a sensitivity of 94% and a specificity of 96% for the recognition of the thrombi, magnetic resonance (MR) performed with contrast media is the most valuable tool in detecting thrombi development. Thrombolysis and heparinization are the suggested treatment modalities for catheter-related thrombus. Initiating the treatment immediately after the development of symptoms may result in a success rate of up to 70%. When the treatment is delayed, the success rate decreases, and the treatment is considered ineffective after ten days.

In conclusion, catheter-related DVT and VCS syndrome are rare but serious complications that require specific care in these selected renal transplant recipient. That minimizing the duration of the procedure can potentially cause complications, so an experienced physician is recommended to perform the procedure. Since thrombus development has a multi-factorial etiology, careful risk assessment and individualized treatment strategies are required for minimization of complications.

Conflict of interest

All authors declare no conflict of interest regarding this manuscript

Acknowledgments

No competing financial interests exist.

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Case Report

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General anesthesia application with the patient who has kabuki make-up syndrome

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Abstract

Kabuki Syndrome is disease derived from a rare genetic mutation that is particularly characterized by distinctive facial features, musculosketal malformations, mental retardation and cardiopulmonary anomalies and several pathologies. From anesthetic aspect, this syndrome may cause both cardiovascular and inspiratory problems, defects in palate and collum and also a number of difficulties in selecting medications and invasive procedures. Difficult intubation, prolonged neuromuscular blockage and malignant hyperthermia are frequently encountered problems in the patients with Kabuki Syndrome. An attentive examination of the patient in preoperative stage and appropriate medication preference is essential in order to prevent complications.

Keywords: Kabuki make-up, congenital anomaly, malignant hyperthermia, difficult intubation

1. Introduction

Kabuki Syndrome is a rare genetic syndrome which has distinct dysmorphic facial findings, postpartum growth restriction, mental retardation, skeletal and organ anomalies and anomalous dermatoglyphic patterns (1). For the first time in 1969, as a consequence of having reservations about an underlying undiscovered genetic disorder in a patient who has a different facial feature and mental retardation, it was studied by a Japanese genetic specialist Norio Niikawa (2). In the years that followed, as a result of the consideration of similar cases by being identified with two different groups from Japan in 1981, it took its place in literatüre (3). Due to the resemblance of characteristic facial features to Kabuki dance drama which belongs to the traditional Japanese theater, it is named after that.

First cases are reported in Japan and although the prevalence of Kabuki Syndrome according to Japanese data is estimated 1/32000, after that in New Zealand it is calculated as 1/86000 (4, 5). It is typically sporadic and has no family history (2). Despite the fact that many cytogenetic anomalies related to the syndrome are indicated, the most common mutation is seen in X chromosome (1). The genes whose pathogenic variants are determined as the cause of Kabuki Syndrome are KMT2D (MLL2) ve KDM6A (1, 6). The characteristics of facial features in patients are may be sorted as; long palpebral fissures, ectropion, thinness in the 1/3 lateral of eyebrows, short nasal septum, large and forward angled ears and preauricular sinus.

Moreover, these patients have additional pathologies as microcephalia, cleft palate and lips, tooth abnormalities, hypotony, joint laxity, cardiac anomalies (typically VSD, bicuspid aorta, coarctation of aorta), skeletal anomalies (scoliosis, shortness in the 4th and 5th metacarpals, costa anomalies, hip dislocation et cetera) and urinary system malformations (7, 8).

2. Case Report

2.1. Medical history and physical examination

A 19 years old female patient who is diagnosed with Kabuki Make-up Syndrome consulted to our clinic for consideration whose operation is planned by orthopedy and traumatology clinic due to ulna distal fracture. According to the medical history received from the patient's relatives, being born weighing 2700 gr at the end of a eight month of pregnancy, the patient is diagnosed with Kabuki Make-up Syndrome when she was 23 months old as a result of the examinations made due to neuromotor growth deficiency and dysmorphism. In the 31st axis of the MLL-2 gene, heterozygous C6794delG mutation was detected in the gene analysis. As a result of the static kidney scintigraphy (DMSA), taken due to frequent urinary tract infection, stage 2 vesicourethral reflux was monitored and left kidney's functional capacity recorded as 20%. Despite the fact that premature thelarche was observed, based upon the normal hormone levels, the patient was followed up and patient's condition improved by itself at the age of 3. At the age of 2 years, the patient had bacterial pneumonia resulted in hospitalization with a frequent upper respiratory tract infection history. The patient was diagnosed with epilepsy

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by an electroencephalogram when she had seizures two times in one month apart with tremors in the body and fixation in the eyes. In the cranial computed tomography (CT) a mass was monitored in the left ear and as a result of the biopsy performed on suspicion of glomus tumor. At the age of 7, the patient started primary school and learn to read and write in the first year. The patient was good et memorizing and she could keep the close relative's phone numbers in her mind. The patient's early IQ test score was stated as 62.

The patient has no cardiac and gastrointestinal system anomalies recorded. The patient had no operation, but before CT was taken at the age of 6, she was sedated and recovered in approximately 6 hours.

In the physical examination, significantly long palpebral fissures and thinness in the 1/3 lateral of the highly curved eyebrows was observed. She had eversion in her lower eyelids and ptosis in her left eye (Fig. 1).

Fig. 1. Lower eye lids, ptosis in her left eye, obese appearence

Her tooth gaps were wide, her nasal septum was low and her ears was low-set (Fig. 2).

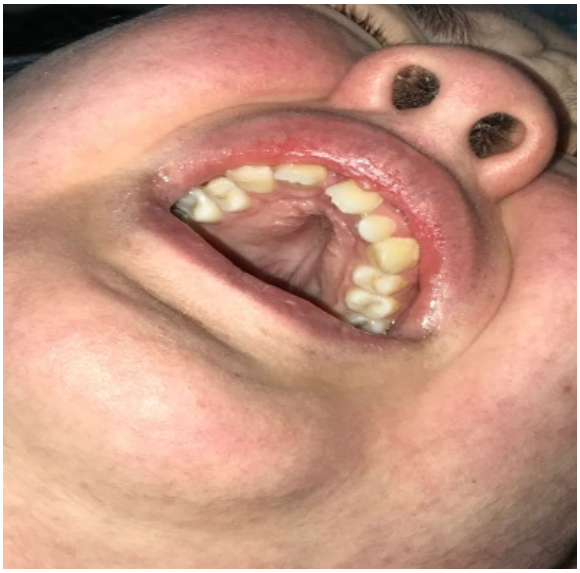

Fig. 2. High palate

The patient's appearance was obese and her weight recorded as 90 kilograms. She had no scoliosis. The patient's hemithorax both took part in breathing and lung sounds were bilaterally normal on auscultation. In the cardiac examination, no additional sound or murmur was recorded. Neck movements were natural, mallampati score were 2 and mouth opening were normal. The patient had joint laxity and it was confirmed that her fingers were shorter then normal (Fig. 3).

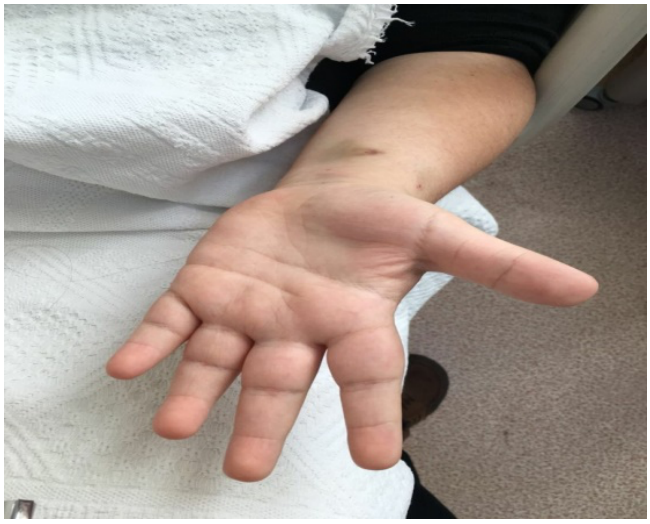

Fig. 3. Short fingers, joint laxity

In the anterior posteriorchest X-Ray, no pathological image was detected. The patient's electrocardiography was in normal sinus rhythm. In the hemogram and routine biochemical blood tests no pathological results were taken.

2.2 Anesthesia application

On the operation day, despite the fact that the patient's mallampati score was 2, essential precautions were taken against the potentiality of difficult intubation and because of the risk of malignant hyperthermia, dantrolene sodium vials were kept ready. The patient was monitored, blood pressure was 112/76 mmHg, heart rate was 92 beats/min, heart rhythm was regular and oxygen saturation was 98% in the room air. Opening the patient's vascular access, 0,5 mg/kg lidocaine, 1 mg/kg propofol and 1mcg/kg fentanyl were administered and induction was ensured. The patient was intubated with size 7.0 intubation tube without curarization due to the fact that the patient had no muscle biopsy history. Vital signs observed stable. After anesthesia, 4-6mg/kg/hour propofol and 0,05-0,2mcg/kg/min remifentanil infusion was administered. There was not any complications observed. In the last half an hour of the operation, 1mg/hour paracetamol and 20 mg tenoxicam were administered to the patient to achieve analgesia. At the end of the operation, medication infusions were turned off and the patient was awakened due to the fact that there were no need for decurarization.

3. Discussion

Applying anesthesia to the patients with Kabuki Syndrome can actually be difficult in consequence of many

pathologies that may involve with this syndrome. Accompanied by micrognathia, cleft and high palate can cause diffucult intubation. Despite the fact that pulmonary functions are generally normal, in hypotonic childs obstructive apnea syndrome may go along with this syndrome. In the meantime scoliosis may also accompany with this syndrome and may cause respiratory restrictivenesses. In addition immundeficiency and associated recurrent pneumonias should not be overlooked. Many cardiac pathologies as coarctation of aorta, bicuspid aorta, mitral valve prolapse, ventricular septal defect, valvular stenosis, tetralogy of Fallot, transposition of great arteries may pose a risk in terms of anesthesia.[10] In this regard, it is highly essential to consider these patients about cardiac and pulmonary issues in detail before anesthesia. Another significant point on selecting anesthesia agent is the risk of deepening of neuromuscular blockage and the possiblity of malignant hyperthermia in hypotonic patients. In this respect, remifentanil is considered as a low risk alternative from the point of complications.[9] Additionally, there are also examples in the literature that neuromuscular blocking agents must be administered at higher doses in the patients with Kabuki Syndrome, due to their regular anticonvulsant treatment.[9,10] In this case, in the pre-anesthetical examination, despite the fact that cardiac and pulmonary complication risks were lower then the cases with severe Kabuki Syndrome, precautions were taken particularly in terms of malignant hyperthermia. As recommended in the literature, remifentanil infusion was preferred and the patient was awakened without any complication.

Although Kabuki Syndrome is rarely seen, patients with Kabuki Syndrome has significant pathognomonic phenotype features and therefore they should be carefully evaluated in preoperative evaluation in terms of possible anesthesia risks. Necessary precautions should be taken in these patients, particularly in terms of cardiac and pulmonary complications, difficult intubation possibility and malignant hyperthermia.

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A case report: Successful management of pulmonary aspergillosis associated with COVID - 19 ARDS

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Abstract

The recent global outbreak of coronavirus disease-19, also known as COVID-19, has infected more than 142 million people worldwide, causing more than 3 million deaths. It has been shown that up to 40% of hospitalized COVID-19 patients may develop ARDS. Although not proven, anti-inflammatory and anti-cytokine treatments are recommended to suppress the cytokine storm that develops in the early stages of the disease.In this case report, a case of pulmonary aspergillus developed as a complication of treatment for ARDS caused by covid 19 in a 50-year-old male patient will be presented in the light of current literature.

Keywords: acute respiratory distress syndrome, covid-19-associated pulmonary aspergillosis, pulmonary aspergillosis, steroid treatment

1. Introduction

From last year to today, the covid-19 pandemic continues to fluctuate worldwide. Although there have been remarkable advances regarding vaccines, there is no specific treatment for the disease. Currently, the primary approach to prevent hyperinflammation caused by the disease is systemic steroid administration. In this case report, a case of pulmonary aspergillus developed as a complication of treatment for ARDS caused by covid 19 in a 50-year-old male patient will be presented in the light of current literature.

