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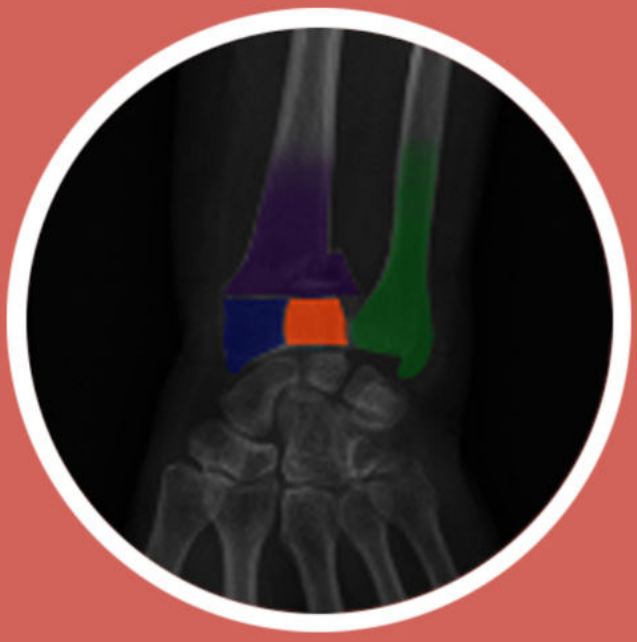

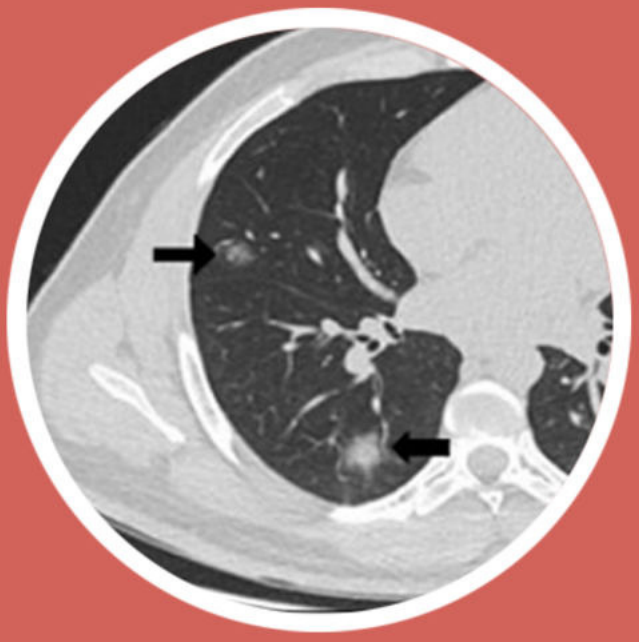

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Original Articles

The European Research Journal 2022;8(2):145-154 Original Article

DOI: 10.18621/eurj.894631 *Medical Genetics*

The road from mutation to next generation phenotyping: contribution of deep learning technology (Face2Gene) to diagnosis neurofibromatosis type 1

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ABSTRACT

Objectives: Genetics is one of the fastest growing medical fields in the last 10 years. While new analysis methods such as Next Generation Sequencing have been developed, the use of artificial intelligence like Face2Gene in this field has also been developed. The aim of this study is to evaluate the clinical, genetic and dysmorphic findings of Neurofibromatosis type 1 (NF1) patients, a disease of the RASopathy group. At the same time, another aim of this study is to evaluate and compare with other RASopathies diseases the success of Face2Gene application which is one of the NGP technologies, in this group of diseases.

Methods: This study is a retrospective archive scan. Fourteen patients from 3 different patient groups were selected for the study. Face2Gene analysis was performed for these groups. Detailed clinical, genetic and dysmorphic findings of NF1 patients were also examined.

Results: As a result of the genetic analysis of NF1 patients, one patient had novel mutation. The most detected mutation type is nonsense mutation (42.8%). The most common finding in magnetic resonance imaging was hamartoma (29%). Face2Gene suggested that NF1 in top-3 for 10 of 14 NF1 patients. Additionally, at the comparison of NF1 patients and non-NF1 RASopathies patients resulted as AUC was 0.749 and p value was 0.134.

Conclusions: Considering the developments in technology in the last 10 years, it is thought that artificial intelligence applications such as Face2Gene will be used a lot in the routines of medical doctors in the next 10 years.

Keywords: Neurofibromatosis 1, cafe-au-lait spots, deep learning, artificial intelligence

Human facial features are an important part of identity. The face was seen as an important part of the body. We recognize and define ourselves and others with facial features. However, in some cases the facial features are quite different from the "normal" facial features and these are very conspicuous. This situation has led to the rise of the "Dysmorphology" field. Dysmorphology refers as "birth defects and result from malformations, deformations, or disruptions, which generally have a significant and obvious effect on appearance" [1].

Dysmorphology has been curious and fantastic field since prehistoric times. The best examples of this are Tumaco-La Tolita Figurine in Colombia and

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Ecuador showing the characteristic facial features of Down syndrome [2]. Additionally, in the literature, characters with dysmorphic features have gave inspire to the authors like Quasimodo in Victor Hugo's novel The Hunchback of Notre-Dame. In this novel, Quasimodo represents Neurofibromatosis type 1 (NF1) patient [3].

Presenting a disease-causing mutation to the phenotype is the greatest aid to clinical geneticists in diagnosis. 30-40% genetic disorders have characteristic and distinct facial features. [4]. The importance of dysmorphology has increased in recent years with the development of new computer-based databanks (London Dysmorphology Database, Pictures of Standard Syndromes and Undiagnosed Malformations Database, Online Mendelian Inheritance in Man, etc.). With use these databases, the success of the prediagnosis is increasing with dysmorphic and physical examination findings [5]. One of these databases developed in recent years is the Face2Gene (FDNA Inc, Boston, USA) application. Face2Gene is one of the best examples of the next-generation phenotyping (NGP). This application is developed using computer vision and deep learning algorithms on the basis of Deep Gestalt technology [6]. This technology provides a community-driven phenotyping trained on thousands of patient images and used to analyze hundreds of syndromes. It also provides an analysis based on the clinical findings of the patients (Feature Match). In recent studies, the success rate of Face2Gene for the correct syndrome has been reported to be 86-91% in the top 10 recommendation disease list [7, 8]. In this study, we considered both types of analysis and included an in-silico analysis in which photos of our research group were compared with 2 control groups.

One of the disease groups with dysmorphic facial features is RASopathies. The common features of this group of diseases are developmental delay, congenital heart disease, dysmorphic facial features and various degrees of intellectual disability. This is caused by germline mutations in genes encoding components or regulators of RAS / MAPK (mitogen activated protein kinase) signaling pathway that lead to dysregulation of cell signal transmission. The diseases of the RASopathies group include neurofibromatosis type 1, Noonan syndrome, Noonan syndrome with multiple lentigines, Leopard syndrome, hereditary gingival fibromatosis type 1, capillary malformation–arteriovenous malformation syndrome, Costello syndrome, cardio-facio-cutaneous syndrome, and Legius syndrome [9].

Neurofibromatosis type 1 (NF1) is a syndrome in group of RASopathies is one of the most common Mendelian diseases. It was first described in 1882 by Friedrich Danie Von Recklinghausen as a case report. Therefore, the other name of the disease is Von Recklinghausen disease. The incidence of disease is approximately 1 in 2600 to 3000 individuals [10]. The disease is inherited as autosomal dominant. Half of the affected individuals (50%) had a de novo mutation in NF1 gene. NF1 syndrome is caused by mutations in the NF1 gene [11]. Genetic variants caused for the disease are mostly mutations that cause truncated protein production (complete gene deletions, insertions, stop, and splicing mutations) [12]. NF1 clinical symptoms and signs are caf´e-au-lait maculae, skin fold freckling, neurofibromas and plexiform neurofibromas, iris Lisch nodules, scoliosis, dysplasia of the long bone or sphenoid, optic pathway glioma, cardiac malformations, cardiovascular disease, vasculopathy, hypertension, and seizures. This syndrome also causes dysmorphic craniofacial features, mild intellectual disability, and a predisposition to developing some malignancies. Dysmorphic facial features are telecanthus, down-slanting palpebral fissures, eversion lower lateral eyelid fissures, large nose, high broad nasal bridge, thick ears helices, small and pointed chin. Diagnosis is provided with the presence of 2 of the disease suggestion criteria's. Suggestion criterias are (1) cafe´-au-lait spots (six or more and > 5 mm in greatest diameter in prepubertal individuals and > 15 mm in greatest diameter in postpubertal), (2) skin freckling (axillary or inguinal regions), (3) Lisch nodules (Two or more), (4) neurofibromas (two or more any type or one plexiform), (5) optic gliomas, (6) distinctive bony lesions, and (7) a first-degree family relative with NF1 [13]. Genetic diagnosis of NF1 is made by sequence analysis and gene-targeted deletion / duplication analysis in NF1 gene [14].

The aim of this study was to evaluate the clinical presentation of NF1 syndrome which is the one of common Mendelian disease and to present it to the literature. At the same time, another aim of this study is to evaluate and compare with other RASopathies diseases the success of Face2Gene application which is one of the NGP technologies, in this group of diseases.

METHODS

This study was planned as a retrospective study. The files of the patients who applied to Medical Genetics Department of Afyonkarahisar Health Science University between 2012 and 2020 were re-reviewed. Patients included in the study were divided into 3 groups. Group 1 consist with patients have pre-diagnose as NF1 disease and detected mutation in the NF1 gene by molecular genetic analysis. The patients included in Group 2 have clinically diagnosed as RASopathies except NF1. Group 3 patients have Down syndrome. Inclusion and exclusion criterias for patients were determined as in Table 1. Consent was obtained from all patients.

Selected 14 patients for all 3 groups (Total count 42). The photos and relevant clinical features were uploaded to Face2Gene. In the suggestion list presented by the application, the presence of NF1 and non-NF1 RASopathy group diseases was annotated for Group 1 and Group 2. We also looked how the correct diagnosis is ranked by both types of analysis, DeepGestalt and Feature match. In addition, the RESEARCH application of Face2Gene was used to understand whether the tool can recognize the group of patients from control groups [15]. In a series of filtrations, we compared our test group to 2 different control groups - a cohort comprised of frontal facial photos of Down

Table 1. Inclusion and exclusion criterias for study

Group 1	
Inclusion Criterias	**Exclusion Criterias**
•Patient consulted to the Afyonkarahisar Health Science University, Medical Genetics Department between 2012-2019	•Patient has not consulted to the Afyonkarahisar Health Science University, Medical Genetics Department
•Patients that have symptoms and signs for NF1 disease.	•Patients that do not have symptoms and signs for NF1 diseases
•Patients that have mutation in NF1 gene that detected by molecular genetics analysis.	•Patients do not have mutation in NF1 gene that detected by molecular genetics analysis or have not any genetics results.
•In patient files, having at least one frontal facial picture for analyzing in Face2Gene application	•Patient does not have enough pictures for analyzing in Face2Gene application
Group 2	
Inclusion Criterias	**Exclusion Criterias**
•Patient consulted to the Afyonkarahisar Health Science University, Medical Genetics Department between 2012-2019	•Patient that were not consulted to Afyonkarahisar Health Science University, Medical Genetics Department
•Patients were clinically diagnosed as one of RASopathies diseases except NF1 (non-NF1 RASopathies)	
•In patient files, having at least one frontal facial picture for analyzing in Face2Gene application	•Patients that do not have enough pictures for analyzing in Face2Gene application
Group 3	
Inclusion Criterias	**Exclusion Criterias**
•Patients that were consulted to the Afyonkarahisar Health Science University, Medical Genetics Department between 2012-2019	•Patients that were consulted to the Afyonkarahisar Health Science University, Medical Genetics Department
•Patients that received diagnosis based on G-banding karyotyping result as Down Syndrome.	•Patients that did not receive diagnosis based on G-banding karyotyping result as Down Syndrome.
•In patient files, having at least one frontal facial picture for analyzing in Face2Gene application	•Patients that do not have enough pictures for analyzing in Face2Gene application

syndrome patients (Group 3) and a cohort comprised of photos of unaffected cohort, of the same sex and age distribution.

In the NF1 disease the distinctive findings which are cafe´-au-lait spots, Lisch nodules, neurofibromas, optic gliomas, bony lesions and family history are re-evaluated for Group 1 patients. For this reason, presenting symptoms, pedigree and MRI findings of patients were reached from hospital records. In addition, from the photos of Group 1 patients, the dysmorphic facial features were detected. In this process, The Elements of Morphology: Human Malformation Terminology was used [16].

The aim of this study is to evaluate the power of DeepGestalt algorithm that is one of the NGPs, to estimate NF1. We studied that this application could guide for medical geneticists in this group of diseases. We also aimed to present the clinical findings of patients with definite diagnosis NF1 to the literature.
This study approved by Afyonkarahisar Health Sciences University Ethic committee.

Statistical Analysis

Collected data were analyzed by Statistical Package for Social Sciences version 18.0 (SPSS Inc., SPSS IBM, Armonk, NY, USA). Continuous data were expressed as mean ± standard deviation (range: minimum-maximum) whereas categorical data were denoted as numbers or percentages where appropriate. Chi-square test was used for the statistical comparisons. Two-tailed *p* values less than 0.05 were accepted to be statistically significant.

RESULTS

The in forms of mutation in the NF1 gene and pedigrees of patients are presented in Table 2. In this study, 2 (14.2%) of 14 patients are female. According from pedigree analysis of patients, only one patient (Case 12) has de novo mutation. Other 13 patients have another affected family member in their family. In this cohort the rate of de novo mutation is 7.14%. Case 5 - 6 are uncle and nephew, Case 10 - 11 are siblings and Case 12 - 13 are mother and son. Two patients have intronic mutation, one of these is non-coding mutation (Case 3) and the other is splicing mutation (Case 7). Other 12 patients have mutation in

Table 2. Genetics and demographic informs in Group 1 patients

MODE OF TRANSMISSION	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	De novo	Autosomal dominant	Autosomal dominant
IS THERE ANOTHER AFFECTED INDIVIDUAL?	Son, brother, mother	Aunt	Father	Mother, sister	Father, grandfather, uncle	Father, brother, 2 offsprings, 2 son of brother	2 daughter, 2 maternal uncle	1 daughter, 1 son and maternal grandmother	2 brother, mother, maternal uncle, maternal grandmother	2 brother, father, paternal grandmother	2 brother, father, paternal grandmother	1 sibling	Mother	Father, paternal uncle, paternal grandmother
ZYGOSITY	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous	Heterozygous
MUTATION (S) ACMG CLASSIFICATION	Pathogenic	Pathogenic	Uncertain Significance	Pathogenic	Heterozygous	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Pathogenic	Novel mutation
TYPE	Nonsense	Missense	Non-coding	Nonsense	Nonsense	Nonsense	Splicing	Nonsense	Nonsense	Frameshift	Frameshift	Frameshift	Frameshift	Frameshift
EXON / INTRON NUMBER	Exon 35	Exon 21	Intron 22	Exon 47	Exon 9	Exon 9	Intron 12	Exon 30	Exon 45	Exon 2	Exon 2	Exon 14	Exon 14	Exon 23
ALTERATION	NF1 c.4537 C>T p.Arg1513X	NF1 c.2531 T>G p.L844R	NF1 c.2990+5 G>A	NF1 c.6955 C>T p.Q2319*	NF1 c.910 C>T p.R304*	NF1 c.910 C>T p.R304*	NF1 c.1392+1G>T	NF1 c.4084C>T p.R1362*	NF1 c.6772C>T p.R2258*	NF1 c.109_110delGA p.Glu37Alafs*29	NF1 c.109_110delGA p.Glu37Alafs*29	NF1 c.1541_1542 delAG p.Q514Rfs*43	NF1 c.1541_1542 delAG p.Q514Rfs*43	NF1 c.3011_3011 delA p.N1004Ifs*8
AGE AT TESTING (YEARS)	37	23	27	40	10	32	29	48	8	22	16	36	6	2
DATE OF BIRTH (YEAR)	1978	1992	1992	1979	2006	1985	1987	1971	2007	1993	1999	1980	2010	2014
CASE ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14

Table 3. Clinical, dysmorphic and radiological findings of Group1 patients

CASE ID	PRESENTING SYMPTOMS	DYSMORPHIC FEATURES	MRI FINDINGS
1	Multiple cafe au lait spots, neurofibromas, lisch nodules	Prominent supraorbital ridges, cheekbones prominence, deeply set eyes, prominent antihelix stems, protruding ears, macrotia, low insertion columella	Nonspecific hyperintense signal in T2-FLAIR A sequences which is oval configuration measured as 7x5 mm in the right frontal white matter at the centrum semiovale level, L2-S1 vertebra perineural cyst
2	Multiple cafe au lait spots, neurofibromas, unilateral hearing loss	Long face, broad forehead, deeply set eyes, broad eyebrows, thick eyebrows, long palpebral fissures, prominent antitragus, long ears, narrow nasal bridge, fullness paranasal tissue, deep philtrum, exaggerated Cupid's Bow	Pontocerebellar arachnoid cyst, mega cisterna magna, right cerebellar hamartoma
3	Multiple cafe au lait spots	Long face, cheekbones prominence, broad chin, deeply set eyes, narrow nasal ridge, deep philtrum, exaggerated Cupid's Bow, thin lower lip vermilion	N/A
4	Multiple cafe au lait spots, neurofibromas	Long face, malar flattening, prominent nasolabial fold, broad chin, deeply set eyes, thick eyebrows, telecanthus, enlarged nares, wide nasal base, wide nasal bridge, deep philtrum, exaggerated Cupid's Bow, thin lower lip vermilion	Normal
5	Multiple cafe au lait spots, seizure, neurdevelopmental delay, lisch nodules	Malar flattening, thick eyebrows, telecanthus, thick ala nasis, bulbose nose, long philtrum, thick lower lip vermilion, thick upper lip vermilion	Arachnoid cysts, cavum septum pellucidum et vergae
6	Multiple cafe au lait spots, neurofibromas	Long face, narrow face, prominence cheekbone, tall chin, thick eyebrows, low hanging columella, wide nasal base, thick upper lip vermilion, thick lower lip vermilion	N/A
7	Multiple cafe au lait spots, neurofibromas	Brachycephaly, frontal balding, long face, prominence cheekbones, long chin, deeply set eyes, hypotelorism, sparse eyebrow, prominent antitragus, thick ala nasi, low insertion columella, narrow nasal bridge, smooth philtrum	Cerebellar hamartoma, neurofibromas
8	Multiple cafe au lait spots, neurofibromas, sarcoma excision from arm	Long face, cheekbones prominence, malar flattening, broad chin, tall chin, deeply set eyes, downslanted palpebral fissures, high insertion columella, malaligned philtral ridges	Triceps muscle sarcoma, bladder mesenchymal sarcoma
9	Multiple cafe au lait spots, ataxic gait	Malar prominence, deeply set eyes, sparse eyebrows, infraorbital creases, upslanted palpebral fissures, ptosis, thick ala nasi, wide nasal bridge, wide nasal ridge, deep philtrum, exaggerated Cupid's Bow	Hamartomas in superficial and deep white matter, periventricular white matter, left cerebellar hemisphere, corpus callosum, bilateral globus pallidus
10	Multiple cafe au lait spots, neurofibromas	Full cheeks, midface prominence, tall chin, downslanted palpebral fissures, wide nasal base, thick lower vermilion	Normal
11	Multiple cafe au lait spots, neurofibromas	Triangular face, full cheeks, midface prominence, pointed chin, downslanted palpebral fissures, wide nasal base, thick lower vermilion	N/A
12	Multiple cafe au lait spots	Broad chin, tall chin, smooth philtrum, thin lower lip vermilion	Normal
13	Multiple cafe au lait spots, short stature	Midface prominence, pointed chin, tall chin, wide spaced eyes, upslanted palpebral fissures, telecanthus, overfolded helix, narrow nasal ridge, exaggerated Cupid's Bow	Hamartomas in brain stem, cerebellar hemisphere and cerebral hemispheres, thickening of optic nerve
14	Multiple cafe au lait spots, developmental delay	Broad forehead, short chin, prominent antihelix stem, serpenginous antihelix stem, wide nasal base, wide mouth	Normal

exon. The most detected mutation is nonsense that has 6 patients. Five mutations are occurred as frameshift. One of these is a novel mutation (Case 14). In this study, there is only one missense mutation. Twelve patients of 14 have pathogenic mutations which are according to American College of Medical Genetics (ACMG) classification of mutations. One patient has "uncertain significance" variant. The range of age that patient have definitive diagnosis is between 2-48.

All of NF1 patients have consulted cause of multiple cafe au lait spots. Other presenting symptoms are neurofibromas, lisch nodules, neurodevelopmental delay, unilateral hearing loss, ataxic gait, short stature, seizure respectively. The most seen dysmorphic facial feature is both long face and deeply set eyes (42.8%). The second is both exaggerated Cupid's Bow and tall chin (35.7%) and the third is thick eyebrows (28.5%). 3 patients didn't have any MRI. Four of 14 patients have hamartomas or hamartoma like image at brain MRI. Also 4 patients had "Normal" MRI. The patient who had pontocerebellar arachnoid cyst (Case 2) that's maybe why he had unilateral hearing loss and he was the only patient who have missense mutation in this study. At the same time Case 2, Case 7 and Case 13 had cerebellar hamartoma but he didn't have any cerebellar sign. Only one patient (Case 13) had thickening of optic nerve. The patient who had novel mutation in NF1 gene had developmental delay but he had normal MRI. All these informs are in Table 3.

The frontal facial photographs of each 14 NF1, Down syndrome and non-NF1 RASopathy patients were uploaded to Face2Gene application. The composite photos of each group are shown in picture 1. The application also provides binary comparisons. According to application, the success of NF1 and 2 other disease groups (Down syndrome and non-NF1 RASopathies) of diagnosis was compared. In addition, 14 unaffected control cases were compared with NF1 patients. According to the binary comparison between NF1 and Down syndrome patients, area under the curve (AUC) value was calculated as 0.965 and p value 0.007. At the comparison of NF1 patients and non-NF1 RASopathies patients resulted as AUC was 0.749 and p value was 0.134. Also, at the comparison of 14 unaffected control cases and NF1 patients, AUC was calculated as 0.932 and p value as 0.032. When compared with Down syndrome and unaffected controls, AUC was 0.989 and p value was 0.000. In comparison of NF1 patients and 3 other groups, AUC resulted as 0.855 and p value as 0.034. The Receiver operating characteristic (ROC) curve of these calculations is shown in picture 2.

At the final of analysis Face2Gene application provides a list which 30 possible diseases for diagnosis. This list is presented depend on Gestalt Score and Feature Score. Accordingly, Gestalt Score is a number obtained according to the analysis of patients' photographs. Feature Score is the other number obtained by entering the clinical findings of the patients. Combined Score is calculated according to these two scores. For 14 patients with NF1, rank of NF1 disease at suggested syndromes list by the application, Gestalt score, Feature score and combined score are presented in Table 4. In addition, these scores and the rank for non-NF1 RASopathies diseases in the suggestion list which recommended by the application for these 14 patients are presented in Table 4. The application suggested this disease in top-3 for 10 of 14 NF1 patients. For 5 patients, non-NF1 RASopathies diseases were suggested at higher rankings than NF1 disease.

DISCUSSION

In this study, we presented genotype and phenotype findings of NF1 patients. According to aim of the study, success of new approach for phenotyping like DeepGestalt (Face2Gene application) technology evaluated. This new generation genetics disease diagnosis techniques may use in routinely at clinical practice for medical genetics doctors.

For autosomal dominant disorders, de novo mutations which is mean an alteration in a gene that is present for the first time in one family member, have high rate [17]. NF1 is one of in this group disease. Almost half of NF1 disease occurs as de novo [18]. In this study, we could not do segregation analysis. But according to pedigree analysis de novo mutation rate found as 7.14%. Possible cause of this condition may be the fitness of NF1 disease is high.

The mutation type is one of elements that are benefited for classification of mutation. That's why, when genotyping, mutation type is one of important stage. Mutation type rates in NF1 gene are reported as for nonsense mutation is between 21%-38% [19, 20]. According to ClinVar genetic database, 407 of 6254 vari-

ants are reported as nonsense. In this study, nonsense mutations rate was 42.8%. Additionally, second most detected mutation type in this study is frameshift mutation (35.7%). In the literature, frameshift mutation rate is reported between 47%-26% [19, 21]. The missense mutation rate in the NF1 gene has been reported as between 60 and 12% [19, 22, 23]. In our study, the rate of this mutation type is lowest one (7%). The rate of mutations occurring in the intronic region of the NF1 gene, which constitute regions of gene that are not translated to protein, has been reported to be 43-20% [21, 23]. In this study, the intronic mutation rate was found as 14%. Considering that variants that cause NF1 disease may occur not only in exons but

Table 4. Face2Gene analysis results of patients with NF1

	NF1 Scores					NON-NF1 RASopathy Scores				
CASE ID	Face2Gene Detected NF1	Rank at Suggested Syndromes List	Gestalt Score	Feature Score	Combined Score	Face2Gene Detected Non-NF1 RASopathies Disease	Rank at Suggested Syndromes List	Gestalt Score	Feature Score	Combined Score
P1	+	1	0.140658	1	0.58	Noonan Syndrome	3	0.17825	0.5	0.26
P2	+	1	0.24933	0.56	0.56	LEOPARD Syndrome	2	0.171426	0.73	0.33
P3	+	3	0.200005	0.84	0.29	LEOPARD Syndrome	8	0.0931721	1	0.11
P4	+	2	0.246332	0.75	0.33	Noonan Syndrome	1	0.26077	0.45	0.51
P5	+	2	0.095214	1	0.3	Noonan Syndrome	1	0.139438	0.5	0.51
P6	+	3	0.184519	0.75	0.21	Legius Syndrome	5	0	0.87	0.17
P7	+	1	0.690764	0.99	0.57	LEOPARD Syndrome	3	0.355832	1	0.21
P8	+	1	0.272886	0.8	0.58	Noonan Syndrome	3	0.236196	0.55	0.18
P9	+	6	0.107819	0.55	0.14	LEOPARD Syndrome	7	0.050874	0.92	0.13
P10	+	4	0.169717	0.75	0.17	Noonan Syndrome	1	0.247422	0.45	0.51
P11	+	6	0.143984	0.75	0.15	Noonan Syndrome	1	0.209742	0.45	0.51
P12	+	1	0.0717643	1	0.6	LEOPARD Syndrome	4	0.0586419	1	0.22
P13	+	1	0.111643	0.51	0.55	LEOPARD Syndrome	4	0.0741118	0.78	0.2
P14	+	8	0.0683091	0.79	0.12	LEOPARD Syndrome	6	0.0490429	0.9	0.14

also that may be occur in the intronic region, genetic analysis should be selected. For this reason, it is recommended to choose genetics analysis methods such as next generation sequencing which can detect changes in the intronic region.

Variants determined by genetic analysis are divided into 5 classes according to ACMG criteria. Class 2 is "Likely pathogenic" and Class 1 is reported as "Pathogenic". Variants in these two criteria groups are considered to be responsible for possible disease [24]. Until now, 96 Likely pathogenic and 1753 Pathogenic variants of the NF1 gene have been reported in the ClinVar database. Also, more than 2.800 different pathogenic variants in NF1 gene have been identified in the University of Alabama cohort [25]. In the literature, pathogenic mutation detection rate is between 89% and 96% [19, 22, 26]. In this study, as a result of 14 NF1 analyzes, only 1 of them was “likely pathogenic” which is a novel mutation, while the other 13 analyzes resulted as a "pathogenic" variant (92%). The detected novel mutation is NF1 c.3011_3011delA p.N1004Ifs*8. The detected mutation causes frameshift, creating an early stop codon and it is occurred in exon 23.

With the advances in technology, the success of medical doctors in diagnosing genetic diseases is increasing. DeepGestalt technology (Face2Gene), which uses artificial intelligence, is one of them. The success of this application in diagnosis has been reported to be 86-91% [7, 8]. All NF1 patients analysis results (14/14 - 100%) are in the top-10 suggestion list recommended by the application. When compared to NF1 patients and unaffected controls at Face2Gene analysis, significant result was found ($p = 0.032$). However, the success of the application in distinguishing between NF1 and non-NF1 RASopathies patients was not significant in this study ($p = 0.134$). The reason for this may be that not enough RASopathies patients have been registered to the app. Therefore, next-generation phenotyping (NGP) programs such as Face2Gene are recommended to be used in routine examinations, especially by medical genetics doctors and pediatricians. In addition, there is an excellent separation when comparing the Down syndrome and the unaffected control group ($p < 0.001$). This shows that Face2Gene's success is high in patients with distinct dysmorphic facial features.

The brain is the control center of our whole body like the maestro. Perhaps for this reason, it is protected by a very tight and protected bone layer that is skull. Therefore, it was not easy to detect morphological changes in the brain until MRI was invented. Nowadays, we can almost take a picture of the brain with MRI. NF1 disease also causes some changes in the brain. In the study by Rosenbaum *et al*. [27], MRI was reported as normal in 6.5% of NF1 patients. In our study, this rate is 28%. This is an example of NF1 patients can be in a wide spectrum. In genetics, this situation is described as variable expressivity and NF1 is one of the genetic diseases that have high variable expressivity [28]. In a study made in Spain in 2019, arachnoid cysts were detected in 3 (3.5%) of 85 NF1 patients in brain MRI [29]. In our study, arachnoid cysts were found in 3 (%21) of 14 patients. In the study of Kelesoglu *et al*. [30], hamartomatous lesions in the central nervous system were reported in 16 of 19 patients (84%) followed up with diagnosed with NF1 [30]. In our study, this rate was found as 29%. As can be seen from these rates, it is not possible to diagnose NF1 only with MRI. There is no specific brain MR image for this disease. However, because of this disease causes various lesions in the brain, brain MRI may be recommended for all patients diagnosed with NF1.

CONCLUSION

One of the most important lessons we learned in our education at the medical school is that diagnosing diseases is one step ahead of treating. Because no disease can be cured without being diagnosed. In the past, diseases were evaluated generally, but with the advancement of technology, they can now be evaluated in more detail and individually. Eric Topol's following sentence expresses this situation well. Medicine is still all about treating populations, not people - one-size-fits all treatments and diagnosis. Therefore, "Next generation phenotyping" is gaining importance day by day and helps diagnose diseases.

Authors' Contribution

Study Conception: ME; Study Design: BG; Supervision: ME; Funding: BG; Materials: ME; Data Collection and/or Processing: BG; Statistical Analysis and/or Data Interpretation: ME; Literature Review:

BG; Manuscript Preparation: ME and Critical Review: BG.

Ethics Declarations

All participants gave their informed consent and were studied under a protocol approved by the Health Sciences University Medical Ethics Committee.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created in this study.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Can the blood urea nitrogen to serum albumin ratio be used as a mortality predictor in patients with pneumonia after cardiac surgery?

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ABSTRACT

Objectives: Serious complications are seen after cardiac surgery operations. Postoperative pneumonia is one of the most important of these complications. Some biomarkers have been examined in the prediction of mortality in special groups such as hospital-acquired pneumonia or aspiration pneumonia. In addition to parameters such as blood-urea nitrogen and albumin, the blood urea nitrogen to albumin ratio obtained by the ratio of these two parameters is also used as a mortality predictor. In this study, it was aimed to investigate the effect of the blood urea nitrogen to albumin ratio at the time of diagnosis of pneumonia on mortality in patients who developed pneumonia in the early period after cardiac surgery.

Methods: In this study, 138 patients who developed pneumonia in the early period after cardiac surgery were examined. Complete blood count and biochemical test results were analyzed for all patients, and differences between groups were investigated. The patients who developed in-hospital pneumonia and were discharged as survivors were classified as Group 1, and non-survivor patients were determined as Group 2.

Results: Patients who did not develop in-hospital mortality were included in Group 1 (n = 105, mean age = 63.7 ± 9.2 years), and those with non-survivor were included in Group 2 (n = 33, mean age = 66.9 ± 9.6 years). At the time of diagnosis neutrophil-lymphocyte ratio, C-reactive protein, blood-urea nitrogen and blood urea nitrogen to albumin ratio values were significantly higher in Group 2 ($p < 0.001$, $p < 0.001$, $p = 0.004$ and $p < 0.001$; respectively) ROC curve analysis was performed to evaluate blood urea nitrogen to albumin ratio in predicting mortality. The cut-off value of blood urea nitrogen to albumin ratio was 4.1 (Area under the curve [AUC]: 0.740, 95% CI: 0.690-0.820, $p < 0.001$, with sensitivity of 72.5% and specificity of 68.6%).

Conclusions: In pneumonia developing after cardiac surgery, we found that the peripheral blood blood urea nitrogen to albumin ratio at the time of the first symptom in the patient has a high predictive power for the development of mortality in this particular patient group.

Keywords: Cardiac surgery, postoperative pneumonia, mortality, prediction

Cardiac surgery is a procedure that is applied with high success rates in the treatment of cardiovascular diseases, and various serious complications after these operations still maintain their importance [1]. Postoperative pneumonia is one of the most important complications [2]. Due to this complication, the length

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of hospital stay is prolonged, and the risk of morbidity and mortality increases. Previous studies reported that the rate of development of postoperative pneumonia has been shown to be between 5% and 21%, and mortality rates in these cases range from 6.2% to 28% [2-5].

Various inflammatory markers obtained from routine blood parameters have been the subject of research in cardiovascular surgery. These markers have been used both in the diagnostic sense and in predicting the prognosis of developing complications [6, 7]. Albumin, as a negative acute phase reactant, is an important inflammatory marker and plays an important role in maintaining osmotic pressure and in interstitial transport of vital molecules [8]. Increased blood urea nitrogen (BUN) levels in blood is also an important indicator of dehydration and has poor prognostic importance in pneumonia patients [9]. In the light of this information, blood urea nitrogen to albumin (B/A) ratio seems to be an important marker. In two recent studies, B/A ratio has been shown as an independent predictor of mortality in patients with hospital-acquired pneumonia and aspiration pneumonia [10, 11].

In this current study, we aimed to investigate the effect of the B/A ratio at the time of diagnosis of pneumonia on mortality in cases who developed early pneumonia after cardiac surgery.

METHODS

This study was approved with the protocol dated 09.06.2021 and numbered 2011-KAEK-25 2021/06-16 of the Bursa Yüksek İhtisas Training and Research Hospital Clinical Research Ethics Committee. In this study, which was planned as a single center, patients between the ages of 20-90 who underwent open heart surgery at Bursa Yüksek İhtisas Training and Research Hospital between January 01, 2014 and January 01, 2020 were included in the study. The patients who had undergone redo cardiac operation, emergency cases, those with a known history of lung disease, those with chronic renal failure, and those with a history of pneumonia were excluded from the study. A total of 138 patients were evaluated for the study.

Laboratory values, demographic characteristics and blood values on the day they were diagnosed with pneumonia were recorded for all patients at the time of admission to the hospital. The patients who developed in-hospital pneumonia and were discharged as survivor were classified as Group 1, and non-survivor patients were classified as Group 2.

Variables

Variables were recorded as of the first admission of the patients to the hospital. Demographic data, identity information, age, gender, smoking were determined and recorded. Their medical histories were analyzed in detail. Presence of hypertension, diabetes, chronic obstructive pulmonary disease, congestive heart failure and coronary artery disease were recorded. By following the clinical outcome; Discharge or death information, duration of intensive care stay and total hospital stay were noted. Laboratory data including complete blood count values (white blood cell [WBC], hemoglobin [Hb], neutrophil, lymphocyte, platelet [PLT]), neutrophil-lymphocyte ratio (NLR), C-reactive protein (CRP), biochemical studies (BUN, Albumin, B/A ratio) was recorded. In addition, inflammatory blood markers were recorded on the basis of the day of diagnosis of pneumonia, and the B/A ratio was recalculated.

Postoperative Pneumonia Diagnosis

In patients with clinically suspected pneumonia, newly detected infiltration on chest X-ray or an increase in the current infiltration degree were taken into account. In addition, pneumonia was diagnosed with the presence of at least two of the following criteria [12]: 1) Fever (> 38.5˚C) or hypothermia (< 36.0˚C); 2) Presence of purulent tracheo-bronchial secretion or an increase in the amount of existing secretion; and 3) Leukocytosis (12,000/μL) or leukopenia (4,000/μL).

Statistical Analysis

Data were analyzed by SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) program. "Kolmogorov-Smirnov test and Shapiro-Wilk test" were used for normality distribution analysis. While “Student's t test was used for the data presenting normal distribution, Mann-Whitney U test was used for data that did not conform to normal distribution. These data were shown as mean ± standart deviation or as median (minimum-maximum) respectively. Categorical variables were shown as frequency and percentage, and

"Chi Square test" was used for analysis. Multivariate binary logistic regression analysis was utilized to analyze mortality predictors. A *p* value's being less than 0.05 was accepted statistically significant. In predicting in-hospital mortality, receiver operating characteristics (ROC) curve analysis was performed for B/A ratio and area under the curve (AUC) was calculated.

RESULTS

A total of 138 patients were included in the study. Patients who did not develop in-hospital mortality were included in Group 1 (n = 105, mean age = 63.7 ± 9.2 years), and those with non-survivor were included in Group 2 (n = 33, mean age = 66.9 ± 9.6 years). There were no statistically significant differences between the two groups in terms of age, gender, body mass index, smoking, hypertension and chronic obstructive pulmonary disease rates ($p > 0.05$). Also preoperative blood parameters of the patients were similar between two groups. Demographic characteristics and preoperative blood parameters of all patients are presented in Table 1.

Operative and postoperative features and blood parameters of the patients at the time of diagnosis were shown in Table 2. The two groups were similar in terms of perfusion times, need of positive inotropic support and use of blood products. There were no statistically significant differences between the two groups in terms of (at the time of diagnosis) WBC, creatinine, neutrophil counts, lymphocyte counts and albumin values ($p > 0.05$). At the time of diagnosis NLR, CRP, BUN and B/A ratio values were signifi-

Table 1. Preoperative features and preoperative laboratory variables of the patients

Variables	Group 1 (Survivor) (n = 105)	Group 2 (Non-Survivor) (n = 33)	*p* value
Age (years)	63.7 ± 9.2	66.9 ± 9.6	0.179
Male gender, n (%)	73 (69.5%)	25 (75.8%)	0.491
BMI (kg/m2)	26.4 (22.4-38)	27.2 (21.6-39)	0.293
Hypertension, n (%)	61 (58.1%)	21 (63.6%)	0.572
Diabetesmellitus, n (%)	30 (28.6%)	14 (42.4%)	0.136
COPD, n (%)	25 (23.8%)	11 (33.3%)	0.277
Smoking, n (%)	23 (21.9%)	8 (24.2%)	0.779
Hiperlipidemia, n (%)	54 (51.4%)	15 (45.5%)	0.549
Ejection fraction (%)	54.2 ± 9.7	50.2 ± 9.6	0.209
White blood cell (103/µL)	9.2 (4.9-12.4)	8.9 (5.1-13.7)	0.259
Hemoglobin (mg/dl)	12.8 (10-15.7)	12.2 (10.4-16)	0.314
Platelet (103/µL)	254.2 (129-460.4)	258.5 (128-450)	0.204
Neutrophil (103/µL)	4.2 (1.8-5.7)	4.4 (2.5-6.9)	0.251
Lymphocyte (103/µL)	2 (0.8- 4.1)	1.8 (0.9- 4.5)	0.102
NLR	2.3 (1.4-13.4)	2.4 (1.3-11.9)	0.096
Creatinine (mg/dL)	1.1 ± 0.8	1.3 ± 0.7	0.495
BUN, (mg/dL)	12 (9-18)	13 (10-20)	0.229
Albumin, (g/dL)	4.2 (3.9 5.5)	4.3 (3.8-5.4)	0.375
CRP (mg/L)	6.9 (0.5-12)	6.2 (0.6-15)	0.194
B/A ratio (mg/g)	1.96 (0.4-4.1)	2.08 (0.5-4.9)	0.174

BMI = Body mass index, COPD = Chronic obstructive pulmonary disease, BUN = Blood urea nitrogen, NLR = Neutrophil to lymphocyte ratio, CRP = C-reactive protein, B/A ratio = Blood urea nitrogen to albumin ratio

cantly higher in Group 2 ($p < 0.001$, $p < 0.001$, $p = 0.004$ and $p < 0.001$; respectively).

Logistic regression analysis was performed to evaluate the predictive value of certain parameters in terms of in-hospital mortality (Table 3). In univariate analysis, age > 70 years (OR [odds ratio]: 1.125, 95% CI [confidence interval]: 1.080-1.548, p = 0.014), ejection fraction< 35% (OR: 1.956, 95% CI: 1.318-2.865, $P = 0.002$), need for inotropic support (OR: 0.875, 95% CI: 0.582-0.961, $p = 0.036$), Time of di-

Table 2. Operative and postoperative features of thepatients

Variables	Group 1 (n = 105)	Group 2 (n = 33)	*P* value
Total perfusion time (min)	86 (65-210)	88 (68-196)	0.148
Cross-clamp time (min)	55 (22-145)	52 (25-150)	0.362
Combined surgery, n (%)	23 (21.9%)	8 (24.2%)	0.779
Packed blood products (units)	6 (4-12)	7 (4-14)	0.194
Inotropic support, n (%)	30 (28.6%)	16 (48.5%)	**0.034**
At the time of diagnosis			
White blood cell (103/µL)	12.9 (13.2- 21.8)	13.1 (11.3- 25.6)	0.107
Neutrophil (103/µL)	4.2 (2.8- 8.4)	4.4 (2.6-9.7)	0.075
Lymphocyte (103/µL)	1.5 (0.9- 2.1)	1.2 (1- 2.5)	0.152
NLR	3.2 (2.1- 15.4)	4.9 (2.4- 22.6)	**< 0.001**
Creatinine (mg/dL)	1.2 (0.9- 1.6)	1.1 (0.7- 2)	0.192
BUN (mg/dL)	12 (8.5- 28.6)	15.6 (8- 46.8)	**0.004**
Albumin (g/dL)	3.6 (2.6- 4.4)	3.5 (2.4- 4.2)	0.076
B/A ratio (mg/g)	3.36 (0.38-10.08)	4.89 (1.18-18.9)	**< 0.001**
CRP (mg/L)	154 (85- 350)	238 (120-450)	**< 0.001**

NLR = Neutrophil to lymphocyte ratio, BUN = Blood urea nitrogen, B/A ratio = Blood urea nitrogen to albumin ratio, CRP = C-reactive protein

Table 3. Logistic regression analysis to identify factors affecting postoperative pneumonia mortality

	Univariate analysis			Multivariate analysis		
Variables	***p* value**	**Exp (B) Odds Ratio**	**95% C.I. Lower Upper**	***p* value**	**Exp (B) Odds Ratio**	**95% C.I. Lower Upper**
Age >70 years	**0.014**	1.125	1.080- 1. 548	0.276	1.345	0.844- 1.694
Ejection fraction < 35%	**0.002**	1.956	1.318- 2.865	0.019	1.127	1.045- 1.539
COPD	0.304	0.696	0.538- 1.183	--	--	--
Inotropic support	**0.036**	0.875	0.582- 0.961	0.332	0.976	0.882- 1.145
Preop NLR	0.098	0.763	0.594- 1.110	--	--	--
Preop B/A ratio	0.175	0.976	0.775- 1.194	--	--	--
Td NLR	**< 0.001**	1.554	1.196- 2.872	0.094	0.887	0.697- 1.148
Td B/A ratio	**< 0.001**	1.668	1.441- 2.152	**< 0.001**	1.224	1.090- 1.792
Td CRP	**< 0.001**	3.336	2.178- 4.894	**< 0.001**	2.628	1.945- 4.136

COPD = Chronic obstructive pulmonary disease, NLR = Neutrophil to lymphocyte ratio, B/A ratio = Blood urea nitrogen to albumin ratio, CRP = C-reactive protein, Td = Time of diagnosis

agnosis (Td) NLR (OR: 1.554, 95% CI: 1.196-2.872, $p < 0.001$), Td B/A ratio (OR: 1.668, 95% CI: 1.441-2.152, $p < 0.001$) and Td CRP (OR: 3.336, 95% CI: 2.178-4.894, $p < 0.001$) values were found to be significantly correlated with the development of in-hospital mortality. As a result of multivariate analysis, ejection fraction< 35% (OR: 1.127 CI 95%: 1.045-1.539, $p = 0.019$), Td B/A ratio (OR: 1.224, CI 95%:1.090-1.79452, $p < 0.001$) and Td CRP (OR: 2.628, CI 95%: 1.945-4.136, $p < 0.001$) values were determined as independent predictors for predicting in-hospital mortality.

ROC curve analysis was performed to evaluate B/A ratio in predicting mortality. The cut-off value of B/A ratio was 4.1 (Area under the curve [AUC]: 0.740, 95% CI: 0.690-0.820, $p < 0.001$, with sensitivity of 72.5% and specificity of 68.6%) (Fig. 1).

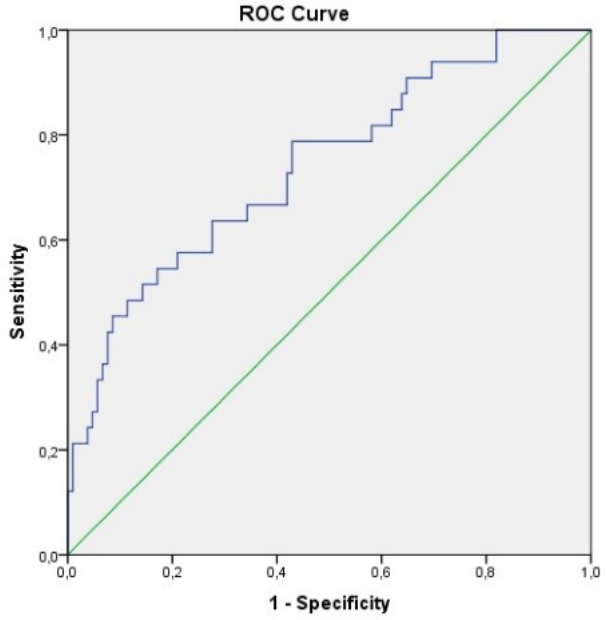

Fig. 1. The area under the curve (AUC), confidence interval (CI), and cut-off values in receiver-operating characteristic (ROC) curve analysis for B/A ratio to predict mortality (cut off:4.1, AUC: 0.740, 95%CI: 0.690- 0.820, $p < 0.001$, with 72.5% sensitivity and 68.6% specificity).

DISCUSSION

Postoperative pneumonia is one of the most important complications after open heart surgery. In addition to prolonging hospitalizations, this may result in mortality rates up to 50%. In this current study, it was shown for the first time in the literature that the B/A ratio is an independent predictor of mortality in cases of pneumonia occurring in the early period after cardiac surgery. In addition to this marker, CRP value and ejection fraction below 35% at the time of diagnosis of pneumonia were also determined as independent predictors of mortality.

Serum albumin plays a key role in maintaining physiological homeostasis. It undertakes important tasks such as balancing osmotic pressure and transporting some components in the blood. The presence of low albumin levels in some chronic diseases such as heart failure, COPD and diabetes, as well as in malignancies with a predominant course of catabolism, has been associated with increased mortality and morbidity [13]. In a study by Yayla *et al*. [14], albumin levels were found to be significantly lower in patients who developed saphenous vein occlusion after CABG operations. In other studies, significant correlations were found between atrial fibrillation developing after cardiac surgery and low albumin [15, 16]. In our study, we found that albumin levels at the time of pneumonia diagnosis were low in patients who developed mortality, although it was not statistically significant ($p = 0.076$).

Dehydration may occur in patients who need hospitalization, especially in infectious diseases where inflammation is at the forefront. The resulting increase in urea reabsorption from the kidneys results in increased BUN levels. This value is an important parameter indicating the state of dehydration in individuals and has been associated with poor clinical outcomes in patients with heart failure and pneumonia [9, 17]. In a study by Akgül *et al*. [16], a significant relationship was found between the development of postoperative atrial fibrillation, which is closely related to inflammation, and high BUN values after CABG operations. In our patients, BUN values at the time of diagnosis of pneumonia were significantly higher in the mortality group ($p = 0.004$).

In line with all this literature information, the B/A ratio emerges as a valuable prognostic marker. There are various studies on various medical problems and B/A ratio in the literature. In a study conducted by Bae *et al*. [18] on patients with ischemic stroke, the B/A ratio was shown as a poor prognostic marker. In a study conducted by Dundar *et al*. [19], the B/A ratio at the time of admission was shown as an independent predictor of mortality in patients over the age of 65 who applied to the emergency department. In addition,

the authors emphasized in this study that the B/A ratio is a stronger predictor than albumin, BUN, creatinine, and glomerular filtration ratio alone [19]. In another study by Fang and XU [20], B/A ratio was found to be a strong predictor of mortality in critically ill patients in intensive care units who developed pulmonary embolism.

Recently, the relationship between B/A ratio and mortality in various pneumonia cases has been the subject of research. In the article published by Feng *et al*. [10] in 2019, the effect of B/A ratio on mortality in hospital-acquired pneumonia cases was investigated. In the study, which included 1158 cases, 150 patients (13%) died within 30 days. At the end of their study, the authors determined the high B/A ratio as an important value in predicting 30-day mortality [10]. In a study by Ryu *et al*. [11], at the beginning of 2021, the relationship between B/A ratio and mortality in aspiration pneumonia cases was investigated. In the study, which included 443 patients, mortality was observed in 90 (20.3%) patients in the first 28 days. As a result of the multivariate analysis, a B/A ratio above 7 was shown as a strong and independent predictor of mortality (OR 3.40, 95% CI 1.87-6.21, $p < 0.001$). In another recent study by Ata *et al*. [21], B/A ratio was found to be an independent predictor for mortality in intensive care patients with COVID-19 pneumonia.

In our study, the other independent predictors of mortality in patients who developed pneumonia, apart from the B/A ratio, were preoperative ejection fraction below 35% and high CRP at the time of diagnosis. Comprehensive studies and meta-analyses have similar results with our study. Having a low ejection fraction in pneumonia that develops after cardiac surgery plays an important role in both the development of postoperative pneumonia and mortality after pneumonia [2, 12, 22-24]. Similarly, there are studies showing that increased CRP levels are also important in the development of postoperative pneumonia and associated mortality [25-27].

Limitations

The most important limitations of our study are that it is single-centered, retrospective, and the number of patients is low. More comprehensive publications with larger numbers of patients are needed to support existing data.

CONCLUSION

In our study, we examined a patient group that developed pneumonia after open heart surgery, which has not been evaluated in the literature before. In pneumonia developing after cardiac surgery, we found that the peripheral blood B/A ratio at the time of the first symptom in the patient has a high predictive power for the development of mortality in this particular patient group. This predictive ability will enable us to predict the risk of pneumonia-related mortality in patients undergoing cardiac surgery and to prevent adverse outcomes by taking necessary precautions in these patients.

Authors' Contribution

Study Conception: AKA, AAP; Study Design: AKA, AAP; Supervision: AKA, AAP, ŞY; Funding: AKA, AAP, OG; Materials: AKA, AAP, OG; Data Collection and/or Processing: AKA, AAP, OG; Statistical Analysis and/or Data Interpretation: AKA, AAP, OG, ŞY; Literature Review: AKA, AAP, OG, ŞY; Manuscript Preparation: AKA, AAP, OG, ŞY and Critical Review: AKA, AAP, OG, ŞY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Hepatitis B and C virus reactivations under biologic treatments in patients with rheumatic diseases: long-term results from a single-center

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ABSTRACT

Objectives: To find out the effects and prevalence of disease-modifying antirheumatic drugs (DMARDs) and anti-TNF agents on hepatitis B virus (HBV) reactivation in hepatitis B surface antigen (HBsAg)-positive patients with rheumatic diseases (RD).

Methods: This retrospective study was conducted on 1,548 RD patients. Patients' medical records regarding immunological profiles, clinical courses, and outcomes, were obtained. In this research, the patient used conventional DMARDs (cDMARDs) and biological DMARDs (bDMARDs). A drug exposure was considered when a patient was administered GC, cDMARDs, or bDMARDs for > 4 weeks. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin were measured. HBsAg, HBV DNA assay, anti-HCV and HIV were identified.

Results: HBsAg was positive in 19 (37.3%) patients. Anti-HBs in 5 (9.8%) patients and anti-HBc IgG in 35 (68.6%) patients were positive. All patients with HBsAg positivity were receiving antiviral prophylaxis. Anti-HCV was positive in 25.5% (n = 13) of individuals . There was not any reactivation among the patients. No HBV reactivation was observed.

Conclusions: Screening before treatment and give prophylaxis to patients who have occult hepatitis or hepatitis B, may be an important factor in the absence of reactivation. Hepatitis screening should be performed in all patients prior to biological treatment is initiated.

Keywords: Hepatitis, rheumatic disease, reactivation, biologic treatment. Disease-modifying antirheumatic drugs, occult Hepatitis.

The primary cause of chronic hepatitis, end-stage liver disease, and hepatocellular carcinoma (HCC) is hepatitis B virus (HBV) infection [1-3]. Around 350 million people worldwide are afflicted with HBV, which causes between 0.5 and 1 million fatalities each year [4]. Similarly, hepatitis C virus (HCV) infects around 170 million people [5].

HBV infection is a significant issue for rheumatologists, as reactivation of HBV can occur as a side effect of immunosuppressive medications (ISDs) [6].

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Numerous conventional disease-modifying antirheumatic medications (cDMARDs), such as glucocorticoids, methotrexate (MTX), hydroxychloroquine, sulfasalazine, and leflunomide, as well as biological DMARDs, such as etanercept, adalimumab, golimumab, infliximab, certolizumab, tocilizumab, TNF-alfa is significant because it inhibits HBV replication and is capable of eradicating the virus [7]. Notably, rituximab, a B cell depleting drug, is frequently used to treat rheumatic disorders. However, prolonged use of potentially hepatotoxic DMARDs, such as MTX, is likely to result in HBV reactivation, and a link between anti-TNF therapy and HBV activation has been established [8, 9].

The American Gastroenterological Association (AGA) Institute emphasized the possibility of HBVr infection associated with chemotherapeutic treatments and immunosuppressive medicines in 2015 [10-11]. As a result, immunocompromised patients should be evaluated for HBV and HCV infection [12]. The prophylactic antiviral medication is extremely useful since it prevents HBV reactivation in HBsAg-positive patients receiving anti-TNF or DMARD therapy [7]. The purpose of this study is to determine the effect and prevalence of DMARDs and anti-TNF medications on HBV and HCV reactivation in patients with rheumatic illnesses who are HBsAg positive.

METHODS

Patients

Between January 2006 and December 2012, we retrospectively analyzed 1,548 individuals with RD who had available HBsAg and HCV data at a university hospital. Without taking anti-HBV prophylaxis, 19 patients tested positive for HBsAg at the time of diagnosis or prior to immunosuppressive treatment. We received medical documents pertaining to immunological profiles, clinical courses, and results.
The inclusion criteria for our patients to participate in the present research were (i) patients with RD (rheumatoid arthritis [RA], ankylosing spondylitis [AS], psoriatic arthritis [PsA], spondyloarthropathy [SpA], vasculitis, systemic lupus erythematosus, behcet disease, and systemic sclerosis); (ii) the intervention consisted of anti-TNF agents, Rituximab, Tocilizumab, Abatacept, Ustekinumab, Tofacitinib, Cyclophosphamide, and DMARDs; (iii) sufficient data on patience regarding the effects of anti-TNF agents or DMARD on HBV reactivation.

Immunosuppressive Therapy

Methotrexate, hydroxychloroquine, and sulfasalazine were used as cDMARDs in this study. Anti-TNF medicines, rituximab (anti-CD20 monoclonal antibody), tocilizumab (anti–interleukin 6 receptor monoclonal antibody), and abatacept (cytotoxic T lymphocyte–associated antigen 4 immunoglobulin) were listed among the bDMARDs. When a patient got GC, cDMARDs, or bDMARDs for a period of more than 4 weeks, exposure to medicines was assessed.

Serological Tests of Viral Hepatitis Markers

We determined serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin using a 24-factor automated chemical analyzer and standard reagents. The Architect-plus 2001 chemiluminisans method was used to determine the hepatitis B surface antigen. Plasma samples from patients were purified using the automated m2000sp (Abbott Molecular, USA) instrument for DNA extraction. The acquired DNA was amplified using the Real-Time PCR on a m2000rt (Abbott Molecular, USA) equipment using an Abbott Real-Time HBV kit.

The study protocol was approved by the Local Clinical Research Ethics Committee (decision number: 2021-6/43).

Statistical Analysis

Statistical analysis was performed with the SPSS program, version 23. The demographic data of the patients were presented as frequency and percentage for qualitative variables and mean and standard deviation for qualitative variables. For all tests, probability values (values) of < 0.05 were considered to indicate statistical significance.

RESULTS

The mean age of the 51 patients was 50.9 ±13.51 years (range: 20-69 years). Out of 51 patients, 58.8% of them were females and 41.2% of them were males (see Appendix 1 for patient characteristics).

HBsAg positivity was observed in 37.3% of pa-

tients (n = 19), Anti-HBs positivity was observed in 9.8% of patients (n = 5), and Anti-HBc IgG positivity was observed in 68.6% of patients (n = 35). It is worth noting that data for Anti-HBc IgG were absent. There were no patients who tested positive for Anti-HBc IgM. All patients with HBsAg positivity were receiving antiviral prophylaxis.

HBsAg was negative in 68.6% of patients (n = 35), although Anti-HBc IgG was positive (occult hepatitis). Anti-HCV was positive in 25.5% of individuals (n = 13). Among the patients, 19 were tested for HIV, and the results revealed that none of the patients had the virus.

When the patients were investigated, eight unique diagnoses were made: RA (35.3%), AS (33.3%), PsA (13.7%), Vasculitis (7.8%), Systemic Lupus Erythematosus (5.9%), Behcet Disease (2%), and Systemic Sclerosis (2%).

Our data indicated that eleven distinct immunosuppressive agents were present in the patients: Etanercept (33.3%), Infliximab (15.7%), Rituximab (15.7%), Adalimumab (9.8%), Golimumab (5.9%), Tocilizumab (5.9%), Abatacept (3.9%), Cyclophosphamide (3.9%), Certolizumab (2%), Ustekinumab (2%), and Tofacitinib (2%). Table 1 summarizes the duration of biological treatment, the duration of steroid treatment, and the steroid doses.

Eight patients received Rituximab (RTX) (15.7%). The average length of RTX use was 39.87 ± 27.48 months (range from 6 to 96 months). Antiviral prophylaxis was administered to all eight individuals. In none of the eight patients was reactivation observed.

DISCUSSION

Hepatitis virus infections are a significant issue for rheumatologists, given the difficulties associated with treatment [12-15]. Numerous studies have demonstrated that methotrexate and biologic treatments, such as infliximab, etanercept, adalimumab, and rituximab, can reactivate HBV in dormant HBV carriers [16-21]. Thus, the ACR recommends screening for HBV and HCV prior to initiating immunosuppressive medication, whether non-biologic or biologic [12]. Although other studies have demonstrated HBV reactivation in patients receiving immunosuppressive therapy for cancer or transplantation at a rate of 20-50%, our investigation found no evidence of HBV reactivation in any of our 51 patients (n = 51) [22].

Notably, TNF-a is required for immunological responses as a pro-inflammatory cytokine. Thus, when TNF-a inhibitors are administered, the virus is able to evade the host's immune protection systems against infection [9]. Prior to initiating treatment, all patients with rheumatic illnesses should be tested for HBV, as HBsAg carriers must get antiviral prophylaxis [6, 7, 11]. Chronic autoimmune illnesses require long-term immunosuppressive medication, but chemotherapy is frequently used for brief periods [23]. It is worth noting that, despite immunosuppressive therapy's benefits, long-term use is likely to compromise host immunological functioning. Lee *et al*. conducted a review of nine studies that comprised 122 individuals with rheumatic illness who tested positive for HBsAg. 15 (12.3%) of 122 individuals acquired HBVr [6]. Etanercept (33.3%), Infliximab (15.7%), Adalimumab (9.8%), Golimumab (5.9%), and Certolizumab (5.9%) were utilized by 34 individuals (2%). There was no evidence of reactivation in any of the patients.

Although Rituximab is the most hazardous medicine due to its HBVr-related side effects, a study found that due to its longer dose interval, Rituximab therapy was safe in individuals with RD [24]. Another study

Table 1. Period of treatment and steroid dose

	Period of biological treatment (month)	Period of steroid treatment (month)	Steroid dose (mg)
HBsAg positive	36.89 ± 19.55 (6-72)	41.89 ± 110.93 (0-480)	1.71 ± 2.89 (0-10)
HBsAg negative Anti-HBc IgG positive	48.47 ± 30.76 (4-120)	54.36 ± 109.36 (0-480)	3.42 ± 4.72 (0-20)
Anti-HCV positive	29.07 ± 25.22 (3-96)	138.84 ± 183.17 (0-552)	2.69 ± 2.78 (0-7.5)

found that the incidence of HBVr was 40% to 100% in HBsAg positive RA patients receiving rituximab without or with GC therapy, arguing in favor of antiviral prophylaxis in HBsAg positive RA patients receiving rituximab [25]. The surprising finding in this study was the absence of reactivation among the 51 patients, notably among the eight individuals who received antiviral prophylaxis for a period spanning from 6 to 96 months. This finding implies that appropriate antiviral prophylaxis is critical for the health of patients.

Tocilizumab and Abatacept are likely to have an influence on the patient's immune response to HBV, as mentioned in the literature. However, we should keep in mind that the majority of GC research on HBVr in patients treated with tocilizumab or abatacept has been hampered by small sample sizes [25]. As a result, additional research with a larger cohort of patients is required.

ISDs (e.g., biologics, steroids, and MTX) are highly likely to reactivate HBV. It is worth noting that assessing the risk of reactivation for each treatment is critical for preventing HBV reactivation [12-23].

In a case–control study including RA patients approved by the US Food and Drug Administration, the odds ratio for HBV reactivation was 2.3 for steroids and much lower for TNF blockers than for steroids or MTX [26].

Fukuda *et al*. [23] found that MTX had a reduced risk ratio for HBV reactivation than steroids and biologics. The time period between ISD onset and HBV reactivation varied, and the clinical outcome following reactivation was not always aggressive [23]. Chen *et al*.'s [24] study discovered that HBVr is prevalent in HBsAg-positive RA patients, even more so when combined immunosuppressive therapies with GC are used. Physicians in particular should exercise caution, as antiviral treatment must be justified in light of the risk of HBVr infection in rheumatic patients receiving various immunosuppressive regimens [25, 27].

