e-ISSN: 2636-8579

JHSM

Journal of Health Sciences and Medicine

VOLUM: 5 ISSUE: 4 YEAR: 2022

PUBLICATION BOARD

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Sincerely yours.

Assoc. Prof. Ercan YUVANÇ, MD
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DOI: 10.32322/jhsm.1105826
J Health Sci Med 2022; 5(4): 938-941

The recovery of ocular surface after bariatric surgery in morbid obese patients

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Cite this article as: Şahin Vural G, Çay F. The recovery of ocular surface after bariatric surgery in morbid obese patients. J Health Sci Med 2022; 5(4): 938-941.

ABSTRACT

Aim: To evaluate the alterations of the ocular surface in morbid obese patients after bariatric surgery.

Material and Method: The morbid obese patients who underwent sleeve gastrectomy surgery between February 2019 and September 2020 at Department of General Surgery in Balıkesir University Medicine Faculty were evaluated were evaluated in preoperative/postoperative 6th month period. The body-mass index (BMI), abdominal circumference (AC), Ocular Surface Disease Index (OSDI) questionnaire, tear osmolarity, Oxford ocular surface staining score, and Schirmer's test were performed. Preoperative and postoperative values were compared.

Results: The study included 68 eyes of 68 patients (33.76±9.85 years). The BCVA was improved from 0.98±0.11 to 1.00, the BMI was changed from 45.11±2.23 to 30.70±4.92 kg/m^2 ($p<0.05$) while AC was decreased from 134.97±6.07 to 109.38±6.26 cm ($p<0.05$) after surgery. In preoperative and postoperative period, OSDI was 12.33±20.57 and zero, tear osmolarity was 301.89±12.98 and 293.57±15.65 mOsm/L, Oxford grading was 0.42±0.69 and 0.04±0.20, Schirmer's test was 13.66±7.71 and 19.26±6.48 mm (in all, $p<0.05$), respectively. The change in BMI was correlated with postoperative tear osmolarity (r:0.251, p: 0.039), and T-BUT (r: -0.254, p: 0.037). In preoperative values, the preoperative BMI was correlated with OSDI scores and corneal staining score (r:0.292, r:0.388; $p<0.05$ respectively).

Conclusion: The decrease in BMI after surgery improves dry-eye disorder. Bariatric surgery is also crucial in the recovery of ocular surface parameters.

Keywords: Bariatric surgery, dry eye disorder, obesity

INTRODUCTION

Obesity is associated with increased morbidity and early mortality related to the increased prevalence of chronic diseases. There are more than 1 billion overweight adults and at least 300 million obese all over the world (1). Bariatric surgery is the most effective choice in weight loss and has been an increasing treatment modality in morbid obesity which is described as body mass index (BMI) >40 or ≥35 kg/m^2 when associated with comorbidities such as arterial hypertension, dyslipidemia, sleep apnea, or diabetes (2,3). The surgical approaches are described as malabsorptive (Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch) or restrictive (adjustable gastric banding, sleeve gastrectomy) bariatric techniques. Sleeve gastrectomy is the most performed method because it is relatively easier, has fewer complication rates, and has shorter operation duration. After bariatric surgery, patients generally receive excessive lifestyle changes, loss of weight, and dietary restrictions. Also, the eye and ocular surface may be influenced by these alterations (4).

Obesity is known as a systemic inflammatory syndrome, and similarly dry eye syndrome (DES) is an inflammatory process of the ocular surface. The Study Group for Environmental Eye Disease showed that obesity is a risk factor for symptomatic DES (5). Although the effect of obesity on the ocular surface has been mentioned in previous studies (6,7), the effect of bariatric surgery is still unclear. In our opinion, obesity may cause ocular surface disorders, and the alterations in BMI after sleeve gastrectomy may improve ocular surface disturbances by recovering to a non-inflammatory process. The aim of this study is to compare the ocular surface alterations after bariatric surgery in morbid obesity patients.

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Received: 19.04.2022 **Accepted:** 09.05.2022

MATERIAL AND METHOD

The study was carried out with the permission of Balıkesir University Clinical Researchs Ethics Committee (Date: 09.10.2019, Decision No: 2019/136). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this prospective study, seventy-six (n:76) patients who have been diagnosed with morbid obesity (BMI >40 or ≥35 kg/m^2 when associated with comorbidities such as arterial hypertension, dyslipidemia, sleep apnea, or diabetes) and performed bariatric surgery between February 2019 and September 2020 at Department of General Surgery in Balıkesir University Medicine Faculty were evaluated. All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration. All participants were consulted to the department of ophthalmology for routine ophthalmic examinations at the immediate preoperative period and postoperative sixth months. The patients who have been performed sleeve gastrectomy were included while five patients who underwent Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch were excluded. Three patients have not completed the follow-up period. Other exclusion criteria were being under the age of 18, history of the ocular surface disorder, previous ocular surgery, any type of topical or systemic (diuretics, antihistamines, vitamins, antidepressants, or anticholinergics) drug use and contact lens wear, history of keratitis, blepharitis, ocular trauma, patients with the corneal punctate epithelial erosion, accompanying systemic disease outside of obesity, Steven-Johnson syndrome, history of thermal/chemical/radiation damage. After strict exclusion criteria, the study included 68 eyes of 68 patients. All participants underwent a detailed ophthalmic examination including best-corrected visual acuity (BCVA), intraocular pressure (IOP), (TONOREF III, Nidek, Gamagori, Aichi, Japan), biomicroscopic examination, and non-dilated fundus examination. Firstly, the ocular surface disease index questionnaire (OSDI-includes 12 questions about the effect of dry-eye symptoms on life quality; Allergan, Irvine, California, USA) has been performed by themselves. Besides, tear osmolarity (quantified by TearLab Osmolarity System; San Diego, California, USA), tear break-up time (T-BUT), Oxford grading score of ocular surface staining (with Lissamine Green), and Schirmer's test was performed at preoperative and postoperative period. In each visit, BMI, abdominal circumference (AC), and follow-up period were recorded. The data obtained from patients in the pre&post operative period were compared.

Statistical Analysis

Statistical analysis was conducted using SPSS statistical software, version 23.0. Patient age and BMI were reported as means and Standard deviation and medians and range and compared by chi-quare tests. The gender distribution was reported by absolute and relative frequency. Mean OSDI scores, mean tear film BUT, Schirmer's and Oxford scores were reported by group means and standard deviation and medians and range and paired samples t-test. Results were shown for each value using tables. The tests were conducted with a significance level of 5%. The correlation between parameters was evaluated with Pearson correlation analysis.

RESULTS

In this study, 48 of the participants were female (70.5%) and 20 of them were male (29.4%). The mean age of the patients was 33.76±9.85 years. The BCVA was 0.98±0.11 preoperatively while 1.00 was in the postoperative period. In the preoperative period, the average BMI was 45.11±2.23 kg/m^2, and the AC 134.97±6.07 cm while the average BMI was decreased to 30.70±4.92 kg/m^2 ($p<0.05$), and the mean of AC was decreased to 109.38±6.26 cm ($p<0.05$) postoperatively. The average BMI change was 14.70±5.32 kg/m^2.

Ocular surface properties were summarized in **Table**. In Pearson correlation analysis, the change in BMI was significantly correlated with postoperative tear osmolarity (r:0.251, p: 0.039), and T-BUT (r: -0.254, p: 0.037). In preoperative values, the BMI was significantly correlated with OSDI scores and corneal staining score (r:0.292, r:0.388; $p<0.05$ respectively).

Table. The ocular surface properties in morbid obese patients in preoperative and postoperative period

	Preoperative	Postoperative	p value
OSDI	12.33±20.57	0	<0.05*
T-Osmolarity (mOsm/L)	301.89±12.98	293.57±15.65	<0.05*
T-BUT (sec)	8.35±13.61	13.61±2.46	<0.05*
Oxford grading	0.42±0.69	0.04±0.20	<0.05*
Schirmer's test (mm)	13.66±7.71	19.26±6.48	<0.05*

OSDI: Ocular Surface Disease Index Questionnaire Score, T-Osmolarity: Tear osmolartiy, T-BUT: Tear break-up time.
p value: Statistically significant ratio

DISCUSSION

In this prospective study, all ocular surface parameters were improved after sleeve gastrectomy. The changes in ocular surface properties after bariatric surgery were investigated in a few studies. These studies found any change in the ocular surface after surgery. Brandao et al. (8) compared the effect of sleeve gastrectomy and Roux en Y on ocular surface parameters, and they resulted that there was no significant change in ocular surface parameters between groups. Marques et al. (9) performed a dry eye-specific questionnaire, the tear ferning test, T-BUT,

Schirmer's test, ocular surface staining, and impression cytology before and after surgery. They resulted in any change in ocular surface parameters and evaluated the ocular surface up to 5 years after surgery compared with preoperative results. In our study, the participants were symptomatic in the preoperative period, the dry-eye symptoms were decreased after surgery.

The systemic inflammation and overactivity in the immune system were observed in obesity, and the amount of C-reactive protein and fibrinogen, the indicators of inflammation, has increased (10). The inflammation affects certain organs as well as the eyes. DED is defined as tear film instability, hyperosmolarity, ocular surface inflammation, and damage (11). The relationship between obesity and DED has been evaluated in several studies. In animal studies, Osae et al. (6) declared that meibomian gland hypertrophy and excessive tearing were found in obese mice that have fed with the high-fat diet, and associated dyslipidemia and obesity with altered meibum composition, a key feature of meibomian gland disease (MGD). Baser et al. (7) evaluated 92 polycystic ovarian syndrome (PCOS) patients with high BMI and compared the Schirmer's test, T-BUT, and OSDI with healthy subjects, and resulted that patients with high BMI are associated with tear film instability due to MGD. The animal studies showed that obesity may lead to corneal nerve degeneration and progression in corneal neuropathy independently of hyperglycemia. Besides, the alterations in corneal nerves can be used in the diagnosis of peripheric neuropathy in non-diabetic obese mice (12). They explained that it is still not certain how obesity impacts the ocular surface. The indicators related to inflammation were increased in obesity, and most of them are mainly produced by adipose tissue. (13–18). The incapacitated adipose tissue volume after bariatric surgery results in decreased inflammatory markers.

The tear osmolarity was significantly decreased after surgery. It is accepted as a gold standard quantitative method in the diagnosis of DED (18). The new description of DED includes increased tear inflammation, and the osmolarity is correlated with ocular surface inflammation. Even there was no significant correlation between ocular surface symptoms and the tear osmolarity in the preoperative period, and the mean of tear osmolarity was in the normal range (275-307 mOsm/L), and it was improved after surgery.

Brandao et al. (8) found T-BUT as 7.5 sec in patients who underwent sleeve gastrectomy at least 6 months ago. In our study, the average of T-BUT was 8.35 sec preoperatively and increased up to 13.61 sec postoperatively. This results that tear film integrity improves after bariatric surgery and indicated the recovery in meibomian gland activity. The effects of obesity on meibomian glands have been published in previous studies (7,20,21). Baser et al. (7) have indicated that there is a relationship between the increase of BMI and meibomian gland dysfunction, thus causing the development of dry eye disease. Additionally, lagophthalmos may exacerbate evaporative dry eye syndrome in obese patients. Lagophthalmos, especially in the night, is caused by floppy eyelid syndrome (FES) and obesity is one of the most important issues in FES (21). After surgery, both floppiness in eyelids may reverse, and symptoms disappear. We focused on dry-eye parameters so we were not recorded the lid laxity. For this reason, it is not possible to mention a certain relationship according to our results.

According to the OSDI questionnaire, 38.2% of the patients had dry-eye symptoms preoperatively. After surgery, OSDI was decreased and only two patients were still symptomatic. In previous studies, the OSDI questionnaire was applied to obese patients after bariatric surgery and reported as symptomatic in most of the patients (60.7%) (8). In a prospective study, Marques et al. (9) were evaluated 89 obese patients for about 12 months and resulted in no change in OSDI in the postoperative period. In the preoperative period, ocular hyperemia and complaints of a foreign body sensation were reported, but the complaints did not differ after surgery. The contrast in our study may be related to improvement in the quality of life following bariatric surgery (4). When patients feel satisfied with their general health status, the complaints may be decreased related to the ocular surface.

In this study, Schirmer's test showed that 60.2% of patients had decreased tear production and improved to 19.1% after surgery. This shows us that there is a failure in tear production in obese patients, and even the bariatric surgery and weight loss improve tear production, the patients still have low Schirmer's scores. The main source of tear production is the lacrimal gland. In obese patients, the inflammation in the lacrimal gland may be a component of systemic inflammation. The relationship between BMI and lacrimal gland inflammation has been investigated in previous studies (23) and has been claimed that inflammation (which directly affects the epithelium cells) may play an important role in the development of the DED. The commonly accepted opinion in the literature about the relationship between DED and obesity is inflammation (13–16). The immune homeostasis of the ocular surface is regulated with the balance of lymphocytes and anti-inflammatory factors such as IL-1 receptor antagonists, transforming growth factor (TGF)-β2, and matrix protease inhibitors like tissue inhibitors of metalloproteinase (TIMP)-1 (24). In the literature, there is not enough data about the change in the level of inflammatory mediators after bariatric surgery.

CONCLUSION

There are several mechanisms that are considered about ocular surface disorders in obesity, and the effect of bariatric surgery on the ocular surface is still controversial. According to our results, the decrease in BMI after bariatric surgery improves dry-eye disorder if Bariatric surgery is not only beneficial in weight loss, anatomical and physiological changes; it is also crucial in the recovery of ocular surface parameters. Further studies with larger-scaled patients should be designed with the inclusion of biochemical, histological, and functional parameters.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Balıkesir University Clinical Researchs Ethics Committee (Date: 09.10.2019, Decision No: 2019/136).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1112941
J Health Sci Med 2022; 5(4): 942-948

Surgical treatment of liver hydatic cyst and evaluation of cystobiliary fistula: experience of two centers

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Cite this article as: Dizen H, Yalınbaş Kaya B. Surgical treatment of liver hydatic cyst and evaluation of cystobiliary fistula: experience of two centers. J Health Sci Med 2022; 5(4): 942-948.

ABSTRACT

Objective: Intrabiliary rupture or cystobiliary fistula is the most common complication of hepatic hydatid cyst. In this article, our objective is to evaluate the clinical, laboratory, imaging, surgical treatment and results of cystobiliary fistulas, which is the most common complication of hydatid cysts.

Material and Method: In our study, patients who underwent open surgery and were followed up and treated for hydatid cyst in the gastroenterology and general surgery outpatient clinic and service between years 2015-2021 were included. The clinical, laboratory, radiological and surgical results of 171 patients with hydatid cysts were retrospectively analyzed.

Results: The mean age of 171 patients who underwent surgery for hydatid cyst was 44.8 (18-71), 68 of whom were men and 103 were women. Bile leakage was present in 50 patients (50 (29.23%)). There were 24 (48%) men and 26 (52%) women with bile leakage. The cyst diameter was 74.2 (36-170) mm and the number of cysts was 1.2 (1-2). The cysts were located in the right lobe of the liver in 116 (79%) patients, in the left lobe in 30 (15%) patients, and in both lobes in 25 (6%) patients. Cystobiliary fistula developed more frequently, especially in cysts located in the right lobe(36 (72%)). Cystobiliary fistula was most common in CE3 (Gharbi type 2) type (30 (60%)). Cystectomy+drainage was performed in 137 (80%) patients in all groups. Cystectomy and drainage were the most common surgical procedures. The cyst diameter was 10 cm in the group with cystobiliary fistula and was significant compared to the group without fistula ($p<0.001$). Aminotransferase (AST and ALT) levels were high in patients with cystobiliary fistula ($p=0.012$, $p=0.054$). However, there was no significant difference between the two groups in alkaline phosphatase, total bilirubin, and gamma glutamyl transferase ($p=0.231$, $p=0.097$, $p=0.544$).

Conclusion: Liver hydatid cyst is endemic in our country as well as in many other countries in the world. Complicated hepatic hydatid cysts require timely and appropriate treatment because of their life-threatening complications. Cytobiliary fistula is the most common complication. In the surgical treatment of hydatid cyst disease, the earlier the diagnosis of occult cystobiliary fistulas is made (especially in the preoperative or peroperative period), the easier the treatment is, and the risk of bile leakage and consequently the morbidity and mortality decreases. Our results and experience showed that treatment and complications are related to the location and size of the cyst, occult/large cystobiliary fistula, detectability of occult fistulas, experienced center and surgeon.

Keywords: Liver hydatid cyst, surgical treatment, cystobiliary fistula

INTRODUCTION

Hepatic cystic echinococcosis (HCE), caused by *Echinococcus granulosus (E. granulosus)*, is a zoonotic parasitic disease and approximately 4000 patients are diagnosed with hydatid cyst per year in Turkey (1-3). It is endemic in Mediterranean countries, the Middle East, Central Asia, South America, Africa, Australia and New Zealand. *E. granulosus* is a parasite that is found as larva in the canine intestine and in cyst forms in nature, dogs are the main host and humans are the intermediate host (4,5). The cycle of the parasite in humans starts with the opening of orally ingested cysts in the intestine, and then the parasite larvae join the blood circulation through the portal system and settle in the target organs, especially the liver. Echinococcal groups; *E. granulosus*, *E. multilocularis*, *E. oligarthrus* and *E. vogeli*. *E. granulosus* is most frequently responsible for cystic formation. It is usually localized in the liver (68.8-80%) and lungs (10-22.4%). Spleen (0.9–8%), skeleton (0.2–3%), kidney (0.4–3.7%), brain (0.4–1%), cardiac muscle (0.02–1.1%), peritoneum (2-5.2%) are localizations where it is rarely

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Received: 05.05.2022 **Accepted:** 16.05.2022

localized (4-6). The pericyst, the outermost layer of the cyst, is a fibrous layer. Inside, there is acellular, laminar membrane. Cellular germinative membrane covers the inner surface of the laminar membrane. They are cystitatic, spherical, fluid-filled, unilocular vesicles. It is usually asymptomatic. Infection and continuous growth of the cyst may cause compression, erosion, and adhesion to adjacent structures. As the intracystic pressure rises from 30-35 cm H_2O to 80 cm H_2O, inflammation leads to necrosis, causes rupture or fistulization (7,8). The most common symptoms are abdominal pain, palpable mass in the right upper quadrant, hepatomegaly. Cholangitis, jaundice, fever, anaphylaxis and acute abdominal pain are symptoms of complicated hydatid disease (9,10). The most common complications of hepatic hydatid cyst are fistulization to the intrahepatic bile ducts, pressure on the surrounding organs and infection. The rates of intrabiliary rupture or cystobiliary fistula vary between 2% and 42% in various studies in the literature (11,12). Ultrasonography (USG) is the basic imaging method for the diagnosis of echinococcosis. However, computed tomography (CT) and magnetic resonance imaging (MRI/MRCP) are important in determining the characteristics of the cyst and its relationship with adjacent structures. In addition to imaging methods, serological tests such as enzyme-linked immunosorbent assay (ELISA), immunoblotting (IB) and indirect immunofluorescent antibody test (IFA) are used for diagnosis (13). The World Health Organization's Working Group on Echinococcosis (WHO-IWGE) standardized the classification system for liver hydatid cysts in 2001. The WHO classification is now used for staging and treatment selection. While cysts smaller than 5 cm (WHO stages CE1 and CE3a) are treated with only albendazole, PAIR and albendazole therapies are recommended for cysts larger than 5 cm. There is frequent relapse in PAIR therapy for patients with CE2 and CE3b cysts. While surgical treatment was once the most common treatment modality, it is now largely applied for complicated cysts (such as biliary fistula or perforated cysts) (CE2, CE3b). In addition, surgical treatment is a suitable treatment option for superficial cysts larger than 10 cm or at risk of rupture and for patients who are not suitable for percutaneous treatment. Surgical treatment options include open surgery and laparoscopic surgery (14-16).

Our aim in this study was to compile the frequency of association between hydatid cyst and biliary tract, clinical and laboratory features, diagnosis and treatment results.

MATERIAL AND METHOD

The study was initiated with the approval of the Eskişehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 18.01.2022, Decision No: 05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Between years 2015 and 2021 Patients who were followed up and operated due to hydatid cyst in gastroenterology and general surgery were included in the study by screening retrospectively. Age, gender, laboratory data, cyst structure and staging according to imaging, cyst diameter and location (right lobe (V, VI, VII, VIII), left lobe (II, III, IV), bilateral), perioperative results, the operative results of the patients who were operated on for hydatid cysts were documented by examining the records of the patients. Complete blood count and liver function tests (alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) of all patients were taken from the system. The type of operation (cystectomy drainage+omentoplasty, cystectomy drainage, resection) and whether there was a biliary fistula during the operation were recorded. The cysts were classified radiologically with the WHO (Gharbi) classification (**Table 1**) (**Figure 1**).

Table 1. WHO-IWGE (Gharbi) classification (13,16)

CL. Anechogenic uniloculated cyst, without echo or internal septa
CE 1(Gharbi type 1). Anechogenic cyst with fine echoes inside
CE 2(Gharbi type 2). A multivesicular appearance with multiple septums- active cyst
CE 3(Gharbi type 3). Fluid between the cyst membrane("waterlily sign") (CE3a) or (Gharbi type 2), Daughter vesicles (CE3b) associated with hypo/hyperechoic images-cyst in the transitional phase
CE 4 (Gharbi type 4). Mixed content, hypo/hyperechocenic, no offspring vesicle cyst-"wool clew" apperance-cyst in degenerative phase
CE 5 (Gharbi type 5). Partial or completely calcified wall cyst-inactive cyst

Patients who were diagnosed with hydatid cyst preoperatively by imaging (CT/MRI, ultrasound) and laboratory (ELISA, biochemistry tests) tests and operated were included in the study. Patients with a lack of imaging and pathological diagnosis and who had a large cystobiliary fistula in the preoperative period who showed cholangitis clinic were excluded from the study. All patients received albendazole treatment for at least 3 months, starting 10 to 15 days before the operation.