2. Case Report

A 50-year-old male patient with a known history of asthma bronchiale was admitted to the emergency room and then to the intensive care unit after respiratory distress increased on the 7th day of Covid 19 (polymerase chain reaction) PCR positivity. While taking O_2 with a reservoir mask and nasal cannula at the time of admission, sat O_2 was measured as 84%, fever was 37.8°C, respiratory rate was 25-30 breaths/min, cardiac apex beat was 120 beats/min, and blood pressure was 145/90 mmHg. Laboratory findings were detected as follows: Sedimentation rate: 56 mm/h, Ferritin: 539.60 µg/l, C-reactive protein (CRP): 86.7 mg/l, WBC: 14600 x 10^9 /mm^3, Neutrophil count: 13.53 x 10^9 /mm^3, Lymphocyte count: 440 x 10^9 /mm^3, Platelet count: 145000 x 10^9 /mm^3, LDH: 495 Iu/mL, Fibrinogen: 645 mg/dL, Procalcitonin: 0.26 ng/mL, pH: 7.23, pCO_2:66 mmHg, pO_2:38 mmHg, Lactate: 3.4 mmol/L. PA radiography and thorax tomography revealed ground glass-consolidation areas and linear atelectasis (Fig 1 A, B). The patient was treated with FiO_2: 100%, 60 L/min nasal high flow oxygen therapy (NHFO), and non-invasive ventilation (NIV) (FiO_2: 100% Peep: 7 cm/H_20 above Peep: 18 cm/H_20) treatment. CRP and ferritin levels increased in consecutive measurements. Medical treatment was started with piperacillin-tazobactam 3x4.5 gr, moxifloxacin 1x400 mg, methylprednisolone 500 mg 2x1, anakinra 3x100 mg, lansoprazole 2x40 mg, enoxiparin 2x 6000 IU, and budesonide 2x1 mg. On the 2nd day of the treatment, the patient whose saturation decreased and tachypnea increased, was intubated and connected to a mechanical ventilator. The ventilator setting was adjusted to be Fio_2: 1.0, Peep:9 cm/H_20, Above Peep:20 cm/H_20, respiratory rate:20/min, and i/e:1.80 in Synchronized intermittent mandatory ventilation (PSIMV) mode.

The dose was adjusted for the patient whose PaO_2/FiO_2 ratio was around 100 during the first week of intubation, and midazolam (0.1 mg/kg/h) and rocuronium (0.1 mg/kg/h) infusion was administered. Methylprednisolone was administered to the patient at 1000 mg for the first 3 days, 4000 mg in total, and for 20 days during hospitalization. Anakinra treatment was administered at 300 mg/day for 10 days. After two unsuccessful extubation attempts on the 21st day of hospitalization, percutaneous tracheostomy with bedside bronchoscopy was performed. After tracheostomy, all sedation was terminated, and the patient started weaning. Control thorax (computed tomography) CT was performed on the 50th day of hospitalization of the patient whose secretion from the tracheostomy cannula did not decrease and CRP and ferritin levels did not decrease (Fig. 2 A, B). Along with partly localized pneumothorax in the right hemithorax, an irregularly shaped, cavitary, abscess-like lesion measuring 6.5x 5.5 cm was detected in the anterior left upper lobe of the left lung.

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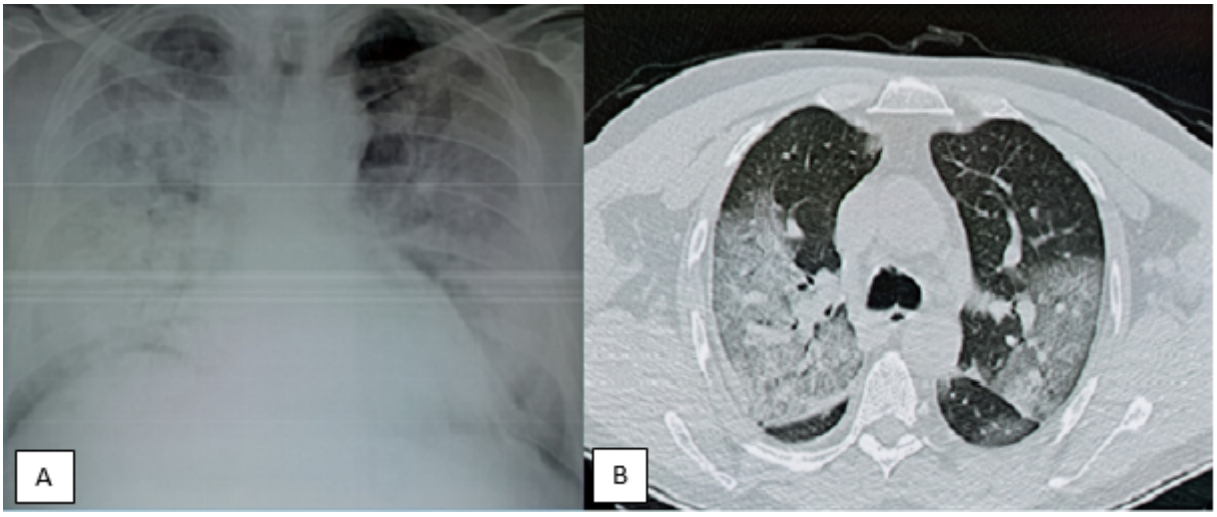

Fig 1. (A.B). PA radiography and thorax tomography revealed ground glass-consolidation areas and linear atelectasis

The dose was adjusted for the patient whose PaO_2/FiO_2 ratio was around 100 during the first week of intubation, and midazolam (0.1 mg/kg/h) and rocuronium (0.1 mg/kg/h) infusion was administered. Methylprednisolone was administered to the patient at 1000 mg for the first 3 days, 4000 mg in total, and for 20 days during hospitalization. Anakinra treatment was administered at 300 mg/day for 10 days. After two unsuccessful extubation attempts on the 21st day of hospitalization, percutaneous tracheostomy with bedside bronchoscopy was performed. After tracheostomy, all sedation was terminated, and the patient started weaning. Control thorax CT was performed on the 50th day of hospitalization of the patient whose secretion from the tracheostomy cannula did not decrease and CRP and ferritin levels did not decrease (Fig. 2 A, B). Along with partly localized pneumothorax in the right hemithorax, an irregularly shaped, cavitary, abscess-like lesion measuring 6.5x5.5 cm was detected in the anterior left upper lobe of the left lung.

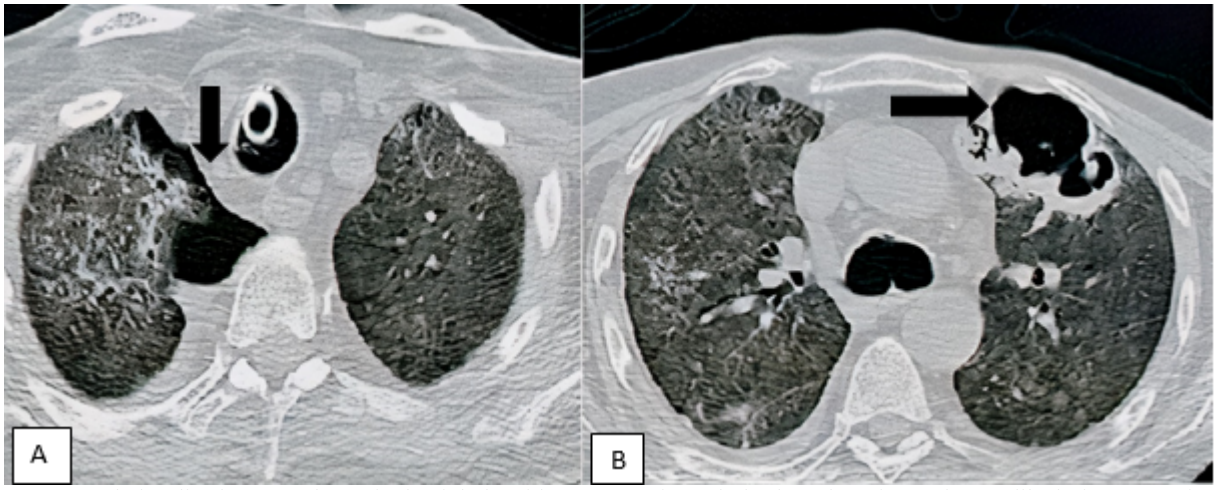

Fig 2. A partly localized pneumothorax in the right hemithorax, B. an irregularly shaped, cavitary, abscess-like lesion measuring 6.5x5.5 cm was detected in the anterior left upper lobe of the left lung

In the follow-up, the culture result obtained from the bronchoscopic lavage sample was compatible with Aspergillus fumigatus, while galactomannan antigen was detected as Aspergillus (3.01, optical index).

The intervention was not considered for the patient who was referred to the department of thoracic surgery. The patient's antibiotic therapy was arranged as iv voriconazole 2 × 6 mg/kg loading for the first 5 days, after which 2 × 4 mg/kg maintenance was administered, and then 2x200 mg oral administration.

He was transferred to the chest disease service as being conscious, cooperative-oriented, Glasgow coma scale (GCS):15, tracheostomized, and received O_2 from the tube at a rate of 4-5 l/min.

3. Discussion

The recent global outbreak of coronavirus disease-19, also known as COVID-19, has infected more than 142 million people worldwide, causing more than 3 million deaths. It has been shown that up to 40% of hospitalized COVID-19 patients may develop ARDS (SARS-CoV-2), although it may create a wide spectrum of clinical manifestations depending on the presence of the underlying disease (1)

The World Health Organization (WHO) has reported that there is currently no scientifically proven specific treatment for COVID-19. Although not proven, anti-inflammatory and anti-cytokine treatments are recommended to suppress the cytokine

storm that develops in the early stages of the disease. In the COVID-19 treatment guidelines of the Turkish Ministry of Health, steroid use is included in patients with macrophage activation syndrome (MAS) or cytokine storm. Recovery study showed that the use of dexamethasone reduced the 28-day mortality rate (2). The Surviving Sepsis Campaign recommends the use of short-term systemic corticosteroids. Several studies have shown that pulse methylprednisolone application is beneficial as it was applied in our case. It is known that while it suppresses hyper-inflammation during periods such as cytokine storm with steroid treatment, it also causes side effects.

In the pre-pandemic period, pulmonary aspergillosis was observed in patients with severe immunosuppression, particularly those associated with hematological malignancies and transplantation. Most recent studies have emphasized the epidemiology and importance of aspergillosis after severe viral infections, especially influenza and COVID-19 (3). However, increasing rates of bacterial, fungal, and viral infections have been detected in COVID-19 patients. In line with this, in the study of Borman et al. in which they examined the samples of 719 undiagnosed critically ill patients, they detected approximately 5% to 15% of COVID-19-associated pulmonary aspergillosis (CAPA) (4).

Current guidelines recommend diagnostic procedures for the diagnosis of Aspergillus, such as respiratory culture and galactomannan index of Bronchoalveolar lavage (BAL) samples (5). Despite the high risk of transmission of Covid 19 due to aerosol exposure during bronchoscopy, a bronchoscopic lavage culture was sent from the patient. The culture result was determined as A. fumigatus, and the GM antigen sent afterward was also detected as positive.

According to the treatment part of the same guideline, voriconazole or echinocandin combination is recommended in patients without azole resistance (5). In our patient, azole resistance was not detected, oral monotherapy after IV voriconazole was sufficient, and no side effects were detected.

Severe COVID-19 infection is associated with an irregular immune response that affects not only the clinical worsening of patients but also alters susceptibility to secondary infections such as Aspergillus infection by impairing host defenses. Pharmacological agents applied for treatment have effects that increase the immunosuppressive effect. Pulmonary aspergillosis is a serious and life-threatening complication in patients with severe COVID-19 receiving immunosuppressive therapy. Clinicians should be aware of new secondary infections and should be more careful to avoid possible complications with the duration and dose of immunosuppressive therapy.

Conflict of interest

The authors declare no conflicts of interest

Acknowledgments

The patient provided informed consent for the publication of this case. In accordance with the provisions of the Ministry of Health of the Republic of Turkey, the ethics committee of the Ministry of Health was applied and approval was obtained with the number DURSUN FIRAT ERGÜL-2021-06-02T11_51_11. Attached is the e-mail printout showing that it was accepted.

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Postpartum intracerebral hematoma following in vitro fertilization

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Abstract

To contribute to the literature with a case of postpartum intracerebral hemorrhage following in vitro fertilization (IVF) treatment. A 41-year-old female patient presented to our clinic with the complaint of headache lasting for four days. It was determined that the patient underwent a cesarean section 10 days earlier and had received preoperative IVF treatment. Her general condition was moderate. She was cooperative and oriented but apathetic and drowsy. There was 4/5 paralysis in the right lower extremity and right arm. Her blood pressure was 197/115 mmHg. In the brain CT, there was an approximately 6x1.5 cm parenchymal hematoma and subarachnoid hemorrhage in the deep white matter in the left frontal region. The patient was followed up in the intensive care unit for five days, and then admitted to the ward following the improvement in her general condition and apathic findings. Although there are no risk factors for intracerebral hemorrhage that occurs after IVF, it can present with neurological sequelae during recovery. There is a need for detailed studies and meta-analyses that will guide both the treatment approach to these patients and preventive measures.