The literature is unanimous in recommending that all patients initiating DMARD medication be screened for HCV infection using anti-HCV antibodies. If the test results are positive, HCV RNA testing should be performed to validate the finding. Patients who have been infected with HCV for an extended period of time should be referred to a hepatologist. It's important emphasizing two critical points: I it is critical to understand the severity of the underlying chronic HCV infection before making a therapy option. These patients could be assessed for advanced fibrosis or cirrhosis. (ii) When a hepatologist diagnoses HCV, he or she should determine whether or not to initiate antiviral medication [8, 12, 28].

Limitations

Our study has some limitations. A retrospective study, for instance, was described. Second, the sample size for HBV carriers was limited to 19 individuals with RD. This is because hepatitis screening has become more prevalent in recent years. However, multicenter trials with a larger number of patients can provide more trustworthy findings.

CONCLUSION

In summary, HBV infection is screened for all patients receiving immunosuppressive therapy for rheumatic diseases, and antiviral prophylaxis should be administered if necessary.

Authors' Contribution

Study Conception: BNC, BY, HED, YP; Study Design: BNC, HED, YP; Supervision: BNC, HED, YP; Funding: N/A; Materials: N/A; Data Collection and/or Processing: ESÖ, ANT; Statistical Analysis and/or Data Interpretation: YP, SE, ANT; Literature Review: HED, ESÖ, SE; Manuscript Preparation: BNC, BY and Critical Review: BNC, BY, HED, YP, SE, ANT, ESÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Appendix 1. **Patient characteristics**

No	Age/Sex	Diagnosis	Serological markers				AST/ALT (IU/L)	HBV DNA (IU/mL)	HCV RNA (IU/mL)	Steroid dose	Steroid duration (months)	ISD	IST Duration (months)	Hepatitis Treatment
			HBsAg	Anti-Hbs	Anti-HBc IgG	Anti-HCV								
1	28/M	PsA	-	-	+	-	17/25	ND		5	48	ADA	50	-
2	49/M	AS	+	-	+	-	14/8	112		-	-	INF	6	TNV
3	53/M	GPA	-	-	+	-	16/17	NEG		5	48	RTX	48	-
4	37/F	AS	-	-	+	-	39/97	NEG		-	-	ETA	42	LAM
5	48/F	SLE	-	-	ND	+	19/23		504.544	5	552	RTX	36	-
6	66/F	AS	-	-	-	+	22/21		35.064	-	-	ETA	19	-
7	36/F	PsA	-	-	+	-	14/11	NEG		-	-	ETA	21	ENT
8	59/M	PAN	+	-	+	-	30/48	NEG		5	480	RTX	45	LAM
9	66/F	RA	-	-	+	-	18/9	NEG		5	480	ABA	35	-
10	25/M	AS	+	-	+	-	22/26	NEG		-	0	GOL	39	TNV
11	20/F	SLE	-	+	-	+	24/18		NEG	5	72	RTX	6	-
12	36/M	AS	-	-	+	-	27/46	NEG		-	0	ADA	25	-
13	46/F	RA	+	-	+	-	19/9	NEG		-	0	ETA	48	TNV
14	57/M	EGPA	-	-	+	-	14/7	ND		5	32	RTX	31	-
15	45/M	PsA	+	-	-	-	19/27	NEG		-	0	UST E	24	LAM
16	31/M	SLE	-	-	-	+	28/42		NEG	7.5	60	CYC	4	-
17	29/F	PsA	-	-	-	+	11/7		NEG	5	48	ETA	36	-
18	69/F	RA	+	-	+	-	19/20	418		5	101	TOCI	37	LAM
19	56/F	RA	+	-	ND	-	22/30	48.1		-	0	ETA	13	TNV
20	63/F	PsA	+	-	+	-	19/14	NEG		-	0	TOCI	72	LAM
21	65/F	RA	+	-	ND	ND	28/24	NEG		2.5	86	ABA	32	LAM
22	63/F	RA	-	-	+	-	29/27	ND		5	106	RTX	96	-
23	53/F	Ssc	+	+	+	-	17/7	NEG		5	66	CYC	9	LAM
24	65/F	RA	-	+	+	+	53/65		1.239.342	5	384	ETA	3	IFN + RBV
25	66/F	PsA	-	-	+	-	16/2	NEG		5	84	ADA	60	-
26	52/M	AS	+	-	+	-	18/9	30		-	0	ETA	60	TNV
27	55/F	RA	-	-	-	+	16/12		NEG	-	240	ETA	36	-
28	36/F	AS	-	-	+	-	14/15	NEG		-	0	ADA	39	-
29	67/M	AS	-	-	+	-	21/21	ND		-	0	INF	85	-
30	45/M	BD	-	-	-	+	41/102		NEG	15	52	INF	32	-

Appendix 1. Continued

No	Age/Sex	Diagnosis	Serological markers				AST/ALT (IU/L)	HBV DNA (IU/mL)	HCV RNA (IU/mL)	Steroid dose	Steroid duration (months)	ISD	IST Duration (months)	Hepatitis Treatment
			HBsAg	Anti-Hbs	Anti-HBc IgG	Anti-HCV								
31	66/M	RA	-	-	+	-	23/21	NEG		5	96	GOL	27	-
32	54/F	PsA	-	-	+	-	27/17	ND		5	88	CERTO	34	-
33	66/F	RA	-	-	+	-	19/10	NEG		5	168	TOFA	33	-
34	62/F	RA	-	+	-	+	18/15		NEG	-	0	TOCI	42	-
35	27/M	AS	-	-	+	-	17/43	NEG		-	0	INF	48	-
36	63/F	AS	+	-	+	-	26/21	NEG		-	0	GOL	50	LAM
37	47/M	AS	+	-	+	-	15/10	18171		-	0	ETA	34	TNV
38	49/M	AS	+	-	+	-	20/20	238		-	0	ETA	48	TNV
39	59/F	AS	-	-	+	-	35/56	NEG		-	0	INF	60	TNV
40	53/F	AS	+	-	+	-	19/13	NEG		-	0	ETA	52	LAM
41	57/F	RA	-	-	-	+	29/42		NEG	2.5	360	ETA	8	-
42	38/M	PsA	+	-	+	-	20/18	114		-	0	ETA	12	TNV
43	63/F	PAN	-	-	-	+	25/22		NEG	-	21	RTX	45	IFN+ RBV
44	63/F	RA	-	+	-	+	26/21		NEG	5	2	ETA	96	-
45	47/F	RA	-	-	+	-	12/18	ND		15	15	INF	4	-
46	29/M	AS	+	-	+	-	32/35	NEG		0	0	INF	48	LAM
47	66/M	RA	+	-	ND	-	20/16	275		10	15	RTX	12	LAM
48	48/M	AS	-	-	+	-	19/12	NEG		-	0	INF	120	-
49	35/M	AS	-	-	+	-	14/10	ND		-	0	ETA	96	-
50	62/F	RA	-	ND	ND	+	16/13		NEG	-	24	ETA	15	-
51	56/F	RA	+	-	+	-	19/21	90		5	48	ADA	60	TNV

PsA = Psoriatic Arthritis, AS = Ankylosing Spondylitis, GPA = Granulomatous Polyangiitis, SLE = Systemic Lupus Erythematosus, PAN = Polyarteritis nodosa, RA = Rheumatoid Arthritis, EGPA = Eosinophilic granulomatosis with polyangiitis, SSc = Systemic Sclerosis, BD = Behcet Disease, ISD = Immunosuppressive drug, ADA = Adalimumab, INF = Infliximab, RTX = Rituximab, ETA = Etanercept, ABA = Abatacept, GOL = Golimumab, USTE = Ustekinumab, CYC = Cyclophosphamide, TOCI= Tocilizumab, CERTO = Certolizumab, TOFA = Tofacitinib, TNV = Tenofovir, LAM = Lamivudine, ENT = Entecavir, IFN+RBV = Interferon+ribavirin.

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Carotid atherosclerosis and lectin-like oxidized low density lipoprotein receptor-1 levels in hemodialysis patients

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ABSTRACT

Objectives: Atherosclerotic cardiovascular disease risk is increased in hemodialysis patients. Oxidized low density lipoprotein has an important role in atherosclerotic process and it exerts this effect via lectin like oxidized low density lipoprotein-1 (LOX-1). Carotid artery intima-media thickness (CIMT) is accepted as a god indicator of subclinical atherosclerosis. In this study, we aimed to investigate LOX-1 and CIMT levels in hemodialysis patients.

Methods: Twenty-eight patients treated with hemodialysis at least 6 months and 19 healthy subjects were enrolled in this study. Serum LOX-1 levels and simultaneously with CIMT were measured in hemodialysis patients and healthy control group.

Results: CIMT value was found to be statistically significantly higher in the hemodialysis group compared to control group (0.9 mm in hemodialysis group vs. 0.7 mm in control group, $p < 0.001$). There was no statistically significant difference between groups in terms of LOX-1 levels. (0.172 ng/ml in hemodialysis group vs. 0.213 ng/ml in healthy control group, $p > 0.05$).

Conclusions: Although cardiovascular risk markers like CIMT, CRP were higher in hemodialysis group as expected, increase in LOX-1 levels was not detected.

Keywords: Atherosclerosis, Carotid intima-media thickness, Hemodialysis, Lectin-like oxidized low densitiy lipoprotein receptor-1

Cardiovascular diseases constitute the major cause of morbidity and mortality in patients with chronic kidney failure [1, 2]. Even when variables such as age, gender, and the presence of diabetes mellitus are adjusted, cardiovascular mortality is still 10-20 times higher in these patients compared to the normal population [3]. In chronic kidney disease, traditional cardiovascular risk factors alone are inadequate to explain the increase in cardiovascular mortality. Some unconventional risk factors associated with uremia are thought to play an important role in the development of atherosclerosis in these patients [4, 5]. Non-invasive sensitive indicators are needed to clarify these mechanisms and to recognize cardiovascular complications early.

Atherogenesis; which plays an important role in the pathophysiology of cardiovascular diseases, is characterized by the accumulation of plasma lipids, fibrous tissue, and cell components comprising mostly macrophages, smooth muscle cells, and lymphocytes

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in large arteries. Traditional risk factors for atherogenesis include age, gender, diabetes mellitus, hypercholesterolemia, and smoking. Currently, high plasma and tissue levels of oxidized low-density lipoprotein (oxidized LDL) have been added to these factors.

Oxidized LDL has been shown to increase the expression of proinflammatory genes, causing monocyte entry into the vascular wall and vascular endothelial cell dysfunction. Oxidized LDL also takes part in the transformation of macrophages into foam cells in atherosclerotic plaque. In some pathological conditions, such as acute myocardial infarction (AMI) and coronary artery disease (CAD), elevated levels of oxidized LDL have been reported. Oxidized LDL inhibits nitric oxide production, causing endothelial dysfunction. Oxidized LDL also induces proatherogenic genes such as endothelium-leukocyte adhesion molecules and smooth muscle growth factors [6].

Lectin-like oxidized LDL receptor-1 (LOX-1) has been identified as the major receptor for oxidized LDL. This receptor is considered to be an important molecule responsible for the binding and entry of oxidized LDL into endothelial cells. In large arteries; LOX-1 has been shown to be expressed in endothelial cells, macrophages, vascular smooth muscle cells, monocytes, platelets, and fibroblasts to bind oxidized LDL [7, 8].

Increased carotid artery intima-media thickness (CIMT) is associated with many cardiovascular risk factors [9]. CIMT has been shown to reflect the distribution and the severity of atherosclerosis, correlating well with coronary artery atherosclerosis. Therefore, the measurement of CIMT is considered a very good indicator of subclinical atherosclerotic cardiovascular disease (CVD) [10].

In our study, we aimed to demonstrate whether LOX-1 and CIMT; which are the indirect biomarkers of atherosclerosis, are correlated with cardiovascular risk markers in hemodialysis patients.

METHODS

The study included 28 patients, who had undergone hemodialysis treatment for more than 6 months and 19 healthy individuals as the control group.

Patients with documented atherosclerotic cardiovascular disease, peripheral vascular disease, nicotine and alcohol use, active infection, severe liver and heart failure, and diabetes mellitus were excluded. The study protocol was approved by the Research Review Board of the Ministry of Health Bursa Yuksek Ihtisas Training and Research Hospital (Date: 01.10.2010, Decision no: 2010/2). Informed consent was obtained from all individuals participating in the study.

Medical history was obtained from all participants and general physical examinations were performed. Age, gender, smoking status, drug use, height, weight, and body mass index of the participants were noted. After the participant rested for 20 minutes; the arterial blood pressure was measured from the brachial artery with a mercury sphygmomanometer with an adult-type cuff, while the patient was in the sitting position. A systolic blood pressure of more than 140 mmHg and a diastolic pressure of more than 90 mmHg were accepted as hypertension. The participants with serum total cholesterol levels of > 200 mg/dl and/or triglyceride levels of > 150 mg/dl and/or patients taking lipid-lowering drugs were considered hyperlipidemic patients. The body weight, height, and waist circumference of the participants were measured. Body mass index (BMI) was calculated using the following formula: weight (kg)/height (m) [2].

Biochemical Analysis

Venous blood samples were collected from the participants for testing the levels of serum creatinine, urea, sodium, potassium, calcium, phosphorus, albumin, total protein, uric acid, total cholesterol, triglyceride, HDL, LDL, fasting blood sugar (FBS), parathormone, C-reactive protein (CRP), and LOX-1. Blood samples collected at least 8 hours of fasting in the morning. In hemodialysis patients, the samples were collected in the same time interval but before the hemodialysis session. To test LOX-1 levels, 5 cc blood was drawn into anticoagulant-free tubes and centrifuged for 5 minutes at 5000 rpm to separate the sera. Then, all samples were stored at -80°C by the time of the analysis of all samples together. Other laboratory analyses were performed daily. Serum LOX-1 levels were determined by using commercially available human lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) ELISA kit (Uscn Life Science Inc. Wuhan).

Carotid Artery Ultrasound Examinations

Carotid artery ultrasound examinations of the participants were performed by an experienced cardiology specialist at Bursa Yuksek Ihtisas Training and Research Hospital. The right and left carotid arteries were visualized when the participants were in the supine position and their heads were extended. Toshiba Nemio 20 high-resolution B-mode ultrasound and an 8 MHz probe were used for the measurements. The interfaces between the intima and lumen and between the media and adventitia are expressed as intimal media thickness (IMT). IMT values were calculated by taking the mean of a total of 12 measurements; which comprised two measurements at the main carotid artery level (2 cm proximal to the bulbous), two at the level of the carotid bulb, and two from the internal carotid arteries all from both sides in each participant.

Statistical Analysis

'SPSS for Windows version 13.0' software of the Department of Biostatistics of Uludag University School of Medicine was used for the statistical analyses in our study. In the study; continuous variables have been presented as median and minimum and maximum values, while categorical variables have been presented as numbers and percentages. The conformity of the continuous variables to a normal distribution was examined with the Shapiro Wilk test. Based on the results obtained from the Shapiro Wilk test, the Mann-Whitney U test was used for comparisons between the groups. Pearson's chi-square and Fisher's exact chi-square tests were used for comparing the categorical variables between the groups. Correlation analysis was performed in order to determine the associations of the variables. Pearson's and Spearman's correlation coefficients were calculated. A p - value of < 0.05 was considered statistically significant in the study.

RESULTS

A total of 47 individuals, including hemodialysis patients and the healthy control group participants, were included in the study. The hemodialysis group consisted of 28 (59.6%) individuals and the control group consisted of 19 (40.4%) individuals and. The mean age in the hemodialysis and control group was 46.5 and 40 years, respectively. When the control group and the hemodialysis group were compared, significant differences were observed in the mean systolic and diastolic blood pressure between the groups (Table 1). The hypertensive nephropathy is the most cause of disease in the hemodialysis group (Table 2).

Urea, creatinine, parathormone, phosphorus, potassium, serum triglyceride, serum CRP and uric acid levels were higher in the dialysis group compared to the control group and these elevations were statistically significant. Serum total cholesterol, LDL-cholesterol, and HDL-cholesterol levels were higher in the control group compared to the dialysis group with statistically significant differences (Table 3). The mean IMT value were significant higher in dialysis group compared with control group (0.90 mm and 0.70 mm,

Table 1. Clinical charasteristic features of patient and control group

Charasteristics	Hemodialysis (n= 28)	Control (n= 19)	*p value*
	Median (min-max.)	Median (min-max.)	
Age (years)	46.5 (22-67)	40 (33-68)	> 0.05
Gender (female/male)	10/18	16/3	> 0.05
BMI (kg/m²)	23 (16-39)	26 (20-31)	> 0.05
Dialysis duration(month)	48(12-132)	-	
SBP (mmHg)	130 (100-160)	110 (90-130)	**< 0.01**
DBP (mmHg)	80 (60-90)	70 (60-90)	**0.03**
Smoke	9	3	> 0.05

P value: for comparison of hemodialysis patients and controls (t test for continues variables and χ^2 test for categorical, as variables). The patients with hemodialysis and controls were similar according to the socioeconomic status, racial and ethnic background, and, dietary and/or physical activity habits, religion

Table 2. Causes of chronic kidney disease

	n	%
Hypertensive nephropathy	10	35.7
Glomerular disease	6	21.4
Unknown etiology	**5**	17.8
Obstructive uropathy	**5**	17.9
Chronic tubulointerstitial nephritis	2	7.2

$p < 0.001$) (see Table 3).

The mean serum LOX-1 levels of the control and dialysis groups were 0.213 ng/ml and 0.172 ng/ml, respectively. There was not a statistically significant difference in the levels of LOX-1 between the two study groups (Table 3).

DISCUSSION

The role of atherosclerosis in the aetiology of many diseases and the resulting high morbidity and mortality rates have increased the interest in this subject matter with growing importance. Prevention of atherosclerosis-associated disorders and inhibition of atherogenesis in cases with emergent diseases, or even the regression of atherogenesis, can be made possible by eliminating risk factors [11].

Carotid arteries are appropriate sites to detect the thickening; which is a good indicator of general atherosclerosis. Several studies that demonstrate the relationship between cardiovascular diseases and carotid atherosclerosis are available in the literature. High CIMT is considered an indicator of generalized ather-

Table 3. Biochemical parameters and carotis intima media thickness in study group

	Hemodialysis (n= 28)	Control (n= 19)	*p value*
	Median (min-max.)	Median (min-max.)	
Hemoglobin (g/dL)	11.35 (9.2-15.59)	12.6 (10.1-14.9)	**007**
Hematocrit (%)	33.8 (27- 45.3)	38.2 (32.2-43.9)	**< 0.001**
Leukocyte (mm³)	5950 (3200-13500)	6300 (4400-10200)	>0.05
Sodium (mEq/L)	139 (130-144)	139 (137-145)	> 0.05
Potassium (mEq/L)	4.95 (3.80-6.60)	4.40 (3.80-4.90)	**< 0.001**
Calcium (mg/dL)	8.80 (7.20-10.10)	9.10 (8.20-9.90)	0.34
Phosphorus (mg/dl)	5.45 (3.50-16)	3.67 (2.20-4.25)	**< 0.001**
Glucose (mg/dL)	88.5 (56-172)	96 (76-116)	> 0.05
Urea (mg/dL)	127 (35-190)	25 (15-36)	**< 0.001**
Creatinine (mg/dL)	9.20 (1.90-13.0)	0.70 (0.48-1.02)	**< 0.001**
Uric acid (mg/dL)	5.80 (3.70-8.80)	3.70 (2.80-6.70)	**< 0.001**
Total cholesterol (mg/dL)	147.5 (97-304)	184 (110-253)	**0.001**
Triglycerides (mg/dL)	138 (63-264)	67 (41-175)	**< 0.001**
LDL (mg/dL)	83.50 (42-225)	120 (40-182)	**0.02**
HDL (mg/dL)	38 (23-64)	54 (36-73)	**< 0.001**
Total protein (g/dL)	6.70 (5-8.10)	7.20 (6.20-7.80)	**0.013**
Albumine (gr/dl)	3.80 (2.70-4.90)	4.50 (3.80-4.90)	**< 0.001**
Parathormone (pg/mL)	237 (6-1656)	42 (10-114)	**< 0.001**
CRP (mg/L)	5.25 (1.00-34.00)	1.00 (0.10-12.70)	**< 0.001**
LOX-1 (ng/mL)	0.172 (0.12-0.54)	0.213 (0.11-0.42)	> 0.05
CIMT (mm)	0.90 (0.60-1.30)	0.70 (0.50-0.80)	**< 0.001**

P value: for comparison of patients with hemodialysis and controls (t test for continuos variables and χ^2 test for categorical, as variables).

osclerosis [10]. Several studies are available in the literature demonstrating increased CIMT in dialysis patients compared to the normal population. Kumar *et al*. [12] in 2009; in a study on 30 hemodialysis patients and a healthy control group, found significantly higher values of CIMT in hemodialysis patients compared to the healthy control group. Prasad *et al*. [13] compared CIMT of 62 diabetic and nondiabetic peritoneal dialysis patients and 62 healthy individuals in the control group and demonstrated that CIMT was higher in the patient group compared to the healthy control group. In our study, in accordance with the studies in the literature, the CIMT value in the dialysis group was found to be statistically significantly higher than that of the control group (0.90 mm vs 0.70 mm in; $p < 0.001$).

Many studies have supported that LOX-1 and atherosclerosis are closely associated. Most of the toxic effects of oxidized LDL are regulated by the LOX-1 receptor. LOX-1 expression has been shown to increase in atherosclerotic lesions in humans and experimental animal models [14].

In a study by Sakurai *et al*. [15] on endothelial dysfunction, LOX-1 was demonstrated to be closely associated with high levels of oxidative stress. Hayashida *et al*. [16] showed that; compared to the healthy control group, the serum LOX-1 level was significantly higher in acute coronary syndrome patients with symptomatic coronary heart disease. In our study, LOX-1 levels were compared between hemodialysis patients and healthy individuals. No significant differences were found in LOX-1 levels between the groups. Studies have demonstrated that both statins, angiotensin converting enzyme (ACE) inhibitors and angiotensin-2 receptor (AT-2) blockers reduce serum LOX-1 levels. Li *et al*. [17] showed that both simvastatin and atorvastatin therapy reduced the LOX-1 expression in coronary artery endothelial cells. In vitro studies have demonstrated that statins and angiotensin converting enzyme (ACE) inhibitors, inhibit oxidized LDL-induced oxidative stress, the expression of adhesion molecules, and the release of LOX-1 [18]. In our study, some of the patients in the dialysis group were receiving treatment for statin and ACE inhibitors/AT-2 blockers for hypertension and hyperlipidemia. We thought that the low levels of lox-1 in hemodialysis patients may be due to these drugs.

Determining the presence of conventional risk factors, besides uremia-specific clinical and metabolic abnormalities is highly important in chronic kidney disease-associated premature atherosclerosis. Conventional risk factors are found to increase in uremia but still inadequate alone to explain the presence of accelerated atherosclerosis. In addition to recent studies showing that atherosclerosis and inflammation are closely associated, many studies report that CRP is also closely associated with CIMT or other indicators of atherosclerosis [19-21]. This relationship is reported to exist in patients with chronic kidney failure and in patients receiving hemodialysis, too. Zoccali *et al*. [19] investigated the relationship between inflammatory processes and atherosclerosis in 138 chronic dialysis patients and concluded that CRP was found high in patients with carotid atherosclerosis (high CIMT) and that inflammation could play a role in the pathogenesis of atherosclerosis. Stenvinkel *et al*. [20] study showed that compared to the control group of healthy individuals, chronic kidney failure patients had high CIMT along with high prevalences of carotid plaques and malnutrition and that CRP was found high in malnutrition. Owen *et al*. [22] showed that serum CRP levels were significantly higher in hemodialysis patients compared to the healthy control group and that CRP as a marker of inflammation had a predictive value for cardiovascular mortality. In our study, serum CRP levels were found to be significantly higher in the hemodialysis group compared to the control group consistent with the information in the literature. Although the small number of patients causes limitations, the fact that it was more specifically performed on hemodialysis patients adds value to the study.

CONCLUSION

In conclusion, cardiovascular risk markers of CIMT and CRP were found high in the hemodialysis patient group of our study as expected. No significant differences were detected in serum LOX-1 levels; which is an important atherosclerosis marker. It will be appropriate to interpret the results of the present study by carrying out further extensive studies on this subject matter.

Authors' Contribution

Study Conception: TD, SK; Study Design: TD,

SK; Supervision: TD, SK; Funding: TD; Materials: TD, SK; Data Collection and/or Processing: TD; Statistical Analysis and/or Data Interpretation: SK; Literature Review: TD; Manuscript Preparation: TD, MGG and Critical Review: TD, MGG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Investigation of the effect of coronary collateral circulation quality on postoperative atrial fibrillation after coronary artery bypass graft operations in patients with right coronary artery total occlusion

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ABSTRACT

Objectives: Postoperative atrial fibrillation (PoAF) may occur in 25-50% of patients after coronary artery bypass graft (CABG) surgery. The severity of coronary artery disease and the quality of coronary collateral circulation (CCC) in the coronary artery with chronic total occlusion (CTO) are known as indirect indicators of myocardial ischemia. In this study, we aimed to investigate the effect of CCC quality on PoAF in patients with right coronary artery (RCA) total occlusion who underwent CABG operation.

Methods: Patients who underwent isolated CABG operation between May 15, 2016 and June 15, 2020 and had RCA CTO were included in the study retrospectively. The patients were recorded as Group 1 who developed PoAF in the postoperative period and Group 2 who did not.

Results: A total of 99 patients were included in the study. Those who develop PoAF were determined as Group 1 (n = 32, mean age = 66.9 ± 11 years), and those who did not were determined as Group 2 (n = 67, mean age = 54.4 ± 12.8, years). There were no statistically significant differences between the two groups in terms of gender, smoking, diabetes mellitus, hypelipidemia and chronic obstuctive pulmonary disease rates. In multivariate analysis, being over 70 years old (OR: 1.396, 95% CI: 1.080-2.190, $p = 0.007$), poor CCC (OR: 1.090, 95% CI: 1.045-1.338, $p = 0.014$) and left atrial diamater (OR: 0.557, 95% CI: 0.471-0.783, $p = 0.032$) were determined as independent predictors of development of PoAF.

Conclusions: In this current study, we demonstrated that low CCC quality increases the risk of POAF in patients with right coronary CTO. CCC quality can be used as an evaluation parameter in identifying groups at risk for PoAF in these special patient groups.

Keywords: Coronary artery disease, surgery, atrial fibrillation, coronary collateral circulation

Coronary artery bypass graft (CABG) surgery is the most valuable method in the treatment of advanced coronary artery disease (CAD). Although mortality is a catastrophic risk in these operations, there are also morbid risks such as postoperative atrial fibrillation (PoAF), cognitive disorders, and end-organ

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damage [1]. Atrial fibrillation may occur in 25-50% of patients after CABG surgery. In addition, PoAF includes a cerebrovascular risk, prolongs hospitalizations and increases treatment costs [2]. Therefore, it is very important to reveal the risk factors for PoAF before CABG operations.

There are many factors that affect the development of PoAF after CABG surgery. These include inflammatory processes, advanced age, and perioperative ischemic events [3]. The severity of CAD and the quality of circulation in the coronary artery with chronic total occlusion (CTO) are known as indirect indicators of myocardial ischemia [4]. In a study, it was shown that preoperative poor coronary collateral circulation (CCC) increased the risk of PoAF after CABG operations [5]. Other studies have also shown that right coronary artery (RCA) disease or its severity is associated with PoAF [6, 7].

In this current study, we aimed to investigate the effect of CCC quality on PoAF in patients with RCA total occlusion who underwent CABG operation.

METHODS

Patients who underwent isolated CABG operation between May 15, 2016 and June 15, 2020 and had right coronary artery CTO were included in the study retrospectively. The study was initiated after the approval of the local ethics committee. The study was carried out in accordance with the Helsinki Declaration criteria. The data of the patients were obtained from the hospital digital record archive and patient files. Preoperative demographic characteristics (age, gender, comorbidities, etc.), operative (perfusion times) and postoperative (hospital and intensive care unit stays, inotropic needs, blood transfusion amounts, etc.) characteristics of all patients were recorded. Those who had emergency operations, combined cardiac surgeries, reoperations, those without RCA disease or rudimentary RCA, those who did not undergo right coronary bypass, those who used preoperative amiodarone, those with thyroid hormone disorders and those with atrial fibrillation were excluded from the study. As a result of exclusion criteria, 99 consecutive patients were included in the study. Coronary angiography of all patients was followed and the CCC of RCA was graded. The patients were recorded as Group 1 who developed PoAF in the postoperative period and Group 2 who did not. In the study, the factors affecting the risk of in-hospital PoAF after the operation were analyzed.

Evaluation of Coronary Collateral Circulation

Coronary collateral circulation was determined by the Rentrop classification. This evaluation was made by two individuals, an interventional cardiologist and a cardiovascular surgeon. Classification was performed as follows [5]: (a) Grade 0: No filling; (b) Grade 1: Inability to visualize the epicardial main vessel structure even though the lateral branches are filled with collaterals; (c) Grade 2: Partial filling of the epicardial main vessel structure with collaterals; and (d) Grade 3: Complete filling of the epicardial main vessel. As a result of this classification, patients with Grade 2 and Grade 3 fillings were included in the study. Right coronary bypass was performed in all patients.

Diagnosis of Postoperative Atrial Fibrillation

All patients were observed in the intensive care unit with continuous heart rhythm monitoring. Also, the 12-lead electrocardiography (ECG) was performed when the patients had complaints such as palpitation, dyspnea, or angina pectoris. Atrial fibrillation was verified via 12-lead ECG. The diagnosis of AF was based on guidelines of the European Society of Cardiology [8]. Postoperative atrial fibrillation was defined as irregular waves in place of typical p waves on ECG. An AF episode > 60 seconds was accepted as PoAF.

Statistical Analysis

In our study, SPSS 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc. version 21.0, Chicago, IL, USA) program was used to analyze the data. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate normality distribution. Continuous data and data with normal distribution were given as the mean and standard deviations. Data that did not distributed with normally were recorded as median (minimum-maximum). Student's t-test was used for the analysis of normally distributed data, while Mann Whitney U test was used for the analysis of non-normally distributed data. Frequency and percentile analysis were performed for nominal data and Chi

Square test was used for comparison. Univariate and multivariate logistic regression analysis was performed to analyze the factors affecting the development of PoAF. A $p < 0.05$ was considered statistically significant in all evaluations.

RESULTS

A total of 99 patients were included in the study. Those who develop PoAF were determined as Group 1 (n = 32, mean age = 66.9 ± 11 years), and those who did not were determined as Group 2 (n = 67, mean age = 54.4 ± 12.8, years). There were no statistically significant differences between the two groups in terms of gender, smoking, diabetes mellitus, hypelipidemia, chronic obstuctive pulmonary disease rates, cerebrovascular event/trans-ischemic attack history, body mass index, ejection fraction and beta blocker/angiotensin- converting enzyme inhibitor/angiotensin receptor blocker use rates. Rates of hypertension (HT), age and left atrial diamater were significantly higher in Group 1 compared with Group 2 ($P = 0.007$, $p < 0.001$ and $p = 0.006$, respectively). Rentrop grade was significantly lower in Group 1 ($p < 0.001$). Demographic characteristics and preoperative data of all patients were summarized in Table 1.

Peroperative features of the patients were presented in Table 2. There was no statistically significant difference between the two groups, in terms of perfusion times, blood product use rates and drainage amounts. Intensive care stay, total hospital stay days and positive inotropic support rates were statistically significantly higher in Group 1 ($p < 0.001$, $p < 0.001$ and p = 0.023).

Univariate and multivariate logistic regression analysis was utilized to predict parameters supporting development of PoAF (Table 3). In univariate analysis being over 70 years old (OR [odds ratio]: 1.921, 95% CI [confidence interval]: 1.345-3.190, $p < 0.001$), hypertension (OR: 1.290, 95% CI: 1.058-2.040, $p = 0.008$), inotropic support (OR: 0.578, 95% CI: 0.345-0.776, $p = 0.024$), poor CCC (OR: 1.428, 95% CI: 1.145-1.944, $p < 0.001$), and left atrial diameter (OR:

Table 1. Demographic and preoperative features of the patients

Variables	Group 1 (n = 32)	Group 2 (n = 67)	*p* value
Age (years) (mean±SD)	66.9 ± 11	54.4 ± 12.8	**< 0.001**†
Male gender, n (%)	23 (71.9)	40 (59.7)	0.239*
Smoking, n (%)	10 (31.3)	17 (25.4)	0.539*
Hypertension, n (%)	26 (81.3)	34 (50.7)	0.007*
Diabetes mellitus, n (%)	9 (28.1)	25 (37.3)	0.358*
Hyperlipidemia, n (%)	14 (43.8)	30 (44.8)	0.923*
COPD, n (%)	7 (9.9)	6 (16.6)	0.144*
Previous CVA, n (%)	2 (6.3)	3 (4.5)	0.711*
BMI (kg/m^2)	26.9 (25-40.8)	28.1 (25- 36.5)	0.441‡
Ejection fraction (%)	45 (30-65)	50 (30-60)	0.158‡
β-Blocker therapy, n (%)	26 (81.3)	58 (86.5)	0.490*
ARB/ACE-I therapy, n (%)	9 (28.1)	17 (24.4)	0.614*
Left atrial diameter (mm)	38 (28-50)	33 (24-50)	**0.006**‡
Rentrop state			**< 0.001***
Grade 2, n (%)	22 (68.7)	18 (26.8)	---
Grade 3, n (%)	10 (31.2)	49 (73.1)	---

Data are expressed as mean±SD or median (minimum-maximum) or n (%). *Chi-square test, †Student's t-test, ‡Mann-Whitney U test, ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = Body mass index, CVA = Cerebrovascular accident, COPD = Chronic obstructive pulmonary disease, SD = standard deviation

Table 2. Peroperative features of the patients

Variables	Group 1 (n = 32)	Group 2 (n = 67)	*p* value
Total perfusion time (min)	88 (60-130)	85 (55-120)	0.304‡
Cross-clamp time (min)	57 (30-80)	61 (29-94)	0.227‡
Inotropic support, n (%)	12 (37.5)	10 (14.9)	0.023*
Packed blood products (units)	5 (4-13)	5 (4-10)	0.219‡
Total chest tube drainage (ml)	700 (450-1500)	850 (400-1600)	0.104‡
Total ICU stay (days)	3 (2-18)	2 (2-7)	**< 0.001**‡
Total hospital stay (days)	11 (9-28)	7 (6-15)	**< 0.001**‡

Data are expressed as median (minimum-maximum) or n (%). *Chi-square test, ‡Mann-Whitney U test

0.670, 95% CI: 0.490-0.866, $p = 0.007$) were found to be significantly correlated with the development of PoAF. In multivariate analysis, being over 70 years old (OR: 1.396, 95% CI: 1.080-2.190, $p = 0.007$), poor CCC (OR: 1.090, 95% CI: 1.045-1.338, $p = 0.014$) and left atrial diamater (OR: 0.557, 95% CI: 0.471-0.783, $p = 0.032$) were determined as independent predictors of development of PoAF.

DISCUSSION

Coronary artery disease severity and poor CCC have also been implicated as indirect indicators of ischemic status [4]. Studies have shown that the prevalence of CAD increases the risk of PoAF after CABG operations [9]. Coronary collateral circulation is an adaptation mechanism developed by the heart against ischemia as a result of myocardial tissue being exposed to ischemia. As a result, the severity of ischemia suffered by the myocardial area with good collateral circulation will be less. It has been demonstrated that patients with good CCC have less tissue damage in myocardial infarction cases [10]. In a recent study, it was revealed that stroke and mortality rates after CABG operations are lower in patients with good CCC [11]. In this current study, we investigated the effect of CCC quality on PoAF in patient groups with RCA total occlusion. At the end of the study, we showed that poor CCC status is an independent predictor of PoAF after CABG operations, in addition to known risk factors such as being over 70 years of age and large left atrial diameter.

In a study by Gungor *et al*. [5], the role of CCC in predicting the development of PoAF after CABG operations was investigated. In their study, a total of 165

Table 3. Logistic regression analysis to identify factors affecting development of postoperative atrial fibrillation

	Univariate analysis			Multivariate analysis		
Variables	*p* value	Exp(B) Odds Ratio	95% CI Lower-Upper	*p* value	Exp(B) Odds Ratio	95% CI Lower-Upper
Age > 70 years	**< 0.001**	1.921	1.345-3.190	**0.007**	1.396	1.080-2.190
Hypertension	**0.008**	1.290	1.058-2.040	0.116	1.790	0.890-1.995
Diabetes mellitus	0.376	0.990	0.770-1.180	--	--	--
COPD	0.146	1.115	0.895-1.170	--	--	--
Inotropic support	**0.024**	0.578	0.345-0.776	0.352	0.884	0.779-1.154
Poor CCC	**< 0.001**	1.428	1.145-1.944	**0.014**	1.090	1.045-1.338
Left atrial diameter	**0.007**	0.670	0.490-0.866	**0.032**	0.557	0.471-0.783

COPD = Chronic obstructive pulmonary disease, CCC = Coronary collateral circulation

patients were divided into two groups as those with poor CCC (Grade1 and 2, n = 79) and those with good CCC (Grade 2 and 3, n = 89). The incidence of PoAF was significantly higher in patients with poor CCC (37 [49%] vs. 12 [14%], $p < 0.001$). In the multivariate analysis, poor CCC was found to be an independent predictor of PoAF (OR: 11.500; 95% CI, 3.977-33.253, $p < 0.001$) [5]. The effect of coronary vascular structure on PoAF was investigated in the study conducted by Polat *et al*. [12] in which 94 CABG patients were included. Although there was no statistically significant difference ($p = 0.065$), the rate of PoAF was found to be high in patients with poor CCC [12]. Unlike these two studies, we included only the patient group with RCA total occlusion, and all patients in our study underwent RCA bypass. Therefore, poor CCC Rentrop Grade 2 and good CCC Rentrop grade 3 were determined in our study. As a result of our study, we revealed poor CCC as an independent predictor of PoAF in patients who underwent CABG with right coronary collateral total occlusion.

Pathophysiological events that occur as a result of the exposure of the atrial wall to intraoperative ischemia may lead to the development of PoAF [13]. Although atrial branches may originate from the heads of the three main coronary arteries, RCA may contribute more to this supply [14]. In this direction, in the study by Mendes *et al*. in which 104 patients who underwent CABG were included, the patients with severe RCA stenosis (> 70% or = 70%) and those without it were divided into two groups and the risk factors for PoAF were investigated. At the end of this study, the authors revealed that severe RCA stenosis as an independent predictor of the development of PoAF in addition to factors such as age and male gender [6]. In a recent study, the relationship between right coronary artery disease severity calculated by Gensini score and PoAF in patients with RCA stenosis was investigated. In this retrospective study, which included 283 CABG patients, right coronary artery disease with a high Gensini score was found to be an independent predictor of PoAF.

In our study, the presence of HT and positive inotropic support were also significantly correlated with the development of PoAF (OR: 1.290, $p = 0.008$ and OR: 0.578, $p = 0.024$). Hypertensive patient groups have increased inflammation status and these patients are also more vulnerable to myocardial ischemia. In a study, the frequency of atrial fibrillation was found to be approximately 1.6 times higher after CABG operations in hypertensive patients [15]. Positive inotropic support may also lead to atrial fibrillation due to increased sympathetic stimulation. Studies have shown that the use of increased positive inotropic support increases the risk of PoAF [16, 17].

In our study, in addition to the presence of poor CCC, other parameters that we showed independent predictors for PoAF were advanced age and left atrial diameter. Enlargements in the left atrial structure can also increase the risk of PoAF by causing various histopathological changes in the atrial conduction pathways and atrial structure. In a study by Karimi et al., its relationship with PoAF was also shown [18]. Structural and electrophysiological changes occur in the atrial tissue due to increased age. This situation also increases the risk of developing PoAF [18].

Limitations

Although our study included a special group of patients with RCA total occlusion, the limited number of patients is an important limitation. In addition, the study was conducted as a single center and retrospective study.

CONCLUSION

In conclusion, the most important treatment method of atherosclerotic heart disease is CABG operations. Atrial fibrillation is an important mortal and morbid condition that can occur after these operations, and it is important to reveal the risk factors. In this current study, we demonstrated that low CCC quality increases the risk of PoAF in patients with right coronary CTO. Collateral circulation quality can be used as an evaluation parameter in identifying groups at risk for PoAF in these special patient groups. Our study needs to be supported by multicenter prospective studies with different patient groups.

Authors' Contribution

Study Conception: MA; Study Design: MA; Supervision: MA, SY; Funding: MA; Materials: MA, SY; Data Collection and/or Processing: MA; Statistical Analysis and/or Data Interpretation: MA, SY; Literature Review: MA, SY; Manuscript Preparation: MA,

SY and Critical Review: MA, SY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(2):181-190 Original Article

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Initial computed tomography features of known inpatient ward versus intensive care admission COVID-19 cases: is there any difference?

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ABSTRACT

Objectives: The aim of this study was to evaluate initial computed tomography (CT), basic clinical and demographic features of cases with COVID-19 pneumonia with known inpatient ward and intensive care unit hospitalization.

Methods: A total of 200 cases (103 males, 97 females; age range: 18-92 years) were retrospectively and randomly collected whom were hospitalized and followed up at infectious disease inpatient ward and intensive care unit (ICU). The initial CT findings were interpreted by two radiologists at the same session by consensus.

Results: Cough (61%) and fever (54%) were the main symptoms at the onset presentation. Initial chest CT imaging revealed that 79.5% ground-glass opacities. Bilateral distribution (62.5%), peripheral and central distribution (45.5%), dorsal and ventral involvement (52.5%) were identified in all cases. CT features predominantly were at right and left lower lobes (69.5%, 62.5%; respectively). Cases with known ICU admission had statistically significant differences with inpatient ward admission cases in regards to CT features included mixed GGO and consolidation, bronchial wall thickening, pleural effusion, subpleural band, emphysema, coronary calcification, cardiothoracic ratio, aorta diameter.

Conclusions: Initial CT features may be helpful for foreseeing admission to ICU as in clinical features.

Keywords: COVID-19, CT, ICU, inpatient, features

Coronavirus 2019 disease (COVID-19) was officially named by the World Health Organization (WHO) on 11 February, 2020 after cases of pneumonia unknown etiology was identified in Wuhan, China in December 2019 [1, 2]. The novel coronavirus (2019-nCoV) was isolated by Chinese authorities on 7 January, 2020 [1]. On 11 March, 2020 WHO announced COVID-19 as a pandemia [3], on the other hand The Ministry of Health, Turkey reported first laboratory-confirmed novel coronavirus (2019-nCoV) case on 10 March, 2020 [4]. By May 31, 2020, a total of 163,942 confirmed cases, 2.77% case fatality rate, 648 critical or serious ICU follow-up cases have been reported in Turkey at daily official announcement [4,

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Reverse transcription-polymerase chain reaction (RT-PCR) is the gold standart diagnostic method for COVID-19, however high false-negative results make managing difficulties in disease course. At this point, radiological methods such as chest x-ray and computed tomography (CT) play important role and are helpful for clinicians in both supporting diagnosis and monitoring the cases even if PCR is negative, but COVID-19 is highly clinically suspected [6, 7]. CT imaging findings of laboratory-confirmed COVID-19 cases in detail from many countries, mainly from China, were to be reported as small or large case sample series [8, 9].

Older adults and cases with concomitant diseases such as hypertension are at a significant risk of severe outcome related to COVID-19 disease [10, 11]. CT has not only pivotal role in the diagnosis, but also has significant role on management of temporal changes of the disease both clinically and radiologically [12]. In this point of view, we hypothesized if there was a difference between initial CT manifestations with known inpatient ward or intensive care unit (ICU) hospitalization history.

In this study, we aimed to evaluate and compare the initial CT, basic clinical and demographic features of laboratory-confirmed sample of 200 COVID-19 cases with known inpatient ward and ICU admission in Ankara City Hospital, Turkey.

METHODS

Turkish Ministry of Health approval was obtained on 21 May, 2020 and local ethics committee approval was received from Ankara City Hospital Ethical Committee, Turkey (approved number: E1/666/2020) on 28 May, 2020. Informed consent was waived due to the retrospective nature of this study.

Cases

A total of 1,800 cases with laboratory-confirmed COVID-19, 5500 highly clinically suspected cases who were admitted to Ankara City Hospital in Turkey from March 11, 2020 to May 31, 2020. As a sample 200 laboratory-confirmed COVID-19 cases were retrospectively and randomly collected who were hospitalized and followed up at infectious disease inpatient ward and ICU. The study included 103 males and 97 females with a median age of 45 years (range, 18-92). The basic demographic, clinical and radiological data including gender, age, exposure history, onset symptoms, underlying diseases, CT features were screened, interpreted and analyzed. The study sample had at least one positive results of RT-PCR with nasopharyngeal swab testing and chest CT examination in their electronic health records. Chest CT examinations and admissions were at the same day for study sample. Flow chart of the study was shown in Fig. 1.

Imaging Technique

The chest CT examinations were acquired by using 128-slice Revolution Evo CT (GE Healthcare) scanners in the supine position at full inspiration from lung apices to the inferior level of the costophrenic angle. The acquisition parameters were as follows: 100 or 120 kVp; 80-400 mAs; 1.375, pitch; 0.625 reconstruction interval; 0.5 seconds (sec) rotation time. Slice thickness was 1.25 mm. Automatic exposure control system (ASiR, GE, Healthcare) regulated the tube current. All chest CT examinations were obtained without intravenous contrast material.

Imaging Interpretation

The chest CT examinations were reviewed at the picture archiving and communication systems (PACS) by two radiologist blinded to the radiology report and clinic data at the same session by consensus. The conventional lung and mediastinal window settings were used by radiologists (window width: 1500 hounsfield unit (HU), window level: -600 to -700 HU; window width: 350-450 hounsfield unit (HU), window level: 40-50 HU, respectively). Multiplanar reconstruction (MPR) techniques were also used at the image interpretation sessions.

The chest CT features were interpreted in the view of presence of CT features, number of lung lobes involved, frequency of lung lobe involvement, lesion distribution by side (bilateral or unilateral), anterior-posterior localisation (ventral, dorsal or both), transverse localisation (central, peripheral or both) and scattering (focal, multifocal or diffuse), lesion characteristics and other findings. We evaluated lesion characteristics defined in previous studies and in accordance with glossary of Fleischner Society [13-16]. We measured main pulmonary artery and aorta di-

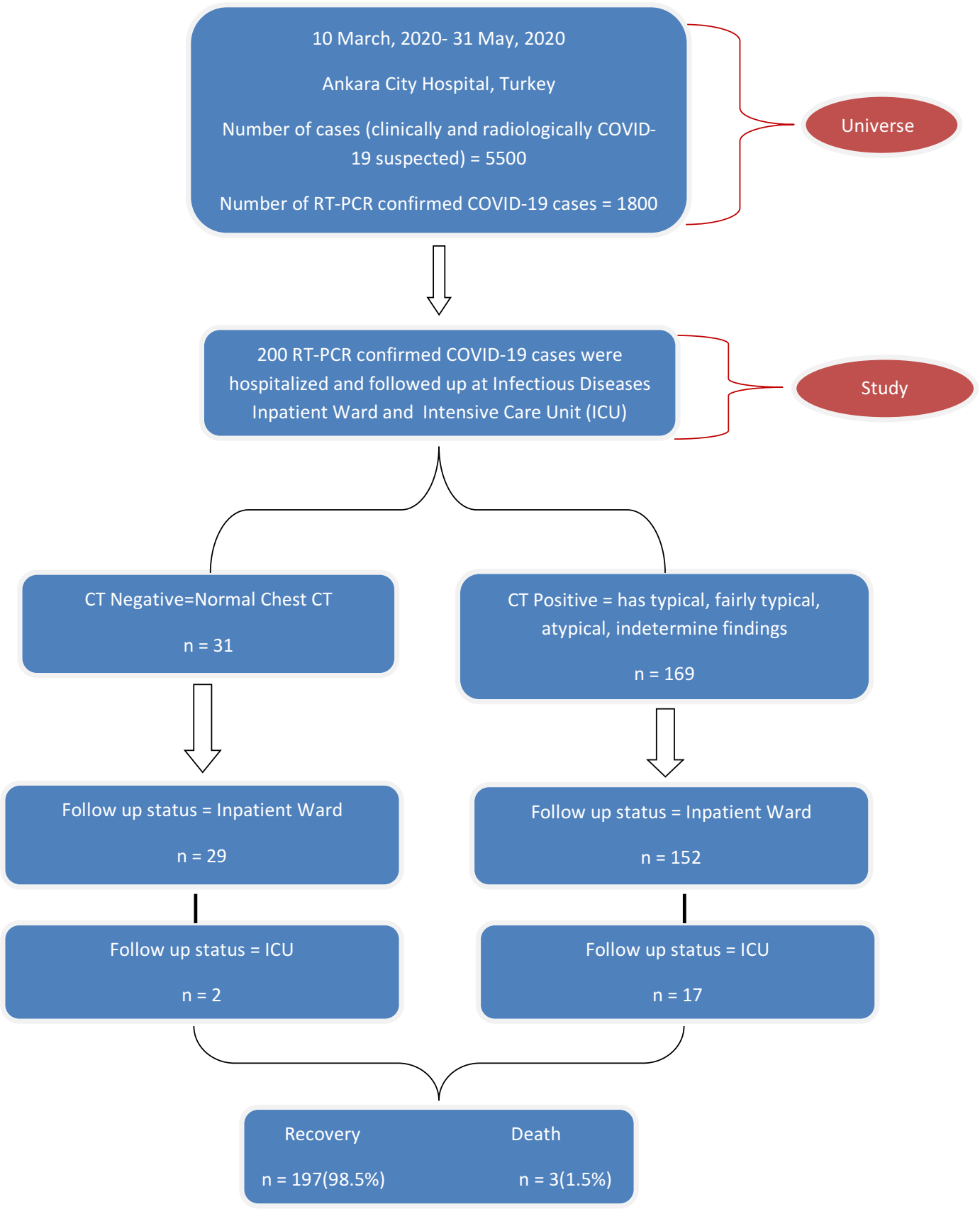

Fig. 1. Flow chart of the study.

Table 1. Basic demographic and clinical features

Features	All Cases (n = 200)
Sex	
Male	103 (51.5)
Female	97 (48.5)
Age (years)	
Median	45
Range	18-92
Age group (years)	
18-29	31 (15.5)
30-39	47 (23.5)
40-49	39 (19.5)
50-59	33 (16.5)
60-69	20 (10)
> 69	30 (15)
Exposure history	
Exposure	98 (49)
No exposure	102 (51)
Onset symptoms[a]	
Time since symptoms onset (day)	3 (0-10)
Cough	122 (61)
Fever	108 (54)
Dyspne	59 (29.5)
Myalgia	55 (27.5)
Malasie/Debility	57 (28.5)
Headache	33 (16.5)
Anosmia	20 (10)
Loss of taste	11 (5.5)
Diarrhea	9 (4.5)
Chest Pain	5 (2.5)
Back pain	2 (1)
No symptoms	39 (19.5)
Underlying disease[b]	
Hypertension	45 (22.5)
Coronary artery disease	36 (18)
Diabetes	25 (12.5)
Chronic obstructive pulmonary disease	15 (7.5)
Others (Asthma,CKD[c], PAD[d], Alzeimer)	5 (2.5)
None	142 (71)

Note-Except for age and time since symptoms onset (median with minimum-maximum range) data are numbers with percentage in parentheses.

[a,b]Some cases had more than one symptoms and underlying disease.

[c,d]Chronic kidney disease, peripheral artery disease

ameters at the level of the bifurcation of the main pulmonary artery in the transverse plan. Cardiothoracic ratio assessed as maximum diameter of heart divided by maximum thoracic diameter in the axial CT images of chest. Coronary calcifications, scoliosis and kyphosis were interpreted via MPR images as present or absent.

Statistical Analysis

Categorical and nominal datas were presented as numbers and percentages, numeric datas as medians with minimum-maximum range. Comparison of categoric and nominal datas was evaluated by chi-square or Fisher exact test, on the other hand numeric datas by Mann Whitney U test between inpatient ward and ICU admission cases. P value < 0.05 was accepted as statistically significant. SPPS for Windows software package (version 21.0, SPSS Inc.) was used for statistical analysis.

RESULTS

Demographic and Clinical Features

A total of 200 cases were included in this study. Our group of cases consisted of 103 (51.5%) males, 97 (49.5%) females, with an age range of 18-92 (median age, 45 years). 41.5% of total cases were older than 50 years. The time between onset of symptoms and hospital presentation ranged from 0 to 10 days (median, 3 days). 49% (n = 98) of total cases had an exposure history to patients with laboratory confirmed COVID-19. Common onset symptoms were cough (61%) and fewer (54%). Thirty-nine cases had no symptoms. The basic demographic and clinical features are given in Table 1.

Initial CT Features

Thirty-one cases (15.5%) had normal CT without any findings. Five lobes involvement were identified 38.5% (n = 77) of total cases. Right and left lower lobes were more likely to be involved (69.5% versus 62.5%). Lesion distribution characteristics in lung parenchyma are given in Table 2. Typical features such as ground-glass opacities (GGOs) (79.5%), round-shaped lesions (44%) and vascular enlargement (38%) were presented on the CT images in most of the cases (Figs. 2 and 3). Reversed halo sign and crazy-paving

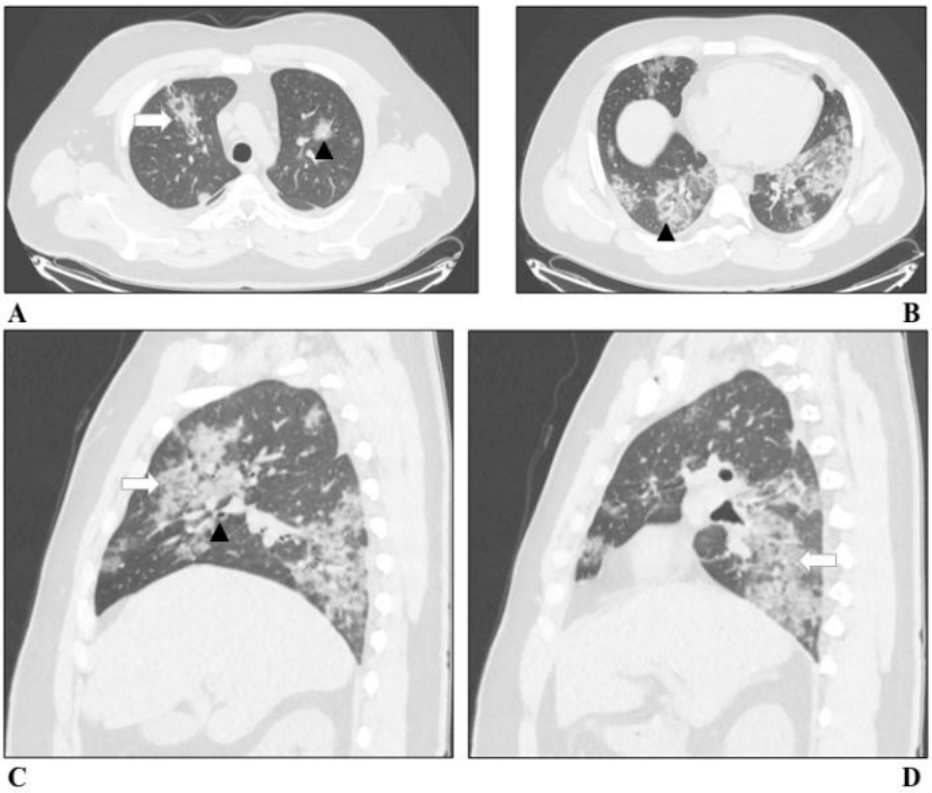

Fig. 2. (A-D) A 55-year-old man with coronavirus disease (COVID-19). Patient had onset symptoms of fever, cough and dyspnea. CT was performed on day of admission. CT images show bilateral multifocal ground-glass opacities (GGOs) and GGOs with superimposed consolidations (white arrows: A, C and D). Vascular enlargements and bronchial wall thickenings (black arrowheads: A, B, C) are also present.

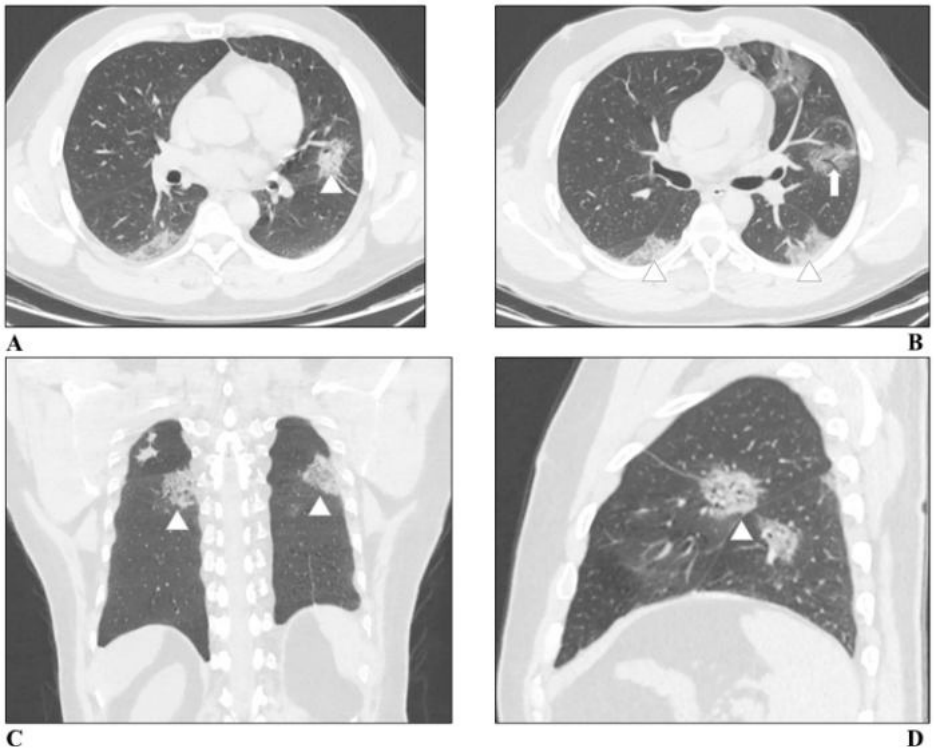

Fig. 3. (A-D) A 45-year-old man with cough. Axial (A and B), coronal (C) and sagittal (D) CT images show bilateral multiple ground-glass opacities (GGOs) and consolidations with thickened intralobular and interlobular septum (white arrowheads: A, C and D). Air bronchogram sign is also present (white arrow: B).

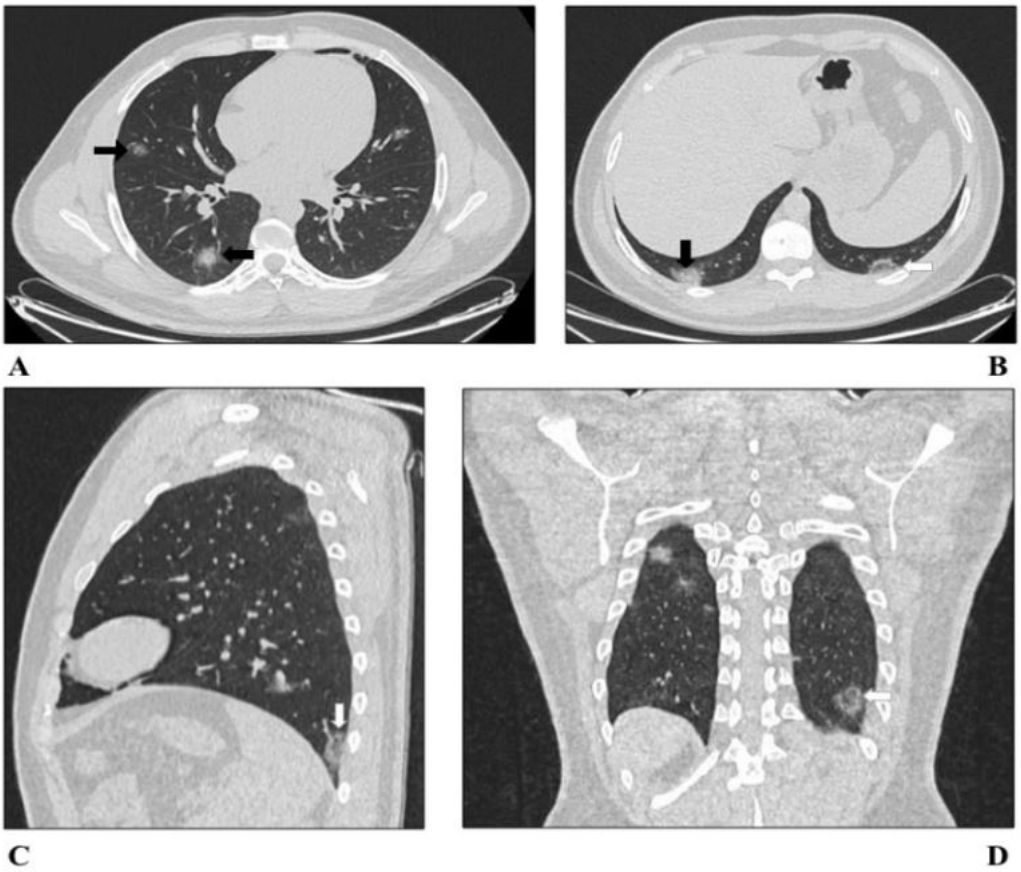

Fig. 4. (A-D) A 38-year-old man with laboratory confirmed coronavirus disease (COVID-19). Patient presented with fever and cough for two days. CT was performed on day of admission. Axial CT images show peripheral round-shaped ground-glass opacities(GGOs) (black arrows: A and B). Reverse halo sign is also present in axial, sagittal and coronal images (white arrows: B, C and D).