The operation procedures were chosen by the surgeons. In all operations, prophylactic antibiotics (cefazolin 1 g) were given to the patients 20 minutes before general anesthesia. All patients were operated on by open surgery method. After entering the abdomen by applying a midline, subcostal or makuuchi incision, abdominal exploration was performed. Liver ligaments were cut and mobilized sufficiently for the exploration

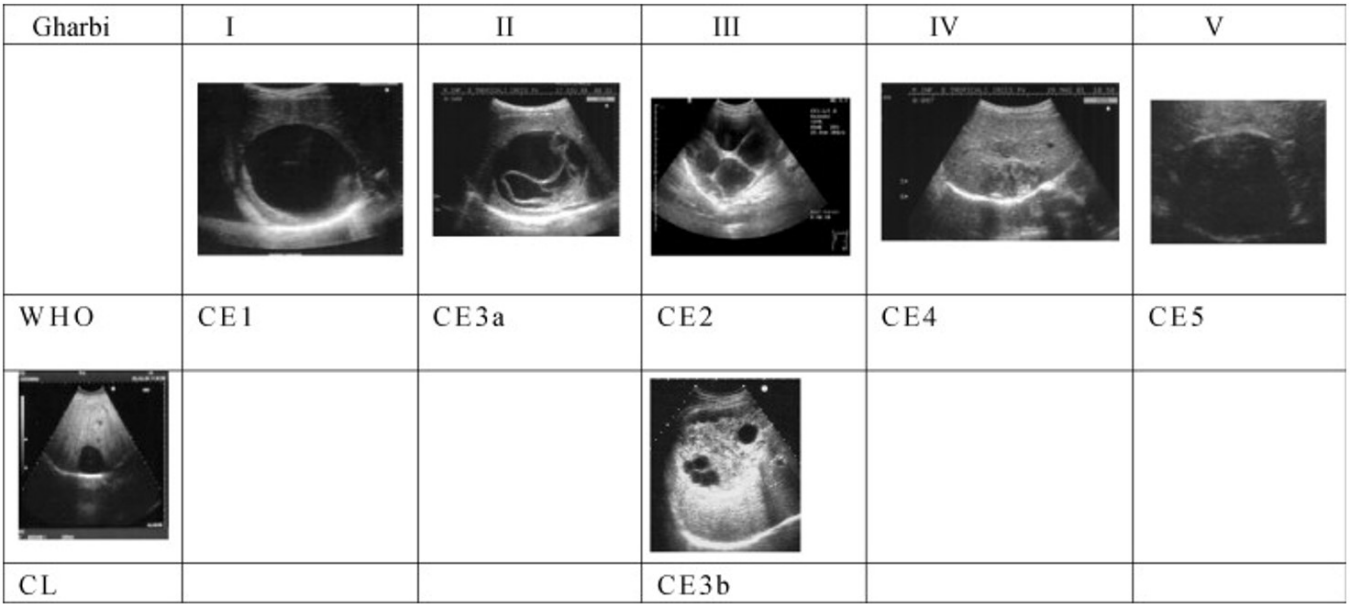

Figure 1. Comparison of Gharbi and WHO-IWGE ultrasound classification (16)

of the cyst cavity and ligation to be performed on the wall. During the evacuation of the cyst, compresses or gas pads impregnated with 3% hypertonic saline solution were placed around the cyst in order to prevent the spread of the parasite. The cyst content was aspirated by puncture into the cyst, and the aspirated cyst content was examined for bile contamination. Three percent hypertonic solution was filled from the puncture site to the cyst until high pressure was created. After waiting for about 10 minutes, the cyst was opened wide from the dome and its contents were evacuated in a controlled manner. If there were areas with apparent bile leakage in the cavity wall, they were sutured with 3/0 prolene. Then, long gas pads impregnated with 3% hypertonic solution were placed into the cavity to control both the repaired areas and detect occult fistulas. After waiting for about 5 minutes, the gas buffers placed in the cavity in a controlled manner were removed and it was checked whether there was bile contamination. Repairs were made to the places where bile contamination was detected until the bile contamination was over. After the cavity wall was sutured for hemostasis with absorbable sutures, a drain was placed into the cyst and the operation was terminated. Patients with apparent cystobiliary fistula of the biliary tract are diagnosed with radiology and laboratory examinations before the operation. However, preoperative diagnosis of occult cystobiliary fistula is very difficult. Occult cystobiliary fistulas can usually be diagnosed by the presence of bile leakage in the cyst cavity during the operation or by the bile flow from the patient's drains after the operation. In patients with large cystobiliary fistulas, if intraoperative bile leakage persisted despite suturing, T-tube drainage and choledochoduodenostomy were performed. A Roux-en-Y type pericystojejunostomy may be preferred in large fistulas opened to the main biliary tract or if the cavity is large. Patients with high-volume (over 300 cc) biliary drainage were followed up for an average of 7-10 days after surgery. ERCP was planned in cases with no decrease in biliary drainage and bile leakage was treated through ERCP by sphincterotomy, nasobiliary drainage or biliary stent placement. The drains were kept for three days after surgery and were removed when there was no bile leakage. If bile drainage continued, the drains were held in place until drainage stopped.

Statistical Analysis

SPSS 23.0 package software was used for statistical analysis of the data. Categorical measurements are presented as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum when necessary). Chi-square or Fisher's exact tests were used to compare categorical variables. The Mann-Whitney U test was used to compare continuous variables with variables such as the type of surgery. Statistical significance level was accepted as less than 0.05 in all tests.

RESULTS

The mean age of 171 patients who underwent surgery for hydatid cyst was 44.8 (18-71), 68 of whom were male and 103 were female. Bile leakage was present in 50 patients (50 (29.23%)). There were 24 (48%) male and 26 (52%) female with bile leakage. The cyst diameter was 74.2(36-170) mm and the number of cysts was 1.2 (1-2) (**Table 2**). The cysts were located in the right lobe of the liver in 116 (79%) patients, in the left lobe in 30 (15%) patients, and in both lobes in 25 (6%) patients. Cystobiliary fistula developed more frequently, especially in cysts located in the right lobe (36 (72%)). Cystobiliary fistula was

most common in CE3a (Gharbi type 2) type (30 (60%)). Cystectomy+drainage was performed in 137 (80%) patients in all groups. Cystectomy and drainage were the most common surgical procedures. Demographic, laboratory and clinical features of patients with and without cystobiliary fistula were compared (**Table 3**, **Table 4**). There was no statistically significant difference in age and gender between the two groups, respectively (p=0.903, p=0.214) (**Table 3**). Nine (18%) patients with cystobiliary fistula were bilateral, 36 (72%) on the right, 5 (10%) on the left, and it was not statistically significant (p=0.543). In subgroup analysis, right lobe location was statistically significant compared to left (p=0.003). The cyst diameter was 10 cm in the group with cystobiliary fistula and was significant compared to the group without fistula (p<0.001). Aminotransferase (AST and ALT) levels were high in patients with cystobiliary fistula (p=0.012, p=0.054). However, there was no significant difference between the two groups in alkaline phosphatase, total bilirubin, and gamma glutamyl transferase (p=0.231, p=0.097, p=0.544) (**Table 4**).

Table 3. Comparison of patient groups with and without cystobiliary fistula

	Cystobiliary fistula, Yes N %	Cystobiliary fistula, No N %	Total N %
*Age	44.9 (18-71)	45.01 (15-70)	44.8 (15-71)
Gender			
Male	24 (48%)	44 (36.4%)	68 (39.8%)
Female	26 (52%)	77 (63.6%)	103 (60.2%)
Total	50 (100%)	121 (100%)	171 (100%)
Cyst location			
Bilateral	9 (18%)	21 (17.4%)	30 (17.5%)
Right	36 (72%)	80 (66.1%)	116 (67.8%)
Left	5 (10.0%)	20 (16.5%)	25 (14.6%)
Total	50 (100%)	71 (100%)	171 (100%)
**Cyst type			
1(CE1)	1 (2.0%)	4 (3.3%)	5 (2.9%)
2(CE3a)	4 (8.0%)	27 (22.3%)	31 (18.1%)
3(CE2;C3b)	30 (60%)	68 (56.2%)	98 (57.3%)
4(CE4)	14 (28%)	22 (18.2%)	36 (21.1%)
5(CE5)	1 (2.0%)	0 (0.0%)	1 (0.6%)
Total	50 (100%)	121 (100%)	171 (100)
Cyst size(mm)	100 (60-170)	63.92 (36-110)	74.2 (36-170)
Number of cyst	1.41 (1-2)	1.34 (1-2)	1.2 (1-2)
Surgical procedure			
Cystectomy+ -omentoplasty	10 (20.4%)	14 (11.6%)	24 (14.1%)
Cystectomy drainage	38 (77.6%)	99 (81.8%)	137 (80.6%)
Resection	1 (2%)	8 (6.6%)	9 (5.3%)
Total	49 (100%)	121 (100%)	170 (100%)

*Mean(Max-Min) **Gharbi classification

Table 2. Demographic and clinical data of liver hydatid cysts

	N %	Total N	P value
Gender		171	
Male	68 (39.77%)		0.398
Female	103 (60.23%)		0.602
*Age	44.8 (18-71)	171	0.903
Cyst size(mm)	74.2 (36-170)	171	<0.001
*Number of cyst	1.2 (1-2)	171	0.372
Cyst location		171	
Bilateral	30 (17.5%)		0.175
Right	116 (67.8%)		0.678
Left	25 (14.6%)		0.146
Cystobiliary fistula		171	
Positive	50 (29.23%)		0.292
Negative	121 (70.77%)		0.708
**Cyst type		171	
1 (CE1)	5 (2.9%)		0.029
2 (CE3a)	31 (18.1%)		0.181
3 (CE2;C3b)	98 (57.3%)		0.573
4 (CE4)	36 (21.1%)		0.211
5 (CE5)	1 (0.6%)		0.006
Surgical procedure		170	
Cystectomy+ omentoplasty	24 (14.1%)		0.141
Cystectomy drainage	137 (80.6%)		0.806
Resection	9 (5.3%)		0.053

*Mean(Max-Min) **Gharbi classification

Table 4 . Cystobiliary fistula and laboratory results

	Cystobiliary fistula		Total	P value
	Yes	No		
	Median (Min-Max)			
AST (U/L)	44.03 (15-328)	32.9 (11-145)	36.1 (11-328)	0.012*
ALT (IU/L)	45.6 (9-268)	37.1 (10-215)	39.4 (9-268)	0.054
ALP (IU/L)	96.2 (33-281)	105.8 (39-201)	102 (33-281)	0.231
GGT (IU/L)	44.2 (19-95)	46.6 (20-90)	45.7 (19-95)	0.544
Total bilirubin (mg/dl)	2.5 (0.25-9)	4 (0-9)	3.51 (0.25-9)	0.097

DISCUSSION

Intrabiliary rupture or cystobiliary fistula is the most common complication of hepatic hydatid cyst and occurs in 3-42% of cases (11,12,17). While the pressure of a normal bile duct system is 15-20 cm H_2O, there is a pressure of about 35 cm H_2O in the cystic cavity of hydatid cysts. Due to this pressure difference, bile does not fill into the cyst unless the hydatid cyst is drained, even if there is a connection between the hydatid cyst and the bile ducts (11,18,19). If structures belonging to hydatid cysts (membrane fragments, daughter vesicles) ie typical radiological features are seen in the biliary tract, ultrasound and CT are diagnostic for large fistulas, but occult cystobiliary fistulas are usually detected during or after the operation by the discharge of biliary

fluid from their drains (20,21). If cystobiliary fistula is diagnosed before or during surgery, postoperative morbidity and development of bile leakage occur at a lower rate. Cystobiliary fistula may be 3-17% large fistula (major, ≥5 mm) or 10-37% occult (minor, <5 mm) (10,19-21). It is known that large fistulas can cause cholangitis, acute pancreatitis, acute cholecystitis and sepsis (19,20-23). The prevalence of cystobiliary fistula was reported as 27% by Kayaalp et al. (25), 28.4% by Demircan et al. (24), 28.1% by Wang et al. (7). A cytobiliary fistula was detected in 29.2% of 171 patients who underwent open surgery. The frequency of cystobiliary fistula in our study was consistent with the results of the studies in the literature.

There was no statistically significant difference between the groups in terms of gender and age in patients with cystobiliary fistula (P=0.903, p=0.214). However, hydatid cyst operation was performed more frequently in women in the group without cystobiliary fistula (44 (36.4%), 77 (63.6%)). Liver hydatid cyst is common in women. It is usually asymptomatic despite being infected in childhood. The reason for this is that it is determined in decade 3rd-4th due to hydatid cyst grows 1-5 mm per year (14,16, 26-28).

Studies have shown that 85-90% of hydatid cysts involve a single organ and more than 70% of them had a single cyst (27). In our study, the mean number of cysts in the liver was 1.2. Liver hydatid cyst is located in the right lobe in 72%. In our study, the number of hydatid cysts was 116 (67.8%) and cystobiliary fistulas were most frequent in right lobes with the number of 36 (72%). In the literature, cystobiliary fistulas were located in the right lobe in correlation with our study (30-33). Kayaalp et al. (25) reported that cystobiliary fistula was most common (48%) in segments close to the liver hilum (segments I, III, IVb, V and VI), and when Dziri et al. (34) differentiated the cyst according to the position of the cyst relative to the diaphragm (supra-diaphragmatic II, VII, VIII and sub-diaphragmatic III, IV, V, VI), they found cystobiliary fistula under the diaphragm to be common. In addition to cyst localization, cyst diameter was also associated with the development of cystobiliary fistula. The mean cyst diameter was 10 cm in patients with cystobiliary fistula, compared to 6.2 cm in patients without cystobiliary fistula. (p=0.001). In the literature, cyst diameter is associated with the risk of cystobiliary fistula even in asymptomatic patients. There is a 79% probability of cystobiliary fistula in cysts larger than 7.5 cm in diameter (35,36).

The main aim of surgical treatment of hepatic hydatid cyst is to treat the existing disease with minimal complications. It is necessary to clean the contents of the cyst and prevent it from spreading into the abdomen, and to minimize cyst cavity as much as possible. In our clinic, surgical treatment was performed for complicated cysts, large sizes of CE2-CE3b, infected cysts, cysts with intrabiliary rupture, and cysts that cause compression symptoms to adjacent organs (16,37,38). One hundred twenty nine (78.4%) patients those operated on were CE2 CE3b type hydatid cysts. Forty-two (21.6%) cysts were in the CE 1,4,5 group and surgical treatment was applied because there were complicated cysts. Cystobiliary fistula was most frequent in the CE3 patient group (30 (60%)). The reason for this was thought to be related to the fact that the surgical operation indication for hydatid cyst was the most common in the CE3 group. Atlı et al. (21) also stated that Type III cysts are more complicated than other cysts.

Surgical treatments are conservative and radical surgeries (10,39,40). Conservative surgery includes obliteration of the cavity, external or internal drainage, omentoplasty, capitonation and is generally safer than radical surgery. In radical surgery, total or partial pericystectomy and hepatic resection are performed. More intraoperative complications may develop in radical surgery (16,24,41). The choice of surgical technique varies according to the characteristics of the cyst and the experience of the hepatobiliary surgeon. Conservative treatment is the surgical method mostly preferred in endemic areas (10,40). Kayaalp et al. (38) stated that the control of bile leakage during the operation in hydatid cyst surgery reduces biliary complications, especially permanent bile fistulas. Despite conventional methods such as methylene blue, contrast, etc., during the operation, only some of the multiple occult cystobiliary fistulas could be detected. However, in recent years, after our bile leakage controls with lipid solutions in hydatid cyst surgery with cystobiliary fistula, we repaired it with nonabsorbable sutures and no bile leakage was found after the operation. Cystectomy+drainage+omentoplasty, cystectomy+drainage were the most frequently performed surgical procedures in our patients with cystobiliary fistula (10 (20.4%), 38 (77.6%)) (**Table 3**). In patients with large cystobiliary fistulas, T-tube drainage and choledochoduodenostomy were performed if intraoperative bile leakage persisted despite suturing. A Roux-en-Y type pericystojejunostomy may be preferred in large fistulas opened to the main biliary tract or if the cavity is large. Bile leakage was not detected in any of the follow-ups of the patients who underwent T-tube drainage and choledochduedonostomy. Biloma, biliary peritonitis, or abscess development which are secondary complications to bile leakage were not recorded in the postoperative follow-ups.

CONCLUSION

Liver hydatid cyst is endemic in our country as well as in many other countries in the world. Complicated hepatic hydatid cysts require timely and appropriate treatment because of their life-threatening complications. Cytobiliary fistula is the most common complication. In the surgical treatment of hydatid cyst disease, the earlier the diagnosis of occult cystobiliary fistulas is made (especially in the preoperative or peroperative period), the easier the treatment is, and the risk of bile leakage and consequently the morbidity and mortality decreases. Our results and experience showed that treatment and complications are related to the location and size of the cyst, occult/large cystobiliary fistula, detectability of occult fistulas, experienced center and surgeon.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Eskişehir Osmangazi University Non-interventional Clinical Researches Ethics Committee (Date: 18.01.2022, Decision No: 05).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1095045
J Health Sci Med 2022; 5(4): 949-953

Methanol poisoning in the emergency department: a retrospective study

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Cite this article as: Yurtsever G, Arıkan C, Acar H, Sorgun O, Bora ES. Methanol poisoning in the emergency department: a retrospective study. J Health Sci Med 2022; 5(4): 949-953.

ABSTRACT

Aim: Massive methanol poisonings have occurred in the past decades, resulting in a large number of deaths. In this study, our aim is to retrospectively analyze methanol poisoning cases admitted to the emergency department between 2019-2021, to evaluate their demographic characteristics, causes of poisoning, clinical and laboratory findings, treatments applied and mortality, and to contribute to the poisoning data of our country.

Material and Method: The cases of methanol poisoning who applied to the emergency department in a 3-year period were analyzed retrospectively. Medical files of patients aged 18 years and older were reviewed. Patients diagnosed with 'methanol poisoning' as a result of the examination were included in the study.

Results: A total of 59 patients were included in the study. 88% (n=52) of the patients with a mean age of 53±10 were male. The presence of neurological symptoms and GCS were associated with mortality among the symptoms of patients presenting to the emergency department (p=0.017, p<0.001, respectively), it was seen that low pH and $NaHCO_3$, and high lactate, serum sodium and anion gap were associated with mortality (p<0.001, p=0.003, p<0.001, p=0.022, respectively, p=0.001)

Conclusion: Methanol poisoning is a disease with high mortality despite the improved treatment possibilities. Lactate level was found to be an independent factor for mortality, and increased lactate levels are associated with poor clinical outcome. There was no difference in mortality between patients treated with ethanol and fomepizole.

Keywords: Methanol intoxication, mortality, emergency department

INTRODUCTION

Toxic alcohol poisoning is a multifaceted clinical picture that occurs with mild gastrointestinal (nausea, vomiting, abdominal pain) and neurological (headache, change in consciousness, visual disturbance) symptoms, which can result in severe metabolic acidosis, cardiovascular shock, seizures, coma and death (1). The most common ones we encounter as toxic alcohol poisoning are; methanol, isopropyl alcohol and ethylene glycol (1). Methanol is found as a solvent in many household products such as antifreeze, cleaning solutions, paints and paint removers. Consumption of illegally produced or homemade alcoholic beverages containing relatively high levels of methanol carries another risk. In this way, mass methanol poisonings that resulted in many deaths in the past decades have occurred (2).

In the absence of nonspecific symptoms and a reliable anamnesis, diagnosis in the emergency department can be quite difficult (3). Accidental or intentional ingestion of substances containing methyl alcohol may result in high rates of mortality and morbidity. Some survivors may develop permanent blindness, kidney dysfunction and chronic brain damage. However, even with high intakes, a positive outcome is possible if the patient arrives at the hospital early enough and the poisoning is detected in time and treated appropriately (4). In the treatment steps; vital support, the use of antidotes, and hemodialysis (2). Early diagnosis and treatment steps are of great importance in preventing clinical complications and mortality (4).

In this study, our aim is to retrospectively analyze methanol poisoning cases admitted to the emergency department between 2019-2021, to evaluate their demographic characteristics, causes of poisoning, clinical and laboratory findings, treatments applied and mortality, and to contribute to the poisoning data of our country.

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Received: 29.03.2022 **Accepted:** 17.05.2022

MATERIAL AND METHOD

The study was carried out with the permission of İzmir Katip Çelebi University Non-interventional Clinical Researchs Ethics Committee (Date: 18.11.2021, Decision No: 0506). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Settings

This single-center, retrospective cohort study was conducted in the adult emergency department of a tertiary university hospital in the city center of Izmir, located in the west of Turkey. The cases of methanol poisoning admitted to the emergency department during the 3-year period between January 1, 2019 and December 31, 2021 were analyzed retrospectively.

Study Population

According to the International Statistical Classification of Diseases and Related Health Problems10th Revision (ICD-10), among patients admitted to the emergency department, at least one of the diagnostic codes (F10, T51, X45, X65, Y15) containing the word 'alcohol and/or methanol poisoning' Medical files of patients aged 18 years and over, one of which was coded, were reviewed. Patients diagnosed with 'methanol poisoning' as a result of the examination were included in the study. Cases with a definite history of methanol exposure, and patients with suspected methanol intake and diagnosed with methanol intoxication due to clinical findings of methanol intoxication such as unexplained metabolic acidosis, acute kidney failure, neurologic dysfunction, and increased anion gap were included in the study. Patients who did not have a history of methanol intake or whose diagnosis of methanol intoxication was definitively excluded, and patients with missing data were excluded from the study.

Data Collection and Processing

Age, gender, vital signs at admission, symptoms at admission, glaskow coma score (GCS), chronic disease history, mechanism of intoxication (intentional, unintentional, drunkenness), how long after methanol intake, laboratory tests, applied treatments of the patients included in the study and clinical outcomes (admission, discharge, referral, death) will be evaluated. Information about the clinical outcomes of the referred patients was obtained by contacting the institution to which they were sent.

From laboratory tests, pH, lactate and bicarbonate (HCO_3) in blood gas, glucose, blood urea nitrogen (BUN), potassium (K), sodium (Na), chlorine (Cl) levels from biochemical parameters were measured and recorded. With these data obtained, the anion gap was calculated using the formula 'Anion gap = (Na+K) – (HCO_3+Cl) (mmol/L)' (5).

Outcome Measures

The primary outcome of this study was the mortality rate in methanol poisonings admitted to the emergency department. The effects of clinical characteristics and laboratory findings on mortality were investigated.

Data Analysis

Data obtained in the study were analyzed using IBM SPSS Statistics for Macos, Version 26.0. Armonk, NY: IBM Corp. Categorical variables were expressed as numbers and percentages, while numerical variables were expressed as mean and standard deviation when presenting the descriptive statistics. Histogram curves, kurtosis -skewness values and a Shapiro-Wilks test were used to test the normal distribution of the data. Mean and standard deviation values were presented since the data were distributed normally. A Student's t-test was used for the comparison of two independent groups. A Chi-square test were used for the comparison of two categorical variables. The results were expressed at a 95% confidence interval. A p value less than 0.05 was considered statistically significant.

RESULTS

A total of 59 patients were included in the study. 88% (n=52) of the patients with a mean age of 53±10 were male. It was determined that the patients applied to the emergency department 18±13 hours after ingestion of methanol, 75% (n=44) of them were poisoned for the purpose of intoxication, and 51% (n=29) had a history of chronic disease. In the physical examination performed at the time of admission, 80% (n=47) of the patients had GIS symptoms, 78% (n=46) had neurological symptoms, and the mean GCS was 12±4.4 points. Ethyl alcohol was given to 81% (n=48) of the patients and fomepizole was given to 19% (n=11) as antidote treatment. Hemodialysis was applied to 76% (n=45) of the patients and bicarbonate was applied to 78% (n=46) of them. Of the patients, 53% (n=31) were hospitalized in the inpatient service, 47% (n=28) in the intensive care unit, and 37% (n=22) were intubated. Morality rate was determined as 25.4% (n=15). Sociodemographic and clinical characteristics of the patients are shown in **Table 1**.