Keywords: intracerebral hematoma, postpartum intracerebral hematoma, IVF, peripartum period

1. Introduction

Physiological and vascular changes during pregnancy are very important in predicting possible complications. A 50% increase in blood pressure results in an increase in cardiac output along with an increase in the permeability of the blood-brain barrier. In addition, propensity to coagulation and changes in fibrinolysis are observed (1).

Vascular changes clearly have an important place in intracerebral hemorrhage that occurs during pregnancy and in the peripartum and postpartum periods. In addition, it has been reported that arteriovenous malformation (2), preeclampsia (3), and hemolysis, elevated liver enzymes and low platelets syndrome (4) are also effective in the etiology. The factors can be listed as hypertension, gestational diabetes, smoking, and chronic liver disease (5, 6).

In vitro fertilization (IVF) treatment was first performed in 1977 by Steptoe and Edwards (7). It has been suggested that risk factors for intracerebral hemorrhage during pregnancy and the peripartum period are similar in patients receiving IVF treatment (1). However, to our knowledge, there are no research articles in the literature on postpartum hemorrhage following IVF treatment and the approach to patients with this complication.

This case report aimed to contribute to the literature by describing a case of postpartum intracerebral hemorrhage that developed after IVF treatment.

2. Case Report

A 41-year-old female patient presented to our clinic with the complaint of ongoing headache lasting for four days. It was determined that she underwent a cesarean section 10 days earlier and had no preoperative preeclampsia or history of intrauterine bleeding but had a history of IVF treatment. The patient's general condition was moderate. She was cooperative and oriented, and completely responded to orders but she was apathetic and inclined to sleep. There was 4/5 paralysis in the right lower extremity and right arm. Her bilateral light reflex was +/+, and there was no sign of meningeal irritation. Her body temperature was 36.5 °C, heart rate was 60/min, saturation was 97% at room air, and blood pressure was 197/115 mmHg. We were informed that her preoperative blood pressure value was 90/60 mmHg. No pathology was found in the thorax and abdominal examinations, and the laboratory test values were as follows: blood glucose, 91 mg/dl; blood urea nitrogen, 25.5 mg/dl; creatinine, 0.44 mg/dl; sodium, 141.4 mEq/L; potassium, 4.19 mEq/L; aspartate aminotransferase, 35 U/L; alanine aminotransferase, 23 U/L; white blood cell count, 9.91x103 U/L; hemoglobin, 13.6 g/dl; platelet count, 330x103 U/L, prothrombin time, 15.4(11-16) sec; international normalized ratio, 1.15(0.8-1.3);and activated partial thromboplastin time, 28.4(25-40) sec. According to the blood gas analysis, her pH value was7.44, partial pressure of carbon dioxide was 34.2 mmHg, and bicarbonate was 23.2 mmol/L. The computed tomography and diffusion-weighted magnetic resonance images of the brain revealed an approximately 6x1.5 cm parenchymal hematoma in the deep white matter in the left

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frontal region and a loss of density compatible with edema around the hematoma, followed by subarachnoid hemorrhage in the sulcus in the left frontotemporal region. There were mild findings of subarachnoid hemorrhage at the inferior gyrus level in the right frontal lobe and a 6-mm shift to the right due to parenchymal edema and hematoma in the left hemisphere (Fig. 1, Fig. 2). However, 3D-Angio imaging showed no signs of stenosis or aneurysm in the brain-neck vascular structures. During the follow-up, esmolol and phenytoin sodium were started for the treatment of hypertension, which reduced the patient's blood pressure to 178/88 mmHg.

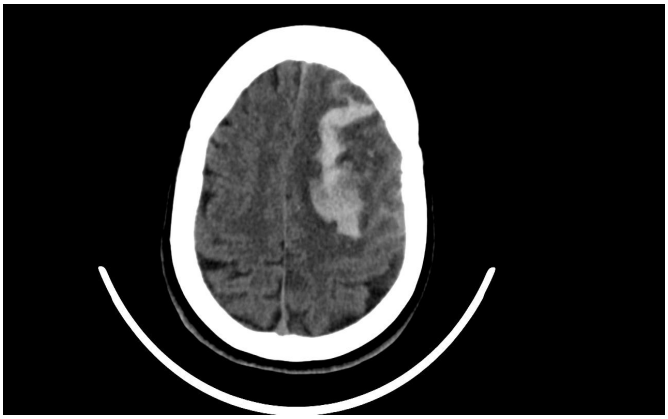

Fig 1. Computed tomography image taken at the time of presentation showing intracranial hematoma and a shift to the right

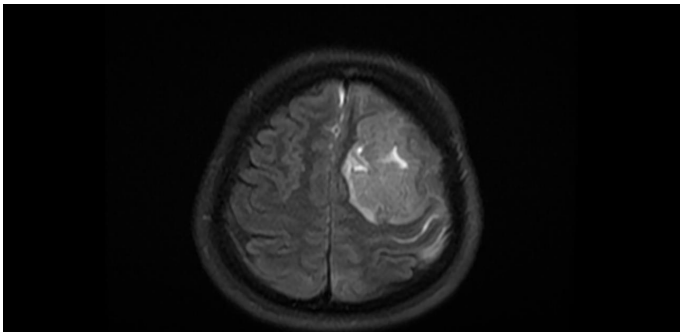

Fig 2. Diffusion-weighted magnetic resonance image taken at the time of presentation showing intracranial hematoma and a shift to the right

Upon consultation with the neurology and neurosurgery departments, intracranial intervention was not considered but it was considered appropriate to admit her to the intensive care unit. The patient was followed up at the intensive care unit for five days, and then moved to the ward with an improvement in her general condition and apathetic findings. After one week of follow-up at the ward, she was discharged with 2/5 hemiplegia in the right lower extremity and 1/5 paralysis of the right arm.

3. Discussion

We consider that our case report will contribute to the literature by describing a case of intracerebral hemorrhage following IVF treatment. In studies performed, intracerebral hemorrhages associated with pregnancy are mostly seen in the third trimester, while those that develop in the postpartum period rank second in terms of frequency (6). Our patient presented to our clinic on the postpartum 10th day. In a previous case report, quadriplegia was reported in a patient who developed epidural hematoma on the postpartum 15th day (8). In our patient, there was significant paralysis in the right arm and right lower extremity and tendency to sleep at first presentation. At the timeshe was discharged, recovery was partially achieved.

If intracerebral hemorrhage is considered to be due to a ruptured vascular lesion, vascular imaging should be requested (1).In our patient, 3D Angio imaging was performed, and no vascular lesion was detected. Although the target blood pressure value is not clear in intracerebral hematoma in pregnant and postpartum patients, hypotension should be avoided due to the risk of fetal hypoxia (1). The blood pressure of our patient was only partially reduced, and thus a significant decrease was prevented.

Although the approach to the case of intracerebral hemorrhage is similar to that of non-pregnant patients (1), the literature contains no research comparing the management of intracerebral hemorrhage during pregnancy and the postpartum period (6). To our knowledge, there is also no study examining the cases of intracerebral hemorrhage after IVF treatment. In addition, we did not find any study comparing intracerebral hematomas observed in the first, second or third trimester or postpartum period with those seen in non-IVF pregnancies.

In a case report, Winarno et al., (2019) described a 42-year-old patient who became pregnant following IVF. The patient was in her third trimester when she developed intracerebral hemorrhage in the midbrain without a history of chronic disease, smoking, operation, or hypertension (9). Similarly, our patient did not have any risk factors, but she did also develop parenchymal hematoma and subarachnoid hemorrhage.

Although pregnancy-related intracerebral hemorrhages are rare, they can result in an increase in the length of hospital stay, morbidity, and mortality, and negatively affect quality of life. However, these complications may also occur in pregnancies after IVF treatment. Although there is no risk factor, patients can remain in a state of recovery with neurological sequelae. There is a need for detailed studies and meta-analyses that will guide both the approach to the treatment of these patients and preventive measures.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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A rare cause of post-ESD pain: Submucosal hematoma at the lesion margin

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Abstract

Submucosal hematoma at the margin of the excised lesion after endoscopic submucosal dissection is extremely rare. These patients may experience persistent epigastric pain after the procedure. In this case, report we will discuss about a rare condition.

Keywords: endoscopic submucosal dissection, gastrointestinal bleeding, submucosal hematoma, post-ESD pain

1. Introduction

Endoscopic submucosal dissection (ESD) is an established effective treatment modality for premalignant and early-stage malignant lesions of the esophagus, stomach and colon (1). ESD is curatively advantageous over endoscopic mucosal resection (EMR) as it allows en bloc resection regardless of tumor size, shape, ulceration or location, which contributes to the reduction in local recurrence rate (2). It is known that bleeding or intramural hematoma may develop after ESD procedure in gastric polyps and subepithelial lesions (3). However, submucosal hematoma is very rare at the margin of the submucosal resected lesion. Here, we present a case of submucosal hematoma at the lesion border in a patient with persistent pain after ESD to a gastric lesion.

2. Case report

A 55 years old female patient, who had a previous history of ESD due to gastric polyp, admitted to our clinic for recurrent lesion. The patient had no chronic disease. In laboratory tests, platelet count, bleeding time and coagulation parameters were normal. ESD was planned for the patient. During the procedure, a recurrent hyperplastic lesion of approximately 4 cm in size was observed in the prepyloric antrum at the site of the previously performed ESD. After submucosal saline injection, circumferential incision was made. However, sufficient elevation could not be achieved, and the lesion was removed using hybrid EMR technique with snare (Fig. 1). After hemostasis control was achieved, the procedure was terminated. The patient developed mild epigastric pain after the procedure, did not have hemoglobin (Hb) decrease, melena/hematemesis and vital disturbances. Control endoscopy was performed 1 day later and a submucosal hematoma of 5 cm in size was observed at the border of the excised lesion (Fig. 2). Oral intake of the patient was stopped, pantoprazole 40 mg BID 0.9% NACL infusion, ciprofloxacin 400 mg bid, metronidazole 500 mg TID and tramadol TID were started. Control endoscopy was performed on the 5th day of the patient whose pain regressed in the follow-ups. It was observed that the epithelial integrity of the mucosa covering the hematoma was impaired, the hematoma was resorbed, and an ulcer with a dirty floor was formed in this area (Fig. 3).

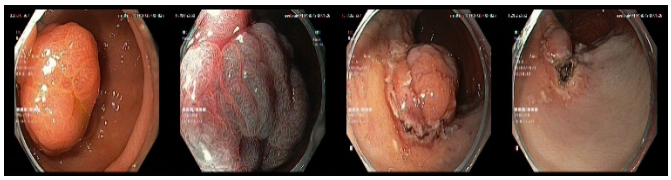

Fig. 1. Hyperplastic lesion and ESD procedure

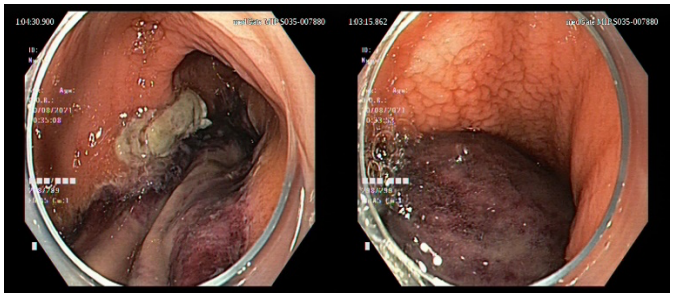

Fig. 2. Submucosal hematoma at the lesion margin

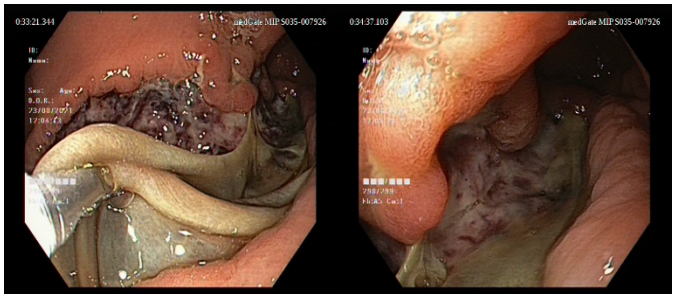

Fig. 3. Resolution of submucosal hematoma

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3. Discussion

The incidence of bleeding after gastric ESD has been reported to range from 1.8% to 15.6% (3). Post-ESD bleeding is defined as melena, hematemesis, and > 2g/dl Hb decrease, requiring endoscopic hemostasis (4, 5). Here, we discussed about a submucosal hematoma at the lesion border after ESD to a gastric lesion. In this case, we followed our patient with conservative treatment and observed that the hematoma regressed in a short time. we did not find any published similar case in the literature. We think that a second look is important in patients who do not have bleeding findings after ESD and who have persistent epigastric pain.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Aortic dissection with cerebral infarction

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Abstract

Aortic dissection is a fatal cardiovascular health problem. Chest and back pain are among the common complaints of the patients, and they may also apply with atypical clinics. It is very difficult to diagnose with examination and anamnesis, especially in patients who present with poor consciousness and stroke symptoms. In this study, we wanted to present a 62-year-old female patient who had syncope at home and was unconscious for about 1 hour, has stroke symptoms, and aortic dissection was detected in her examinations. When no hemorrhage was detected in non-contrast brain CT, neck and brain contrast-enhanced CT angiography imaging was performed. Aortic dissection flap extending to the right carotid communis was detected in the imaging. Clinicians should pay attention to detailed examination and be alert for further examinations in order not to harm the patient in terms of underlying causes, especially in unconscious patients who have a stroke clinic and cannot express their complaints in a healthy way.