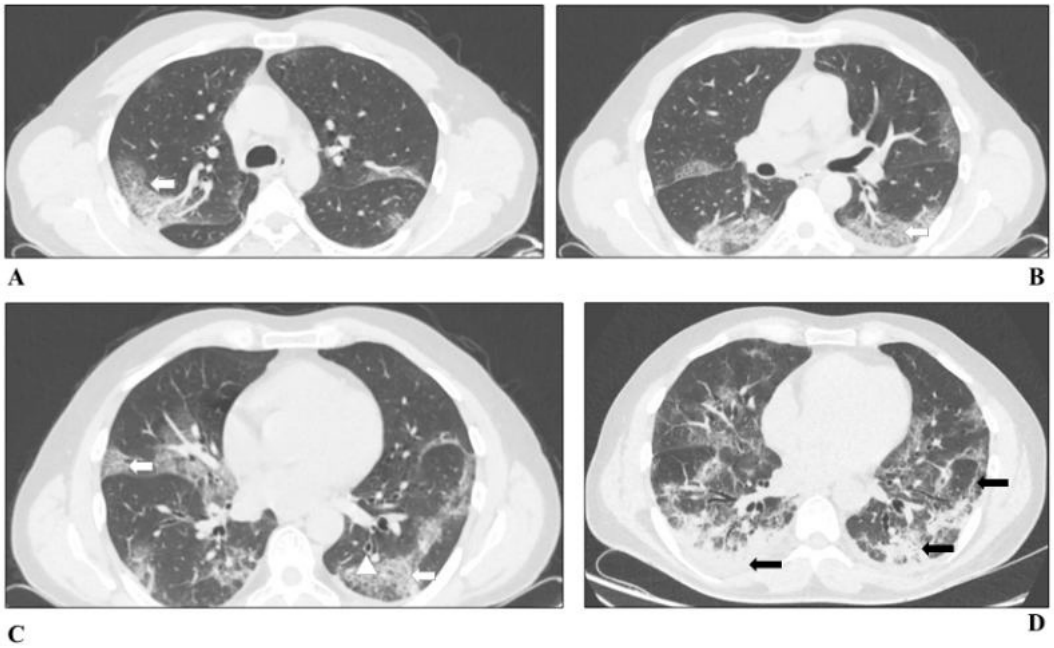

Fig. 5. (A-D) A 60-year-old man with dry cough, dyspnea and fatigue. CT was performed on day of admission (A, B and C) and 10 days later (D). Axial CT scans show interlobular septal thickening in a crazy paving pattern (white arrows: A, B and C) and bronchial wall thickening (white arrowhead: C), while consolidations and subpleural curvilinear bands occur10 days later (black arrows: D).

Table 2. Other chest CT features and measurements

Findings	All Cases (n = 200)	Cases followed-up inpatient ward (n = 181)	Cases with ICU admission (n = 19)	*p value*
Age (years)	45 (18-92)	43 (18-92)	72 (36-92)	**< 0.001**
Sex				0.705
Male	103 (51.5)	94 (51.9)	9 (47.4)	
Female	97 (48.5)	87 (48.1)	10 (52.6)	
Underlying disease	58 (29)	39 (21.5)	19 (100)	**< 0.001**
Without CT findings (%)	31 (15.5)	29 (16)	2 (10.5)	0.744
Time since symptoms onset (day)	3 (0-10)	3 (0-10)	0 (0-8)	**0.006**
Imaging Findings				
Number of lobes involved				0.520
1	38 (19)	33 (18.2)	5 (26.3)	
2	21 (10.5)	18 (9.9)	2 (10.5)	
3	12 (6)	12 (6.6)	1 (5.3)	
4	21 (10.5)	19 (10.5)	2 (10.5)	
5	77 (38.5)	70 (38.7)	7 (36.8)	
Frequency of lobe involvement				
Right upper lobe	108 (54)	99 (54.7)	9 (47.3)	0.542
Left upper lobe	107 (53.5)	99 (54.7)	8 (42.1)	0.295
Middle lobe	104 (52)	95 (52.5)	9 (47.3)	0.671
Right lower lobe	139 (69.5)	127 (70.2)	12 (63.1)	0.528
Left lower lobe	125 (62.5)	113 (62.4)	12 (63.1)	0.950
Lung region distribution				0.564
Bilateral	125 (62.5)	111 (61.3)	14 (73.7)	
Unilateral	44 (22)	41 (22.7)	3 (15.8)	
Transverse distribution				0.483
Central	4 (2)	3 (1.7)	1 (5.3)	
Peripheral	74 (37)	67 (37.0)	7 (36.8)	
Peripheral and central	91 (45.5)	82 (45.3)	9 (47.4)	
Anterior-posterior distribution				0.618
Ventral	12 (6)	11 (6.1)	1 (5.3)	
Dorsal	52 (26)	45 (24.9)	7 (36.8)	
Ventral and dorsal	105 (52.5)	96 (53.0)	9 (47.4)	
Scattered distribution				**0.019**
Focal	38 (19)	32 (17.7)	4 (21.1)	
Multifocal	115 (57.5)	108 (59.7)	9 (47.4)	
Diffuse	16 (8)	12 (6.6)	4 (21.1)	
Round-shaped lesions	88 (44)	82 (45.3)	6 (31.6)	0.144
Ground-glass opacities	159 (79.5)	146 (80.7)	13 (68.4)	**0.010**
Consolidation	60 (30)	52 (28.7)	8 (42.1)	0.294
Mixed ground-glass opacities and consolidation	57 (28.5)	49 (27.1)	8 (42.1)	**< 0.001**
Reticulation	59 (29.5)	52 (28.7)	7 (36.8)	0.568
Centrilobular nodules	17 (8.5)	14 (7.7)	3 (15.7)	0.385
Crazy-paving pattern	43 (21.5)	39 (21.5)	4 (21.1)	0.848
Air bronchogram sign	27 (13.5)	24 (13.3)	3 (15.7)	0.738
Bronchiectasis	15 (7.5)	12 (6.6)	3 (15.7)	0.179
Bronchial wall thickening	17 (8.5)	11 (6.1)	6 (31.6)	**0.003**
Reversed halo sign	15 (7.5)	15 (8.3)	0 (0)	0.368
Halo sign	26 (13)	26 (14.4)	0 (0)	0.078
Subpleural bands	17 (8.5)	11 (6.1)	6 (31.6)	**0.003**
Vascular enlargement	76 (38)	68 (37.6)	8 (42.1)	0.697
Pleural effusion	5 (2.5)	0 (0)	5 (26.3)	**< 0.001**
Pleural thickening	7 (3.5)	5 (2.8)	2 (10.5)	0.148
Mediastinal lymphadenopathy	40 (20)	32 (17.7)	7 (36.8)	0.073
Pericardial effusion	11 (5.5)	8 (4.4)	3 (15.7)	0.084
Cavitation	0 (0)	0 (0)	0 (0)	
Pneumothorax	0 (0)	0 (0)	0 (0)	
Empyhsema	33 (16.5)	26 (14.4)	7 (36.8)	**0.021**
Coronary calcification	55 (27.5)	44 (24.3)	11 (57.9)	**0.002**
Scoliosis	47 (23.5)	37 (20.4)	10 (52.6)	**0.004**
Kyphosis	57 (28.5)	43 (23.8)	14 (73.7)	**< 0.001**
Main pulmonary artery diameter (mm)	26.5 (18-43)	26 (18-43)	28 (20-34)	0.352
Aorta diameter (mm)	31 (21-45)	31 (21-43)	34 (25-45)	**0.006**
Cardiothoracic ratio	0.45 (0.23-0.66)	0.45 (0.23-0.66)	0.52 (0.43-0.63)	**< 0.001**

Note-Except for age, main pulmonary artery, ascending aorta diameter and cardiothoracic ratio (median with minimum-maximum range) data are numbers with percentage in parentheses.

patern were identified 7.5% (n = 15) and 21.5% (n = 43) of total cases, respectively (Figs. 4 and 5). Other chest CT features and measurements are demonstrated in Table 2.

Comparison of Basic Demographic-Clinical and Initial CT Features with Known Inpatient Ward and ICU Admission Cases

Cases with known ICU admission were older than known inpatient ward admission ($p < 0.001$). All of the cases known ICU admission had comorbid diseases. There were statistically significant difference the time between onset of symptoms and hospital presentation ($p = 0.006$). Regarding to lobe number and frequency of lobe involvement, no significant difference were found between two groups. The anterior-posterior, transverse, lung side distributions had no significant difference, on the other hand in regards to scattered distribution diffuse patern was higher frequency (21.1%) in known ICU admission cases. GGOs' were commonly presented in known inpatient ward admission cases ($P = 0.01$), however mixed GGO and consolidations were identified in known ICU admission cases ($p < 0.001$). Other statistically significant and non-significant features and measurements are shown in Table 2.

DISCUSSION

The purpose of this study was to analyzed initial CT features of patient with known hospitalization in ICU and inpatient ward. An outstanding feature of this study is not only comprehensively evaluated initial CT features but also assessed differences in CT findings between known ICU and inpatient ward admission.

Meta-analyses and systematic reviews revealed that gender and age range varied between different sample sizes, countries [14, 17]. In our study cohort, cases were predominantly male and median age was 45. Most of the cases were under the age of 60 could be related to the statement of curfew restriction for people over the age 65. In their review and meta-analysis of 1115 patients, Won *et al*. [18] showed that fever and cough were the main clinical characteristics. We found that the similar clinical characteristics, on the other hand anosmia, loss of taste, diarrhea, chest pain and back pain were less frequently seen. 19.5% of our cases with no symptoms were recurited from filiation method.

In the current study, bilateral, multifocal, periferal and dorsal dominant, five lobes involvement with a lower lobe predominance especially right was the most common lesion localizations. GGOs, round-shaped lesions, vascular enlargement were the main CT features. These findings are in agreement with previous systematic reviews and meta-analyses [14, 16-18]. The typical findings suggesting that progression including consolidation, mixed GGOs and consolidation, crazy-paving patern, reversed halo sign were found less frequently. On the other hand, of our cases, %15.5 had normal CT in their initial imaging. These results may be related to accession of cases to healthcare in the early period and filiation method. In our cases, median day for hospital presentation after the symptoms were started, was 3. The atypical and fairly typical findings, such as bronciectasis, air-brochogram sign, bronchial wall thickening, halo sign, subpleural bands, pleural thickening, pleural effusion, pericardial effusion, centrilobular nodules and lymphadenopathy were also seen but less commonly compatible with previous literature [19]. Cavitation and pneumothorax cases with COVID-19 were rarely reported in literature [20, 21]. These two rare findings were not seen in our cases.

In their study, Meng *et al*. [22] reported that main CT feature was GGOs in asymptomatic cases with COVID-19. Our results suggested that same initial CT findings especially cases known inpatient wards admission. However, CT features of diffuse distribution, mixed GGOs and consolidation were statistically significant initial CT finding in known ICU admission cases than known inpatient wards admission. Pure consolidation was higher at initial CTs with known ICU cases, but it was not statistically significant than with known inpatient ward admission. Subpleural bands or lines which may be associated to pulmonary edema or fibrosis and bronchial wall thickening which usually related to inflammation of airways [23], we found these findings higher in their initial CTs with known ICU admission cases. Pleural effusion indicating severity were observed higher in cases with known ICU admission. Other findings, such as pericardial effusion and mediastinal lymphadenopathy suggesting severity [24] showed higher frequencies in their initial CTs with known ICU admission cases, but it was not

statistically significant.

Older age and comorbidities are major risk factors leading to poor prognosis for patients with COVID-19 [25, 26]. In accordance with these factors, in our cohort known ICU admission cases had older median age and underlying diseases which were statistically significant than with known inpatient ward admission. These cases showed early hospital presentation. Moreover, these group of cases had significant findings in regard to CT features such as emphysema, coronary calcifications, scoliosis, kyposis, aorta diameter and cardiothoracic ratio which were also related to age and underlying diseases. We should give attention these findings at image interperations.

Limitations

Our study has some limitations. Firstly, we did not evaluate laboratory findings. Secondly, we only interpreted the initial CTs, not follow-up CTs. Liu *et al*. [27] revealed that CT quantification of lesion might early predict the progression and severity. Our study was based on predominantly qualitative CT features. Therefore lastly, visual assessments might cause under- or over-estimation some of CT features.

CONCLUSION

Initial chest CT imaging features may give an idea whether patients may need intensive care admission in the COVID-19 course like demographic features such as elderly or clinical features such as having hypertension history.

Authors' Contribution

Study Conception: ÖÜ, UK, EÖ, İH, AAS, HRG; Study Design: ÖÜ, UK, EÖ, İH, AAS, HRG; Supervision: ÖÜ, UK, EÖ, İH, AAS, HRG; Funding: N/A; Materials: ÖÜ, UK, EÖ, İH; Data Collection and/or Processing: ÖÜ, UK, EÖ, İH; Statistical Analysis and/or Data Interpretation: ÖÜ, UK, EÖ, HRG; Literature Review: ÖÜ, UK, HRG; Manuscript Preparation: ÖÜ, UK, EÖ, İH, AAS and Critical Review: İH, AAS, HRG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The relationship between burnout syndrome and low back pain, neck pain and mood status in hospital workers in the COVID-19 pandemic

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ABSTRACT

Objectives: Burnout syndrome is expected among healthcare workers facing extended periods of physical and psychological stress. Physical and psychosocial factors affect the aetiology of healthcare workers' musculoskeletal pain. This study aimed to determine healthcare workers' burnout syndrome levels at a hospital during the COVID-19 pandemic, investigating burnout syndrome's relationship with lower back pain, neck pain, depression and anxiety.

Methods: This prospective observational study employed a Google Forms questionnaire, and 120 training and research hospital employees volunteered to participate. The questionnaire included the Maslach Burnout Inventory, Pain-Visual Analog Scale, Neck Disability Index, Oswestry Disability Questionnaire and Hospital Anxiety and Depression Scale.

Results: Fifty-four participants (45%) had moderate emotional exhaustion, and 20 (16%) had severe emotional exhaustion. Eighty-two (68%) had mild depersonalisation and 38 (32%) had moderate depersonalisation, and 120 (100%) had severe reduced personal accomplishment. Moreover, 68.3% of volunteers complained of neck pain over the last year, while 51.7% complained of lower back pain. Relationships were observed between: emotional exhaustion, lower back pain, neck pain, lower back disability, neck disability, anxiety scores and depression scores; depersonalisation, neck pain, anxiety scores and depression scores; and personal accomplishment, neck pain, neck disability, back disability, anxiety scores and depression scores. Lower back disability was significantly higher among participants not infected with the SARS-CoV-2. Anxiety was significantly higher among participants infected with the SARS-CoV-2.

Conclusions: Burnout is a risk factor for musculoskeletal pain among healthcare workers. Therefore, healthcare workers require physical and psychological support during crises such as pandemics.

Keywords: Burnout syndrome; COVID-19; healthcare workers; lower back pain; neck pain; depression

Since the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) to be a pandemic, millions of cases and thousands of deaths have been confirmed [1]. For healthcare providers, working during an epidemic can have positive effects, improving post-traumatic growth through saving lives and improving patient outcomes [2]. However, due to COVID-19, a worldwide public

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health problem, healthcare workers also faced negative effects, such as the risk of transmission, inadequate medical equipment and devices, and particularly stressful workplace activity and intensity compared to the rest of society [3]. According to WHO data, more than 35,000 healthcare workers worldwide were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the pandemic, some of whom died as a result [1]. These difficulties and risks sparked fear, physiological stress and psychological stress among healthcare professionals [4]. Studies have reported that anxiety, depression, insomnia and high stress levels have been common among healthcare professionals during this pandemic [5-7]. These experiences can lead to post-traumatic stress disorder among healthcare workers. Post-traumatic stress disorder is expected to cause healthcare workers to feel burnt out after working under physical and psychological stress for long periods [2]. Burnout syndrome sufferers' mental state deteriorates alongside their work, family lives and social lives, negatively affecting their quality of life [8]. As a result, work-related tension and burnout can cause: psychological problems, such as chronic irritability, anxiety and depressive complaints; physical problems, such as fatigue, insomnia, stomach ailments, breathing difficulties and body aches; and decreased productivity and creativity with organisational consequences, such as workplace accidents [9]. Musculoskeletal disorders are a common occupational problem for healthcare professionals. In addition to physical factors – such as manual use, static tasks and repetitive tasks – psychosocial factors, such as work stress, monotonous tasks, high perceived workloads and time pressure, have been defined as work-related risk factors for musculoskeletal pain [10, 11]. Back pain, lower back pain and neck pain are among healthcare workers' most common musculoskeletal problems [12]. Given this information, burnout levels caused by intense workloads and psychological stress may share a relationship with lower back and neck pain among healthcare workers during the COVID-19 pandemic.

Accordingly, this study aimed to determine healthcare workers' burnout syndrome levels at a hospital during the COVID-19 pandemic, investigating burnout syndrome's relationship with lower back pain, neck pain, depression and anxiety.

METHODS

This prospective observational study was planned in accordance with the Declaration of Helsinki and approved by our local ethics committee (2011-KAEK 25 2021/07-01). Participants' consent was obtained. The studied population comprised healthcare professionals aged 18-60 years who were working at a training and research hospital and who agreed to answer our questionnaire. Workers with less than one year of professional healthcare experience and workers who did not want to participate in our survey were excluded from the study. After providing necessary preliminary explanations and information to volunteers, we conducted a preliminary questionnaire with ten participants under observation. Subsequently, research data were collected online using an e-survey through Google Forms. In addition to questions about participants' socio-demographic information, the questionnaire used the following evaluation scales: the Maslach Burnout Inventory (MBI), the Visual Analogue Scale (VAS), the Oswestry Disability Questionnaire (ODQ), the Neck Disability Index (NDI) and the Hospital Anxiety and Depression Scale (HAD).

Maslach Burnout Inventory (MBI)

The MBI was developed to determine burnout levels. It comprises 22 items, and each item is scored between 0 and 6. The composite score for each scale represents a participant's total score for each dimension. There are three components of this inventory: emotional exhaustion, depersonalisation and lack of personal accomplishment. Participants who score 0-16, 17-26 and ≥ 27 on the emotional exhaustion scale exhibit low, moderate and high levels of emotional exhaustion, respectively. Those who score 0-6, 7-12 and ≥ 13 on the depersonalisation dimension have low, moderate and high levels of depersonalisation, respectively. Items measuring lack of personal accomplishment are reverse-coded; participants with scores of 0-31, 32-38 and ≥ 39 exhibit high, moderate and low lack of personal accomplishment, respectively [13].

Visual Analogue Scale (VAS)

Participants were asked to answer the following questions pertaining to the VAS: 'Did you have lower back pain last year?' and 'Did you have neck pain last year?' The VAS was used to evaluate the pain intensity

of participants who reported experiencing lower back or neck pain. Patients were asked to rate their pain severity on a 10-point scale (0: I have no pain; 10: very severe pain).

Oswestry Disability Questionnaire (ODQ)

The ODQ was used to assess disability due to lower back pain [14]. The questionnaire's validity and reliability were confirmed by Yakut *et al*. [15]. The ODQ comprises ten questions in total, each consisting of six options. The six options for each question are scored between 0 and 5 points. A score of 0-4 is considered to indicate no disability, versus 5-14 indicating mild disability, 15-24 indicating moderate disability, 25-34 indicating severe disability and > 35 indicating total disability.

Neck Disability Index (NDI)

The NDI is used to evaluate disability due to neck pain. Its validity and reliability were confirmed by Telci *et al*. [16]. Total NDI scores were used to determine participants' disability levels using the following assessment: 0-4 points: no disability; 5-14 points: mild disability; 15-24 points: moderate disability; 25-34 points severe disability; and > 35 points: full disability.

Hospital Anxiety and Depression Scale (HAD)

The HAD is a self-assessment questionnaire comprising 14 questions. Seven questions (the odd-numbered items) measure anxiety (HAD-A), and the other seven (evenly numbered) measure depression (HAD-D). The HAD is a four-point Likert-type scale that is valid and reliable [17]. The HAD-A and HAD-D scores are calculated separately, yielding two scores that range between 0 and 21. High scores indicate high levels of anxiety or depression. Scores of 0–7 points indicate normal levels, 8-10 points indicate borderline abnormal levels and 11-21 points indicate abnormal levels.

Patients' burnout levels were calculated using three different components: emotional exhaustion, depersonalisation and lack of personal accomplishment. First, patients were divided into groups for participants with and without neck pain and with and without lower back pain. Then, they were further divided into two groups: participants exposed to SARS-CoV-2 (COVID-positive) and those not exposed to SARS-CoV-2 (COVID-negative) (Fig. 1).

Statistical Analysis

Data were analysed using the IBM SPSS 23.0 statistics software package. Descriptive statistical methods (frequency, percentage, mean, standard deviation, median and min-max) were used to assess the data. Categorical variables were expressed as percentages n (%). A chi-square test and Fisher's exact test were used to compare categorical data. The normal distribution of variables was calculated using the Shapiro-Wilk test. The data showed no normal distribution. A Mann-Whitney U test and Kruskal-wallis test were used for intergroup comparisons. The relationships between variables were assessed using Spearman's rho correlation test. The results were evaluated with a confidence interval of 95%, and statistical significance was set at $p < 0.05$.

RESULTS

This study's survey was sent to 130 healthcare professionals. Seven refused to answer the questionnaire. Three were excluded from the study because they had not completed one year of professional healthcare work experience (Fig. 1). A total of 120 professionals – including 36 (30%) physicians, 44 (36.70%) nurses, 24 (20%) medical secretaries, eight (6.70%) housekeepers and eight (6.70%) administrative staff members – participated in this study. Ninety-four (78.30%) participants were women, and 86 (71.7%) participants were over 30 years old. Participants' demographic and clinical data are shown in Table 1.

Fifty-four (45%) participants had moderate burnout levels, and 20 (16%) had severe levels of emotional exhaustion. Eighty-two (68%) had mild levels of depersonalisation, and 38 (32%) had moderate levels of depersonalisation. One hundred and twenty (100%) had severe levels of reduced personal accomplishment. Participants' distribution by MBI score is presented in Table 1. Emotional burnout levels were statistically significantly higher among female participants than male participants and among participants working more than 40 hours per week compared to those working fewer than 40 hours per week ($p < 0.05$). Lack of personal accomplishment was higher among participants who were under 30 years old, female, single and working over 40 hours per week

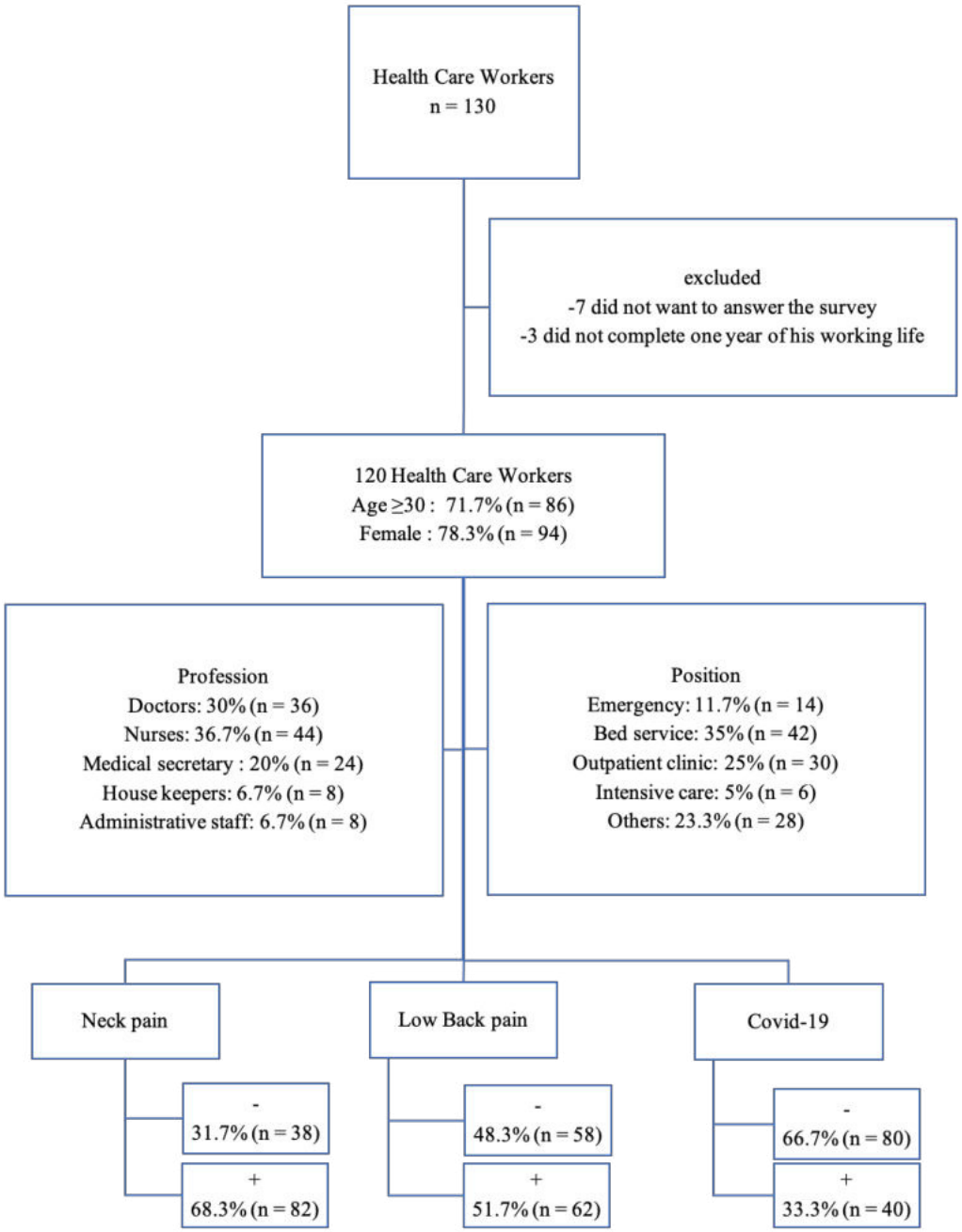

Fig. 1. Flow chart.

(Table 2).

Additionally, 68.3% of participants (n = 82; VAS = 2.86 ± 2.70) complained of neck pain within the last year, and 51.7% (n = 62; VAS = 4.25 ± 2.18) complained of lower back pain within the last year (Fig. 1). When participants with and without neck pain were compared, no statistically significant difference in burnout levels was observed. When participants with and without lower back pain were compared in terms of burnout levels, only depersonalisation was statistically significantly higher among those with lower back pain (Table 3).

While a significant correlation was observed between neck pain (VAS) and all burnout scores, a significant correlation was found between lower back pain (VAS) and emotional burnout only. Both lower back and neck disability levels were found to correlate with emotional exhaustion and lack of personal accomplishment levels. A close relationship was also observed between emotional exhaustion, depersonalisation and lack of personal accomplishment levels and anxiety and depression scores (Table

Table 1. Sociodemographic, clinical data and burnout levels of the participants

Variables		n	%	Mean ± SD
Age (years)	< 30	34	28.3	-
	≥ 30	86	71.7	-
Gender	Female	94	78.30	-
	Male	26	21.70	-
Marital status	Married	78	65	-
	Single	42	35	-
Education status	High school/associate degree	44	36.70	-
	Undergraduate	44	36.70	-
	Postgraduate	32	26.70	-
Profession	Doctor	36	30	-
	Nurse	44	36.70	-
	Medical secretary	24	20	-
	Housekeepers	8	6.70	-
	Administrative staff	8	6.70	-
Position	Emergency	14	11.70	-
	Bed service	42	35	-
	Outpatient clinic	30	25	-
	Intensive care	6	5	-
	Other	28	23.30	-
Weekly working hours	< 40	28	23.30	-
	≥ 40	92	76.70	-
Way of working	Daytime	56	46.70	-
	Shift	32	26.70	-
	24 hours	32	26.70	-
Covid-19	I did not experience	80	66.70	-
	I experienced it as a mild illness.	32	26.70	-
	I experienced it as a severe illness.	6	5	-
	I experienced without symptoms.	2	1.70	-
Neck pain	None at all	**38**	**31.7**	-
	Pandemic evolved during	28	23.30	-
	Increased during the pandemic	54	45	-
Low back pain	None at all	**58**	**48.30**	-
	Pandemic evolved during	36	30%	-
	Increased during the pandemic	26	21.70	-
Burnout levels				
Emotional exhaustion	Mild 0-16	46	39	10.17 ± 2.54
	Moderate 17-26	54	45	20.74 ± 2.38
	Severe ≥ 27	20	16	28.10 ±1.25
Depersonalization	Mild 0-6	82	68	3.19 ± 1.87
	Moderate 7-12	38	32	8.15 ± 1.05
	Severe ≥ 13	0	0	-
Lack of personal accomplishment	Severe 0-31	120	100	20 ± 3.69
	Moderate 32-38	0	0	-
	Mild ≥ 39	0	0	-
NDI				11.18 ± 7.47
ODQ				7.28 ± 6.59
HAD-D				6.96 ± 3.72
HAD-A				9 ± 3.96

NDI = Neck Disability Index, ODQ = Oswestry Disability Questionnaire, HAD-D = The Hospital Anxiety and Depression Scale-Depression, HAD-A = The Hospital Anxiety and Depression Scale- Anxiety, Mean ± SD; Rate %

Table 2. **Comparison of participants' sociodemographic data according to their burnout levels**

Variables		n	Burnout levels								
			Emotional exhaustion			Depersonalization			Lack of personal accomplishment		
			x	SD	p value	x	SD	p value	x	SD	p value
Age (years)[a]	< 30	34	17.11	7.35	0.332	5.08	2.85	0.55	19.57	4.21	**0.006**
	≥ 30	86	19.04	6.45		5.21	3.03		20.6	2.75	
Gender[a]	Female	94	19.4	6.48	**< 0.001**	4.94	2.91	0.146	19.91	3.15	**0.005**
	Male	26	12.53	6.38		6.12	2.94		21.76	4.9	
Marital status[a]	Married	78	18.82	6.78	0.055	4.86	2.78	0.389	20.51	3.54	**0.038**
	Single	42	16.23	7.25		5.53	3.23		19.04	3.83	
Education status[b]	High school/ associate degree	44	18.00	7.12	0.054	5.38	2.74	0.644	20.09	4.55	0.319
	Undergraduate	44	20.44	6.58		4.92	3.65		19.09	2.97	
	Postgraduate	27	14.37	6.12		5.06	2.50		21.12	3.00	
Profession[b]	Doctor	36	13.77	6.01	0.189	5.05	2.92	0.223	20.88	2.9	0.264
	Nurse	44	21.09	6.39		4.18	2.50		18.72	4.12	
	Medical secretary	24	18.83	6.87		6.10	2.73		19.33	3.59	
	Administrative staff	8	17.12	6.74		6.00	3.54		22.50	2.47	
	Housekeepers	8	17.32	6.54		6.04	2.89		21.87	3.10	
Weekly working hours [a]	< 40	28	14.5	6.17	**0.003**	5.23	3.79	0.873	21.78	2.91	**0.003**
	≥ 40	92	18.95	6.97		5.12	2.55		19.45	3.75	

x = mean, SD = standard deviation, $p < 0.05$ = Significant, [a]Mann-Whitney U test, [b]Kruskal wallis test

Table 3. Comparison of those with and without neck-low back pain in terms of burnout levels

		n	Burnout levels								
			Emotional exhaustion			Depersonalization			Lack of personal accomplishment		
			x	SD	*p value*	*x*	SD	*p value*	*x*	SD	*p value*
Neck pain	+	82	17.17	7.12	0.081	4.97	2.68	0.271	19.68	3.94	0.132
	-	38	19.92	6.64		4.31	3.17		20.68	3.05	
Low back pain	+	62	18.27	7.05	0.591	6.03	2.64	**< 0.001**	19.41	4.21	0.097
	-	58	17.58	7.05		3.58	2.51		20.54	3.07	

x = mean, SD = standard deviation, $p < 0.05$ = Significant, Mann-Whitney U test

Table 4. Relationships between burnout and neck-back pain (VAS), disability, depression, and anxiety in hospital workers

		Correlation					
		Neck pain VAS	NDI	Low back pain VAS	ODQ	HAD-D	HAD-A
Emotional exhaustion	R	0.447	0.541	0.280	0.553	0,678	0,642
	p value	**< 0.001**	**< 0.001**	**0.02**	**< 0.001**	**< 0.001**	**< 0.001**
Depersonalization	R	0.214	0.101	-0.137	0,074	0,393	0,261
	p value	**0.019**	0.338	0.136	0.485	**0.002**	**0.042**
Lack of personal accomplishment	R	-0.194	-0.294	-0.28	-0.428	-0.506	-0.433
	p value	**0.034**	**0.001**	0.761	**< 0.001**	**< 0.001**	**< 0.001**

NDI = Neck Disability Index, ODQ = Oswestry Disability Questionnaire, HAD-D = The Hospital Anxiety and Depression Scale-Depression, HAD-A = The Hospital Anxiety and Depression Scale-Anxiety,
$p < 0.05$ = Significant, Spearman's rho correlation test

Table 5. Comparison of burnout, depression, anxiety, neck and low back pain (VAS)-disability levels between survivors of covid-19 disease and those who did not experience covid-19 disease.

	COVID +	COVID -	*p* value
Emotional exhaustion	17.50 ± 7.60	17.74 ± 6.88	0.656
Depersonalization	4.30 ± 3.92	5.28 ± 2.74	0.127
Lack of personal accomplishment	20.63 ± 2.64	19.85 ± 3.83	0.371
neck pain VAS	2.66 ± 2.62	3.01 ± 2.76	0.485
NDI	7.63 ± 5.95	12.94 ± 8.03	0.105
low back pain VAS	4.45 ± 1.94	4.10 ± 2.34	0.375
ODQ	5.10 ± 5.84	8.04 ± 6,83	**0.008**
HAD-D	7.63 ± 3.71	6.13 ± 3.66	0.050
HAD-A	10.16 ± 4.64	8.26 ± 3.76	**0.048**

NDI = Neck Disability Index, ODQ = Oswestry Disability Questionnaire, HAD-D = The Hospital Anxiety and Depression Scale-Depression, HAD-A = The Hospital Anxiety and Depression Scale-Anxiety,
$p < 0.05$ = Significant, Mann-Whitney U test

4).

Forty participants (33.3%) had previously had COVID-19. Eighty (66.70%) had never had COVID-19. Anxiety levels among participants who had had COVID-19 were statistically significantly higher than the corresponding levels among participants who had not had COVID-19. Lower back disability scores were statistically significantly higher among participants who had not had COVID-19 than among participants who had had COVID-19 (Table 5).

DISCUSSION

The results of this study showed that lower back and neck pain are common among healthcare workers experiencing the pandemic's physical and psychological burdens. Moreover, the groups who had and had not contracted COVID-19 were equally affected by lower back pain, neck pain and burnout syndrome scores. Sixteen per cent of participants exhibited high levels of emotional burnout, while all participants exhibited high levels of a lack of personal accomplishment. High levels of emotional burnout were common among women and participants working more than 40 hours per week, while a lack of personal accomplishment was common among participants who were under 30 years old, female, single and working over 40 hours per week. Positive correlations were observed between emotional exhaustion and lower back and neck pain, lower back and neck disability, anxiety scores and depression scores. A positive correlation was also observed between depersonalisation and neck pain, anxiety scores and depression scores. A negative correlation was observed between personal accomplishment and neck pain, neck disability and lower back disability, anxiety scores and depression scores. Additionally, participants who had not had COVID-19 had higher lower back disability scores than participants who had contracted the disease. Anxiety scores were higher among participants who had had COVID-19 than among participants who had not.

Pandemics have physiological effects as well as psychological effects. Factors such as increased numbers of daily cases and rising death rates, inadequate medical equipment and devices, an active and intense work pace and stress can cause feelings of burnout among healthcare professionals [2, 3]. Giusti *et al.* [18] reported that 67.6% of healthcare workers struggling with COVID-19 had moderate or severe emotional exhaustion, while 26% had moderate or severe depersonalisation and 74.4% experienced a moderate or severe decrease in personal accomplishment. In this study [18], predictors of all three components of burnout were work hours, psychological comorbidities, fear of infection and perceived support by friends. Additionally, the female gender, nursing, hospital work, and contact with COVID-19 patients were found to predict both emotional exhaustion and depersonalisation, while decreased personal accomplishment was estimated by age. In the current study, 61% of the participants had moderate or high levels of emotional exhaustion, while all participants had significant declines in personal accomplishment. Also, all participants exhibited mild or moderate depersonalisation. Factors such as duration of exposure to the pandemic's burdens, differences in working conditions and differences in the intensity of accompanying psychological comorbidities may explain these different results.

In the fight against COVID-19, nurses, women and frontline health workers have faced especially high psychological burdens [19]. Working life conditions contribute to burnout levels. Burnout is defined as a condition that mostly affects women [20]. In the COVID-19 pandemic, the results of a study of healthcare workers showed that gender has a major impact on emotional exhaustion and that women have higher levels of emotional exhaustion than men [21]. A study of Egyptian doctors found that older doctors were less likely to develop burnout during the COVID-19 pandemic. While the male gender predicted depersonalisation, the female gender was significantly associated with higher emotional exhaustion. Exposure to or death from COVID-19 among colleagues or relatives was significantly associated with high emotional exhaustion and decreased personal accomplishment, respectively. In this study, no relationship was observed between working hours and burnout [22]. In European countries, healthcare professionals – especially nurses – have been reported to exhibit high levels of stress, emotional fatigue and depressive symptoms [23]. A scoping study that included a total of 50 studies evaluated depression, anxiety, psychological trauma, sleep disorders, workplace burnout and fatigue among healthcare workers during the COVID-19 outbreak. It showed that the female gender, young elders, frontline

workers and non-physician workers were more affected than other subgroups [24]. Factors such as nurses' working in close contact with infected patients, a lack of work experience among young people, a high number of women working in positions such as nurses or nursing assistants and a higher prevalence of mood disorders among women have been found to cause these results [25]. In the current study, in accordance with the literature [18, 20-22], participants' emotional exhaustion levels were statistically significantly higher among women than in men. Our result supported Giusti *et al*.'s [18] conclusion. However, contrary to a study by Abdelhafiz *et al*. [22], in the current study, emotional exhaustion levels were statistically significantly higher among participants working more than 40 hours per week compared to those working fewer than 40 hours per week. Though not to a statistically significant degree, nurses exhibited higher emotional burnout than other healthcare professionals. This result was also compatible with the literature [18, 22]. In addition, in line with the literature [18, 24], in the present study, we also observed a decrease in personal accomplishment among participants who were under 30 years old, female, single and working over 40 hours per week.

Musculoskeletal disorders are a common occupational problem for healthcare professionals. In addition to physical factors (such as manual use, static tasks and repetitive tasks), psychosocial factors (such as work stress, monotonous tasks, high perceived workloads and time pressure) have been defined as work-related risk factors for musculoskeletal diseases [10, 11]. According to the results of a study investigating the prevalence of musculoskeletal pain among Norwegian nurses' assistants, neck, shoulder, elbow, high back and hip pain were more common among women than men. The prevalence of neck pain increased with increasing weekly work hours. Lower back pain was most common among people working in nursing homes [26]. In a study of 1,162 nurses in Japan, the prevalence of lower back pain during the previous 12 months was 71.3%, versus 54.7% for neck pain and 33.9% for back pain. Neck pain was associated with tobacco smoking and high mental stress, while upper back and lower back pain were associated with bending or twisting, hard physical work, premenstrual tension, high mental pressure and insufficient staffing [27]. A study examining the relationship between psychosocial work environments and musculoskeletal pain among nurses and nurses' assistants showed that lower back pain appeared to be associated with work fatigue. In contrast, symptoms in the neck and shoulders were mostly associated with relational and emotional factors [28]. The rates of neck pain and lower back pain in our study population were 68.3% and 51.7%, respectively. When participants with and without neck pain were compared, we found no statistically significant difference in burnout component levels. However, correlations were observed between neck pain severity and emotional exhaustion, depersonalisation and a lack of personal accomplishment. When participants with and without lower back pain were compared in terms of burnout components, we found that only depersonalisation was statistically significantly higher among participants with lower back pain. Additionally, a significant relationship was found between the severity of lower back pain and emotional exhaustion. Moreover, we found a positive relationship between lower back and neck disability and emotional exhaustion, and we found a negative relationship between lower back and neck disability and a lack of personal achievement.

COVID-19 has been reported to cause musculoskeletal pain and sometimes last a long time [29]. The current study's results did not show significant differences in neck pain and lower back pain between participants who had contracted COVID-19 and participants who had not. Also, no significant difference was found in burnout or neck disability between participants who had contracted COVID-19 and participants who had not. Lower back disability was higher among participants who had not had COVID-19. Some participants who had contracted COVID-19 had been absent from their work environment for a while due to illness. However, others had continued to work without interruption. This difference may explain the higher incidence of lower back disability among participants who had not had COVID-19.

Iacovides *et al*. [30] found a significant relationship between depression and burnout in their study of 368 nurses. These researchers stated that there are two different types of burnout that are either related to depression or not related to depression. They argued that depression, which is associated with burnout, creates more severe burnout and develops among individuals who are prone to developing burnout [30]. During the

COVID-19 pandemic, a study of Spanish medical personnel associated emotional exhaustion and depersonalisation with post-traumatic stress, while reduced personal accomplishment was associated with symptoms of anxiety and depression [25]. In the current study, we found a relationship between depression and anxiety scores and all burnout types. Additionally, we found that the anxiety scores of participants who had contracted COVID-19 were significantly higher than the corresponding scores of participants who had not.

Limitations

To the best of our knowledge, the present study is the first to investigate neck pain and lower back pain among healthcare workers professionally active during the COVID-19 pandemic and this pain's relationship with burnout, depression and anxiety that developed under the pandemic's burden. The limitations of our study are its relatively low number of participants and our lack of subgroup analysis. More comprehensive studies with subgroup analyses are needed.

CONCLUSION

During the COVID-19 pandemic, healthcare workers have had to work under more physical and psychological stress than normal. Our results reflected this situation: back and neck pain was common among healthcare personnel who were professionally active during the COVID-19 pandemic. Burnout levels were also high. The severity of lower back pain, neck pain and disability – as well as depression and anxiety – may affect burnout levels among healthcare personnel experiencing heavy workloads during the pandemic. Emotional burnout levels were especially high among nurses who worked in close contact with infected people, female participants and participants working more than 40 hours per week. Participants who had contracted COVID-19 had worse lower back disability because they had worked longer than those who had not, and their anxiety levels were also higher. Given these results, burnout among healthcare workers can be considered a risk factor for musculoskeletal pain. For this reason, healthcare workers should be supported physically and psychologically during crises such as pandemics.

Authors' Contribution

Study Conception: İAK; Study Design: İAK; Supervision: İAK, MKA; Funding: İAK, MKA; Materials: İAK, MKA; Data Collection and/or Processing: İAK, MKA; Statistical Analysis and/or Data Interpretation: İAK, MKA; Literature Review: İAK; Manuscript Preparation: İAK and Critical Review: İAK, MKA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Evaluation of clinico-radiological factors affecting morbidity and mortality in peptic ulcer perforation surgery

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ABSTRACT

Objectives: Peptic ulcer perforation (PUP) remains a surgical emergency with high early period morbidity and mortality. In this study, it was aimed to evaluate clinico-radiological factors affecting morbidity and mortality in peptic ulcer perforation surgery.

Methods: Patients who were operated for PUP at Erzurum Regional Training and Research Hospital General Surgery Clinic, Erzurum, Turkey between 2010 and 2020 were selected retrospectively. The patients' clinical and radiological parameters were retrieved from their medical records. Patients who developed complications in the 30 days after surgery were considered the morbidity-positive group, and the patients who developed mortality in the 30 days after surgery were considered the mortality-positive group. The relationship between investigated factors and morbidity and mortality was investigated with suitable statistical tests. A p value < 0.05 was considered statistically significant.

Results: The study included 81 patients and, 74 (91.4%) patients were males. Complications were observed in 15 (18.5%) patients and mortality was seen in 3 (3.7%) patients in the first 30 days postoperatively. Preoperative comorbidity, low systolic blood pressure, high Boey score had negative effect on both morbidity and mortality. In addition, lower amylase levels played a protective role in both morbidity (p = 0.011) and mortality (p = 0.018). Mortality increased significantly with increasing age. However, no radiological factor affected either morbidity or mortality.

Conclusions: Both morbidity and mortality increased in cases with poor clinical condition at the time of diagnosis. In addition, the mortality rate was higher in patients with comorbidities and postoperative complications.

Keywords: Amylase, Boey score, comorbidity, morbidity, mortality, peptic ulcer perforation

Peptic ulcer perforation (PUP) is one of the most important complications of peptic ulcer disease (PUD) [1]. Although the incidence of PUD decreased during the last few decades due to the successful treatment of Helicobacter pylori, the decrease in perforation cases was not as desired [2]. Perforation accounts for most deaths associated with PUD [3, 4]. PPU remains a surgical emergency, with high early period mortality of 10-30% and early period morbidity of 21-43% [4, 5].

Surgical repair with or without omentum is the most common surgical technique in PUP surgery. While surgical repair is most commonly performed with open surgery, laparoscopy are preferred in appropriate cases [6]. The laparoscopic treatment of PUP has been shown to be applicable and safe, but its im-

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plementation into routine clinical practice has been slow [5]. A Denmark study reported that only 6% of patients with PPU were treated with laparoscopic surgery [7].

The aim of this study is to evaluate clinico-radiological factors affecting morbidity and mortality in PUP surgery.

METHODS

Patients who were operated for PUP at Erzurum Regional Education and Research Hospital General Surgery Clinic, Erzurum, Turkey, between 2010 and 2020 were selected for the study retrospectively. Age and gender of the patients, preoperative comorbidity, systolic blood pressure (above or below 100 mm Hg), time from pain to hospital admission (longer or shorter than 24 hours) were evaluated. Since smoking is an important parameter in perforation etiology, the smoking of the patients was also evaluated. Boey scores of all patients were calculated. The components of the Boey score are as follows: concomitant medical illness, preoperative shock, perforation time greater than 24 hours. Each factor scores 1 point if positive. The total Boey score is calculated based on the individual scores of the parameters.

Preoperative laboratory parameters and imaging tools were also investigated. In hematological analysis, white blood cell (WBC) and platelet counts, hemoglobin values, leukocyte and lymphocyte counts were searched. In addition, amylase and lactate dehydrogenase (LDH) levels were investigated in biochemical analysis. Presence of free air both X-Ray radiograph and computed tomography (CT) scan were investigated. Also, on CT scan, presence of intra-abdominal fluid was searched.

Surgery type, perforation location, postoperative complications, hospital stay, and mortality were also evaluated. After collecting the evaluated parameters, the relationship between the parameters and morbidity and mortality was analyzed.

Ethics committee approval was received from Non-invasive Clinical Research Ethics Committee of Erzurum Regional Education and Research Hospital, Erzurum, Turkey (Decision No: 2021/05-84).

Statistical Analysis

Statistical evaluation was made with SPSS v22.0 (IBM, Armonk, NY, USA). The normality distribution of quantitative variables were checked with Shapiro-Wilk test. The Mann-Whitney U test was used according to the results of the Shapiro-Wilk test. In addition, Chi-square test, and Likelihood ratio test were used to compare qualitative variables. A p value below 0.05 was considered statistically significant.

RESULTS

Between 2010 and 2020, 94 patients were operated on for PUP in Erzurum Regional Training and Research Hospital General Surgery Clinic, Erzurum, Turkey. Thirteen patients were excluded from the study because all data of these patients were not accessible. Thus, 81 patients were included in the study. After collecting the evaluated parameters, the effect of the collected parameters on morbidity and mortality was investigated. Complications were observed in 15 (18.5%) patients and mortality was seen in 3 (3.7%) patients in the first 30 days postoperatively. Patients were divided into groups according to morbidity and mortality.

74 (91.4%) patients were males and 7 (8.6%) were females, and male to female ratio was 10.57. The mean age of all patients was 44.81 years (range: 18-

Table 1. Comorbid diseases of the patients

Comorbidity	n (%)
Hypertension	10 (62.5)
Chronic obstructive pulmonary disease (COPD)	3 (18.75)
Hypertension with COPD	2 (12.5)
Hypertension with diabetes mellitus	1 (6.25)
Total	16 (100)

Table 2. Comparison of clinical parameters according to morbidity

Preoperative factors	Morbidity positive n = 15	Morbidity negative n = 66	*p* value
Age (years) (mean)	46.27	39.80	0.337*
Gender			0.114**
Female	3 (42.9%)	4 (57.1%)	
Male	12 (16.2%)	62 (83.8%)	
Comorbid disease			**0.001****
Yes	8 (50%)	8 (50%)	
No	7 (10.8%)	58 (89.2%)	
Preoperative systolic blood pressure			**0.001****
< 100 mmHg	7 (58.3%)	5 (41.7%)	
≥ 100 mmHg	8 (11.6%)	61 (88.4%)	
Time from pain to admission			0.932**
≥ 24 hours	8 (18.2%)	36 (81.8%)	
< 24 hours	7 (18.9%)	30 (81.1%)	
Boey score			**0.004*****
0	5 (15.2%)	28 (84.8%)	
1	2 (6.3%)	30 (93.8%)	
2	4 (40%)	6 (60%)	
3	4 (66.7%)	2 (33.3%)	
Cigarette usage			0.701**
Yes	9 (20%)	36 (80%)	
No	6 (16.7%)	30 (83.3%)	
Laboratory test results (mean)			
WBC (10^3/mm^3)	15.27	13.02	0.484*
Neutrophil (10^3/mm^3)	10.87	10.46	0.670*
Lymphocyte (10^3/mm^3)	3.44	1.83	0.555*
Platelet (10^3/mm^3)	292.53	274.23	0.870*
Amilase (U/L)	58.07	95.70	**0.011***
LDH (U/L)	261.20	247.67	0.359*
Free air on X-Ray			0.983**
Yes	8 (18.6%)	35 (81.4%)	
No	7 (18.4%)	31 (81.6%)	
Free air on CT scan			0.113**
Yes	15 (22.1%)	53 (77.9%)	
No	0 (0%)	13 (100%)	
Fluid at CT scan			0.742**
Yes	10 (19.6%)	41 (80.4%)	
No	5 (16.7%)	25 (83.3%)	
Operative factors			
Type or surgery			0.464**
Open	14 (17.9%)	61 (82.1%)	
Laparoscopic	1 (33.3%)	2 (66.7%)	
Perforation localization			**0.001*****
Pre-pyloric area	9 (39.1%)	14 (60.9%)	
Juxta-pyloric area	4 (23.5%)	13 (76.5%)	
Post-pyloric area	2 (4.9%)	39 (95.1%)	

* Mann-Whitney U Test, **Chi-square test, ***Likelihood ratio test. WBC = White Blood Cell, LDH = Lactate Dehydrogenase, CT = Computed Tomography

Table 3. Comparison of clinical parameters according to mortality

	Mortality positive n = 3	Mortality negative n = 78	*p* value
Preoperative factors			
Age (years) (mean)	78.17	39.57	**< 0.001***
Gender			0.240**
Female	1 (14.3%)	6 (85.7%)	
Male	2 (2.7%)	72 (97.3%)	
Comorbid disease			**0.007****
Yes	3 (18.8%)	13 (81.2%)	
No	0 (0%)	65 (100%)	
Preoperative systolic blood pressure			**0.003****
< 100 mmHg	3 (25%)	9 (75%)	
≥ 100 mmHg	0 (0%)	69 (100%)	
Time from pain to admission			0.246**
≥ 24 hours	3 (6.8%)	41 (93.2%)	
< 24 hours	0 (0%)	37 (100%)	
Boey score			**< 0.001*****
0	0 (0%)	33 (100%)	
1	0 (0%)	32 (100%)	
2	0 (0%)	10 (100%)	
3	3 (50%)	3 (50%)	
Cigarette usage			0.084**
Yes	0 (0%)	45 (100%)	
No	3 (8.3%)	33 (91.7%)	
Laboratory test results (mean)			
WBC (10^3/mm^3)	17.38	13.33	0.934*
Neutrophil (10^3/mm^3)	13.58	10.42	0.480*
Lymphocyte (10^3/mm^3)	3.38	2.08	0.953*
Platelet (10^3/mm^3)	272.67	277.81	0.543*
Amilase (U/L)	36.00	90.76	**0.018***
LDH (U/L)	360.33	245.94	0.053*
Free air on X-Ray radiograph			0.598**
Yes	1 (2.3%)	42 (97.7%)	
No	2 (5.3%)	36 (94.7%)	
Free air on CT scan			> 0.999**
Yes	3 (4.4%)	65 (95.6%)	
No	0 (0%)	13 (100%)	
Fluid at CT scan			0.292**
Yes	3 (5.9%)	48 (94.1%)	
No	0 (0%)	30 (100%)	
Operative Factors			
Type or surgery			> 0.999**
Open	3 (3.8%)	75 (96.2%)	
Laparoscopic	0 (0%)	3 (100%)	
Perforation localization			0.258***
Pre-pyloric area	1 (4.3%)	22 (95.7%)	
Juxta-pyloric area	2 (11.8%)	15 (88.2%)	
Post-pyloric area	0 (0%)	41 (100%)	
Morbidity			**0.005****
Yes	3 (20%)	12 (80%)	
No	0 (0%)	66 (100%)	

*Mann-Whitney U Test, **Chi-square test, ***Likelihood ratio test. WBC = White Blood Cell, LDH = Lactate Dehydrogenase, CT = Computed Tomography

84 years). While no relationship was found between age and morbidity, mortality increased with increasing age ($p < 0.001$). Sixteen (19.8%) patients had at least one comorbid disease. Comorbid diseases of the patients are shown in Table 1.

In 12 (14.9%) patients, preoperative systolic blood pressure was under 100 mm/Hg. In 44 (54.3%) patients, time from pain to hospital admission was longer than 24 hours. The most common Boey score of the study was Boey 0 (n = 33, 40.7%). The percentages for Boey 1, 2, and 3 were 39.5%, 12.3% and 7.4%, respectively. In addition, cigarette consumption was present in 55.6% (n = 45) of all patients. There was a correlation between the presence of comorbid disease, low systolic blood pressure, high Boey score, and both morbidity and mortality. While the morbidity rate was 66.7% in patients with Boey 3 score, the mortality rate was 50%. As the Boey score increased, the possibility of both morbidity and mortality increased.

On laboratory, 58 (71.6%) patients had leukocytosis, and 57 (70.4%) patients had neutrophilia. According to laboratory evaluation, only amylase levels played a role in both morbidity ($p = 0.011$) and mortality ($p = 0.018$). Both morbidity and mortality were inversely proportional to the rising amylase level.

On imaging tools examination, subdiaphragmatic free air on right side was observed in 43 (53%) patients on plain radiography. Plain radiography was not taken in 20 (24.7%) patients under emergency conditions. However, free air was also present on tomography in all patients with free air on plain radiography. On CT scan, 68 (84%) patients had intra-abdominal free air, 51 (63%) patients had free fluid in the abdomen. On the other hand, there was no pathological finding on CT scan in 13 (16%) patients. The presence of free air and free fluid in imaging methods affected neither morbidity nor mortality.

Open surgery was preferred surgery type in 78 (96.3%) patients. The remaining operations were performed via laparoscopy. Graham's omental patch closure was performed in all patients to close the perforation defect. Most of the surgery notes could not be evaluated because there was no information about the perforation diameter in operation notes. In addition, the most common area of perforation was the post-pyloric area (n = 41, 50.6%). Other perforation areas and percentages were as follows: 28.4% at pre-pyloric area, and 21% at juxta-pyloric area. Morbidity rate was higher in pre-pyloric area perforations with 39.1% ($p = 0.001$). In the patients with morbidity, mortality was also higher ($p = 0.005$). Evaluation of morbidity and mortality according to clinical and radiological parameters is shown in Table 2 and Table 3.

The morbidity rate of the study was 18.5%. The most common postoperative complication was surgical site infection with 46.7%. The incidence of pulmonary complications was 33.3%. Postoperative complications and treatment of these complications are shown in Table 4. The mean length of hospital stay was 8.23 days (3-16 days). Mortalite rate of our study was 3.7% (n = 3). All patients died because of multi organ failure and sepsis.

DISCUSSION

This study's results demonstrate that morbidity of PUP surgery was higher at the patients with preoperative comorbidity, shock, higher Boey score, and perforation localized pre-pyloric area. In addition, mortality of PUP surgery was higher at the patients with advanced age, preoperative comorbidity, shock,

Table 4. Postoperative complications and treatment of these complications

Postoperative complications	Treatment	n (%)
Surgical site infection	Local drainage with daily cleaning	7 (46.7)
Multi organ failure and sepsis (all these patients died)	Combine antibiotherapy with fluid support therapy	3 (20)
Atelectasis	Breathing exercises	2 (13.3)
Pleural effusion	Drainage without chest tube	2 (13.3)
	Drainage with chest tube	1 (6.7)
Total		15 (100)

higher Boey score, and morbidity. However, lower amylase level had a protective effect on both morbidity and mortality.

In literature, PUP cases are more likely to be seen in male gender and are mostly seen in the 4th and 5th decades [8-11]. In the present study, the male/female ratio was 10.57, which was consistent with the literature. On the other hand, the mean age of all patients was 44.81 years, which was consistent with the literature too.

There was no consensus on a specific gender and age limit that determined morbidity and mortality. In the study of Kim *et al*. [12], age above sixty and female gender were affected morbidity. However, Kocer *et al*. [10] showed that PUP cases were mostly seen in the male gender (88.8 vs. 11.2). Yıldırım *et al*. [13] showed that age over 50 years increased both morbidity and mortality. In this study, gender did not affect both morbidity and mortality. However, advanced age only affected mortality.

Since smoking is more preferred in male gender and the incidence of smoking increases, perforation rates are higher in male gender [14, 15]. The smoking prevalence of present study was 55.6% and was not correlated with higher morbidity and mortality. On the contrary, Kocer *et al*. [10] showed that smoking increased mortality but did not affect morbidity. Contrary to the literature, smoking did not affect both morbidity and mortality in the present study.

As in the literature, the presence of preoperative shock increases mortality like our study [10, 16, 17]. Tas *et al*. [18] did not identified correlation between shock and morbidity. In contrast, preoperative shock increased morbidity in the present study. Comorbidities, higher ASA (American Society of Anesthesiologist) score and from pain to hospital application are also important factors for morbidity and mortality [5, 9-11, 19]. However, in the recent study, no relationship was found between the time of onset of pain and both morbidity and mortality. But comorbid diseases played an important role in increasing morbidity and mortality. As a limitation of our study, ASA scores of the patients could not be accessed and evaluated.

Boey score is a useful tool for assessing the prognosis of operated cases due to PUP and helps in the evaluation of both morbidity and mortality [14]. While mortality is between 30-60% in patients with a Boey score of 2, in Boey score 3 cases, mortality reaches 100%. In our study, all deaths had a Boey score of 3.

Laboratory parameters can also help to predict PUP. Yamamoto *et al*. [20] showed that while serum WBC count and platelet count were higher in perforation group, hemoglobin level, total protein and albumin levels, AST and ALT levels were higher in non-perforation group. Amylase levels were higher in patients with morbidity and mortality in follow-up and higher amylase levels were correlated with duration of perforation, size of perforation, and amount of fluid determined intraoperatively [21]. However, in contrast to the literature in the present study, both morbidity and mortality were high in patients with low serum amylase levels.

In plain radiography, 47.2-80% of patients with perforation had sub-diaphragmatic free air on the right side [10, 22]. On the other hand, CT scan has a high diagnostic accuracy of 98% in the diagnosis of PUP [12]. In 35% of gastroduodenal perforations, there is no direct or indirect finding in imaging methods [23]. In this study, while subdiaphragmatic free air on right side was observed in 53% of the patients on plain radiography, free air was also present on tomography in 84% of all patients. On the other hand, there was no pathological finding on CT scan in 16% of the patients.

In the studies of Tas *et al*. [18] and Yıldırım *et al.* [13] free air on plain radiograph and perforation localization were not affected both morbidity and mortality. There was no relationship between the presence of free air in imaging tools and morbidity and mortality.

Type of surgery, perforation diameter wider than 5 mm and performing definitive procedures for treatment were also factors on morbidity and mortality [10, 18]. However, Yıldırım *et al*. [13] showed that the perforation diameter larger than 5 mm and the amount of fluid detected intraoperatively did not affect morbidity, but did affect mortality. Additionally, one study showed that even intra-abdominal fluid above 200 cc affected morbidity [24]. Effects on morbidity and mortality could not be evaluated since most of the surgery notes did not have any information about the perforation diameter and intra-abdominal fluid in our study. In addition, surgical procedures could not be compared since all patients were operated with primary closure with omental patch. But in the study of Yıldırım *et al*. [13], treatment with only primary suture increased both morbidity and mortality.

The post-operative morbidity rate in PUP surgery ranges between 21-42% [10, 25]. Pulmonary and surgery site infections are often the main cause of post-operative complications [11]. The morbidity rate in the presented study was 18.5%, which was partially lower than the literature.

In literature, length of stay after surgery in patients with PUP ranges between 7-12.5 days [9, 26]. In line with the literature, the average length of hospital stay in this study was 8.23 days.

Limitations

There were some limitations in this study. This study was a retrospective study, and the patients were excluded because the data of 13 patients were not available. The relationship between ASA score, perforation diameter and amount of intra-abdominal fluid and early outcomes could not be evaluated due to the lack of information. In addition, the small number of patients included in the study is an important limitation.

CONCLUSION

Peptic ulcer perforation (PUP) is a serious disease that every surgeon may encounter. PUP remains a surgical emergency with high early period morbidity and mortality. From our study's results, both morbidity and mortality increased in cases with poor clinical condition at the time of diagnosis. In addition, the mortality rate was higher in patients with comorbidities and postoperative complications. Diagnosis and necessary surgical treatment should be done as early as possible to prevent morbidity and mortality.

Authors' Contribution

Study Conception: MY, TK; Study Design: MY, MK; Supervision: MY; Funding: MK, TK; Materials: MY, MK; Data Collection and/or Processing: MY, TK; Statistical Analysis and/or Data Interpretation: MY, TK; Literature Review: MY, MK, TK; Manuscript Preparation: MY, TK and Critical Review: MY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(2):210-217 Original Article

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The role of microductectomy in the diagnosis and treatment in women with pathologic nipple discharge

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ABSTRACT

Objectives: Approximately one tenth of the patients who apply to the breast polyclinics complain of nipple discharge. Apart from pregnancy and lactation, spontaneous, unilateral, bloody or serous discharge originating from a single duct describes the pathological nipple discharge (PND). The aim of this study is to show that precancerous breast lesions, which can be easily overlooked by conventional diagnostic methods, are detected with the microductectomy performed with the correct indication and it is possible to complete the appropriate treatment.

Methods: Fifty-five microductectomy procedures were performed in 55 female patients who applied to the relevant clinic with the complaint of nipple discharge between January 2013 and August 2018 and who met at least two of the three criteria of pathological nipple discharge (spontaneous, single ductus, bloody or serous) except pregnancy and lactation. Prospectively collected information was evaluated retrospectively.

Results: The average age of the patients in the study ranged from 23 to 73 years (mean age: 45.5 years; median age: 47 years). Out of 55 procedures, 28 (50.9%) were performed in women of reproductive age, 27 (49.1%) were performed in women in menopause. The discharge was localized to the right breast in 28 patients, and to the left breast in 27 patients. Forty-one of the 55 patients included in the study met all of the criteria for pathological nipple discharge, while the other 14 patients had at least two of the three criteria. Final pathologies were classified as follows; intraductal papilloma/papillomatosis with atypia, intraductal papillary carcinoma (IPC), ductal carcinoma in situ (DCIS), and potential neoplastic and malignant lesion (PNML).