It was observed that the gender, age, admission to the hospital after methanol intake, the presence of chronic disease and the type of poisoning were not associated with mortality (p=0.259, p=0.838, p=0.412, p=0.576). While only the presence of neurological symptoms and GCS were associated with mortality among the symptoms of patients presenting to the emergency department (p=0.017, p<0.001, respectively), GIS symptoms were not associated with mortality (p=0.435) (**Table 2**)

Table 1. Sociodemographic and clinical characteristics of the patients

		Number (n)	Percentage (%)
Gender	Female	7	12
	Male	52	88
Form of poisoning	Willful	15	25
	inebriation	44	75
Chronic disease	Yes	30	51
	No	29	49
Hospitalization status	Service	31	53
	Intensive care	28	47
Hemodialisis	Yes	45	76
	No	14	24
Entubation	Yes	22	37
	No	37	63
Mortality	Yes	15	25
	No	44	75

Table 2. Effects of gender, age, symptoms and type of intoxication on mortality mortality

		Number (%)	Available	None	p
Gender	Female	7 (12)	3 (43%)	4 (57%)	0.259
	Male	52 (88)	12 (23%)	40 (76%)	
Gastrointestinal symptom	Yes	47 (80)	13 (28%)	34 (72%)	0.435
	No	12 (20)	2 (17%)	10 (83%)	
Neurological symptom	Yes	46 (78)	15 (33%)	31 (67%)	0.017*
	No	13 (22)	0 (0%)	13 (100%)	
Chronic disease	Yes	30 (51)	9 (30%)	21 (70%)	0.412
	No	29 (49)	6 (21%)	23 (79%)	
Form of poisoning	Intentional	15 (25)	3 (12%)	20 (80%)	0.576
	Unintentional	44 (75)	12 (27%)	32 (73%)	
Age	(Mean±SD)	NA	54±11	53±10	0.838
GCS (point)	(Mean±SD)	NA	6.2±4	14±2.3	<0.001
Application time (hour)	(Mean±SD)	NA	18.3±9.5	18.5±14	0.952

Chi-square test was applied, * p<0.05,NA: Not applicable.

When the effect of vital signs measured at the first admission to the emergency department on mortality was investigated; Systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and oxygen saturation measured by pulse oximetry were found to be unrelated to mortality (p=0.840, p=0.404, p=0.204, p=0.576, p=0.596, respectively) (**Table 3**).

When the mortality rates of the patients were compared according to the laboratory values checked in the emergency department, it was seen that low pH and $NaHCO_3$, and high lactate, serum sodium and anion gap were associated with mortality (p<0.001, p=0.003, p<0.001, p=0.022, respectively). , p=0.001). It was observed that blood glucose, BUN, potassium and chlorine values were not associated with mortality (p=0.062, p=0.500, p=0.084, p=0.336), respectively (**Table 4**). According to the logistic regression analysis performed with the factors found significant from the laboratory values, only lactate level was found to be an independent indicator in terms of mortality (p=0.042).

Table 3. Relationship between vital signs and mortality

	Mortality (Mean±SD)		p
	Yes	No	
Systolic TA (mmHg)	138±36	137±25	0.840
Diastolic TA(mmHg)	75±20	79±12	0.404
Pulse (beat/dk)	103±22	96±14	0.204
Respiration rate (min)	22±6	23±5	0.576
Saturasyon (SO_2%)	98±2	97±3	0.596

Table 4. The Relationship of Laboratory Parameters with Mortality

	Mortality (Mean±SD)		
Test name	Yes	No	p
pH	6.9±0.2	7.2±0.2	<0.001
$NaHCO_3$	8.7±5.6	15±7	0.003
Lactate	9±3.7	3±2.3	<0.001
Glucose	244±117	176±110	0.062
BUN	12.7±5.2	15.3±14.3	0.500
Potassium	4.9±1.5	4.3±0.8	0.084
Sodium	138±4.4	134±6.3	0.022
Clor	100.3±5.5	98±9	0.336
Anion Gap	34±9.8	25.2±7.6	0.001

There was no correlation between ethyl alcohol and fomepizole given as antidote treatment in the emergency department in terms of mortality (p=0.549).

DISCUSSION

Although methanol poisoning is not seen very frequently in the emergency department, it is an important and requires urgent treatment because the cases usually apply collectively from a common source of poisoning and have high mortality and morbidity (6,7). This study is one of the most recent studies on methanol poisoning with a large case series in our country. In our study, clinical features and laboratory findings that may be associated with mortality were investigated retrospectively and some important results were obtained.

Neurological symptoms and GCS (respectively p=0.017, p<0.001) from clinical findings, low pH and $NaHCO_3$ among laboratory findings, and high lactate, serum sodium and anion gap were associated with mortality (respectively; p<0.001, p= 0.003, p<0.001, p=0.022, p=0.001). Low GCS, pH and $NaHCO_3$, high lactate and anion gap levels are clinically expected to increase mortality and are not unique to methanol poisoning. In addition, according to logistic regression analysis, only lactate level was found to be an independent factor in terms of mortality. The data of this study alone may not be sufficient to determine the precise threshold value of serum lactate level in terms of mortality, but a serum lactate level >3±2.3 is a warning for negative results.

Although the difference between serum sodium levels is statistically significant, the value in one group was found to be within the normal range (135-145 mEq/L) and the

other was found to be very close to the normal range and is not considered clinically significant. Although some studies have reported a relationship between high sodium value and mortality (8,9,10,11), according to the logistic regression analysis performed in our study, sodium alone was not an independent factor. The emergence of neurological symptoms and the decrease in GCS are interrelated and have been shown to increase mortality (12,13). However, the time between methanol exposure and hospital admission was quite similar in both groups, and its relationship with mortality could not be demonstrated. This suggests that the occurrence of neurological symptoms is not only related to time but also probably to the amount of methanol ingested .

In our study, ethanol was administered to 81% (n=48) of the patients and fomepizole was administered to 19% (n=11) as an antidote. In a study conducted in our country, it was reported that 58% of the patients were treated with ethanol, and fomepizole was not used in any of the patients (14). In international studies, it has been reported that 80% of ethanol and 16% of fomepizole are used, quite similar to our study (15,16). There was no correlation between ethyl alcohol and fomepizole used as antidotes in terms of mortality (p=0.549). This situation is similar to previous studies (2,10,17). Bicarbonate treatment was applied to 78% (n=46) of the patients, and hemodialysis was applied to 76% (n=45) of them. In a study conducted in our country, it was reported that 87% of the patients were treated with bicarbonate and 84% of them were treated with hemodialysis (10,11). In the USA, the rate of patients undergoing hemodialysis is about half of that in our country (10,11).

In our study, the mortality rate was determined as 25.4% (n=15). This rate is similar to the studies conducted in Turkey (7,14), but it is considerably higher than the studies conducted abroad (10,11,15). Such a high mortality rate may be related to the number of patients who need hemodialysis and mechanical ventilation. The rate of patients undergoing hemodialysis and intubated in our study is approximately twice that of the aforementioned study (10,11,17). More research is needed to determine the factors affecting mortality and the level of impact.

Limitations

It is not possible to directly measure methanol concentrations or their toxic metabolites in our hospital and in any hospital within the borders of our province. For this reason, history, clinical features and laboratory findings were used instead of direct measurement in the diagnosis of patients.

CONCLUSION

Methanol poisoning is a disease with high mortality despite the improved treatment possibilities. Lactate level was found to be an independent factor for mortality, and increased lactate levels are associated with poor clinical outcome. There was no difference in mortality between patients treated with ethanol and fomepizole.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İzmir Katip Çelebi University Non-interventional Clinical Researchs Ethics Committee (Date: 18.11.2021, Decision No: 0506).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version they have no conflicts of interest to report regarding the present study

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1100677
J Health Sci Med 2022; 5(4): 954-960

The determinants of sleep effectiveness: a survey study in young adult Turkish population

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Cite this article as: Şilek H, Kartufan FF. The determinants of sleep effectiveness: a survey study in young adult Turkish population. J Health Sci Med 2022; 5(4): 954-960.

ABSTRACT

Aim: In this study, we aimed to reveal the major parameters and sleeping habits such as sleep onset, duration, frequency of night awakenings on sleep in a healthy active population.

Material and Method: This survey study included a total of 1033 volunteer participants, The survey form included demographic data such as age and gender, and questions about the sleep quality and sleep quantity to measure sleep effectiveness via both subjective and objective assessment. In addition, among the questioned conditions, those that could be associated with having night sleep problems were determined with a logistic regression analysis.

Results: Of all participants, 38.2% experienced problems related to night sleep. The sleep duration was reported as <6 hours by 17.6%, between 6-8 hours by 51.4% and >8 hours by 31% of the participants. The COVID-19 pandemic affected sleep patterns in 66.9% of the participants. Age ($p=0.007$), gender ($p=0.038$), falling asleep immediately when going to bed at night ($p<0.001$), waking up from sleep, even for a short time at night ($p<0.001$), time to go to bed to sleep at night ($p<0.001$) and affected sleep patterns after the COVID-19 pandemic ($p<0.001$) were found as the determinants of sleep effectiveness.

Conclusion: The most important determinants of sleep problems were sleep latency, nocturnal awakenings, time to go to bed and affected sleep patterns after the COVID-19 pandemic. This study can be a reference for preparation of programs to increase sleep quality of employees and guidance for further more comprehensive epidemiological studies.

Keywords: Sleep, sleep effectiveness, sleep quality, sleep latency, sleep patterns, COVID-19

INTRODUCTION

Sleep is defined as a state of immobility with highly diminished physical responsiveness that enables reorganization of neural activity (1). Sleep is one of the major physiological processes involved in human survival (2). Enough and undisturbed sleep is essential for an individual's personal well-being and the ability to perform efficiently (3). Sleep efficiency has a significant impact on the physical and mental health of the working population. However, community managers, employers and government authorities are usually unaware of sleep efficiency on the performance of employees.

Long working hours, chronic drug use and presence of chronic diseases, lack of exercise, and excessive use of psychostimulants such as caffeine and nicotine result in decreased sleep efficacy (4). The sleep effectiveness is usually addressed in two parameters: sleep quality and sleep quantity, namely duration. The quality and quantity of sleep have major implications for motor functioning, cognitive performance and long-term physical health (5). A decrease in sleep quality or quantity will lead to similar impacts, including sleep loss and sleep deprivation. Sleep deprivation (SP) can be resulted from lifestyle habits and sleep disorders. SP often leads to excessive daytime sleepiness, which has significant negative impacts on personal and working life, with an estimated incidence of 23.2% (6).

In modern society, sleep is often not made a priority due to the competing interests such as sports, social media usage etc., resulting in sleeping for a shorter time and feeling more sleep deficit (7). In the USA, the prevalence of short sleep duration rose to 35.6% in 2018 from 30.9% in 2010 among working Americans (8). Sleep medicine specialists dealing with sleep diseases constantly warn people who do not have insomnia complaints and restrict

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Received: 09.04.2022 **Accepted:** 17.05.2022

sleep times to less than 6 hours for detrimental impacts of SP on physical and mental health (9). Habitual short sleep duration has been associated with serious adverse outcomes, including obesity, type II diabetes mellitus, hypertension, cardiovascular disease, depression and all-cause mortality (10). The American National Sleep Foundation recommends an appropriate sleep duration of 7-9 hours/day for young adults and 7-8 hours/day for older adults (11).

Good quality sleep depends on many factors such as sleeping for more time, falling asleep in 30 min or less and less awakening at night. Sleep quality can be measured based on the objective and subjective determinants (12). Objective parameters for the evaluation of sleep quality include total duration of sleep, the amount of wake during the sleep episode, and the frequency and duration of awakenings across the night (13). Whereas, subjective assessment consists of reported difficulties falling asleep, sleep latency, waking up frequently during the night, or feeling tired during the day (14).

In this study, we aimed to reveal the major parameters and sleeping habits such as sleep onset, duration, frequency of night awakenings and other related information and to investigate the effects of the ongoing COVID-19 pandemic on sleep in a healthy active population that does not describe any sleep problems.

MATERIAL AND METHOD

The study was carried out with the permission of Yeditepe University Clinical Researches Ethics Committee (Date: 30.12.2020, Decision No: 1337). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This survey study included a total of 1033 volunteer participants, aged 18-50 years who responded to the questionnaire forms. The questionnaire form was prepared by the researchers by searching the relevant literature on the sleep effectiveness and sleep quality. The questions were limited to 18 considering that otherwise the participants may be bored, not accept or not interested in the survey. In addition, the survey questions were written as multi-choice short, easy to understand and reply items and the non-directive questioning technique was preferred. When preparing the survey questions, attention was paid to not imply medical terms or disease diagnosis in order to avoid causing suspicion or confusion in participants.

Although face-to-face interview technique yields more objective results in the surveys, this was impossible due to the ongoing COVID-19 pandemic. So, we chose a remote access survey compulsorily. The survey form was prepared via the Google forms application (https://docs.google.com/forms/u/0/?tgif=d). The questionnaire forms were sent to some participants via remote access to their corporate emails and others to their mobile phones. The participants were asked to fill the survey forms based on their sleep habits within the last five years. Participants who work in shifts, who had serious chronic sleep problems or who used medication that could affect their sleep were not included in the survey.

The survey form included demographic data such as age and gender, and questions about the sleep quality and sleep quantity to measure sleep effectiveness via both subjective and objective assessment. More than one option could be marked in question 15, which investigated the conditions that could have negative effects on the quality and quantity of sleep. The last question was an additional item questioning the effects of COVID-19 pandemic on sleep patterns. In addition, among the questioned conditions, those that could be associated with having night sleep problems were determined with a logistic regression analysis.

Statistical Analysis

Data obtained in this study was statistically analyzed using SPSS version 23.0 (SPS Statistical Package for Social Sciences, IBM Inc., Chicago, IL, USA). When the study data were evaluated, categorical variables were expressed as frequencies (number, percentage). The relationship between two independent variables was evaluated with the Chi-square test. The Binary Logistic Regression Model was constructed to examine the factors affecting a two-state independent variable. $p<0.05$ values were considered statistically significant.

RESULTS

Of the 1033 participants, 36.3% were male and 63.7% were female. Age distribution of the participants is shown in **Figure 1**.

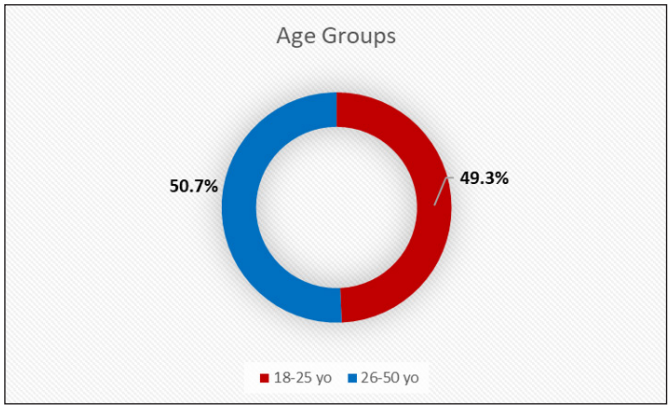

Figure 1. Age distribution of the participants

None of the participants presented to a physician due to sleep problems previously. Of all participants, 38.2% experienced problems related to night sleep. 25.1% of the participants fell asleep immediately, while 43.2% fell asleep between 10 to 20 minutes, 16.3% in half an hour and 15.3% within 30 minutes to one hour. Of all participants, 11.4% woke up for >2 hours at night. Participant's times to go to bed at night is shown in **Figure 2**.

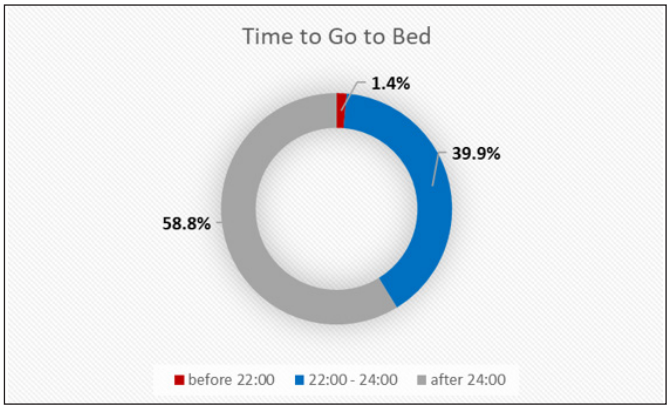

Figure 2. Participants' times to go to bed at night

The sleep duration was reported as <6 hours by 17.6%, between 6-8 hours by 51.4% and >8 hours by 31% of the participants. 83.6% of the participants stated that healthy and sufficient night sleep affects themselves during the day. The ideal sleep duration for feeling well and happy was reported as 4-6 hours by 5.4%, at least 6 hours by 26.9%, at least 8 hours by 49.6% and at least 10 hours by 8.1% of the responders. 82.4% of the participants reported that they need daytime sleep or napping. The COVID-19 pandemic affected sleep patterns in 66.9% of the participants. Distribution of the study parameters is given in **Table 1.**

The COVID-19 pandemic affected sleep patterns in 46% of the participants with problems related to sleep at night and 54% of those without sleep related problems (p<0.001) (**Figure 3**).

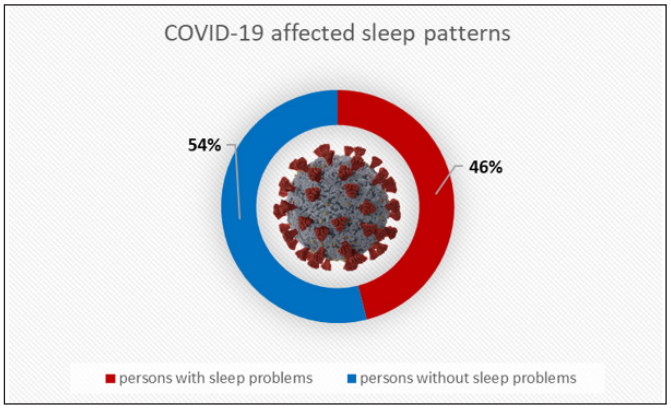

Figure 3. Effect of the COVID-19 pandemic on sleep patterns

Table 1. Distribution of the variables

(n=1033)	N	%
Gender		
Male	375	36.3
Female	658	63.7
Age		
18-25	509	49.3
26-50	524	50.7
Seeing a doctor for sleeping problems before		
Yes	0	0
No	1033	100
Having problems with night sleep		
Yes	395	38.2
No	638	61.8
Time to falling asleep when going to bed at night		
Evet, i fall asleep immediately	259	25.1
10-20 minutes	446	43.2
In half an hour	168	16.3
30 Minutes-1 hour	158	15.3
It varies	2	0.2
Falling asleep immediately when going to bed at night		
Yes	259	25.1
No	774	74.9
Waking up from sleep, even for a short time at night		
Yes, 1-2	558	54
Yes, >2	118	11.4
It varies No	346	33.5
Wake up time in the morning		
<6:00	123	11.9
06:00-08:00	597	57.8
>8:00	313	30.3
Time to go to bed to sleep at night		
<22:00	14	1.4
22:00-24:00	412	39.9
>24:00	607	58.8
Daily sleep duration		
<6 h	182	17.6
06-08 h	531	51.4
>8 h	320	31
Self-assessment when waking up in the morning		
Fresh	131	12.7
Tired, sleep duration dependent	501	48.5
Tired, sleep duration independent	401	38.8
Thinking that a healthy and sufficient night sleep affects yourself during the day		
Yes	864	83.6
No	169	16.4
The reason why sleep pattern is important in your life		
Vigour and performance	628	60.8
Mood	260	25.2
Professional career	47	4.5
Not affect	98	9.5
Ideal sleep duration to feel good and happy		
4-6 hours	56	5.4
At least 6 hours	381	36.9
At least 8 hours	512	49.6
At least 10 hours	84	8.1
*Situations that may negatively affect sleep quantity and quality		
Evening, social activities	140	13.6
Traffic and rush	139	13.5
Too much tea, coffee, or smoking	176	17
Housework due to working until late hours	276	26.7
My job	323	31.3
Needing daytime sleep or napping		
Yes	851	82.4
No	182	17.6
Taking a technological device with you as a habit when going to bed at night		
Yes, clock for alarm	109	10.6
Yes, actively used	827	80.1
No	97	9.4
Were sleep patterns affected after the covid-19 pandemic?		
Yes	691	66.9
No	342	33.1

*Participants were able to give more than one answer to this question

According to the Chi-square analysis; no statistically significant correlation was found between having sleep problems at night and age, gender, daily sleep duration, ideal sleep duration to feel good and happy, needing daytime sleep or napping, and taking a technological device with oneself as a habit when going to bed at night (for all, p>0.05). On the other hand, statistically significant correlations were found between having sleep problems at night and falling asleep immediately when going to bed at night, waking up from sleep even for a short time at night, wake up time in the morning, time to go to bed to sleep at night, self-assessment when waking up in the morning, thinking that a healthy and sufficient night sleep affects oneself during the day, the reason why sleep pattern is important in one's life and affected sleep patterns after the COVID-19 pandemic (for all, p<0.05). The correlations between having sleep problems at night and the survey parameters are given in **Table 2**.

Table 2. Relationships of having sleep problems at night with the study parameters.