Keywords: stanford type A, stroke, syncope, emergency

1. Introduction

Aortic dissection (AoD) is a fatal aortic disease and prompt diagnosis is essential for prompt surgical intervention and good patient outcomes. Mortality of Stanford type A AoD is greater than 50% if early surgical intervention is not performed. Especially in Stanford type A AoD, the ascending aorta is affected and sometimes accompanies acute ischemic stroke. Patients with ischemic stroke as a complication of Stanford type A dissection; often do not complain of chest or back pain, possibly due to impaired consciousness, amnesia, or aphasia. It has a fatal course following inappropriate intravenous rt-PA therapy, and delayed proper surgical treatment also increases mortality (1). The latest guidelines indicate AoD as a contraindication to the use of intravenous thrombolytics for acute cerebral infarction (CI). A case of AoD with a rare CI occurring at our emergency department has been analyzed and summarized. This case will serve as a reference for the management of similar patients.

2. Case Report

A 62-year-old female patient was admitted to the emergency service by ambulance after fainting at home and unconscious for about 1 hour. The patient's Glasgow Coma Score was 5 and other vital parameters were normal, and direct and indirect light reflexes could not be detected in the neurological examination. Left Babinski reflex was positive, right upper and left lower extremity distal pulses could not be palpated. There were known diagnoses of hypertension, diabetes mellitus and atrial fibrillation. Rapid serial intubation was performed to maintain cardiopulmonary stability. Brain CT imaging was performed to detect central events.

Blood tests showed C-reactive protein 3.6 mg/L, D-dimer 19.6 mg/L, white blood cells 9.69 × 103/uL, red blood cells 3.98 × 106/uL, and hemoglobin 3.98 g/L. When no hemorrhage was detected in non-contrast brain CT (Fig. 1a) neck and brain contrast-enhanced CT angiography imaging was performed. It was observed that there was no blood supply in the right cerebral hemisphere and decreased blood supply in the left cerebral hemisphere (Fig.1b). AoD flap extending to the right carotid communis was detected in the imaging (Fig. 2ab). The ascending aorta of the patient, whose echocardiography was performed, was measured 54 mm and a dissection flap was seen. The patient was taken to intensive care follow-up for further examination and treatment. He died after 15 hours of intensive care follow-up.

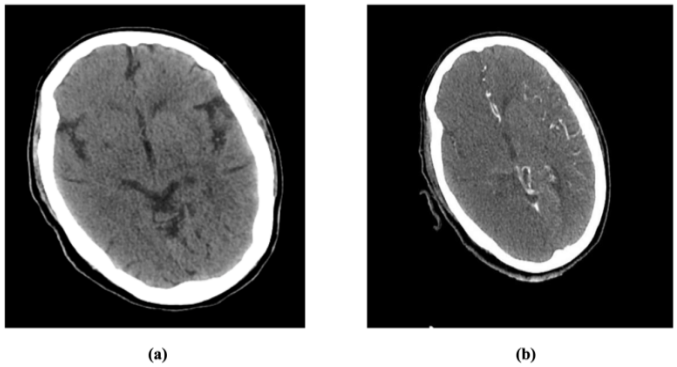

Fig. 1. Non-contrast brain CT (a), Lack of contrast material passage in the right cerebral hemisphere (b)

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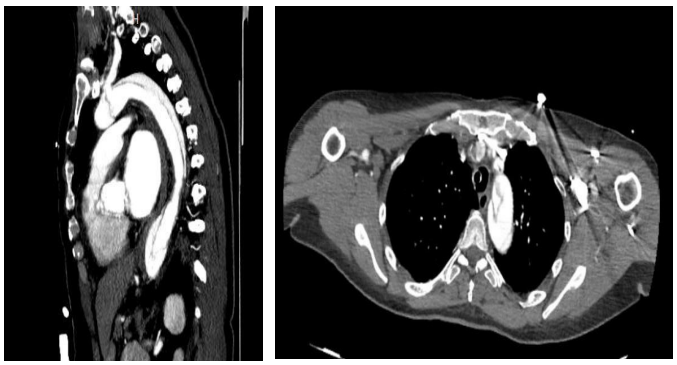

Fig. 2. Stanford type A dissection (a), dissection flap starting from the brachiocephalic artery and extending to the right common carotid artery (b)

3. Discussion

The most frequent causes of AoD are hypertension, atherosclerosis, trauma, Marfan syndrome, arteritis, and pregnancy. This patient had there was a history of only hypertension. Clinical symptoms are intimately related to pathophysiological development. The most classic clinical symptom in AoD is chest or back pain. However, only about half of the patients with CI have such a complaint (chest or back pain), likely due to the presence of amnesia or cortical symptoms such as aphasia and/or impaired consciousness (1,2). Some auxiliary examinations can also provide remarkable clinical information. If symptoms such as unexplained hypotension, shortness of breath, chest discomfort, asymmetry of blood pressure between the arms, loss of consciousness, and cold limbs are present, aortic CT angiography and echocardiography should be added to determine if AoD is present. The guidelines have suggested intravenous thrombolysis as the top level of therapy for CI within the time window. If a patient has AoD, intravenous thrombolysis can have catastrophic results. For example, new embolic events caused by the disintegration of emboli in the dissection, pericardial effusion, tamponade due to aortic rupture, and the delay of life-saving surgery. Published reports on aortic steering warnings in intravenous thrombolytic therapy emphasize the importance of keeping in mind the potential existence of AoD as a cause of ischemic stroke (3). Depending on the extent of involvement of AoD, it can cause various organ disorders and clinical symptoms. Approximately 6% of patients experience a transient ischemic attack (TIA) due to accompanying ischemic stroke or spread to the cervicocerebral arteries or embolism from the dissection site (4, 5). A study of 1637 consecutive patients with suspected stroke found a total of 5 patients with ischemic stroke as a complication of type A aortic dissection (1). AoD patients need to preserve low blood pressure to prevent further tearing. In contrast, low blood pressure will decrease stroke hemisphere perfusion and then grow the CI (6). The presence of ischemic stroke has been accepted as an indicator of poor prognosis (7,8). In addition, it has been reported that with early diagnosis of AoD and appropriate surgical treatment, accompanying neurological symptoms are not associated with increased mortality (2,9,10). Patients may present with a combination of various neurological manifestations such as hemiplegia, impaired consciousness, syncope, convulsions, amnesia, spinal cord ischemia, and peripheral neuropathy (11). Clinicians should pay attention to detailed examination and be alert for further examinations in order not to harm the patient in terms of underlying causes, especially in unconscious patients who have a stroke clinic and cannot express their complaints in a healthy way.

Today, due to intensive care occupancy, the first treatment of most ischemic stroke patients is performed in the emergency room conditions. In particular, patients who are candidates for fibrinolytic therapy and present with stroke symptoms should be investigated for etiology. Although it is not common in stroke patients, as in our case, the presence of underlying AoD changes the course of treatment. Otherwise, the fibrinolytic therapy given can be fatal.

Conflict of interest

None to declare

Acknowledgments

None to declare

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Case Report

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Acute encephalopathy associated with anaphylactic shock caused by angiographic radiocontrast media: An unusual case

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Abstract

Radiocontrast media have been used with increasing frequency for centuries. Radiocontrast media may have the spectrum up to anaphylaxis as a side effect. The case presented here is of a patient with acute encephalopathy, associated with the anaphylactic shock of angiographic radiocontrast media. A 67-year old male patient with a diagnosis of abdominal aortic aneurysm (AAA) was referred for coronary and peripheral angiographic evaluation before the AAA operation. After the angiographic examination was completed, the patient developed complaints of dyspnea, stridor, flushing and eruption. The patient recovered totally after a successful medical intervention was performed for anaphylaxis. Decorticated posture gradually developed, and the patient lost consciousness again. After cranial computed tomography, diffusion magnetic resonance imaging and electroencephalography were performed, levetiracetam treatment was started to the patient after the patient had a tonic-clonic convulsion. The patient recovered completely after a seizure with antiepileptic treatment without. Nonconvulsive status epilepticus must be considered after the allergic reaction, and anti-epileptic agents should be taken into consideration in addition to preventing hypoxia and hypoperfusion.

Keywords: radiocontrast media, anaphylaxis, hypoxia, nonconvulsive status epilepticus

1. Introduction

The first iodinated radiocontrast media (IRM) was introduced in 1929, and IRMs are today used in >50 million radioscopic examinations per year (1). IRMs can be classified into two groups, ionic and non-ionic. These are both structurally based on tri-iodinated benzene rings. Non-ionic monomers have much lower osmolality. Hyper osmolality is known to have a role in the pathogenesis of physiological reactions. Hypersensitivity reactions (HR) can be classified as 1) allergic-like, 2) pseudoallergic, and 3) anaphylactoid reactions (1).

Because of mast cell activation in anaphylactic reactions, cerebral hypoperfusion due to vasoconstriction in brain vessels (Kounis-like syndrome) or directly caused by systemic hypotension can cause brain disorders and encephalopathy (2).

The case presented here is of a patient with acute encephalopathy, which could not be detected with imaging methods, associated with the anaphylactic shock of angiographic radiocontrast media.

2. Case Report

A 67-year old male patient with a diagnosis of abdominal aortic aneurysm (AAA) was referred for coronary and peripheral angiographic evaluation before the AAA operation. We performed abdominal computed tomography angiography (CTA) for AAA diagnosis. There was no allergic reaction during this CTA, and we detected the diameter of the infrarenal abdominal aorta was 45 mm, increased in compliance with aneurysmatic enlargement, and we observed mural thrombus areas reaching a thickness of 20 mm observed on CTA (Fig. 1 a-b).

With radial artery access, coronary angiography indicated non-critical coronary arterial disease and 70-80% lesion on bilateral superficial femoral arteries. We detected an infrarenal AAA (Fig. 1c-d) on peripheral angiography. Both CTA and coronary angiography examinations were performed with the iohexol which was a non-ionic low-osmolar IRM. After completing the angiographic examination, the patient was taken to the recovery room and followed for bleeding. The patient developed complaints of dyspnea, stridor, flushing and eruption. The patient lost consciousness during this time. We urgently administered methylprednisolone 40 mg + diphenhydramine 50 mg + adrenaline 1 gr intra-venosus to the patient, who was then admitted to the intensive care unit. The patient's aspiration and consciousness improved. There was no motor sensorial deficit, but decorticated posture gradually developed, and the patient lost consciousness again.

An anaesthetist and neurologist examined the patient, and respiratory support was provided. The patient underwent cerebral CT (CCT) at 6-hour intervals, but we observed no pathology other than chronic ischaemic changes (Fig. 2a). There was no pathology on diffusion magnetic resonance

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imaging (DMRI) (Fig. 2b). As there was no ischaemic or hemorrhagic lesion on CCT or DMRI, we performed electroencephalography (EEG) for non-convulsive status epilepticus. We determined moderate-heavy ground rhythm pathology on EEG (Fig. 2c).

Almost 24 hours after the angiography, the patient had a tonic-clonic convulsion detected by a doctor. After this convulsion, we started levetiracetam treatment as the recommendation of the neurology clinic. On the post-convulsion control DMRI and flair sequences, we observed cortical diffusion restriction at the vertex level of the frontoparietal in the right hemisphere, which could represent a postictal signal change (Fig. 2d).