Conclusions: In cases where direct intraductal imaging methods cannot be applied in patients admitted to the polyclinic with pathological nipple discharge, microductectomy emerges as an effective diagnosis and treatment method that can be applied with low morbidity.

Keywords: Pathological nipple discharge (PND), microductectomy, surgery

Intermittent or continuous nipple discharge is the third most common cause of complaints (up to 10%) in women who apply to medical institutions with complaints of the breast, after breast pain and palpable mass. Most of the nipple discharge is physiological [1, 2]. Apart from pregnancy and lactation, spontaneous, unilateral discharge originating from a single duct describes pathological nipple discharge (PND) [3]. The secretion can be a serous, serosanguinous, bloody and purulent character. The most common cause of nipple discharge is benign breast lesions such as solitary intraductal papilloma and papillomatosis [4]. A rare but

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important cause of pathological nipple discharge is breast cancer, which accounts for 5 -21% of these discharge [4-6].

In the diagnostic approach of PND, the imaging methods , following the complete history and physical examination, play a major role. The classical modalities preferred in these patients are mammography, ultrasonography (USG), magnetic resonance imaging (MRI), cytology of the discharge, fine needle aspiration biopsy (FNAB) and core biopsy. Mammography and USG are methods with low sensitivity in detecting very small intraductal lesions [7]. MRI may not always be successful in detecting all intraductal neoplasms [8, 9]. Galactography is an imaging method used to visualize the lactiferous ducts, but the image is evaluated indirectly, not directly. Although the use of this modality increases the reliability of the diagnosis, it is insufficient to distinguish intraductal lesion from intraductal debris. Because galactography reports both situations as filling defects. Therefore, the general approach, used in the final diagnosis of women with pathological nipple discharge, is "canal excision" [10, 11]. Although its added value has not been accepted all over the world, breast ductoscopy is a new method that is increasingly used in the investigation of nipple discharge compared to other methods [12, 13]. Unfortunately, ductoscopy can not be used due to uncommon and difficult to reach.

Within the scope of this study, among women who applied to the polyclinic with the complaint of nipple discharge, patients who described at least 2 criteria of pathological nipple discharge underwent microductectomy in the operating room environment. Pathology results of the patients were compared with preoperation imaging methods and cytology results. The adequacy of the surgical procedure was evaluated in patients with malignancy reported as a result of pathology. The relationship between the discharge criterion and malignancy was investigated and also the adequacy of microductectomy in symptomatic relief was examined.

METHODS

This study was conducted Breast and Endocrine Surgery Unit. It was approved by the local ethics committee of the institute. In addition, all patients were informed about the procedure and then signed an informed consent form.

Fifty-five microductectomy procedures were performed in 55 female patients who applied to the relevant clinic with the complaint of nipple discharge between January 2013 and August 2018 and who met at least two of the three criteria of pathological nipple discharge (spontaneous, single ductus, bloody or serous) except pregnancy and lactation. Prospectively collected information was evaluated retrospectively. The patients included in the study were divided into groups according to how many PND criteria they met (PND 2 +: those who meet any 2 of 3 criteria, PND 3 +: those who meet 3 criteria). Patients who had a palpable mass on physical examination, a solitary mass with suspicion of malignancy by imaging methods, and those who were found to have malignancy as a result of imaging-guided biopsy were excluded from the study.

The patients were divided into 3 groups according to their pathology results; Those with no intraductal lesions (ductal ectasia/periductal mastitis), those with benign intraductal lesions (intraductal papilloma and intraductal papillomatosis), those with pathogenic neoplastic and malignant lesions (DCIS, intraductal papillary carcinoma, atypical intraductal papilloma and atypical papilloma with atypical papilloma). The cytology results of nipple discharge of the patients were collected under 4 groups. These groups are; cytological findings including blood cells, cytological findings including inflammatory and normal ductus cells, papilloma suspicious cytological findings and cytological findings with atypical ductus cells. The USG and MRI results of the patients were coded under 4 groups. These 4 groups; normal USG and MRI findings, ductal ectasia, intraductal lesion, and malignancy suspicious findings. Mammography was coded according to the BIRAD-S system.

Isolated ductal lobular unit excision (microductectomy) was performed in patients who meet at least two criteria of pathological nipple discharge and who wanted symptomatic relief. The mentioned procedure was performed under general anesthesia and in the operating room. Stages of the microductectomy procedure are shown in Figs. 1 and 2).

Statistical Analysis

SPSS version 21 for Windows was used for statis-

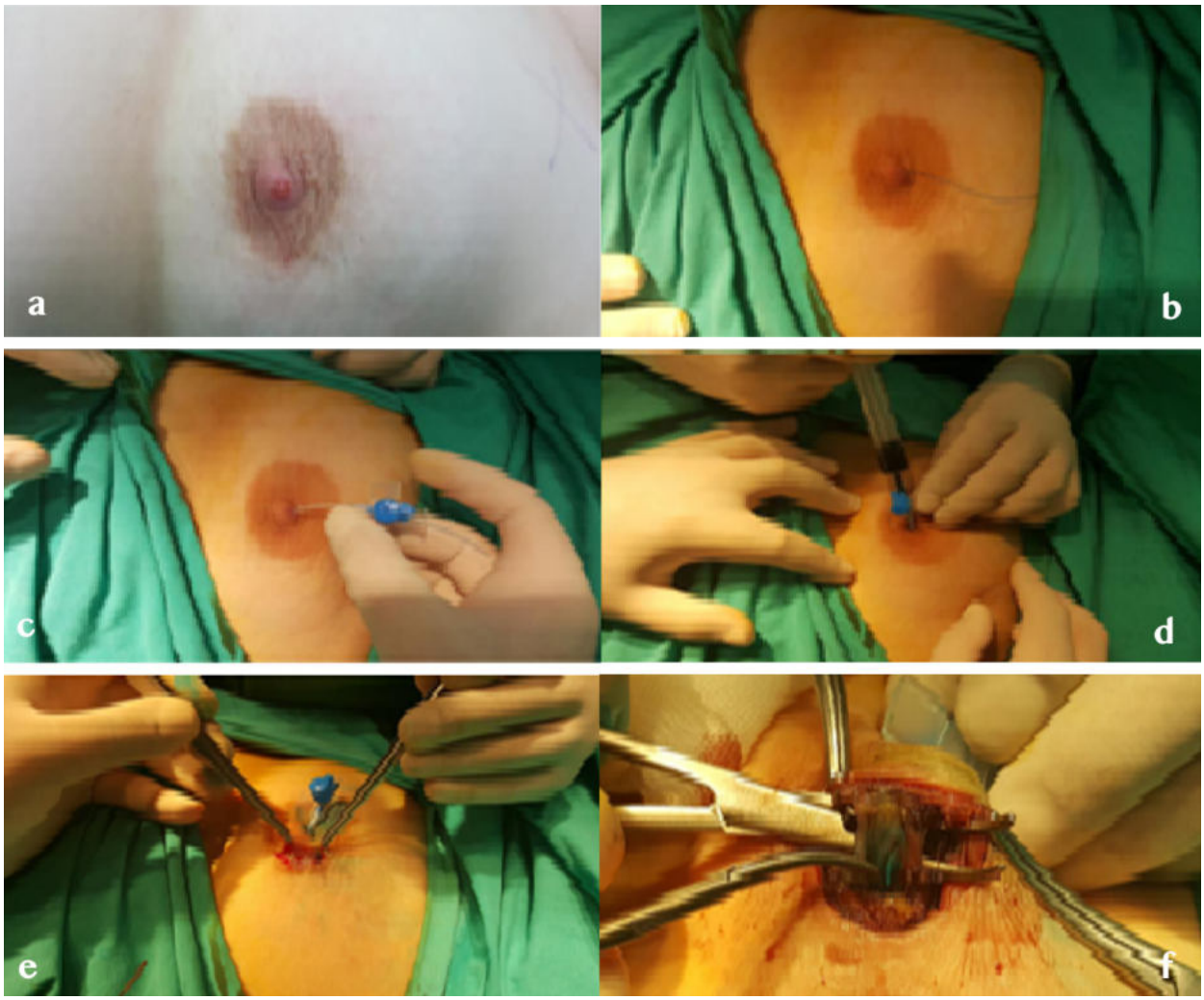

Fig. 1. Stages of the microductectomy procedure. (a) İsolated nipple discharge, (b) Cannulation of the duct with prolene, (c) Dilation of the duct with a branul cannula, (d) Staining of the duct with methylene blue, (e) Exploration with periareolar excision, and (f) Isolating the dyed duct.

tical calculations. Chi-Square and Fisher's exact tests were used for statistical analysis. A value of $p < 0.05$ was considered significant.

RESULTS

Fifty-five patients who were operated on were evaluated postoperatively. The discharge of 54 patients stopped after the operation. A patient whose pathology had intraductal papillomatosis continued to discharge after the operation, and subareolar excision was performed as a second operation. The pathology result of the second operation was reported as a foreign reaction. No postoperative complications were observed in other patients. In one of the patients, re-excision was required when the surgical margin was positive DCIS was seen in the pathology result.

The average age of the patients in the study ranged from 23 to 73 years (mean age: 45.5 years; median age: 47 years). Out of 55 procedures, 28 (50.9%) were performed in women of reproductive age, 27 (49.1%) were performed in women in menopause. The discharge was localized to the right breast in 28 patients, and to the left breast in 27 patients. Forty-one of the 55 patients included in the study met all of the criteria for pathological nipple discharge, while the other 14 patients had at least two of the three criteria (Tables 1 and 2).

Final pathologies were classified as follows; intraductal papilloma/papillomatosis with atypia, intraductal papillary carcinoma (IPC), ductal carcinoma in situ (DCIS), and potential neoplastic and malignant lesion (PNML).

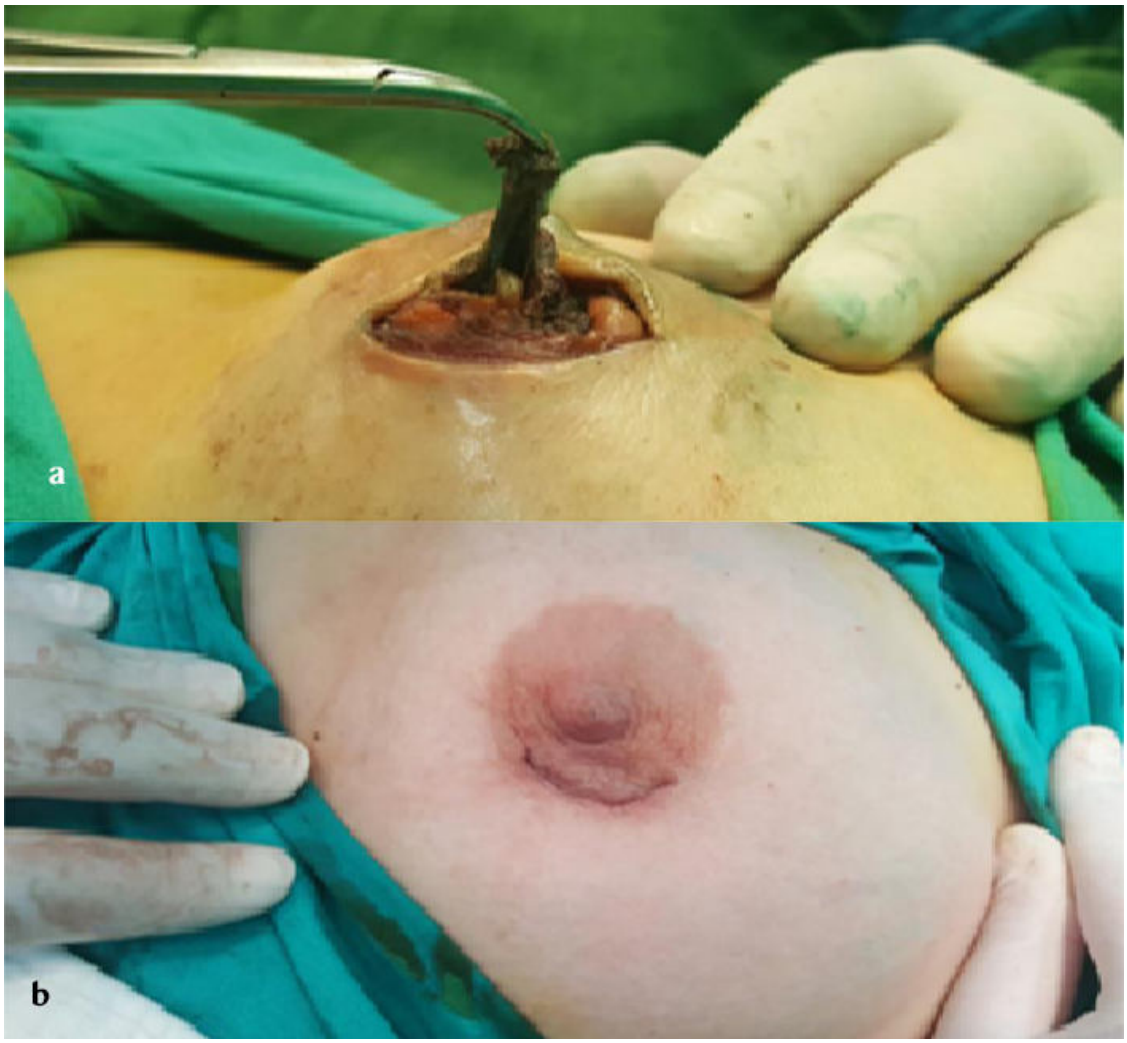

Fig. 2. The last stage of the procedure: isolated ductus excision. (a) Complete isolation and excision of the duct, (b) Closure of the skin.

All patients were evaluated ultrasonographic before the operation. Lesions (papillomatous lesion/PNML) were found in the pathologies of 21 (61.7%) of 34 patients whose USG was reported as normal. Twelve of these patients were reported as intraductal papilloma, 4 as intraductal papillomatosis, and 5 as PNML. Seventeen patients with intraductal lesions detected on USG were reported. When the pathologies of these patients were examined, it was found that the following were reported; Ductal ectasia/periductal mastitis in 5 (29.4%) patients, papillomatous lesion in 7 (41.2%) patients, and PNML in 5 (29.4%) patients.

Mammography was performed in 41 of 55 patients before the operation. Mammography was not requested for the other 14 patients due to their age. The pathology of 2 of 14 patients who did not undergo mammography were reported as DCIS. In 25 of 41 patients who had mammography, its result was reported as BIRADS 0. DCIS was found in the pathology of 2 of these patients, intraductal papillary carcinoma in 1, intraductal papilloma with atypia in 2 patients, and intraductal papillomatosis with areas of atypia in 1. Mammography results of 8 of the other 16 patients were reported as BIRADS 1, 5 of them as BIRADS 2, 1 of them as BIRADS 3, and 2 of them as BIRADS 4a. In 7 out of 8 patients reported as BIRADS 1, intraductal lesion was shown pathologically. In 2 of 5 patients reported as BIRADS 2 and 1 patient reported as BIRADS 3, intraductal lesion was shown pathologically. PNML was not detected in any patient reported as BIRADS 1-2 and 3. DCIS was detected in one of the 2 patients reported as BIRADS 4a, and intraductal papillary carcinoma was detected in the other.

MRI could not be performed in 2 of 55 patients included in the study due to claustrophobia. Pathology

Table 1. Distribution of patients by discharge type

	Total patients	Number of patients with lesions	*p* value
Pathological discharge (cerotic, serosanguinous and bloody)	47	34 (72.3%)	***p* < 0.01**
Non-pathological discharge (milky, green and brown)	8	1 (12.5%)	

results of these patients were reported as ductal ectasia/periductal mastitis. In the pathology of 12 of 20 patients whose MRIs were reported as intraductal lesions, intraductal papillomatous lesions (9 solitary papilloma, 3 multiple papillomas), 2 had DCIS, 2 had intraductal papilloma with atypia, and 1 had papillomatous with atypical areas of papilloma.

In the other 3 patients, no intraductal lesions were detected (ductal ectasia/periductal mastitis). In the pathologies of 3 patients whose MRIs were reported as suspected malignancy; DCIS was found in 1 and ductal ectasia/periductal mastitis in the other 2. In the pathologies of 30 patients whose MRI results were reported as normal; 13 had intraductal papillary lesions (solitary papilloma/multiple papillomas in 10 patients), DCIS in 2, intraductal papillary carcinoma in 2, and ductal ectasia/periductal mastitis in the other 13 patients.

Preoperative nipple discharge cytology examination made in all patients included in the study. In the pathology of 7 of 9 patients with red blood cells on cytological examination, intraductal papilloma (77.8%), intraductal papillary carcinoma (11.1%), and ductal ectasia/periductal mastitis were detected in 1 (11.1%). In the pathologies of 20 patients whose cytology results were reported as suspicious papilloma; While 10 had intraductal papillary lesions (solitary papilloma in 7 patients, multiple papillomas in patients), 6 patients PNML (2 patients DCIS, 1 patient intraductal papillary carcinoma, 2 patients intraductal papilloma with atypia, 1 patient papillomatosis with atypical areas of papilloma). In 4 patients, no intraductal lesions were detected (ductal ectasia/periductal mastitis). Papillomatosis was detected in 1 of 2 patients and DCIS was detected in 1 of 2 patients with atypical ductus cells on cytological examination. When the pathologies of 24 patients with inflammatory cells and normal ductus cells on cytological examination were examined; There were no intraductal lesions in 15 of them (ductal ectasia/periductal mastitis), 7 had intraductal papillary lesions (solitary papillomas in 5 patients, multiple papillomas in 2 patients), and DCIS in 2 patients.

If 5 patients who underwent microductectomy and whose pathology result was reported as DCIS, and 2 patients whose pathology result was reported as intraductal papillary carcinoma, were examined, in six of these patients, adequate surgical margins were provided by microductectomy. Re-excision was performed in a patient with DCIS due to a positive surgical margin. After radiotherapy was applied to all patients, Tamoxifen or Aromatase inhibitor treatment was started depending on the menopause status.

DISCUSSION

Imaging methods are always helpful diagnostic methods. Physical examination and anamnesis are the most important elements in the correct diagnosis. Even

Table 2. Distribution of patients according to pathological nipple discharge

Pathological Nipple Discharge -PND Single duct-Spontaneous-Pathological discharge	Total patients	Number of patients with lesions	*p* value
3+criteria	41	29 (70.7%)	$P > 0.05$
2+criteria	14	6 (42.8%)	

if methods such as USG, mammography, breast MRI are found to be normal, it should always be kept in mind that there may be an underlying pathology.

Apart from pregnancy and lactation, spontaneous, unilateral, bloody or serous discharge originating from a single duct describes PND. Although the most common cause of pathological nipple discharge is benign breast lesions (35-48%) such as solitary intraductal papilloma and papillomatosis, this discharge can rarely be a sign of malignancy. For this reason, surgeons should carefully evaluate the patient's complaints and symptoms.

Although the definition of PND is clear, there is no consensus on who will undergo microductectomy. Within the scope of this study, the rate of intraductal lesion detection by microductectomy was 63.6% (35/55: 21 SP, 7 MP, 5 DCIS, 2 intraductal papillary carcinomas) in the whole patient group. It is seen that this rate is higher when compared with the other in the literature. The reason for this is that patients who meet all PND criteria are given priority in order to avoid unnecessary surgery when making a surgical decision, since there is no possibility to perform ductoscopy. The primary criterion for the surgical decision was the color of the discharge. Also, the discharge of all patients in the study was a single duct.

In the literature, when the color of the discharge is not taken into account, the rates of PNML in patients who are decided to be operated according to the results of ductoscopy are between 7% and 13% [14-16]. If the color of the discharge is bloody, this rate increases up to 31% [17, 18]. This rate has been reported as 10% in patients who underwent ductus excision, considering classical imaging methods, cytology and pathological discharge criteria without ductoscopy [19, 20]. In this study, the PNML rate was 18.1% (10/55) in the whole patient group. The PNML rate was 19.5% (8/41) in patients with PND 3+ and 14.2% (2/14) in patients with PND 2+. Considering these results, the reason why PNML rates were higher than the examples in the literature was that 2 patients with intraductal papilloma with atypia and 1 patient with intraductal papillomatosis with atypia were included in the PNML group. In addition, if ductoscopy was performed in 1 patient with intraductal papilloma + DCIS, DCIS could be skipped by performing ductoscopic papillectomy. If these 4 patients are excluded from the PNML group, the new rate changes to 10.9% (6/55) and it can be seen that this rate is compatible with the literature. While these results show that ductoscopy is useful in removing single papilloma in an office environment without the need for surgery, it is insufficient to detect PNMLs and the patient may skip it. Nevertheless, when looking at the series in the literature to reach such an opinion, it is seen that the patient group in the study is insufficient. Cytological examination of nipple discharge may be helpful in diagnosis, but alone cannot distinguish ADH, intraductal papilloma and DCIS. In a retrospective study by Kalu *et al*. [21], The sensitivity of cytology was 74.5% and the specificity was 30%. Ohlinger *et al*. [22], İn their retrospective study, found the sensitivity of cytology as 57.8% and the specificity as 85.2%. In this study, the sensitivity of cytology in detecting intraductal lesions was 74% and its specificity was 75%.

In the literature, the sensitivity of ultrasonography in detecting the intraductal lesion varies between 56% and 83%, and the specificity varies between 18% and 75% [22, 24, 25]. In this study, the sensitivity of ultrasonography was 45.2% and the specificity was 75%. The reason for the difference of the sensitivity percentage from the literature is that USG is thought to be a subjective imaging method based on the experience of the person performing it. The specificity of the study was found to be consistent with the literature. The sensitivity of mammography in detecting intraductal lesions in nipple discharge varies between 15% and 60% in various studies, and its specificity varies between 65% and 98% [23, 24]. Mammography was used in this study to rule out malignancy. The use of MRI is more common in evolving nipple discharge. When looking at the literature, it can be seen that the sensitivity of MRI in various studies varies between 65% and 100%, and the specificity varies between 12% and 68% [22, 24, 25]. In the study conducted, the sensitivity of MRI was found to be 72.2% and its specificity as 51.4%, and these rates were found to be compatible with the literature.

CONCLUSION

The findings of this study show that microductectomy performed with the correct indication enables the completion of appropriate treatment by detecting precancerous breast lesions that can be easily missed with

classical diagnostic methods. At the same time, it provides symptomatic treatment of patients in lesions without malignancy risk. It is thought that it is not a wrong view to consider microductectomy as a priority in women who meet the 2 criteria of nipple discharge. In cases where direct intraductal imaging methods cannot be applied in patients admitted to the polyclinic with pathological nipple discharge, microductectomy emerges as an effective diagnosis and treatment method that can be applied with low morbidity.

Authors' Contribution

Study Conception: AEK, MMA, FM; Study Design:AEK, MMA, FM; Supervision: AEK, MMA, FM; Funding:AEK, MMA, FM; Materials: AEK, MMA, FM; Data Collection and/or Processing: AEK, MMA, FM; Statistical Analysis and/or Data Interpretation: AEK, MMA, FM; Literature Review: AEK, MMA, FM; Manuscript PreparationAEK, MMA, FM and Critical Review: AEK, MMA, FM.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(2):218-224 Original Article

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The factors affecting the redisplacement in distal radius fractures

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ABSTRACT

Objectives: Many instability criteria have been described in the literature to predict loss of reduction in distal radius fractures. However, the effect of the column location of the fracture on loss of reduction has not been investigated. The aim of this study is to investigate the effect of fracture column location and other radiological parameters on the loss of reduction of the distal radius fractures.

Methods: A total of 106 patients who were treated conservatively for displaced distal radius fractures were included in the study. The average age of the patients included in the study is 54.9 years (range: 18-91 years). Anteroposterior and lateral radiographs of the wrist were taken in each patient at the time of first admission, immediately after reduction and casting, and at the 1st, 2nd and 6th weeks. Intraarticular fracture were evaluated by computed tomography (CT). Radial length, volar tilt angle and column location of the fracture were obtained by evaluating the radiographs and CT. The effects of post-reduction radiological parameters and column location of the fracture on loss of reduction were analyzed.

Results: Reduction loss was detected in 23 (21.7%) of 106 patients. Metaphyseal fracture in 83 (78.3%) patients, intermediate volar column fracture in 76 (71.7%) patients, intermediate dorsal column fracture in 86 (81.1%) patients, ulnar column fracture in 52 (49.1%) patients and radial column fracture in 25 (23.6%) patients were determined. It was observed that having a fracture in the ulnar column or radial column caused a significant loss in radial length ($p < 0.05$). Metaphyseal and the intermediate column fractures did not make a statistically significant difference in reduction loss.

Conclusions: Column location of the fracture can also be used to predict loss of reduction in the conservative treatment of distal radius fractures.

Keywords: distal radius fracture, instability, loss of reduction, redisplacement, column theory

Distal radius fractures account for approximately one-fifth of fractures treated in emergency departments [1]. The first treatment of patients with distal radius fractures is usually conservative treatment consisting of closed reduction and plaster immobilization [2, 3]. However, loss of reduction occurs in up to 64% of patients after closed reduction [4].

It is a widely accepted opinion that surgical fixation will benefit patients in distal radius fractures with loss of reduction other than acceptable parameters (> 10° dorsal angulation, radial shortening > 3 mm or intra-articular step-off) (American Academy of Orthopaedic Surgeons Board of Directors, 5 December 2009), considering the patient-related factors.

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Lafontaine *et al*. [5] has defined five basic criteria to identify patients with unstable distal radius fractures: dorsal angulation exceeding 20° at presentation; dorsal comminution; extension of the fracture into the radiocarpal joint; an associated ulnar fracture; and age over 60 years. In cases where three or more of these criteria are present, the fracture is considered unstable [5]. After this study, many studies were conducted to determine the instability criteria in distal radius fractures. Some of them confirmed these five criteria, while others rejected them [6, 7]. An other study identified different radiological and clinical risk factors and developed scoring systems to predict loss of reduction [8]. As a result, the factors determined about instability in the literature are; patient age 60 or above, metaphyseal comminution, dorsal angulation greater than 20°, shortening of radius greater than 5 mm/positive ulnar variance, associated ulnar fracture, severe osteoporosis, radial inclination less than 15°, 2 mm joint stepping and widening of the joint surface more than 50% [5, 8, 9]. Although there are many risk factors used in the literature to predict the loss of reduction in distal radius fractures, the evidence regarding them is still limited [10]. In addition, the effect of the column location of the fracture on loss of reduction has not been investigated. Therefore, we determined the main research question as ' Does the column localization of the fracture have an effect on reduction loss in conservatively treated distal radius fractures?'. The primary aim of this study is to investigate the effect of fracture column location on the loss of reduction of the distal radius fractures. The secondary aim of this study is to investigate the effects of age, post-reduction radiological parameters on reduction loss in patients with conservatively treated distal radius fractures. The hypothesis of the present study is 'The column localization of the fracture can be used to assess the stability of distal radius fractures.

METHODS

The patients were informed verbally and written with a consent form describing the procedure. The study was conducted according to the Helsinki Declaration and approved by Local Commitee of Medical Ethics for human studies (03.08.2018/10).

One hundred and six out of a total of 123 patients,

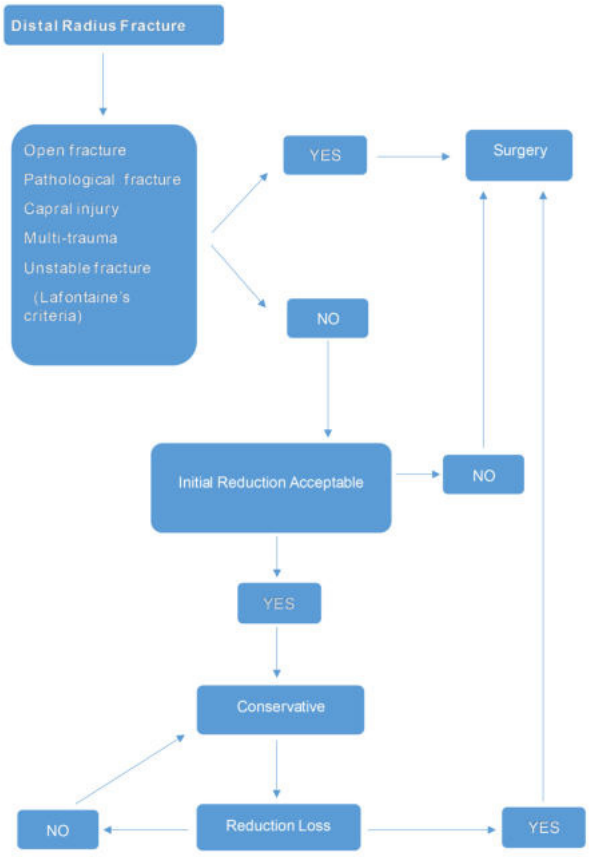

Fig. 1. Flowchart of patient selection and treatment algorithm.

75 females and 31 males, who were treated conservatively for distal radius fractures in our clinic between May 2018 and October 2019 were included in the study. Seventeen patients who were lost to follow up were excluded from the study. Patients with multiple fractures, pathological fractures, open fractures, carpal injuries and unstable fractures (according to Lafontaine's criteria [5]) were not included in the study. In addition, patients who could not achieve acceptable reduction after the first reduction were not included in the study (Fig. 1). The average age of the patients included in the study is 54.9. (18-91 range). Closed reduction under sedation and long arm circular cast were applied to all patients. Anteroposterior and lateral direct radiographs of the wrist were taken in each patient at the time of first admission, immediately after reduction and casting, at the 1st week, 2nd week and 6th week. Computed tomography (CT) was performed to determine the column localization of the fracture only in intra-articular fractures. Patients were followed until union was observed. Radial length and volar tilt angle were measured by examining all direct graphs. In addition, the distal forearm was divided into five basic anatomical regions, considering the column theory [11] and Melone [6] classification. These regions were; the extrarticular metaphyseal part was classified as metaphyseal region, the area lateral to the Lister's tubercle containing the scaphoid fossa as the radial column, the area medial to the Lister's tubercle containing the lunate fossa as the intermediate column, and the distal ulna as the ulnar column. In addition, the intermediate column was divided into two as volar and dorsal regions. Considering these five main regions, graphies and CT scans were evaluated and the column locations of the fractures were determined (Fig. 2). All the measurements were conducted by one independent orthopedic surgeon.

In the measurements made on the radiographs obtained during the follow-up of the patients; according to AAOS criteria, patients with a dorsal angulation of the volar tilt angle over 10 degrees and shortening of more than 3 mm in radial length were evaluated as reduction loss [12].

Statistical Analysis

The effects of age, fracture column location, radial length and volar tilt after first reduction parameters on reduction loss were analyzed. Shapiro Wilk test was used to investigate the compatibility of the data to normal distribution, the two-way repeated measures ANOVA test was used for repeated measures, the McNemmar test was used for the comparison before and after the analysis of the cross tables, and the standard SPSS for Windows (version 21.0, IBM Corp., Armork, New York) was used for the analysis. $P < 0.05$ value was accepted as the criterion for statistical significance.

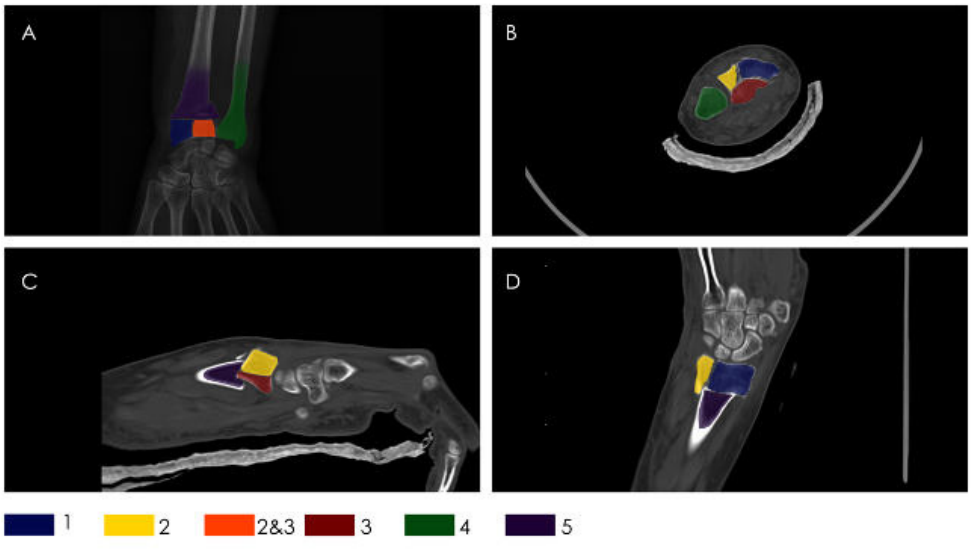

Fig. 2. (A) AP view distal radius X-Ray, (B) Axial view distal radius CT, (C): Sagittal view distal radius CT, (D) Coronal view distal radius CT. Distal radius column illustration: 1) Blue = Radial column, 2) Yellow = Dorsal intermediate column, 2&3) Orange = Intermediate column, 3) Red= Volar intermediate column, 4) Green = Ulnar column, and 5) Purple = Metaphyseal region.

RESULTS

Examining the anatomical location of 106 distal radius fractures, it was determined that 83 (78.3%) patients had metaphyseal fractures, 76 (71.7%) patients had intermediate volar colon fractures, 86 (81.1%) patients had intermediate dorsal colon fractures, 52 (49.1%) patients had ulnar colon fractures and 25 (23.6%) patients had radial column fracture. In the first radiographs after reduction, the radial height was detected as an average of 12.35 mm (3.92-20.68 mm), and the average volar tilt angle was 5.23° (-17.50 - 21.90°). In the last control radiographs of the patients, the radial height was detected as an average of 9.25 mm (-1.12 - 18.80 mm), and the mean volar tilt angle was 1.55° (-22.10 - 25.10°) (Table 1).

Reduction loss was detected in 23 (21.7%) of 106 patients. It was observed that 19 (17.9%) of them had reduction loss in radial length and in 4 (3.8%) of them in volar tilt. There was no statistically significant difference between reduction loss and age (OR; 95% confidence interval (CI): 0.224 [0.936-1.022]). There was no statistically significant difference between reduction loss and after reduction measurements of the radial length (OR; 95% CI: 0.935 [0.734-1.191]) and volar tilt angle (OR; 95% CI: 0.979 [0.893-1.074]). It was found that ulnar (OR; 95% CI: 6.993 [2.5-19.607]) or radial (OR; 95% CI: 3.871 [1.264-11.904]) column fractures of the distal radius causes significant loss of radial length ($p < 0.05$). There was no statistically significant relationship between the fractures in the metaphyseal region (OR; 95% CI: 0.253 [0.051-1.262]), intermediate volar column (OR; 95% CI: 1.012 [0.303-3.381]) and intermediate dorsal column (OR; 95% CI: 1.874 [0.486-7.224]) with radial length ($p > 0.05$) (Table 2). Among the criteria investigated, no statistically significant parameter effective in volar tilt loss was observed ($p > 0.05$) (OR; 95% CI: 0.169).

DISCUSSION

In this study, in conservatively treated distal radius fractures, the effect of the fracture's column location on loss of reduction was investigated and it was concluded that the radial length loss was greater in fractures involving the radail and ulnar column. The rate of reduction loss in conservatively treated distal radius fractures is 9-32% [13]. Factors causing reduction loss in conservatively treated distal radius fractures have been investigated in many studies in the literature. The colon theory has been defined as the concept of stable fixation in the surgical treatment of distal radius fractures. However, the effect of the column theory on reduction loss in conservative treatment has not been examined in the literature.

In order to classify distal radius fractures, there are more than twenty classification systems that have been

Table 1. Radiographic parameters in each session

	After Reduction (min-max)	Final Follow-up (min-max)
Radial Length	12.35 mm (3.92-20.68)	9.25 mm (-1.12-18.8)
Volar Tilt	5.23° (-17.5-21.9)	1.55° (-22.1-25.1)

Table 2. Fracture column location with radial length displacement on logistic regression analysis

	Odds Ratio	95% CI for OR Lower	95% CI for OR Upper	*p* value
Metaphyseal Fracture	0.253	0.051	1.262	0.094
Intermediate Dorsal Column Fracture	1.874	0.486	7.224	0.362
Intermediate Volar Column Fracture	1.012	0.303	3.381	0.985
Ulnar Column Fracture	6.993	2.5	19.607	**0.0001**
Radial Column Fracture	3.871	1.264	11.904	**0.018**

defined so far according to the surgeon's name, the mechanism of the fracture, the area of the fracture, and the stability. Although classifications are useful in academic use, they remain inadequate due to the deficiencies in guiding the treatment method and the inability to form a common consensus. There are many articles comparing surgical and conservative treatment. Arora *et al*. [2] compared the results of surgical and conservative treatment options in patients over 65 years of age with distal radius fractures and found that there was no difference between the two groups in range of motion and pain level. In the same study, they showed that surgical treatment had better results in grip strength, volar tilt angle measurements and radial length measurement. They stated that conservative treatment had better results in complication rates. Zengin *et al*. [14], in their study comparing volar plating and plaster treatment in patients aged 60 and over with AO type c distal radius fractures, reported that the surgical method yielded better grip strength and radiological results and there was no statistically difference between clinical and functional results. Surgical and conservative treatment options were also compared in terms of cost. In their study, Shauver *et al*. [15] showed that the cost of conservative treatment was much lower when they compared the treatment costs, although surgery was preferred more in the treatment of distal radius fractures in elderly patients. Toon *et al*. [16] compared open reduction and internal fixation with conservative treatment in the treatment of distal radius fractures and found that there was a 37-times difference between these two methods in the treatment cost. For this reason, finding certain criteria for conservative treatment in distal radius fractures will provide an economically important advantage.

The concept of stability gains importance in the conservative treatment of distal radius fractures. There are many studies investigating the instability criteria in distal radius fractures [17]. It is claimed that; patient age 60 or above, comminution of metaphyseal dorsal cortex, dorsal angulation greater than 20°, shortening of radial length more than 5 mm/positive ulnar variance, associated ulnar fracture, severe osteoporosis, radial inclination less than 15°, joint stepping of more than 2 mm and an enlargement of more than 50% in the joint face are important in instability [12, 18]. Leone *et al*. [19] claimed that the degree of radial shortness and volar tilt angle are associated with early instability, radial inclination, age, shortening of the radial length and volar tilt angle are associated with late instability. Nesbitt *et al*. [9] argued that there is a 50% risk of loss of reduction in patients over the age of 58. In our study, there was no significant difference between ages in terms of loss of reduction. In many studies, shortening of the radial length is stated to be the most important radiological instability factor affecting the prognosis, so correction of the radial length should be the primary goal [20, 21]. Volar tilt angle is also claimed to be one of the important radiological instability criteria [22]. Perugia *et al*. [23] reported that volar tilt angle and ulnar variance are the most important radiological parameters that need to be corrected in order to achieve good functional results in patients with distal radius fractures. In addition, associated ulnar styloid fracture is an important radiological parameter that increases the possibility of functional limitation [24]. Lyu *et al*. [25] investigated the risk factors causing radial shortening in patients with distal radius fractures who were followed up conservatively. They stated age, time between injury and reduction, fracture classification and early weight bearing as risk factors that will cause shortening of the radial length. Similarly, in our study, it was observed that fractures in the radial and ulnar colon created a significant difference in radial length. However, it was determined that a fracture in any column does not cause a statistically significant change on the volar tilt angle.

There are very few theories regarding clinical evaluation with respect to the anatomical columns in the distal radial region. The column concept was defined for surgical fixation stability but was omitted in the stability assessment for conservative management of distal radius fractures. In the examination performed over the columns in our study, it was observed that radial and ulnar column involvement were important risk factors for loss of reduction. There are studies in the literature showing that the ulna styloid fracture accompanying the distal radius fracture causes instability [24]. Similarly, in our study, it has been shown that ulna styloid fracture, therefore, fracture in the ulnar column is one of the effective factors in reduction loss.

The radius and ulna styloid regions in the radial and ulnar columns are the attachment sites of the important ligaments that provide wrist stability (radial collateral ligament, radioscaphocapitate ligament, ra-

diolunotriquetral ligament, ulnar collateral ligament, triangular fibrocartilage complex). In our study, it has been shown that fractures in these regions are associated with subsequent loss of reduction by causing radial length loss. Again, in a recent study, it was shown that radial shortening during conservative follow-up is a parameter that can be used to predict poor outcomes [25]. Further investigations are required between distal radius fractures and fracture instability, including wrist ligaments.

Limitations

Our study has a few limitations. Most importantly, our sample size is small and our study is retrospective. Besides, the initial displacement degree of the fracture is ignored. Another limitation is that measurements are made by a single independent surgeon. The subject that we want to focus on in our study is the relationship between the colon theory and the loss of reduction in the conservative treatment of distal radius fractures, which has not been studied in the literature, so other factors may have been ignored.

CONCLUSION

Column location of the fracture can also be used to predict loss of reduction in the conservative treatment of distal radius fractures. In our study, a significant relationship between radial length loss and radial and ulnar colon location of the fracture was demonstrated.

Authors' Contribution

Study Conception: AÖ; Study Design: AÖ; Supervision: AÖ; Funding: Osmangazi University Scientific Research Proect Unit; Materials: AOT; Data Collection and/or Processing: AOT; Statistical Analysis and/or Data Interpretation: AOT, MK; Literature Review: MK; Manuscript Preparation: MK and Critical Review: MK, AÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(2):225-231 Original Article

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A rare missense Duchenne muscular dystrophy gene variant in a family with muscular dystrophy from Turkey

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ABSTRACT

Objectives: Duchenne and Becker muscular dystrophies (DMD/BMD) are muscle diseases that show X-linked recessive inheritance. The disease occurs depending on large mutations, deletions/duplications, small mutations, point mutations and mid-intronic mutations of the gene encoding the protein called dystrophin. Therefore, in this study, we aimed to investigate the pathogenic variants of DMD in the affected family.

Methods: A 23-year-old male who had weakness in the muscles, difficulty climbing the stairs, frequent falls at the age of seven was referred to the Medical Genetics department for an initial diagnosis of DMD/BMD. His siblings also suffered from similar symptoms. Therefore, eight individuals from the same family were included in the study. MLPA analysis was performed to evaluate deletion/duplication and variants of the DMD gene were evaluated by targeted NGS. Sophia DDM algorithms were used for the bioinformatics analysis of data, and the pathogenicity of the mutations was evaluated based on in silico prediction tools.

Results: Allelic variants were identified in 8 individuals of the family including two suspected patients and six suspected obligatory carriers. NGS analysis revealed that proband and his nephew were hemizygous for pathogenic c.10018T > C (p.Cys3340Arg, C3340R) mutation and mother, two sisters and niece were carriers.

Conclusions: C3340R mutation was first reported in a Taiwanese BMD patient among the 23 different pathologic changes. This variant identified as pathogenic because of being highly conserved cysteine substitution in the dystroglycan-binding domain of dystrophin. This study has the importance of reporting an infrequent pathogenic mutation, C3340R, in two patients and four suspected obligatory carriers of a Turkish family.

Keywords: Duchenne muscular dystrophy, next-generation sequencing, multiplex ligation-dependent probe

Dystrophinopathies refers to a group of X-linked muscle diseases caused by an absent or deficient sarcolemmal protein, dystrophin. Duchenne muscular dystrophy (DMD) gene mutations cause Dystrophinopathies. The DMD gene is one of the largest genes with 79 exons.

There are two main phenotypes. A severe form is DMD, and a mild form is Becker muscular dystrophy (BMD). It has been shown that DMD is 1:3500, whereas BMD is 1:20000 male births and one-third of the mutations occur de novo [1]. DMD is usually characterized in early childhood, whereas BMD is later

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onset with the symptoms, including the skeletal muscles' proximal weakness that causes a frequent fall, difficulty climbing stairs, jumping, running, shuffling gait, and getting up from a lying or sitting position. Clinical appearance ranges mild (increase in the concentration of creatine kinase (CK) and muscle cramps) to severe (progressive muscle disease, wheelchair dependence, cardiac involvement, etc.) Typically BMD patients have milder symptoms, later-onset skeletal muscle weakness, and slower progression than DMD patients. The distinction between DMD and BMD is made depending on the age of wheelchair addiction: DMD occurs before age 13, and BMD is after age 16 [2].

The disease occurs due to defects in the DMD gene consisting of 79 exons that have been localized to the band Xp21 and encoding the dystrophin protein. The full-length dystrophin protein has four functional domains: N-terminal actin-binding domain (exons 2–8), central rod domain (exons 8-61), cysteine-rich domain (exons 63-69), and C-terminal domain (exons 70-79) [3]. Since the discovery of the gene in 1986, thousands of genetic alterations have been described worldwide [4, 5].

Deletions or duplications cause approximately two-thirds of the DMD/BMD, but point mutations, especially missense mutations, are rare. Deletions account for 60-70% of all DMD cases, whereas 80-85% of BMD cases [6] and point mutations are responsible for approximately 26% of DMD and 13% BMD cases [7]. However, Aartsma-Rus *et al*. [8] showed that DMD-related in-frame deletions/duplications were present in 7% of BMD-associated out-of-frame variants in 2% of all patients, reporting that 9% of mutations did not conform to the reading frame rule. It is also recommended that these discrepancies be confirmed at the RNA level. Depending on the variable levels of alternative insertion, one or more exons can restore or disrupt the reading frame [8].

DMD/BMD is inherited in an X-linked recessive manner. The diagnosis of DMD/BMD is based on the characteristic clinical findings and by identifying a pathogenic variant. Still, it may be necessary to use many different genetic analysis methods due to various pathogenic variants. Approximately two-thirds of the muscular dystrophies are caused by deletions or duplication in the DMD gene. The remaining variants are insertions or deletions, splice site changes, and single nucleotide variants. Among these changes, pathogenic missense variants are infrequent.

Here we report a family with a rare pathogenic missense variant, c.10018T > C (p.Cys3340Arg) in exon 69 of the DMD gene with the clinical appearances of affected males the carrier females.

METHODS

Eight individuals from the same family were included in the study. A 23-year-old male proband was referred to the Medical Genetics department for an initial diagnosis of DMD/BMD. He was born after an uneventful pregnancy at 40 weeks of gestation by standard vaginal delivery. Her parents were non-consanguineous but originated from the same small village. The neuromotor development of the patient was normal until the age of 7 years. The patient then started to suffer from weakness in the muscles, difficulty climbing the stairs, frequent falls, and difficulty getting up from a lying or sitting position. Electromyography (EMG) examination at eight years old revealed myopathic findings in both extremities. The echocardiography of the patient was normal at the age of 9 years. Respiratory function tests showed severe restrictive pulmonary function at the age of 19. The patient was tested for genetic analysis for DMD/BMD (22 exons by multiplex PCR were performed) at the age of 10 in an external center and was found to be normal. In the family history; it was learned that his older brother, the son of his older sister and the son of the other older sister who suffered from similar symptoms, died at 14 years old, 22 years old, and 21 years old (the last one died while our genetic analysis was performing) respectively. We have been informed that nobody has similar family symptoms, especially in his grandmother's family. The Ethics Committee approved all protocols used in this study of Pamukkale University Hospital with the number E-60116787-020-9709. The procedures performed in this study involving human participants were applied according to the ethics committee's standards.

MLPA Analysis

The multiplex ligation-dependent probe amplification (MLPA) was performed using the MLPA DMD kit (Salsa MLPA kit DMD/Becker, MRC Netherlands)

following the manufacturer's protocol. The SALSA MLPA Probemix P034-B2 DMD-1 contains 49 MLPA probes, while the SALSA MLPA Probemix P035-B1 DMD-2 contains 48 MLPA probes.

Targeted Next-Generation Sequencing (NGS)

Eight individuals from the family (I:2 grandmother, II:1 mother, III:3 older sister, III:4 older sister, III:5 older sister, III:6 affected male PROBAND, IV:5 affected male nephew, IV:7 niece) were included to NGS study. DNA library was prepared using the DMD master kit (Multiplicom). First, PCR was performed using a 20ng genomic template to amplify all coding regions of the DMD gene and control amplicons in four separate plexes with multiplex PCR amplification reactions containing 118 amplicons per sample. Second, PCR has performed to label the amplicons with molecular descriptors. Each pooled amplicon was purified using Agencourt AMPure XP beads. The library was prepared from each amplicon (280-400 bp) using equimolar concentration. Fluorometric quantitations of DNA samples and purified libraries were determined using Qubit dsDNA Kit (ThermoFisher MA). Sequencing was performed on the Miseq instrument by using Illumina MiSeq Nano Kit v2.

Statistical Analysis

Sophia DDM® (v4.3.1) platform was used for the bioinformatics analysis of data, enabling SNV and Indels (Sophia Genetics SA, Switzerland). Generated FastQ files were then aligned against the reference sequence specified in a manifest file and trimmed to remove primer sequences. Besides, SOPHIA DDM® (v4.3.1) holds a CNV module allowing the CNV analysis for amplicon-based NGS. The pathogenicity of the mutations was evaluated based on in silico prediction tools (SIFT, MutationTaster, Polyphen2) the inheritance (OMIM), database entries (ClinVar, HGMD), and ACMG recommendations.

RESULTS

For the initial diagnosis of DMD/BMD, we first performed deletion/duplication analysis (79 exons) for the DMD gene by MLPA technology, and we did not detect deletion or duplication. The patient was subjected to laboratory and radiological testing. The serological analysis showed creatine kinase (CK) level to be elevated to 933 U/L and lactate dehydrogenase to 252 µg/dl. Polyphasic motor unit action potential (MUAPs) were detected in the left tibialis anterior, left vastus lateralis, right gastrocnemius muscles in the needle electromyography examination.

Genetic data for the family are shown in Fig. 1. Allelic variants were identified by NGS analysis in 8 individuals of the family (demonstrated in the pedigree) who were suspected patients (n = 2) and suspected obligatory carriers (n = 6). The rare pathogenic mutation we detected, c.10018 T > C (p. Cys3340Arg; C3340R), was found in 6 out of 8 individuals (hemizygous in males (III:6, IV: 5) and heterozygous in fe-

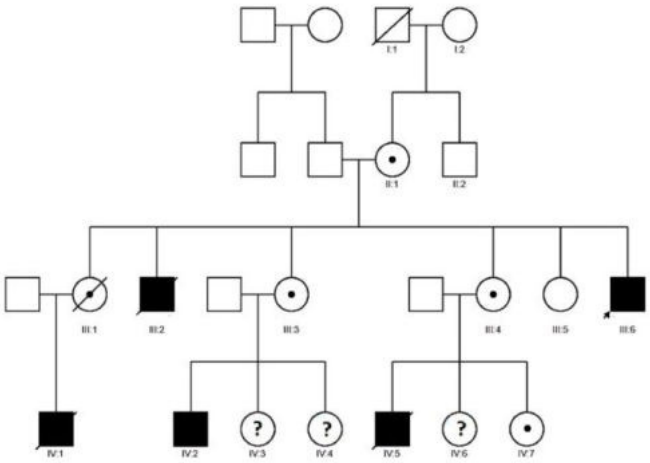

Fig. 1. Pedigree of the family with muscular distrophy: Proband and his nephew (III:6, IV:5) were hemizygous and mother, two sisters and his niece (II:1, III:3, III:4, IV: 7) were heterozygous for C3340R mutation. Eight individuals from the family (I:2 grandmother, II:1 mother, III:3 older sister, III:4 older sister, III:5 older sister, III:6 affected male PROBAND, IV:5 affected male nephew, IV:7 niece) were included to NGS study.

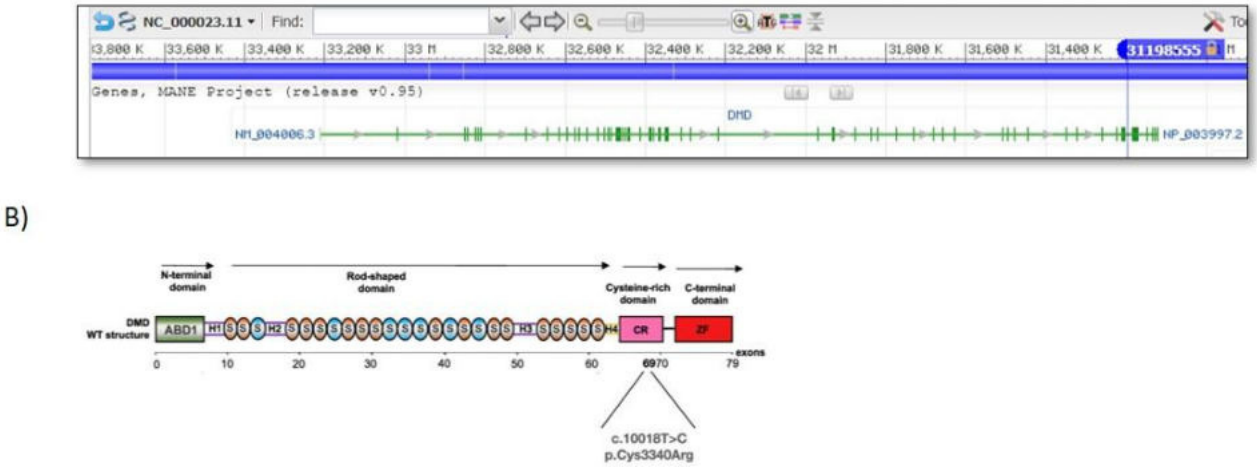

Fig. 2. Overview of the functional domains the Dystrophin protein (A) and genomic and location (B) of c.10018T > C mutation.

males (II: 1, III: 3, III:4, IV: 7) except in grandmother and elder sister. The coding sequence and genomic location of c.10018 T > C mutation is represented in Fig. 2.

DISCUSSION

Muscular dystrophy is a collection of more than 30 genetic diseases causing progressive weakness and degeneration in the skeletal muscles. DMD and BMD are X-linked recessive inherited muscular dystrophies. DMD/BMD symptoms are similar, such as the proximal muscles' weakness that cause a waddling gait, frequent falls, running, jumping, difficulty climbing stairs, and getting up from a lying or sitting position. Affected men use the Gower maneuver to rise from the prone position, using their arms to support the weak pelvic girdle muscles. Calf muscles are hypertrophic and intact during palpation, and calf pain is sometimes observed. There are myopathic changes in EMG examination and increased serum CK levels. Respiratory complications and progressive cardiomyopathy are the most common causes of death. However, BMD is distinguished from DMD by the dependence on the wheelchair after 16 years of age (before age 13 in DMD), the late onset of symptoms, and milder course.

The first report of a missense mutation associated with DMD was published by Prior *et al*. in 1993 [9]. In the UMD-DMD France database, which provides up-to-date information about the DMD gene's mutations, 2898 variants have been reported [10-12]. A comprehensive study involving 1497 patients with dystrophinopathy in Japan revealed the spectrum of mutations identified in the DMD gene. According to this spectrum, exon deletions (61%), duplications 13%), and nonsense (13%) mutations are seen with the highest frequency [13]. However, in some studies, the rate of large deletions was reported to be less (nearly 43%) than generally reported. However, a higher rate for missense mutations was observed (1.4%) due to the diversity in the patients' selection [6]. In a study conducted on a Turkish family of DMD/BMD without 56 detected DMD deletions, Eraslan *et al*. [14] scanned the eighteen deletion-prone exons of the dystrophin gene using modified non-isotopic multiplex single-strand conformation analysis (SSCA). They reported that they identified five unique mutations, 2 of which were responsible for the onset of disease phenotype in DMD [14]. Flanigan *et al*. [6] reported that Point mutations account for 46% of all mutations in their study. However, contrary to previous studies, they could not observe point mutation hotspots due to the nearly evenly distribution of point mutations across the exons [6].

In our family, we found a rare missense mutation, c.10018T > C(p.Cys3340Arg) in exon 69, which is predicted as pathogenic according to in-silico databases (SIFT, PolyPhen and Mutation Taster) and the UMD-DMD France database (record ID: 1607). This mutation has not been reported previously in Turkish population and this substitution affects the highly conserved and substantial cysteine-rich domain for the functions of dystrophin isoforms. In addition, this mutation was first reported in a Taiwanese BMD patient

by Hwa *et al*. among the 23 various pathologic changes including 7 substitutions of which C3340R is the only missense mutation, 6 small deletions and 2 small insertions. This variant has been reported to be pathogenic in that dystrophin has a highly conserved cysteine substitution in the second half of the dystroglycan binding domain [15]. For this mutation, another nucleotide changes in 3340. amino acid position of the dystrophin protein (p.Cys3340Tyr and p.Cys3340Trp) was also reported as pathogenic [16, 17]. Lenk *et al*. [17] reported a G10227A transition, which resulted in a highly conserved cysteine substitution at position 3340 in a child with DMD. They concluded that the patient's mental retardation and absence of b-wave in his electroretinogram could indicate central nervous functions of dystrophin isoforms also depend on cysteine presence 3340 [17]. Second report was from India revealing that C3340R, F590R, C3207R and C3319R have a higher potential to cause DMD than other mutations [18]. Mutations with cysteine residues mutated to some other amino acids such as C3207R, C3313F, C3319R, and C3340R significantly altered the secondary structure of the dystrophin. Another interesting fact is that any mutation containing a basic amino acid instead of a relatively hydrophobic one (like F590R, C3207R, C3319R, and C3340R) has a higher potential cause DMD than other mutations.

The diagnosis of DMD/BMD depends on clinical features and genetic analysis. For genetic diagnosis, a two-step procedure as MLPA to detect deletions and duplications and sequencing of the coding region and splice sites to detect point mutations were usually performed [19]. MLPA analysis alone in DMD/BMD yields approximately 71% [20]. However, the sensitivity of MLPA in combination with sequencing is about 97.3% [19]. These rates are variable among studies. Ballo *et al*. [21] confirmed the genetic diagnosis of DMD in 42% of the affected males (by detection of deletions in the dystrophin gene). In another study from Iran, the genetic diagnosis rate was 81% in DMD [22]. MLPA analyses of our patient were normal. We performed sequencing of the DMD gene by NGS technology, depending on his clinical findings and family history. As a result, we did not detect C3340R mutation in grandmother even though there are female carriers in our family, consistent with the X-linked recessive inheritance of DMD. These situations, like ours, were being studied for several years. Haldane was the first to suggest a mutation-selection equilibrium in X-linked recessive disorders. In DMD, affected males can not inherit their defective allele to the next generation depending on the reduced life expectancy. In every generation, one-third of mutated alleles are expected to be 'lost' from the population leading to a rapid decrease in the disease incidence. Therefore, the conclusion of Haldane [23] was if there is an equivalent rate of de novo mutations, then the selection of mutated alleles from the population can be compensated. After that, Haldane [23] enlarged on a formula for mutation-selection balance, and according to this genetic model, three ways for the inheritance of DMD mutations were accepted: (1) Mothers are female carriers because their mother is already a carrier; (2) A de novo mutation has occurred in meiosis either in the grand-parental generation (in spermatogenesis of the grandfather or oogenesis of the grandmother; or the mother (de novo mutation in oogenesis); and (3) Mitotic de novo mutations because of germline mosaics can occur in the spermatogenesis of the grandfather, in the oogenesis of the grandmother or the oogenesis of the mother [19].

Grimm *et al*. [24]reported that most deletions arise in oogenesis, while most point mutations are welded from spermatogenesis. In our family, c.10018 T > C mutation was not detected in grandmother (I: 2), and grandfather (I: 1), who died at 87 years old, did not have any muscle problem. So it was intensely estimated that he was not a DMD/BMD patient, and mutation was firstly detected in proband's mother (II: 1) due to the second or third way of the inheritance of DMD mutation.

In family studies for DMD/BMD, rates of inherited variants or de novo variants can differ due to criteria such as variant types, patient selection, or patient number. In Consistence with Haldanes' theoretical model, Ma *et al*. [11] reported a genetic analysis on mothers of 442 patients revealing that 297 (67.2%) of them owned the same mutations as their children, while 145 (32.8%) of them did not. In a study in 106 Taiwanese families with DMD/BMD in 19 mother–patient pairs, 21.1% (4/19) of cases were found to be de novo [15]. Yang *et al*. [20] also reported that DMD gene defects were inherited in 51.72% of their mothers' patients. According to Prior and Bridgeman [25], deletions in the gene's proximal part are more likely

to turn into a familial hereditary mutation. In contrast, distal deletions are more frequently seen sporadically.

Our analysis also revealed 4 missense mutations besides c.10018T > C(p.Cys3340Arg) in our family including c.2645 A > G (p.Asp882Gly), c.5234G > A (p.Arg1745His), c.8810G > A (p.Arg2937Gln) and c.7096A > C (p.Lys2366Gln). These variants are predicted to be benign according to in-silico algorithms and online databases and reported as polymorphisms in the literature [26]. But C3340R mutation is predicted as pathogenic mutation depending on the scores of SIFT, POLYPHEN2 and Mutation Taster. SIFT and POLYPHEN2 reported this variant as "affect protein function" and "probably damaging" whereas MutationTaster as "disease causing". Despite the fact that all males in our family had DMD phenotype of whom their mothers' were carriers, this variant can be considered as "pathogenic". Detection of large deletions and large duplications was performed using MLPA or multiplex PCR. Because most deletion/duplication variants cause DMD, copy number variation analysis such as MLPA is recommended as the first step. In addition, Sanger or NGS was used to identify point mutations and small insertions or duplications [27, 28]. Studies in the literature have reported that it can identify approximately 92% of dystrophin mutations through NGS [29, 30]. However, by combining MLPA and DNA sequencing analysis, the genetic diagnosis rate in DMD/BMD patients can be increased. It can be possible to detect rare variants as in our family.

CONCLUSION

As a conclusion; This study has the importance of reporting an infrequent pathogenic mutation, c.10018T > C (C3340R), for the first time in two patients and four suspected obligatory carriers in a Turkish family. The identification of new mutations could be increasing awareness among parents and physicians with early identification of DMD cases and genetic counseling.

Authors' Contribution

Study Conception: OT, BA, ÇE; Study Design: OT, BA, NK, HA; Supervision: OT, ÇE, AD, HA; Funding: OT, AD, HA; Materials: BA, ÇE; Data Collection and/or Processing: OT, NK, ÇE, AD; Statistical Analysis and/or Data Interpretation: OT, BA, NK, HA; Literature Review: OT, BA; Manuscript Preparation: OT, BA and Critical Review: OT, BA.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Early period maladaptive schemas, psycological symptoms and examining the tendency of deception

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ABSTRACT

Objectives: There are relationships between early maladaptive schemas, psychological symptoms, and deception structures. Researches have not examined all these structures collectively in a single study. The aim of this study is to investigate the relationship between early maladaptive schemas, psychological symptoms and deception tendency according to various sociodemographic features. This research also aims to contribute to clinical studies. Many counselees who receive psychotherapy have problems in their relationships. Therefore, it is important to understand what is causing these problems.

Methods: The research was carried out with a total of 407 non-clinical participants, 200 women and 207 men who aged between 18 and 45 live in Istanbul. Data were collected from the participants using the Sociodemographic Information Form, the Young Schema Scale, the Brief Symptom Inventory, and the Deception Tendency Scale.