	Having problems related to night sleep				Chi-square	p
	Yes		No			
	n	%	n	%		
Gender					3.782	0.052
Male	158	42.1	217	57.9		
Female	237	36	421	64		
Age					2.509	0.113
18-25	207	40.7	302	59.3		
26-50	188w	35.9	336	64.1		
Falling asleep immediately when going to bed at night					92.291	<0.001
Yes	34	13.1	225	86.9		
No	361	46.6	413	53.4		
Waking up from sleep, even for a short time at night					53.031	<0.001
Yes 1-2	195	34.9	363	65.1		
Yes >2	80	67.8	38	32.2		
No	109	31.5	237	68.5		
Wake up time in the morning					35.018	<0.001
<6	31	25.2	92	74.8		
06-8	204	34.2	393	65.8		
>8	160	51.1	153	48.9		
Time to go to bed to sleep at night					52.931	<0.001
<22	3	21.4	11	78.6		
22-24	104	25.2	308	74.8		
>24	288	47.4	319	52.6		
Daily sleep duration					4.216	0.117
<6	70	38.5	112	61.5		
06-8	217	40.9	314	59.1		
>8	108	33.8	212	66.3		
Self-assessment when waking up in the morning					86.7	<0.001
Fresh	39	29.8	92	70.2		
Tired, sleep duration dependent	132	26.3	369	73.7		
Tired, sleep duration independent	224	55.9	177	44.1		
Thinking that a healthy and sufficient night sleep affects yourself during the day					3.878	0.049
Yes	319	36.9	545	63.1		
No	76	45	93	55		
The reason why sleep pattern is important in your life					15.363	0.002
Vigour and performance	211	33.6	417	66.4		
Mood	118	45.4	142	54.6		
Professional career	19	40.4	28	59.6		
Not affect	47	48	51	52		
Ideal sleep duration to feel good and happy					5.793	0.122
4-6 hours	25	44.6	31	55.4		
At least 6 hours	138	36.2	243	63.8		
At least 8 hours	191	37.3	321	62.7		
At least 10 hours	41	48.8	43	51.2		
Needing daytime sleep or napping					0.548	0.459
Yes	321	37.7	530	62.3		
No	74	40.7	108	59.3		
Taking a technological device with you as a habit when going to bed at night					2.471	0.291
Yes, clock for alarm	37	33.9	72	66.1		
Yes, actively used	326	39.4	501	60.6		
No	32	33	65	67		
Were sleep patterns affected after the covid-19 pandemic?					53.522	<0.001
Yes	318	46	373	54		
No	77	22.5	265	77.5		

A binary logistic regression analysis was performed to determine the variables affecting the status of having problems related to sleep at night (**Table 3**). As seen in the table, age (p=0.007), gender (p=0.038), falling asleep immediately when going to bed at night (p<0.001), waking up from sleep, even for a short time at night (p<0.001), time to go to bed to sleep at night (p<0.001) and affected sleep patterns after the COVID-19 pandemic (p<0.001) were found to statistically signşificantly affect the status of having problems related to sleep. Odds ratio (OR) for having sleep problems was 1.541 folds higher in the male participants than female participants, 1.430 folds higher in the participants aged between 26-50 years compared to those aged between 18-25 years, 5.034 folds higher in the participants who reported that they falling asleep immediately when going to bed at night compared to those who could not, 2.472 fold higher in participants who go to the bed after 24:00 compared to those going to bed before 22:00, and 2.769 folds higher in the participants with sleep patterns affected by the COVID-19 compared to those with sleep patterns that were not affected.

Table 3: examining the variables affecting the status of having problems related to night sleep

	B	St. Error	P	Odds ratio	95% Condfidence interval	
					Lower	Upper
Gender (female)						
Male	0.433	0.160	0.007*	1.541	1.127	2.108
Age (18-25)						
26-50	0.358	0.173	0.038*	1.430	1.019	2.007
Immediate sleepinh when going to bed (yes)						
No	1.616	0.219	0.000*	5.034	3.276	7.736
Waking up from sleep, even for a short time at night (no)			0.000*			
Yes 1-2 times	0.128	0.168	0.446	1.136	0.818	1.579
Yes >2 times	1.652	0.268	0.000*	5.215	3.083	8.824
Morning wake up time (<6)			0.289			
06:00-08:00	0.250	0.279	0.370	1.284	0.743	2.218
>8	0.544	0.363	0.134	1.722	0.846	3.507
Time to go to bed to sleep at night (<22)			0.000*			
22-24	-0.515	0.813	0.527	0.598	0.121	2.942
>24	0.905	0.233	0.000*	2.472	1.565	3.906
Daily sleep time (<6)			0.165			
6-8 Hours	-0.418	0.247	0.091	0.659	0.406	1.069
>8	-0.153	0.198	0.441	0.858	0.582	1.266
Thinking that a healthy and sufficient night sleep affects oneself during the day						
(No)						
Yes	0.055	0.247	0.824	1.057	0.651	1.714
Why sleep pattern is important in your life (does not affect)			0.072			
My stamina and performance	-0.531	0.318	0.095	0.588	0.315	1.097
Emotions	-0.132	0.329	0.689	0.877	0.460	1.672
Meslek kariyer	-0.152	0.440	0.730	0.859	0.363	2.035
Ideal sleep time to feel good and happy (4-6 hours)			0.765			
At least 6 hours	-0.229	0.410	0.577	0.796	0.356	1.778
At least 8 hours	-0.190	0.288	0.509	0.827	0.471	1.453
At least 10 hours	-0.036	0.280	0.897	0.964	0.557	1.670
Needing or sleeping in the daytime (no)						
Yes	0.174	0.200	0.384	1.190	0.804	1.763
Taking a technological device with you as a habit when going to bed at night (yes, clock for alarm)			0.871			
Yes, active usage	0.131	0.255	0.608	1.140	0.691	1.880
No	0.147	0.368	0.691	1.158	0.563	2.383
Situation of affecting sleep patterns after the covid-19 outbreak (no)						
Yes	1.018	0.179	0.000*	2.769	1.950	3.932

:P<0.05 (Statistically significant). Omnibus chi square =259,532, p=0,000, dependent variable: having problems with night sleep (1: yes 0:no)

DISCUSSION

This survey study provides evidence regarding the determinants of sleep quality and quantity among healthy individuals without any chronic disease. The rate of the participants who stated to have problems related to night sleep was found as 38.2%. Ramaswamy et al. (15) found the rate of having sleep problems as 36.3% among Sothern Indian 15-60 year old population. These data were determined in accordance with the data we obtained in the survey.

In a systematic review on sleep quality by Crivello et al. (16) the appropriate sleep onset latency was reported as 0-30 minutes for adults. In the same study, the appropriate number of awakenings was stated as 0-1, while more than 3 awakenings were reported to be inappropriate. In a study by Saferzade et al. (17) with adolescents, the mean sleep patency was reported as 21.41 minutes. In our study, sleep latency was reported as 30 minutes by 84.6% of the participants, while %15.3 reported the sleep latency as 30 minutes-1 hour. Again in our study, the number of self-reported awakening was found as 1-2 in 54% of the participants, while 33.5% reported no awakening during night sleep. Within this context, our findings are consistent with the literature.

According to the Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society, the appropriate sleep duration is 7-9 hours, while ≤ 6 hours is inappropriate for optimal health in adults (18). Young adults who slept <7 hours are more likely to report poor general health and low overall physical and mental health-related quality of life (19). In the present study, self-reported sleep duration was found as < 6 hours in 17.6%, 6-8 hours in 51.4% and >8 hours in 31% of the participants. In a survey study includingw over 15.000 American adults, Jean-Louis et al. (20) found the mean sleep duration as < 6 hours in 15.0%, 6-8 hours in 73% and >8 hours in 12% of the participants.

In the present study, binary logistic regression analysis revealed the determinants of having problems related to sleep at night as age (p=0.007), gender (p=0.038), falling asleep immediately when going to bed at night (p<0.001), waking up from sleep, even for a short time at night (p<0.001), time to go to bed to sleep at night (p<0.001) and affected sleep patterns after the COVID-19 pandemic (p<0.001). Similarly, studies in the literature have reported the determinants of poor sleep quality as ease of falling asleep, frequency of awakening and sleep continuity (21, 22). In a study by Silva et al. (23) with nursing students, the determinants of sleep quality were found as time to falling asleep and sleep duration, and duration of travel from school to the home. Wesselius et al. (24) found the most significant factor affecting sleep problems as nocturnal awakenings in the hospitalized patients. Rocha et al. (25) reported the factors affecting sleep quality as sleep latency and fragmented sleep. In general, the results of our study and those of the previous studies are consistent in terms of the determinants of sleep efficiency with sleep latency and nocturnal awakening was more common in the reviewed studies.

Traumatic events such as those caused by the COVID-19 pandemic can lead to anxiety and psychological distress that negatively affect sleep quality (26). One important finding of our study was the fact that the ongoing COVID-19 pandemic affected sleep patterns negatively in 66.9% of all participants. This effect was seen in 46% of the participants with sleep problems and 54% of those without sleep problems. Cellini et al. (27) investigated the changes in sleep patterns caused by COVID-19 outbreak and found that people went to bed and woke up later, and spent more time in bed with a lower quality of sleep. Li et al. (28) showed that time in bed and total sleep duration, and thuse sleep efficiency significantly decreased due to the COVID-19 pandemic. In a more recent study, Marelli (29) found that the rate of early morning awakening decreased from 78.6% to 70% in students and from 75.6% to 61.3% in workers after the COVID-19 pandemic. These results are consistent with our findings.

Study Limitations

The major limitation of this study is the inability to conduct the survey through face-to-face interviews due to the ongoing pandemic. In addition, the number of participants is relatively low for such an online survey. Finally, different groups (age, gender etc.) could be created to compare the survey results. However, this can be a subject for future studies. On the other hand, being the first study conducted on sleep quantity and quality, namely sleep effectiveness in Turkey is a strong aspect of the study.

CONCLUSION

A considerable portion of the study population had problems related to nocturnal sleep. Majority of the participants went to bed after 24:00, which causes inappropriate sleep duration especially in the working population. The most important determinants of sleep problems were sleep latency, nocturnal awakenings, time to go to bed and affected sleep patterns after the COVID-19 pandemic. We believe that this study can be a reference for preparation of programs to increase sleep quality of employees and guidance for further more comprehensive epidemiological studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Yeditepe University Clinical Researches Ethics Committee (Date: 30.12.2020, Decision No: 1337).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare. Financial Disclosure: The authors declared that this study has received no financial support.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1112225
J Health Sci Med 2022; 5(4): 961-965

Single fraction image guided radiation therapy for management of bone metastases during the COVID-19 pandemic

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Cite this article as: Akın M, Düzova M. Single fraction image guided radiation therapy for management of bone metastases during the COVID-19. J Health Sci Med 2022; 5(4): 961-965.

ABSTRACT

Aim: Radiation therapy (RT) plays a major role in management of bone metastases, however, various dose-fractionation schemes are utilized taking into account patient, tumor, and treatment characteristics. The aim of this study was to assess Image Guided Single Fraction Radiation Therapy (IG-SFRT) for management of painful bone metastases during the COVID-19 pandemic.

Material and Method: Patients receiving IG-SFRT for painful bone metastases were assessed for age, gender, primary cancer diagnosis, location of metastases, performance status, analgesic intake, pain relief, and overall treatment efficacy in this study.

Results: Out of the total 65 patients treated with IG-SFRT during the course of COVID-19 pandemic at our department, 54 patients were evaluable for overall treatment efficacy analysis. Based on the international consensus on palliative RT endpoints, rates of complete response (CR), partial response (PR), pain progression (PP), and indeterminate response (IR) were 16.67%, 59.26%, 9.26%, 14.81%, respectively corresponding to an overall response rate of 75.93%. IG-SFRT was well tolerated by all patients without toxicity.

Conclusion: For patients with bone metastases, pain palliation is a critical aspect of management. In view of the high rate of overall treatment efficacy achieved with IG-SFRT in our study, we suggest routine utilization of this image guided radiotherapeutic approach for management of painful bone metastases which additionally allows for minimization of treatment visits thereby improving patient and treatment facility convenience under the special circumstances of the recent COVID-19 pandemic.

Keywords: Radiation therapy (RT), image guided radiation therapy (IGRT), bone metastasis, COVID-19 pandemic

INTRODUCTION

Pain is the most common symptom of bone metastasis which leads to quality of life impairment in affected patients. Along with pain, bone metastases may also lead to several deteriorating consequences including pathological fractures, spinal cord compression, bone marrow aplasia and hypercalcemia which may be severe and fatal (1). Bone metastases constitute a frequent complication of systemic cancer and a leading cause of pain in affected patients (2). Various factors may be involved in occurrence bone metastasis, nevertheless, it is considered that osteoclasts play a critical role in pathophysiology of pain by several mechanisms including damage of bone and nerve fibers along with acidotic stimulation of pH-sensitive receptors (3-5).

A considerable proportion of patients with cancer suffer from bone metastases during the course of their disease, and prompt management may be required to provide symptomatic relief. Radiation therapy (RT) plays a major role in treatment of bone metastases with satisfactory results (6,7). Nevertheless, patterns of RT practice in terms of dose-fractionation schemes vary widely among treatment centers. Management of patients using single fraction radiation therapy (SFRT) has not been considered as the standard irradiation strategy for palliative treatment of painful bone metastases in several centers despite high level of evidence suggesting comparable efficacy of SFRT for pain relief (6-11). Selection of fractionation pattern for RT of bone

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Received: 02.05.2022 **Accepted:** 17.05.2022

metastases may be affected by many factors including patient, tumor, and treatment characteristics (7). Affected patients' life expectancy, compliance with treatment, and performance status are important considerations. Primary tumor histology, time interval between primary diagnosis and bone metastasis, location of metastasis, perceived risk of pathological fracture, presence or absence of accompanying neurological deficits, soft tissue involvement and spinal cord compression are among the critical tumor related factors. Logistical issues including source availability, distance to treatment center, facility workload, and reimbursement may be considered among different aspects of palliative management of bone metastases with RT (7,8). While multifraction RT of bone metastases has been common practice in majority of private and public RT centers in different parts of the world, utility of single fraction treatments may be justified for management of selected patients taking into account the comparable efficacy in pain relief along with other factors including source availability, patient convenience and compliance, treatment cost, staff and facility workload (6-11). Palliative irradiation of bone metastasis comprises a large proportion of the total workload in RT centers given its high frequency. From another standpoint, the recent coronavirus disease 2019 (COVID-19) pandemic has resulted in incorporation of certain administrative measures along with modification of treatment facility practice patterns accordingly (12,13). Since high dose of radiation is delivered in a single session with SFRT, incorporation of contemporary RT technologies such as Image Guided Radiation Therapy (IGRT) may be considered to improve the accuracy and precision of treatments. IGRT refers to use of advanced imaging techniques at several steps of the treatment process including RT simulation and data acquisition, radiation treatment planning (RTP), setup verification and precise target localization. This advanced technology allows for minimizing setup margins which may reduce exposure of normal tissues and radiation induced toxicity. We adopted IG-SFRT for prompt management of bone metastases during the critical course of the COVID-19 pandemic and report our treatment results in this study.

MATERIAL AND METHOD

The study was carried out with the permission of Selçuk University Hospital Clinical Research Ethics Committee (Date: 15.03.2022, Decision No: 2022/135). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients receiving IG-SFRT for management of pain due to bone metastases during the course of COVID-19 pandemic were assessed for age, gender, primary cancer diagnosis, location of metastases, performance status, analgesic intake, pain relief, and overall treatment efficacy. Written informed consents of all patients were acquired prior to treatment, and this retrospective study was performed in compliance with the Declaration of Helsinki principles and its later amendments. All patients had histologically proven cancer diagnosis with radiologically confirmed bone metastases causing a pain score of 5 or more on the Brief Pain Inventory (BPI) scale (14). Patients who did not receive hormone therapy at least 9 months before RT were included to assess the effect of IG-SFRT, concurrent hormone therapy was not used.

All patients underwent computed tomography (CT)-simulation at the CT-simulator (Siemens Somatom Emotion, Siemens Healthcare, Germany) at our department. Acquired planning CT images were transferred to the delineation workstation (MonacoSim, Elekta, UK) for contouring of treatment volumes and critical structures. A margin of 5 to 10 milimeters was used to generate the planning target volume. Delineation data sets were sent to the Elekta Monaco treatment planning system (Elekta, UK) for RTP. IGRT was routinely utilized for setup verification of each patient. Radiation dose was 8 Gray for IG-SFRT and all treatments were delivered by VersaHD (Elekta, UK) Linear Accelerator (LINAC) using 6 MV photons.

Primary endpoint of the study was overall treatment efficacy assessed by the pain response with BPI at baseline before IG-SFRT and 1 month after treatment. Briefly, a score of 0 refers to no pain and a score of 10 refers to the worst possible pain on the BPI scale. Response categories based on the international consensus on palliative RT endpoints are shown on **Table 1** (15).

Table 1. Response categories based on the international consensus on palliative radiation therapy endpoints

Category	Definition
Complete response	A pain score of zero without any increase in analgesic intake 1 month after single fraction radiation therapy
Partial response	A decrease of at least 2 points on the Brief Pain Inventory pain score without any increase in analgesic intake, or at least a 25% reduction in analgesic intake without an increase in pain score
Pain progression	An increase of 2 points or more in pain score without reduction in analgesic use, or as at least a 25% increase in analgesic use without accompanying decrease in pain score
Indeterminate response	A response which does not reflect the definitions of complete response, partial response, and pain progression

Complete response (CR) was categorized as a pain score of zero without any increase in analgesic intake 1 month after IG-SFRT. Partial response (PR) was categorized as a decrease of at least 2 points on the BPI pain score without

any increase in analgesic intake, or as at least a 25% reduction in analgesic intake without an increase in pain score. Pain progression (PP) was defined as an increase of 2 points or more in pain score without reduction in analgesic use, or as at least a 25% increase in analgesic use without accompanying decrease in pain score. A response which did not reflect the definitions of CR, PR, or PP was categorized as indeterminate response (IR).

Overall treatment efficacy was determined based on the rate of responding patients with CR or PR. Any adverse effects occurring as treatment toxicity were recorded.

Statistical Analysis

Data analysis was performed by using Statistical Package for the Social Sciences, version 15.0 (SPSS, Inc., Chicago, IL) software with the level of significance set at $p < 0.05$. Descriptive analysis was performed for quantitative variables, mean and median values were calculated along with the range. Qualitative variables including CR, PR, PP, and IR indicating the overall treatment efficacy were presented as percentages. Paired t-test was used for comparison between BPI scores before and after IG-SFRT.

RESULTS

Patient, disease, and treatment characteristics are shown on **Table 2**. All patients suffered from multiple metastases in lungs, liver, skeleton and other regions. However, bone metastases were uncomplicated without clinical or radiological findings suggestive of spinal cord compression, pathological fracture, or imminent fracture requiring surgical fixation. Number of metastases was 6 in 30 patients (55.56%), 7 in 11 patients (20.37%), 8 in 7 patients (12.96%), and 9 in 6 patients (11.11%). Out of the total 65 patients treated with IG-SFRT at our department, 54 patients were evaluable for overall treatment efficacy analysis using the BPI pain scores acquired at baseline before IG-SFRT and 1 month after IG-SFRT. Median age was 65 years (range: 38-84 years). Thirty one patients (57.41%) were male and 23 patients (42.59%) were female. Primary diagnosis was prostate cancer, breast cancer, lung cancer, and other for 20 patients (37.04%), 16 patients (29.63%), 11 patients (20.37%), and 7 patients (12.96%), respectively. Hormone therapy was utilized for 30 patients (55.56%) at least 9 months before RT and bisphosphonate therapy was used for 50 patients (92.59%).

Site of metastatic involvement included the hips and pelvis in 21 patients (38.89%), lumbar spine in 10 patients (18.52), thoracic spine in 9 patients (16.67%), lower limbs in 7 patients (12.96%), and other locations in 7 patients (12.96%). Type of bone metastasis was osteolytic in 16 patients (29.63%), osteosclerotic in 20 patients (37.04%), and mixed in 18 patients (33.33%). Median Karnofsky Performance Status was 60 (range: 40-90).

Table 2. Patient, tumor and treatment characteristics

Characteristic	Number	%
Number of patients with pain response assessment	54	
Median age (range)	59 (38-84) years	
Median Karnofsky Performance Status (range)	60 (40-100)	
Radiation dose	8 Gray	100
Gender		
Man	31	57.41
Woman	23	42.59
Primary tumor histology		
Prostate Cancer	20	37.04
Breast Cancer	16	29.63
Lung Cancer	11	20.37
Other	7	12.96
Site of metastatic involvement		
Hips and pelvis	21	38.89
Lumbar spine	10	18.52
Thoracic spine	9	16.67
Lower limbs	7	12.96
Other	7	12.96

Treatment outcomes with IG-SFRT are summarized in **Table 3**. Median BPI pain score was 7 (range: 5-10) before IG-SFRT at baseline, and median BPI pain score was 4.5 (range: 0-10) 1 month after IG-SFRT. There was a median decrease of 40.18% (range: 0%- 100%) in BPI pain scores 1 month after IG-SFRT, which was statistically significant ($p < 0.05$). Based on the international consensus on palliative RT endpoints, rates of CR, PR, PP, and IR were 16.67%, 59.26%, 9.26%, 14.81%, respectively corresponding to an overall response rate of 75.93%. Treatment requirement rate was 37.04%. IG-SFRT was well tolerated by all patients without toxicity.

Table 3. Summary of treatment outcomes with IG-SFRT

Characteristic	
Median BPI score (range)	7 (5-10) before IG-SFRT 4.5 (0-10) one month after IG-SFRT
Median decrease in BPI score one month after IG-SFRT	40.18% (range: 0%-100%)
Rate of Complete Response	16.67%
Rate of Partial Response	59.26%
Rate of Pain Progression	9.26%
Rate of Indeterminate Response	14.81%
Overall response rate based on BPI scores before and one month after IG-SFRT	75.93%

DISCUSSION

Bone metastases constitute a major health concern as a frequent complication of systemic cancer resulting in considerable morbidity and even mortality. Radiotherapeutic management of pain due to bone metastasis is still a matter of debate in terms of optimal dose and fractionation schemes. Despite the

accumulating high level evidence, there appears to be underutilization of SFRT for palliative management of bone metastases (16). Although there may be plausible justifications in favor of multifaction RT for selected patient subgroups, emerging pertinent and important aspects of radiotherapeutic management under the special circumstances of the recent COVID-19 pandemic should include minimization of treatment visits thereby improving patient and treatment facility convenience through prioritization of expedited irradiation protocols such as single fraction RT regimens.

In a recent study by McDonald et al. (17) assessing the effect of RT on painful bone metastases, pain reduction and improved quality of life indices were achieved as early as 10 days after SFRT, justifying the utility of this approach for management of all patients regardless of performance status and life expectancy. Although there may be controversies regarding the incorporation of patients in the decision-making process for their management, a study by Szumacher et al. (18) about palliative RT of bone metastases revealed that a higher proportion of patients favored SFRT particularly due to the convenience of the treatment plan. Focusing on a less addressed perspective, Saito et al. (19) investigated the influence of RT schedule on decisions of physicians from various specialties to refer their patients suffering from bone metastases for palliative irradiation. The study underscored that referring physicians preferably considered SFRT particularly for management of patients with poor performance status and prognosis, which may have implications for increased utilization of palliative irradiation with wider adoption of SFRT (19). From a different standpoint, cost-utility analysis based on the large randomized Dutch bone metastasis study revealed that SFRT provided equivalent palliation and quality of life compared to multiple fraction RT with lower medical and societal costs (20,21).

In our study, three-quarters of the 54 evaluable patients had an overall pain response 1 month after 8 Gray IG-SFRT with one-sixth of patients being completely free of pain. A satisfactory rate of overall treatment efficacy has been achieved by use of SFRT, which is consistent with the literatüre (6-11, 21-23). SFRT dose was 8 Gy as suggested by the IAEA randomised trial (23) investigating the optimal SFRT dose for management of pain due to bone metastases.