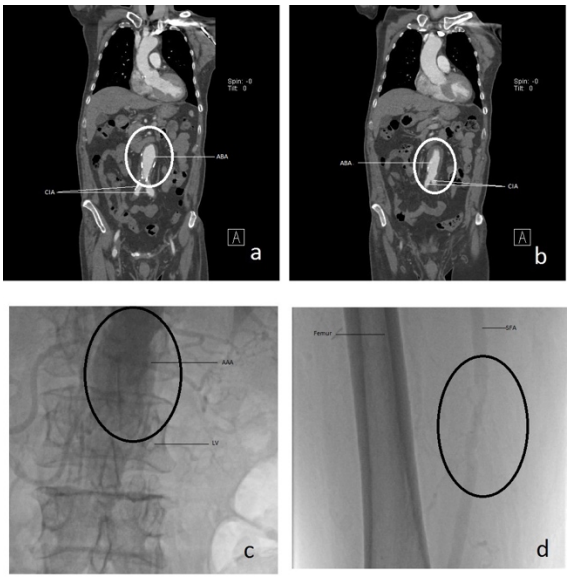

Fig. 1. Aneurysmatic dilatation and atherosclerotic calcification detected on CT(a-b), and conventional angiography (c), 70-80% peripheral lesion detected on conventional angiography (d). (ABA: Abdominal aorta, CIA: Common iliac artery, SFA: superficial femoral artery, LV: lumbar vertebra)

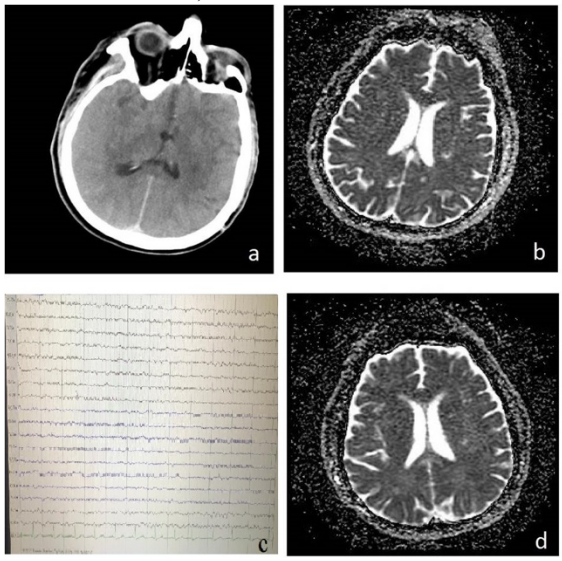

Fig. 2. No acute pathology on CCT (a) and DMRI (b), but there was moderate-heavy ground rhythm pathology on EEG (c), after convulsion, cortical diffusion restriction was observed at the vertex level of the frontoparietal in the right hemisphere, which could represent a postictal signal change (d)

The decorticated posture and unconsciousness improved after 6 hours of levetiracetam treatment. Although quadri-paresis continued, the patient responded to verbal stimuli. The quadri-paresis improved at 72 hours after angiography.

3. Discussion

Hyper sensitivity reactions (HR) are serious allergic reactions, which may be a response to any substance and sometimes lead to death due to anaphylactic shock and systemic hypoperfusion. HRs due to IRM are not dependent on the dose of IRM. HRs can be classified as acute and late phase reactions (1).

Symptoms include urticaria, erythema, bronchospasm, and shock. The action on first encountering a substance may result in sensation and lead to a weak-reaction, which can then result in a serious acute-reaction on the second encounter with the same substance. IRM-activated mast cells and basophils, complementary and kinin systems mediate all of these reactions (2).

HR is a systemic disorder due to anaphylaxis, hypotension and systemic perfusion and can affect all organs. Although rare, encephalopathy is the most threatening complication. The reasons for brain injury in HRs can be cerebral hypoxia caused by hypoperfusion because of anaphylactic shock or cerebral hypoxia caused by local allergic vasculitis secondary to HR (3).

Kounis syndrome (KS) is associated with HR, caused by acute myocardial injury (4). Furthermore, Kounis-like syndrome (KLS) has been described for other organs, meaning that this vascular phenomenon is not restricted to coronary injuries. As ischemia-sensitive organs, cerebral arteries and mesenteric arteries can be affected by KLS (5,6). There may be ischemic lesions or findings on MRI or CCT in KLS in relation to the duration of ischemia.

Reports in the literature about encephalopathy after HR and anaphylaxis include papers by Peláez et al. with the association of amoxicillin-clavulanic acid (7), Ding et al. presented formocresol (3), Speach et al. hymenoptera venom (8), Schabitz et al. diclofenac (9), and Arishima et al. an insect bite (10). In these cases, ischaemic lesions were present after the events on imaging tests.

The current case differs from the literature as there was no ischaemic lesion on CT or MRI, but there were ischaemic findings on EEG, and clinical improvement was obtained after anti-convulsive therapy after a convulsion, which may have been due to this clinic being nonconvulsive status epilepticus after a KLS.

The pathogenesis in this case may be associated with temporary vasoconstriction without sequelae because of early intervention for anaphylaxis and hypotension, and to KLS of the cerebral vessels. This situation with no-ischaemia on CT or MRI may have been due to nonconvulsive status epilepticus, and this situation can be masked by the heavy ground rhythm

pathology on EEG.

Even when a patient has previously been exposed to a drug with no problems, the allergic side-effects of each drug should be considered for each repeated procedure. In some cases, there may be an unexplained loss of consciousness with non-diagnostic imaging tests or EEG findings can be masked by hypoxia. In such a situation, nonconvulsive status epilepticus must be considered after the allergic reaction, and anti-epileptic agents should be taken into consideration in addition to preventing hypoxia and hypoperfusion.

Informed Consent

Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

Conflict of Interest

The authors declared no conflict of interest.

Acknowledgments

None to declare.

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Covid-19 infection mimicking postpartum pulmonary embolism: A case report

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Abstract

The case was a 32-year-old, nulliparous pregnant woman, after in-vitro fertilization (IVF) pregnancy. Her contractions started, and the amniotic fluid membrane ruptured at 38 gestational ages. The patient developed shortness of breath and lower oxygen saturation which started suddenly at the 8th hour after the cesarean section procedure under general anesthesia. Thrombotic conditions that may appear during the postpartum period should be diagnosed early and immediate treatment should be started to resolve the actual cause.

Keywords: Covid-19, acute pulmonary embolism, IVF

1. Introduction

Coronavirus Disease (Covid-19) was first identified as a result of research conducted in a group of patients who developed respiratory symptoms (fever, cough, shortness of breath, etc.) in Wuhan, China. In this case report, we aimed to present a case of Covid-19 infection mimicking postpartum pulmonary embolism.

2. Case Report

The case was a 32-year-old, nulliparous pregnant woman, after in-vitro fertilization (IVF) pregnancy. Our patient was a non-smoker and had a body mass index (BMI) of 26.3 kg /m². Her past medical history was unremarkable and she had a negative family history of venous thromboembolism. She revealed no risk factors during her gestational follow-ups. When her contractions started and amniotic fluid membrane ruptured at 38 gestational ages, the patient was admitted to Medistate Hospital Gynecology and Obstetrics Clinic for cesarean section indication due to inadequate pelvis and IVF pregnancy in March; 2021. An alive and healthy female baby with birth weight and birth length of 3000 g and 47 cm, respectively, and an APGAR score of 9/10 was delivered under general anesthesia.

The patient developed shortness of breath and lower oxygen saturation which started suddenly at the 8th hour after the cesaeran section procedure under general anesthesia. Blood pressure was 110/70 mmHg; vaginal bleeding and postpartum uterus involution were normal. We considered pulmonary embolism first, and therefore took, a computed tomography (CT) of the thorax to conduct the diagnosis. We regarded; the appearance detected on the pulmonary parenchyma was considered as atypical viral pneumonias belonging to pandemic infection. Clinical assessment was recommended. We detected no finding for pulmonary embolism.The laboratory analyses revealed the following findings; arterial blood gas: pO_2:97,1 mmHg, ph:7,44 lactate:3,5 mmol/L, D-Dimer: 6943 ng/ml , sedimentation:31 mm/hour AST:19 U/L, ALT:6 U/L, LDH: 299 U/L, leukocyte:24,680, lymphocyte:1510, Hb: 11.5 gr /dl, Htc:31.8 %, PLT:182.000, Pro-BNP:335 pg/ml. Covid-19 (SARS-CoV) reverse transcriptase was negative.

Upon progression of respiratory distress at the 12th hour after surgery, the patient was transferred to the intensive care unit after detection of Covid-19 appearance on the CT scan. The baby was discharged home. The patient had no medical condition and was taken to isolation in the general intensive care unit due to the suspicion of Covid-19 when frosted glass appearance consistent with Covid-19 was detected in the pulmonary parenchyma after exclusion of pulmonary embolism in the contrast CT pulmonary angiography. However, although the PCR and further tests for Covid-19 were negative, the patient was isolated and Covid-19 protocol followed when an appearance consistent with Covid-19 was obtained by Thorax CT findings. Fig. 1 and 2 show Thorax CT images improvement of the ground-glass opacities.

There was no need for intubation and the patient was discharged safely on the 12th postoperative day. Low molecular weight heparin treatment continued until the fortieth post-op day.

3. Discussion

SARS-CoV2 affects cells by binding to ACE2 (angiotensin converting enzyme 2) receptors, which are highly expressed in lung alveoli, cardiac myocytes, vascular endothelium and other cells (1).

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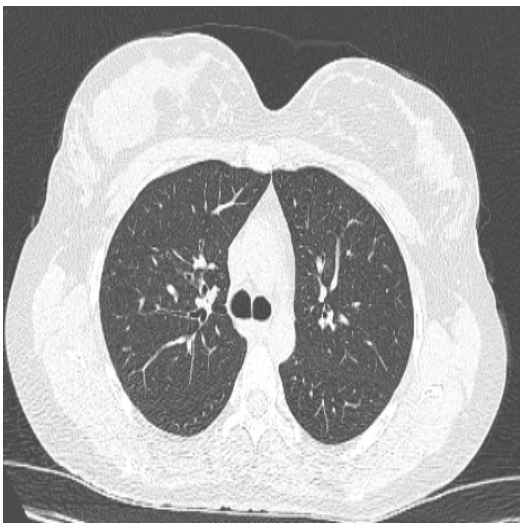

Fig. 1. Thorax CT image improvement of the ground-glass opacities.

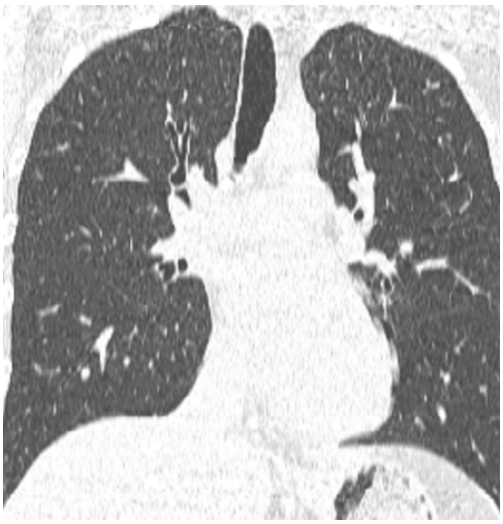

Fig. 2. Another thorax CT image improvement of the ground-glass opacities.

The disease starts with symptoms such as fever, weakness, headache, cough and/or myalgia. It can progress to a serious disease such as systemic inflammatory response syndrome (SIRS), acute respiratory distress syndrome (ARDS), diffuse intravascular coagulation and shock with multi-organ involvment (2). Changes in the hemostasis system and the development of thrombosis are increasing in patients with Covid-19(3).

Coagulopathy becomes evident with minimal changes in increased D-dimer and fibrinogen levels, prothrombin time (PZ), activated partial thromboplastin time (aPTZ), and platelet count. A high initial D-dimer level is associated with increased mortality (4).

In conclusion, thrombotic conditions that may appear during the postpartum period should be diagnosed early and immediate treatment should be started to resolve the actual cause. This should be considered for tailoring antithrombotic prophylaxis.

Conflict of interest

We declare no conflict of interest.

Acknowledgments

We received no financial support for the research, authorship, or publication of this article. We asked the patient to help us publish the case report in an international journal for discussion, including disease symptoms, diagnosis, and image related content. The patient agreed to allow us use her medical records and signed the consent form.

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Case Report

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Hyperpigmentation-Ashy dermatosis

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Abstract

Abstract metni, tek paragraph şeklinde 9 punto, Times New Roman, iki yana yaslı şekilde düzenlendi. Başlıkla metin arasında boşluk bulunmuyor, metin sonunda 6 nk aralık bulunuyor.

Yazar isimleri ilk harf büyük olacak şekilde yazılırken, yazar soyadları büyük harflerle yazılmalıdır. Yazar kurum bilgileri, önce departmandan başlamak üzere, fakülte, üniversite ismi, şehir ve ülke ile devam etmelidir. Tümü tümce düzeni ile yazılmalıdır (ilk harfler büyük).