Results: According to the results of the applied correlation analyzes, it was found that there was a significant positive correlation between the components of early maladaptive schemas, psychological symptoms and infidelity tendency. The findings were interpreted and discussed within the framework of the literature.

Conclusions: An effective treatment plan can be developed that specifically addresses the etiological factor for problems that arise in close relationships. There is no significant positive relationship between the brief symptom inventory and the deception tendency scale. The base of this weak relationship is most likely to be associated with The Brief Symptom Inventory sub-dimensions of depression, anxiety, negative self, somatization, and hostility. We propose a research design to predict the relationship between EMS, personality, personality disorders, and the tendency of deception for other studies.

Keywords: Early maladaptive schemas, deception, close relationship, psychological symptom

Our early childhood experiences occur our story and this story continues to resonate throughout our lives [1]. Early maladaptive schemas show up mostly in relational processes. Early maladaptive schemas (EMS) are pervasive life patterns that widely affect cognitions, emotions, memories, social perceptions, interactions, or behavioral patterns. EMS is being considered to developing during childhood. In this schema model, cognitive variables were accepted as key elements for understanding mental disorders [2]. Based on the assumptions of Beck's Cognitive Therapy [3], automatic thoughts, beliefs, and schemas influence emotions and behaviors. Therefore, it has been suggested that different cognitive levels contribute to the maintenance of different forms of psychopathology. Young *et al*. [4, 5], determined that the

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formation of cognitive schemas occurs in early childhood and extended Beck's original work by naming it with Early maladaptive schemas. EMS is elaborated during the childhood or adolescence and reenacted throughout life. It is also characterized as memories, emotions, and bodily sensations that contribute to a cognitive consistency about oneself or others [6]. EMS may increase or decrease throughout life depending on the person's individual coping mechanisms, life conditions, and interpersonal patterns. They often continue to exist because of these factors [7]. Schemas which are being grounded in childhood and adolescence are triggered by events in adulthood. These schemas play an important role in people's thoughts, feelings, behaviors, relationships with others, self-perceptions, and moods. This paradoxically leads a person to direct unintentionally recreate the conditions that hurt them in their childhood [4, 5]. It seems that most of the problems between close relationships which are experienced are close relationships needs, spouse's needs, schemas, ways of dealing, and prisms which is composed with modes [6].

When we look at Young *et al*. [5] perspective of early maladaptive schemas, we can see that irrational, dysfunctional beliefs may lead to a view of unhealthy relationships and this may lead to reduced relationship satisfaction. Similarly, dysfunctional relationships with early age caregivers can predispose a person to hold beliefs about relationships and this care can tend to occur EMS's. As well as it leads to insecure attachment styles and specifically relationship loyalty problems.

People who have an insecure attachment style established with early caregivers are more likely to experience lower satisfaction in their relationships than people with a secure attachment style [8]. According to Harris and Curtin [9], conclude that certain EMS's are associated with negative affect and having negative core beliefs can predict depression or anxiety. It shows a relationship between EMS's and internalization problems in puberty including depression and anxiety [2, 10, 11]. EMS serves to guide later patterns of information processing and behavior that arise from early family interaction patterns. It is defined as stable and persistent dysfunctional beliefs about oneself in relation to the environment. Although there is no empirical link has been established between these EMS's, psychological symptoms, and the tendency of deception, they have much in common with internal models of the attachment system. Also, schema theory shows that schemas which are known as schema modes and relevant relationship coping styles that establish dominance on self and different aspects of the self-show that how it separates from other aspects. The theory explains that how a person transitions among these things [12].

Deception involves various lies which show up the consequences of unfaithfulness inevitably or it involves discourses and behaviors which stay out of honesty borders [13]. Deception is the one of the most important factor which threats stability and survival of marriage and romantic relationship [14]. Concept of deception along with marriage is a part of violation of obligations which is regulated couples' relationships because of extramarital interaction. Also, it causes sanction deception may harbour sexual, emotional or both of them inside. The possibility of establishing an emotional relationship is higher for women. In marriage circumstances, sexual and emotional elements which are concomitant involve more threats than situations in which the only one exist [15]. Deception strongly affects the functioning and stability of the relationship [16]. There are lots of factors influence come into existence of unfaithfulness. For example, these include the nature of the relationship like dissatisfaction [17] and the context of the relationship such as opportunities and factors which related to being person including beliefs about love and gender [18].

There is a significant correlation with attachment style which involves deception, early maladaptive schemas, and emotional deprivation schemas. In Fricker's study [19], predicted that avoidant and anxious attachment and decepiton were highly correlated. The anxious attachment was found the correlation to be positively related to the list of extramarital behaviors and also, an avoidant attachment was correlated with a scale of propensity to deception. With regard to sexuality, a person's perception style of the sexual self is assumed to be closely linked to the individual's early attachment schemas. With the expanding attachment experiences that characterize adolescence and early adulthood, especially. Attachment behaviors in romantic relationships may be affected by sexual self-schemas which were developed during this period [20].

Main Points

1. All schema domains were positively associated with different severity of psychological symptoms, such as depression, anxiety, negative self, somatization, and hostility.

2. A positive and significant relationship was observed between unrelenting standards, insufficient self-control/ self dicipline schemas, and the tendency to deception.

3. The Dependence/ Incompetence and Defectiveness/ Shame schemas Abandonment/ Instability, Mistrust/Abuse, Social Isolation schemas were associated with the severity of depression.

4. Outpatients who were diagnosed with depression and without any clinical diagnosis found that Defectiveness/Shame, Insufficient Self-Control, and Self-Sacrifice schemas differed between those with and without a diagnosis of depression.

5. A certain event in an individual's life may trigger early maladaptive schemas that manifest themselves with the appearance of anxiety disorder or depression, depending on which schema is activated.

METHODS

Universe and Sample

In this study, 407 volunteer participants between the ages of 18-45 from the province of Istanbul took part. Participants, 49.1% were female, 50.9% male, 4.7% primary school graduate, 5.7% secondary school graduate, 14.3% high school graduate, 58.7% university graduate, 16.7% postgraduate or higher, 41.0% are married and 59.0% are single.

Model of the Research

In the research, "relational screening model" was used. Research designs aim to show the existence and/or degree of co-variation among more than one variable are defined as "a relational screening models".

Data Collection

Ethics committe approval of this study was obtained from Istanbul Aydın University. The data which was used in the research was collected in 2021. Sociodemographic Form, Young Schema Scale, the Brief Symptom Inventory, and Deception Tendency Scale were transferred to Google Forms in order to apply the data collection tools. In addition, it was distributed to 407 participants over the age of 18 who were selected by a simple random method. Data collection took approximately 40 days. It was explained to participants that do not need to give in information about their identities for answering data collection tools correctly and faithfully. When, the aim of research and data collection tools fill faithfully by participants, the reliability of research will increase. This situation is explained too.

Data Collection Tools

Sociodemographic Data Form

This is a personal data form consisting of gender, age, marital status, and educational status.

Young Schema Scale

The Turkish version of the Young Schema Questionnaire (YSS-SF3) (Young Schema Questionnaire YSQ-SF3) was used to measure the maladaptive schemas formed in the early period in the study. The Original Young Schema Scale (YSQ) is a scale consisting of 16 schemas and 205 items [5]. Later, a shorter form consisting of 15 schemes and 75 items was created (YSQ-SF 2) [21]. The Young Schema Scale Short Form-3 (YSQ-SF3) was created by adding Approval/Recognition-Seeking, Punitiveness, and Pessimism schemes to YSS-SF2 [5]. The validity and reliability study of the 90-item short form of the scale in our country was carried out by Soygüt *et al* [22] in a university sample. As a result of the analyzes which made to reveal the construct validity of the scale, it was seen that 16 schema dimensions were formed.

Brief Symptom Inventory (BSI)

The Brief Symptom Inventory is a Likert-type self-assessment inventory developed by Derogatis [23] upon the need for a short but valid and reliable scale to evaluate general psychopathology. The Brief Symptom Inventory is the short form of SCL-90-R that emerged as a result of studies with SCL-90-R. The reliability of the Brief Symptom Inventory was checked in the studies conducted by Şahin and Durak [24].

Deception Tendency Scale

The Deception Tendency Scale was developed by Polat [25] to evaluate the deception tendencies of mar-

ried individuals and there are a total of 30 items on the scale.

Statistical Analysis

Statistical evaluations were analyzed using SPSS (Statistical Package for Social Sciences) 25.0 package program. The assumption of normal distribution, which is one of the first steps of the analysis, was checked. In this process, the kurtosis and skewness values of the scale and subscales were checked. When taking the study of George *et al*. [26] as a reference, these values are being in the reference range of -2 +2 provides a normal distribution. By using Pearson Correlation analysis, the relationships between Young Schema Scale, the Brief Symptom Inventory, and Deception Tendency Scale were examined. The p value which will be referenced is 0.05 and the confidence interval value is 95%.

RESULTS

When we analyzed the findings, we found a middle level and positive relationship between Emotional Deprivation and the Brief Symptom Inventory scores (r = .34, $p < 0.01$), a weak and positive relationship between Emotional Deprivation and Anxiety scores (r = .30, $p < 0.01$), middle level and positive relationship between Emotional Deprivation and Depression scores (r = .35, $p < 0.01$), middle level and positive relationship between Emotional Deprivation and Negative Self scores (r = .39, $p < 0.01$), weak and positive relationship between Emotional Deprivation and Instability scores (r = .22, $p < 0.01$), a weak and positive relationship between Emotional Deprivation and Hostility scores (r = .25, $p < 0.01$) (Table 1).

Middle level and positive relationship between Social Isolation/Mistrust and the Brief Symptom Inventory scores (r = .57, $p < 0.01$), middle level and positive relationship between Social Isolation/Mistrust and Anxiety scores (r = .51, $p < 0.01$), middle level and positive relationship between Social Isolation/Mistrust and Depression scores (r = .58, $p < 0.01$), middle level and positive relationship between Social Isolation/Mistrust and Negative Self scores (r = .63, $p < 0.01$), middle level and positive relationship between Social Isolation/Mistrust and Instability scores (r = .34, $p < 0.01$), and a middle level and pos-

Table 1. Relationships Between Young Schema Scale and The Brief Symptom Inventory

	The Brief Symptom Inventory	Anxiety	Depression	Negative Self	Somatization	Hostility
Emotional Deprivation	.34**	.30**	.35**	.39**	.22**	.25**
Social Isolation/Insecurity	.57**	.51**	.58**	.63**	.34**	.49**
Defectiveness	.41**	.38**	.41**	.44**	.28**	.30**
Emotional Inhibition	.46**	.41**	.43**	.50**	.33**	.38**
Nesting/Dependency	.44**	.40**	.42**	.48**	.39**	.28**
Abandonment	.47**	.44**	.46**	.53**	.34**	.35**
Vulnerability to Harm / Illness	.56**	.53**	.55**	.59**	.41**	.43**
Failure	.39**	.37**	.40**	.40**	.30**	.26**
Pessimism	.56**	.54**	.57**	.52**	.43**	.45**
Self Dicipline /Insufficient Self-Control	.35**	.31**	.33**	.37**	.24**	.33**
Self-Sacrifice	.28**	.26**	.27**	.31**	.20**	.22**
Punitiveness	.43**	.41**	.40**	.44**	.28**	.37**
Unrelenting Standards	.27**	.25**	.23**	.31**	.15**	.25**
Approval/Recognition Seeking	.38**	.36**	.37**	.42**	.25**	.30**

**$p < 0.01$, *$p < 0.05$ used test: Pearson Correlation Test

itive relationship between Social Isolation/Mistrust and Hostility scores. (r = .49, $p < 0.01$) (see Table 1).

Middle level and positive relationship between Defectiveness and the Brief Symptom Inventory scores (r = .41, $p < 0.01$), middle level and positive relationship between Defectiveness and Anxiety scores (r = .38, $p < 0.01$), middle level and positive correlation between Defectiveness and Depression scores (r = .41, $p < 0.01$), middle level and positive correlation between Defectiveness and Negative Self scores (r = .44, $p < 0.01$), weak and positive relationship between the Defectiveness and Somatization scores (r = .28, $p < 0.01$), weak and positive relationship between the Defectiveness and Hostility scores (r = .30, $p < 0.01$) (see Table 1).

Middle level and positive relationship between Emotional Inhibition and the Brief Symptom Inventory scores (r = .46, $p < 0.01$), Middle level and positive relationship between Emotional Inhibition and Anxiety scores (r = .41, $p < 0.01$), Emotional Inhibition and Depression scores (r = .43, $p < 0.01$) were middle level and positively correlated, Emotional Inhibition and Negative Self scores (r = .50, $p < 0.01$) were middle level and positively correlated, Middle level and positive relationship between Emotional Inhibition and Somatization scores (r = .33, $p < 0.01$), Middle level and positive relationship between Emotional Inhibition and Hostility scores (r = .38, $p < 0.01$) (see Table 1).

Middle level and positive correlation between Incompetence/Dependence and the Brief Symptom Inventory scores (r = .44, $p < 0.01$), middle level and positive between Incompetence/Dependence and Anxiety scores (r = .40, $p < 0.01$), middle level and positive correlation between the scores of Incompetence/Dependence and Depression scores (r = .42, $p < 0.01$), middle level and positive relationship between Incompetence/Dependence and Negative Self scores (r = .48, $p < 0.01$), middle level and positive relationship between Incompetence/Dependence scores (r = .39, $p < 0.01$), weak and positive correlation between the scores of Incompetence/Dependence and Hostility scores (r = .28, $p < 0.01$) (see Table 1).

Middle level and positive relationship between Abandonment and the Brief Symptom Inventory scores (r = .47, $p < 0.01$), middle level and positive relationship between Abandonment and Anxiety scores (r = .44, $p < 0.01$), middle level and positive relationship between Abandonment and Depression scores (r = .46, $p < 0.01$), middle level and positive relationship between Abandonment and Negative Self scores (r = .53, $p < 0.01$), middle level and positive correlation between Abandonment and Instability scores (r = .34, $p < 0.01$), middle level and positive correlation between Abandonment and Hostility scores (r = .35, $p < 0.01$) (see Table 1).

Middle level and positive correlation between Vulnerability to Harm/Illness and the Brief Symptom Inventory scores (r = .56, $p < 0.01$), middle level and positive correlation between Vulnerability to Harm/Illness and Anxiety scores (r = .53, $p < 0.01$), middle level and positive correlation between Vulnerability to Harm/Illness and Depression scores (r = .55, $p < 0.01$), middle level and positive correlation between Vulnerability to Harm/Illness and Negative Self scores (r = .59, $p < 0.01$), middle level and positive correlation between Vulnerability to Harm/Illness and Instability scores (r = .41, $p < 0.01$), middle level and positive correlation between Vulnerability to Harm/Illness and Hostility scores (r=.43, $p < 0.01$) (see Table 1).

Middle level and positive relationship between Failure and the Brief Symptom Inventory scores (r = .39, $p < 0.01$), middle level and positive relationship between Failure and Anxiety scores (r = .37, $p < 0.01$), middle level and positive relationship between Failure and Depression scores (r = .40, $p < 0.01$), middle level and positive relationship between Failure and Negative Self scores (r = .40, $p < 0.01$), middle level and positive relationship between Failure and Instability scores (r = .30, $p < 0.01$), weak and positive relationship between Failure and Hostility scores (r = .26, $p < 0.01$) (see Table 1).

Middle level and positive correlation between Pessimism and the Brief Symptom Inventory scores (r = .56, $p < 0.01$), middle level and positive correlation between Pessimism and Anxiety scores (r = .54, $p < 0.01$), middle level and positive correlation between Pessimism and Depression scores (r = .57, $p < 0.01$), middle level and positive correlation between Pessimism and Negative Self scores (r = .52, $p < 0.01$), middle level and positive relationship between Pessimism and Instability scores (r = .43, $p < 0.01$), middle level and positive relationship between Pessimism and Hostility scores (r = .45, $p < 0.01$) (see Table 1).

Middle level and positive relationship between Self Dicipline/Insufficient Self-Control and the Brief

Symptom Inventory scores (r = .35, $p < 0.01$), middle level and positive relationship between Self Dicipline/Insufficient Self-Control and Anxiety scores (r = .31, $p < 0.01$), middle level and positive correlation between Self Dicipline/Insufficient Self-Control and Depression scores (r = .33, $p < 0.01$), middle level and positive correlation between Self Dicipline/Insufficient Self-Control and Negative Self scores (r = .37, $p < 0.01$), weak level and positive relationship between Self Dicipline/Insufficient Self-Control and Instability scores (r = .24, $p < 0.01$), middle level and positive correlation between Self Dicipline/Insufficient Self-Control and Hostility scores (r = .33, $p < 0.01$) (see Table 1).

The weak and positive relationship between Self Sacrifice and the Brief Symptom Inventory scores (r = .28, $p < 0.01$), weak and positive relationship between Self-Sacrifice and Anxiety scores (r = .26, $p < 0.01$), weak and positive relationship between Self-Sacrifice and Depression scores (r = .27, $p < 0.01$), middle level and positive relationship between Self-Sacrifice and Negative Self scores (r = .31, $p < 0.01$), weak and positive relationship between Self-Sacrifice and Instability scores (r = .20, $p < 0.01$), weak and positive relationship between Self-Sacrifice and Hostility scores (r = .22, $p < 0.01$) (see Table 1).

Middle level and positive relationship between Punitiveness and the Brief Symptom Inventory scores (r = .43, $p < 0.01$), middle level and positive relationship between Punitiveness and Anxiety scores (r = .41, $p < 0.01$), middle level and positive relationship between Punitiveness and Depression scores (r = .40, $p < 0.01$), middle level and positive relationship between Punitiveness and Negative Self scores (r = .44, $p < 0.01$), weak and positive relationship between Punitiveness and Instability scores (r = .28, $p < 0.01$), middle level and positive relationship between Punitiveness and Hostility scores (r = .37, $p < 0.01$) (see Table 1).

Weak and positive relationship between Unrelenting Standards and the Brief Symptom Inventory scores (r = .27, $p < 0.01$), weak and positive relationship between Unrelenting Standards and Anxiety scores (r = .25, $p < 0.01$), weak and positive relationship between Unrelenting Standards and Depression score (r = .23, $p < 0.01$) s, middle level and positive relationship between Unrelenting Standards and Negative Self scores (r = .31, $p < 0.01$), weak and positive relationship between Unrelenting Standards and Instability scores (r = .15, $p < 0.01$), weak and positive relationship between Unrelenting Standards and Hostility scores (r = .25, $p < 0.01$) (see Table 1).

Middle level and positive correlation between Approval/Recognition Seeking and the Brief Symptom Inventory scores (r = .38, $p < 0.01$), middle level and positive relationship between Approval/Recognition Seeking and Anxiety scores (r = .36, $p < 0.01$), middle level and positive correlation between Approval/Recognition Seeking and Depression scores (r = .37, $p < 0.01$), middle level and positive correlation between Approval/Recognition Seeking and Negative Self scores (r = .42, $p < 0.01$), weak and positive relationship between Approval/Recognition Seeking and Instability scores (r = .25, $p < 0.01$), middle level and positive correlation between Approval/Recognition Seeking and Hostility scores (r = .30, $p < 0.01$) (see Table 1).

The weak and positive relationship between Deception Tendency Scale and Emotional Deprivation scores (r = .15, $p < 0.01$), weak and positive relationship between Deception Tendency Scale and Social Isolation/Mistrust scores (r = .27, $p < 0.01$), weak and positive relationship between Deception Tendency

Table 2. Relationships between Young Schema Scale and Deception Tendency Scale

	Deception Tendency Scale
Emotional Deprivation	.15**
Social Isolation/Insecurity	.27**
Defectiveness	.16**
Emotional Inhibition	.22**
Incompetence/Dependence	.16**
Abandonment	.19**
Vulnerability to Harm/Illness	.23**
Failure	.16**
Pessimism	.19**
Self Dicipline /Insufficient Self-Control	.30**
Self-Sacrifice	.07
Punitiveness	.13**
Unrelenting Standards	.33**
Approval / Recognition-Seeking	.21**

**$p < 0.01$, *$p < 0.05$ used test: Pearson Correlation Test

Scale and Defectiveness scores (r = .16, $p < 0.01$), weak and positive relationship between Deception Tendency Scale and Emotional Inhibition scores (r = .22, $p < 0.01$), weak and positive relationship between Deception Tendency Scale and Incompetence/Dependence scores (r = .16, $p < 0.01$), weak and positive relationship between Deception Tendency Scale and Abandonment scores (r = .19, $p < 0.01$), weak and positive relationship between the Deception Tendency Scale and the Vulnerability to Harm/Illness scores (r = .23, $p < 0.01$), weak and positive relationship between the Deception Tendency Scale and Failure scores (r = .16, $p < 0.01$), weak and positive relationship between Deception Tendency Scale and Pessimism scores (r = .19, $p < 0.01$), middle level and positive relationship between Deception Tendency Scale and Self Dicipline/Insufficient Self-Control scores (r = .30, $p < 0.01$), weak and positive correlation between Deception Tendency Scale and Punitiveness scores (r = .13, $p < 0.01$), middle level and positive relationship between Deception Tendency Scale and Unrelenting Standards scores (r = .33, $p < 0.01$), weak and positive correlation between Deception Tendency Scale and Approval/Recognition-Seeking scores (r = .21, $p < 0.01$) (Table 2).

The weak and positive correlation between Deception Tendency Scale and the Brief Symptom Inventory scores (r = .23, $p < 0.01$), weak and positive relationship between Deception Tendency Scale and Anxiety scores (r = .20, $p < 0.01$), weak and positive correlation between Deception Tendency Scale and Depression scores (r = .21, $p < 0.01$), weak and positive relationship between Deception Tendency Scale and Negative Self scores (r = .22, $p < 0.01$), weak and positive relationship between the Deception Tendency Scale and the Instability scores (r = .16, $p < 0.01$), weak and positive relationship between the Deception Tendency Scale and Hostility scores (r = .24, $p < 0.01$) (Table 3).

Table 3. Relationships between the Brief Symptom Inventory and Deception Tendency Scale

	Deception Tendency Scale
The Brief Symptom Scale	.23**
Anxiety	.20**
Depression	.21**
Negative Self	.22**
Somatization	.16**
Hostility	.24**

**$p < 0.01$, *$p < 0.05$ used test: Pearson Correlation Test

DISCUSSION

The research was made to examine the relationship between early maladaptive schemas, psychological symptoms, and deception with each other. To reach research findings, the research was made on 407 non-clinical volunteer participants aged between 18-45 from the province of Istanbul. Also, these findings are being argued with literature.

The severity of the relationship between EMS and psychological symptoms and the relationship between these structures and the tendency to deception were evaluated. In the non-clinical sample, all schema domains were positively associated with different severity of psychological symptoms, such as depression, anxiety, negative self, somatization, and hostility. According to the research findings, emotional deprivation, social isolation/mistrust, defectiveness, emotional deprivation, abandonment, vulnerability to harm/illness, pessimism, dependence/incompetence were found to be significantly positively correlated with the severity of EMS and depression, anxiety, and negative self-perception symptoms. Vulnerability to harm/illness, pessimism, social isolation/mistrust is significantly positively associated with EMS and somatization and hostility. These findings are compatible with van Genderen [27] relationship between depressive personality structure and social isolation/mistrust, defectiveness/shame, vulnerability to harm/illness, pessimism, and failure schemas. A study conducted by Shah and Waller [28] on a sample of outpatients who were diagnosed with depression and without any clinical diagnosis found that Defectiveness/Shame, Insufficient Self-Control, and Self-Sacrifice schemas differed between those with and without a diagnosis of depression.

In studies conducted with a sample of non-clinical individuals, the Dependence/Incompetence and Defectiveness/Shame schemas [29], Abandonment/Instability, Mistrust/Abuse, Social Isolation [9] schemas

were associated with the severity of depression. The findings of these studies and the findings that have not been researched show compatibility.

A certain event in an individual's life may trigger early maladaptive schemas that manifest themselves with the appearance of anxiety disorder or depression, depending on which schema is activated. For example, an individual with the Vulnerability to Harm/Illness schema will be more likely to show signs of anxiety disorder than to show signs of depression [30-32] evaluate those personality traits as inherited tendencies that influence the actions of early caregivers. The repetitive dysfunctional behaviors of early caregivers contribute to the development of unconditioned, negative self, others, and worldviews. This EMS can cause personality problems in several ways. First, the experience of these belief systems can trigger depressive, anxiety, or anger symptoms. Secondly, EMS may predispose individuals to seek problematic close, social, and professional relationships that reinforce the power of the schema. Thirdly, when the experience of affectivity and memories which be associate with EMS is troubled, individuals develop maladaptive coping styles including avoidance [30].

In our research findings, the positive relationship between emotional deprivation, social isolation/mistrust, defectiveness, emotional deprivation, abandonment, vulnerability to harm/illness, pessimism, dependence/incompetence, and the severity of EMS with depression, anxiety, and negative self-perception symptoms a consistent with Young's [30] explanations. There is a theoretical link between EMS and psychopathology. EMS is mediating variable which takes a turn on the relationship between adult psychopathology and negative childhood experiences [33].

In our research findings, a positive and significant relationship was observed between unrelenting standards, insufficient self-control/self sicipline schemas, and the tendency to deception. The significant positive relationship between the tendency to deception and unrelenting standards seems contradictory at first glance. Unrelenting standards are characterized by inflexible rules which are including unrealistic moral, ethical and cultural, religious instructions in many areas of life, perfectionism, excessive attention to detail, and underestimation of one's performance compared to the norm [6].

However, this always involves a deterioration in the areas of enjoyment, relaxation, health, self-esteem, perception of success, and satisfying relationships. On the other hand, the insufficient self-control/self dicipline schema involves the individual having a pervasive difficulty or refusal to maintain adequate self-control and tolerate frustration to achieve personal goals and to restrain overexpression of emotions and impulses. People who have this schema do not exhibit sufficient self-control. They cannot show tolerance for disappointment. If they cannot achieve their individual goals, and they have difficulty in regulating their emotions and impulse expressions. Those who have this schema at a milder level show avoidance of pain, conflict, challenge, responsibility or they make exaggerated efforts in matters of personal satisfaction, commitment, and integrity [4].

CONCLUSION

The research was made to examine the relationship between early maladaptive schemas, psychological symptoms, and deception with each other. Outpatients who were diagnosed with depression and without any clinical diagnosis found that Defectiveness/Shame, Insufficient Self-Control, and Self-Sacrifice schemas differed between those with and without a diagnosis of depression. The severity of the relationship between EMS and psychological symptoms and the relationship between these structures and the tendency to deception were evaluated. An effective treatment plan can be developed that specifically addresses the etiological factor for problems that arise in close relationships. There is no significant positive relationship between the brief symptom inventory and the deception tendency scale. The base of this weak relationship is most likely to be associated with the Brief Symptom Inventory sub-dimensions of depression, anxiety, negative self, somatization, and hostility. We propose a research design to predict the relationship between EMS, personality, personality disorders, and the tendency of deception for other studies.

Authors' Contribution

Study Conception: KG; Study Design: KG; Supervision: KG; Funding: KG; Materials: KG; Data Collection and/or Processing: KG; Statistical Analysis

and/or Data Interpretation: KG; Literature Review: KG; Manuscript Preparation: KG and Critical Review: KG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

Ethics Committee Approval

Ethics committee aproval was received fort his study from the Istanbul Aydın University (Approval Date: June 9, 2021; Approval Number:2021/7).

Informed Consent

Written informed consent was obtained from the individuals who participated in this study.

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Beneficial effects of linagliptin in cell culture model of Parkinson's disease

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ABSTRACT

Objectives: We aimed to investigate the neuroprotective effects of linagliptin in an in vitro 6-hydroxydopamine (6-OHDA) Parkinson's disease model.

Methods: 6-OHDA (200 µM) were administered to the SH-SY5Y cells for 24 h to induce Parkinson's disease model in vitro. Cells were treated with linagliptin (1, 10, 50 and 100 nM) 30 minutes before 6-OHDA administration. Cell viability was examined by 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide (MTT) method and lactate dehydrogenase (LDH) analysis. Superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA) and reactive oxygen species (ROS) analyses were conducted to assess oxidative stress. Apoptosis was evaluated with Caspase-3 mRNA expression levels.

Results: It was observed that 6-OHDA elevated LDH levels and cell death. Oxidative stress was exaggerated with increased ROS and MDA levels and substantially apoptosis was proven with increased Caspase-3 levels in SH-SY5Y cells. Pretreatment with linagliptin alleviated oxidative stress and apoptosis.

Conclusions: Given its neuroprotective role as well as its effects on oxidative stress and apoptosis, linagliptin may be a drug candidate in Parkinson's disease.

Keywords: 6-OHDA, DPP-4 inhibitor, linagliptin, Parkinson's disease, SH-SY5Y cells

Parkinson's disease (PD) is a progressive and common neurodegenerative disease [1]. Characteristic feature of PD is progressive death of neuronal populations, primarily dopaminergic neurons [1]. Even though neuropathological processes of PD are well defined, its etiology is still largely undefined [2]. Furthermore, multiple mechanisms have been investigated as triggers of neuron loss in PD, including oxidative stress, mitochondrial dysfunction, apoptosis, and inflammation [3, 4]. PD patient's key symptoms are tremor, bradykinesia, stiffness. Also, postural instability, behavioral and cognitive problems such as dementia, depression, anxiety, and sleep disturbances also occur in the late stages of PD [5].

Levodopa and/or dopamine agonists are used as the first choice in the treatment of PD, and the treatment has remained symptomatic [6]. These treatments are capable of slowing the progression of PD and most of them only relieving symptoms, and after a certain period most Parkinson's patients suffer from side effects such as motor and non-motor fluctuations and dyskinesia [7].

Linagliptin (LNG) is a dipeptidyl peptidase-4 (DPP-4) inhibitor which can be chosen for the type 2

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diabetes management. Several studies in recent years have demonstrated the strong neuroprotective properties of LNG in various neurodegenerative disorders, like Alzheimer's disease, dementia and stroke [8, 9]. These effects are based on the antioxidant and anti-inflammatory features of LNG, as well as its capability to modify the crucial neurotransmitters' activity. It is also well known that glucagon-like peptide-1 (GLP-1) exerts neuroprotective activity by attenuating neuroinflammation [10, 11].

6-hydroxydopamine (6-OHDA) is a neurotoxicant that has been extensively utilized to induce in vivo and in vitro experimental PD models. Together with other free radicals, it produces H_2O_2, O2- and OH radicals, which determine mitochondrial membrane permeability loss and consequently results in oxidative stress [12, 13].

On this basis, this research was planned to assess the beneficial effects of LNG in 6-OHDA-induced in vitro PD model.

METHODS

Cell Culture

SH-SY5Y cells were incubated with 10 % FBS and antibiotic solution in DMEM. The flask was cultivated at 37 °C with 5% CO2. Then, 0.5 × 10^4 cells were seeded into 96 well-plates. To form PD in cell line, 6-OHDA (200 µM) was administered to each well for one day. Firstly SH-SY5Y cells were treated with LNG (1, 10, 50 and 100 nM) and then thirty minutes later 6-OHDA was administered to each well [14-16].

MTT Analysis

In order to evaluate the cell viability, 3-[4,5-dimethylthiazole-2-yl]-2,5-diphenyltetrazolium bromide (MTT) method was utilized. 20 µl MTT solution (Sigma-Aldrich) was added to each well. After four hours supernatants were exchanged with 150 µm DMSO and the absorbance was measured at 490 nm.

LDH Analysis

Lactate dehydrogenase (LDH) is an intracellular enzyme which reflects cytotoxicity. LDH leakages from cells when membrane integrity is disrupted. LDH activity were assessed by an LDH assay kit (Elabscience, US). Absorbance was calculated at 450 nm.

Oxidative Stress Markers

Superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA) and reactive oxygen species (ROS) were analyzed by ELISA kits (Elabscience, US) as described before [17]. Levels of ROS were measured using ELISA kit (LSBio, United states) and the optical density was assessed at 450 nm.

Molecular Analysis

mRNA extraction and cDNA synthesis were carried out as previously described with RNeasy easy kit (Qiagen, Germany) Real-time PCR analysis also was carried out as previously described [18]. Relative mRNA caspase-3 expression levels were determined by Rotor-Gene Q (QIAGEN). *β*-actin was utilized as the reference gene. The target gene expression levels were compared with the housekeeping gene *β*-actin. The sequences of specific primers were as follows: Caspase-3: forward, 5′-TTTTCAGTCCGGGGACAAAC-3′, reverse,5′-GGGCAGCCGAGAATAACAAT-3′, β-actin: forward, 5′- CAAGGTGGGTGTCTTTCCTG-3′, reverse, 5′-GATCCACACGGAGTACTTGC-3′. The obtained results were analyzed as fold changes using the $2^{-\Delta\Delta Ct}$ method.

Statistical Analysis

All data were analyzed with one-way analysis of variance (ANOVA) followed by the Tukey post hoc test (IBM SPSS 21.0) $p < 0.05$ assumed meaningful. Results are mean ± SD.

RESULTS

MTT and LDH Analyses

6-OHDA lead to marked reduction of cell viability in the MTT assay and increased LDH leakage. Also, LNG increased the cell proliferation and our findings proved that LNG markedly increased viable cell ratio. Additionally, LNG significantly reduced LDH levels (Fig. 1).

Oxidative Stress Results

SOD and CAT levels were markedly decreased in 6-OHDA group while MDA and ROS levels significantly increased in comparison to control group. Activities of SOD and CAT were significantly increased

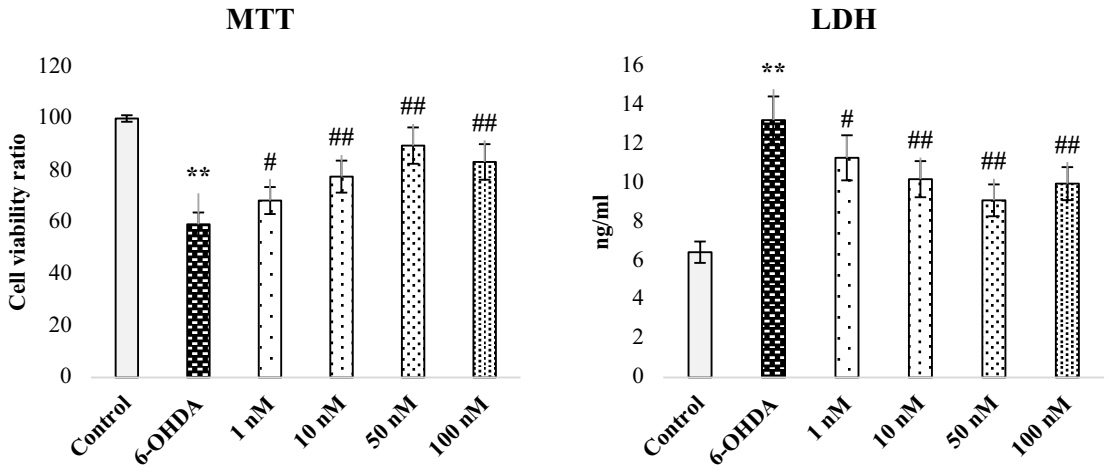

Fig 1. Cell viability test results. Results are mean ± SD. **$p < 0.001$ versus control, # $p < 0.05$ versus 6-OHDA, ## $p < 0.001$ versus 6-OHDA.

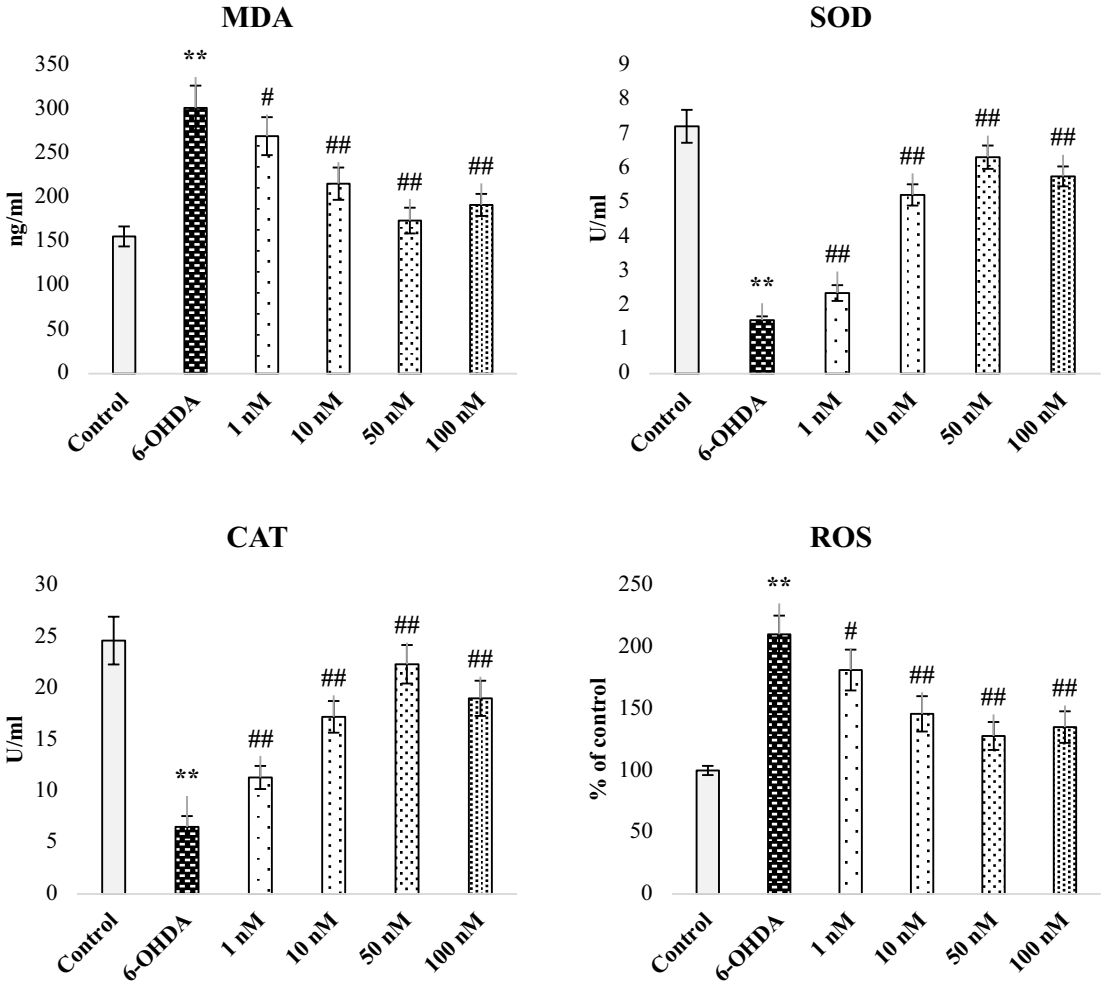

Fig 2. Oxidative stress results. Results are mean ± SD. **$p < 0.001$ versus control, #$p < 0.05$ versus 6-OHDA, ##$p < 0.001$ versus 6-OHDA.

in LNG groups, whereas MDA and ROS concentrations were markedly decreased in comparison with 6-OHDA group (Fig. 2).

mRNA Expressions of Caspase-3

The mRNA expression of Caspase-3 was markedly increased in the 6-OHDA group. LNG ad-

ministration significantly reduced caspase-3 expression in comparison with 6-OHDA group (Fig. 3).

DISCUSSION

In this research, the neuroprotective effects of LNG against 6-OHDA neurotoxicity in SH-SY5Y cells was examined for the first time.

In this study, we observed that 6-OHDA significantly reduced SH-SY5Y cell viability, and treatment with LNG increased cell viability. In addition to our observations of cell viability, we also demonstrated a significant reduction of apoptosis in LNG groups.

GLP-1, an incretin hormone which has been proven to be effective in neurodegenerative disorders like Alzheimer's disease and GLP-1 is immediately de-activated by DPP-4 enzyme. Thus, inhibition of DPP-4 is used for elevation of GLP-1. There are studies confirming that GLP-1 analogs improve neurodegeneration by reversing cognitive deficits in neurodegenerative disorders like Alzheimer's disease [19, 20]. Also, DPP-4 inhibition is supposed to exert neuroprotective effects by elevating GLP-1 levels in circulation. De-activation of DPP-4 has been shown to modulate the levels of glucose-dependent insulinotropic polypeptide, neuropeptide Y, brain natriuretic peptide, and stromal-derived factor-1, which have neuroprotective effects [21-23]. These data revealed that by inhibiting the DPP-4 enzyme, neuroprotective effects can be obtained in neurodegenerative diseases such as PD.

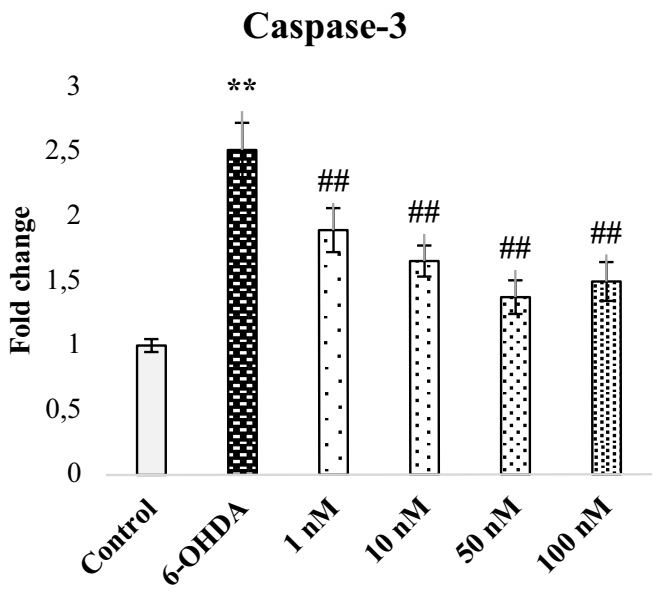

Fig 3. Relative expression of Caspase-3. Results are mean ± SD. **$p < 0.001$ versus control, ##$p < 0.001$ versus 6-OHDA.

Oxidative damage is known to take part in pathological processes associated with neurodegenerative disorders like PD [24]. Previously, it has been proven that overproduction of ROS in PD can destroy neuronal cell function, cause oxidative DNA damage, disrupt the respiratory chain, and disrupt mitochondrial DNA mutations in the brain of patients with PD [25]. Inhibiting ROS formation and increasing antioxidant enzyme activity are valuable strategies to reduce oxidative stress. In this report, LNG decreased the ROS and MDA concentrations and elevated SOD and CAT activity. Besides, similar to our results, LNG has been reported to have a broad antioxidant effect by reducing ROS production and increasing the activities of antioxidant enzymes [16]. Also, it has been previously reported that LNG exerts an indirect antioxidant effect by increasing the level of circulating GLP-1, which has strong antioxidant, anti-inflammatory and neuroprotective effects in the central nervous system [9].

A substantial amount of evidence indicates that 6-OHDA also induces apoptosis through caspase activation following oxidative stress with excessive ROS increase. Caspase-3 is a substantial component of the cysteine protease class concerned with in the mitochondrial apoptotic pathway [26]. We found that LNG down-regulated caspase-3 expression and showed antiapoptotic effects, confirming previous studies. Previously it has been reported that LNG has a marked neuroprotective, anti-apoptotic and cognitive improving properties in in-vitro cerebral ischemia model [27].

CONCLUSION

In the light of all these data, LNG may be a promising agent in Parkinson's disease with its anti-oxidant and anti-apoptotic properties.

Authors' Contribution

Study Conception: IFO, UO; Study Design: IFO, UO; Supervision: IFO, UO; Funding: N/A; Materials: N/A; Data Collection and/or Processing: IFO, UO; Statistical Analysis and/or Data Interpretation: IFO, UO; Literature Review: IFO, UO; Manuscript Preparation: IFO and Critical Review: IFO, UO.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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The European Research Journal 2022;8(2):247-255 Original Article

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Effects of subclinical hypothyroidism on maternal and obstetric outcomes during pregnancy

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ABSTRACT

Objectives: Subclinical hypothyroidism has been defined as normal free thyroxine (FT4) with elevated thyroid stimulating hormone (TSH) levels. The aim of this study is to examine the relationship between the first trimester subclinical hypothyroidism with adverse obstetric outcomes in pregnant women.

Methods: This retrospective cohort study was conducted by examining the pregnant women who applied to the Gynecology Department of Okmeydani Training and Research Hospital at their 6th to 14th gestational weeks and had antenatal follow-ups between February 1, 2017 and December 31, 2020.

Results: Fetal weight (OR: 1; 95% CI, 0.99-1.03, $p = 0.023$), gestational age at delivery (OR: 0.91; 95% CI, 0.83-0.99, $p = 0.022$), and preterm delivery (OR: 0.79; 95% CI, 0.48-1.06, $p = 0.005$) were found to be statistically significant parameters in univariate risk analyses performed in the group whith patients normal T4 levels and TSH levels ≥ 2.5-4 mIU/L. Lower gestational age at delivery (OR: 1; 95% CI, 0.93-1.88, $p = 0.016$), and higher preterm delivery rates (OR: 0.99; 95% CI, 0.96-1.01, $p = 0.003$) were found to be statistically significant in multivariate risk analysis.

Conclusions: The rate of preterm delivery was statistically higher, and fetal weight and week of delivery were significantly lower in the group of pregnant women diagnosed with SCH having TSH values between 2.5 and 4 mIU/L.

Keywords: Pregnancy, preterm birth, subclinical hypothyroidism

Thyroid diseases are frequently seen during pregnancy. The frequency of thyroid disorders in pregnancy is 2-3%. It can be overt hypothyroidism, subclinical hypothyroidism or hyperthyroidism [1]. Elevated serum levels of thyroid stimulating hormone (TSH) greater than 10 mIU/L and/or lower free thyroxine (fT4) levels are observed in overt hypothyroidism. However, subclinical hypothyroidism has been defined as normal FT4 with elevated TSH levels [2, 3]. Size of the thyroid gland increases by 10% in iodine-rich, and by 20-40% in iodine deficient countries [4]. Maternal thyroid hormone regulates fetal growth and development through transplacental transfer between the first 18-20 weeks of pregnancy and plays an important role in the development of fetal brain [5].

Since fetal thyroid tissue does not mature before 12-14 weeks of pregnancy, maternal fT4 is the only source of thyroid hormone for the developing fetus. In early pregnancy, maternal thyroid hormones are required for neural proliferation and migration. From mid-pregnancy, both maternal and fetal thyroid hormones are crucial for neurogenesis, neuronal migration, axonal growth, dendritic arborization, and synaptogenesis [6].

During pregnancy, many physiological changes

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occur in the thyroid gland in women. From the 4th-8th weeks of pregnancy, thyroxine-binding globulin (TBG) levels double in circulation due to the increase in estrogen production and total T4 and T3 concentrations increase in the first half of pregnancy and reach a plateau at the 20th gestational week. Human chorionic gonadotropin (hCG) hormone shows thyrotropic activity [7]. During the first trimester, a temporary increase in free thyroxine (FT4) and a decrease in thyroid-stimulating hormone (TSH) levels are observed. Later on, while FT4 concentration decreases by 10-15%, TSH returns to normal values. With these variations the reference intervals of both FT4 and TSH change throughout pregnancy [8].

According to recommendations of 2011 American Thyroid Association (ATA) guidelines, trimester specific- reference ranges have been established. Indeed, TSH values should be 0.1-2.5 mIU/L in the first, 0.2-3.0 mIU/L in the second, and 0.3-3.5 mIU/L in the third trimesters [9]. In some studies, as recommended by the National Academy of Clinical Biochemistry (NACB), values ranging between 2.5th and 97.5th percentiles are accepted as normal [10]. However, ATA revised its recommendations in 2017 and if the pre-pregnancy TSH value is unknown, 4.0 mIU/L has been accepted as the upper limit of normal (ULN) of cut-off value [4].

There are studies showing the relationship between maternal thyroid diseases and preterm birth, birth weight, gestational diabetes mellitus, and preeclampsia [11, 12]. Overt hypothyroidism is treated without hesitation, but there is no clear consensus on the treatment of subclinical hypothyroidism.

In the present study, universal screening of thyroid function was conducted in a pregnant population and the prevalence of SCH in antenatal pregnant women was investigated. The aim of this study is to examine the relationship between the first trimester subclinical hypothyroidism with adverse obstetric outcomes in pregnant women.

METHODS

This retrospective cohort study was conducted by examining the pregnant women who applied to the Gynecology Department of Okmeydani Training and Research Hospital at their 6th to 14th gestational weeks and had antenatal follow-ups between February 1, 2017 and December 31, 2020. Gestational age was calculated according to the last menstrual period or findings of ultrasound performed before the 20th gestational week. Gravida, parity, number of abortions, gestational weeks of all patients were recorded. Written consent was obtained from all pregnant women for delivery. Multipl pregnancy, smokers, alcohol users, pregnant women under 18 years old, those with diagnoses of chromosomal anomalies, maternal heart disease, history of autoimmune disorders, chronic drug users, overt thyroid disorder, or pregnants who were treated previously or presently with thyroxin or antithyroid drugs, were not included in this study.

Maternal blood samples were obtained from all mothers at first trimester visit after an also overnight fasting. Maternal thyroid stimulating hormone (TSH) and free thyroxine (fT4) levels were measured in routine antenatal follow-ups. All data were entered in a computerized database.

In our laboratory, reference ranges for serum TSH (0.27-4.2 mIU/L), and f T4 (0.93-1.6 ng/dl) were determined as indicated. However, since in some studies, normal T4 values in pregnant women were accepted as ranging between 0.8-1.53 ng/dl for the first trimester, these values were also taken as normal values in our study [13].

The 2011 American Thyroid Association (ATA) guidelines accepted the upper limit of normal of the first trimester TSH as 2.5 mIU/L, but in 2017 the ULN was revised as 4 mIU/L [4, 9].Therefore, both values were used separately in our study.

Pregnant women with normal TSH and fT4 levels were considered to be euthyroid and served as control subjects (Group 1). Patients with normal T4 levels and TSH levels ≥ 2.5-4 mIU/L were included in Group 2, and patients with normal T4 levels and TSH levels ≥ 4-10 mIU/L were included in Group 3.

Although our study started with 878 pregnant women, 804 patients were selected as the study group because 74 patients did not have subclinical hypothyroidism and normal values. Gestational week at delivery, fetal weight, type of delivery, indications for cesarean section and gender of the newborns were recorded. Besides, maternal, and obstetric outcomes as preeclampsia, oligohydramios, polyhydramnios, large for gestational age (LGA) ,small for gestational age (SGA), preterm birth, postterm birth, preterm pre-

mature rupture of membranes (PPROM), premature rupture of membranes (PROM), low birth weight (LBW), gestational diabetes mellitus (GDM), fetal demise, macrosomia were recorded.

The diagnosis of oligohydramnios was defined ultrasonographically as the amniotic fluid index less than 2 cm in a single quadrant and less than 5 cm in the total of 4 quadrants. Polyhydroamnios, on the other hand, was defined as amniotic fluid index over 8 cm in a single quadrant and over 20 cm in total of 4 quadrants. The diagnosis of GDM was made with a 2 step procedure as recommended by the American College of Obstetricians and Gynecologists (AGOC) [14].

Intrauterine fetal death after 24 weeks of gestation was defined as fetal demise. Macrosomia was defined as fetal weight above 4000 g and low birth weight was considered when it was below 2500 g. Births before 37 weeks of gestation were termed as premature births, and deliveries over 42 weeks were called post-term births. Birthweights below the 10th percentile were termed as SGA, and LGA if they were over the 90th percentile.

The diagnosis of preeclampsia was made according to the criteria set by the International Society for the Study of Hypertension in Pregnancy [15].

Rupture of fetal membranes before the onset of labor was termed as premature rupture of membranes (PROM), while rupture of membranes before 37th gestational week was designated as preterm premature rupture of membranes (PPROM).

Ethical Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University of Health Sciences , Okmeydanı Training and Research Hospital (Date: 10/08/2021/No: 48670771-514.10./297).

Statistical Analysis

In this study, statistical analyzes were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean, standard deviation, median, interquartile range) used in the evaluation of the data, the distribution of the variables was examined with the Shapiro-Wilk normality test. For pairwise comparison of the variables with normal distribution, the independent t-test, while for pairwise comparison of the groups of non-normally distributed variables the Mann-Whitney U test were utilized. Chi-square and Fisher's exact tests were used in the comparison of qualitative data. Univariate and multivariate risks of the groups were determined by logistic regression analysis. The results were evaluated at the significance level of $p < 0.05$.

RESULTS

A total of 804 patients included in our study were divided into 3 groups according to their T4 and TSH values. Group 1 was chosen as the control group, while Groups 2 and 3 were defined as the groups with subclinical hypothyroidism as follows: Group 1 (n = 592) T4 normal and TSH = 0.1-2.5 mIU/L; Group 2 (n = 146) T4 normal and TSH ≥ 2.5-4 mIU/L; Group 3 (n = 66), T4 normal and TSH ≥ 4-10 mIU/L.

Demographic characteristics of the patients and maternal and fetal adverse obstetric outcomes are shown in Table 1 and Table 2. When Groups 1 and 2 were compared with each other, no statistically significant difference was observed between the 2 groups as for maternal age, delivery type, cesarean section indications, gravida, parity and abortion averages, test week, and gender distributions. For all these parameters, no significant difference was found when Groups 1 and 3 were compared with each other.

Fetal weight averages and mean gestational age at delivery in Group 2 were found to be statistically significantly lower than Group 1 ($p = 0.023$ and $p = 0.044$ respectively). However, no statistically significant difference was observed between Groups 1 and 3 as for fetal weight averages and mean gestational age at delivery.

Regarding obstetric outcomes, any statistically significant difference was not observed between Groups 1 and 2 and also between Groups 1 and 3 as for abruptio placentae, preeclampsia, GDM, PPROM, PROM, SGA, fetal demise, macrosomia, LBW, post-term birth, need for neonatal intensive care unit, oligohydramnios, polyhydramnios, and LGA.

The frequency of preterm births in Group 2 was statistically significantly higher than Group 1 ($p = 0.004$). However, no statistically significant difference was observed between Groups 1 and 3 as for the the

Table 1. Demographic characteristics

		Group 1 (n = 592)	Group 2 (n = 146)	Group 3 (n = 66)	*p* value G1-G2	*p* value G1-G3
Age (mean ± SD)		29.42 ± 5.81	29.34 ± 5.95	29.7 ± 6.84	0.886*	0.715*
Delivery, n (%)					0.847⁺	0.532⁺
Vaginal		281 (47.47)	68 (46.58)	34 (51.52)		
Cesarean		311 (52.53)	78 (53.42)	32 (48.48)		
Indications for cesarean sections, n (%)					0.346⁺	0.928⁺
Previous Cesarean		179 (57.37)	49 (62.82)	22 (68.75)		
Fetal Distress		50 (16.03)	13 (16.67)	3 (9.38)		
Progress failure		24 (7.69)	5 (6.41)	2 (6.25)		
Cephalopelvic disproportion		24 (7.69)	5 (6.41)	3 (9.38)		
Macrosomia		14 (4.49)	0 (0.00)	1 (3.13)		
Malpresantation		17 (5.45)	4 (5.13)	1 (3.13)		
Placenta previa		2 (0.64)	0 (0.00)	0 (0.00)		
Cord prolapsus		0 (0.00)	1 (1.28)	0 (0.00)		
Maternal factor		2 (0.64)	1 (1.28)	0 (0.00)		
Gravida	**Mean ± SD**	2.75 ± 1.48	2.75 ± 1.36	2.53 ± 1.36	0.689‡	0.234‡
	median (IQR)	3 (2-4)	3 (2-4)	2 (2-3)		
Parity	**Mean ± SD**	1.36 ± 1.17	1.33 ± 1.08	1.17 ± 0.97	0.960‡	0.295‡
	median (IQR)	1 (0.25-2)	1 (0-2)	1 (0-2)		
Abortus	**Mean ± SD**	0.4 ± 0.84	0.42 ± 0.75	0.36 ± 0.8	0.564‡	0.627‡
	median (IQR)	0 (0-1)	0 (0-1)	0 (0-1)		
Test weeks (mean ± SD)		8.06 ± 2.29	7.94 ± 2.44	8.08 ± 2.62	0.597*	0.929*
Fetal Weight (mean ± SD)		3272.16 ± 544.02	3156.61 ± 560.61	3299.02 ± 443.94	**0.023***	0.699*
Gestational age (mean ± SD)		38.59 ± 1.83	38.17 ± 2.31	38.76 ± 1.44	**0.044***	0.463*
Gender, n (%)					0.268⁺	0.337⁺
Female		306 (51.69)	68 (46.58)	30 (45.45)		
Male		286 (48.31)	78 (53.42)	36 (54.55)		

*Independent t test, ⁺Chi-Square test, ‡Fisher's Exact Test, Group 1 = T4 normal (0.8-1.53 ng/dl), TSH = 0.1-2.5 mIU/L, Group 2 = T4 normal (0.8-1.53 ng/dl), TSH ≥ 2.5-4 mIU/L, Group 3 = T4 normal (0.8-1.53 ng/dl), TSH ≥ 4-10 mIU/L

distribution of preterm births.

Univariate and multivariate logistic regression risk analyzes were performed for Group 2 (Table 3). Fetal weight (OR: 1; 95% CI, 0.99-1.03, $p = 0.023$), gestational age at delivery (OR: 0.91; 95% CI, 0.83-0.99, $p = 0.022$), and preterm delivery (OR: 0.79; 95% CI, 0.48-1.06, $p = 0.005$) were found to be statistically significant parameters in univariate risk analyses performed in Group 2.

Maternal age and parity were adjusted by performing a multivariate risk analysis. Lower gestational age at delivery (OR: 1; 95% CI, 0.93-1.88, $p = 0.016$), and higher preterm delivery rates (OR: 0.99; 95% CI, 0.96-1.01, $p = 0.003$) were found to be statistically significant in multivariate risk analysis.

Univariate and multivariate logistic regression risk analysis were performed for Group 3 (Table 4). No statistical significance was observed in the variables examined in Group 3 ($p > 0.05$)

Table 2. **Adverse obstetric outcomes**

	Group 1 (n = 592)		Group 2 (n = 146)		Group 3 (n = 66)		*p* value	*p* value
	n	%	n	%	n	%	G1-G2	G1-G3
Abruptio placentae	4	0.68	0	0.00	0	0.00	0.319ǂ	0.503ǂ
Preeclampsia	23	3.89	8	5.48	0	0.00	0.390+	0.103ǂ
GDM	52	8.78	16	10.96	8	12.12	0.416+	0.372+
PPROM	12	2.03	1	0.68	2	3.03	0.270ǂ	0.592ǂ
PROM	45	7.60	11	7.53	5	7.58	0.978+	0.994+
SGA	30	5.07	10	6.85	5	7.58	0.394+	0.389+
Fetal demise	4	0.68	0	0.00	0	0.00	0.319ǂ	0.503ǂ
Makrosomia	43	7.26	5	3.42	5	7.58	0.092+	0.926+
LBW	40	6.6	13	8.90	1	1.52	0.368+	0.095ǂ
Preterm birth	62	10.47	28	19.18	7	10.61	**0.004**+	0.973+
Postterm birth	1	0.17	1	0.68	0	0.00	0.283ǂ	0.738ǂ
Neonatal intensive care	26	4.39	6	4.11	1	1.52	0.881+	0.264ǂ
Oligohydramnios	8	1.35	4	2.74	2	3.03	0.235+	0.290ǂ
Polyhidramnios	14	2.36	5	3.42	0	0.00	0.469+	0.207ǂ
LGA	89	15.03	14	9.59	12	18.18	0.089+	0.501+

+Chi-square test, ǂFisher's Exact Test.LGA = Large for gestational age, SGA = Small for gestational age , GDM = Gestational Diabetes Mellitus, PROM = Premature rupture of membrane, PPROM = Preterm premature rupture of membrane, LBW = Low birth weight

Group 1 = T4 normal (0.8-1.53 ng/dl) , TSH = 0.1-2.5 mIU/L

Group 2 = T4 normal (0.8-1.53 ng/dl), TSH ≥ 2.5-4 mIU/L

Group 3 = T4 normal (0.8-1.53 ng/dl), TSH ≥ 4-10 mIU/L

Table 3. **Results of univariate and multivariate logistic regression risk analysis performed for Group 2 with TSH levels ≥ 2.5-4 mIU/L**

	Univariate risk		Multivariate risk	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Fetal weight	1.00 (0.99-1.03)	**0.023**	1.01 (0.87-1.57)	0.058
Gestational age	0.91 (0.83-0.99)	**0.022**	1.09 (0.93-1.88)	**0.016**
Preterm delivery	0.79 (0.48-1.06)	**0.005**	0.99 (0.96-1.01)	**0.003**

In multivariate analysis ORs adjusted for maternal age and parity.

Group 2 = T4 normal (0.8-1.53 ng/dl), TSH ≥ 2.5-4 mIU/L

DISCUSSION

Subclinical hypothyroidism is a condition characterized with increased thyroid stimulating hormone (TSH) levels with normal free thyroxine (fT4) levels without any symptoms of hypothyroidism. Although a correlation was found between adverse maternal outcomes and overt maternal hypothyroidism, the relationship between subclinical hypothyroidism (SCH) in pregnancy and perinatal complications is not clear. There is no clear consensus on the normal and cut-off values of TSH in pregnancy. Therefore, in our study we found it appropriate to examine pregnant women with SCH in 2 separate groups.

In our study, the rate of preterm delivery was statistically higher, and fetal weight and week of delivery

Table 4. Results of univariate and multivariate logistic regression risk analysis performed for Group 3 with TSH levels ≥ 4-10 mIU/L

	Univariate risk		Multivariate risk	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Fetal weight	1.00 (0.94-1.07)	0.698		
Gestational age	1.06 (0.91-1.23)	0.462		
Preterm delivery	0.99 (0.43-2.25)	0.973		
LBW	2.71 (0.65-4.83)	0.129	0.99 (0.97-1.02)	0.715

In multivariate analysis ORs adjusted for maternal age and parity.
Group 3 = T4 normal (0.8-1.53 ng/dl), TSH ≥ 4-10 mIU/L

were significantly lower in the group of pregnant women diagnosed with SCH having TSH values between 2.5 and 4 mIU/L, when compared to pregnant women with normal thyroid function test results. However, no statistically significant adverse obstetric outcomes were encountered in pregnant women with SCH having TSH values between 4 and 10 mIU/L.

There is no clear consensus on universal application of thyroid function screening tests before pregnancy. Some clinicians recommend testing especially around the 9th gestational week at the first antenatal visit, while others recommend screening high-risk women. The optimal time for thyroid function tests is at the end of the first trimester or before pregnancy in high-risk pregnant women [16]. In our study group, we performed this screening test at a mean 8.02 gestational weeks namely at the first trimester antenatal visit as recommended.