Our study may add to the existing literature in the context of routine IGRT utilization as a viable radiotherapeutic approach for irradiation of bone metastases, which is a poorly addressed treatment concept in palliative RT setting. A critical objective to consider in SFRT is avoidance of geographical miss and excessive toxicity which may be more relevant given the high dose of radiation delivered in a single session. IGRT is a contemporary technique to achieve this goal since it allows for precise treatment delivery with volumetric imaging guidance for accurate setup verification and reduced setup margins for decreased exposure of normal tissues. Incorporation of IGRT in RT of bone metastases may improve the accuracy, precision, and toxicity profile of RT without extending the overall treatment time (24-26).

CONCLUSION

In conclusion, pain palliation is a critical aspect of management for patients with bone metastases. In view of the high rate of overall treatment efficacy achieved with IG-SFRT in our study, we suggest utilization of this image guided radiotherapeutic approach for management of pain due to bone metastases which additionally allows for minimization of treatment visits thereby improving patient and treatment facility convenience under the special circumstances of the recent COVID-19 pandemic.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Selçuk University Hospital Clinical Research Ethics Committee (Date: 15.03.2022, Decision No: 2022/135).

Informed Consent: Written informed consents of all patients were acquired prior to treatment.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1086679
J Health Sci Med 2022; 5(4): 966-968

The effect of the COVID-19 pandemic period on the cases of acute cholecystitis

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Cite this article as: Türkmen Sarıyıldız G. The effect of the COVID-19 pandemic period on the cases of acute cholecystitis. J Health Sci Med 2022; 5(4): 966-968.

ABSTRACT

Aim: A gallstone is a stone formed within the gallbladder out of precipitated bile components. Risk factors for gallstones include a family history of gallstones, age, genetic and environmental factors, sedentary lifestyle, high-fat diet, obesity. In this study, it was aimed to determine the effects of the pandemic process on acute cholecystitis cases.

Material and Method: Patients who applied to hospital between 1st January 2018 and 1st January 2022 and were diagnosed with Acute Cholecystitis were retrospectively screened. The demographic data as age and sex were recorded by dividing the patients into two groups, two years before and two years after the COVID-19 pandemic period.

Results: The 2-year retrospective evaluation before and after the COVID-19 pandemic, a significant increase was found in cases of acute cholecystitis after the pandemic ($p<0.05$).

Conclusion: Sedentary lifestyle and obesity are important factors in the etiology of acute cholecystitis. The COVID-19 pandemic, an increase in the number of acute cholecystitis have been clearly demonstrated by this single center data.

Keywords: Acute cholecystitis, COVID-19, pandemic period

INTRODUCTION

Cholecystitis or inflammation of the gallbladder, is a clinical condition that describes inflammation of the gallbladder with symptoms of right upper quadrant pain, nausea, vomiting, and sometimes fever (1). Acute cholecystitis is caused by obstruction of the cystic duct by gallstones or particles in more than 90% of cases (2). Important risk factors leading to gallstones include age, genetic and environmental factors, sedentary life, high-fat diet, obesity, birth control pills, pregnancy, presence of this condition in other family members, diabetes mellitus, liver disease or rapid weight loss (3). Additionally, etiology of acute cholecystitis other than stone includes vasculitis, chemotherapy, major trauma and malignant processes, albeit rarely (3,4).

The diagnosis of acute cholecystitis is made by clinical symptoms, laboratory and radiological tests. Abdominal ultrasound is one of the leading radiological methods used to confirm the diagnosis (5). In addition to Murphy's sign in clinical physical examination, increase in leukocyte level, liver function tests, gallbladder wall thickness, gallbladder fullness, pericholecystic fluid and air in the gallbladder wall can be counted among the data supporting the diagnosis of cholecystitis by USG (6).

Although there are a sufficient number of studies in the literature examining demographic, clinical, and laboratory data in patients with acute cholecystitis, immobilization, sedentary life, and obesity status due to quarantine during the COVID-19 pandemic period may suggest increased gallbladder stone pathologies and the risk of acute cholecystitis diagnoses.

In this study, it was aimed to determine the effects of the pandemic process on acute cholecystitis cases.

MATERIAL AND METHOD

The study was carried out with the permission of Medicana International Ankara Hospital Academic and Ethics Committee (Date: 05.02.2022, Decision No: BŞH-05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Received: 12.03.2022 **Accepted:** 19.05.2022

Patients who applied to our Hospital between 1st January 2018 and 1st January 2022 and were diagnosed with Acute Cholecystitis were retrospectively screened.

Patients diagnosed with acute cholecystitis were determined clinically, laboratory, and radiologically, regardless of age. The first COVID-19 case in Turkey was announced on March 11, 2020. The patients were divided into two groups, 2 years before and two years after this period. The demographic data as age and sex were recorded by dividing the patients into two groups, two years before and two years after the COVID-19 pandemic period.

Statistical Analysis

SPSS software (SPSS 18.0, Chicago, Illinois, USA) was used for statistical analyses. Data were expressed as mean±SD. T-test was used to compare the parameters of patients. A P-value cutoff less than 0.05 was considered statistically significant.

RESULTS

Patients who applied to Medicana International Ankara Hospital between 1st January 2018 and 1st January 2022 and were diagnosed with Acute Cholecystitis were retrospectively screened. Total of 4,403 patients diagnosed with Acute Cholecystitis were investigated for the study.

The mean age of the patients was 39.75±16.8 years, and 18.78 (42.65%) of the patients were male. Since it was considered as 2 years before and two years after the pandemic, a total of 1,878 patients were diagnosed with acute cholecystitis between January 2019 and January 2020, and 1,096 (58.36%) of the patients were women.

Considering the pandemic period from January 2020 to January 2022, a total of 2,525 (57.35%) patients were diagnosed with acute cholecystitis, and 1,429 (56.6%) of the patients were women. The demographic characteristics of the patients with acute cholecystitis are summarized in **Table 1**.

The 2-year retrospective evaluation before and after the COVID-19 pandemic, a significant increase was found in cases of acute cholecystitis after the pandemic (p <0.05).

Acute cholecystitis was more common in women in both groups in the pre-pandemic and post-pandemic 2-year period, but there was no statistically significant difference between the groups since age was taken into account (p>0.05).

DISCUSSION

Cholelithiasis is seen at a rate of 10-15% in the general population, and they have common risk factors including type 2 DM, hyperlipidemia, insulin resistance, metabolic syndrome, rapid weight loss (7). Also, obesity is a risk factor for the formation of cholesterol gallstones and exposes patients to increased risk of gallstone-related complications and cholecystectomy (8, 9).

A systematic review of 17 prospective studies involving 1,921,103 participants found two-fold increased risk of gallbladder disease from the lower to the upper limit of the normal BMI range (18.5–24.9 kg/m²). They also suggest that even moderate increases in adiposity increase risk of gallbladder disease. Also, hormone changes and gallbladder dysmotility are the most immportant mechanisms to explain the association between obesity and gallbladder disease (10). Together, lifestyle and dietary factors, in particular, might either indirectly (e.g., inducing overweight, obesity, insulin resistance and the metabolic syndrome) or directly (e.g. dietary content in fiber and specific macronutrients) interfere with the pathogenesis of cholesterol gallstones acting on common pathogenic pathways (9, 10).

Additionally, insulin resistance is an important risk factor in the formation of cholelithiasis. In recent experimental studies, Mendez-Sanchez et al. (11) reported that insulin resistance causes cholesterol gallstone formation by increasing cholesterol secretion into bile. Thus, Ata et al. (12) reported that insulin resistance increases gallstone formation in non-obese and non-diabetic patients. In addition, a sedentary lifestyle is considered one of the main causes of insulin resistance. While a sedentary lifestyle is the source of many diseases, it also accelerates the increase in obesity, which is an important social health problem.

Table 1. Demographic characteristics of patients with Acute Cholecystitis

Date	Number of patients		Male /female	p
Jan 2018-Jan 2020	4403	1878 (42.65%)	782 (41.64%)/1096 (58.36%)	<0.05
Jan 2020-Jan 2022		2525 (57.35%)	1096 (43.40%)/1429 (56.6%)	

Table 2. Age distribution of patients with Acute Cholecystitis

Date	Number of patients		Male /female age		p
Jan 2018-Jan 2020	4403	1878 (42.65%)	39.75±16,8	43.3/47.6	>0.05
Jan 2020-Jan 2022		2525 (57.35%)		53.1/57.4	

Besides a close relationship can be established between COVID-19 infection and sedentary life. Amongst these immune-debilitating diseases, COVID-19 infection is common in diabetic patients related to the absence of a normal active immune system to fight the COVID-19. Recovery of patients having a history of diabetes from COVID-19 has several complications, and their management becomes cumbersome (13). Furthermore, cholesterol lewel can indirectly increase the susceptibility of patients to COVID-19 and increase the risk of death from COVID-19 (13-15). Thus, COVID-19 confers an increased risk for type 2 diabetes (16).

All together, during COVID-19 infection the inactivity triggered by the epidemic immobility process can be considered as the main source of the increase in obesity. In the light of all these data, our study supported the hypothesis that the sedentary life caused by the COVID-19 pandemic process causes an increase in hiperlipidemia, insulin resistance as a result, an increase in gallbladder pathologies and acute cholecystitis.

Our study has some limitations. The first was a single-center, retrospective study, and the small number of the study population was an important limiting factor. Second, laboratory, BMI, and radiological imaging were not investigated in the study. In addition, patients diagnosed with acute cholecystitis were included in the study regardless of whether they were positive or negative for COVID-19. However, these restrictions did not affect the results.

CONCLUSION

The superior aspects of our work; it is important in showing the increase in acute cholecystitis cases and presenting local data during the pandemic process. As a result; a sedentary life, immobility, and obesity are important factors in the etiology of acute cholecystitis. The COVID-19 pandemic process, gallstone formation, and an increase in the number of acute cholecystitis have been clearly demonstrated by single-center data. For data with higher levels of evidence, multicenter studies with more parameters are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medicana International Ankara Hospital Academic and Ethics Committee (Date: 05.02.2022, Decision No: BŞH-05).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1109966
J Health Sci Med 2022; 5(4): 969-972

Effect of chitosan application on lung tissue in rats with experimental fluorine toxicity

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Cite this article as: Bulduk B. Effect of chitosan application on lung tissue in rats with experimental fluorine toxicity. J Health Sci Med 2022; 5(4): 969-972.

ABSTRACT

Aim: The aim of this study is to investigate the effects of chitosan application on lung tissue in rats with experimental fluorine toxicity.

Material and Method: In the study, 21 healthy male wistar albino rats were used. Prior to the trial, the acclimation of the rats was provided. 3 groups were randomly generated in a way that there were 7 rats in each group. These were determined as the control group (C), the fluorosis group (NaF) and the fluorosis + chitosan (NaF+CS) group.

Results: In the NaF group, CAT, SOD and GSH values were found to be low compared to other groups and MDA values were found to be high. It was found that the chitosan application reduced the CAT, SOD and GSH values, and increased the MDA value.

Conclusion: It has been predicted that chitosan application may be beneficial in preventing cellular damage that may occur with fluorine exposure.

Keywords: Chitosan, sodium fluoride, antioxidant, lung

INTRODUCTION

Fluorine is an important substance that must be taken from the outside in terms of human health. Fluorine, which is naturally found on earth, is taken into the body as a result of consuming water, inhaling industrial gases, eating plant and animal foods. Approximately 80% of the fluorine taken into the body passes into the blood by a simple diffusion route. A small part of the fluorine is excreted from the kidneys, while a large part is stored in bone tissue. Therefore, we see the beneficial and harmful effects of fluoride mostly in the skeletal system. Fluorosis occurs if fluorine is taken too much (1-3). Fluorosis especially damages bone tissue, as well as heart, muscle, nerve, kidney, and lung tissues (4,5). In a study conducted, it was reported that the application of 4,5 and 9 mg fluorine/kg/day sodium fluorine caused necrosis in the rabbit lung parenchyma (6).

Chitosan is an environmentally friendly biopolymer that has no toxic effect, has an antimicrobial effect, accelerates wound and bone healing, and also reduces pain (7). It is known that chitosan and its derivatives have antioxidant, antidiabetic, and anticancer properties (8).

The aim of this study is to investigate the effects of chitosan application on lung tissue in rats with fluorosis.

MATERIAL AND METHOD

Animals and Experimental Design

In the study, 21 healthy male Wistar Albino rats provided from Van Yüzüncü Yıl University Experimental Animal Unit were used. Prior to the trial, the acclimation of the rats was provided. Experimental applications in the study were carried out in accordance with the conditions of care of laboratory animals (12 hours of light: 12 hours of dark and 22±1°C and 60% humidity). During the experimental applications, rats were given standard commercial rat feed (pellet feed) and drinking water ad libitum. 3 groups were randomly generated in a way that there were 7 rats in each group. The experiment lasted 12 weeks. The study was conducted with the approval of Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (Date: 31/03/2022, Decision No: 2022/03-08). All procedures were performed adhered to the ethical rule.

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Received: 24.04.2022 **Accepted:** 19.05.2022

1. **Control group (C):** The control group was fed with drinking water and standard pellet feed.
2. **Fluorosis Group (NaF):** 100 ppm fluorine was applied to rats in the form of NaF by adding to their drinking water.
3. **Fluorosis and the Chitosan Group (NaF+CS):** 100 ppm fluorine was applied to rats in the form of NaF by adding to their drinking water. At the same time, 250 mg/kg/day of chitosan was administered daily by oral gavage.

Application

At the end of 12 weeks, all rats were anaesthetized with a combination of ketamine and xylazine through intramuscular (i.m) route and dissected. Later, lung tissues were taken to determine the levels of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and malondialdehyde (MDA) and washed using sodium phosphate buffer (pH 7.2). The tissues were stored at -80°C until the time of the study. In the homogenization buffer (pH 7.4), the tissues were homogenized using a homogenizer. The obtained homogenates were centrifuged and prepared to determine the amount of SOD, CAT, GSH and MDA. In the spectrophotometer, the antioxidant enzyme activities, and the amount of MDA of the samples were measured and their absorbance was determined in accordance with the literature (9-12).

Statistical Analysis

In the study, one-way variance analysis (ANOVA) was used to compare the group averages from various angles. After analyzing the characteristics and variance, the Duncan test was used to determine the different groups. The statistical significance level was taken as P<0,05 in the calculations. All analyses were done using the SPSS package program (Ver. 22).

RESULTS

The difference between the groups of chitosan application in rats with fluorine toxicity is shown in **Figure 1**.

The CAT value in the NaF group was found to be statistically different compared to the control and NaF+CS group. It was found that the decreasing CAT value in the NaF group increased in the Naf+CS group and was parallel to the control group. SOD values were similar in the control and NaF+CS groups, while they were found to be low in the NaF group. When the groups were examined in terms of GSH value, it was found that the value was low in the NaF group compared to the control group, and the GSH value in the NaF+CS group was similar compared to the control group. It was observed that the GSH value decreased in rats with fluorosis increased with the application of chitosan.

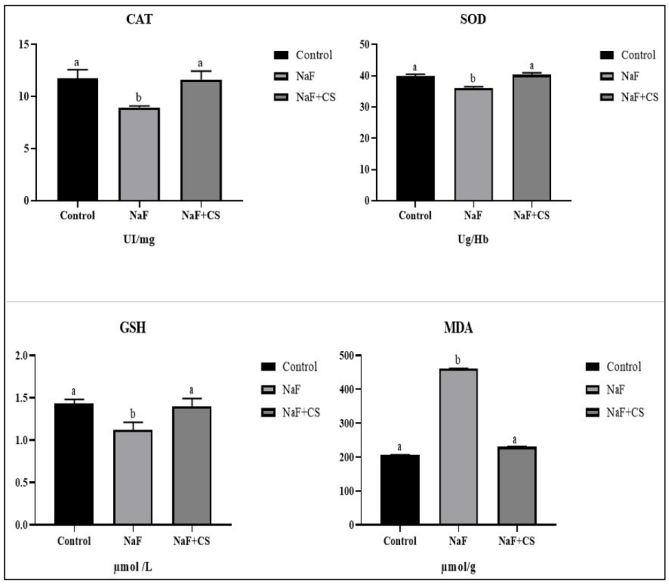

Figure 1. CAT, SOD, GSH and MDA values in the lung tissue of rats with fluorosis

When the MDA value was analyzed, the NaF group was found to be higher than the control group. The NaF+CS group was found to be similar compared to the control group and low compared to the NaF group.

DISCUSSION

It is known that excessive fluorine exposure causes cellular damage in the organism (13). With the decrease of Ca+2 levels in organisms with fluorosis, cellular oxygen use also decreases and hence causes various disorders (14). Aydın et al. (15) conducted a study in which they applied 10, 50 and 100mg/l fluoride to drinking water of Wistar albino male rats for 6 months. At the end of the study, they reported that necrosis, desquamation, and alveolar obstruction were observed when the lung tissue was examined. They also observed that CAT activity decreased. In the same study, it was revealed that the degree of lung damage also varied depending on the dose of fluorine. Nabavi et al. (16) showed that there was a decrease in CAT and SOD values in rats administered 600 ppm fluoride intraperitoneally. In another study, they reported that CAT and SOD values decreased significantly in rats with fluorosis (17). In a study conducted on people living in areas with an excessive fluorine concentration, it was found that the SOD value was low (18). It was revealed that there was a significant decrease in GSH levels in mice with chronic fluorine toxicity (19). In a study conducted on rats applied with 25 ppm fluorine daily by mixing it into their drinking water for 16 weeks, it was reported that GSH and other antioxidant activities decreased, and lipid peroxidation increased (20). CAT, SOD and GSH are among important antioxidants. A decrease in their

level indicates the formation of free radicals (21). It was found that antioxidant values are decreased in people living in endemic areas and in studies on experimental fluorine toxicity (22,23). In our study, we also found that the NaF application reduced the values of CAT, SOD and GSH, which are antioxidants. It was assumed that this was caused by oxidative stress caused by flora-related intoxication. It was believed that CAT, SOD and GSH enzymes decreased due to their use in the defense system against cellular damage by free radicals. It was reported in previous studies that chitosan application prevented oxidative damage by strengthening the antioxidant defense mechanism (24). Chitosan has antioxidant properties by affecting free radicals (25). It was found that chitosan application had a protective effect against oxidative stress in rats (26). In this study, it was observed that chitosan application affected the oxidative stress caused by fluorine. It was found that the application of fluorine alone reduced the CAT, SOD and GSH values, but the application of chitosan together with fluorine increased these antioxidant enzymes. It is thought that chitosan protects lung tissue by preventing oxidative stress.

When we looked at the MDA values, it was found to be quite high in the fluorine-applied group. It is known that MDA is a lipid peroxidation marker, it causes intracellular ion imbalance, and disruption of enzyme activities and leads to changes in the structure of DNA (27,28). In a study conducted on rabbits, it was reported that fluorine poisoning caused kidney damage, a decrease in the levels of SOD, GSH-Px, CAT, GSH-Rd, and an increase in the level of MDA (29). In another study conducted on rats, it was shown that fluorosis caused a fairly significant increase in the level of MDA (30). In this study, we found that fluorine application caused an increase in the level of MDA. We found that the application of chitosan reduced the MDA level, which increased with fluorine. In a study conducted on mice, it was found that chitosan oligosaccharide and its derivatives had a protective effect against liver damage caused by carbon tetrachloride. It was stated that the antioxidant ability of the organ was regained with chitosan (31). It is believed that the application of chitosan suppresses lipid peroxidation, thereby reducing MDA values.

CONCLUSION

It was found that experimental fluorine toxicity in rats reduced antioxidant enzyme values, increased MDA value, chitosan application regulated these values and may reduce cellular damage caused.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the approval of Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (Date: 31/03/2022, Decision No: 2022/03-08).

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author has participated in the design, execution, and analysis of the paper, and approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1087030
J Health Sci Med 2022; 5(4): 973-976

The relationship of breast cancer deaths with age groups and urbanization of the population: a multi-country analysis

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Cite this article as: Altunal Ç, Şahiner İT. The relationship of breast cancer deaths with age groups and urbanization of the population: a multi-country analysis. J Health Sci Med 2022; 5(4): 973-976.

ABSTRACT

Aim: In this retrospective observational study, it was aimed to evaluate the relationship between breast cancer deaths and demographic properties of countries.

Material and Method: The research was conducted on World Health Organization (WHO) 10th International Classification of Diseases (ICD-10) mortality list and World Bank Country Reports (WBCR). Total breast cancer-related deaths, age groups and urban population rates of 14 countries between 1996 and 2017 were evaluated.

Results: Both uncontrolled and controlled correlation analysis results showed that population age distribution had a significant correlation with total breast cancer-related deaths ($p<0.01$). Population percentage at 0-14 ages had a negative correlation with breast cancer-related deaths, whereas other age groups had positive correlations. Correlation between the urban population and total breast cancer-related deaths was insignificant at an uncontrolled level ($p>0.05$). Generalized Linear Model (GLM) results showed that only the country had a significant effect on total breast cancer related deaths ($p<0.05$). However, age group effects were insignificant at the multivariate level ($p>0.05$).

Conclusion: Although reasons such as age and urbanization play an important role among breast cancer risk factors, it is found that they do not affect mortality rates. A total of 22 years of WHO data and 14 country results showed that deaths due to breast cancer are only related to the country. Therefore, countries can minimize deaths due to breast cancer by carrying out more effective struggles, early diagnosis, treatment and awareness activities.

Keywords: Breast cancer, mortality, age, urban population

INTRODUCTION

Breast cancer, which is characterized by malignant lesions in the breast tissue, is a type of cancer especially seen in women. Breast cancer, which has a high prevalence and incidence all over the world, is also an important public health problem (1-3).

Despite advances in imaging, diagnosis and treatment methods, breast cancer still has high mortality rates today (4-7). Early diagnosis in breast cancer is of vital importance in reducing the treatment process and mortality (8-11). For early diagnosis, first of all, it is necessary to reveal which variables are affected by the disease, risk factors and risk levels.

Although studies have been conducted on environmental risk factors and age in breast cancer in the literature (12-14), these studies are mostly clinical or meta-analysis studies. On the other hand, the results of these studies reveal the need for a wider monitoring and analysis of the disease.

In this observational study, it was aimed to evaluate relationship between breast cancer deaths and demographic properties of countries.

MATERIAL AND METHOD

For this study, World Bank data, which is available as open access on the internet, was used. Since patient files and records are not used, there is no need for an ethics committee. No human/animal participant is avaible so no ethics approve is mandatory. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Received: 13.03.2022 **Accepted:** 22.05.2022

The research was conducted on World Health Organization (WHO) 10th International Classification of Diseases (ICD-10) mortality list and World Bank Country Reports (WBCR). Total breast cancer-related deaths, age groups and urban population rates of 14 countries between 1996 and 2017 were evaluated. Parameters used in the research and related data repositories were:

- -1036- Malignant neoplasm of breast-WHO ICD-10
- -Population ages 0-14, female (% of female population)-WBCR
- -Population ages 15-64, female (% of female population) -WBCR
- -Population ages 65 and above, female (% of female population) -WBCR
- -Urban population (% of total population)
- -WBCR

Since the country populations were different, rates were used in the research, in order to eliminate effects of country differences. Female proportions were used for age, since breast cancer related deaths are more common in female, and very rare in males. Since the research is conducted on public data, no ethical approval is needed.