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Keywords: anahtar kelimeler küçük harflerle yazılır, virgülle ayrılır ve n az 4 tane olmalıdır, xxx, yyy, zzz

1. Introduction

Ashy dermatosis-like hyperpigmentation Erythema dyschromicum perstans (EDP), also known as ashy dermatosis, is a hypermelanotic condition characterised by the development of a slate-grey macula in otherwise healthy individuals (1). The disease is not characterised by systemic or internal organ involvement; instead, it affects the skin only. Patients often request treatment due to cosmetic concerns (2). The EDP rate is the same in men and women (1, 3). Here, we describe sudden-onset EDP in a 19-year-old male patient.

2. Case Report

A 19-year-old male patient applied to the outpatient clinic with discoloration on the trunk and back. His lesions had started 3 months ago and increased in the last 2 weeks. Dermatological examination revealed pigmented macules and patches of different sizes, which tended to coalesce, on the back and anterior aspect of the trunk (Fig. 1 and 2).

The patient reported that the lesions had previously been more erythematous and purplish. The lesions did not regress after local treatment with a prescribed corticosteroid cream of moderate potency. The patient was free from systemic disease, was not taking any drugs and had no relevant family history. The complete blood count, liver and kidney function, erythrocyte sedimentation rate, and thyroid function were normal, as were all urine analyses. The anti-HBs, anti-HCV, anti-HIV, VDRL, and ANA tests were all negative.

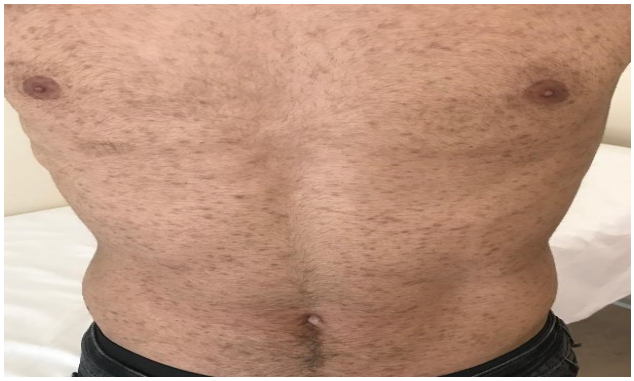

Fig. 1. Hyperpigmented macular eruption on the anterior aspect of the trunk

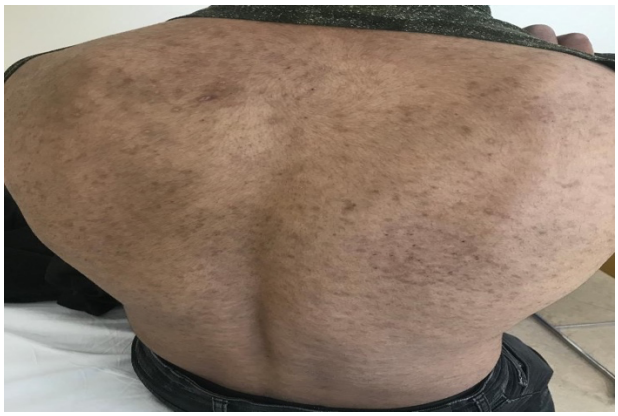

Fig. 2. Diffuse pigmented macules and patches on the back

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Histopathological examination of lesional biopsy tissue from the back and anterior of the trunk revealed EDP, characterised by vacuolar degeneration of the basal layer, mild lymphohistiocytic inflammatory cell infiltration around the vessels in the upper dermis, melanophages, pigment incontinence, and low-level lymphocyte exocytosis in the epithelium (Fig. 3). Dapsone (100 mg/day) controlled the lesions.

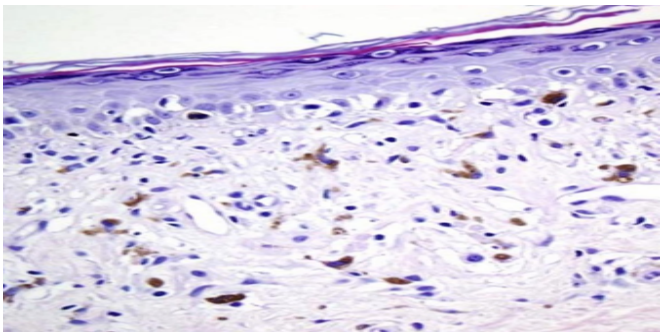

Fig. 3. Mild interphase dermatitis and pigment incontinence with perivascular lymphocytic infiltrate in the dermis (H&E 40X)

3. Discussion

Ashy dermatosis (EDP) is a rare dermal melanosis first described by Ramirez in 1957, and represents an example of acquired pigmentation (4, 5). Although the cause of EDP is unknown, Tlougan et al. (6) suggested that triggers might include infections (parasites and HIV), drugs (penicillin, ethambutol, and benzodiazepines), radiocontrast agents, ammonium nitrate, cobalt and fungicides. It is possible that thyroid dysfunction and endocrinopathies (such as diabetes mellitus, atopy and dyslipidaemia) may also cause the disease. Immunopathological examinations of active lesions suggested that immune-mediated mechanisms might play roles in the pathogenesis of EDP (5, 6). Hyperpigmentation refers to pigment deposition in the epidermis and/or dermis. As well as EDP and postinflammatory hyperpigmentation (PIH), primary cutaneous amyloidosis (PCA), neuralgia paresthetica (NP) and certain drug reactions may trigger hyperpigmentation (7). Few studies on EDP treatment have appeared. Silverberg et al. (8) found that sun screen, chemical peeling agents, antibiotics, and topical and systemic steroids were ineffective. Odom et al. (9) described partial responses to griseofulvin, clofazimine, and dapsone. EDP is a rare dermatosis, for which differential diagnosis and treatment may thus sometimes be inadequate. More clinical studies are needed.

Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Case Report

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Abciximab-induced thrombocytopenia: Correct management

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Abstract

Thrombocytopenia is a possible side effect of routinely administered medical agents. Abciximab is one of the three potent intravenous glycoprotein IIb/IIIa receptor inhibitors (along with eptifibatide and tirofiban) that have shown significant positive outcomes when used in patients with intracoronary thrombus. The use of abciximab was associated with the risk of thrombocytopenia. This case reported the development of thrombocytopenia and treatment management after using abciximab.

Keywords: Abciximab, thrombocytopenia, glycoprotein IIb/IIIa receptor inhibitors, side effect

1. Introduction

Glycoprotein (GP) IIb/IIIa receptor inhibitors are antiplatelet agents used in interventional cardiology in acute coronary syndrome. Thrombocytopenia may develop as a side effect due to these agents, and its incidence has been reported as 8-10%.

Thrombocytopenia can be considered pathophysiologically, as decreased production, increased destruction, and a disorder in platelet distribution. Many etiological factors can cause thrombocytopenia with different mechanisms, and drug-induced thrombocytopenia can also be observed. Drug-induced antibodies cause immune destruction of platelets. One of these drugs is abciximab, a glycoprotein (GP) IIb/IIIa receptor inhibitor that prevents platelet aggregation. This case aimed to review thrombocytopenia that developed after abciximab treatment.

2. Case Report

The patient, who applied at the emergency department with an epileptic seizure complaint, was hospitalized as we detected inferior myocardial infarction (MI) in their electrocardiography (ECG). We performed the right and left selective coronary arterial intervention procedure through the right femoral route on October 11, 2021, and administered 7500 UFH, 300 mg acetylsalicylic acid, 180 mg ticagrelor and one vial of abciximab. The patient was admitted to the Coronary Intensive Care Unit on October 11, 2021, discharged without any bleeding, hematoma or other complications at the intervention site. We hospitalized the patient after the outpatient visit on November 2, 2021, as we noticed thrombocytopenia, besides intraoral bleeding and hematuria. In the examinations of the patient, the values were WBC: 10000 mm^3 HGB: 10.1 g/dl PLT: 1000 mm^3. We performed a peripheral smear evaluation to differentiate pseudothrombocytopenia and evaluated the platelet level, which was in accordance with the peripheral smear. We started prednol 40 mg on November 3, 2021, and gave IVIg treatment as 1 mg/kg on November 3-4, 2021. We observed an increase in the course of thrombocytes in the follow-ups. On November 8, 2021, we discharged the patient with 107.000 mm^3 platelets in the examinations. We found the platelet as 247000 mm^3 in the examinations during the November 15, 2021 outpatient visit.

3. Discussion

Thrombocytopenia is defined as when circulating platelets are below the typical number. Pseudothrombocytopenia should be differentiated from true thrombocytopenia by repeating the platelet count using citrate anticoagulated blood. Acute thrombocytopenia is usually caused by pseudothrombocytopenia, drug-induced, idiopathic thrombocytopenic purpura gestational and less often chronic liver disease, myelodysplastic syndrome, congenital syndromes, or viral infections (1).

Today, drug-induced thrombocytopenia (DIT) is an increasingly common cause of isolated thrombocytopenia. Antibody-mediated platelet destruction should be suspected in patients who experience an acute decrease in platelet levels, usually within one or two weeks of starting a new drug (2). More than 300 drugs have been implicated in DIT. In the systematic review of individual patient data, the most commonly reported drugs with a definite or probable causal relationship to thrombocytopenia are quinine, quinidine, trimethoprim/sulfamethoxazole, vancomycin, penicillin, rifampin, carbamazepine, ceftriaxone, ibuprofen, myralaminplatin, and oxalimintazapine. GPIIb/IIIa inhibitors such as abciximab, tirofiban, and eptifibatide, have also been demonstrated. However, the most common drug involved in

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DIT is heparin (3). Abciximab is a potent antiplatelet agent that blocks platelet aggregation. It effectively prevents and treats acute ischemic complications of percutaneous coronary angiography and improves outcomes of high-risk procedures by reducing the incidence of major adverse cardiac events (4). The incidence of profound thrombocytopenia caused by abciximab is 8.5% and occurs rapidly (within 2-4 hours) after drug infusion; platelet values return to normal within 2-5 days after discontinuing abciximab but may take up to 10 days (5). Abciximab-induced acute severe thrombocytopenia (platelet count <20,000/μL) represents a rare, unpredictable, adverse severe complication that can cause fatal haemorrhagic events, including intracranial haemorrhage (6). Most cases are usually mild, but deaths have also been reported in some cases of severe thrombocytopenia (7). The reported incidence of thrombocytopenia is greater than 1% at the first exposure and more than 10% at the second exposure. Thrombocytopenia onset can take up to 8-10 days after the first dose of the drug, as in our patient (7, 8). The diagnosis of abciximab-induced thrombocytopenia should generally be considered after heparin-induced thrombocytopenia (HIT), pseudothrombocytopaenia, and disseminated intravascular coagulation (DIC) have been excluded (9). Since the immune response is drug-dependent, thrombocytopenia usually resolves after discontinuing the drug, removing the drug from the circulation and forming new platelets by the bone marrow (10). Treatment includes immediate discontinuation of the drug if the platelet count falls below 50 000/μL. Platelet transfusion should be considered if there is bleeding or if the platelet count falls below 20 000/μL. Although data on the efficacy of these supportive measures in acute situations is still lacking in severe thrombocytopenia cases, it may be reasonable to consider intravenous immunoglobulin (IVIg) and high-dose corticosteroids, as in our case (11).

Drug-induced thrombocytopenia is a severe condition that should be considered in the differential diagnosis of a patient with thrombocytopenia receiving drug therapy. It can be difficult to diagnose drug-induced thrombocytopenia, especially in its immune-mediated forms definitively. It was primarily diagnosed by excluding other causes of thrombocytopenia. The timing of thrombocytopenia is correlated with the administration of the high-risk drug (12). There are many case reports of thrombocytopenia in the literature after abciximab treatment (13). In this case, we aimed to present the development of severe acute thrombocytopenia caused by abciximab, its successful management, and treatment with discontinuation of abciximab. Therefore, patients who are given GP IIb/IIIa receptor blockers should be hospitalized and followed hematologically as these blockers may cause life-threatening adverse outcomes.

Informed consent

We obtained informed consent from all individual participants included in the study.

Conflict of interest

None to declare.

Acknowledgments

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Dasatinib: A rare cause of recurrent cardiac tamponade

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Abstract

Dasatinib is one of the second-generation tyrosine kinase inhibitors (TKI) that used as the first line for the treatment of Philadelphia chromosome (Ph) positive chronic myeloid leukemia (CML). Several cardiovascular side effects such as pleural-pericardial effusion, pulmonary hypertension, prolonged QTc interval, and platelet dysfunction have been reported. A 59-year-old female with worsening dyspnoea was diagnosed with cardiac tamponade twice in six months period after initiation of Dasatinib 100 mg per day for CML. She was successfully treated with drainage of effusion percutaneously and discontinuation of Dasatinib. Recurrent cardiac tamponade is a rare complication related to the use of Dasatinib. It should be kept in mind that Dasatinib is a potential agent for pericardial effusion, especially when other possibilities are excluded.