SCH is considered as a milder thyroid function test abnormality and is seen more frequently than overt maternal hypothyroidism. Overt hypothyroidism has a prevalence of 0.2-0.5%. However, the prevalence of SCH in pregnancy is between 2% and 2.5% [17]. In our study, when all SCH cases with TSH cut-off values above 2.5 mIU/L were examined, the prevalence rate was found to be 24.14%. However, when the TSH cut-off value was taken as 4 mIU/L, the prevalence of SCH was found to be 7.5%. Unlike other studies, these rates were extremely high. The reason may be that our hospital is a tertiary center and too many patients are followed up during the antenatal period.

It is not always easy to determine cut-off values for normal TSH levels. Geographic and ethnic diversity may also have a significant effect on TSH and FT4 reference limits in pregnancy [18, 19]. In a study from India the authors used 5th to 95th percentile as normal reference range. The upper limit of normal for TSH in the first trimester was 5.0-6.0 mIU/L [20, 21]. However, in another study from India, the researchers concluded that it was more accurate to accept 3.0 mIU/L as the cut-off value of TSH for SCH instead of 4.0 mIU/L as accepted in the revised ATA 2017 guidelines [22]. However, we examined fetal and maternal outcomes in 2 separate groups by taking both 2.5 mIU/L and 4 mIU/L as TSH cut-off values for SCH. We thought that we could get more accurate results in this study.

In the study by Chen *et al*. [23], 4.63% of pregnant women were diagnosed with SCH when all trimesters were examined without discrimination. Risks of gestational hypertension, SGA, LBW and PROM were relatively higher in pregnant women with SCH. There was no significant difference in the incidence of fetal distress, stillbirth, GDM, placenta previa, placental abruption, and preterm birth. However, when the first trimester was examined separately, and normal TSH levels were taken as 0.09-3.47 mIU/L, any difference was not found between groups with SCH and euthyroid in terms of obstetric outcomes [23].

In the study of Casey *et al*. [24], premature birth before 34 weeks of gestation was observed 2 times more frequently in women with SCH. However, in other studies, no significant difference was found regarding rates of preterm delivery in SCH [23, 25]. In our study, preterm birth was seen at a rate of 19.18% in the group with TSH values ranging between 2.5 and 4 mIU/L which were found to be statistically significantly higher when compared to the euthyroid group. ($p = 0.004$) In the univariate and multivariate logistic regression analyses, statistically significantly higher

rates of preterm birth (p = 0.005, p = 0.003 respectively) were detected. However, no significant difference was found as for preterm birth rates in the group with TSH levels ranging between 4 and 10 mIU/L. It was suprising that there was less premature birth in this group.

In one study, an increased risk of severe preeclampsia was found in pregnant women with SCH compared to the euthyroid group [26]. In another study, placental abruption was observed 3 times more frequently in pregnant women with SCH compared to the normal group [24]. However, in our study, no increased risk was found in rates of either preeclampsia or placental abruption in pregnant women with SCH.

In the study of Monen *et al*. [27], maternal TSH ≥ 97.5th percentile in the first and third trimesters was correlated with SGA, but no relationship was found between maternal FT4 levels and SGA. In another study, 16.52% of pregnant women who gave birth to babies with SGA were in the SCH group [28]. In our study, SGA was found at a rate of 7% in the SCH group and 33.33% of the pregnant women who gave birth to a baby with SGA were detected in the SCH group. However, any statistically significant difference was not found between the group with SCH, and the euthyroidism as for the rate of SGA.

In the study of Cleary-Goldman *et al*. [29], no relationship was found with subclinical hypothyroidism and adverse outcomes. In their studies, a relationship was found between overt hypothyroidism and GDM, but no relationship was detected between GDM, and SCH in pregnant women [29]. However, in a large population-based study, the risk of GDM was found to be associated with increased TSH during pregnancy [30]. In our study, GDM was found at rates of 10.96%, and 12.12% in the groups with TSH levels between 2.5-4 mIU/L, and 4-10 mIU/L, respectively without any increased risk in GDM in all patients with SCH.

In another study, pregnants under 20 gestational weeks were examined and the 5-95th percentile was considered normal for TSH. No correlation was found between thyroid status and stillbirth rate. While stillbirth rate increased at TSH levels above10 mU/L, any corresponding increase was not observed in the incidence of SCH [24]. In our study, fetal demise was not observed in the SCH patient group. In the study of Negro *et al*. [25], the group with TSH levels between 2.5 and 5.0 mIU/ L group was compared with the euthyroid group, and pregnancy loss was found to be significantly higher in the SCH group. They found an increased risk in gestational diabetes and stillbirth in subsequent pregnancies in patients who were diagnosed with SCH in their previous pregnancies [31].Therefore, it is important to diagnose SCH during pregnancy and follow up these patients after delivery.

In a meta-analysis of 18 cohort studies, pregnant women with SCH were found to be at a higher risk for pregnancy loss, placental abruption, premature rupture of membranes, and neonatal death [32]. However, in this meta-analysis, the studies were performed in different trimesters. However, our study was conducted by screening only first trimester pregnant women and no increase in risk was detected in any of these adverse effects.

Limitations

We acknowledge that this study has some limitations Data related to race, ethnicity, iodine intake, maternal pre-pregnancy body mass index and socioeconomic status, were not analyzed in this study. When diagnosing SCH, factors that affect TSH values such as gestational age and the time of day when the blood sample is obtained should also be considered. All the patients in our study were in the first trimester, and blood samples were drawn in the morning. We acknowledge that TSH cut-off values for the diagnosis of SCH differ in previous studies. Our study, unlike other studies, was conducted with two separate cut-off values and obstetric and maternal outcomes were examined separately.

CONCLUSION

The current study was performed to gain insight into the impact of SCH on maternal and perinatal outcomes. In pregnant women diagnosed with SCH, and TSH values between 2.5 and 4 mIU/L, the rate of preterm delivery was statistically significantly higher, and fetal weight and gestational week at birth were significantly lower. Routine maternal thyroid function testing is necessary to improve maternal and perinatal outcomes during the antenatal period, and especially in the first trimester. However, further prospective multicenter studies with large patient groups are needed. Performing thyroid function tests only on

pregnant women with symptoms of thyroid disease or with a relevant personal history may be insufficient to predict pregnant women who may be in the high-risk pregnancy group.

Authors' Contribution

Study Conception: SG, BC; Study Design: SG, BC; Supervision: SG, BC; Funding: N/A; Materials: N/A; Data Collection and/or Processing: SG, BC; Statistical Analysis and/or Data Interpretation: SG; Literature Review: SG; Manuscript Preparation: SG and Critical Review: SG, BC.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Common complications and their managements after penoscrotal hypospadias repairs: comparison of one-stage and staged repairs

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ABSTRACT

Objectives: Surgical repair of hypospadias is challenging and the risk of complications is high, even for the most experienced specialists. In this study, we aim to present our experience with the management of the most common postoperative complications in patients who underwent proximal hypospadias repair.

Methods: We retrospectively reviewed the data of patients underwent proximal hypospadias surgery between December 2011 and February 2021. Patients who were repaired with single and staged methods were divided into two groups. Treatment methods of postoperative complications including wound dehiscence, fistula, stricture and diverticulum were examined and the results were noted and statistically compared.

Results: Forty-four patients, with a mean age of 34 months at the first surgery were reviewed, 17 of whom underwent a single-stage repair and 27 of whom staged. Except for a patient who underwent Onlay island flap urethroplasty, long TIPU was used in all single-session repairs, and Byar's and Bracka methods in 19 and 8 patients of the staged group, respectively. The overall complication rate was 34% at a mean follow-up of 41 months, and 18% in single-stage repair, and 44% in staged. Glans dehiscence, urethrocutaneous fistula, urethral stricture, and diverticula were seen 2 (4%), 4 (9%), and 4 (9%), respectively. All glans dehiscence and two fistulae along with distal stricture treated with Mathieu urethroplasty. Two proximal short strictures were relieved by single session dilation. Diverticula were repaired by urethroplasty. The complications were successfully treated, and no recurrence developed.

Conclusions: The risk of complications is higher due to proximal hypospadias, long urethroplasty and defective penile tissue. Hypoplasic glandular urethra, distal stricture and a neourethra devoid of spongiosum appear to be related for complications. Despite the more encountered, postoperative complications of proximal hypospadias repairs have been shown to be successfully treated with the appropriate techniques.

Keywords: proximal hypospadias, postoperative complications, glans dehiscence, urethrocutaneous fistula, urethral diverticulum, urethral stricture

In about 20% of cases with hypospadias, the urethral orifice is proximal, and it is opened anywhere from the penoscrotal region to the perineum [1]. Various techniques have been described to repair proximal hypospadias. Among the most popular are the single-stage long Snodgras and Duckett's methods as the vascularized preputial island flap technique [2, 3]. As staged technique, Bracka repair consists of a free preputial graft with orthoplasty and urethral bed replacement, and the urethral plate formed from the free

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graft is then tubularized to create the neourethra [4]. The Byars technique involves that vertical incision of the dorsal preputium and translocation of the preputial flaps to the ventral penile surface to provide adequate urethral plate for the subsequent tubularization [5]. In spite of developing techniques, hypospadias is one of the most difficult surgical procedures, and recent publications have shown that the complication rates ranged between 32-68% [6-9]. In addition to the most common complications such as fistula, glans dehiscence (GD), and urethral stenosis, other rare complications such as urethral diverticula, residual ventral penile curvature (VPC), hairy neouretra, and poor cosmetic appearance are encountered in proximal hypospadias repair [6-10]. Current surgical principles have significantly reduced complication rates; however, the knowledge about the management of postoperative complications is limited. In this study, we aim to present the results of our series of proximal hypospadias patients, and the managements of the most common postoperative complications.

METHODS

Following approval by the institutional ethics board of clinical research, we retrospectively analyzed the patients who underwent penoscrotal hypospadias repair in our clinic between December 2011 and February 2021. Data retrieved from the medical records of our institution included age at first surgery, additional anomalies, the outcomes of hormonal and genetic screen, the number of stages, the type of operations at each stage, the postoperative complications, and the managements and the results of complications which required surgical intervention. All patients whose stages was not completed, less than six months since their last surgery, and sexual development disorders in hormonal and genetic screenings were excluded from the study. Patients were divided into two groups, as single stage repaired and as staged.

Surgical Techniques

The proximal hypospadias was defined exactly during surgery after an artificial erection test. The patients whose meatus opened to the penoscrotal region or more proximal and whose meatus displaced to the penoscrotal region after transection of the urethral plate were considered as proximal hypospadias. Urethroplasty with preserving urethral plate which described by Snodgrass and Prieto [7] (Fig. 1) and the

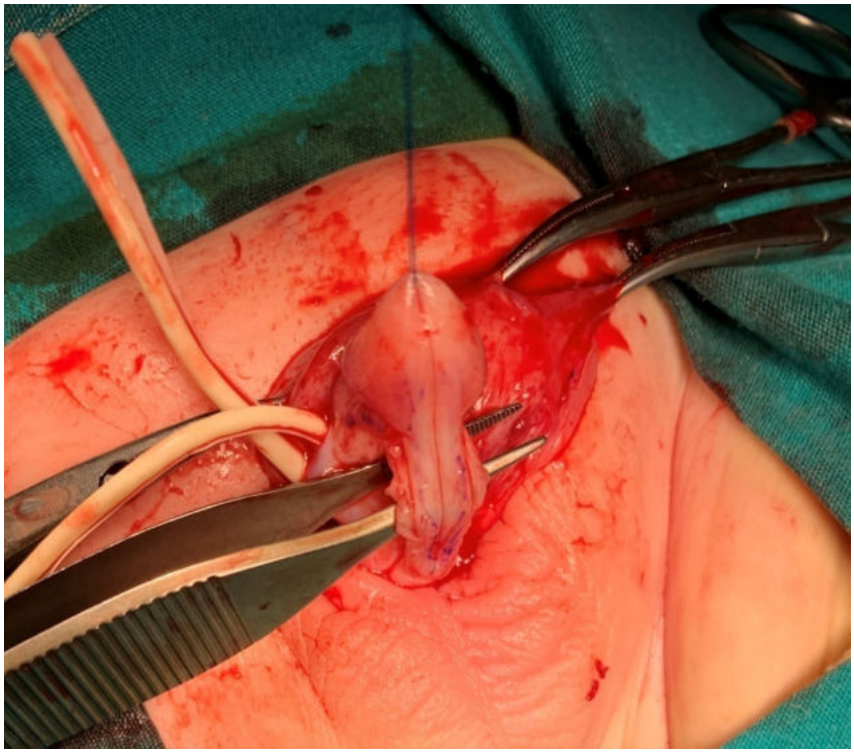

Fig. 1. Photo showing that was sufficiently straightened for urethroplasty by excision of the fibrous chordee on the corpus cavernosum, while preserving the urethral plate.

onlay island flap urethroplasty were used for single-stage repairs, and preputial flaps (Byar's) or graft (Bracka) methods (Fig. 2) for staged. The selection of repair type was made based on the evaluation of VPC and urethral plate quality during surgery. Whether in single-stage or staged repairs, all tethering fibrous chordee on the corporal bodies from the glans to the proximal normal membranous urethra were excised. If VPC persists more than 30o, it was corrected by the methods of Nespit or dorsal midline plication. The neo-urethras were covered by dartos flaps prepared from the dorsal preputial tissue. In second stages, urethral plate tubularization (Tiersch-Duplay) were performed with7/0 polydioxanone suture, by using a continuous subcuticular inverting technique over 6 or 8 Fr catheter (Fig. 3). We left glanuloplasty to the third stage in the patients who have hypoplastic glans and/or required very long urethroplasty. TIP or Mathieu method was performed in the third stage. The dressing and catheters were removed on ambulatory basis at the third and sixth postoperative day, respectively. Suprapubic drainage was not utilized. Staged repairs were performed at intervals of at least six months.

The patients were followed up for 2 weeks, 6 weeks, 3 months, 6 months and then annually to evaluate the outcome of the operation and to control any late complication. The postoperative complications requiring surgical correction were defined such as GD, urethrocutaneous fistula, urethral stricture which could be calibrated less than 6 Fr, residual VPC above 15o after repair, and urethral diverticulum which expanded with urine accumulation during urination.

Management of Postoperative Complications

Glans Dehiscence

All cases with GD were re-operated in single stage. Urethroplasty were performed by using Mathieu method along with deeply dissection of the glans wings.

Urethrocutaneous Fistula

If an urethrocutaneous fistula was encountered, the urethral calibration performed initially to be sure the adequate size of the urethra and to exclude any distal obstruction. Patients who developed fistula and urethral stenosis together underwent urethroplasty

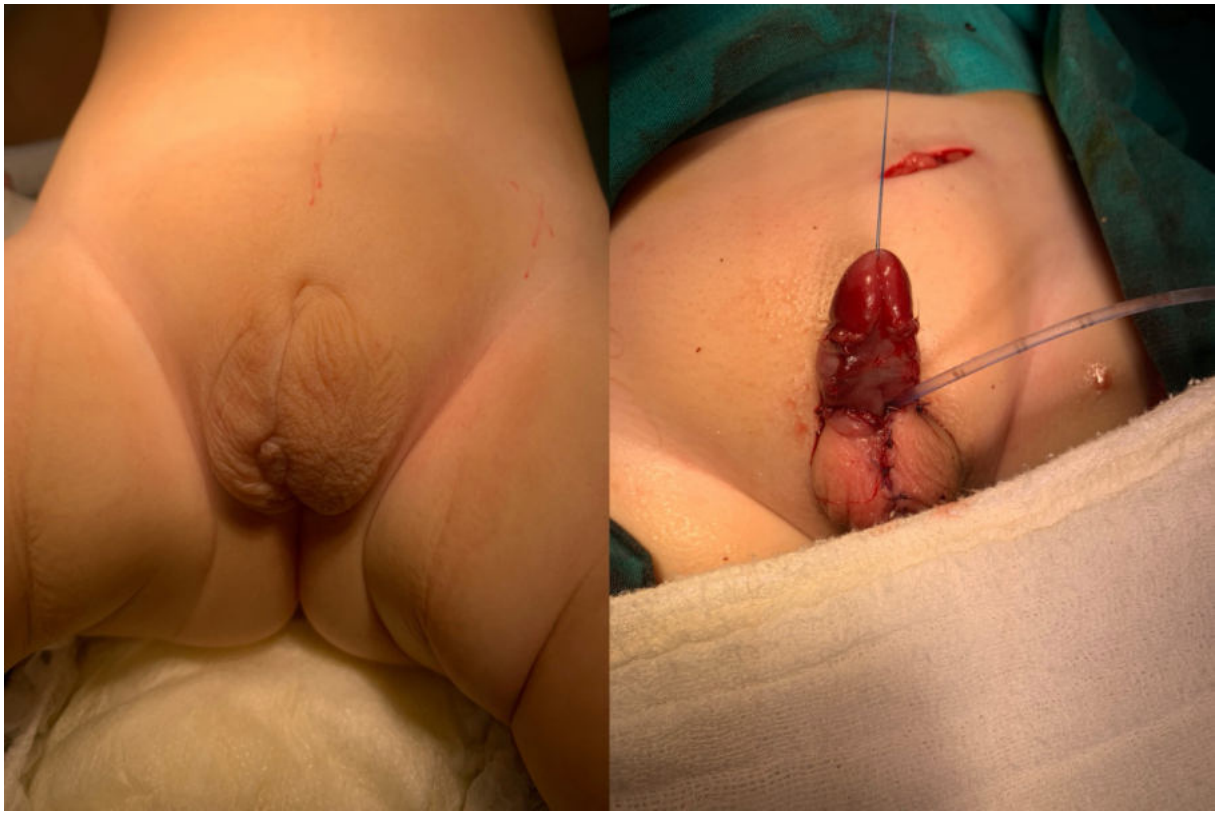

Fig. 2. Urethral plate formations with free preputial graft (Bracka method) along with Glenn-Anderson method in a patient with penoscrotal transposition at the first stage.

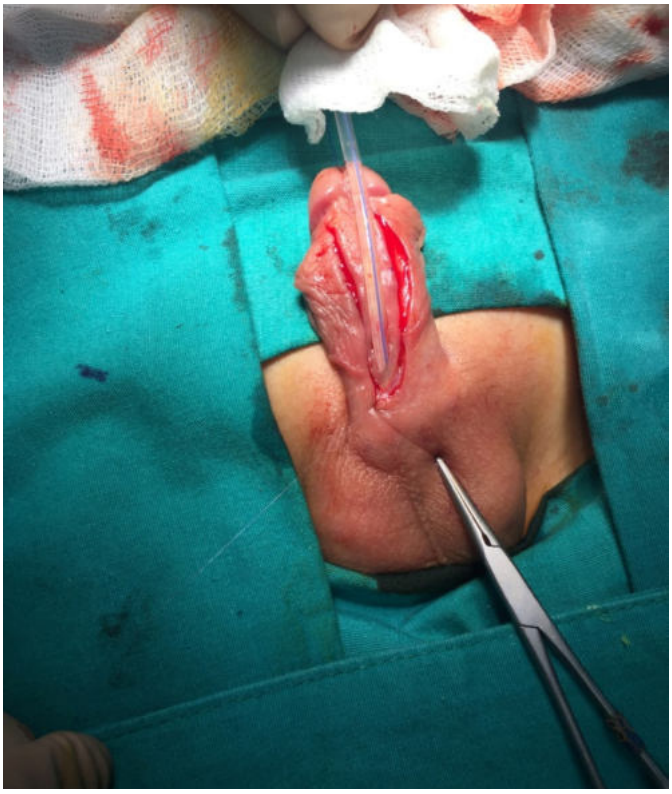

Fig. 3. Uretroplasty in the second stage with the Duplay-Tiersch method

using the Mathieu method. Otherwise the exact location of the fistula was detected by using methylene blue, the orifice of the fistula incised circumferentially and the tract removed. Fistula closure was performed by using subcuticular running suture without tension as to be inverted the epithelial edge into the lumen on transverse plane. A second layer of vascularized local tissue flap (dartos or soft subcutaneous tissue) was interposed over the suture line, and the penile skin sutured with a 7-0 polydioxanone suture in an interrupted vertical mattress closure. The urethral catheter was left in place for 6 days.

Urethral Stricture

The patients presenting with any voiding difficulty or low-calibration voiding, and those with a calibration less than 6F were accepted urethral stricture. To repair for severe distal urethral strictures, re-do urethroplasty performed by using Mathieu method. Visual urethrotomy was not performed, but cystourethroscopy by the 7 and 9 Fr cystoscopes was performed to visualize the neourethra directly and avoid the false passage (Fig. 4). After passing through the stricture by using cystoscope, urethral dilation was performed by using bougie probes.

Urethral Diverticulum

In patients who developed a urethral diverticulum, presence of distal obstruction, length of the diverticulum and luminal septations of the neourethra was investigated by urethrogram or cystourethroscopy. To restore diverticulated urethra, aventral midline incision was made on the urethral diverticulum, dilated urethra opened in same fashion, and excessive lateral mucosal walls were removed (Fig. 5). A suitable catheter introduced, urethroplasty carried out by using subcuticular running suture technique accompanied with a second layer covering of subcutaneous tissue or dartos flaps, and skin closed by using interrupted mattress sutures.

Residual Ventral Penile Curvature

Whether the cause of the residual VPC was due to fibrous chordee was investigated by performing artificial erection test. More than 15o degree of VPC at any stage accepted as residual. If the etiology of the VPC considered owing to fibrous chordee, the neourethral plate re-transected just below the glans, all fibrotic tissues removed, a new urethral plate created by using lateral prepitual flaps, and partial tubularization performed. Otherwise, dorsal midline plication or Nesbit procedure was done in the patients who have a residual VPC.

Statistical Analysis

Demographic and clinical characteristics of the patients were compared. All statistical analyses were per-

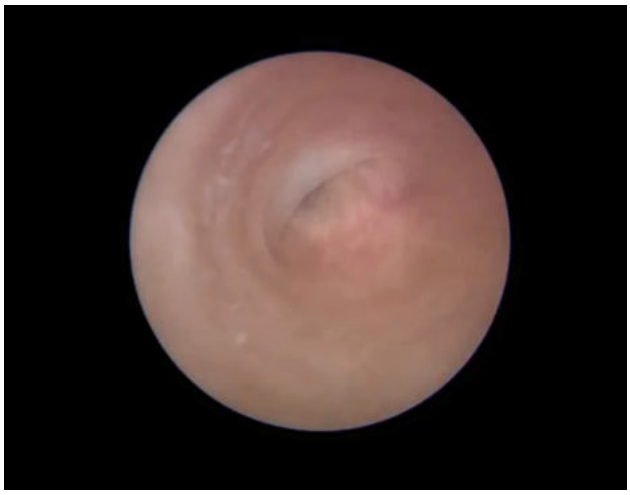

Fig. 4. Stricture in the proximal urethra during urethroscopy

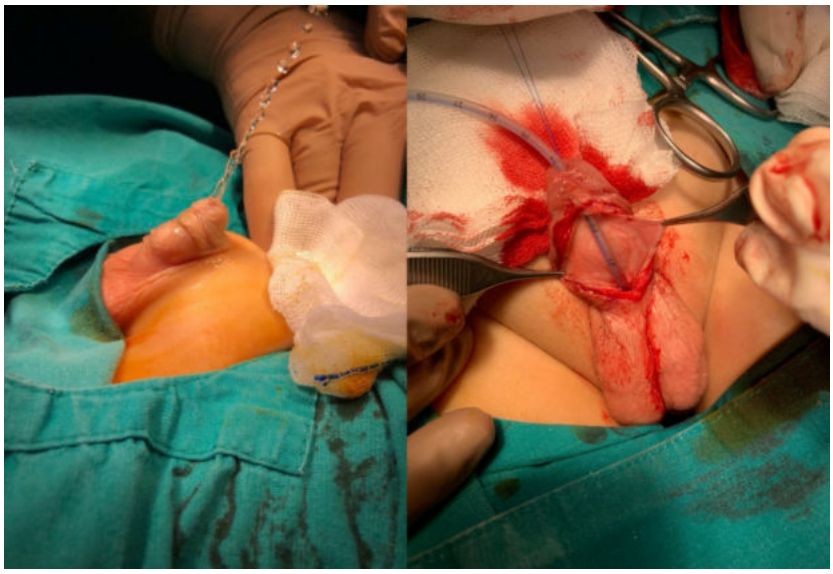

Fig. 5. **Uretroplasty in a patient with postopertive urethral diverticulum**

formed using the Statistical Package for the Social Sciences (SPSS 21.0; IBM, Armonk, NY). Comparisons between pre- and post-standards subgroups for categorical variables were compared using chi-square test, and using Mann-Whitney U tests for continuous variables. Data were expressed as means, standard deviation, frequency and percentages. Statistical significance was defined as a *p* value of less than 0.05.

RESULTS

Out of 49 patients, 44 who underwent penoscrotal hypospadias operation in our department from December 2010 to February 2020 were included in the study. Demographic, preoperative and operative characteristics of the patients are displayed in Table 1. The mean age at initial surgery was 34 months (range: 5-168

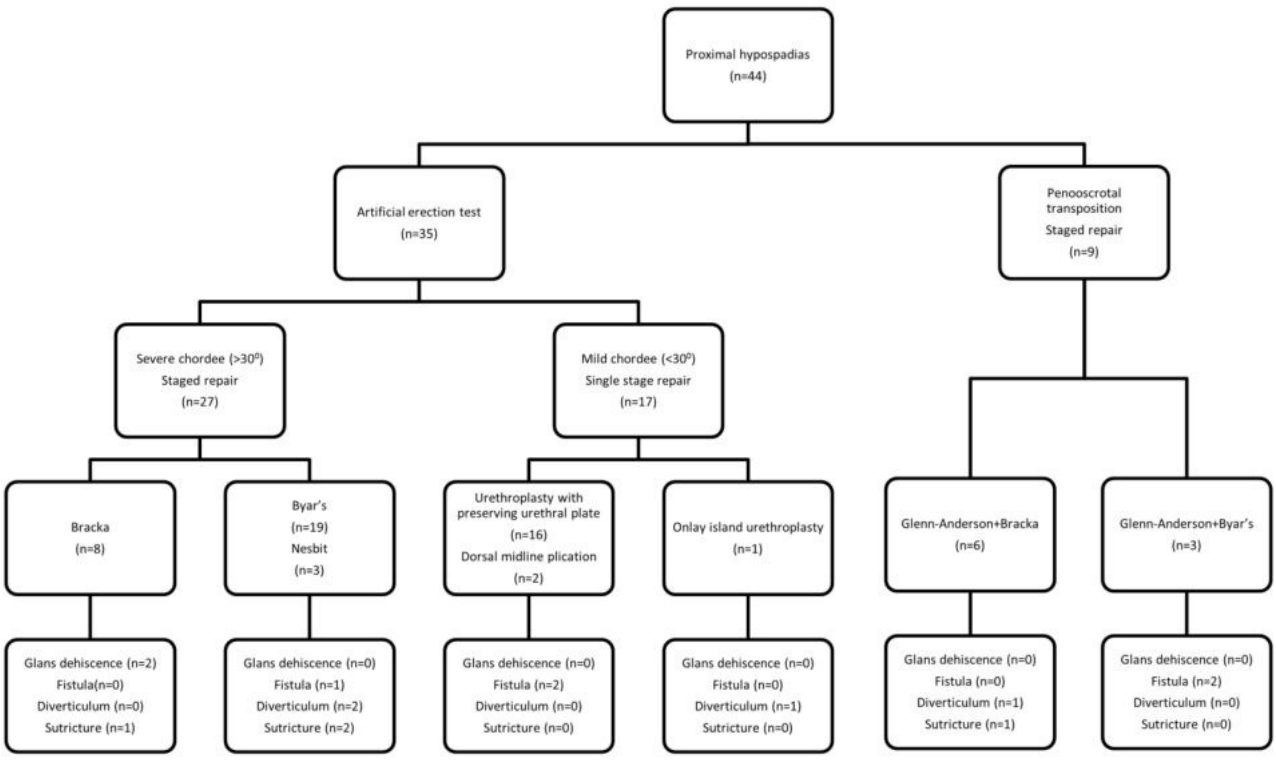

Fig. 6. **Flow diagram showing our management and outcomes for 44 patients with proximal hypospadias**

months). The mean age of the patients who underwent a single stage was significantly lower than those who underwent staged ones ($p < 0.05$). Our approaches to proximal hypospadias and the complications summarized in simplified flow diagram (Fig. 6). The single stage hypospadias repair was performed in 17 (39%) while a planned staged repair in 27 (61%) patients (Table 2). Preoperative testosterone treatment was not given except one patient with penoscrotal transposition and micropenis.

There was no significant difference between the groups in terms of the presence of additional anomaly ($p > 0.05$). Twenty-two proximal hypospadias cases were accompanied with additional anomaly such as penoscrotal transposition/bifid scrotum (n = 9, 21%), undescended testicle (n = 8, 18%), inguinal hernia (n = 4, 9%), and imperforate anus (n = 1, 2%).

Urethral plate was preserved in all of the single stage repairs, except one case was underwent with onlay island flap. In the staged group, Byar's method was applied to 19 patients for first stage, while 8 patients were applied Bracka. An aggressive chordee resection was enough to provide a straight penis in most of patients; a dorsal plication was required in 3 patients in staged group and 2 in single stage. Staged repairs were completed in two stages in 15 patients, and three stages in 12 patients. The planned third stage was carried out by TIPU method in 10 patients and by

Table 1. Patient's age at first operation, and clinical features of the patients summarized

	Single stage (n = 17)	Staged (n = 27)	Total (n = 44)
Mean age at first surgery (months), mean (min-max)	14 (6-39)	56 (6-168)	34 (5-168)
Additional anomaly, n (%)			
Penoscrotaltransposition	-	9 (33%)	9 (21%)
Undescended testis	1 (6%)	7 (26%)	8 (18%)
Inguinalhernia	2 (12%)	2 (7%)	4 (9%)
Anal atresia	-	1 (4%)	1 (2%)
Total	**3 (18%)**	**19 (70%)**	**22 (50%)**
Chordee, n (%)			
Mild/moderate	15 (88%)	20 (74%)	35 (80%)
Severe	2 (12%)	7 (26%)	9 (20%)

Table 2. Types of operations performed at each stage

	Single stage (n = 17)	Staged (n = 27)
First operation, n (%)		
Urethroplasty preserving urethral plate	16 (94%)	-
Tubularized islang flap	1 (6%)	-
Byar'sfalp		19 (70%)
Bracka (prepitual graft)	-	8 (30%)
Second operation, n (%)		
Tiersch-Duplay	-	24 (89%)
Mathieu	-	3 (11%)
Planned third operation, n (%)		
TIPU	-	10 (37%)
Mathieu	-	2 (7%)

Mathieu method in 2.

The mean follow up period in our series was 41months. . There was no significant difference between the groups in terms of the mean follow-up period ($p > 0.05$). All complications are shown in Table 3, the overall complication rate was 34% (15/44 patients), and most of them was in staged group (44%). The most seen complication was urethrocutaneous fistula, (12%). GD, urethral stricture, and diverticulum were occurred 2 (4%), 4 (9%), and 4 (9%), in rates, respectively. In two cases, distal urethral stricture and fistula developed together. Although the number of complications was higher in the staged group, there was no difference between the groups in terms of the total number of complications ($p > 0.05$).

Patients who developed GD were cripple hypospadias that had a failed repair elsewhere and we applied the staged Bracka method. In these patients, the glans hypoplasic and urethral groove was very shallow. They were repaired by performing urethroplasty with the Mathieu method. Any GD did not recur in these patients.

Fistulectomy and multilayer repair were performed in two patients. A meatotomy was performed in the same session with fistula repair in one case. Distal urethroplasty was performed by Mathieu method in two patients of the staged group who developed fistula associated with distal stricture. Neither stricture nor fistula occurred again.

Strictures developed in 4 cases (9%) requiring reoperation, and all of them in staged group. The two had glandular localization that did not allow 6Frcalibrations, and a fistula developed proximally. The entire distal urethra was opened up to the fistula, and the re-urethroplasty was performed by Mathieu method. Cystourethroscopy revealed proximal anastomotic stenosis at the level of the natural urethra. The 7 and 9 Fr cystoscopes were easily passed through the stricture and expanded with suitable size probes. Strictures were dilated in two times, but not persisted.

Urethral diverticulum occurred in four patients (9%). One of them was in the single stage group which was performed tubularized onlay island flap urethroplasty (6%), and three were in the staged group (11%), one underwent Bracka method, and two Byar's. Urethrography and cystourethroscopy revealed no distal stricture, but we noticed the very stiff glandular urethra. Diverticulum was successfully excised and urethroplasty was completed by performing a tight tubularization. There was occurred no postoperative recurrence or any other complication.

No residual VPC was observed in any patient in this series, with the exception of one patient who detected a residual fibrous chordee in the second stage. In this patient, more than 30o of VPC still remained, the neourethral plate was re-transected just below the glans, a dorsal plication was performed after all fibrotic tissues removing, urethral plate re-formed by using lateral prepitual flaps.

DISCUSSION

In present series, overall complication rate for 44 patients was 34% at mean 41 months follow-up period. Since we prefer single-stage repair in the patients who have better penile development and less VPC, we believe that we achieve better results in these patients than in the staged group. A linear relationship has been found between hypospadias severity and complications regardless of the type of repair, therefore it is ob-

Table 3. Complications which required surgical intervention

	Single stage (n = 17)	Staged (n = 27)	Total (n = 44)
Mean follow-up (months), mean (range)	44 (6-107)	39 (6-96)	41 (6-107)
Complications (treatment), n (%)			
Dehiscence (Mathieu [n = 2])	-	2 (7%)	2 (4%)
Fistula (Mathieu [n = 2], multilayer repair [n = 3])	2 (12%)	3 (11%)	5 (12%)
Urethral stricture (Mathieu [n =2], dilation [n = 2])	-	4 (15%)	4 (9%)
Diverticulum (urethroplasty [n=4])	1 (6%)	3 (11%)	4 (9%)
Total	**3 (18%)**	**12 (44%)**	**15 (34%)**

vious that a repair of proximal hypospadias may result in increased risk of complications caused by the defective penile tissues [11, 12]. However, the most postoperative complications are related to the techniques, the surgeon's experience, and the underlying anatomical abnormalities [13]. Recently, it has also been reported the greater likelihood of complications in hypospadias patients with congenital anomalies suggests that the complications may partly to be have a biological basis [14]. Although not statistically large enough to compare, the most of the patients who occurred a complication in our series had an accompanied genital anomaly.

In our series, GD developed in two cases that were cripple hypospadias, and have not enough glans wings for urethroplasty (4%). It has been reported that the risk factors of GD include proximal hypospadias, reoperations and the host's wound healing ability [15, 16]. The width of the urethral plate, the size of the glans, and the depth of the groove has been also suggested to be other predisposing factors. Various staged inlay mucosal graft techniques have been reported to reduce the risk of GD in cases [16, 17]. Snodgrass and Bush [18] have stated that additional dissection of the glandular wings from the urethral plate reduces the approximation tension and GD. White and Hanna [16] have also suggested that a grooveless glans penis should be converted to a deep grooved plate to prevent recurrent GD. Although it has been suggested that preoperative testosterone therapy may decrease the risk of GD by increasing the glans size, there is insufficient randomized data to prove this theory [15]. In order to prevent GD formation, we postponed glanuloplasty to the third stage in case of narrow grooved and hypoplastic glans. Two of our cases who developed GD were cripple, and a forced glanuloplasty performed at former stage. However, these cases were successfully repaired using the Mathieu method.

Urethrocutaneous fistula is one of the most common complications encountered after hypospadias repair, with rates up to 55% [13, 19]. In the presented series, it was found that the total incidence of fistula was 12%. Interposition of tissue flaps such as buccal mucosa, tunica vaginalis flaps, dartos flaps, spongious tissue, external spermatic fascia, adipose tissue and spermatic cord between layers has been reported to be important in reducing fistula formation [20-22]. Additionally, it has also been suggested that there are many factors affecting fistula development, such as distal obstruction, diverticulum, repair under magnification, stent use, suture technique, and tension in the suture line [19, 23]. While simple closure techniques are sufficient in small fistulas, it has been suggested that if local tissue cannot be used due to severe scar formation, mucosal grafts are a reliable option for repairing large urethrocutaneous fistulas [22, 23]. The success rate of first simple closure of fistula after hypospadias surgery is over 90% [13, 23]. Large fistula was not developed in our series, small fistulas repaired in three layers. We believe that subcuticular closure of the urethral lumen without tension also affects success in fistula repair. It is well known that simple closure may cause recurrence in the presence of fistula with distal stricture. In two patients who developed fistula associated with distal glandular stricture, we performed urethroplasty with Mathieu method instead of fistula repair. No recurrence was observed in any patient during the follow-up period.

Urethral stricture is the second most common complications of hypospadias surgery. It has been reported that 7-12% urethral stricture develops after hypospadias repairs, in which most of them used graft or flap for repair [7, 8, 24]. Devascularization is always a possible risk when pedicled flaps are used, which can cause scarring and urethral stricture [25]. Our practices include the formation wide enough for urethral plate, the tubularization with appropriate calibration, and the repair in 3 stages instead of 2 in the patients with requiring long urethroplasty. Notwithstanding, a stricture requiring intervention was occurred in our four cases (9%), and all of them in staged group. There were typically two different localizations of the strictures which are at the border of native urethra in two patients, and at the glandular urethra in others. Possible reasons of strictures were that circular anastomosis in the first one, and that hypoplasic glans in the next. The traditional treatment of the urethral strictures has always begun with dilation or visual urethrotomy, but it has been suggested that dilations have no role in the management of urethral structures in children [24]. Nevertheless, dilation was found successful for short proximal anastomotic strictures in our series. We think that anastomotic strictures respond to dilation due to its short and ring-like nature.Although we have not used, the success of urethrotomy in the literature ranges from 0 to 72% regardless of the type

of hypospadias, used tissue, and the method of urethroplasty, however, early urethroplasty recommended in those who do not respond to urethrotomy once [26, 27]. Dilatation was not attempted in two patients who developed glandular stricture along with fistula, and re-do urethroplasty was performed by Mathieu method.

It has been reported that the incidence of diverticulum formation after hypospadias repair is 7-23%, and the most of them has been seen especially in the patients who have a perineal/proximal defect [7, 13, 28]. It has been suggested that diverticulum formation is associated with distal stenosis and flap / graft use (e.g., preputial, buccal or bladder mucosa) [29-31]. In addition other factors such as excessive use of plate for long tubularization, urine flow with high pressure and artificial thick urethral plate are associated with diverticulum formation. Diverticulum developed in 4 (9%) of our patients. The glandular urethra was normally calibrated in these cases, but it was too tight. There is no standard approach for the treatment of urethral diverticulum. Snyder *et al*. [13] have reported that if there is no other complication, simple partial excision with multi-layer closure is sufficient for diverticulum repair. If there are other complications such as stricture or fistula, other techniques such as 'pants over vest' closure could be applied. In our cases, simple closure of the diverticulum was easily performed and no recurrence occurred. However, it cannot be guaranteed that the distal stiffy glans will not cause re-expansion of the urethra, which is deprived of spongious tissue at an older age.

Snodgrass and Bush [32] have proposed that residual VPC was detected in 83% of patients who presented with complications after hypospadias surgery. Many techniques have been described to correct penile curvature. Dorsal plication performed easily and produces reliable straight erection. However, recently, the results show that this process is not durable to severe VPC [32]. The excision of the dysplastic ventral chordee with or without transecting the urethral plate is the second most common method for VPC correction [33]. Additionally, ventral lengthening with serial corporotomies with or without grafts is rarely used [32]. In our series, adequate excision of ventral fibrous cords was sufficient for VPC correction in most patients, five patients required dorsal plication, and no residual VPC was detected.

Limitations

The limitations of this study are that it is retrospective and relatively few cases. In addition, our study does not include the effects on hairy urethra, psychological problems and sexual function and the results of operations that may be encountered in the long term.

CONCLUSION

In conclusion, proximal hypospadias has a higher risk for complications due to long urethroplasty and defective penile tissue. Complications are thought to be related to each other, such as narrow glandular plate-GD, fistula-distal stricture and diverticulum-stiffy glandular urethra. Despite the high rates, postoperative complications of proximal hypospadias repairs have been shown to be successfully treated with the appropriate techniques.

Ethics approval and consent to participate

All procedures performed in this retrospective study and data analysis were in accordance with the ethical standards of our IRB (Bursa Yuksek Ihtisas Training and Research Hospital Ethical Committee) with approval reference number of 2011-KAEK-25 2020/03-19, dated 18.03.2020. The IRB waived the need for informed consent for this retrospective study.

Authors' Contribution

Study Conception: EO, STO, MK; Study Design: EO, MK; Supervision: MK; Funding: N/A; Materials: EO, STO, MK; Data Collection and/or Processing: EO, STO, MK; Statistical Analysis and/or Data Interpretation: EO, MK; Literature Review: EO, MK; Manuscript Preparation: EO, MK and Critical Review: MK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Baseline characteristics of outpatients with heart failure according to phenotype: preliminary analysis from SMYRNA-HF registry

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ABSTRACT

Objectives: SMYRNA-HF study is a prospective multicenter registry study to determine the profiles of patients with heart failure (HF) in Turkey. This study aimed to present the baseline characteristics of preliminary cohort by comparing them according to different HF phenotypes.

Methods: The first SMYRNA-HF cohort included outpatients with HF from 9 centers. Patients were classified into three HF phenotypes as HF with reduced ejection fraction (HFrEF), mildly reduced EF (HFmrEF), and preserved EF (HFpEF) as recommended by guidelines.

Results: Overall, 298 patients were included in this preliminary analysis that 57% of the patients were classified as having HFrEF, 33.3% as having HFpEF, and 9.7% as having HFmrEF. Female gender was more common in HFpEF (p = 0.003). Age, frequency of diabetes mellitus, use of angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, use of beta-blocker, use of daily loop diuretic, heart rate, blood urea nitrogen levels, lipid profiles, hemoglobin, white blood cell, platelet levels were similar among three HF phenotypes. Body mass index (BMI) ($p < 0.001$), frequency of hypertension (HT) ($p < 0.001$), and atrial fibrillation (AF) ($p = 0.015$) were higher in HFpEF. Ischemic etiology ($p < 0.001$) was less frequent in HFpEF. Use of mineralocorticoid receptor antagonist was higher in HFrEF ($p < 0.001$).

Conclusions: Our study presented the baseline characteristics of outpatients with HF in Turkey. There were

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significant differences among HF phenotypes in terms of gender, BMI, frequency of HT, AF, and ischemic etiology. Treatment implementations seem to follow the guidelines. Although the rates are low, new treatment approaches recommended in the most recent guidelines seem to enter clinical practice.
Keywords: Heart failure, registries, Turkey, phenotypes, outpatients, baseline characteristics

Heart failure (HF) is a fatal disease that occurs as a result of deterioration of cardiac functions. It is estimated that there are approximately 40 million patients with HF in the world. The number of patients with HF is anticipated to increase in the coming years [1]. Many notable improvements have been observed in the treatment of HF, and there has been a remarkable increase in the life expectancy of patients with HF [2, 3]. Nevertheless, these patients still are at risk of death or acute decompensation requiring recurrent hospitalization.

Large-scale multicenter HF cohort registry studies have been conducted in many countries [4-13]. These studies provide important data regarding the basic profiles of patients, the distribution of HF phenotypes, risk factors, treatment, mortality, and morbidity characteristics of patients with HF from different countries. The "SELFIE-TR study" that includes the basal characteristics, treatments [14], and mortality data [15] of patients with different HF phenotypes has been recently published in Turkey.

More registry studies are required to understand better the profile of the patients with HF in our country. In this multicenter HF registry study called SMYRNA-HF, it was aimed to determine the profile of outpatients with HF in our country, to define the baseline characteristics of the patients, to examine whether these features differ between different HF phenotypes, and to evaluate the treatment of the patients.

METHODS

The SMYRNA-HF study is an ongoing prospective national registry study including outpatients with HF with a plan to recruit patients from centers in Turkey under the leading role of Izmir. In this registry study, long-term follow-up of the patients is aimed. The current study, which provides the data from the preliminary cohort of the SMYRNA-HF registry, recruited patients from 9 centers between October 2019 and January 2021. Patients with acute decompensated HF and hospitalized with acute decompensation within the last month were not considered.

Demographic and clinical characteristics of the patients, laboratory, electrocardiographic and echocardiographic findings, and medications at the time of enrolment were recorded. The diagnosis and phenotype categorization of patients with HF were made according to the current guidelines. The patients were classified into three HF phenotype groups; HF with reduced ejection fraction (HFrEF) if they had left ventricular ejection fraction (LVEF) ≤ 40%, HF with mildly reduced ejection fraction (HFmrEF) if they had LVEF between 41% and 49%; and HF with preserved ejection fraction (HFpEF) if they had LVEF ≥ 50% [16, 17]. The New York Heart Association (NYHA) class was used to determine the functional capacities of patients.

Ethical approval for this study was provided by the Non-Invasive Research Ethics Committee of Dokuz Eylül University (date: 16.09.2019, approval No: 2019/23-39), the coordinating center, and each center approved participation in the study in accordance with established legislation.

Statistical Analysis

The Kolmogorov-Smirnov test was used to evaluate whether the data showed a normal distribution. Since all continuous variables showed a non-normal distribution, non-parametric analysis methods were used. The continuous variables were expressed as median (quartile 1-3), and the categorical variables were presented as numbers (%). Differences in continuous variables between the three groups according to HF phenotype were analyzed with the Kruskal Wallis-H test. Differences between categorical variables were analyzed with the chi-square test. The significance level for all tests was determined as $p < 0.05$. Statistical analysis was performed using the IBM SPSS Statistics for Windows (Version 25.0. Armonk, NY: IBM Corp.).

RESULTS

A total of 298 patients with HF were included in this analysis. 57% of the patients were classified as having HFrEF, 33.3% as having HFpEF, and 9.7% as having HFmrEF (Fig. 1). The median age of the patients was 67 (59-76) years, and 37% of them were female. Previous acute coronary syndrome (ACS) was present in 54.7% of the patients. In addition, 30.9% of the patients had hypertension, and 28.2% had diabetes mellitus (DM). In the whole cohort, the median LVEF was 40% (30%-52%).Beta-blocker use was reported in 85.6%, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin receptor blocker (ARB) use was reported in 63.4%, mineralocorticoid receptor antagonist (MRA) use was reported in 40.9%, and daily loop diuretic use was reported in 79.2%. In the whole cohort, the frequency of use of angiotensin receptor neprilysin inhibitors (ARNI) and sodium-glucose co-transporter-2 (SGLT2) inhibitors was 4.4% and 1.3%, respectively. The frequency of implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy with defibrillator (CRT-D) was 10.4% and 2.3%, respectively. The rhythm was atrial fibrillation in 24.2% of the patients. The baseline characteristics of patients, including demographic, clinical features, electrocardiographic and echocardiographic findings, laboratory parameters, and medications are presented in Table 1.

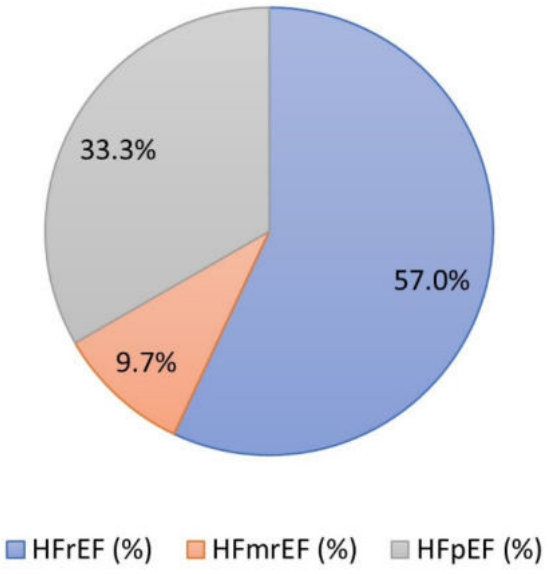

Fig. 1. Ratio of patients according to heart failure phenotypes. HFrEF = heart failure with reduced ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction.

Median LVEF was 31.5% in the patients with HFrEF, 45% in HFmrEF, and 55% in HFpEF ($p < 0.001$). Age, frequency of DM, use of ACEI/ARB, use of beta-blocker, use of daily loop diuretic, heart rate, blood urea nitrogen levels, lipid profiles, hemoglobin, white blood cell, platelet levels were similar among three HF phenotypes (Table 2). Female gender was more common in the patients with HFpEF ($p = 0.003$). The median body mass index (BMI) value ($p < 0.001$) and the frequency of hypertension, atrial fibrillation was higher ($p < 0.001$ and $p = 0.015$, respectively), and the frequency of previous ACS was lower in the patients with HFpEF ($p < 0.001$). The median systolic blood pressure (SBP), diastolic blood pressure (DBP), and sodium level were lower in patients with HFrEF ($p < 0.001$, $p < 0.001$, $p = 0.002$, respectively). The median creatinine level and the frequency of use of MRA were higher in patients with HFrEF ($p = 0.003$, $p < 0.001$, respectively). In addition, there were no significant differences among the groups with regard to frequency of poor NYHA functional class (NYHA class III-IV) ($p = 0.210$) and echocardiographic parameters, including left atrium diameter, right ventricle diameter, and systolic pulmonary artery pressure (SPAP) ($p = 0.272$, $p = 0.094$, $p = 0.309$, respectively). Left ventricle end-diastolic diameter (LVEDD), end-systolic diameter (LVESD) were higher ($p < 0.001$, $p < 0.001$), and tricuspid annular plane systolic excursion (TAPSE) was lower in patients with HFrEF ($p = 0.024$). The comparison results of patients' characteristics according to HF phenotypes are presented in Table 2.

DISCUSSION

The SMYRNA-HF study provides a real-life dataset of chronic HF outpatients with different HF phenotypes in reference to the European Society of Cardiology (ESC) guidelines published in 2021 [17]. SMYRNA-HF registry study aimed to reflect outpatients with HF in our country. The characteristics of the patients for each HF phenotype were determined and whether patients were on guideline-directed medical therapy or not considered thoroughly in this analysis. Of note, these patients have been on follow-up for outcomes. This registry overall purposes of determin-

Table 1. Baseline characteristics of the whole cohort (n = 298)

	Median (Quartiles 1-3)
Age (years)	67 (59-76)
Female gender, n (%)	110 (37.0)
Body mass index (kg/m^2)	27.26 (24.24-31.33)
NYHA functional classification, n (%)	
Class I/II	218 (73.2)
Class III/IV	80 (26.8)
Systolic blood pressure (mmHg)	120 (110-136.5)
Diastolic blood pressure (mmHg)	70 (69.5-80)
Previous acute coronary syndrome, n (%)	163 (54.7)
Diabetes mellitus, n (%)	84 (28.2)
Hypertension, n (%)	92 (30.9)
Atrial fibrillation, n (%)	72 (24.2)
Heart rate (beats/min)	75 (66-83.5)
ICD, n (%)	31 (10.4)
CRT-D, n (%)	7 (2.3)
Echocardiography characteristics	
LV end-diastolic diameter (mm)	53 (48-58)
LV end-systolic diameter (mm)	39.5 (34-46)
LVEF (%)	40 (30-52)
SPAP (mmHg)	38 (34.5-45)
TAPSE (mm)	16 (14-18)
Left atrium (mm)	44 (41-48)
Right ventricle (mm)	37 (32-40.3)
Medication, n (%)	
Use of ACEI/ARB	189 (63.4)
Use of betablocker	255 (85.6)
Use of MRA	122 (40.9)
Use of daily loop diuretic	236 (79.2)
Use of SGLT2 inhibitor, n (%)	4 (1.3)
Use of ARNI, n (%)	13 (4.4)
Laboratory findings	
Glucose (mg/dL)	110 (95-145)
Blood urea nitrogen (mg/dL)	18.5 (15-27.8)
Creatinine (mg/dL)	1.0 (0.8-1.3)
Sodium (mEq/L)	139 (136-141)
Potassium (mEq/L)	4.4 (4.1-4.8)
Hemoglobin (g/dL)	13.0 (11.4-14.2)
Platelet ($\times 10^9$/L)	245.5 (201.0-311.8)
White blood cell ($\times 10^9$/L)	8.0 (6.7-10.0)
Low-density lipoprotein (mg/dL)	100.5 (75.8-128.0)
High-density lipoprotein(mg/dL)	43.0 (36.0-54.0)
Triglyceride (mg/dL)	115.0 (90.8-170.0)
Total cholesterol (mg/dL)	172.0 (141.8-200.0)

NYHA = New York Heart Association, ICD = implantable cardioverter defibrillator, CRT-D = cardiac resynchronization therapy-defibrillator, LV = left ventricle, LVEF = left ventricular ejection fraction, SPAP = systolic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion, ACEI = angiotensin- converting enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist, SGLT2 = sodium-glucose cotransporter-2, ARNI = angiotensin receptor neprilysin inhibitor

Table 2. Comparison of baseline characteristics according to heart failure phenotypes (n = 298)

	HFrEF (n = 170)	HFmrEF (n = 29)	HFpEF (n = 99)	*p* value
Age (years)	66 (58-75)	67 (57-75)	69 (62-77)	0.289
Female gender, n (%)	51 (30.2)	9 (31.0)	50 (50.5)	**0.003***
Body mass index (kg/m^2)	25.9 (23.4-29.4)	28.1 (25.1-32.1)	29.4 (26.3-33.5)	**< 0.001***
NYHA functional classification – Class III/IV, n (%)	46 (27.1)	4 (13.8)	30 (30.3)	0.210
Systolic blood pressure (mmHg)	120 (110-130)	130 (120-140)	130 (115-140)	**< 0.001***
Diastolic blood pressure (mmHg)	70 (62-75)	80 (70-90)	70 (70-80)	**< 0.001***
Previous acute coronary syndrome, n (%)	110 (64.7)	21 (72.4)	32 (32.3)	**< 0.001***
Diabetes mellitus, n (%)	42 (24.7)	11 (37.9)	31 (31.3)	0.240
Hypertension, n (%)	30 (17.6)	13 (44.8)	49 (49.5)	**<0.001***
Atrial fibrillation, n (%)	35 (22.7)	3 (11.1)	34 (35.4)	**0.015***
Heart rate (beats/min)	75.5 (67-85)	70 (61-80)	76 (67-84)	0.177
Echocardiography characteristics				
LV end-diastolic diameter (mm)	56 (52-61.5)	52 (48-56)	48 (43-51)	**< 0.001***
LV end-systolic diameter (mm)	44 (40-50)	38.5 (37-41)	33 (30-36)	**< 0.001***
LVEF (%)	31.5 (25-40)	45 (45-46.5)	55 (51-60)	**< 0.001***
SPAP (mmHg)	40 (34-46)	35 (30-40)	38 (35-45)	0.309
TAPSE (mm)	16 (13-18)	16.5 (16-19)	17 (15-19)	**0.024***
Left atrium (mm)	44 (41-48)	43 (38-46)	45 (42-48)	0.272
Right ventricle (mm)	38 (33-40)	32 (28-39)	37 (31-41)	0.094
Medication, n (%)				
Use of ACEI/ARB	108 (63.5)	20 (69.0)	61 (61.6)	0.769
Use of betablocker	151 (88.8)	26 (89.7)	78 (78.8)	0.063
Use of daily loop diuretic	137 (80.3)	19 (65.5)	80 (80.8)	0.161
Use of MRA	90 (52.9)	12 (41.4)	20 (20.2)	**< 0.001***
Laboratory findings				
Glucose (mg/dL)	110.5 (96-148)	111 (85.5-138)	108 (94.5-131)	0.491
Blood urea nitrogen (mg/dL)	20 (16-30)	17.5 (16.5-20.5)	17 (14-24)	0.059
Creatinine (mg/dL)	1.1 (0.9-1.4)	1.0 (0.8-1.3)	1.0 (0.8-1.2)	**0.003***
Sodium (mEq/L)	138 (136-140)	140 (138-142)	140 (137-141)	**0.002***
Potassium (mEq/L)	4.4 (4.08-4.8)	4.4 (4.2-4.6)	4.4 (4.1-4.8)	0.986
Hemoglobin (g/dL)	13 (11.5-14.3)	12.7 (11-13.8)	12.9 (11.4-14.1)	0.878
Platelet ($\times 10^9$/L)	242 (193-307)	234 (207-299)	255 (209-319.5)	0.253
White blood cell ($\times 10^9$/L)	7.9 (6.8-9.5)	9.4 (7-11.4)	8.1 (6.4-10)	0.210
Low-density lipoprotein (mg/dL)	99 (77.5-124.5)	90 (63-143)	104 (77-128)	0.801
High-density lipoprotein(mg/dL)	44 (36-53)	41 (35-56)	43.5 (37-54)	0.905
Triglyceride (mg/dL)	113 (83-155)	139 (105-195)	114.5 (91-161)	0.541
Total cholesterol (mg/dL)	173 (142-210)	161 (144-200)	170.5 (141-194)	0.804

Data are presented as median (Quartiles 1-3) unless otherwise stated. *$p < 0.05$. HFrEF = heart failure with reduced ejection fraction, HFmrEF = heart failure with mildly reduced ejection fraction, HFpEF = heart failure with preserved ejection fraction, NYHA = New York Heart Association, LV = left ventricle, LVEF = left ventricular ejection fraction, SPAP = systolic pulmonary artery pressure, TAPSE = tricuspid annular plane systolic excursion, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker, MRA = mineralocorticoid receptor antagonist

ing the barriers to the management of HF and identifying predictors of mortality and recurrent hospitalization. Baseline characteristics of this preliminary cohort were presented herein.

In the ESC registry study, including outpatients with HF, 60% of the patients had HFrEF, 24% had HFmrEF, and 16% had HFpEF [18]. Similar to the ESC registry study, 57% of the patients were found to have HFrEF in our study. While 42.9% of patients with HF had ischemic etiology in the ESC registry study, this rate was 54.7% in our study. Similar to our study, ischemic etiology was found in more than half (52.6%) of the patients in the chronic HF group of the SELFIE-TR study [14]. The higher rate of ischemic etiology in HF (i.e., previous ACS) in our country compared to Europe indicates that we need to move faster in diagnosis and hyperacute treatment, especially in ST-segment elevation myocardial infarction, and improve the quality of primary percutaneous coronary interventions [19]. In our study, the frequency of HFpEF was found to be 33.3%. In the SELFIE-TR study, the frequency of HFpEF was only 7.3% in the whole cohort [14]. In general, patients with HFpEF have multiple comorbidities; the diagnosis with HF and follow-up by a cardiologist is delayed due to overlapping symptoms. Compared to the SELFIE-TR study, the higher frequency of HFpEF in our study can be interpreted as an increased awareness of HFpEF in both physicians and patients.

In general, patients with HFpEF are older and more frequently women than patients with HFrEF and HFmrEF. Patients with HFpEF have more frequent atrial fibrillation compared to patients with HFrEF and HfmrEF [20]. In the HAPPY study investigating the prevalence of HF in Turkey, the male gender ratio was higher in the subgroup of HF with LVEF < 50%, and the female gender ratio was higher in the subgroup of HF with LVEF ≥ 50% [21]. In our study, half of the patients with HFpEF were women; although the median age was numerically higher in patients with HFpEF, it did not reach statistical significance.

HFmrEF is more akin to HFrEF than the HFpEF phenotype; patients with these two phenotypes (HFmrEF and HFrEF) have a higher male gender ratio, younger age, are more likely to have ischemic etiology, and are less likely to have atrial fibrillation compared to patients with HFpEF [22-24]. In the APOLLON study comparing the clinical features of patients with HFmrEF and HFpEF in Turkey, the mean ages of the two groups were similar; the female gender ratio was higher in patients with HFpEF, and the ratio of previous myocardial infarction was higher in those with HFmrEF [25]. Consistent with the literature, in our study, approximately 70% of patients with HFmrEF and HFrEF were male, their median age was similar, and the underlying ischemic etiology was higher in patients with HFmrEF and HFrEF than in those with HFpHF. While more than half of the patients with HFmrEF and HFrEF had previous ACS, this rate was 32.3% in those with HFpEF.

Obesity is one of the major causes of HFpEF [20, 26-28]. BMI assessment is important in patients with HF. In our study, the HF phenotype with the highest BMI was HFpEF. Hypertension is the most important cause of HFpEF [29]. In our study, nearly half of the patients with HFpEF were found to have hypertension. In our study, the proportions of patients with NYHA functional class III-IV were similar in patients with HFrEF and HFpEF (27.1% vs. 30.3%, respectively) along with similar age distribution. However, the NYHA functional class assessment is based on symptoms only. Non-cardiac comorbidities are more common in HFpEF, and it may be difficult to distinguish whether symptoms are primarily and solely caused by HF or by other non-cardiac diseases [30]. Therefore, the frequency of patients with poor NYHA functional class may have been found to be similar in patients with HFrEF and HFpEF.

In our study, SBP and DBP were found to be lower in patients with HFrEF. Similarly, in the ESC registry study, SBP was lower, and hypotension (SBP ≤ 110 mmHg) was more frequent in patients with HFrEF [13]. These results may simply be associated with a high frequency of hypertension in patients with HFpEF.

Most of the deaths are caused by electrical disturbances, including ventricular arrhythmias in patients with HFrEF. ICD or CRT-D are recommended to reduce mortality in these patients when specific indications are provided [17]. In our study, all patients with ICD/CRT-D were in the HFrEF phenotype. The rate of ICD and CRT-D were 18.2% and 4.1%, respectively in patients with HFrEF. In the ESC registry study, the same rates were 34.8 % and 22.4 %, respectively [18]. Although it is difficult to make a comparison due to the small number of patients, the rate of patients with

ICD/CRT-D was low in our cohort. In the CRT Survey-II study, 11,088 patients who are candidates for CRT were recruited from 288 centers, the median number of CRT implantations per year in Turkey was found to be significantly lower than in other European countries [31]. Management of HF especially device threapy is expensive [32]. The lower rate of device therapy in HF in our country may be due to cost-effectiveness problem. Conservative approach of patients and physicians may also be another reason. Nevertheless, it would be appropriate to improve the implementation of ICD and CRT-D in eligible patients.