Frequency analysis was used for description of normally distributed data. Scale parameters were described with mean percentages. Kolmogorov Smirnov Test was used for normality of scale parameters. Spearman's rho correlation and partial correlation analysis were used for relationship between total breast cancer-related deaths and cofounders. Generalized Linear Model (GLM) was used for multivariate level analysis. SPSS 17.0 for windows was used for analysis at 95% confidence interval with 0.05 significance level.

RESULTS

In 1999, a sharp increase in total death was reported around the world, whereas its rate was low during 1996-1998 periods. After this peak, level of total breast cancer related deaths was in high trend, except in 2015. In 2015, a sharp decrease was reported, followed by a sharp increase (**Figure 1**).

Russian Federation has the highest breast cancer caused death rates among other countries in which breast cancer-related deaths were reported by WHO ICD-10 Mortality list. Ukraine is the second country having high breast cancer related deaths, followed by Kazakhstan, Belarus and Azerbaijan (**Figure 2**).

Population at 0-14 age percentage was the highest in Syrian Arab Republic, at 15-64 ages percentage was the highest in Russian Federation, and at 65 or above age percentage was the highest at Ukraine. Urbanization percentage was the highest in San Marino, followed by Andorra, and Belarus (**Table 1**).

Figure 1. Total breast cancer caused deaths according to years for all countries

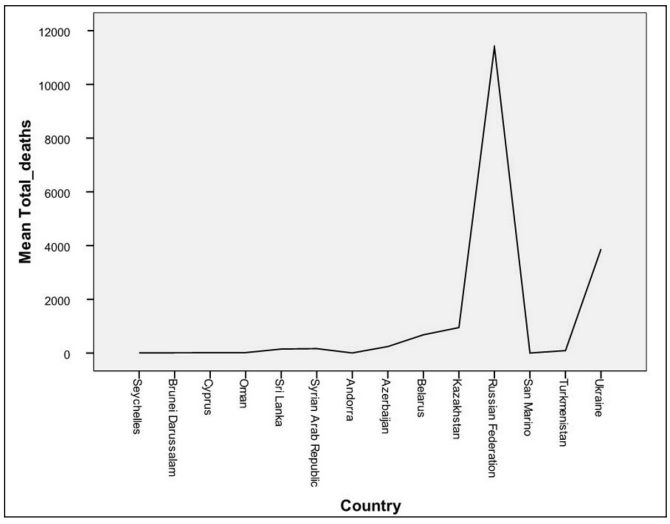

Figure 2. Total breast cancer caused deaths according to countries (1996-2017)

Table 1. Age structure and the urban population percentages of countries (1996-2017 mean percentages)

Country	Population ages between 0-14	Population ages between 15-64	Population ages between 65 or above	Urban population
Seychelles	24.03	67.03	8.94	52.84
Brunei Darussalam	28.77	68.27	2.96	72.50
Cyprus	22.17	66.40	11.44	68.59
Oman	32.09	64.81	3.10	74.62
Sri Lanka	26.36	67.07	6.57	18.38
Syrian Arab Republic	39.46	57.02	3.51	53.19
Andorra	-	-	-	88.55
Azerbaijan	27.31	65.48	7.21	51.85
Belarus	14.22	67.80	17.99	73.89
Kazakhstan	22.89	68.00	9.11	56.65
Russian Federation	14.60	68.57	16.82	73.56
San Marino	-	-	-	96.36
Turkmenistan	30.96	64.01	5.02	47.88
Ukraine	13.17	67.31	19.52	68.46
Total	23.25	69.49	10.46	61.11

Both uncontrolled and controlled correlation analysis results showed that population age distribution had a significant correlation with total breast cancer related deaths (p<0.01). Population percentage at 0-14 ages had a negative correlation with breast cancer related deaths, whereas other age groups had a positive correlation. The urban population had significant correlation with total breast cancer-related deaths, according to controlled correlation (p<0.01). However, correlation between urban population and total breast cancer-related deaths was insignificant at an uncontrolled level (p>0.05) (**Table 2**).

Table 2. Spearman's rho and partial controlled correlation analysis results between total deaths and demographic properties

Total deaths	Uncontrolled		Controlled[a]	
	r	p	r	p
Population ages between 0-14	-0.442**	0.000	-0.463**	0.000
Population ages between 15-64	0.268**	0.000	0.314**	0.000
Population ages between 65 or above	0.443**	0.000	0.443**	0.000
Urban population	0.100	0.160	0.289**	0.000

a. Controlled for year, gender and country ** p<0.01

Generalized Linear Model (GLM) results showed that only country had a significant effect on total breast cancer-related deaths (p<0.05). However, age group effects were insignificant at multivariate level (p>0.05) (**Table 3**).

DISCUSSION

Although there are extensive research and diagnostic studies on breast cancer today, it is still one of the important causes of death. In addition to deaths due to breast cancer, the treatment process of the disease in advanced stages emerges as an important problem both in terms of the patient's quality of life and public health (15-18). Although clinical studies and meta-analyzes have been conducted on this problem, there have not been sufficient studies that take a picture and evaluate the disease in general.

Family history and gender are the leading risk factors in studies on breast cancer (19-25). In our study, gender was one of the most important risk factors and the disease was mostly female. The proportion of male patients was statistically negligible when compared with the data of all countries.

The most important finding in our study is the findings regarding the relationship between age and breast cancer. Although there are not enough studies in the literature to establish a direct relationship between age and breast cancer, the general opinion is that breast cancer and breast cancer deaths are more common in older ages. In our study, this information in the literature was supported by the correlation analysis results. However, according to the multivariate analysis results, it was seen that only the country was an effective parameter in deaths due to breast cancer. However, it is a known fact that environmental factors play a role in the etiology of cancer. Although there is no relevant scientific data in the literature, the Chernobyl disaster, in which radiation leakage occurred, is one of the first factors that come to mind, especially in the background of the increase in the disease in countries such as Russia and Ukraine. This situation shows that the results of studies establishing a relationship between age and deaths due to breast cancer are local and that there is no such relationship in the general picture.

Another point that needs to be emphasized in the study is that the relationship between WHO and WB data is not at a sufficient level and therefore sufficient studies cannot be done globally. This is the most important limitation of both the research and the studies and field practices in terms of public health. Other limitations of the study are that the mortality rates due to breast cancer are taken only from any official institution, the related risk factors are not known sufficiently and there are no comorbidities.

Although reasons such as age and urbanization play an important role among breast cancer risk factors, it is found that they do not affect mortality rates. A total of 22 years of WHO data and 14 country results showed that deaths due to breast cancer are only related to the country. Therefore, countries can minimize deaths due to breast cancer by carrying out more effective struggle, early diagnosis, treatment and awareness activities.

Table 3. Generalized Linear Model (GLM) results for breast cancer-related deaths and demographic factors

Parameter	B	Std. Error	95% Wald Confidence Interval		Hypothesis Test	
			Lower	Upper	Wald Chi-Square	p
(Intercept)	4737841.64	8372728.99	-11672405.63	21148088.91	0.32	0.571
Population ages between 0-14	-44725.77	83579.98	-208539.52	119087.98	0.29	0.593
Population ages between 15-64	-44532.77	83557.36	-208302.19	119236.66	0.28	0.594
Population ages between 65 or above	-44434.21	83594.19	-208275.81	119407.39	0.28	0.595
Urban population	58.68	32.02	-4.08	121.44	3.36	0.067
Year	-142.55	93.36	-325.53	40.42	2.33	0.127
Country	1.07	0.53	0.02	2.12	4.02	0.045
(Scale)	31448109.56	3243624.84	25692112.09	38493666.51		

ETHICAL DECLARATIONS

Ethics Committee Approval: This study is retrospective observational research. No human/animal participant is avaible so no ethics approve is mandatory.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1109926
J Health Sci Med 2022; 5(4): 977-983

Ear, nose and throat specialists' awareness on oral and dental health and orthodontic problems in children with mouth breathing due to adenotonsillar hypertrophy

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Cite this article as: Arat Maden E. Ear, nose and throat specialists' awareness on oral and dental health and orthodontic problems in children with mouth breathing due to adenotonsillar hypertrophy. J Health Sci Med 2022; 5(4): 977-983.

ABSTRACT

Introduction: Considering the nature of oral healthcare needs for children with adenotonsillar hypertrophy (ATH) and mouth breathing and the increased risk of oral disease faced by the children, we aimed ascertain the perception and experience of ear, nose and throat (ENT) specialists to dental referral for such children.

Material and Method: A descriptive, cross-sectional survey was sent to a sample of ENT specialists in Turkey. The questionnaire, consisted of 27 questions in five domains. A total of 123 ENT specialists participated in the survey.

Results: In the evaluation of the examination of the oral cavity of children with ATH, a low frequency of examination for the malocclusion (57.7%) and oral functional habits (68.3%) was found. Reasons ENT specialists referred patients to orthodontists varied from missing teeth 15.4% to sounds from tmj 66.7%. In the chi-square test for the effect of gender and the location of practice in the orthodontic referral of ENT specialists we could identify significant predictors ($p<0.05$).

Conclusion: Although the majority were aware that ENT specialists has an important role in the prevention of parafunctional oral habits and orthodontic anomalies, they did not have the pertinent knowledge and practice to apply a complete and systematic examination for oral and dental health, parafunctional oral habits and malocclusion.

Keywords: ATH, ENT specialists, malocclusion, oral and dental health, referral

INTRODUCTION

ATH has been reported as the most important factor causing partial or complete obstruction of the upper respiratory tract in childhood (1). In general, it has been observed most frequently and severely between the ages of 4 and 8 years (2). Adenotonsillar hypertrophy can affect children in many ways, causing craniofacial changes such as maxillary growth retardation, mandibular retrusion, crossbite, dolichocephalic face, as well as myofunctional changes such as chewing, swallowing and speech disorders (3,4). Additionally, adenoid and tonsil hypertrophy is the most important factor of mouth breathing in pediatric patients (5). Mouth breathing due to ATH has been shown to cause "Adenoid face" that defined most dentofacial changes such as V-shaped narrowing of the maxillary arch, opening of the lips and lowering of the tongue, retrognathic mandible, increased overjet, anterior and posterior crossbite, anterior open bite, and displacement of the contact points (6,7). Therefore, it is necessary to intervene these etiological factors early to prevent the development or worsening of the malocclusion and if it has already developed, correct it with early orthodontic treatment to stimulate eugnatic skeletal growth (8). Also, regarding oral health problems, mouth breathing can increase the risk of dry mouth, tooth decay and gingivitis due to evaporation of saliva. Some authors reported that significantly higher number of initial lesions in all teeth was observed in the mouth breather children (9,10). A multi-disciplinary management approach involving general and pediatric dentists, otolaryngologists and orthodontists is essential for the early diagnosis and treatment of oral health problems in mouth breathing children (1).

Dentofacial appearance has a significant impact on individuals, especially children (11,12). Shaw et al. (13) reported that children were teased about their dentition more than any other factors. Malocclusion may therefore

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Received: 27.04.2022 **Accepted:** 22.05.2022

affect the individual's quality of life and self-esteem. Early intervention and preventive orthodontics perform the same functions and prevent or reduce progression to fully developed malocclusion later in life and also remove factors that hinder the regular development of dental arches (14). Furthmore, early orthodontic treatment has been found to improve both psychosocial development and masticatory function in children. The referral is also important for planning the individual remineralization therapy and to prevent the progression of the caries lesions. (1). Thus, a referral may significantly and positively change an individual's life.

ENT specialists may help in early diagnosis of orthodontic problems and other oral and dental health problems in children with mouth breathing due to ATH and this may advance the treatment effect and its constancy over the years. In these children, early detection of caries is the basic principle in order to reduce the loss of tooth structure and to establish an appropriate treatment plan (15). To the best of our knowledge, there is no study published worldwide focusing on the assessment of awareness of ENT specialists regarding oral and dental health and orthodontic problems in children with mouth breathing due to ATH.

This study aimed to determine the knowledge, attitudes and practices of ENT specialists who work in Turkey, concerning the prevention of oral and dental health problems and malocclusion and to raise awareness about the importance of ENT specialists in preventing oral and dental health and orthodontic problems in mouth breathing children due to ATH.

MATERIAL AND METHOD

A descriptive cross-sectional study was carried out among ENT specialists including those with post-graduation levels, working in government, private, and other healthcare sectors who are currently practicing in Turkey. Ethical permission required for the study to be carried out was obtained from Gaziosmanpaşa Training and Research Hospital, Medical Researches Ethics Committee (Date: 28.04.2021, Decision No: 268). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The instrument for the study was a self-made comprehensive questionnaire that consists of five chapters containing questions about the sociodemographic information of the participants, the risk factors of malocclusion and oral and dental health, the evaluation of the attitudes of ENT specialists towards the prevention of malocclusions, parafunctional habits and dental and gingival diseases, the evaluation of the behaviors of ENT specialists on the examination and treatment of malocclusion, parafunctional habits and dental and gingival diseases, and the evaluation of knowledge levels and sources of information on malocclusion and oral and dental health of ENT specialists. The first section of questionnaire included sociodemographic data such as age, gender, title, years of clinical experience, hours of patient care per week, and the number of patients with ATH seen per month and the number of operation of ATH per month. The second part included questions measuring the level of knowledge of ENT specialists about risk factors related to malocclusion and oral and dental health. In the third and fourth sections, physicians were asked about the attitudes and practices regarding the prevention of malocclusion and dental and gingival diseases and orthodontic examination practices (knowledge about orthodontic problems, whether they have performed oral and dental examinations); and in the fifth part, it was questioned if ENT specialists received training on dental and gingival diseases and orthodontic problems and prevention of these and the source of their knowledge.

The questionnaires were combined into a form on Google forms and sent to the participants via e-mail, WhatsApp, and private social network platforms starting April 28, 2021, and the questionnaires were closed on May 28, 2021. Before starting the study, to test the comprehensibility and consistency of the questionnaire within the scope of the study, the questions were sent to 5 experts, 2 pediatric dentists, 2 ENT specialist, and 1 biostatistician. Therefore, biased and confusing questions were omitted. A pilot study was conducted before the questionnaires were uploaded online to assess the relevance and intelligibility of the questions. The pilot study sample included participants representing nine ENT specialists, and each received a hard copy of the questionnaire. A brief introduction was presented at the beginning of the survey to inform the respondents of the purpose and content of this study, and electronic informed consent was obtained if they agreed to complete the questionnaire. In the OpenEpi power analysis program, with an estimated margin of error is 5% and sample power is 80%, the required minimum number of responders is estimated to be 120. A total of 123 Turkish ENT specialists, all volunteers, answered the questionnaire.

Statistical Analyses

Statistical analyses were performed using Statistical Package for the Social Sciences 20.0 (SPSS 20.0) program. The demographic characteristics of the participants were evaluated with the Chi-square test. The Shapiro-Wilk test was used to analyze the assumptions of normal distribution of the quantitative results. A p value less than 0.05 was considered as 'statistically significant'.

RESULTS

A-hundred twenty three ENT specialists completed the questionnaires. Among the responding ENT specialists, 64.2% were male while 35.8% were female. Their location of practice varied between governmental hospitals (38.2%), academic institutions (50.4%) and private clinics (9.8%). According to the duration of practice, 27.6% reported experience of more than 20 years. Many reported working duration up to 40 hours a week (75.6%). Ratio of eleven or more patients admitted within a month due to ATH were 52%. Various sociodemographic details of the study participants are available in **Table 1**.

Table 1. Socio-demographic characteristics of respondents

	(n=123)	(%)
Gender		
Male	79	64.2
Female	44	35.8
Age		
20-29	43	35.0
30-39	34	27.6
40-49	27	22.0
50-59	14	11.4
>=60	5	4.1
Location of practice		
Govermental hospital	47	38.2
University	62	50.4
Private hospital	12	9.8
Don't work	2	1.6
Years at work		
0-9	59	48.0
10-19	30	24.4
>=20	34	27.6
Hours per week		
31-40	30	24.4
>=40	93	75.6
Patients per day		
0-10	5	4.1
11-20	10	8.1
21-30	19	15.4
>30	89	72.4
Patients with ATH per month		
0-5	32	26.0
6-10	27	22.0
>=11	64	52.0
ATH operation per month		
0-5	48	39.0
6-10	42	34.1
>=11	33	26.8

ATH: Adenotonsillar hypertrophy

Of the total sampling, 95.9% knew that ATH is a risk factor for maloclusion. More than half of the sample, 79.7% had sufficient knowledge regarding that decreasing savigation in children with mouth respiratory and ATH promotes an aciduric and acidogenic microflora. Regarding ENT specialists' knowledge levels about various orthodontic problems, knowledge of retrognatism was the most (92.7%), while knowledge of overbite was the least (50.4%) (**Table 2**).

Table 2. ENT specialists' knowledge levels about orthodontic problems and risk factors of malocclusion and oral and dental health in children with ATH

Knowledge levels		**n=123**	**(%)**
1. Children with ATH are more likely to develop malocclusion. Do you have any information about this?	Yes	118	95.9
	No	5	4.1
2. Since the decrease in the amount of saliva in children with ATH will reduce the mechanical clearance of saliva, it may cause the accumulation of food residues and dental plaque, leading to an aciduric and acidogenic oral microflora, which leads to the development of caries and bad breath. Do you have any information about this?	Yes	98	79.7
	No	25	20.3
Orthodontic problems			
		n=123	**(%)**
Crowding			
I know		92	74.8
I don't know		31	25.2
Crossbite			
I know		76	61.8
I don't know		47	38.2
Overbite			
I know		62	50.4
I don't know		61	49.6
Anterior openbite			
I know		89	72.4
I don't know		34	27.6
Prognathism			
I know		105	85.4
I don't know		18	14.6
Retrognathism			
I know		114	92.7
I don't know		9	7.3
Missing teeh			
I know		78	63.4
I don't know		45	36.6
Spaces			
I know		89	72.4
I don't know		34	27.6
None			
I know		5	4.1
I don't know		118	95.9

* Participants marked more than one option.

A total of 95.1% believed that they played important roles in preventing malocclusion, dental caries and gingival diseases in children. Also, 95.1% considered dental visits for preventing malocclusion and dental and gingival diseases. About the fact that ENT specialists have to examine children's teeth and oral cavities, 95.9% of the participants responded positively (**Table 3**).

Table 3. Questions related to attitude domain among the ENT specialist

		(n=123)	(%)
1. ENT specialists have to examine oral cavity of children with ATH.	Yes	118	95.9
	No	-	-
	I don't know	5	4.1
2. Dental examination is important in the prevention of malocclusion and dental and oral diseases.	Yes	117	95.1
	No	2	1.6
	I don't know	4	3.3
3. ENT specialists play an important role in the prevention of malocclusion and oral and dental diseases in children with ATH.	Yes	117	95.1
	No	2	1.6
	I don't know	4	3.3
4. A multidisciplinary approach management that includes pediatric dentists, ENT specialists and orthodontists is important for the early diagnosis and treatment of oral health problems in children with ATH.	Yes	118	95.9
	No	-	-
	I don't know	5	4.1

* ENT: Ear, Nose, Throat ATH: Adenotonsillar hypertrophy

They were also asked if they evaluated the oral functional habits of their patients. While 21.1% of the sample indicated that they evaluated when the patient had a complaint about this subject, 68.3% of the sample indicated that they evaluated every time. 57.7% of the participants reported performing routine oral examinations. Participants were asked if they would refer children to the dental practioner when they decided to adenotonsilectomy. 84.6% indicated that they would refer.

Moreover, participants were asked if they would refer a child with ATH to dentists when they identified a child with malocclusion or any parafunctional habits. Most of the sample (85.4%) indicated that they would refer (**Table 4**). On the other hand participants were asked if they had any patient that they referred to ortohodontist or dental practioner. 57.7% indicated that they had orthodontic referral 30.9% indicated that they referred children to dental practioner (**Table 4**).

Their answers for the reasons for referral due to orthodontic and dental problems to orthodontist or dental practioner differed for each condition from 15.4% for missing teeth to 66.7% for temporamandibular diseases (**Table 5**).

The participants preferred several methods to receive dental education and training on parafunctional oral habits and orthodontic anomalies. Scientific journals and colleagues were the most preferred method, (40.7%; 44.7%). Furthermore, previous dental training about orthodontic problems in children was reported by only 17.8% of participants. On the other hand, their responses for receiving dental education regarding oral and dental diseases and protective measures in children during their medical or specialty training were mostly "I did not receive any dental education and training" (82.9%). Most of the participants (86.2%), indicated that they needed more knowledge about oral and dental diseases and prevention of malocclusion.

Table 4. Questions related to practice domain among ENT specialists

		(n=123)	(%)
1. Do you evaluate the oral functional habits of your patients with ATH?	Yes	84	68.3
	No	13	10.6
	If any problem	26	21.1
2. Do you perform oral health examinations for malocclusion for your patients with ATH?	Yes	71	57.7
	No	10	8.1
	If any problem	42	34.1
3. Do you refer your patient with ATH that you decide to make adenotonsillectomy to a dentist when you diagnose dental caries or any gingival problems?	Yes	104	84.6
	No	19	15.4
4. Do you refer your patient with ATH to a dentist when you diagnose malocclusion or any parafunctional oral habit?	Yes	105	85.4
	No	18	14.6
5. Did you have any patient with ATH that need oral apliance for treatmetnt of obstuctive sleep apne (OSA), you consult with dentistry?	Yes	41	33.3
	No	54	43.9
	I think this appliance is not successful for OSA	8	6.5
	I don't know this appliance	19	15.4
	No response	1	0.8
6. Did you have any patient you consult with orthodontics?	Yes	71	57.7
	No	49	39.8
	No response	3	2.4
7. Did you have any patient you consult with dentistry?	Yes	38	30.9
	No	82	66.7
	No response	3	2.4

* ATH: Adenotonsillar hypertrophy

Table 5. Responses of ENT specialists in relation to the reason for orthodontic referral

	(n=123)	(%)
Sounds from tmj		
Yes	82	66.7
No	41	33.3
Jaw deviation		
Yes	80	65.0
No	43	35.0
Retrognathism		
Yes	75	61.0
No	48	39.0
Prognathism		
Yes	73	59.3
No	50	40.7
Crowding		
Yes	72	58.5
No	51	41.5
Grinding at sleep		
Yes	65	52.8
No	58	47.2
Early tooth loss		
Yes	51	41.5
No	72	58.5
Crossbite		
Yes	47	38.2
No	76	61.8
Difficulty in biting		
Yes	43	35.0
No	80	65.0
Overbite		
Yes	36	29.3
No	87	70.7
Spaces		
Yes	36	29.3
No	87	70.7
Mouth breathing/snoring		
Yes	25	20.3
No	98	79.7
Delayed eruption		
Yes	23	18.7
No	100	81.3
Missing teeth		
Yes	19	15.4
No	104	84.6
None		
Yes	5	4.1
No	118	95.9

ENT: Ear, Nose, Throat tmj: temporomandibular joint, *Participants marked more than one option.