Keywords: dasatinib, recurrent cardiac tamponade, cardiac effects

1. Introduction

Dasatinib is one of the second-generation tyrosine kinase inhibitors (TKI) used for the treatment of Philadelphia chromosome (Ph) positive chronic myeloid leukemia (CML) by hematologists as a first-line treatment option. It also can be used when developing intolerance or resistance to other treatments in CML and Ph (+) acute lymphoblastic leukemia (ALL) (1). Its effectiveness is significantly higher compared to imatinib, the first generation of this group of drugs. It shows 325-fold more activity against the native BCR-ABL gene that is the target of the drug (1). However, in opposition to positive features, several cardiovascular side effects such as pleural-pericardial effusion, pulmonary hypertension, prolonged QTc interval, and platelet dysfunction are increasingly reported (2, 3).

Several clinical conditions can cause pericardial effusions, such as viral infections or other infections, metabolic diseases, reduced lymphatic drainage (congestive heart failure, cirrhosis, nephrotic syndrome), autoimmune diseases, cardiac injury, uremia, drug hypersensitivity, traumatic or idiopathic (5). In addition, pericardial effusion is common in malignant diseases. This could be as a result of the spreading of the primary disease or as a side effect of antineoplastic drugs or radiation therapy (4). Also, pericardial effusion may be the first manifestation of the disease. The patient could be presented with cardiac tamponade as a result of rapidly increasing pericardial effusion.

Here, we discussed a case that presented with a drug-associated recurrent cardiac tamponade who have treated with Dasatinib 100 mg per day for chronic myeloid leukemia.

2. Case Report

A 59-year-old female patient has been admitted cardiology outpatient clinic with several complaints such as shortness of breath, palpitations, and fatigue. It was learned from her medical history that she was treated with the diagnosis of cardiac tamponade in another cardiology clinic three months ago after the onset of similar symptoms and had been using colchicine dispert. She was treated with Nilotinib up to six months ago with the diagnosis of CML three years ago. Upon admission on physical examination, she was hemodynamically unstable and had the signs of cardiac tamponade, which are cold and sweaty extremities, pronounced jugular venous distention, reduced heart sounds, hypotension (blood pressure was 100/60mmHg), tachycardia (heart rate was 110/min) and abdominal tenderness. Electrical alternans with heart rate 100/min were revealed in electrocardiography (Fig. 1a). Laboratory data were as follows: white blood cell count 5.06 bin/uL (26.2% neutrophils and 62.9% lymphocytes); platelet count 166 bin/uL; haemoglobin 8.2 g/dl; creatinine 0.57 mg/dl; AST 19 U/lt; ALT 12 U/lt; total protein 5.5 gr/dl; albumin 3.41 g/dl; LDH:234 U/lt; CRP <3.14 mg/L and sedimentation 26 mm/h. The urinalysis was unremarkable. Echocardiography revealed large pericardial effusion which surrounds all around the heart, with the collapse of the right atrium and right ventricle occurring early diastole (Fig. 1b). Initial echocardiography-guided pericardiocentesis was performed, and approximately 1000 ml of fluid was percutaneously drained. The exudative nature of the fluid (fluid total protein 4.2 g/dl; fluid albumin 2.83 g/dl, serum-fluid albumin gradient 0.58; fluid LDH level 305 U/lt and serum-fluid LDH ratio 1.5)

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was revealed after pericardial fluid analysis.

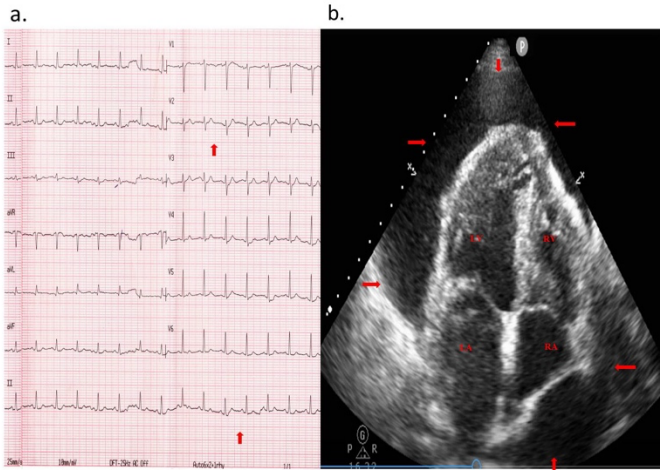

Fig 1: (a) The electrocardiography showing electrical alternans with sinus tachycardia (arrows indicate the alterne QRS waves). (**b)** Transthoracic echocardiography (apical four chamber view) showing the pericardial effusion (arrows indicate the fluid). **LV:** Left ventricle; **RV:** Right ventricle; **LA:** Left atrium; **RA:** Right atrium

It was learned from the first center that the effusion drained three months ago was also exudative. Etiological evaluations were made. There was no infection history or sign and no pathological findings were detected in thorax, abdomen and breast imaging in terms of malignancy. Cytological analysis of pericardial fluid was non-specific. The patient's symptoms began six months ago after changing Nilotinib therapy to 100 mg Dasatinib per day. As the etiology of pericardial effusion is unknown, we considered that there might have been a Dasatinib-associated pericardial effusion after literature research. (6-7). We directed the patient to hematology, and dasatinib therapy was replaced with Nilotinib again after BCR/ABL gene evaluation. The patient was discharged uneventfully with colchicine dispert therapy. Pericardial effusion was not repeated in the patient's three- and six-month follow-up after discontinuation of Dasatinib therapy.

3. Discussion

To the best of our knowledge, this is the first case report of recurrent cardiac tamponade as a complication associated with Dasatinib.

KML has transformed from a deadly disease into a controllable form with the treatment of BCR-ABL tyrosine kinase inhibitors. The first approved imatinib from this group was followed by many new generations such as Dasatinib, Nilotinib, Bosutinib, Ponatinib. Dasatinib, which is one of the new generation TKIs generally used cases in which imatinib treatment cannot be continued, is among the first-line treatment options due to its effectiveness (8). Cardiovascular effects have been investigated in detail in CML patients due to the significant effect on the success of treatment and overall survival. In this context, several cardiovascular effects, including pulmonary artery hypertension, congestive heart failure, pleural and pericardial effusion, QTc prolongation, and sudden cardiac death, have been reported related to Dasatinib (9).

The most common non-hematological adverse event in patients treated with Dasatinib is the occurrence of pleural effusions (7). Dasatinib-related pleural effusions are usually lymphocyte-dominant exudates. Concomitant pericardial effusion can be detected in 29% of cases (9, 10). The pathogenesis of effusions is still uncertain. However, the hypotheses focused on immune-mediated increased permeability and serositis due to Dasatinib which is not only tyrosine kinase but also a strong inhibitor of Src kinases and platelet-derived growth factor receptor β (PDGFR-β) (11). In previous studies, the presence of concomitant heart or lung diseases, hypertension, hypercholesterolemia, autoimmune diseases, skin rash related to treatment, and advanced age were identified as high-risk conditions for the development of effusions (12). Wattal et al. reported a case of a CML patient who received 100 mg Dasatinib daily, presented with pleural and pericardial effusion and regressed after Dasatinib treatment interruption (6). In a review of the 13 CML patients treated with 50 or 100 mg Dasatinib, Krauth et al. reported that four of the patients developed clinically significant pleural or pericardial effusion, and one of these patients had life-threatening massive pericardial effusion. (7). The treatment approach typically includes dose interruption or reduction, diuretics, short-term corticosteroid therapy, fluid drainage, and modification in CML maintenance therapy (13,14). In our case, we detected isolated cardiac tamponade, which we think is related to Dasatinib. As a result of continuing the drug, it was repeated twice within six months. However, no pericardial effusion occurred after the switching of the treatment.

As a complication of Dasatinib, cardiac tamponade, especially recurrent ones, is rarely seen. When other possibilities are excluded, it should be kept in mind that Dasatinib is a potential etiologic agent for pericardial effusion.

Conflict of interest

None to declare.

Acknowledgments

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Bispectral index

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Dear Editor,

We have read the article titled "Relationship between the national institutes health stroke scale score and bispectral index in patients with acute ischemic stroke" prepared by Özdemir et al. with great interest (1). We thank the authors and the editorial board for publishing this informative and successful manuscript. We also would like to mention a few important points about bispectral index.

Despite the modern methods and new drugs developed in surgery and anesthesia, anesthesia application and surgical intervention continue to be a stress factor for the human organism. These applications cause neuroendocrine response along with hemodynamic changes (2). These changes are largely dependent on stimulation of the sympathetic and adrenal systems. With the stimulation of this system, the level of catabolic hormones such as adrenaline, noradrenaline, and cortisol increases, while inhibition occurs in anabolic hormones such as insulin and testosterone (2). This stimulation and inhibition cause different clinical findings.

While fasting blood glucose and blood lactate levels increase in parallel with the increase in hemodynamic parameters, plasma levels of hormones such as adrenaline, noradrenaline and cortisol also increase. There are many factors that affect these results (2). The patient's age, weight, type and duration of the operation, position, experience of the surgery and anesthesia team, the tools and equipment used, the anesthesia method and the anesthetic drugs used are some of these factors (2).

Evaluation of depth of anesthesia in anesthesia induction and maintenance is an ongoing and highly complex problem (3). With the discovery that the brain generates electrical activity, the fact that anesthetic drugs alter electroencephalography (EEG) became evident (3, 4). For this reason, the interest in the use of EEG for anesthesia monitoring has increased and EEG has been recommended in many studies as a valuable method for determining the depth of anesthesia. BIS is an interpretation method that quantifies the degree of acute phase coupling among the components of the EEG signal, largely reflecting the cortical EEG (3, 4). Bispectral index monitoring, which enables the measurement of the sedative and hypnotic effects of anesthetic drugs on the central nervous system, is provided with the help of a sensor placed on the frontotemporal region (4, 5). In this way, neuroendocrine side effects of anesthetic drugs can be reduced by monitoring the depth of anesthesia (4, 5). As Özdemir et al. suggested in their study, a second area of use for the bispectral index could be the neurological monitoring of the patient under sedation (1). We believe that it will provide the opportunity to evaluate acute strokes, especially during major cardiovascular surgical procedures.

Conflict of interest

None to declare.

Acknowledgments

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Emergency services and health literacy

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Dear Editor,

According the current definition of the world health organization health literacy is the desire and capacity of people to form opinions and make decisions about health services throughout their lives, to access health-related information resources in order to protect, maintain, improve and improve their health, and to perceive health-related information and messages correctly (1).

The emergence of the heath literacy has been with the increase in the frequency of chronic and degenerative diseases such as cardiovascular diseases, cancers, chronic lung diseases, diabetes, while infectious diseases have lost their importance as the leading causes of death since the middle of the last century (2). In this case, it came to the fore that those who provide health services should develop services for these diseases (2, 3). However, the control of chronic and degenerative diseases is not as easy as the control of infectious diseases. While communicable diseases can be controlled by measures such as vaccination, timely and appropriate antibiotic treatment, and providing healthy drinking and potable water, different methods are required for the prevention and control of non-communicable diseases. Because, unlike communicable diseases, various factors have a role in the formation of non-communicable diseases (4). The factors that affect chronic diseases are the changes that occur in the organism due to advancing age, as well as genetic factors have a role in some diseases. Therefore, interventions for the control of non-communicable diseases must be multifaceted (4). Some of these factors require the improvement of the environment and services, while others require people to make changes in their health-related behaviors. In the formation of chronic and degenerative diseases, the health-related behaviors of people are of great importance (4). Failure to comply with the principles of healthy living, which can be summarized as healthy nutrition, active life and not smoking, poses a risk for the development of various chronic diseases (1). As the pandemic period reveals, people's behavior is important in the spread of infectious diseases. These behaviors can have consequences that affect not only the individual's own health, but also the public health, even the economy and social life (5).

The main thing in emergency service is to give this service to the most urgent as soon as possible. Application of non-emergency patients increases the emergency room crowd (6). Approximately 30% of the total hospital admissions in our country are emergency services (1). Although the crowdedness of the patients in the emergency services is relatively less in the hospital where the research was conducted in our country, this situation always emerges as a national and local health problem. It is known that this problem has both sociological (emergency concept perception in patients) and administrative and physical inadequacy reasons. In addition, non-urgent emergency applications exacerbate this problem. The tendency of those who applied to the emergency service to think about their own situation as an emergency, to use the emergency room as an outpatient clinic because all examinations can be done in the same day in the emergency services and fast results can be obtained, has been shown in the studies conducted on this subject (6). On the other hand, it is a separate public health problem that patients try to solve their chronic diseases in the emergency department due to the ease of access (7). These patients cannot be followed up regularly and cannot reach quality health care. For health problems that require further examination, such as rectal bleeding, repeated admissions to the emergency room instead of the relevant health unit cause a delay in the diagnosis. These delayed diagnoses can cause mortality and morbidity from time to time (1, 3).