The ACE-I/ARB/ARNI, beta-blocker, and MRA triad are the cornerstone of treatment for patients with HFrEF [13, 33, 34]. In these study, 63.5% of patients with HFrEF were on ACE-I or ARB and 88.8% of those on beta-blocker. In the ATA study, including patients with HFrEF from Turkey, renin-angiotensin system (RAS) inhibitors and beta-blocker usage were 78.2% and 90.2%, respectively [35]. In our country, the rate of use of beta-blocker was satisfactory in patients with HFrEF, but the same cannot be said for RAS inhibitors. Replacement of ACE-I or ARB with ARNI is recommended in symptomatic patients with ambulatory HFrEF [17], but only 7.6% of patients with HFrEF were on ARNI in this cohort. The low usage rate of this drug can be explained by the lack of reimbursement in our country. SGLT2 inhibitors have been reported to reduce the risk of death in patients with HFrEF [36, 37]; thus, SGLT2 inhibitors were recommended for all patients with HFrEF in the recent ESC guideline [17]. In our study, only 2.3% of the patients with HFrEF were on SGLT2 inhibitors. This rate was quite low. However, SGLT2 inhibitors have recently entered the guidelines. We think that the use of SGLT2 inhibitors will increase significantly in the coming years.

There are no specific studies on medical therapy in patients with HFmrEF [17]. However, many patients with HFmrEF are also treated with ACE-I/ARBs because of ischemic heart disease, hypertension, or systolic dysfunction after ACS. A beta-blocker is used in many patients with HFmrEF because of atrial fibrillation or angina [17]. Of note, to date, only empagliflozin has been demonstrated to improve outcomes in patients with HFpEF [38]. Nevertheless, most of the patients with HFpEF have hypertension and atrial fibrillation; these patients are also on ACE-I/ARBs and beta-blockers. In a large randomized controlled study involving 4822 patients with HFpEF, it was reported that 86% of the patients were on ACE-I/ARBs, and 80% of them were on beta-blockers [39]. In our study, we think that the rate of use of ACE-I/ARBs and beta-blockers was similar in all three HF phenotypes due to other compelling cardiovascular indications. MRAs are recommended for all patients with HFrEF to reduce mortality [40, 41], but MRAs do not have clear-cut indications for patients with HFpEF and HFmrEF. Consistent with these findings, the use of MRAs was found to be significantly higher in patients with HFrEF in our study. However, only 52.9% of the patients with HFrEF were on MRAs; this ratio was 55.4% in the ATA study [35]. In the light of these data, it should be aimed to increase the use of RAS inhibitors and MRAs in patients with HFrEF unless severe renal dysfunction, symptomatic hypotension and hyperkalemia. In the Hit-Point trial, the clinical benefits of enhanced HF education with a telephone follow-up program were demonstrated in patients with HFrEF [42]. Therefore, these patients should be monitored more closely to improve patient compliance and optimize medical therapy.

Limitations

First, our study has a small sample size. In addition, the patients were recruited only from cardiology clinics, and we did not consider patients with chronic HF examined by other physicians such as internists. Since echocardiography was administered during routine outpatient practice, it was limited to assessing cardiac functions and structure. Detailed echocardiography and hemodynamic assessment were not part of the evaluation of these patients in the majority of the cases. Due to the multicenter nature of our study, standardization could not be made for LVEF measurement. Some patients with LVEF values, especially close to the cutoff values, may have been misclassified due to the differences between the performing physicians.

CONCLUSION

Our study presented the baseline characteristics of patients with HF in our country. It was determined that there were significant differences in patients with dif-

ferent HF phenotypes in terms of BMI, gender, frequency of having ischemic etiology, hypertension, and atrial fibrillation. Treatment approaches were generally in accordance with the guidelines. In addition, although the rates are low, new treatment approaches recommended in the most recent guidelines seem to enter clinical practice.

Authors' Contribution

Study Conception: BŞ, Ah.Çe., LB, UU, SYT, HG, MK, Al.Ço., BK, NÇ, Ay.Ço., BA, İG, CA, YÖ, MKK, EK, MÖ, TE, NY, MBY; Study Design: BŞ, Ah.Çe., LB, UU, SYT, HG, MK, Al.Ço., BK, NÇ, Ay.Ço., BA, İG, CA, YÖ, MKK, EK, MÖ, TE, NY, MBY; Supervision: BŞ, Ah.Çe., MBY; Funding: N/A; Materials: BŞ, Ah.Çe., LB, UU, SYT, HG, MK, Al.Ço., BK, NÇ, Ay.Ço., MÖ, TE, MBY; Data Collection and/or Processing BŞ, Ah.Çe., LB, UU, SYT, HG, MK, Al.Ço., BK, NÇ, Ay.Ço., MÖ, TE; Statistical Analysis and/or Data Interpretation: BŞ, MBY; Literature Review: BŞ, MBY; Manuscript Preparation: BŞ, MBY and Critical Review: BŞ, Ah.Çe., LB, UU, SYT, HG, MK, Al.Ço., BK, NÇ, Ay.Ço., BA, İG, CA, YÖ, MKK, EK, MÖ, TE, NY, MBY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The association between triglycerides/high-density lipoprotein cholesterol ratio, insulin resistance and serum androgen levels in patients with polycystic ovary syndrome

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ABSTRACT

Objectives: Insulin resistance and dyslipidemia are common comorbidities of polycystic ovary syndrome. We aim to evaluate the association between triglycerides/high-density lipoprotein cholesterol ratio, insulin resistance, and serum androgen levels in patients with polycystic ovary syndrome.

Methods: We enrolled a total of 40 polycystic ovary syndrome patients and 20 healthy control subjects in this cross-sectional study. The polycystic ovary syndrome patients were divided into two subgroups obese and non-obese. The triglycerides/high-density lipoprotein cholesterol ratio and homeostatic model assessment of insulin resistance were calculated for all individuals. Demographic characteristics, serum levels of metabolic parameters, and androgens were compared between the study subgroups. *P* - value < 0.05 was accepted as statistically significant.

Results: The triglycerides/high-density lipoprotein cholesterol ratio was higher in obese polycystic ovary syndrome patients than in other groups (3.64 ± 3.06 vs. 1.07 ± 0.36 in control and 1.18 ± 0.53 in non-obese group, $p < 0.005$). The triglycerides/high-density lipoprotein cholesterol ratio was positively correlated with homeostatic model assessment of insulin resistance (r = 0.546, $p < 0.001$), total testosterone (r = 0.402, $p = 0.010$), and free androgen index (r = 0.609, $p < 0.001$) while was negatively correlated with sex hormone-binding globulin (r = -0.497, $p = 0.001$). Obese polycystic ovary syndrome patients had higher serum total testosterone levels, higher free androgen index, and lower sex hormone-binding globulin than non-obese polycystic ovary syndrome patients (0.71 ± 0.49 ng/mL vs. 0.45 ± 0.16 ng/mL, $p = 0.006$; 3.1 ± 1.91 vs. 1.01 ± 0.49, $p < 0.005$; and 26 ± 10.3 nmol/L vs. 59.6 ± 43.7 nmol/L, $p < 0.005$, respectively). Obese polycystic ovary syndrome patients had also worse lipid parameters, including high triglycerides and low high-density cholesterol when compared with other groups.

Conclusions: The triglycerides/high-density lipoprotein cholesterol ratio was correlated with the homeostatic model assessment of insulin resistance, and androgenic hormonal profiles including total testosterone and free androgen index in patients with polycystic ovary syndrome.

Keywords: Insulin resistance, TG/HDL-C ratio, hyperandrogenism, obesity, polycystic ovary syndrome

Polycystic Ovary Syndrome (PCOS) is a common metabolic disease. The Rotterdam criteria including clinical and/or biochemical findings of hyperandrogenism, oligomenorrhea or oligo-ovulation, and/or

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existence of polycystic ovaries on ultrasound are commonly used to diagnose patients with PCOS. The presence of at least two criteria is essential for the diagnosis [1].

Patients with PCOS have an increased risk for the development of type 2 diabetes mellitus (T2DM) and cardiovascular events due to concurrent insulin resistance (IR). Also, dyslipidemia and metabolic syndrome are more often seen in PCOS patients with IR than those without IR [2]. IR has been detected in most patients with PCOS beyond that predicted by their body mass index (BMI). In contrast, PCOS per se has been shown to confer a risk of IR [3]. Although definitive pathogenic mechanisms are currently not clear, IR and hyperinsulinism play a contributory role in the pathogenesis of hyperandrogenism [4]. An expert panel by clinicians recommended screening glucose intolerance in PCOS patients [5]. In the light of all this information, investigation of insulin resistance in addition to screening fasting lipid profiles, measurement of blood pressure, and determination of body mass index (BMI) may contribute to the determination of initial cardiovascular risk in these patients. Currently, there are no validated methods for indicating IR in daily practice. There are several complicated, expensive, and time-consuming diagnostic tests and methods such as the euglycaemic hyperinsulinaemic clamp technique. Homeostatic model assessment of insulin resistance (HOMA-IR) has a lower cost and is more practical [6]. Practical measurements that evaluate simultaneously IR and cardiovascular risk are essential for PCOS patients. Hyperlipidemia related to IR presents with high levels of triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) in addition to lower high-density lipoprotein cholesterol (HDL-C) levels. Nur Zati Iwani *et al*. [7] showed a great sensitivity of the TG/HDL-C ratio in diagnosing metabolic syndrome and in the determination of IR and cardiometabolic risk in obese children. Although few studies suggested the association between the TG/HDL-C ratio and IR in PCOS patients, the knowledge does not gain yet a clear recommendation for clinical practice [8]. Therefore, we aimed to evaluate TG/HDL-C ratio in Turkish PCOS patients as a predictor of IR, and its relationship with serum androgen levels. We hypothesized to obtain a practical formula from lipid parameters that are available in daily practice.

METHODS

We enrolled a total of 40 PCOS patients who fulfilled the 2004 revised Rotterdam Criteria in this cross-sectional study [10]. The PCOS patients were divided into two subgroups obese and non-obese. Patients with at least two of the subsequent criteria were accepted as PCOS; (i) oligo- or anovulation, (ii) clinical and/or biochemical hyperandrogenism, (iii) polycystic ovaries. Polycystic ovarian morphology was confirmed via ultrasound. Twenty healthy subjects with no symptoms of hirsutism, oligo-anovulation, or infertility were enrolled in the control group. Serum androgen levels were normal, and there were no pathological hyperandrogenemia signs on physical examination. The control group was selected from individuals examined by the same physician in the same time frame, not affecting the examination, especially the Ferriman-Gallwey Score (FGS) [11]. The non-obese PCOS patients and healthy controls were matched in terms of anthropometric measurements such as BMI. The detailed medical history (menstrual order, infertility, hirsutism) and systemic examination notes of all patients were examined. The exclusion criteria were also set as being pregnant and/or postmenopausal woman, having an incomplete diagnosis, using hormone preparations such as oral contraceptive drugs within the last six months, or having any concomitant confounding endocrinological diseases such as hypothyroidism, T2DM, and dyslipidemia, or systemic disorders such as coronary artery disease, renal or hepatic insufficiency or tumors of the pituitary, ovary or adrenal glands. The study was performed by following the local Ethics Committee approval and the Helsinki Declaration. All participants approved a written- and informed- consent form.

For physical measurements, height, weight, and BMI were measured. The waist circumference (WC), hip circumference (HC), and waist-to-hip ratio (WHR) were calculated for anthropometric measurements. Bodyweight was measured on a scale without shoes and extra clothing. BMI was calculated as the bodyweight (in kilograms) divided by the height (in meters) squared. BMI of at least 30 kg/m^2 was determined as the cut-off for obesity [9]. The midpoint between the lower border of the rib cage and the iliac crest was determined for the measurement of the waist circumference. For the hip circumference, the maximum

diameter over the buttocks was measured with a measuring tape according to the WHO Guidelines [12, 13]. Blood samples for levels of serum gonadotropins were taken from the patients between the second and fourth days of the menstrual cycle between 08 a.m. and 10 a.m. For amenorrheic patients with PCOS, they were prescribed oral medroxyprogesterone acetate 5 mg, once a day for five days. After the initiation of the menstrual cycle, the blood samples were taken as above-mentioned. Blood samples that investigate serum levels of glucose, insulin, and lipid profile were also collected after eight-hour overnight fasting. TG/HDL-C and HOMA-IR were calculated for all individuals. The following formula 'fasting glucose (mg/dL)×fasting insulin (μU/mL)/405' was used to calculate HOMA-IR [14].

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS version 21.0 (SPSS Inc.) software. Categorical variables were compared with the Chi-square test. The Student's t-test and One-way ANOVA and Tukey post hoc HSD tests were used for the analysis of independent, normally distributed parametric variables, and the Mann-Whitney U test with Bonferroni correction and the Kruskal-Wallis test were used for the analysis of numerical variables not normally distributed. Spearman's correlation coefficients were calculated to assess the associations between variables. Data were expressed as mean ± standard deviation (SD), median, minimum and maximum values or number (n), and percentage (%) as appropriate. A value of $p < 0.05$ was considered statistically significant. In correlation comparisons where each group was evaluated separately, it was evaluated with Bonferroni correction ($p = 0.05/3 = 0.0167$).

RESULTS

The mean age was 26.7 ± 7.5 years among 40 patients with PCOS while 28.1 ± 4.4 years among healthy controls. The demographic and anthropometric measurements of all the study subjects are shown in Table 1. There was no difference between the healthy group and the non-obese patient groups in terms of height, weight, WC, and BMI. Hirsutism was more prominent in PCOS patients compared to the healthy control subjects, and there was no difference between the obese and non-obese PCOS groups [FGS: 15.8 ± 6.61 (in non-obese PCOS), FGS: 17.30 ± 4.92 (in obese PCOS); $p > 0.05$]. Comparisons were made of hormonal parameters. The serum androgen levels are given in Table 2. Obese PCOS patients had higher serum total testosterone levels, higher free androgen index, and lower sex hormone-binding globulin than non-obese PCOS patients (0.71 ± 0.49 ng/mL vs. 0.45 ± 0.16 ng/mL, $p = 0.006$; 3.1 ± 1.91 vs. 1.01 ± 0.49, $p < 0.005$; and 26 ± 10.3 nmol/L vs. 59.6 ± 43.7 nmol/L, $p < 0.005$, respectively). Non-obese PCOS patients

Table 1. Comparisons of demographic and anthropometric measurements of patients according to the groups

	Control group (n = 20)	Non-obese PCOS group (n = 20)	Obese PCOS group (n = 20)	*p* value
Age (years)	28.10 ± 4.48	23.10 ± 5.60	30.40 ± 7.60	< 0.005[1,3]
Height (cm)	161.10 ± 7.67	163.20 ± 5.25	161.40 ± 6.31	0.038[2]
Weight (kg)	61.40 ± 7.72	58.60 ± 8.17	95.00 ± 12.35	< 0.005[2,3]
BMI (kg/m^2)	21.80 ± 2.64	21.70 ± 3.04	36.10 ± 4.24	< 0.005[2,3]
WC (cm)	74.10 ± 5.43	71.00 ± 4.97	99.50 ± 10.30	< 0.005[2,3]
WHR	0.77 ± 0.03	0.75 ± 0.02	0.84 ± 0.04	< 0.05[1,2,3]
Ferriman Gallwey Score	2.85 ± 1.18	15.8 ± 6.61	17.30 ± 4.92	< 0.005[1,2]

Data are shown as mean ± standard deviation. PCOS = polycystic ovary syndrome, BMI = body mass index, WC = waist circumference, WHR = waist-hip ratio, FGS = Ferriman Gallwey score

p^1 = Comparison of the control group and non-obese PCOS group

p^2 = Comparison of the control group and obese PCOS group

p^3 = Comparison of obese and non-obese PCOS groups

Table 2. Comparisons of hormonal and biochemical data of the patients according to the groups

	Control group (n = 20)	Non-obese PCOS group (n = 20)	Obese PCOS group (n = 20)	*p* value
Total testosterone (ng/mL)	0.29 ± 0.08	0.45 ± 0.16	0.71 ± 0.49	**< 0.005**[1,2,3]
Sex hormone binding globülin (nmol/L)	55.20 ± 31.10	59.60 ± 43.70	26.00 ± 10.30	**< 0.005**[2,3]
Free androgen index	0.62 ± 0.28	1.01 ± 0.49	3.10 ± 1.91	**< 0.05**[1,2,3]
Androstenedione (ng/mL)	1.96 ± 0.64	3.73 ± 1.41	4.20 ± 1.71	**< 0.005**[1,2]
Dehydroepiandrosterone-sulfate (µg/dL)	261.40 ± 111.70	360.40 ± 143.70	348.40 ± 107.00	**<0.005**[1,2]
Follicular stimulating hormone (mIU/mL)	5.98 ±5.36	4.28 ± 3.61	6.62 ± 6.95	**0.049**[3]
Luteinizing hormone (mIU/mL)	6.25 ± 7.90	9.57 ± 18.61	8.20 ± 5.30	**0.03**[2]
Fasting plasma glucose (mg/dL)	71.60 ± 12.55	83.30 ± 4.69	88.30 ± 8.29	**< 0.05**[1,2,3]
Fasting plasma insulin (mIU/L)	7.06 ± 2.39	8.01 ± 1.57	16.6 0± 7.65	**< 0.005**[2,3]
Aspartate transaminase (IU/L)	17.20 ± 2.30	16.40 ± 3.20	18.30 ± 4.90	**0.723**
Alanine transaminase (IU/L)	14.30 ± 6.50	12.70 ± 6.70	21.80 ± 8.20	**< 0.005**[2,3]
Triglyceride (mg/dL)	64.60 ± 20.80	67.40 ± 25.70	150.20 ± 99.70	**< 0.005**[2,3]
Low-density lipoprotein cholesterol (mg/dL)	95.40 ± 20.30	103.00 ± 28.30	129.50 ± 36.90	**< 0.05**[2,3]
High-density lipoprotein cholesterol (mg/dL)	60.50 ± 9.70	58.80 ± 11.10	44.10 ± 9.70	**< 0.005**[2,3]
TG/HDL-C	1.07 ± 0.36	1.18 ± 0.53	3.64 ± 3.06	**< 0.005**[2,3]
HOMA-IR	1.24 ± 0.49	1.62 ± 0.35	3.59 ± 1.62	**< 0.005**[1,2,3]

PCOS = polycystic ovary syndrome, TG/HDL-C ratio = triglycerides: high-density lipoprotein-cholesterol ratio, HOMA-IR = homeostatic model assessment insulin resistance

p^1 = Comparison of control group and non-obese PCOS group

p^2 = Comparison of control group and obese PCOS group

p^3= Comparison of obese and non-obese PCOS groups

had higher free androgen index, androstenedione and DHEAS levels than the healthy control group (1.01 ± 0.49, p =0.012; 3.73 ± 1.41, $p < 0.005$; 360.4 ± 143.7, $p = 0.028$).

When the groups were evaluated in terms of laboratory data, LDL-C and triglyceride levels were significantly higher, and HDL-C levels were significantly lower in the obese PCOS group when compared to the other two groups (Table 2). While there were no differences in aspartate transaminase (AST) levels between groups, serum ALT levels were higher in the obese PCOS group than in the other two groups. (21.8 ± 8.2 IU/L, $p < 0.005$). The TG: HDL-C ratio and HOMA-IR values were significantly higher in obese patients with PCOS than non-obese PCOS patients (3.64 ± 3.06 vs. 1.18 ± 0.53, $p < 0.005$ and 3.59 ± 1.62 vs. 1.62 ± 0.35, p < 0.005; respectively).

In addition, non-obese PCOS patients had significantly higher serum fasting glucose and HOMA-IR than healthy individuals (83.3 ± 4.69, $p < 0.005$; 1.62 ± 0.35, $p < 0.005$, respectively). When all the patients were evaluated, according to the results of correlation analysis, the TG/HDL-C ratio was positively correlated with HOMA-IR (r = 0.546, $p < 0.001$), total testosterone (r = 0.402, p = 0.010), and FAI (r = 0.609, $p < 0.001$) while was negatively correlated with sex hormone-binding globulin (r = -0.497, $p = 0.001$) (Table 3). We detected no significant correlation when each group was separately examined.

Table 3. Correlation between hormonal parameters and the TG/HDL-C ratio in the patients

	All obese and non-obese patients with PCOS		Obese PCOS		Non-obese PCOS		Healthy controls	
TG/HDL-C	**r**	***p* value**	**r**	***p* value**	**r**	***p* value**	**r**	***p* value**
HOMA-IR	0.546	**< 0.001**	0.064	0.787	0.099	0.676	0.193	0.416
Total testosterone	0.402	**0.010**	0.098	0.682	0.148	0.533	0.077	0.746
Sex hormone-binding globulin	-0.497	**0.001**	-0.046	0.846	-0.207	0.381	0.226	0.338
Free androgen index	0.609	**< 0.001**	0.059	0.806	0.344	0.138	-0.071	0.767
Dehydroepiandrosterone	0.161	0.321	-0.129	0.589	0.461	0.041	-0.015	0.950
Androstenedione	0.122	0.452	0.091	0.703	-0.081	0.735	-0.318	0.172

HOMA-IR = homeostatic model assessment insulin resistance, TG/HDL-C ratio = triglycerides: high-density lipoprotein-cholesterol ratio. Spearman's rho correlation coefficient with Bonferroni correction ($p = 0.05/3=0.0167$).

DISCUSSION

Obesity and IR are well-known risk factors contributing to the complex pathophysiological mechanisms in PCOS. A vast majority of patients with PCOS (40-88%) are overweight/obese and insulin-resistant [15]. IR is an insufficient glucose response to insulin and is often diagnosed with clinical manifestations, including T2DM and metabolic syndrome [16]. There is a need for a reliable, practical, valid parameter that can indicate IR. HOMA-IR is a commonly used tool for IR. The analysis of serum fasting insulin is not possible and practical in every health center to calculate HOMA-IR. Also, no clear cut-off value has been established for HOMA-IR. The euglycemic clamp technique is another reported method performed in specialized centers but is also impractical for routine use [17]. Both of the-mentioned methods have not been placed for routine clinical use in detecting IR because of limitations related to cost, reliability and standardization. Mc Laughlin *et al*. [18] showed that a TG/HDL-C ratio of at least 3 was more diagnostic than TG or insulin levels alone in determining IR in overweight patients. The number of 1.8 in SI units (3.0 in traditional units) was reported as a cut-off point for TG/HDL-C (with a sensitivity and specificity; 57%, and 71% respectively). Song do *et al*. [19] recommended OGTT for Korean women with PCOS with TG/HDL-C ratio > 2.5, and this cut-off was calculated as a predictor of IR. Greenwood and Huddleston [20] showed that the cut-off value of 2.64 had a sensitivity of 87% and a specificity of 75% for diagnosing metabolic syndrome in PCOS patients. The mean TG/HDL-C ratio was 3.64 in obese PCOS patients in our study. We noticed again that the TG/HDL-C ratio was positively correlated with HOMA-IR in our population despite this correlation may be explained by the presence of obesity alone. The TG/HDL-C ratio was similar between non-obese PCOS patients and healthy controls. These results may have been also affected by the low patient numbers in each group and the patient characteristics.

The average BMI, WC, and WHR, were similar in the non-obese PCOS patient and the healthy control groups. Ovesen *et al*. [21] found no difference in IR in non-obese PCOS patients compared to an age and weight-matched control group. Although the TG/HDL-C ratio was similar between the two subgroups, non-obese PCOS patients had higher HOMA-IR values than the control group without a statistical significance. It is possible to say that HOMA-IR can detect IR earlier than the TG/HDL-C. This condition may be explained by increased levels of serum fasting insulin before dyslipidemia occurs.

There are many complex pathogenetic pathways in the underlying mechanism of hyperandrogenism and IR. Higher levels of different androgens may contribute to IR or vice versa. It is well-known that patients with hyperinsulinemia have marked hyperandrogenemia [22]. Excess insulin levels reduce hepatic sex hormone-binding globulin and increase ovarian androgen production via stimulation of ovar-

ian insulin growth factor-1 receptors in the presence of the adequate luteinizing hormone [23]. As a result, IR and obesity aggravate hyperandrogenism's clinical and laboratory findings, and losing weight reduces androgen levels in patients [24]. Nevertheless, hyperandrogenemia has a negligible effect on IR [25]. Holte *et al*. [26] reported that the body fat ratio had been shown to worsen hyperandrogenism findings in women with PCOS, regardless of BMI. According to that cross-sectional study, obese PCOS patients with a higher body fat ratio also have a higher free androgen index, higher total testosterone, and lower SHBG [26]. The conclusion drawn from our study is also that obese PCOS patients had higher total testosterone levels, higher FGS, and higher TG/HDL-C ratio values than non-obese PCOS patients and healthy control subjects.TG/HDL-C ratio was positively correlated with serum androgen levels and free androgen index, and negatively correlated with SHBG. Previous studies have indicated that SHBG can be used as a marker of IR [27]. The SHBG values were lower in obese PCOS patients than in the other groups. This condition might be a causative factor for more severe hirsutism and hyperandrogenism findings. Ain *et al*. [28] also investigated the TG/HDL-C ratio in a study of 350 participants without comorbidity or chronic illness. The TG/HDL-C ratio was correlated with carotid intimal thickness. They noticed that TG/HDL-C ratio can be used as an early predictor of cardiometabolic events. TG/HDL-C ratio was also shown as an indicator of atherosclerotic risk, even in chronic inflammatory diseases such as ankylosing spondylitis and familial Mediterranean fever [29].

Limitations

The limitations of the study were as follows: A major limitation of the study was the evaluation of IR with HOMA-IR. Secondly, the sample size was limited. More patients are needed to determine a specific cut-off value for the TG/HDL-C ratio and compare non-obese PCOS and healthy control subjects. Another limitation was that it was a cross-sectional study in which causal relationships cannot be evaluated. However, determination of the TG/HDL-C ratio in patients with PCOS can be used as a good predictor as a surrogate marker for IR and cardiometabolic risk. The assessment of the FGS was performed only by one of the researchers at one time was another limitation preventing determining intra- and inter-observer variations.

CONCLUSION

This study demonstrated a higher TG/HDL-C ratio and IR in obese PCOS patients. The TG/HDL-C ratio was also correlated with hyperandrogenism and HOMA-IR in PCOS patients. The TG/HDL-C ratio is easily calculated from the lipid parameters, and it may be practical to use TG/HDL-C ratio to predict IR in PCOS patients.

Authors' Contribution

Study Conception: ÖÖG, SC; Study Design: ÖÖG, SC, FV; Supervision: ÖÖG, SC, FV; Funding: ÖÖG, SC, FV; Materials: ÖÖG, SC, FV; Data Collection and/or Processing: ÖÖG, SC, FV; Statistical Analysis and/or Data Interpretation: ÖÖG, SC, FV; Literature Review: ÖÖG, SC; Manuscript Preparation: ÖÖG, SC, FV and Critical Review: ÖÖG, SC.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(2):282-289 Original Article

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The relationship between upper extremity pain and ultrasound use in perinatologist

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ABSTRACT

Objectives: To examine the relationship between upper extremity problems and the performance of abdominal sonography to provide an understanding of the prevalence of upper extremity pain among perinatologist.

Methods: This study was conducted as a prospective trial between June-August 2020. The online questionnaire prepared by the researchers was completed by volunteer perinatologists. It included topics such as age, gender, years of perinatology specialist experience, average number of patients per week, minutes each patient's examination lasted and other demographic data is performed. Perinatologists with upper extremity pain were assigned to group 1. Group 2 comprised those who had no upper extremity pain. Patients in group 1 were divided into two subgroups according to pain intensity. All data were compared between groups.

Results: Overall, 115 perinatologists participated in this research. Of all participants, 82 (71.3%) had upper extremity pain, and 33 (28.7%) had no upper extremity pain. No significant relationship was observed for age, gender, average number of ultrasound examinations per day, or time allotted for each patient's examination between group 1 and 2. Providers performed perinatology services for 5 years (range: 1-23 years) in subgroup 1A and for 7 years (range: 1-23 years) in subgroup 1B ($p = 0.02$).

Conclusions: Upper extremity pain caused by intensive ultrasound use is common in perinatologists; as the years in the profession increase, the frequency and severity of these pains may increase.

Keywords: Upper extremity, pain, ultrasound, perinatologist

Musculoskeletal diseases are important causes of morbidity and disability, and the treatment of these diseases represents one of the most important health challenges in the world [1, 2]. In particular, upper extremity pain (at the shoulder, arm, elbow, forearm, wrist, and hand) frequently develops, especially in some professions and office environments [3]. In recent years, publications have increasingly shown that high job stress and demands are positively associated with symptoms and disorders in all upper extremity regions [4, 5]. When we look at the literature, work-related musculoskeletal disorders, overuse syndrome, work-related upper extremity disorders (WRULD), repetitive strain injuries (RSI), musculoskeletal injury (MSI), and cumulative trauma disorder (CTD) are common terms [6]. Pain due to use relates to several risk factors, including medical conditions, biomechanical exposures, work organization factors, work demands, and individual psychosocial variables [7].

In the United States, 81% of sonographers have scanned in pain for half of their careers, and 20% of

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those sonographers will have a career-ending injury with resultant compensation claims [8]. Common musculoskeletal disorders caused by repeated ultrasound use include rotator cuff tendinitis, epicondylitis, carpal tunnel syndrome, hand-wrist tendinitis, and neck and back pain [8]. These complaints subsequently lead to decreased work efficiency, reduced quality of the health service, and psychological damage.

Ultrasonographers in Turkey is not included in the health system. Obstetric ultrasonography is performed by perinatologists, obstetricians, and radiologists. In Turkey, perinatologists spend most of their working hours using ultrasound during patient examination and actively use their upper extremities during the examination. Perinatologists usually sit or stand next to the patient during the examination and constantly use their abdominal semilunar transducers. Fetal anatomical scanning and fetal echocardiography examination represent valuable tools to detect congenital anomalies. To more ideally perform the ultrasound evaluation, perinatologists may need to force their extremities into unusual angles to accommodate maternal and fetal positions. Perinatologists actively use both upper extremities to wield the ultrasound probe and intervention materials for some invasive procedures. As technology becomes more advanced, the level of knowledge and the need for these procedures increase, so new studies are becoming more common worldwide.

In our clinical practice, we observed that upper extremity-related pathologies are common among perinatologists. From this observation, we decided to conduct a study to examine the relationship between upper extremity problems and the performance of abdominal sonography to provide an understanding of the prevalence of upper extremity pain among these physicians.

METHODS

This study was conducted as a prospective trial between June 2020 and August 2020. The online questionnaire prepared by the researchers was completed by volunteer perinatologists who participated. The study protocol was approved by the hospital's ethics committee and was registered with clinicaltrials.gov (NCT04477135). Signed informed consent was obtained from all participants before the start of the study.

Our study group consisted of perinatologists who work as subspecialists in perinatology in Turkey. Perinatologists who completed the questionnaire completely and were actively treating patients were included in the study. Perinatologists who had upper extremity discomfort before perinatology training, who received medical treatment for this reason, or who underwent an operation were excluded from the study. In Turkey, perinatology is positioned as a subbranch of gynecology and obstetrics. Gynecologists and obstetricians are entitled to become perinatology specialists after three years of perinatology training.

The questionnaire form included topics such as age, gender, years of perinatology specialist experience, average number of patients per week, minutes each patient's examination lasted, dominant hand, hand used to perform the ultrasound, and side of the patient from which the examination is performed. In addition to questions about demographic data, the following items were included in the questionnaire: Have you experienced upper extremity pain after starting perinatology? Have you had a radiological examination for this problem? Have you been diagnosed with a disease or any treatment you received? If there is pain, what are the frequency (every day, a few days a week, a few days a month, a few days a year) and the severity (rate it from 1 to 10)? Do you have neck pain? Have you been diagnosed with upper limb impingement syndrome? Do you do sports?

Statistical Analysis

SPSS 20 (IBM Corp. released 2011. IBM SPSS Statistics for Windows, version 20.0, Armonk, NY: IBM Corp.) was used to evaluate the data. The data were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's tests) to determine their normal distribution. Differences between groups were evaluated using Student's t-test for parametric data and the Mann–Whitney U-test for non-parametric data. Relationships between categorical variables were analyzed using a chi-squared test. Bivariate correlations were investigated using Spearman's correlation analysis. A p - value < 0.05 was considered to indicate statistical significance.

RESULTS

Overall, 115 perinatologists participated in this research. When the whole sample was evaluated, 48.6% (n = 56) of the participants were women, and 51.4% (n = 59) were men. Of all participants, 82 (71.3%) had upper extremity pain, and 33 (28.7%) had no upper extremity pain. In our study population, perinatologists with upper extremity pain were assigned to group 1. Group 2 comprised those who had no upper extremity pain. Patients in group 1 were divided into two subgroups according to pain intensity. The upper extremity pain intensity of the patients in subgroup A was four or less, and the pain intensity of the patients in subgroup B was five or greater.

A comparison of the demographic and occupational characteristics of perinatologists with and without upper extremity pain is provided in Table 1. Participants in group 1 were perinatologists for six years (range, 1-23 years); those in group 2 offered perinatology services for four years (range, 1-8 years; $p = 0.01$). Eighty perinatologists (97.6%) in group 1 had dominant right hands compared with 33 (100%) in group 2 ($p < 0.001$). The right hand was used to hold the ultrasound probe for 78 providers (95.1%) in group 1 and 30 providers (90.9%) in group 2 ($p < 0.001$). Eighty-two perinatologists (100%) performed ultrasounds from the right side in group 1 compared with 30 (90.9%) in group 2 ($p < 0.001$). No significant relationship was observed for age, gender, the average number of ultrasound examinations per day, or time allotted for each patient's examination between the two

Table 1. Demographic and occupational characteristics of perinatologists with and without upper extremity pain

	Total cohort (n = 115)	Upper extremity pain present (n = 82)	Upper extremity pain absent (n =33)	*p* value
Age (years)	40 (29-65)	39.5 (29-53)	41 (31-65)	0.102[a]
Number of years performing as a perinatologist	6 (1-23)	6 (1-23)	4 (1-8)	**0.01**[a]
Gender, n (%)				0.780[b]
Female	56 (48.7)	46 (56.1)	10 (30.3)	
Male	59 (51.3)	36 (43.9)	23 (69.7)	
Distribution of ultrasound examination per week	100 (5-1000)	100 (5-1000)	80 (30-150)	0.184[a]
Time allotted for each patient's examination (min)	16 (5-40)	20 (5-40)	15 (5-30)	0.198[a]
Dominant hand, n (%)				**< 0.001**[b]
Right	113 (98.3)	80 (97.6)	33 (100)	
Left	2 (1.7)	2 (2.4)	0	
Hand holding the ultrasound probe, n (%)				**< 0.001**[b]
Right	108 (93.9)	78 (95.1)	30 (90.9)	
Left	7 (6.1)	4 (4.9)	3 (9.1)	
Side that the perinatologist perform ultrasound, n (%)				**< 0.001**[b]
Right	112 (97.4)	82 (100)	30 (90.9)	
Left	3 (2.6)	0	3 (9.1)	

Data are presented as median (minimum-maximum) or n (%).

[a]Mann-Whitney U test

[b]Chi-square test

Table 2. Distribution the investigated parameters among the perinatologists experiencing upper extremity pain

Parameters	Data
Radiological imaging, n (%)	
Yes	12 (14.6)
No	70 (85.4)
Medical treatment, n (%)	
Yes	20 (24.4)
No	62 (75.6)
Pain intensity (number ±SD)	4.73 ± 1.58
Frequency of pain, n (%)	
Every day	10 (12.2)
A few days per week	22 (26.8)
A few days per month	44 (53.7)
A few days per year	6 (7.3)
Work interruption, n (%)	
Yes	10 (12.2)
No	72 (87.8)
Nerve impingement syndrome, n (%)	
Yes	14 (17.1)
No	68 (82.9)
Neck pain, n (%)	
Yes	52 (63.4)
No	30 (36.6)
Sport, n (%)	
Yes	30 (36.6)
No	52 (63.4)

Data are presented as mean ± SD or n (%).

groups.

Table 2 summarizes the distribution of the investigated parameters among the perinatologists experiencing upper extremity pain. Seventy percent of participants with upper extremity pain did not have an examination, and 75.6% did not receive any treatment. The mean pain severity, ranked from a maximum severity value of 8, was 4.73 ± 1.58. Overall, 12.2% of perinatologists with upper extremity pain noted pain every day; 26.8%, a few days a week; 53.7%, a few days a month; and 7.3%, a few days a year. Only ten perinatologists (12.2%) had to take a break because of pain; 52 (63.4%) participants reported neck pain as well. In addition, 85.7% of orthopedics with LBP practiced sports.

Perinatologists with upper extremity pain were divided into subgroups according to pain severity and evaluated (Table 3). The mean age was 37.82 ± 4.7 years in group 1A and was 39.61 ± 4.9 years in group 1B (p = 0.098). Providers performed perinatology services for 5 years (range, 1-23) in subgroup 1A and for 7 years (range, 1-23) in subgroup 1B (p = 0.02). In group 1A, two perinatologists (5%) reported pain every day, and eight (20%) reported pain a few days a week. In group 1B, eight (19%) reported daily pain, and 14 (33.3%) reported pain a few days a week (p <

Table 3. Demographic and occupational characteristics of perinatologists through the upper extremity pain intensity

	The upper extremity pain intensity 4 or less (n = 40)	The upper extremity pain intensity 5 and above (n = 42)	*p* value
Age (years) (mean ± SD)	37.82 ± 4.7	39.61 ± 4.9	0.098 [c]
Number of years performing as a perinatologist (years)	5 (1-23)	7 (1-23)	**0.02** [a]
Distribution of ultrasound examination per week	120 (5-1000)	100 (25-350)	0.126 [a]
Time allotted for each patient's examination (min)	18 (10-40)	20 (5-40)	0.181 [a]
Frequency of upper extremity pain, n (%)			**< 0.001** [b]
Every day	2 (5)	8 (19)	
A few days per week	8 (20)	14 (33.3)	
A few days per month	26 (65)	18 (42.9)	
A few days per year	4 (10)	2 (4.8)	
Gender, n (%)			0.269 [b]
Female	24 (60)	22 (52.4)	
Male	16 (40)	20 (47.6)	
Sport, n (%)			0.534 [b]
Yes	16 (40)	14 (33.3)	
No	24 (60)	28 (66.7)	

Data presented as median (minimum-maximum), n (%) or mean ± SD.
[a]Mann-Whitney U test
[b]Chi-square test
[c]Student T test

Table 4. Correlation of (age, number of years performing as a perinatologist, average number of ultrasound examination per day, time allotted for each patient's examination, spor) some parameters and upper extremity pain

	Upper extremity pain	
	R	*p*
Age	-0.153	0.102
Number of years performing as a perinatologist	**0.320**	**< 0.001**
Average number of ultrasound examination per week	0.124	0.185
Time allotted for each patient's examination	0.120	0.200
Sport	-0.137	0.143

P value < 0.05 was statistically significant.

0.001). No other parameters differed significantly between the two groups. As shown in Table 4, the number of years performing as a perinatologist was weakly associated with upper extremity pain.

DISCUSSION

The results of this study were obtained from an online survey of physicians working as perinatologists in Turkey. According to the results of this study, 71% of perinatologists have upper extremity pain, and this pain is often accompanied by neck pain. Participants with pain have been working as perinatologists for many years, and most do not play sports. Perinatologists with pain severity of 5 or more were older. In addition, people who worked as perinatologists for long periods had pain every day or a few days a week.

Upper extremity and neck pain can be caused by many reasons related to the use of ultrasound (e.g., posture disorder, use of ultrasound without warming movements, wrong probe grip). Repetitive strain injury may actually be the upper headline for ultrasound use and subsequent upper extremity pain [8]. Burnage [9] emphasized that inadequate preparation may cause muscle injury. In a study of Swedish dental personnel by Lindegard *et al*. [10], the prevalence of neck/shoulder pain was 56%. Simonsen *et al*. [11] reported a 61% pain prevalence for beginning sonographers-higher than the existing literature. In addition, among sonographers who did not report neck/shoulder pain at baseline, 35% did so at follow-up after 2.5 years. In our study, the results were similar to the existing literature: 71% of perinatologists who participated had upper extremity pain. However, we focused on a group with ultrasound experience. The use of ultrasonography has a wide place in obstetrics education. Therefore, we can say that the prevalence of pain related to ultrasound use was higher in our study than in the literature. A survey of Canadian and American sonographers (n = 1,621) reported pain or discomfort in the neck (74%), shoulder (76%), upper back (58%), upper arm (38%), forearm (31%), wrist (59%), and hand/fingers (55%) [12]. Unfortunately, because we did not classify locations of upper extremity pain in our study, we cannot mention specific regions.

In a study involving participants from different professions, the number of years that the operator spent scanning did not result in significant pain differences [8]. However, the study demonstrated a positive correlation between the prevalence of symptoms experienced and the number of days worked in ultrasound per week. In our study, participants with upper extremity pain had been working as subspecialists for a longer time than participants without pain. Perinatologists only perform high-risk pregnancy examinations and examine each patient with an abdominal ultrasound. Obstetricians may not be negatively affected by the use of abdominal ultrasounds, as they also perform gynecological ultrasounds and operations. That is, general gynecologists and obstetricians work in different positions during the day, unlike perinatologists, who constantly work in the same position. The variety of work positions may create a natural break. Therefore, we believe that perinatologists are a more accurate population than other branches to explore the relationship between abdominal ultrasound use and upper extremity pain.

In our study, the distribution of ultrasound examinations per week and the time allotted for each patient's examination was not statistically associated with the presence of pain. However, the pain was reported more often as these variables increased. If a physician who examines many patients does various warming movements or works with breaks between examinations, or if the physician is holding the probe with a correct posture by sitting in a more comfortable seat, there may be no upper extremity pain. We attributed the weak relationship between the years of working as a perinatologist and the presence of upper extremity pain to this bias ($r = 0.320$, $p < 0.001$). Most perinatologists participating in our study used their right hands and performed ultrasound by standing on the right sides of the patients. The physicians standing on the right sides versus those on the left sides had more upper extremity pain. This result may represent sampling bias because the left-handed cohort was very small. In a similar study, no significant difference was found between right and left-hand use [8].

Unlike other studies, most of the physicians with upper extremity pain did not have any examinations, did not take a break from work, did not receive any medical treatment, and did not experience nerve compression syndrome. We attributed these results to the severity of pain at a tolerable level (4.73 ± 1.58) and to the frequency of most pain a few days a month. No-

tably, 63.4% of the patients with upper extremity pain had neck pain and did not exercise. During the use of ultrasound, pain, stiffness, or contractions may occur over time in the shoulder and neck muscles that work in correlation with the upper extremity. If these symptoms persist, they predispose to neck problems, such as cervical discopathy, cervical flattening, and arthritis. In addition, intensive wrist use can cause entrapment neuropathy, tendonitis, bursitis, and arthritis [12].

When we subgrouped the participants in our study according to pain intensity, we found that the pain intensity of the physicians who were older and who had worked as perinatologists for many years was greater than five and was more frequent. The perception of pain may increase with age, or people's awareness of pain may increase with age. In addition, pain severity is an objective assessment. Limitations of the survey itself include limited validity, errors resulting from non-response, and potential bias by motivation, honesty, and memory.

Among the strengths of the study was the focus on a specific group using ultrasound repeatedly in patients-namely, perinatologists. Many studies have conducted extremity pain and ultrasound, but we found no previous studies questioning the perinatologists' upper extremity pain. Our analysis showed a correlation between the presence of upper extremity pain and the years spent as a perinatologist.

Limitations

Our study has some limitations. First, we had a small number of participants, and breaks between patients were not assessed. Second, our study was not designed to investigate the posture of the participating physician while performing ultrasounds. Physicians whose back, shoulder, arm, and wrist positions were incorrect and who did not take care to use the correct posture while working may have introduced bias into the results. In addition, the type of ultrasound examination performed was not assessed. Some literature emphasizes that ultrasound type is an independent risk factor for joint pain [13]. Because our study was a nationwide survey, it was difficult to determine ultrasound types or standardize a review of the types. Moreover, depictions of own pain are different with each person.

CONCLUSION

Upper extremity pain caused by intensive ultrasound use is common in perinatologists; as the years in the profession increase, the frequency and severity of these pains may increase. In our study, demographic characteristics and patient-based risk factors were not significant in the prevalence of upper extremity pain. In this sense, personal factors, such as exercising with the correct posture, taking breaks at appropriate intervals, adjusting the lighting of the examination room, or doing sports to strengthen the upper extremity muscles, may be more meaningful. As suggested in the book "Work-related Upper Limb Disorder: A Sonographer's Survival Guide," musculoskeletal problems can be prevented by doing some warming movements. More comprehensive studies are needed to clarify the risk factors of upper extremity pain associated with professional ultrasound use in perinatologists to develop prevention strategies and investigate our recommendations' effectiveness.

Authors' Contribution

Study Conception: AEY; Study Design: AEY; Supervision: AEY, FE; Funding: N/A; Materials: N/A; Data Collection and/or Processing: AEY, FE; Statistical Analysis and/or Data Interpretation: AEY; Literature Review: FE; Manuscript Preparation: AEY and Critical Review: FE.

Conflict of interest

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The European Research Journal 2022;8(2):290-295 Original Article

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Management of the early postoperative PCR positive patients in the COVID-19 pandemic: cardiac surgeon's nightmare

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ABSTRACT

Objectives: In the last 2 years with the new type of coronavirus infection (COVID-19) pandemic, it has become inevitable to adapt to this disease in cardiovascular surgery procedures. In this study, we aimed to investigate the effects of the results of respiratory tract samples taken from different places in patients undergoing cardiac surgery on our postoperative patient follow-up procedures and to share our cardiac surgery experiences during the pandemic period.

Methods: A total of 177 patients who underwent cardiac surgery were included in this study. Endobronchial lavage samples were obtained from the intubated patients through the endotracheal tube in the early postoperative period. According to the Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) results obtained in the early postoperative period, the patients were divided into 2 groups as Group 1 for those with negative PCR and Group 2 for those with positive PCR. After that a total of 59 patients who were found to have COVID-19 were divided into 2 groups as survivors and non-survivors.

Results: There were 118 (66.6%) patients in Group 1 and 59 (33.3%) in Group 2. The mean ages of patients in Group 1 and Group 2 were 64.5 ± 9.8 years and 61.9 ± 10.1 years, respectively ($p = 0.174$). Mortality was significantly higher in Group 2 (n = 24, 40.6%) compared Group 1 (n = 2, 1.6%) ($p < 0.001$). After that a total of 59 patients who were found to have COVID-19 were divided into 2 groups as survivors (n = 35, 59.3%) and non-survivors (n = 24, 40.7%). There was no statistically significant difference between the groups in terms of gender, smoking, diabetes mellitus, hypertension, chronic renal failure, chronic obstructive pulmonary diseas rates and surgery types ($p > 0.05$).

Conclusions: The COVID-19 pandemic has significantly affected our cardiovascular surgery practice. In addition to being negative for PCR at least 2 times in routine preoperative preparations, obtaining endobronchial lavage samples for PCR testing from the endotracheal tube in the early postoperative period plays an important role in patient management.

Keywords: COVID-19, cardiac surgery, endobronchial lavage, nasopharyngeal swab, mortality

The new type of coronavirus infection (COVID-19), which emerged in the Wuhan province of China in December 2019, spread very rapidly and affected the whole world. On March 11, 2020, the World Health Organization (WHO) declared that this disease caused a pandemic. In the last 2 years, the world has developed new strategies to combat this disease and has entered into a restructuring in terms of approach

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to the disease.

As in all medical departments, it has become inevitable to adapt to this new situation in cardiovascular surgery procedures. For this purpose, a series of precautions have been taken for cardiac patients, who are reported as one of the most risky groups. First of all, postponing elective cardiac surgical procedures, applying less invasive procedures if the operation cannot be postponed, and performing the operation within a certain algorithm and taking the high surgical risk into account, if the operation is inevitable, constituted the main approach scheme [1-3]. It has been reported that pulmonary complications related to COVID-19, especially in the postoperative period, have very serious consequences for this critically ill population [4-6]. In order to avoid these fatal outcomes, it is recommended to plan the operation by seeing 2 negative Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) results in the preoperative period [7]. Although the reliability of samples taken by nasopharygeal swab (NFS) is high, it has been shown that the positivity rate is different compared to samples taken from the lower respiratory tract [8]. The COVID-19 pandemic had negative effects on the number of surgical procedures and postoperative morbidity and morbidity rates in our cardiovascular surgery clinic.

The aim of this study is to share our experience in patients who underwent cardiac surgery in our heart center, which has been active since the beginning of the pandemic, and to reveal how endobronchial lavage samples taken from the endotracheal tube in the early postoperative period have changed our postoperative patient management procedures.

METHODS

Data Sources

For this study, approval was obtained from the T.C. Ministry of Health General Directorate of Health Services COVID-19 Scientific Research Evaluation Commission and Bursa Yüksek Ihtisas Training and Research Hospital Clinical Research Ethics Committee with the protocol number 2011-KAEK-25 2021/06-06. In this study, which was planned as a single center, patients aged between 38-91 years who underwent open heart surgery in Bursa Yüksek Ihtisas Training and Research Hospital Cardiovascular Surgery clinic between 01/09/2020 and 31/12/2021 were examined. The laboratory values, radiological image data, demographic characteristics, measured vital parameters, applied treatments and clinical outcomes of the patients were recorded at the time of admission to the hospital. According to our hospital protocol, thoracic computed tomography (CT) has been routinely performed in all patients scheduled for open heart surgery since the beginning of the COVID-19 pandemic. For this reason, routine thoracic CT was performed in all patients included in the study. Patients with positive RT-PCR in the preoperative period, patients with pathological images in radiological imaging, emergency operations, redo operations, previous lung malignancy or pneumonia history, pre-operative diagnosis of COVID-19, and patients less than 1 month from the diagnosis of COVID-19 were not included in the study. Patients who were found to have negative RT-PCR test in two consecutive nasopharyngeal swab samples taken from the nasopharyngeal region in the last 48 hours in the preoperative period were included in the study. In addition, endobronchial lavage from the intubation tube and RT-PCR test were performed in all patients within the first 15 minutes postoperatively. As a result, a total of 548 patients were examined. According to the RT-PCR results obtained in the postoperative period, the patients were divided into 2 groups as Group 1 for PCR negative and Group 2 for PCR positive. While there were 59 patients in Group 2, the sample group was formed with 118 patients by determining the ratio of 2:1 through the computer program among the remaining 489 patients for Group 1.

Variables

Variables were recorded from the time of patients' first admission to the hospital. Demographic data, age, gender, and smoking were recorded. Hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), and chronic renal failure (CRF) were recorded in their medical history. Two consecutive RT-PCR results obtained with NFS in the last 48 hours preoperatively, and RT-PCR results obtained from the endobronchial lavage sample taken from the endotracheal intubation tube and examined within the first 15 minutes after the patient's transfer to the intensive care unit in the postoperative period were recorded.

Statistical Analysis

In our study, SPSS version 21.0 (IBM Statistical Package for the Social Sciences Statistic Inc., Chicago, IL, USA) program was utilized to analyze the data. "Kolmogorov-Smirnov test and Shapiro-Wilk test" were used for normality distribution analysis. Student's t test was used for the data presenting normal distribution and Mann-Whitney U test for those that did not conform to normal distribution. These data were shown as mean±standard deviation or as mean (interquartile range). Categorical variables were shown as frequency and percentage, and "chi-square test" was used for analysis. A $p < 0.05$ was accepted statistically significant.

RESULTS

Endobronchial lavage samples were obtained from the endotracheal tube in the early postoperative period in 177 patients included in the study. There were 118 (66.6%) patients in Group 1 and 59 (33.3%) in Group 2. The mean ages of patients in Group 1 and Group 2 were 64.5 ± 9.8 years and 61.9 ± 10.1 years, respectively ($p = 0.174$). There was no statistically significant difference between the groups in terms of gender, smoking, DM, HT, CRF, COPD rates and surgery types ($p > 0.05$ for all). Mortality was significantly higher in Group 2 (n = 24, 40.6%) compared Group 1 (n = 2, 1.6%) ($p < 0.001$) (Table 1).

A total of 59 patients who were found to have COVID-19 were divided into 2 groups as as survivors (n = 35, 59.3%) and non-survivors (n = 24, 40.7%). The mean ages of patients in survivor and non-survivor were 60.4 ± 10.3 years and 64.1 ± 9.9 years, respectively (p = 0.239). There was no statistically significant difference between the groups in terms of gender, smoking, DM, HT, CRF, COPD rates and surgery types ($p > 0.05$ for all).

DISCUSSION

In this study, we found that in addition to our cardiac surgery experience during the COVID-19 pandemic period, the way RT-PCR was performed creates significant differences in patients who were planned and performed cardiac surgery. The results of endobronchial lavage samples taken from the intubation tube in the early postoperative period have led us to take vitally important decisions in patient and disease management after cardiac surgery. By virtue of the algorithm we developed, we applied a multi-disciplinary approach to this special patient group by taking isolation measures in the postoperative period. Thus, PCR positive patients are isolated from other patients, min-

Table 1. Demographic and peroperative features of the patients

Variables	Group 1 (PCR negative) (n = 118)	Group 2 (PCR positive) (n = 59)	*p* value
Age (years) (mean ± SD)	64.5± 9.8	61.9±10.1	0.174
Male gender, n (%)	59 (50)	34 (57.6)	0.338
Hypertension, n (%)	20 (16.9)	14 (23.7)	0.280
Diabetes mellitus, n (%)	28 (23.7)	10 (16.9)	0.400
COPD, n (%)	5 (4.2)	6 (10.1)	0.123
Smoking, n (%)	24 (20.3)	14 (27.1)	0.605
CRF, n (%)	3 (2.5)	1 (1.6)	0.721
Surgery type, n (%)			0.345
Isolated CABG	93 (78.8)	50 (84.7)	---
Combined surgery	25 (21.2)	9 (15.3)	---
Mortality, n (%)	2 (1.7)	24 (40.7)	**< 0.001**

COPD =Chronic obstructive pulmonary disease, CRF =Chronic renal failure, SD = standard deviation, PCR = Polymerase chain reaction, CABG =Coronary artery bypass graft

Table 2. Demographic and peroperative features of PCR positive patients

Variables	Survivor (n = 35)	Non-survivor (n = 24)	*p* value
Age (years) (mean ± SD)	60.4 ± 10.3	64.1 ± 9.9	0.239
Male gender, n (%)	19 (54.2)	15 (62.5)	0.531
Hypertension, n (%)	8 (22.8)	6 (25.0)	0.849
Diabetes mellitus, n (%)	2 (5.7)	8 (33.3)	0.015
COPD, n (%)	2 (5.7)	4 (16.6)	0.174
Smoking, n (%)	7 (20.0)	7 (29.1)	0.416
CRF, n (%)	0	1 (4.1)	0.848
Surgery type, n (%)			0.626
Isolated CABG	29 (82.8)	21 (87.5)	---
Combined surgery	6 (17.2)	3 (12.5)	---

COPD = Chronic obstructive pulmonary disease, CRF = Chronic renal failure, CABG = Coronary artery bypass graft

imizing the risk of transmission.

As of the COVID-19 pandemic, radical changes have occurred in the practice of cardiac surgery. There has been a significant decrease in the patient population undergoing cardiac surgery. Also it has emerged that elective procedures should be deferred, and interventions that cannot be deferred should be performed under strict precautions and control, especially in patients who need cardiac surgery. Cardiac surgery practices are associated with a high mortality risk during the pandemic, especially in the presence of coronary artery disease [9-11]. This situation emerges as a need for long hospital stays at the patient level, intensive care or service follow-up. For this reason, the group of patients who underwent cardiac surgery constituted a sensitive and unique population for the pandemic period.

As of the beginning of the pandemic, there has been a significant decrease in the patient population undergoing cardiac surgery. These operations were avoided due to the high data on cardiac surgical mortality associated with COVID-19. Surgical procedures were applied under strict precautions for operations that could not be postponed. In our clinic, cardiac surgery applications were performed in accordance with a certain procedure. Especially in the early postoperative period, it became necessary to develop an algorithm after PCR positivity was observed in endobronchial lavage samples taken from the intubation tube. With this algorithm, all patients were considered potential PCR positive in the early postoperative period, until the PCR tests from endobronchial lavage samples were concluded. Care was taken in both the intensive care follow-up of the patient and the personal protection equipment of the healthcare workers. Those with positive RT-PCR tests were immediately transferred to the COVID-19 intensive care unit, while those with negative RT-PCR continued to be followed up in the classic cardio-vascular intensive care unit. A multidisciplinary approach was applied to cardiac surgery patients who were positive for PCR, and their follow-up and treatment was planned with the departments of pulmonary diseases, infectious diseases, anesthesiology and cardiology.

The clinical picture of COVID-19 infection appears in a wide spectrum ranging from asymptomatic disease carrier to pneumonia with diffuse lung involvement, multi-organ failure and sepsis [12]. Although the majority of patients survive the disease with mild to moderate severity, in the study of Guan *et al*. [13], the rate of severe disease and hospitalization among patients was reported to be around 16%. The symptoms of the disease are seen to vary from mild disease findings to severe disease. It has been reported that there are comorbidities such as CAD, HT, DM, immunodeficiency or malignancy in the patient group in which the disease progresses particularly severely [9, 14]. There is no comprehensive study in the literature regarding postoperative mortality rates in patients with COVID-19 infection, especially in patients undergoing cardiac surgery. In studies conducted with a small number of patients, mortality rates have been

reported to range from 8% to 50% [5, 15, 16]. Considering the in-hospital mortality rates, the mortality rate is up to 84% in patients undergoing cardiac surgery who need intensive care again [2].

In our study, mortality rate was found to be 40.7% in RT-PCR positive COVID-19 patients detected in the early period after cardiac surgery. In the study of Lei *et al*. [17] performed on patients who underwent non-cardiac surgery and were in the incubation period for COVID-19 infection, the total mortality rate was 20.6%, while the mortality rate for the patient group requiring intensive care was reported as 46.7%. In this study, it is seen that the high mortality rate detected in patients requiring intensive care follow-up after major surgery, even if they did not undergo cardiac surgery, is also in line with the data of our study.

RT-PCR from nasopharyngeal swab samples is typically used to diagnose COVID-19. In addition, blood, sputum, stool, urine and broncho-alveolar swab samples can also be examined for diagnosis. In a study conducted on 1070 different samples from 205 patients, the highest rate of RT-PCR positivity was found in endobronchial lavage samples (93%). This is followed by sputum (72%), nasal swab (63%) and pharyngeal swab (32%) [8]. As can be seen, endobronchial lavage samples taken from the intubation tube show a high RT-PCR positivity. This also means that endobronchial lavage specimen collection yields a high-confidence result compared to RT-PCR tests from nasopharyngeal swab specimens. In our study, although RT-PCR negativity was detected in all patients in the preoperative period, there were 59 (10.7%) patients with RT-PCR positivity in endobronchial lavage samples taken in the early postoperative period. In a review by Patel *et al*. [18], it is mentioned that there are nearly 20% false positives in RT-PCR tests performed on nasopharyngeal swab samples.

With this study, we have achieved a new gain in the approach to cardiac surgery cases during the COVID-19 pandemic. The RT-PCR positivity detected in the endobronchial lavage samples in the postoperative period showed the necessity of developing a new algorithm in the approach to this particular patient group. In the light of this information, it is very important to take an endobronchial lavage sample in all medical situations requiring endotracheal intubation, regardless of the previous RT-PCR result, in terms of the follow-up and treatment process of the patient's clinic.

Limitations

The most important limitations of our study are that it is single-centered, retrospective, and the number of patients is low. More comprehensive publications with larger numbers of patients are needed to support existing data.

CONCLUSION

With the COVID-19 pandemic, serious changes have occurred in the practice of cardiac surgery, as in many medical conditions. Especially in the intensive care process after open heart surgery, endobronchial lavage samples taken from the endotracheal intubation tube are important in demonstrating the presence of COVID-19, which could not be detected previously in patients. In addition to being negative for PCR at least 2 times in routine preoperative preparations, obtaining endobronchial lavage samples for PCR testing from the intubation tube in the early postoperative period plays an important role in patient management.

Authors' Contribution

Study Conception: AKA, ŞY; Study Design: AKA, ŞY; Supervision: AKA, ŞY; Funding: AKA, ŞY; Materials: AKA, ŞY; Data Collection and/or Processing: AKA, ŞY; Statistical Analysis and/or Data Interpretation: AKA, ŞY; Literature Review: AKA, ŞY; Manuscript Preparation: AKA, ŞY and Critical Review: ŞY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Toxoplasmosis in pregnancy: test, treatment and outcome

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ABSTRACT

Objectives: The aim of this study was to share the results, follow-up, and treatment characteristics of our pregnant women who were followed-up with anti-*Toxoplasma gondii* Immunoglobulin (Ig) M positivity during pregnancy.

Methods: Anti-*T. gondii* IgM- and IgG-positive pregnant women were evaluated between 2014-2018. Demographic characteristics, treatment, and information about pregnancy were obtained from the electronic database. Pregnant women were divided into three groups; primary infection, no infection, and suspected infection in pregnancy. Primary and suspected infection in pregnancy were followed up congenital toxoplasmosis risky pregnancy. Fetal ultrasonography (USG), *T. gondii* DNA polymerase chain reaction (PCR) result in amniotic fluid were recorded.

Results: Twenty-four pregnant women with a mean age of 27.9 years were followed up. IgG avidity results were low in 37.5% (n = 9), intermediate avidity in 8.3% (n = 2), and high avidity in 54.2% (n = 13) of pregnant women. Eleven (45.9%) pregnant women had congenital toxoplasmosis risky pregnancy. Fetal USG was performed on ten pregnant women, and no signs of congenital toxoplasmosis were found. Amniocentesis was performed in 72.7% (n = 8) of the participants, and the amniotic fluid *T. gondii* DNA-PCR result was negative in all of them. Ten (90.9%) pregnancies resulted in mature birth and one (9.1%) resulted in miscarriage.

Conclusions: Anti-*T. gondii* IgM positivity is an indication of acute infection. But IgM can persist for years, and be false-positive in pregnancy. Therefore, additional tests are required, and leading to emotional distress and unnecessary interventions in pregnacy women. These results can aid in developing an approach to screening and diagnosis of *T. gondii* infection in pregnancy.

Keywords: Toxoplasmosis, pregnancy, avidity, congenital toxoplasmosis, *T. gondii* DNA polymerase chain reaction (PCR), fetal ultrasonography

Toxoplasmosis is a common parasitic disease worldwide and is caused by *Toxoplasma gondii.* Although it often causes a self-limited infection with asymptomatic or mild symptoms (such as fever, malaise, lymphadenopathy), it can have a severe course in immunosuppressive individuals (e.g., HIV). Besides, acute infection during pregnancy can pass to the fetus (congenital toxoplasmosis), miscarriage, premature birth, stillbirth may occur and may cause severe sequelae in live-born babies (such as mental

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retardation, chorioretinitis, epilepsy) [1, 2].

It is estimated that more than 30% of the world's population is infected with *T. gondii*. According to countries and regions, this rate varies between 10-80% due to differences in climate, nutrition, and hygiene habits [3, 4]. In the United States, seropositivity has been reported to be 23% in adolescents and adults and 14% in women of childbearing age [2].