We examined the referral patterns of ENT specialists to orthodontists and dentists regarding demographic characteristics such as gender, location of practice, years at work and seen patients with ATH per month. In the chi-square test, there was a statistically significant result for the effect of gender and the location of practice. Orthodontic referral of male participants (70.9%) were statistically higher than female participants (34.1%). Orthodontic referral of ENT specialists working in govermental hospital (48.9%) were statistically lower than ENT specialists working in private hospital (66.%) (**Table 6**). There wasn't any statistically significant dental referral result for the effect of demographic characteristics (**Table 6**).

Table 6. The effect of some sociodemographic factors on orthodontic referrals of ENT specialists

	Referrals			Statistical analysis*
	n/ %	n/ %	n/ %	
Gender				$\chi2$=19.988 df=2, p <.001
Male	56 (70.9)	20 (25.3)	3 (3.8)	
Female	15 (34.1)	29 (65.9)	0 (.0)	
Location of practice				$\chi2$=16.897 df=6, p <.010
Govermental hospital	23 (48.9)	24 (51.1)	0 (.0)	
University	38 (61.3)	23 (37.1)	1 (1.6)	
Private hospital	8 (66.7)	2 (16,7)	2 (16.7)	
Don't work	2 (100.0)	0 (.0)	0 (.0)	
Years at work				$\chi2$=6.899 df=4, p >.05
0-9	29 (49.2)	29 (49.2)	1 (1.7)	
10-19	19 (63.3)	11 (36.7)	0 (.0)	
>=20	23 (67.6)	9 (26.5)	2 (5.9)	
Patients with ATH per month				$\chi2$=7.662 df=4, p >.05
0-5	18 (56.3)	14 (43.8)	0 (.0)	
6-10	11 (40.7)	14 (51.9)	2 (7.4)	
>=11	42 (65.6)	21 (32.8)	1 (1.6)	

*p<.05, $\chi2$=chi-square value, df= degrees of freedom

DISCUSSION

According to the American Academy of Pediatric Dentistry and the American Academy of Pediatrics (16, 17), dental visits for children should begin at 6-12 months of age. This early visit to the dentist and routine oral examination is even more important for the child with a background medical problem to ensure the prevention, early diagnosis and prompt treatment of some of the above-mentioned oral and dental problems that they may be predisposed to (18,19).

ATH, one of the main causes of upper airway obstruction, is considered a common disease among children (20, 21). It has been shown that by providing adequate oral health care in children with ATH, diseases such as dental caries, periodontal diseases and bad breath can be prevented. It is also recommended to start orthodontic treatment as soon as possible, if necessary (22). In this context, ENT specialists, dental practioners and orthodontists should work as a team in the treatment of children with ATH.

The variability of the orthodontic and dental examination practices and possibly the ability to recognize the prevalence of orthodontic and dental problems in children with ATH is reflected in the patient referral patterns from the ENT specialists to the orthodontists and dental practioners. While conditions such as sounds from tmj, jaw deviation, retrognathism, prognathism and crowding were resulted in high referral frequencies, other anomalies were not common reasons for referrals. Orthodontic problems were less likely to result in referral; these include missing teeth, delayed eruption, mouth breathing/snoring, spaces

and overbite. The lack of early age orthodontic screening has been evident for years in all countries. For this reason, it is clear that orthodontic protection should be increased at an early age if possible (23,24).

We could not define any other research regarding orthodontic and dental knowledge, screening and referral in children with ATH from ENT specialists in the literature. Therefore, we could only compare our results with researchs evaluating pediatrician's knowledge and referrals for orthodontic problems, oral hygiene and dental caries (17,25,26). The results of the current study showed that the majority of the sample had admissible level of knowledge and attidue regarding malocclusion, oral and dental health and risk factors. However, the percentage of oral health related practices were fewer among ENT specialists which is line with an American national survey that conducted on pediatricians by Lewis et al (17). According to the results of a previous survey with 96 pediatricians in Greece, the majority were aware that the examination of the oral cavity was important, but did not have the appropriate knowledge to conduct a complete and systematic screening for orthodontic problems (27). In this previous study, a low frequency was detected in the examination of the position of teeth (54%) and jaws (51%), which comply with this study. Similarly, the results of this study show that %57.7 of ENT specialists examine the oral cavity of children with ATH for malocclusion. The reasons pediatricians referred patients to specialists varied from mouth breathing-snoring 24% (23/96) to face or teeth asymmetry 87% (84/96) (27). In this study, the reasons ENT specialists referred patients with ATH to specialists varied from missing teeth 15.4% to sounds from tmj 66.7%.

Mouth breathing/snoring which usually seen in children with ATH and most of the anomalies were not common reasons for referral. Therapeutic options include surgical extraction of hypertrophic adenoids and tonsils, as well as non-surgical alternatives such as oral appliances (OAs) (28). The dental practioners can play an important role in treating those cases with oral appliances, who refuse the surgery, or those with structural abnormality in which myofunctional appliances are beneficial (28). Only 33.3 % of participants consult patients with ATH that need oral appliance for treatment of obstructive sleep apne. %15.4 of them don't know this appliance. Therefore, it might be considered that ENT specialists have limited basic dental training, and this causes low confidence in oral cavity screening, recommendation, or consultation (16). 86.2% of the participants, stated that they needed more knowledge about oral and dental diseases and prevention of malocclusion. This result reveals that ENT specialists should be informed more about the subject both during and after medical education.

Moreover, many participants (95.9%) believed that ENT specialists must examine the teeth of children with ATH. Most participants (95.1%) considered their roles in children's teeth examination, the prevention of malocclusion and oral and dental diseases but few of them reported evaluating children's oral functional habits (68.3%) and the oral health examination for malocclusion (57.7%). Similarly, Alshunaiber et al. (16) and Di Giuseppe et al. (29) reported a low percentage of pediatricians who performed oral health examinations for children. However, the study of Indira et al. (30) found better practice levels, and many pediatricians (98.9%) reported that they included children's teeth examination in routine practice.

The majority of ENT specialists were aware of the importance of referral of patients with dental caries, gingival problems, malocclusion and parafunctional oral habit, but 57.7% of them consult with orthodontics and 30.9% of them consult with dentistry. In the present study, as in the study of Sezer et al. (31) conducted with pediatricians, insufficient knowledge on some aspects of children's parafunctional oral habits and orthodontic problems together with the associated practice among ENT specialists might be related to the lack of required dental training and education of the majority of participants. Also, decreased orthodontic referral frequency among ENT specialists who worked in governmental hospitals may be associated with a lack of clinical time for detailed examination.

CONCLUSION

Ideally, all children should have orthodontic screenings in both dentistry and ENT practices as each specialty can provide care and advice for their patients' orthodontic and oral and dental health. ENT specialists can relate to patients with ATH from an early age. Since they usually examine their patients before orthodontists and dental practioners, they have the opportunity to advise, guide and refer them when necessary. Being aware of the etiology, risk factors and impact of oral and dental diseases and orthodontic problems in children with ATH will support ENT specialists in making informed decisions and implementing comprehensive person-centered care plans.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical permission required for the study to be carried out was obtained from Gaziosmanpaşa Training and Research Hospital Medical Researches Ethics Committee (Date: 28.04.2021, Decision No: 268).

Informed Consent: Informed consent form was obtained from volunteers.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author have no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Acknowledgments: The author thank all ENT specialists for their participation in the study. The author would also like to thank Dr. Doğan Çakan for his kind support.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1113486
J Health Sci Med 2022; 5(4): 984-988

Knowledge and attitudes toward basic life support: survey among school teachers

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Cite this article as: Aldinç H, Gün C. Knowledge and attitudes toward basic life support: survey among school teachers. J Health Sci Med 2022; 5(4): 984-988.

ABSTRACT

Aim: It is known that in cases of cardiac arrest, the chance of survival rates increases by 2-3 times with the bystander basic life support (BLS). Considering that children who spend a significant part of the day apart from their families at school have their teachers with them, it is understood how important the BLS knowledge and skills of teachers are. In our study, we analyzed the knowledge of primary, secondary and high school teachers about BLS and their thoughts about this training.

Material and Method: The study was conducted by face-to-face interview with 200 primary/secondary school and high school teachers working in Istanbul in 2019. The teachers participating in the study were evaluated with questionnaires related to their demographic characteristics, their level of knowledge about BLS and their thoughts about BLS training. Correct answers and "yes" answers were calculated with 1 point, incorrect answers and "no" answers were calculated with 0 points.

Results: In the BLS information levels survey of female participants, it was found that they scored statistically lower for questions "Do you know emergency medical service number?" and "Emergency medical service call-up in critical condition" ($p<0.05$). Again, female participants had a lower score in the answers to all questions in the BLS application/education request questionnaire according to their gender ($p<0.05$). Participants who had previously received BLS training were found to score higher on certain questions in BLS knowledge levels and BLS application/training request questionnaires.

Conclusion: In the study, it was found that primary/secondary and high school teachers lack the available BLS information. It was determined that people who have been trained in this subject are more willing to BLS training and applications than people who have not been trained in BLS.

Keywords: Cardiopulmonary resuscitation, education, cardiac arrest, school teachers

INTRODUCTION

It is known that the chance of cardiac arrest cases being brought back to life increases 2-3 times with the basic life support (BLS) applied by the witnesses at the scene (1). This is called "Bystander Resuscitation" in the literature (2). Considering that children spend most of their time away from their families at school, we can say that teachers play a critical role in emergency situations where BLS is required (3).

There are two factors necessary for a successful BLS: 1) The presence of a bystender with knowledge of BLS 2) The implementation of BLS as soon as possible and with success (4). Therefore, it is important that the teachers who are with the children are qualified to intervene early and correctly. In this way, it will be possible for teachers to provide students with the right BLS training in addition to increasing lifesaving (5).

In a study conducted on the BLS knowledge of teachers in Turkey, it was found that only 33.1% of them received this training. 47.5% of those who did not receive BLS training said that they could apply BLS to the student if necessary (3). Of course, it is not clear how correctly and effectively teachers in this group who do not have BLS training can do the application. The training of teachers in accordance with the current BLS algorithms published by the American Society of Pediatrics and the American Heart Association will be able to prevent erroneous and delayed interventions. As a result of these trainings, the point of view of teachers who avoid the application of BLS for fear of inexperience and ignorance may change to this critical intervention.

There are not many studies examining the relationship between primary/secondary and high school teachers and BLS in Turkey. We conducted a survey study with teachers working in primary/secondary and high schools in Istanbul.

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Received: 07.05.2022 **Accepted:** 23.05.2022

In this study, we examined the current knowledge levels of teachers about what to do in case of cardiopulmonary arrest and the current level of knowledge about BLS and their perspectives regarding receiving BLS training. We aimed to contribute to more effective planning in the standardization of this important training by analyzing the relationship of teachers' knowledge levels and attitudes towards BLS training with participant variables.

MATERIAL AND METHOD

The study protocol was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Research Ethical Committee (Date: 04.11.2021, Decision No: 2021/21-15). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

On November-December 2021, 212 teachers in private/public primary/secondary/high schools located in the Küçükçekmece district of Istanbul were invited to study. 200 teachers who volunteered among these teachers were included in the study signed an informed consent form. The study was conducted in the form of face-to-face interviews.

The teachers participating in the study were questioned in terms of demographic characteristics such as age, gender, class levels where they were teachers, whether they had received BLS training before.

Participants were asked some questions based on the American Heart Association (AHA) 2020 BLS Guide and their knowledge levels were evaluated. Then, questions were asked about their will to participate in BLS training and to practice and receive BLS training in real life. Correct answers and "yes" answer were evaluated with 1 point and incorrect answers and "no" answers were evaluated with 0 points (**Table 1**).

Statistical Analysis

According to the gender of the participants, their level of knowledge about BLS and their BLS application/training requests were analyzed by Pearson Chi-square Independence Test and Fisher Exact Probability Test. Again, according to the fact that they had previously received BLS training with the same method, their BLS knowledge levels and their will to receive training were analyzed.

Spearman's Rho Correlation Test was used to analyze the correlation between the age and the class levels they teach, and their BLS knowledge levels and their BLS application/training request.

In addition, the correlation between BLS knowledge levels and BLS application/training request was analyzed again with Spearman's Rho Correlation Test.

All analyses (IBM Inc., Armonk, NY, USA) were performed using the SPSS Statistics version 21.0.

Table 1. Assessment questionnaire

BLS knowledge assessment questionnaire
1. Do you know the survival rate with the bystander BLS?
2. Do you know the emergency medical service phone number?
3. Assessment of the patient's unresponsiveness, airway and breathing
4. Emergency medical service call
5. The correct ratio of chest compressions and rescue breathing
6. Accurate depth and speed of chest compressions
7. Has he considered using an automatic external defibrillator?
8. Does he know the purpose of using an automatic external defibrillator in patients with cardiac arrest?
Evaluation questionnaire related to BLS application/training request
1. I would like to participate in BLS training
2. I would like to start BLS when I witness cardiac arrest
3. I would like to start BLS and do chest compressions
4. I would like to start BLS and do mouth-to-mouth ventilation
5. I would like to start BLS and do chest compressions + mouth-to-mouth breathing
6. Reasons for not starting BLS;
Lack of information
Being afraid to make mistakes
The risk of infectious diseases
The patient's vomiting
Other reasons
7. I would like to give BLS training

RESULTS

105 male and 95 female participants were evaluated in the study. The general characteristics of the participants and the distribution of their responses to the survey questions are shown below (**Table 2**). There was a statistically significant difference between the groups according to the gender of the participants in terms of their answers to the questions in the BLS information levels survey: "Do you know emergency medical service phone number?" and "Emergency medical service call-up" ($p<0.05$). Again, according to their gender, a statistically significant difference was found between the groups in terms of answers to all questions in the application/training request questionnaire ($p<0.05$) (**Table 3**).

According to the fact that the participants had received BLS training before; in the knowledge levels survey, no statistically significant difference was found between the groups in terms of their answers to the questions: "Do you know the survival rate with the bystander BLS?", "Assessment of the patient's unresponsiveness, airway and breathing", "emergency medical service call" and "The correct ratio of chest pressure and a rescue breathing." ($p<0.05$). Again, according to the state of receiving BLS training, in BLS application/training request questionnaire, there was a statistically significant difference between the groups in terms of the answers ($p<0.05$) given to questions: "I would like

to start BLS and do mouth-to-mouth ventilation," "I would like to start BLS and do chest compressions + mouth-to-mouth ventilation" and "I would like to teach BLS" (**Table 4**).

Table 2. General characteristics of the participants and the distribution of their answers

	n	%
Gender		
Man	105	52.5
Woman	95	47.5
Age	38.13±9.17	36 (23-57)
Class levels		
1	14	7
2	35	17.5
3	26	13
4	19	9.5
5	21	10.5
6	11	5.5
7	6	3
8	17	8.5
9	11	5.5
10	17	8.5
11	12	6
12	11	5.5
Received BLS training before	19	9.5
BLS knowledge assessment questionnaire		
Do you know the survival rate with the bystander BLS?	5	2.5
Do you know the emergency medical service phone number?	187	93.5
Assessment of the patient's unresponsiveness, airway and breathing	8	4
Emergency medical service call	124	62
The correct ratio of chest compressions and rescue breathing	14	7
Accurate depth and speed of chest compressions	-	-
Has he considered using an automatic external defibrillator?	-	-
Does he know the purpose of using an automatic external defibrillator in patients with cardiac arrest?	-	-
Evaluation questionnaire related to BLS application/training request		
I would like to participate in BLS training	183	91.5
I would like to start BLS when I witness cardiac arrest	183	91.5
I would like to start BLS and do chest compressions	183	91.5
I would like to start BLS and do mouth-to-mouth ventilation	94	47
I would like to start BLS and do chest compressions + mouth-to-mouth breathing	94	47
I would like to give BLS training	164	82
Reasons for not starting BLS;		
The risk of infectious diseases	4	2
Being afraid to make mistakes	13	6.5

Table 3. Distribution of BLS knowledge levels and BLS application/training request rates according to gender of the participants

	Gender				X^2	p
	Man		Woman			
	n	%	n	%		
BLS knowledge assessment questionnaire						
Q1	5	4.8	-	-	4.64	0.061
Q2	104	99	83	87.4	11.194	0.001
Q3	5	4.8	3	3.2	0.334	0.724
Q4	84	80.0	40	42.1	30.399	0.000
Q5	5	4.8	9	9.5	1.701	0.192
Q6	-	-	-	-		
Q7	-	-	-	-		
Q8	-	-	-	-		
Evaluation questionnaire related to BLS application/training request						
Q1	103	98.1	80	84.2	12.363	0.000
Q2	103	98.1	80	84.2	12.363	0.000
Q3	103	98.1	80	84.2	12.363	0.000
Q4	67	63.8	27	28.4	25.075	0.000
Q5	67	63.8	27	28.4	25.075	0.000
Q7	98	93.3	66	69.5	19.236	0.000

Pearson Chi-Square Test, Fisher's Exact Test

Table 4. Distribution of BLS knowledge levels and BLS application/training request rates depending on whether they have been trained for BLS before or not.

	Received BLS training before				X^2	p
	No		Yes			
	n	%	n	%		
BLS knowledge assessment questionnaire						
Q1	-	-	5	26.3	48.853	0.000
Q2	168	92.8	19	100	1.46	0.617
Q3	-	-	8	42.1	79.386	0.000
Q4	105	58	19	100	12.868	0.000
Q5	6	3.3	8	42.1	39.744	0.000
Q6	-	-	-	-		
Q7	-	-	-	-		
Q8	-	-	-	-		
Evaluation questionnaire related to BLS application/training request						
Q1	164	90.6	19	100	1.95	0.379
Q2	164	90.6	19	100	1.95	0.379
Q3	164	90.6	19	100	1.95	0.379
Q4	75	41.4	19	100	23.675	0.000
Q5	75	41.4	19	100	23.675	0.000
Q7	145	80.1	19	100	4.609	0.028

Pearson Chi-Square Test, Fisher's Exact Test

A statistically significant correlation was found between the ages of the participants and the answers to the 1st and 2nd questions in the BLS knowledge levels questionnaire in the positive direction and a negative and statistically significant correlation was found between the class levels they teach and the answers to questions 2, 3 and 4 in the BLS knowledge levels questionnaire ($p<0.05$) (**Table 5**).

A statistically significant correlation was found between the ages of the participants and the answers to questions 1, 2, 3, 4 and 5 in the BLS application/training request questionnaire in a negative way and a statistically significant correlation was found in the negative direction between the answers to questions 4, 5 and 7 between application/training request for BLS and the class levels they teach ($p<0.05$)(**Table 5**).

Table 5. Correlation analysis for the age and class level of the participants and the relationship between BLS knowledge levels and BLS application/training request

	Age		Class level	
	r	p	r	p
BLS knowledge assessment questionnaire				
Q1	0.161	0.023	-0.082	0.250
Q2	0.170	0.016	-0.173	0.015
Q3	0.138	0.051	-0.222	0.002
Q4	0.127	0.073	-0.391	0.000
Q5	0.027	0.709	-0.095	0.179
Evaluation questionnaire related to BLS application/training request				
Q1	-0.196	0.005	-0.133	0.060
Q2	-0.196	0.005	-0.133	0.060
Q3	-0.196	0.005	-0.133	0.060
Q4	-0.244	0.000	-0.193	0.006
Q5	-0.244	0.000	-0.193	0.006
Q7	-0.109	0.126	-0.251	0.000

Spearman's Correlation Test

DISCUSSION

In our study, it was found that the proportion of participants who had previously received BLS training was only 6.5%. In a study conducted with a large group of primary, secondary and high school teachers in Belgium in 2013, this figure was found to be 59% (1). In a study conducted among secondary school teachers in 2016 (4) it was 36.7% and in a study conducted with primary, secondary and high school female teachers in 2020 (6) it was 30.5% and this rate was found to be remarkable according to the value of our study.

In our study, the proportion of teachers who knew the emergency medical service phone number was found to be 93.5%, and this proportion was 66% in the study (1), which found that teachers in the study had previously received 59% BLS training. The reason for this may be the lack of BLS training in our country and the associated excess of urgent health care needs. In addition, despite the high rate of knowing the emergency medical service phone number, the rate of people considering calling emergency medical services in case of arrest / unresponsive patient was found to be 62%. When we look at the subgroups, this ratio is 80% for men and 42.1% for women. Although the emergency medical service number is known by women, the fact that the emergency medical service call rate is significantly lower may be due to the fact that they feel more excitement and panic in case of such critical situation. As a matter of fact, in a study published in 2006, it was found that the stress level of female rescuers was significantly higher than that of men (7).

In a study conducted with teacher's training school students in South Africa, the proportion of BLS training received earlier was 8.9%, and the proportion of those who consider this training mandatory for all teachers was 90.5% (8). In our study, the proportion of those who want to study BLS was found to be 91.5% in a similar way. These rates indicate that even if they have not received enough training, teachers are aware of and willing to receive BLS training.

It is noteworthy that in our study, all teachers who had previously received BLS training responded positively to all questions related to the application, training and provision of BLS training. The fact that people with BLS training are more willing to apply BLS if necessary has been shown by similar results in many previous studies (9-12). The most important reasons for this request are to understand the importance of BLS and to be able to apply BLS correctly (12).

Especially in the 4th and 5th questions, where mouth-to-mouth ventilation is included, the positive response rate of people who have not received BLS training is only 41.4%. In an article published by Dobbie at al. (13) in 2018, when reasons for not wanting to practice BLS were examined between people who had not received BLS training and those who had received it, mouth-to-mouth ventilation practice had no relationship with the status of previous training. Nevertheless, in this study, the presence of blood and vomit in the environment as a reason for avoiding BLS was found to be significantly higher in people who did not have BLS training.

In addition to the requirement that secondary/high school teachers should have this training, the European Resuscitation Council and the American Heart Association recommend that BLS training be included in the secondary/high school training curriculum (1,5). There are also some studies related to this. In a study conducted with elementary school students in Thailand, it was found that although their physical strength is not as sufficient as that of adults, they are able to apply adequate BLS after training (14). The cost of providing this training to primary/secondary and high school students is a separate issue. Due to the high cost of the training provided by medical doctors in this regard, the role of medical faculty students in this training has been examined and found to be effective (15). There is even a study that shows that high school students can receive effective BLS training through peer teaching (16). It has been shown in a study that it is also meaningful for school teachers to provide BLS training within the educational curriculum in terms of effectiveness (17). In our study, it was found that most of the teachers participating in the study, especially teachers who had previously received BLS training, wanted to provide BLS training at school.