Misuse and abuse of emergency services is a common problem in our country. As authors, we think that the increase in the level of health literacy may prevent this misuse and abuse.

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Conflict of interest

None to declare.

Acknowledgments

None to declare.

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Letter to the Editor

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A rare early complication of cesarean myomectomy: Uterine rupture

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1. Introduction

A 35-year-old female patient presented to our clinic complaining about abdominal pain with increasing severity in the last 1 day. Her anamnesis revealed that she gave birth to a healthy boy through cesarean section 11 days ago (gravida 1, para 1). The indication for cesarean section was a uterine myoma 6 cm in diameter and she also underwent myomectomy during the same session. In her physical examination, she had generalized tenderness, guarding and rebound in her abdomen. In her laboratory findings, haemoglobin was 11.6 g/dL, leukocytes 15,200/mm^3 and C-reactive protein 149 mg/L. The erect abdominal radiograph was normal and, no pathologies were seen in her ultrasound other than free abdominal fluid. Abdominal tomography revealed minimal free air around the liver and spleen (Fig. 1A and 1B), fluid in the abdomen and a suspicious perforated area on the anterior surface of the duodenum (Fig. 1C). With a prediagnosis of acute abdomen, a nasogastric catheter was placed and an access to the abdomen was gained through a upper midline incision. During exploration, seropurulent fluid and fibrins were seen in the abdomen. No pathologies were found in the stomach, duodenum, or small and large intestines. The gastrocolic ligament was opened and, an access was made to the bursa omentalis.

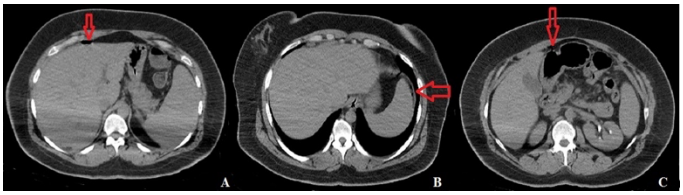

Fig. 1. **a)** Abdominal tomography; minimal free air around the liver on the horizontal plane, **b)** Minimal free air around the spleen, **c)** Suspicious perforated area on the anterior surface of the duodenum

Approximately 300 ml of methylene blue was administered from the nasogastric catheter and no leakage from the gastrointestinal system was seen. The uterus, uterine tubes and ovaries were examined. A perforated area approximately 2 x 1 cm in size involving the endometrium with no active bleeding was detected in the left-lateral side of the isthmus of uterus where the myomectomy had been administered (Fig. 2). The area was debrided and the myometrium and serosa were sutured in two separate layers with 0 polyglactin sutures. The abdominal cavity was washed with normal saline. After a drain was inserted into the Douglas cavity, the operation was completed. The patient was discharged without complications and she was asymptomatic after 6 months of follow-up.

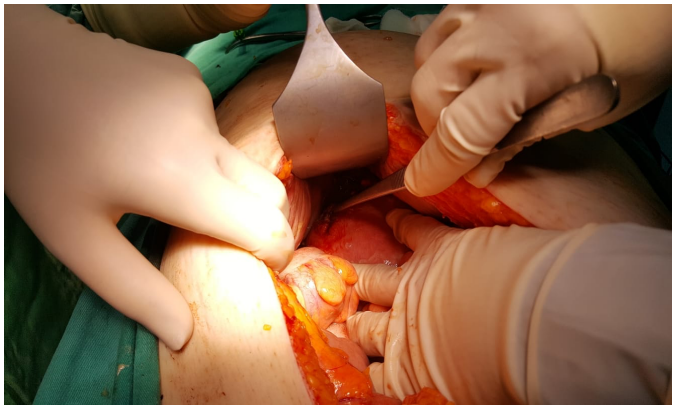

Fig. 2. Image of the ruptured area on the left-lateral side of the perioperative uterine isthmus

Cesarean myomectomy (CM) is defined as resection of the anterior wall, subserous and pedunculated myomas in the uterus during a cesarean section procedure. The frequency of CM procedures has increased recently because the incidence of myoma in pregnancies is high, ranging from 1.6% to 10.7%, the management of haemorrhage in the pregnant uterus is better due to contractions and puerperal involution, and myomectomy is technically easier on a pregnant uterus (1). CM provides these patients with symptom relief and improved quality of life, and eliminates myoma-induced complication risk in the puerperium and subsequent pregnancies. Although CM allows two surgeries with a single incision avoiding the risk of repeated anaesthesia and relaparotomy, it still involves

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high rates of serious early and late complications such as major haemorrhage, uterine rupture, adhesion formation between uterus and neighbouring tissues, and even the risk of maternal death (2).

Uterine rupture (UR) is a rare but dangerous complication requiring full-thickness separation of the uterine wall and the overlying serosa and involving severe maternal and neonatal morbidity and mortality. UR may develop due to splitting of a suture caused by a technical issue in an early period after CM, it may also occur at the scar site of the myometrium in pregnancies occurring many years after CM. The signs and symptoms of UR are usually nonspecific and include sudden onset abdominal pain, intra-abdominal bleeding, hypovolemic shock, fetal distress, protrusion of the fetus or placenta in the abdominal cavity, and atony of the uterus (3). To avoid delay in diagnosis and treatment, UR should always be taken into consideration and the patient should be assessed with abdominal ultrasound, a fast and correct method for UR. A primary repair of the UR site with emergency laparotomy is usually a satisfactory treatment.

The management of myomas during cesarean section is still a controversial issue today due to serious complications such as UR. Being a high-risk surgical procedure, CM should be attempted only for selected cases and by experienced surgeons.

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Letter to Editor

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Novel coronavirus infection and rhabdomyolysis

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Dear editor,

First novel coronavirus infection was seen in Wuhan, China at the end of 2019, as pneumonia cases of unknown etiology. This new type of virus was defined as a new type of coronavirus (2019-nCoV) that has not been seen in humans before on January 7, 2020 (1). Later, the name of the 2019-nCoV disease was named as Coronavirus Disease-2019 (COVID-19), and the virus was named as SARS-CoV-2 due to its close resemblance to the Coronavirus (SARS CoV) related to Severe Acute Respiratory Syndrome (2). The first detected case of the COVID-19 epidemic in Turkey, which has spread around the world, was announced by the Ministry of Health on 11 March. The first death due to the virus in Turkey took place on March 15, 2020 (3).

Rhabdomyolysis is the release of toxic muscle contents into the circulation because of damage to striated muscles due to traumatic or non-traumatic causes and destruction of muscle tissue. Rhabdomyolysis was first described in the 1940s in patients exposed to trauma in the form of crushing under destroyed houses during the war. Toxic substances can cause crush syndrome and acute renal failure, which is one of the most important clinical problems related to this condition (4). Rhabdomyolysis is a clinical and biochemical syndrome caused by acute necrosis of skeletal muscle fibers and leakage of cellular contents into the circulation. In general, the most common causes of rhabdomyolysis include alcohol and substance use, drugs, muscle diseases, trauma, disasters, neuroleptic malignant syndrome, seizures, immobility, infection, heavy physical activity, myositis, and heat-related diseases (5). The blood creatine kinase (CK) value is a significant test for the diagnosis of rhabdomyolysis. Serum CK levels begin to increase 2-12 hours after kidney injury, peak in 1-3 days, and then decrease within 3-5 days. A five-fold increase in serum CK is sufficient for the diagnosis of rhabdomyolysis (6).

Influenza A virus subtype is associated with several viruses, including H1N1 and SARS-CoV-1. It has been reported in the literature that some patients with severe acute respiratory syndrome or H1N1 infection show mild to moderate increases in serum CK levels (7). Similarly, in many case reports in the literature, a case of SARS-CoV-2 associated rhabdomyolysis has been reported (8). Haroun et al. showed that rhabdomyolysis is associated with increased mortality in patients with COVID-19 (9). Gang et al. reported that rhabdomyolysis was associated with in-hospital mortality in their study in hospitalized patients (10). The mechanism of muscle damage in viral infections, especially SARS-CoV-2, is not fully understood. Possible explanations suggested including direct and indirect mechanisms. The most important possible explanation is that the virus directly causes muscle damage. The presence of angiotensin converting enzyme 2, which is defined as the functional receptor for SARS-CoV and SARS-CoV-2, in skeletal muscles is one of the data supporting this theory in the literature (11). However, in postmortem examinations SARS-CoV was not detectable in skeletal muscle, and it is therefore unclear whether SARS-CoV-2 directly infects muscle (12) The second plausible explanation postulates that the cytokine storm-like immune response may lead to skeletal muscle damage (13). The muscle pain seen in patients during viremia and the accompanying high CK levels support the first explanation. Late rhabdomyolysis seen in hospitalized patients support the second explanation.

As a result, rhabdomyolysis can be seen in SARS-CoV-2 infected patients and the mechanism is not clear. Researchers should do new research on this subject and the mechanism should be clearly revealed.

Conflict of interest
None to declare.

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None to declare.

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Letter to Editor

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Ideal predictor studies

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Dear Editor,

We have read the article titled "Evaluation of Covid-19 cases that applied to the hospital at the first peak of the pandemic" prepared by Akdoğan et al. with great interest (1). Firstly, we thank the authors for their research from Turkey that aims create an alternative diagnosis method by using some laboratory parameters in the early phase of COVID-19. Although the study bore negative findings, these studies by academics from Turkey for humanity at a time when the whole world was affected by the pandemic are commendable. Secondly, we thank the authors and the editorial board for their courage in publishing this informative and successful article with negative findings. As mentioned in an article published in Nature, highlighting negative results will improve science (2). We also would like to mention a few important points about ideal predictor studies in the early phase of COVID-19.

COVID 19 is affecting economies, social life, and health systems around the world. It significantly increases the burden on the health system. It is difficult for patients to access medical support at peak periods (3). Various scoring systems and laboratory parameters were studied to determine the priorities of the patients and the severity of the disease (4). The importance of triage practice, used to determine the priority of patients in emergency services, has increased. Research were done on the ideal early warning score for patients with symptoms of COVID-19. Rapid Emergency Medicine, National early warning, Rapid Acute Physiology, and Modified early warning scores are the most studied early warning scores for COVID-19 in literature (5-7). Even vital parameters were combined with laboratory parameters such as lactate in patients with COVID-19-like symptoms to approach the ideal early warning score (8). On the other hand, scoring systems such as Pneumonia Severity Index, CURB, and CURB-65, used in pneumonia and critical patients, were validated against COVID-19 to use scarce resources effectively (9). Many authors, such as Akdoğan et al., research laboratory parameters to detect critical diseases in the early phase of the COVID-19 pandemic (1,10-12). Hematological parameters were the leading ones because they were cheap and easily accessible (11,12). Lymphocyte count, C-reactive protein, D-dimer, ferritin were associated with mortality and critical illness. These parameters were used to decide on hospitalization and admission to the intensive care unit (1,10-12). Weng et al., similar to Akdogan et al., developed the ANDC score by aiming for a quantitative tool for early predicting mortality risk of patients with COVID-19 in the early phase of the pandemic. This score, developed with mathematical and statistical calculations, was calculated with the formula (1.14 × age – 20) (years) + 1.63 × neutrophil/lymphocyte ratio + 5.00 × D-dimer (mg/L) + 0.14 × C-reactive protein (mg/L) (13). Bilge et al. confirmed in their study that ANDC is an independent biomarker (14).

As a result, the effort of researchers to reach the ideal predictor in patients with COVID-19 continues. The ideal predictor should be inexpensive, accessible, and best predictive of COVID-19-related mortality.

Conflict of interest

None to declare.

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None to declare.

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GUIDE FOR AUTHORS

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Manuscripts should be prepared electronically using an appropriate MS Word compatible word-processing package, formatted for A4 or letter page size, double-spaced throughout with 2.5 cm margins on all sides, and using Times New Roman, 12-point font. Text should not be justified, but flush left. Words should not be hyphenated to fit on a line. Pages should be numbered sequentially.

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Author acknowledgments should be written in the third person ("The authors wish to thank...") and written permission should be obtained from all individuals who are listed in the Acknowledgments section of the manuscript.

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Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002, p. 93-113.

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Web page:

Atherton, J. Behaviour modification [Internet]. 2010 [updated 2010 Feb 10; cited 2010 Apr 10]. Available from: http://www.learningandteaching.info/learning/behaviour_mod.htm.

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