In a study investigating the prevalence of *T. gondii* in the world in 2009, our country was among the countries with a high prevalence (30-60%) [4]. *T. gondii* IgG seropositivity was 24.6% in 17,751 women of childbearing age in Istanbul, Adana, Bursa, Kayseri, and Kocaeli, and 30.7% in a study including pregnant women from Denizli [5, 6]. Seropositivity was 69.5% in pregnant women in Şanlıurfa [7]. There are also regional differences in our country. It is noteworthy that these rates are similar to Italy, France, Finland, and Austria, where toxoplasma screening is mandatory [8-11]. The increase in the incidence of congenital toxoplasmosis presentation in newborns brings up a screening in the United States. Massachusetts and New Hampshire are two states that perform routine newborn screening [12]. In our country, information about screening needs to be clarified.

According to estimates obtained from regional data in the USA, 400-4,000 cases of congenital toxoplasmosis and 750 deaths have been reported annually. The fact that 50% of cases are food-borne makes toxoplasmosis the third leading cause of food-borne death in the United States [13]. Since congenital toxoplasmosis is a critical public health problem, the Centers for Disease Control and Prevention (CDC) has made recommendations to reduce the risk of congenital infection [14].

In our country, there is no recommendation for pregnancy screening in the Ministry of Health's Antenatal Care Management Guidelines for toxoplasmosis or the recommendations of the Turkish Perinatology Society [15, 16]. In the age-related prevalence study performed in the province of Hatay, the estimation of the primary infection risk in pregnant women was found to be 6/1,000 [17]. The World Health Organization (WHO) estimated the incidence of congenital toxoplasmosis for Europe in 2013 to be 1.5 per 1,000 births [18].

Enzyme immunoassay methods that detect anti-*T. gondii* Immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies are frequently preferred in clinical practice for the laboratory diagnosis of toxoplasmosis due to their high sensitivity and ease of application. Anti-*T.gondii* IgM may remain positive for a long time in the peripheral blood. Therefore, additional tests such as IgG avidity, *T. gondii* DNA polymerase chain reaction (PCR) in amniotic fluid, and fetal ultrasonography (USG) are required to diagnose acute infection in pregnant women. Sometimes, the diagnosis is unclear even with these, and it is tried to be interpreted with the previous test results.

Our study aimed to interpret the test results of our pregnant women who were followed up with anti-*T. gondii* IgM and IgG positivity, their pregnancy follow-ups, growth retardation in babies. Together with the seropositivity studies, these results were intended to shed light on the screening for toxoplasmosis in pregnancy and guide physicians in interpreting the tests.

METHODS

Pregnant women who applied to our Infectious Diseases and Clinical Microbiology outpatient clinic between 2014-2018 with anti-*T. gondii* IgM and IgG positivity were included in our study. The study was approved by Ankara City Hospital Ethical Committee. Demographic characteristics of the pregnant women, the treatment they received, and information about pregnancy were obtained from the electronic database. After gathering these data, information about the babies of the pregnant women was recorded. The ages of the babies, whether they had was growth retardation in their follow-ups.

The results were interpreted per the evaluation criteria of commercial kits. For anti- *T. gondii* IgM, < 0.8 COI values were considered as negative, COI values between 0.8-0.999 as intermediate, ≥ 1 COI values as positive, < 1 IU/mL values as negative for anti- *T. gondii* IgG, values between 1-2.999 IU/mL as intermediate, ≥ 3 IU /mL values as positive and for IgG avidity test < 50 index value as low avidity, index value between 50-50.9 as intermediate avidity, ≥ 60 index value as high avidity.

The results were interpreted according to the gestational week and previous test results. Low avidity result was interpreted as primary infection in pregnancy. High avidity result was considered as no infec-

tion in pregnancy if in the first 12 weeks of pregnancy, and as infection with undecidable timing- suspected infection- if after 12 weeks. Pregnant women who were evaluated as infection in pregnancy and suspected infection during pregnancy were followed up as congenital toxoplasmosis risky pregnancy. *T. gondii* DNA PCR and fetal USG results were recorded in the amniotic fluid of these pregnant women.

Statistical Analysis

Statistical analysis was performed using SPSS 18.0 version and Microsoft excel. Descriptive statistics were presented as frequency and percentages for categorical variables and as mean ± standard deviation (SD) or median (minimum-maximum values) for continuous variables.

RESULTS

Twenty-four participants with a mean age of 27.9 years (20-38) were included in our study. There was a history of miscarriage in 3 and tuberculosis in one. There was no chronic disease or drug use. The median gestational week was 10.5 (range, 6-34) weeks. Nineteen pregnancies were in the first trimester, four were in the second trimester, and one was in the third trimester. None of the participants had any symptoms. IgG avidity results were low in 37.5% (n = 9) of the pregnant women, intermediate avidity in 8.3% (n = 2), high avidity in 54.2% (n = 13) (Fig. 1). Eleven (84.6%) participants with high avidity were in the first trimester, and it was interpreted as no infection in pregnancy. Two (15.4%) pregnant women were in the second trimester (15 and 16 weeks of gestation), and the timing for infection could not be determined (suspected infection). One of the pregnant women whose IgG avidity resulted as intermediate avidity was interpreted as a primary infection in pregnancy due to a 4-fold increase in *T. gondii* IgG titer, and the other pregnant woman as no infection in pregnancy due to previous results. Since 88.9% (n = 8) of the pregnant women with low avidity results had a primary infection in pregnancy and 11.1% (n = 1) had results from their previous pregnancy, it was interpreted as no infection in pregnancy (Fig. 1).

Spiramycin 3gr/day dose was initiated for all participants who applied to our outpatient clinic with anti-*T. gondii* IgM positivity, and an IgG avidity test was requested. Spiramycin treatment was discontinued in patients who were decided to have an infection before pregnancy.

Fetal ultrasonography results were available in 91.7% (n = 22) of the participants, and no fetal anomaly was determined in any of them. Amniocentesis was performed in 37.5% (n = 9) of the pregnant women,

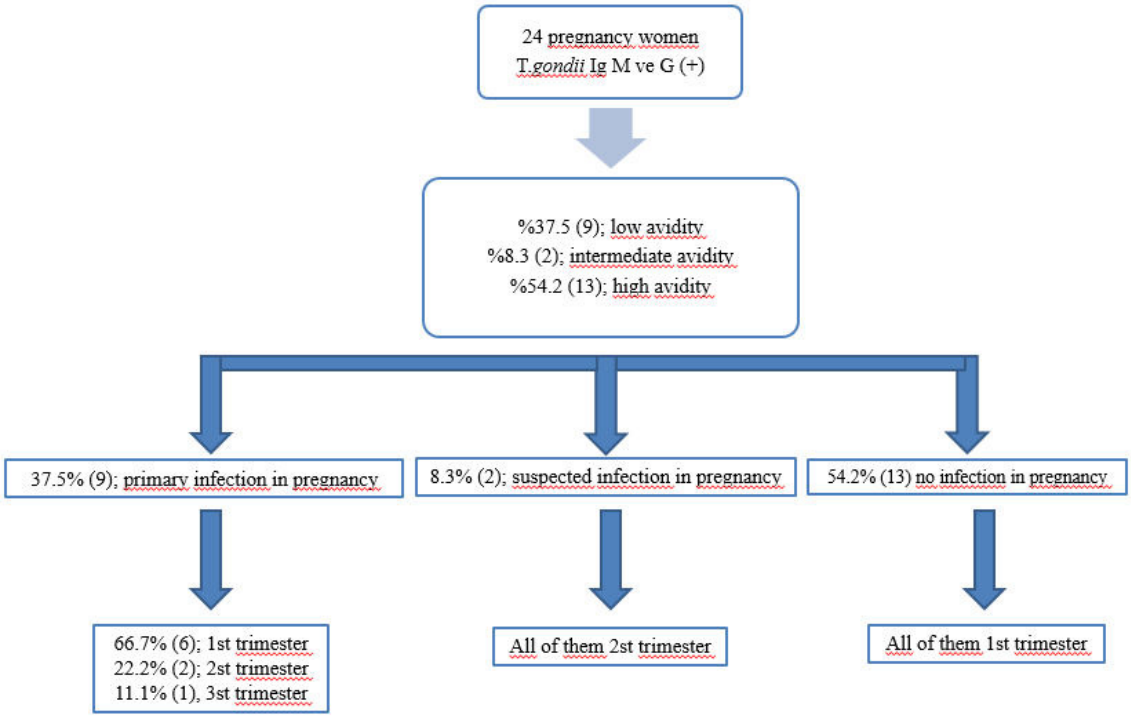

Fig. 1. Immunoglobulin (Ig) G avidity result and infection decision chart.

and the *T. gondii* DNA PCR result in the amniotic fluid of all of them was negative. Considering the pregnancy outcomes, miscarriage developed in 12.5% (n =3). One of the pregnant women who had a miscarriage was diagnosed with a primary infection in pregnancy, and the other two were diagnosed with no infection in pregnancy. 87.5% (n = 21) of babies were born mature.

Eleven (45.9%) pregnant women were congenital toxoplasmosis risky pregnancy (Table 1). Spiramycin treatment was continued in these pregnant women. The mean age of the pregnant women was 28 years. Of the pregnant patients with congenital toxoplasmosis risk, 54.5% (n = 6) were in the first trimester,

Table 1. Follow-up of congenital toxoplasmosis risky pregnant.

No	Age (years)	Pregnancy trimester	IgG avidity result	Infection definition	Fetal USG	Amniotic fluid T. gondii DNA PCR	Pregnancy termination
1	21	II	Low	Primary infection in pregnancy	Normal	Negative	Born mature
2	24	III	Low	Primary infection in pregnancy	Normal	No	Born mature
3	26	I	Low	Primary infection in pregnancy	No	No	Born mature
4	27	II	Low	Primary infection in pregnancy	Normal	Negative	Low
5	33	I	Low	Primary infection in pregnancy	Normal	Negative	Born mature
6	34	I	Low	Primary infection in pregnancy	Normal	No	Born mature
7	25	I	Low	Primary infection in pregnancy	Normal	Negative	Born mature
8	25	I	Low	Primary infection in pregnancy	Normal	Negative	Born mature
9	26	I	Intermediate	Primary infection in pregnancy	Normal	Negative	Born mature
10	34	II	High	Suspected infection in pregnancy	Normal	Negative	Born mature
11	33	II	High	Suspected infection in pregnancy	Normal	Negative	Born mature

IgG = immunoglobulin G, PCR = polymerase chain reaction, USG = ultrasonography

36.4% (n = 4) were in the second trimester, and 9.1% (n = 1) were in the third trimester. In the IgG avidity results, 72.7% (n = 8) had low avidity, 9.1% (n = 1) had intermediate avidity, 18.2% (n = 2) had high avidity. Fetal ultrasonography was performed on ten pregnant women, and no signs of congenital toxoplasmosis were found. Amniocentesis was performed in 72.7% (n = 8) of the pregnant women, and the amniotic fluid T.gondii DNA PCR result was negative in all of them. 90.9% (n = 10) of pregnancies resulted in mature birth, and 9.1% (n = 1) resulted in miscarriage. One of the babies was diagnosed with Bartter syndrome in the examinations performed due to growth retardation and died at sixth month due to aspiration pneumonia. The mean age of 9 living babies was 4.3 (3-5). None of the babies had developmental delay.

DISCUSSION

There is no worldwide consensus for screening for toxoplasmosis during pregnancy. While there are countries that advocate screening all pregnant women, some do not advise screening. Geographical location, cultural practices, feeding habits, socioeconomic status significantly affect the prevalence of the disease. European countries lead the primary toxoplasmosis infections in the world. France reported the highest infection rates in pregnant women (54%), while the remaining European countries reported lower infection rates (46%) [20].

After acute infection, the IgM titer starts to rise on the fifth day and reaches its maximum level in 1-2 months. While IgM antibodies become negative before the sixth month in 25% of cases, they may remain positive for a year or even up to 2 years in other patients, depending on the sensitivity of the test method used [19]. IgG titer begins to be detected 1-2 weeks after acute infection and remains high for life [20]. In pregnant women with positive *T. gondii* IgM and IgG tests, it is recommended to perform an IgG avidity test to determine whether the infection is in the early or late stages [21]. However, since antibodies with low avidity can remain in the serum for months, infection in pregnancy may not always be present when a low avidity value is detected [22, 23]. In such a case, laboratory diagnosis should be confirmed by PCR from amniotic fluid, and it should also be supported by clinical and ultrasonographic findings [22]. In interpreting serological tests, the time of requesting the tests is also important [24]. The high avidity result in the first trimester ensures the exclusion of infection. However, the examinations performed in the second and third trimesters make this decision difficult. In 20.8% (5/24) of the pregnant women in our study, tests were requested in the second and third trimesters. This also made the interpretation of the tests complicated. In this case, previous serological examinations are beneficial in making the diagnosis. No infection in pregnancy was decided because 8.3% (2/24) of the pregnant women who applied to us due to toxoplasmosis had a previous serology analysis. There is no recommendation for routine screening in our country. Furthermore, there is no consensus among doctors due to the lack of a common follow-up plan. These challenges encountered in the interpretation of the tests cause unnecessary tests in pregnant women and increase the anxiety of the prospective parents due to the uncertainty of the baby's prognosis [25, 26]. A study in Italy stated that 51.3% of pregnant women had previous results, making decision-making much easier [27]. They argued that more detailed studies on the tests used in screening policies should be done [27].

In pregnant women diagnosed with acute toxoplasmosis, the use of fetal USG is recommended after serological tests. Neurological anomalies (hydrocephalus, ventriculomegaly, and intracerebral calcifications), splenomegaly, congenital nephrosis, and ascites can be detected in fetal USG [28]. In our study, fetal USG was performed in 90.9% of pregnant women with congenital toxoplasmosis risk, and no finding suggestive of toxoplasmosis was detected in any of them. In the study of Italy, at least one finding suggestive of congenital toxoplasmosis was found in 10.4% of fetuses [27]. As the result of a multicenter study in France, the rate of an anomaly in fatal USG was reported as 4.2%. [29].

Amniocentesis is recommended at the earliest 18th week in pregnant women diagnosed with acute infection during pregnancy. *T. gondii* DNA PCR in amniotic fluid has a positive predictive value close to 100% in determining fetal infection [30]. In the study of Greco *et al.* [31], *T. gondii* DNA PCR was found to be 6% positive in amniotic fluid during primary infection. In a report from our country in 2021, *T. gondii* DNA PCR positivity in amniotic fluid was reported as

16.7% (1/6). This condition has been associated with initiating treatment late in pregnancy [32]. In our study, eight pregnant women underwent amniocentesis, and the *T. gondii* DNA PCR result in amniotic fluid was negative in all of them. This result supports the ultrasound findings showing that there is no fetal involvement.

Fetal transmission generally occurs at the rate of 29% (95% CI 25-33), while it is 6% at 13 weeks of gestation and 72% at 36 weeks of gestation. Congenital infection was determined in a pregnant woman who had seroconversion at 24-30 weeks of gestation, and it was reported that the incidence of her findings would be the highest (10%) [33]. As a result of the meta-analysis performed in 2014, the infection rate in the third trimester was 32% [24]. In the study of Avelino et al. [34], the rate of congenital toxoplasmosis was reported to be as high as 56% in women with suspected infection. However, it was reported that high rates might be due to delayed first-trimester screening of pregnant women [27]. This indicates the importance of antenatal screening time. Apart from this, the rates were reported to be much lower, such as 0.8-7%, in studies performed in pregnant women with Anti-*T. gondii* IgM (+)/ IgG (+) and low avidity [31, 35, 36]. Our study considered no fetal involvement since there was no problem in both the intrauterine tests and the follow-up of the babies after birth. Early treatment in pregnancy reduces fetal transmission by 50% [37, 38]. In our study, 54.5% (6/11) of pregnant women with congenital toxoplasmosis risk were in the first trimester, and all of them were initiated with spiramycin, which may be the reason why we did not see any signs of congenital involvement.

Some findings of fetal involvement of congenital toxoplasmosis can be easily missed at birth. Most babies develop late symptoms months after birth, such as chorioretinitis, seizures, mental retardation, and motor or cerebellar dysfunction. Furthermore, associations between congenital infection and sensorineural hearing loss, congenital nephrosis, hematological abnormalities, hepatosplenomegaly, various endocrinopathies, and myocarditis have been demonstrated [39]. We obtained information from the mothers about the outcomes of the babies and found that there was no developmental delay

One of the pregnancies diagnosed as primary infection in pregnancy ended in miscarriage. In the fetal USG performed in this pregnancy, no fetal anomaly was found to suggest congenital toxoplasmosis. Moreover, *T. gondii* DNA PCR was negative in amniotic fluid. Therefore, the miscarriage developed is not associated with toxoplasmosis, but it cannot be said clearly because the miscarriage material is not screened for toxoplasmosis.

Limitations

Our study has limitations such as being retrospective, the small number of patients, the fact that the miscarried baby was not examined in terms of toxoplasmosis, and it does not provide clear data on seroprevalence. However, it gives information about congenital transmission as it includes the long-term results of babies. A large-scale study has not yet been performed to determine the rate of congenital toxoplasmosis in Turkey [11]. Leading these studies was critical in justifying establishing a consensus on pregnancy screening and follow-up. It is also hoped that it will aid physicians in interpreting serological test results.

CONCLUSION

Toxoplasmosis is a preventable infection that affects millions of women and their children. The difficulty in interpreting serological results in the outpatient clinic causes significant difficulties for us, the physicians, and the mother and father-to-be with the stress it creates. Babies who are not correctly diagnosed and treated for congenital toxoplasmosis are at risk for lifelong brain and ocular abnormalities [20]. Considering the rates in our country, it is vital to evaluate women of childbearing age who are planning a pregnancy and pregnant women in terms of acute toxoplasmosis. In particular, systematic serological screening of pregnant women by establishing a national program will ensure that the cost-effectiveness of the screening is evaluated, and the problems experienced in diagnosis and follow-up will be minimized.

Authors' Contribution

Study Conception: RG, AKK; Study Design: AKK, İH; Supervision: AKK, İH, MA; Funding: N/A; Materials: FYA; Data Collection and/or Processing: AKK, MA, FE; Statistical Analysis and/or Data Inter-

pretation: AKK, BK; Literature Review: YO; Manuscript Preparation: AKK, RG and Critical Review: AKK, FE, RG, YO.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The relationship between smoking dependence, exposure to cigarette smoke, carboxyhemoglobin and perioperative complications in patients who underwent laparoscopic cholecystectomy under general anesthesia

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ABSTRACT

Objectives: The aim of this study; to determine the effects of preoperative smoking dependence and noninvasively measured carboxyhemoglobin (COHb) levels on perioperative complications in patients who underwent elective laparoscopic cholecystectomy.

Methods: Ninety patients (Group I: smoker, Group II: non-smoker, and Group III: passive smoker) who underwent laparoscopic cholecystectomy under general anesthesia were studied. The level of dependence of smokers was evaluated with the Fagerstrom Test for Nicotine Dependence (FNBT). Preoperative COHb level was determined with a pulse CO-oximeter by placing a sensor on the fingertip. Respiratory complications in the perioperative and recovery room and Modified Aldrete Score (MAS) in the recovery room were recorded as 5th, 10th and 15th min.

Results: Female gender was significantly higher in Groups II and III. Significant increases were noted in Group I in terms of increased perioperative secretion and incidence of bronchospasm. In the recovery room, the increase in MAS 5th min in Group I and MAS 10th min and 15th min in Group III was significantly lower. In Group I, positive correlations between the COHb level and the number of cigarettes smoked and the FNBT level, and a negative correlation between MAS and the number of hours past after the last cigarette smoked were determined. In Group II, the COHb level correlated positively with the number of cigarette smokers at home and negatively with MAS. All these correlations were statistically significant.

Conclusions: It was demonstrated that cigarette smoking increased the incidence of perioperative respiratory complications under general anesthesia. Preoperative COHb level estimated by the pulse CO-oximeter can be used as an indicant of the potential risk of perioperative repiratory complications.

Keywords: Smoking, carboxyhaemoglobin, noninvasive pulse CO-oximetry, perioperative respiratory complications, laparoscopic cholecystectomy

Smoking, which threatens health, is a preventable cause of perioperative respiratory complications, wound infection, myocardial infarction, stroke and mortality [1, 2]. It has been reported that there may be increased reactivity in the respiratory system, such as narrowing of the small airways, insufficient clearance

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of pulmonary secretion, and increased mucus secretion in patients who smoke /exposed to cigarette smoke and are to be anesthetized [3]. Lung function may be affected by stimulation of the intra-abdominal organs during laparoscopic cholecystectomy and gallbladder traction, and this may be exacerbated in the lung exposed to cigarette smoke [4].

Clinical studies on smoking have mostly focused on the postoperative period, and complications during the operation and in the recovery room have been neglected [5-8].

In many studies cigarette smoking have relied on self-reporting [9, 10]. Carbon monoxide (CO) is found in tobacco smoke as an exogenous source and is absorbed from the lung to form COHb. Measurable COHb levels can be used to investigate inhalation in passive smokers as well as the accuracy of direct self-reporting. There is a weak but statistically significant relationship between the COHb level and self reported smoking [11]. COHb levels are typically less than 2% in non-smokers and 5-9% in smokers [12]. In this way, the relationship between COHb change and perioperative complications can be revealed in smokers, non-smokers and passive smokers. COHb level that can be measured with a Pulse CO-o0ximeter; It is a simple, non-invasive and rapid method to help confirm the non-smoking interval. In addition, there are publications stating that there is a high positive correlation between COHb pulse and COHb blood test [13, 14].

In this study we determined the effect of preoperative cigarette smoking dependence and the noninvasively measured COHb level on perioperative respiratory complications seen in patients undergoing elective laparoscopic cholecystectomy under general anesthesia.

METHODS

This study was carried out in University of Health Sciences Bursa Yuksek Ihtisas Training and Research Hospital between January 2020 and July 2020, in accordance with the principles of the Declaration of Helsinki, after informed consent of the patients and the approval of the local Ethics Committee (2011-KAEK-25 2019/12-22).

In this prospective and single-blind study, elective laparoscopic cholecystectomy operation was planned, patients aged 18-70 years, with American Society of Anesthesiologists physical condition classification (ASA) I-II-III, smokers, non-smokers and passive smokers (who had not previously used tobacco products but exposed to tobacco smoke at home and/or place of work) were included. Patients with a history of allergy to drugs to be used, known psychiatric disorders, pregnant women, those who were breastfeeding, those who had a respiratory system infection in the last one month, those with drug and alcohol addiction, those with difficult intubation prediction, and those with a body mass index of ≥ 30 kg were excluded from the study.

The patients included in the study were grouped as smokers (Group I, n = 30), non-smokers (Group II, n = 30) and passive smokers (Group III, n = 30). Demographic characteristics of the patients and smoking habits of smokers were learned on the day of the operation (self-reporting). Whether smokers smoked in the last 12 hours and how many cigarettes they smoked, and the number of smokers in the exposed areas (home, workplace, etc.) in passive smokers were questioned and recorded. Nicotine dependence was assessed on the day of surgery by the FTND. Before induction of anesthesia, the COHb level was determined by placing a fingertip sensor with a pulse CO-Oximeter (Rad-57 Masimo Corporation, Irvine, CA).

Anesthesia was administered by an anesthesiologist who did not know the COHb value and FTND level of the patients and who was blind to the study. Routine monitoring was applied to all patients. After the vascular access was established, intravenous (IV) 0.01-0.02 mg/kg midazolam (Zolamid®, Defarma Ankara, Turkey) was given for premedication. For anesthesia induction, 2mg/kg propofol (Pofol®, İlsan-İltaş Kocaeli, Turkey), 0.6mg/kg rocuronium (Jecron® Tüm Ekip İlaç AS. Istanbul, Turkey) and 1-2mcg/kg fentanyl (Talinat®, Vem, Istanbul, Turkey) was applied. In the maintenance of anesthesia, inhalation anesthetic sevoflurane (Sevorane®, Abbvie, Istanbul, Turkey) was used with a mixture of O_2 + air, with a MAC 1.0. Near the end of the surgery, 10 mg metoclopramide HCl (Metpamid®, Sifar İlaç AŞ, Istanbul, Turkey) and 2g paracetamol (Parol®, Atabay, Istanbul, Turkey) IV were administered for postoperative pain. Following spontaneous respiration, 100% O_2 was given and 0.03-0.05 mg/kg neostigmine (Neostigmine®, Adeka, İstanbul, Türkiye) and 0.01 mg/kg at-

ropine (Atropin sülfat®, Osel, İstanbul, Türkiye) were given i.v. for reversal of neuormuscular blockage, followed with extubation under clinical observation.

Primary Outcomes

All patients were followed up routinely. Perioperative peripheral oxygen saturation (SpO_2), hypoxia, apnea, laryngospasm, bronchospasm, use of bronchodilator therapy, increased secretion, nausea, vomiting; In the recovery room, hypoxia, apnea, bronchospasm, use of bronchodilator therapy, increased secretion, nausea and vomiting were recorded. $SpO_2 < 95$ for more than one minute was considered as hypoxia, breath-holding for more than 15 seconds apnea, and the need to remove secretions with an aspirator were considered as increased secretion.

Secondary Outcomes

The duration of general anesthesia and operation from induction to extubation, and the length of stay in the recovery room for recovery after extubation were recorded. MAS was evaluated at the 5th, 10th and 15th minutes after admission to the recovery room. The MAS score was recorded upon completion of the postoperative recovery.

Statistical Analysis

SPSS 21.0 for Windows program (Statistical Package for the Social Sciences, NY, USA) was used for statistical analysis. The Shapiro wilk test was used to determine whether the variables were normally distributed. Continuous variables were defined as mean ± standard deviation, and categorical data were expressed as n (%). Pearson chi-square test was used to detect differences between groups on the basis of categorical variables. The Indipendent Samples T test was used to compare the mean values of age, anesthesia time, surgery time, recovery time, COHb level, Aldarete 5th, 10th and 15th minutes between the groups. The Mann-Whitney U test was used to compare the difference between the 5th minute MAS scores and the 15th minute and the 5th minute MAS scores and the 10th minute and 5th minute MAS scores. The Spearman rho test was used to determine the correlations between the COHb level and the FTND result, the number of cigerettes smoked before the operation, the time of the last cigarette smoked and the MAS score in Group I, MAS score and the number of cigarette smokers present in the area of exposure in Group III. The p values of < 0.05 and < 0.01were accepted to express statistical significance.

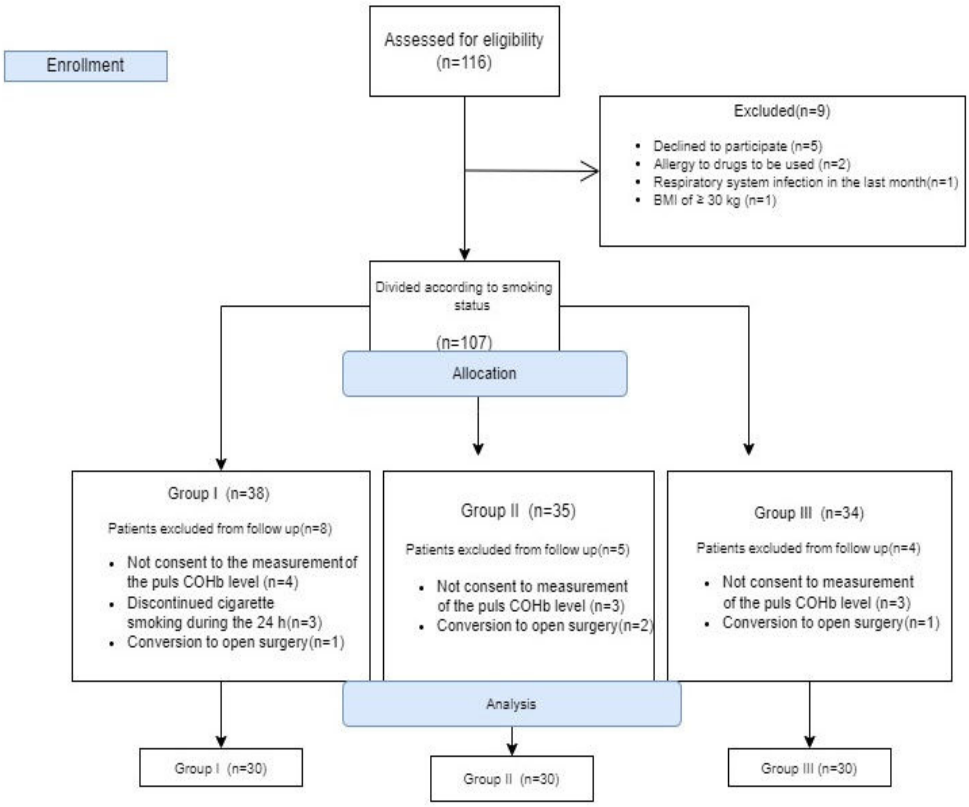

Fig. 1. Flow chart.

RESULTS

Data obtained from 90 patients out of 116 patients who underwent laparoscopic cholecystectomy were included in the study analysis. A total of 9 patients, 5 who did not want to participate in the study, 2 with a history of allergy, 1 with a respiratory tract infection, and 1 with a BMI > 30, were not accepted into the study because they did not meet the criteria. 4 patients in Group I, 3 patients in Group II and 3 patients in Group III who did not approve the measurement of COHb level with Pulse CO-oximeter; 3 patients in Group I who quit smoking 24 hours before surgery; 1 patient in Group I, 2 patients in Group II and 1 patient in Group III who underwent open cholecystectomy were excluded from the study (Fig. 1).

In demographic data of the patients, there was no difference between the groups in terms of age, ASA, comorbidities, duration of anesthesia, operation time, and time spent in the recovery room. Female gender was significantly higher in Groups II and III ($p < 0.001$, Table 1 and 2).

The mean FNBT values were determined as of low dependence (3.67). Preoperative COHb pulse level was found to be statistically significantly higher in Group I compared to Groups II and III (3.23 ± 1.43, 0.63 ± 0.81, and 2.27 ± 1.05; $p < 0.001$, respectively). Comparing the MAS at the 5th, 10th and 15th minutes; The increase in the change in MAS (10-5th min) and MAS (15-5th min) was found to be significantly lower in Group III at MAS 5th min Group I ($p = 0.041$, $p = 0.002$, and $p = 0.005$, respectively) (Table 1).

Table 1. Demographic data

	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	*p* value
Age (years), (mean ± SD)	50.10 ± 10.32	49.53 ± 16.04	47.27 ± 12.17	0.625
Gender, n (%)				**< 0.001**
Female	13 (43.3)	26 (86.7)	27 (90.0)	
Male	17 (56.7)	4 (13.3)	3 (10.0)	
ASA, n (%)				0.158
I	2 (6.7)	8 (26.7)	8 (26.79	
II	26 (86.7)	21 (70)	22 (73.3)	
III	2 (6.7)	1 (3.3)	0 (0.0)	
Comorbidities, n (%)				0.731
Yes	16 (53.3)	15 (50.0)	18 (60,0)	
No	14 (46.7)	15 (50.0)	12 (40.0)	
COHb level (%), (mean ± SD)	3.23 ± 1.43	0.63 ± .81	2.27 ± 1.05	**< 0.001** [b]
Duration of anesthesia (min), (mean ± SD)	63.33 ± 18.16	63.67 ± 21.73	58.60 ± 8.95	0.943 [a]
Duration of surgery (min), (mean ± SD)	52.0 ± 14.54	51.50 ± 21.78	48.33 ± 8.13	0.710 [a]
Time required for recovery (min), (mean ± SD)	28.20 ± 6.36	27.13 ± 6.08	27.0 ± 3.85	0.822 [a]
MAS (5th min), (mean ± SD)	7.20 ± .81	7.23 ± 1.01	7.73 ± .64	**0.041** [a]
MAS (10-5th min), (mean ± SD)	1.10 ± .31	1.43 ± .73	0.97 ± .32	**0.002** [a]
MAS (15-5th min), (mean ± SD)	2.43 ± .73	2.40 ± .86	1.93 ± .37	**0.005** [a]

Data are presented as mean ± standard deviation or n (%). ASA = American Society of Anesthesiologists score, MAS = The Modified Aldrete Score, COHb = Carboxyhemoglobin level in the pulse CO-oximeter, 10-5th = difference score of MAS measurement between 10th and 5th minutes; 15-5th = difference score of MAS measurement between 15th and 5th minutes.
[a] Mann-Whitney U test, [b]Independent samples t-test.

Table 2. Distribution of comorbidities by groups

	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	*p* value
HT	8 (26.7)	6 (20.0)	14 (46.7)	0.067
DM	6 (20.0)	5 (16.7)	7 (23.3)	0.812
Thyroid diseases	3 (10.0)	3 (10.0)	3 (10.0)	1.00
Heart diseases	3 (10.0)	4 (13.3)	2 (6.7)	0.690
Obesity	1 (3.3)	2 (6.7)	1 (3.3)	0.770
Asthma	1 (3.3)	1 (3.3)	2 (6.7)	0.770
COPD	0 (0.0)	0 (0.0)	1 (3.3)	0.364
Kidney diseases	0 (0.0)	1 (3.3)	1 (3.3)	0.600

Data are presented as n (%). HT = Hypertension, DM = Diabetes Mellitus, COPD = Chronic Obtructive Pulmonary Disease. Pearson chi-square test

Table 3. Comparison of the incidence of perioperative complications between groups

Recorded complications	Stages of the surgery	Group I (n = 30)	Group II (n = 30)	Group III (n = 30)	*p* value
Nausea					
	Perioperative	6(20,0)	1 (3.3)	4 (13.3)	0.140
	Recovery room	1 (3.3)	0 (00.0)	4 (13.3)	0.064
Vomiting					
	Perioperative	1 (3.3)	0 (00.0)	0 (00.0)	0.364
	Recovery room	0 (00.0)	0 (00.0)	0 (00.0)	-
Increased secretion					
	Perioperative	14(46.7)	2 (6.7)	8 (26.7)	**0.002**
	Recovery room	0 (00.0)	0 (00.0)	0 (00.0)	
Apnea					
	Perioperative	3(10.0)	0(00.0)	1(3.3)	0.160
	Recovery room	4(13.3)	0(00.0)	2(6.7)	0.117
Laryngospasm					
	Perioperative	4 (13.3)	0 (00.0)	0 (00.0)	**0.015**
	Recovery room	0 (00.0)	0 (00.0)	0 (00.0)	**-**
Bronchospasm					
	Perioperative	0 (00.0)	1 (3.3)	0 (00.0)	0.364
	Recovery room	0 (00.0)	0 (00.0)	0 (00.0)	-
Need for bronchodilators					
	Perioperative	4 (13.3)	1 (3.3)	3 (10.0)	0.383
	Recovery room	0 (00.0)	0 (00.0)	0 (00.0)	
$SpO_2 < 95\%$					
	Perioperative	4 (13.3)	2 (6.7)	2 (6.7)	0.578
	Recovery room	3 (10.0)	0 (00.0)	1 (3.3)	0.160

Data are presented as n (%). Pearson chi-square test

There was no statistical difference between the groups in terms of the incidence of hypoxia, apnea, bronchospasm, bronchodilator therapy, nausea and vomiting in the perioperative and recovery room; however, perioperative laryngospasm and increased secretion were significantly higher in Group I compared to the others ($p = 0.015$ and $p = 0.002$, respectively) (Table 3).

In Group I, there was a positive correlation between COHb pulse level and how many cigarettes smoked and FNBT ($p < 0.05$ and $p < 0.001$, respectively), and a negative correlation between how many hours ago he smoked and MAS ($p < 0.05$); In Group III, there was a positive correlation between the COHb pulse level and the number of people smoking at home, and a negative correlation between the 5*th* and 10*th* minutes of MAS ($p < 0.001$ and $p < 0.05$, respectively) (Table 4). The results were statistically significant.

DISCUSSION

The relationship between preoperative COHb pulse levels and the effects of smoking and/or passive smoking on perioperative respiratory complications was the focus of this study. In our study, the incidence of perioperative laryngospasm and increased secretion was significantly higher in Group I patients. When the recovery room first 15 min MAS recovery was compared; the increase in the change in MAS 5th min Group I, MAS 10th min and 15th min measurement was significantly lower in Group III.

It has been reported that especially the pulmonary mechanics are affected by abdominal organ stimulation and bladder traction during laparoscopic cholecystectomy surgery [4]. In cigarette smoking patients undergoing general anesthesia, hyperactivy in the respiratory system, decreased clearance of pulmonary secretion, increased mucus secretion, coughing and apnea incidences are increased [3, 9, 10]. The respiratory complications of laryngospam and increased secretion observed in our investigation are in agreement with the literature.

Most of the studies evaluating perioperative complications of passive smoking have been performed in children, reporting significantly increased perioperative complication incidences and longer post-anesthesia care unit (PACU) stay [15, 16]. In less number of studies made on adults, Tütüncü *et al*. [17] had only noted significantly increased coughing and excessive secretion in passive smokers. Şimşek *et al*. [18] reported increased incidences of peri- and post-operative respiratory complications due to passive exposure to cigarette smoke that significantly correlated with longer PACU stay and increased risk of coughing, desaturation and hypersecretion in relation to the duration of the exposure. In our study, incidences of secretion increase were 46.7% in smokers, 6.7% in non-smokers and 26.7% among the passive smokers, but the patients of the three groups had similar durations of stay in the recovery room.

Anesthesia and surgery duration and especially upper abdominal surgical procedures are important parameters affecting the risk of respiratory complications [19]. It has been reported that laparoscopic cholecys-

Table 4. In Group I correlation between COHb with how hours ago last cigarette smoked, how many cigarettes smoked, FNBT and MAS. In Group III correlation between COHb with MAS and the number of people smoking at home

	How hours ago last cigarette smoked	how many cigarettes smoked	FNBT	MAS (5th min)	MAS (10-5th min.)	MAS (15-5th min.)	number of people smoking at home
Group I							
COHb level	**- 0.387***	**0.429***	**0.466****	**- 0.437***	**- 0.412***	**- 0.402***	-
Group III							
COHb level	-	-	-	**0.470****	**- 0.395***	- 0.353	**0.629****

COHb = Carboxyhemoglobin, FNBT = Fagerstrom Test for Nicotine Dependence, MAS = Modified Aldrete Score
Spearman's rho *$p < 0.05$, **$p < 0.001$

tectomy durations changed between 30 and 166 minutes and the duration of anesthesia, on a basis of group comparisons, changed between 3.5-4.5 hours [3, 10, 19-21]. Özgünay *et al*. [22] reported that in laparoscopic cholecysctomy the duration of anesthesia was significantly increased among cigarette smokers. In our study; although there was no difference between the groups in terms of duration of operation, duration of anesthesia and waking up for recovery; while the operation time was consistent with the literature, the anesthesia time was shorter. This advantageous situation may have resulted in fewer perioperative complications in smokers and/or passive smokers in our study.

Although smokers are known to have elevated blood COHb levels due to CO inhalation in cigarette smoke, limited data are available on COHb levels in passive smokers exposed to cigarette smoke. Reddy *et al*. [23] in their study in the outpatient clinic; they found COHb pulse levels to be 5.9%+/-4.45% in smokers, 1.95%+/-1.55% in non-smokers, and 1.94%+/-1.55% in passive smokers. In our study, the COHb pulse level was 3.23%+/-1.43% in smokers, 0.63%+/-0.81% in non-smokers, and 2.27%+/-1.05% in passive smokers. Our result was higher than the literature value in passive smokers, but COHb pulse value was significant in Group I in group comparison. COHb pulse measurement has been used for screening purposes in pediatric patients with preoperative passive smoking exposure in a few studies in the literature [24, 25]. However, perioperative or postoperative respiratory complications have not been investigated. Our study is valuable because it includes the perioperative and recovery room under anesthesia.

FTND score has been used to assess the level of nicotine dependence [5, 21], The mean level of FTND determined in our study was 3.67, indicating low level nicotine dependence. Lee *et al*. [21] reported a mean value of 4.3. Moller *et al*. [5] have observed in most patients a medium level of dependence. However, FTND has not been investigated in most studies involving the effects of smoking on perioperative complications [5, 9, 20, 26].

Only one study reported a relationship between MAS scores and the time required for recovery in adults regarding the effect of smoking on perioperative respiratory complications [22]. Ozgünay *et al.* [22] in smokers; MAS 5.10. they stated that the changes in the 15th min were lower and the time required for recovery was also significantly longer. In our study, our results were similar in terms of MAS changes. However, we did not find any difference between the groups in terms of time to awakening.

Yee *et al*. [24] observed in children exposed to parental cigarette smoking that the COHb levels were higher in comparision to the control children. In our study, the COHb level was directly related to the number of cigarettes smoked and the nicotine dependence level and to the exposure of the passive smokers to the number of the smokers in their dwellings; and high levels affected recovery adversely.

Limitations

Low FNDT scores, and not having data on coughing, headache, throat ache and long term respiratory complications are the limitations of our study.

CONCLUSION

The incidence of perioperative respiratory system complications increases in the first minutes in the recovery room. Specifically, it has been shown that the level of COHb is directly related to the amount of cigarettes smoked and the number of people who smoke, and to affect recovery. It should be remembered that detailed interrogation of the preoperative smoking status of the patients, measuring the COHb value with puls CO-Oximeter a simple and non-invasive technique, especially in passive smokers, will be beneficial for the anesthetists in terms of possible perioperative respiratory complications. More comprehensive studies are needed on this subject. More comprehensive studies are needed on this subject.

Authors' Contribution

Study Conception: ŞE, ŞEÖ; Study Design: ŞE; Supervision: ŞE, ŞEÖ; Funding: ŞE; Materials: ŞE; Data Collection and/or Processing: ŞE, ŞEÖ; Statistical Analysis and/or Data Interpretation: ŞE, ŞEÖ; Literature Review: ŞE, ŞEÖ; Manuscript Preparation: ŞE, ŞEÖ and Critical Review: ŞE, ŞEÖ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Do radiological parameters affect quality of life in patients with untreated and symptomatic hallux valgus?

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ABSTRACT

Objectives: The aim of this study is to investigate the effect of the disease on quality of life (QoL) in patients with not operated symptomatic hallux valgus (HV) and the relationship between the degree of deformity classified by radiological parameters and QoL.

Methods: In this prospective study, 100 patients (33 males, 67 females; mean age 49.25 ± 15.20 years; range 18 to 75 years) who were admitted to our institution and diagnosed with HV between March 2019 and February 2020 were included. Hallux valgus angle (HVA) and intermetatarsal angle (IMA) were used to assess the degree of deformity. The Visual Analog Scale (VAS), the Foot Function Index (FFI), and the 36-Item Short-Form Health Survey (SF-36) instruments were used to evaluate patients.

Results: The severity of HVA associated with SF-36 scores for physical health, social functioning, bodily pain, general health, and mental health ($p < 0.05$). Differences were found between the degrees of IMA for social functioning, bodily pain, and general health scores in SF-36 ($p < 0.05$). A significant statistical correlation was observed between pain scores in VAS and severity of HVA and IMA. Higher scores in VAS and FFI were recorded from the participants with high degrees of HVA ($p < 0.05$). However, no relationship was found between the radiographic severity of the IMA and the FFI.

Conclusions: In this study, it was shown that the QoL decreased as the degree of deformity increased in HV patients. In addition, it was concluded that HVA is a more basic radiological predictor than IMA in the evaluation of HV patients.

Keywords: Hallux valgus, radiographic angles, quality of life

Hallux valgus (HV) is one of the chronic progressive foot deformities that can be seen in almost every age group, characterized by the lateral deviation (abduction) of the hallux and by the corresponding deviation (adduction) of the first metatarsal [1]. In a recent large-scale epidemiological study showed that the prevalence of hallux valgus was 23% in adults aged 18-65 and 35.7% in the elderly [2]. Although the etiology of hallux valgus is unclear, inappropriate footwear, the length of the first metatarsal, foot pronation, female sex and hereditary factors have been identified as risk factors [3]. Considering its high incidence in orthopedic foot surgery [4], the fact that it is becoming a major health problem such as osteoarthritis in women [5], and its association with disability [6], increased risk of falling [7], muscle weakness in the toe

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[8], worse physical performance [9], balance and gait disturbances [10].

QoL is defined as an individual's perception of his/her position in life in relation to his/her goals, expectations, standards, and interests within the framework of the surrounding culture and value systems. The main purpose of the services provided in health systems is to provide a positive change in the health of the individual or society. It is important to measure the QoL, in order to manage health policies and conduct medical research.

The effects of diseases on QoL are variable. However, most of the time, the physician has no chance to thoroughly evaluate the patient to make a decision on the treatment of the disease in the outpatient clinic conditions. In such cases, radiological parameters gain importance in the treatment decision of HV disease. The accepted standard radiological measurements to reveal the severity of the disease are hallux valgus angle (HVA) and intermetatarsal angle (IMA) [11]. According to our literature review, studies investigating the correlation between these angles and the patients' QoL are limited.

The aim of our study was to investigate whether the disease really affects the quality of life using standard radiological measurements in symptomatic and non-surgical patients with varying degrees of HV deformities.

METHODS

A total of 100 patients who were 18 to 75 years of age and were diagnosed with HV in the Physical Medicine and Rehabilitation and Orthopedics and Traumatology Clinics at SANKO University Sani Konukoglu Practice and Research Hospital between March 2019 and February 2020 were included in this study. The patients were randomly selected from those who have not undergone surgical treatment and botulinum toxin injections and used any HV orthotic devices (e.g, interdigital reel, night splint) throughout their lives. Patients who were over 75 years old, had rheumatic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and gout, history of foot surgery or trauma, and those with neurological diseases were not included in the study. The study protocol was approved by the SANKO University Clinical Research Ethics Committee (Decision No: 2019/02-04; Date: 04.03.2019). The study was conducted in accordance with the principles of the Declaration of Helsinki. A written informed consent was obtained from each participant. Demographic data of the individuals such as age, gender and body weight index (BMI = kg/m²) were recorded.

The degree of the deformity was evaluated with radiological parameters using the HVA and the IMA. Since the severity of hallux valgus may differ between feet in the same individual, we evaluated the most painful foot.

The measurements of the HVA and IMA angles on standing anterior-posterior foot radiographs were performed by two independent physicians. PACS (PACS Expertise, Marosis, South Korea) computer system in a conventional X-ray machine was used for radiographic evaluations. The HVA was categorized as normal (< 15°), mild (Stage 1) (15-20°), moderate (Stage 2) (20-40°), and severe (Stage 3) (≥ 40°); the IMA as normal (< 9°), mild (Stage 1) (9-11°), moderate (Stage 2) (11–16°), and severe (Stage 3) (≥ 16°) [12].

The Short Form-36 (SF-36) instrument was used to measure the overall QoL. In the SF-36 scale, eight dimensions of health, including physical function, social function, role limitations (due to physical and emotional reasons), mental health, vitality/energy, pain, and general perception of health are examined with 36 items. The scores range from 0 to 100, separately for each subscale. A high score is an indicator of good QoL [13]. Intensity of pain was evaluated using a visual analog scale (0-100) (VAS) [14]. The Foot Function Index (FFI) was used to evaluate foot pain and the functional status of the foot [15]. FFI consists of 23 items on 3 subscales with three subgroups. FFI is scored on a visual analog scale between numeric anchors representing extremes. In calculations, all scores are averaged. Higher scores indicate more pain, disability, and activity restriction.

Statistical Analysis

IBM SPSS Statistics v.23 package program was used for data analysis. In expressing the descriptive statistics, the mean and standard deviation or the median and minimum-maximum values were given for quantitative data, and the frequency and percentage values were given for qualitative data. The compliance

of the quantitative data with normal distribution was evaluated using the Kolmogorov-Smirnov test. In group comparisons of the quantitative data, the independent samples t-test (quality of life comparisons according to gender), one-way ANOVA (FFI) or Kruskal-Wallis variance analysis (quality of life comparisons according to severity of hallux valgus and intermetatarsal angles except FFI) were used according to the suitability of the data. When a significant difference was detected in the ANOVA results, Tukey's or Dunn's test was used to determine the difference. The relationship between two continuous data was evaluated using the Pearson correlation coefficient (correlations between quality of life and patient characteristics). In all evaluations, a p level <0.05 was considered statistically significant.

RESULTS

A total of 100 participants (mean age: 49.25 ± 15.20 years, range: 18 to 75 years) were enrolled in this study. Table 1 shows the characteristics of the patients such as age, education, affected foot, gender, BMI, HVA, IMA, FFI, SF-36, and foot pain levels in VAS. First, we stated that 67% of patients were women and in 57% of the cases the right foot was affected. Mean scores ± SD were significantly high in the assessment of foot pain, foot function, and BMI for all patients.

Regarding HVA, there were 23 cases classified as 'HV3/severe' (> 40°); 51 cases classified as 'HV2/moderate' (20-40°), and 26 cases classified as 'HV1/mild' (15-20°). The classification of the IMA revealed that 22 cases were categorized as 'IMA1/mild' (9-11°), 37 as 'IMA2/moderate' (11-16°), and 41 as 'IMA3/severe' cases (> 16°).

In all patients there was a statistically significant correlation between scores of SF- role physical, SF-energy/fatigue, SF-social functioning and pain (VAS-foot) scores ($p < 0.05$). Additionally, a statistically significant positive correlation was found between FFI, HVA, IMA and VAS-foot pain ($p < 0.001$) (Table 2).

In gender-based comparisons, it was observed SF-energy fatigue, SF-emotional well-being, SF-general health, and SF-mental health scores were significantly lower in females than males ($p = 0.004$, $p = 0.045$, p

Table 1. Sociodemographic and clinical characteristic of patients (n = 100)

	Mean ± SD (Range)
Age (years)	49.25 ± 15.20 18-75
BMI (kg/m²)	25.35 ± 3.94 19.3-36.2
Education level, n (%)	
Untrained	12 (12)
Low	13 (13)
Middle	38 (38)
High	37 (37)
Affected foot, n (%)	
Right	57 (57)
Left	43 (43)
Gender, n (%)	
Female	67 (67)
Male	33 (33)
HVA	32.52 ± 8.07 16.2-53.4
IMA	14.53 ± 2.91 8.5-20.7
FFI	70.27 ± 10.01 31-88
VAS-foot pain	77.20 ± 10.47 60-100
SF-Physical functioning	54.90 ± 12.26 25-75
SF-Role physical	40.5 ± 17.86 25-75
SF-Role emotional	66.1 ± 22.22 33-100
SF-Energy/Fatigue	59.50±19.73 25-100
SF-Emotional well being	49.56 ± 16.63 28-72
SF-Social functioning	65.20 ± 19.74 25-88
SF-Pain	40.30 ± 11.36 25-63
SF-General health	61.30 ± 13.38 30-80
SF-Mental health	56.35 ± 15.56 25-80

BMI = Body Mass Index, HVA = Hallux Valgus Angle, IMA = Intermetatarsal Angle, FFI = Foot Function Index, VAS = Visual Analogue Scale, SF = Short Form, SD = Standart Deviation

Table 2. Correlations between quality of life and patient characteristics.

		Age (years)	BMI (kg/m^2)	VAS-foot pain	FFI	HVA	IMA
SF-Physical functioning	r	0.050	-0.081	-0.144	0.039	-0.101	-0.082
	p	0.624	0.422	0.154	0.701	0,317	0.416
SF-Role physical	r	-0.067	0.067	-0.401	-0.106	-0,429	-0.165
	p	0.507	0.508	**< 0.001**	0.293	**< 0.001**	0.102
SF-Role emotional	r	-0.241	0.093	-0.095	-0.341	-0.195	0.039
	p	0.016	0.360	0.347	**0.001**	0.052	0.702
SF-Energy/Fatigue	r	-0.111	0.100	-0.383	-0.322	-0.290	-0.044
	p	0.270	0.320	**< 0.001**	**0.001**	**0.003**	0.667
SF-Emotional well being	r	0.146	0.246	-0.004	-0.143	0.168	0.181
	p	0.148	0.013	0.971	0.154	0.096	0.071
SF-Social functioning	r	-0.026	0.166	-0,515	-0.413	-0.467	-0.249
	p	0.796	0.098	**< 0.001**	**< 0.001**	**< 0.001**	**0.013**
SF-Pain	r	0.101	-0.117	-0.133	0.092	-0.254	-0.232
	p	0.316	0.246	0.188	0.360	**0.011**	**0.020**
SF-General health	r	-0.386	-0.120	0.185	-0.143	0.240	0.334
	p	**< 0.001**	0.235	0.066	0.156	**0.016**	**0.001**
SF-Mental health	r	-0,483	-0.021	0.101	-0.276	0.265	0.302
	p	**< 0.001**	0.833	0.318	**0.005**	**0.008**	**0.002**

BMI = Body Mass Index, HVA = Hallux Valgus Angle, IMA = Intermetatarsal Angle, FFI = Foot Function Index, VAS = Visual Analogue Scale, SF = Short Form, r= Pearson correlation coefficient

Table 3. Quality of life comparisons according to gender

	Female Mean±SD (n = 67)	Male Mean±SD (n = 33)	*p* value
SF-Physical functioning	55.00 ± 12.43	54.70 ± 12.11	0.908
SF-Role physical	41.04 ±17.78	40.76 ± 18.29	0.940
SF-Role emotional	66.68 ± 21.72	64.65 ± 23.49	0.671
SF-Energy/Fatigue	55.75 ± 20.11	67.12 ± 16.77	**0.004**
SF-Emotional well being	47.22 ±16.30	54.30 ± 16.52	**0.045**
SF-Social functioning	64.10± 20.27	67.42 ± 18.73	0.432
SF-Pain	41.79 ± 10.85	37.27 ± 11.94	0.061
SF-General health	58.81 ± 13.08	66.36 ± 12.70	**0.007**
SF-Mental health	52.69 ± 14.25	63.79 ± 15.66	**0.001**
VAS	77.46 ± 10.74	76.67 ± 10.05	0.723
FFI	69.66 ± 10.35	71.52 ± 9.32	0.386

FFI = Foot Function Index, VAS = Visual Analogue Scale, SF = Short Form, SD = Standart Deviation.
Independent samples t-test.

= 0.007, and $p = 0.001$, respectively) (Table 3).

When the group with HVA3/severe deformity was compared with the mild and moderate groups, VAS-foot pain, SF-role limitations due to physical health, SF-social functioning, SF-bodily pain, SF-general health, and SF-mental health scores were found to be statistically significantly worse ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p = 0.027$, $p = 0.005$, and $p = 0.017$, respectively) (Table 4).

In classification of the deformity based on the IMA, a significant difference was detected in the VAS-foot pain, SF-social functioning, SF-bodily pain, and SF-general health scores in comparison of the IMA3/severe group with the other groups ($p = 0.004$, $p = 0.016$, $p = 0.015$, and $p = 0.008$, respectively) (Table 4).

The FFI was worse in the HVA3/severe deformity group than the HVA1/mild group ($p = 0.042$). However, there was no difference in foot function according to the radiographic severity of the IMA ($p > 0.05$) (Table 4).

DISCUSSION

The results of this study showed that the increase in HVA and IMA decreased the quality of life in HV patients as expected, but the increase in radiological HVA in patients with HV was a more effective parameter than IMA in evaluating QoL and foot function.

HV is associated with diminished QoL [16], and patients often complain of difficulty in walking and standing [17], nail disorders [18], bunions [19], and calluses [20]. HV therapy aims to relieve pain and improve function. Conservative treatment options include padding, splinting, shoe modification, orthosis, and nonsteroidal anti-inflammatory drugs [21]. Botulinum toxin injection is a potentially effective method in reducing HV deformity and associated pain [22]. However, these methods provide short-term relief for the patient. Different qualitative and quantitative evaluations are available to define the severity of the deformity. HVA, IMA, metatarsophalangeal osteoarthritis, metatarsal rotation, and lateral round

Table 4. Quality of life comparisons according to severity of hallux valgus and intermetatarsal angles

	HVA1 Mean ± SD (range) (n = 26)	HVA2 Mean ± SD (range) (n = 51)	HVA3 Mean ± SD (range) (n = 23)	*p* value	IMA1 Mean ± SD (range) (n = 22)	IMA2 Mean ± SD (range) (n = 37)	IMA3 Mean ± SD (range) (n = 41)	*p* value
SF-Physical functioning*	60 (25-70)	60 (25-75)	50 (25-70)	0.532	62.5 (25-70)	55 (25-75)	50 (25-75)	0.500
SF-Role physical*	50 (25-75)	25 (25-75)	25 (25-70)	**< 0.001**	50 (25-75)	50 (25-75)	25 (25-75)	0.239
SF-Role emotional*	66.7 (33.3-100)	66.7 (33.3-100)	66.7 (33.3-100)	0.136	66.7 (33.3-100)	66.7 (33.3-100)	66,7 (33.3-100)	0.645
SF-Energy/Fatigue*	72.5 (40-100)	50 (30-95)	65 (25-85)	0.059	55 (25-85)	65 (30-100)	60 (30-95)	0.562
SF-Emotional well-being*	44 (28-72)	60 (28-72)	60 (28-72)	0.130	44 (28-72)	48 (28-72)	60 (28-72)	0.369
SF-Social functioning*	87.5 (37.5-87.5)	62.5 (25-87.5)	62.5 (25-87.5)	**< 0.001**	81.25 (25-87.5)	75 (25-87.5)	62.5 (25-87.5)	**0.016**
SF-Pain*	50 (25-62.5)	45 (25-55)	32.5 (25-50)	**0.027**	50 (25-62.5)	45 (25-55)	32.5 (25-55)	**0.015**
SF-General health*	50 (30-80)	60 (30-80)	70 (30-80)	**0.005**	55 (30-80)	66 (30-80)	70 (40-80)	**0.008**
SF-Mental health*	50 (25-80)	50 (25-80)	60 (25-80)	**0.017**	50 (25-75)	50 (25-80)	60 (25-80)	0.052
VAS*	70 (60-85)	80 (60-95)	85 (60-100)	**< 0.001**	70 (60-100)	80 (60-100)	80 (60-100)	**0.004**
FFI**	68.19 ± 9.64 (53-88)	69.29 ± 9.92 (31-86)	74.78 ± 9.65 (58-88)	**0.042**	68.95 ± 9.48 (54-88)	69.70 ± 8.95 (53-86)	71.49 ± 11.22 (31-88)	0.580

HVA = Hallux Valgus Angle, IMA = Intermetatarsal Angle, FFI = Foot Function Index, VAS = Visual Analogue Scale, SF = Short Form, SD = Standart Deviation.

*Kruskal-Wallis variance analysis. **One-way ANOVA.

sign of first metatarsal present are among these evaluations. Besides radiographic measurements, clinical evaluation methods such as quality of life can guide the definition and optimal treatment of HV deformity [23].

Our study aimed to objectively evaluate the daily lives of symptomatic and untreated HV patients, depending on the radiological angles of varying degrees. Each domain (physical, mental and social) included in these scales is related to QoL and these domains are closely related to each other. In our study, when the SF-36 values of all patients were examined, it was found that there was a statistically significant impairment in SF-role limitations due to physical health, SF-energy/fatigue, SF-social functioning, and foot pain (VAS) scores ($p < 0.05$). However, a statistically significant positive correlation was found between foot pain (VAS) and the FFI, and radiologically measured deformity degrees in all patients ($p < 0.05$).

Hallux valgus angle is defined as the angle between the shaft axis of the first metatarsal and the proximal phalanx of the hallux. Values of HVA greater than 15° are considered to be pathological. IMA is the angle between the shaft axis of the first and second metatarsal. Values above 9° are generally interpreted as pathological. In general, the appearance of the deformity and the degree of HVA/IMA determine the treatment strategies.

In our study, the SF-36 scores in the SF-role limitations due to physical health, SF-social functioning, SF-bodily pain, SF-general health, and SF-mental health subgroups were significantly different between the HVA3/severe group and the HVA1/mild and HVA1/moderate HVA groups ($p < 0.05$). However, in our study, the SF-social functioning, SF-bodily pain, and SF-general health domains had a significant difference in comparison of the IMA3/severe group with the IMA1/mild and IMA3/moderate groups. There is no consensus in the literature regarding the radiographic parameters. Lazarides et al. [24] found that "The severity of HVA is significantly affected the general health and the severity of IMA affected the SF-role physical, SF-role emotional, and SF-mental health". Another study reporting the emergence of a worse health scenario as deformity increases showed that all SF-36 subscale scores demonstrated a significant decreasing trend as the severity of hallux valgus increased [6].

Hallux valgus deformity is not a disorder that only affects women. In our study, approximately 70% of the patients with HV were females. Anxiety and depression are common disorders reported to be more common in women [25]. Moreover, patients with anxiety and/or depression, and those with a higher percentage of severe deformities than those who are not affected by these mental disorders have lower scores in the mental health domain in QoL assessments [26]. In our study, it was observed that the impairment in SF-energy fatigue, SF-emotional well-being, SF-general health, and SF-mental health scores was more significant in females compared to males. However, although the HV prevalence is higher in women, the predictive effect of HV treatment does not appear to be associated with the gender of the patients. A study involving only female patients showed that there was no clear relationship between the effect of varying degrees of HVA and foot deformity and QoL [27]. Another study showed that the increasing severity of HVA with a progressive decrease in general health and foot health was higher in elderly individuals with HV, regardless of gender [28].

The results of our study also revealed a relationship between the varying degrees of HVA and foot function parameter scores. The increase in the HVA led to higher scores in the FFI, which evaluates pain, difficulty, and disability during different activities, while the increase in IMA did not affect this result. It has been shown that the presence of HV significantly reduces QoL by causing foot pain, disability, and functional restrictions [29].

Pain that cannot be managed by conservative treatment methods is the most important indication for surgery. VAS has been shown to be an approved and reliable method in the evaluation of QoL in patients with HV [30]. In our study, a statistically significant positive correlation was detected between the FFI, HVA, IMA and VAS scores ($p < 0.05$). We also observed that as the deformity of the HVA and IMA increased, the pain scores that affect the QoL of the individuals also increased.

Limitations

Although our study is compatible in terms of the number of patients with other studies, it had some limitations such as the sample size. Social differences, including the genetic and structural foot differences of

the patients and the choice of shoes in women, can be listed among the factors that limited our study.

CONCLUSION

The results of this study showed that radiological HVA is a more effective parameter than IMA on quality of life, pain, and disability in patients with non-surgical HV, and it may be more eligible to use HVA as a reference when assessing foot function. In making a surgical decision, not only the severity of HVA but also the effect of this angle on the patient's quality of life should be considered.

Authors' Contribution

Study Conception: TT, GBS; Study Design: TT; Supervision: TT, GBS; Funding: TT, GBS; Materials: TT, GBS; Data Collection and/or Processing: TT; Statistical Analysis and/or Data Interpretation: TT, GBS; Literature Review: TT; Manuscript Preparation: TT and Critical Review: TT, GBS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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