There are some limitations in our study. It has not been studied how teachers who have received BLS training receive it to a certain standard, how many years ago they received it. Another limitation is that the BLS knowledge of the teachers participating in the study is measured only theoretically.

CONCLUSION

The current BLS training rate among primary/secondary and high school teachers is at a low level. Teachers who receive training have a greater tendency to apply BLS in a critical situation, a greater desire to receive more training and provide BLS training at school. In order for this training to be given to teachers and then to be given to students through teachers, more extensive studies are required.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study protocol was approved by the Acıbadem Mehmet Ali Aydınlar University Medical Researches Ethical Committee (Date: 04.11.2021, Decision No: 2021/21-15).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1080669
J Health Sci Med 2022; 5(4): 989-995

The risk of smartphone addiction in university students and its affecting factors

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Cite this article as: Üstündağ Öcal N, Öztürk A. The risk of smartphone addiction in university students and its affecting factors. J Health Sci Med 2022; 5(4): 989-995.

ABSTRACT

Aim: In this study, it was aimed to determine the risk of smartphone addiction in university students and to reveal the factors affecting it.

Material and Method: This descriptive and cross-sectional study was conducted on first and fourth year students of the Faculty of Health Sciences, Faculty of Economics and Administrative Sciences, and Faculty of Engineering and Architecture of a state university in the Central Anatolia Region. The study was completed with 1181 students who agreed to participate in the research. Data were collected using a sociodemographic information form consisting of 29 questions and a Smartphone Addiction Scale-Short Form (SAS-SF) consisting of 10 questions. Chi-square and logistic regression analysis were used in the comparative analyses, and $p<0.05$ values were considered statistically significant.

Results: 51.6% of the students participating in the study were female and 48.4% were male. The average age of first use of smartphones by students is 15.6±2.6 years. The average score of the students in SAS-SF is 28.12±10.65, According to the evaluation made by considering the cut-off points of the scale (above 31 for men and 33 for women), the risk of smartphone addiction was found in 34.7%.

Conclusion: It has been determined that approximately one third of the students participating in the research are at risk of smartphone addiction, and awareness of the subject should be created in the students.

Keywords: Smartphone addiction, university students, behavioral addiction

INTRODUCTION

With the effect of rapidly developing and advancing technology, mobile phones, which are widely used, have been replaced by smart phones. Smartphones that feature a small pocket computer; In addition to making phone calls, it has the ability to make video calls, connect to the internet, send and receive e-mails, install some applications and programs, and records images and sound (1). The use of smartphones with all these features has become very common in the last ten years (2). For example, it has been reported that 99.3% of internet users in China access it via smartphones (3). Similarly, in Switzerland, almost all adolescents aged 12-19 (97%) have a smartphone (4). In Turkey, the rate of mobile phone use among young people aged 16-24 has been reported as 94.2% in 2020 (5).

When it comes to addiction, the first thing that comes to mind is substance addiction, alcohol addiction, tobacco addiction, but it is known that behavioral addictions such as technology and smartphone addiction can also occur (6-8).

Smartphone addiction, "individual's inability to regulate their smartphone use and eventually leads to negative consequences and clinical deterioration in daily life" (9-12).

In our study, it was aimed to determine the risk of smartphone addiction in university students, one of the groups that use smartphones the most, and to determine the factors that may affect it.

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Received: 28.02.2022 **Accepted:** 24.05.2022

MATERIAL AND METHOD

Ethics Dimension of The Research

In order to carry out the study, the approval of the Erciyes University Clinical Researches Ethics Committee (Date: 09.02.2018, Decision No: 2018/61) and institutional permission were obtained. In addition, before the research, the students were informed about the research and their consent was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Type of Study

This study is descriptive and cross-sectional.

Place/Time of Study

Study was conducted between October and December 2018 on 1st and 4th year students studying Health, Social and Science of a Erciyes University.

Population, Sample and Sampling Research Method

The sample of the research consists of 1st and 4th year students studying at the Faculty of Health Sciences, Faculty of Economics and Administrative Sciences and Faculty of Engineering and Architecture. During the data collection, 260 people who did not attend the classes or did not want to participate in the research could not be interviewed and 28 students who did not use a smart phone were excluded from the study. As a result, a total of 1181 students were reached, including 302 (95.2%) from the Faculty of Health Sciences, 407 (74.4%) from the Faculty of Economics and Administrative Sciences, and 472 (78.1%) from the Faculty of Engineering and Architecture. Participation rate in the study was 80.4%.

Data Collection Tools

The data were collected by giving a 29-question sociodemographic information form prepared by the researchers. In addition, using the Smartphone Addiction Scale-Short Form consisting of 10 questions, it was collected in classroom environments and under the supervision of researchers.

Data Collection

Smartphone Addiction Scale-Short Form (SAS-SF) is a scale developed by Kwon, Kim, Cho and Yang to measure smartphone addiction in adolescents in 2013 and consists of 10 items in total. The scale, which has no sub-factors, is evaluated with a 6-point Likert scale, and the scale items are scored correctly from 1 to 6 (1-Strongly disagree, 2-Disagree, 3-Partly disagree, 4-Partly agree, 5-Agree, 6-Strongly agree). The total score obtained from the scale varies between 10 and 60, and it has been reported that the risk of addiction increases as the score gets higher. The cronbach alpha coefficient of the scale was 0.91, with cut-off points of 31 for men and 33 for women in the Korean sample (13). The Turkish validity and reliability study of the scale was conducted by Noyan et al. (14) and It has been reported as a valid and reliable scale that can be applied to evaluate smartphone addiction in university students and young adults. However, a separate cut-off point was not determined in the relevant study, and cut-off scores of 31 for men and 33 for women in the Korean sample were accepted as valid.

Statistical Analysis

While evaluating the data, the chi-square test was used to compare categorical variables as well as descriptive statistics. In order to show the relationships between smartphone addiction and independent variables, a model containing statistically significant ($p<0.05$) values according to the chi-square analysis was created and logistic regression analysis was performed. The dependent variable in the model is "smartphone addiction"; gender, age, education areas, economic status according to their own evaluations, perception of health status, smoking and alcohol use, sleep quality, frequency of checking smartphones during the day, taking pictures with smartphones, socializing smartphones Media usage status, smartphone use time, age of first use of the smartphone, where the smartphone was left before going to bed at night and the frequency of smartphone replacement were taken as independent variables.

RESULTS

A total of 1181 students participated in the research, and the average age of the students studying in the first year was determined as 19.5, and the average age of the students studying in the fourth year was determined as 22.1. 51.6% of the students are female, 60.5% are in the first class and 69.0% are living in the dormitory. Some features related to smartphone usage are given in **Table 1**.

Table 1. Some characteristics of students' smartphone use.

Characteristics (n=1181)	X±SD
Age of first use of smartphone	15.6±2.6
How long has he used the smartphone (years)	5.1±2.0
How long he uses the smartphone per day (hours)	5.5±3.5
Frequency of checking smartphone during the day (times)	41.7±62.9
Monthly paid invoice/credit amount (TL)	40.9±36.6

It was determined in **Table 2** that the students participating in the study mostly used their smart phones for internet use, communication and social media (90.6%, 90.0%, 87.3%, respectively). The average score of the students participating in the study in SAS-SF is 28.12±10.65. The median value is 27. According to the evaluation made by considering the cut-off points of the scale (above 31 points for men and 33 points for women), 34.7% of the students participating in the research are smartphone addicts.

Table 2. Smartphone addiction risk status by some sociodemographic characteristics of the participants

Feature	n	%	Risk of smartphone addiction				x^2, p
			Yes		No		
			No.	%	No.	%	
Total	1181	100	410	34.7	771	65.3	
Gender							x^2: 9.036 p: 0.003
Male	572	48.4	174	30.4	398	69.6	
Women	609	51.6	236	38.8	373	61.2	
Education area							x^2: 17.602 p: 0.001
Health*	302	25.6	121	40.1	181	59.9	
Social daytime education	316	26.8	90	28.5	226	71.5	
Social evening education*	91	7.7	43	47.3	48	52.7	
Science daytime education	318	26.9	111	34.9	207	65.1	
Science evening education	154	13.0	45	29.2	109	70.8	
Class							x^2:6.330 p:0.012
1st class	714	60.5	268	37.5	446	62.5	
4th class	467	39.5	142	30.4	325	69.6	
Age range							x^2:6.297 p:0.043
18-20	631	53.4	234	37.0	397	63.0	
21-23	459	38.9	154	33.6	305	66.4	
24 and above*	91	7.7	22	24.2	69	75.8	
Self-assessment of sleep quality							x^2:14.228 p:0.007
Good	411	127	30.9	284	69.1	411	
Medium	452	146	32.3	306	67.7	452	
Bad*	318	137	43.0	181	57.0	318	

The risk of smartphone addiction; It was found to be higher in social sciences and health sciences students, younger students, female students, and students who stated that their sleep quality was low. It was determined that the risk of addiction was statistically significantly higher in those who started using a smartphone at a young age, checked their phone frequently, kept the phone in bed or under the pillow at night, and used the phone for social media (**Table 3**).

According to the Logistic Regression analysis results, the risk of smartphone addiction; 1.38 times for women compared to men, 2.22 times for those studying in social evening education compared to those studying at social daytime education, 2.11 times for those with good family economic status, according to their own assessment, According to his own assessment, it was found that those with poor sleep quality were 1.60 times more likely than those with good sleep. The same risk; Those who check their smartphones 50 or more times a day are 1.49 times compared to those who check 20 times or less, 1.54 times those who use their smartphones to take pictures, and 2.19 times those who use a smartphone for 7 hours or more a day (**Table 4**).

Table 3. Smartphone addiction risk status by students' smartphone and ınternet usage characteristics

Feature	n	%	Risk of smartphone addiction				x^2, p
			Yes		No		
			No.	%	No.	%	
Total	1181	100.0	410	34.7	771	65.3	
Age of first use of the smartphone							x^2:7.184 p:0.007
Under 15	637	53.9	243	38.1	394	61.9	
15 years and over	544	46.1	167	30.7	377	69.3	
How many hours of internet use per day							x^2:52.196 p<0.001
0-4 hours*	644	54.6	165	25.6	479	74.4	
5-6 hours	265	22.4	117	44.2	148	55.8	
7 and above	272	23.0	128	47.1	144	52.9	
Frequency of checking the smartphone during the day							x^2:35.770 p<0.001
20 times and below*	616	52.2	168	27.3	448	72.7	
21-49 times*	182	15.4	67	36.8	115	63.2	
50 times or more*	383	32.4	175	45.7	208	54.3	
How many hours a day he uses a smartphone							x^2:54.095 p<0.001
0-4 hours*	582	49.3	146	25.1	436	74.9	
5-6 hours*	278	23.5	107	38.5	171	61.5	
7 hours or more*	321	27.2	157	48.9	164	51.1	
Where the smartphone is left before bed at night							x^2:38.070 p<0.001
Outside the bedroom	14	1.2	2	14.3	12	85.7	
In the bedroom away from the bed*	106	9.0	17	16.0	89	84.0	
Near the bed	824	69.7	277	33.6	547	66.4	
In bed/under pillow*	237	20.1	114	48.1	123	51.9	
Smartphone replacement frequency							x^2:10.049 p:0.002
Less than 2 years	290	24.5	123	42.4	167	57.6	
3 Years or more	891	75.5	287	32.2	604	67.8	
Invoice/credit amount paid monthly to the smartphone							x^2:7.629 p:0.022
30 Tl and below*	612	51.9	191	31.2	421	68.8	
31-99 Tl	519	43.9	197	38.0	322	62.0	
100 Tl and more	50	4.2	22	44.0	28	56.0	
Considering himself a smartphone addicted (n=1113)**							x^2:200.509 p<0.001
Yes i am addicted*	162	13.7	111	68.5	51	31.5	
I'm partially dependent	492	41.7	222	45.1	270	54.9	
No, i am not addicted*	459	38.8	59	12.9	400	87.1	
Using the smartphone for social media							x^2:19.529 p<0.001
Yes	1031	87.3	382	37.1	649	62.9	
No	150	12.7	28	18.7	122	81.3	
Using a smartphone to take photographs							x^2:25.073 p<0.001
Yes	844	71.5	330	39.1	514	60.9	
No	337	28.5	80	23.7	257	76.3	

**: The number of students who answered "I have no idea" is 68, 5.8% is not included.

Table 4. Analysis of variables that may be effective on smartphone addiction with binary logistic regression.

Variable (reference)	B	Exp(B)	%95 G.A	p
Gender (Male)		1.000		
Women	0.323	1.381	1.026-1.859	0.033
Age (24 and over)		1.000		
21-23	0.397	1.488	0.868-2.551	0.149
18-20	0.467	1.595	0.921-2.761	0.095
Field of education (social daytime education)		1.000		
Faculty of health sciences	0.508	1.662	1.168-2.365	0.005
Social evening education	0.800	2.226	1.360-3.644	0.001
Science daytime teaching	0.336	1.399	0.982-1.994	0.063
Science evening education	0.182	1.200	0.759-1.896	0.435
His family's economic situation according to his self evaluation (poor)		1.000		
Middle	0.648	1.912	1.056-3.459	0.032
Good	0.747	2.110	1.129-3.945	0.019
Self-assessment of health (good)		1.000		
Middle	0.298	1.347	0.997-1.818	0.052
Bad	0.069	1.072	0.450-2.554	0.876
Smoking status (not smoking)				
Using	0.151	1.000	0.859-1.573	0.328
		1.163		
Alcohol use status (using)		1.000		
Not using	0.145	1.156	0.763-1.751	0.493
Self-assessment of sleep quality (good)		1.000		
Middle	0.005	1.005	0.746-1.354	0.974
Bad	0.471	1.602	1.152-2.226	0.005
Frequency of checking smartphones during the day (20 or less)		1.000		
21-49 times	0.236	1.267	0.879-1.825	0.205
50 or more times	0.404	1.497	1.119-2.003	0.007
Those who use smartphones to take photos (no)		1.000		
Yes	0.434	1.543	1.118-2.129	0.008
People using smartphone for social media purposes (no)		1.000		
Yes	0.381	1.464	0.907-2.365	0.119
How many hours of smartphone use per day (0-4 hours)		1.000		
5-6 hours	0.412	1.509	1.098-2.075	0.011
7 hours or more	0.786	2.195	1.611-2.993	<0.001
Age of first use of the smartphone (15 years and above)		1.000		
Under	0.215	1.240	0.931-1.651	0.142
Where the smartphone is left before bed at night (outside the bedroom/away from the bed)		1.000		
Near/inside the bed	0.763	2.144	1.265-3.632	0.005
Smartphone replacement frequency (every 3 years or more)		1.000		
Less than 2 years	0.347	1.415	1.061-1.888	0.018

DISCUSSION

In this study, it was determined that the average score of the students in SAS-SF was 28.12±10.65. As a result of the evaluation made by considering the cut-off points of the scale (above 31 for men and 33 for women), it was determined that 34.7% of the students participating in the study had a risk of smartphone addiction. As the scale score average increases, it is considered that the risk for addiction increases (14). In a study conducted with medical school students, the average score of the students from the short form of the smartphone addiction scale was found to be 27.72±11.07 (15).

In another study, the average score of 170 university students from the smartphone addiction scale was found to be 29.60±11.08 (16). In the study conducted with high school students in Kütahya, the average score of the students from the short form of the smartphone addiction scale was found to be 26.60 (17). In a study conducted on individuals aged 18-25 who applied to the family medicine outpatient clinic of a university, the mean SAS-SF score was reported as 31.18±14.59 (18). In the study examining the relationship between sleep quality and smartphone addiction in Pamukkale University students, the mean SAS-SF score was reported as 28.63±10.15. In the same study, 34.6% of the students were found to be at risk of smartphone addiction, and it is possible to say that the result is similar to our study (19). It can be thought that this may be due to the fact that the researched population has similar age groups. In a study conducted with 1,043 young adults at a university in England, the rate of smartphone addiction risk was similar to our study and reported as 38.9% (2). Considering other studies in the literature, 30.5% of the students in a study conducted with 210 university students from Korea, 17.9% of adolescents in another study conducted in Korea in 2013, In a study conducted among 414 Chinese university students, 13.5% of the students, In a study conducted with 249 students studying at a private university in Lebanon, it was shown that 44.6% of the students had the risk of smartphone addiction (9-12).

In the study, when the students' evaluation of themselves as smartphone addicts was examined, it was determined that 68.5% of the students who answered yes, I am addicted, had a risk of smartphone addiction. In another study, similar to our study, it was determined that students who evaluated themselves as smartphone addicts were more addicted to smartphones than other groups, and the difference between the groups was found to be statistically significant (20). In another study conducted on university students, it was reported that 52.69% of the students defined themselves as smartphone addicts (21). Young people's inability to control their time during mobile phone use and their more active use of social platforms cause them to be exposed to the screen for a longer period of time, making them more prone to problematic mobile phone use.

In the study, it was determined that the risk of smartphone addiction was higher in women than in men, and the difference between them was found to be statistically significant (**Table 2**). When the variables that may affect the smartphone addiction of the students participating in the study were evaluated by binary logistic regression analysis, it was determined that the risk of smartphone addiction was 1.38 times higher in women than in men (**Table 4**). In other studies, it was found that smartphone addiction is higher in female students, which supports our study (13,20,22,23). Although men are more inclined to use technological devices than women (24). It is possible to say that smartphone addiction is more common in women (25-27). The reason why smartphone addiction is seen more frequently in women than in men is attributed to the purposes of using the smartphone (26). However, there are opposite results in the literature. For example; in the study conducted by Taylan (28) with 300 university students, it was determined that the average score of male students from the smartphone addiction scale was higher than that of females.

In some studies, no statistically significant difference was found between gender and smartphone addiction (14,15,17,18,20,29).

In the study, when the educational areas of the students and the risk of smartphone addiction were examined, it was determined that the highest rate of smartphone addiction was found among students studying in social sciences evening education with 47.3%, and students studying in health department with 40.1% in the second place (**Table 2**). In our study, when the variables that may affect students' smartphone addiction are evaluated with binary logistic regression analysis (**Table 4**.), it is found that the risk of addiction is 1.66 times higher for those studying at the Faculty of Health Sciences, and 2.22 times for students studying at evening education in social sciences, compared to those studying in daytime education detected. In a study conducted in Lebanon, it was determined that the addiction score average of the students studying in the Health department was higher than the students studying in the Architecture, Engineering, Humanities and Law Departments (22). The fact that students studying in health sciences could spend longer time with a smartphone due to the need to search for more information on subjects such as practice courses and case tracking may have caused a higher addiction score average.

In the study, the risk of smartphone addiction among students aged 18-20 was found to be 37.0% (**Table 2**). When evaluated by logistic regression analysis (**Table 4**), although no significance was demonstrated, the risk of smartphone addiction was found to be 1.59 times higher in students aged 18-20 compared to students aged 24 and over. When the relationship between the class in which the students study and smartphone addiction is examined, it was determined that 37.5% of the first-year students and 30.4% of the fourth-year students were smartphone addicts, and the difference between them was found to be statistically significant. It was determined that the average age of the first-year students was 19.5, and the fourth-year students were 22.1 years old. As it can be seen from **Table 4**, although there is no significant difference, it is seen that the age of first use of the smart phone is below the age of 15 and the use of social media may have an effect on addiction. Earlier acquaintance with the smartphone makes it easier for the individual to adapt to the use of smartphones, which can be predicted to increase the risk of addiction. When the studies in the literature are examined; It has been reported that university students who use social media actively have a high level of smartphone addiction (30).

In another study, it was reported that those who instant messaging with their friends, those who use social media actively, and those who play games with their smartphones are at high risk for smartphone addiction (31).

In the study, when the variables that may affect students' smartphone addiction were evaluated with binary logistic regression analysis (**Table 4**), it was determined that those with good economic status had a 2.11 times higher risk of addiction than those with bad economic status, according to the student's self-assessment. Contrary to our study, when the literature was examined, no difference was found when it was examined in terms of family income (32).

With the developing technology, high-end smartphones with different functional features and hardware are coming to the market and the ease of access to these phones is increasing with the increase in economic income. It can be thought that the young people who want to benefit from these innovations offered by the smart phone world will spend more time with the smart phone and this will increase the risk of addiction.

CONCLUSION

In conclusion; The risk of smartphone addiction; women, those who are studying in the first year, those who start using the smartphone at the age of 15, those who use the internet or smartphone for 7 or more hours a day, those who check their phones 50 times or more during the day, those who change their smartphones in less than one year, those who use their smartphones at night. It is higher in those who keep it near the bed/under the pillow, and in those who use their smartphones for social media and taking photos. The risk of smartphone addiction was determined in 34.7% of the students participating in the study.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Erciyes University Clinical Researches Ethics Committee (Date: 09.02.2018, Decision No: 2018/61).

Informed Consent: Before the interview, the individuals who agreed to participate in the research were explained about the purpose and importance of the research, the time they would spend for the interview, and their consent was obtained. In the study "Informed Consent Principle", "Voluntary Principle" and "Privacy Protection Principle" were fulfilled.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: This study was produced from doctoral thesis and was supported by a Erciyes University Scientific Research Projects Unit with the code TDK-2018-8143.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgments: The authors thank all students who participated in the study for their contributions to this study.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm. 1109188
J Health Sci Med 2022; 5(4): 996-1001

Denervation injury of scalp hair due to trigeminal ganglion ischemia: the first experimental study

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Cite this article as: Olğun A, Karadağ MK, Zeynal M, et al. Denervation injury of scalp hair due to trigeminal ganglion ischemia: the first experimental study. J Health Sci Med 2022; 5(4): 996-1001.

ABSTRACT

Aim: Scalp hairs are mainly innervated by sensitive fibers of trigeminal nerves. Ischemic neurodegeneration of trigeminal ganglion can cause denervation injury of scalp hairs. We investigated if there is a relationship between the degenerated neuron densities of trigeminal ganglion neuron densities and the numbers of degenerated hair follicles numbers following subarachnoid hemorrhage (SAH).

Material and Method: Five normal (n=5), five SHAM (n=5), and ten (n=10) male rabbits were chosen from formerly experimental SAH created by cisternal homologous blood injection (0.75cc) group, which followed for three weeks. Degenerated neuron numbers of trigeminal ganglion and atrophic hair follicles numbers in the frontal areas of the scalp were examined by stereological methods. Degenerated neuron densities of trigeminal ganglions and atrophic hair follicles numbers were analyzed by the Mann-Whitney U test.

Results: The mean degenerated neuron densities trigeminal ganglions (n/mm^3) and atrophic hair follicles (n/mm^2) were determined as $5\pm2/m^3$ and$12\pm4/mm^2$ in control; $12\pm3/m^3$ and $41\pm8/mm^2$ in Sham and, $168\pm23/m^3$ and $79\pm14/mm^2$ in the study group ($p>0.001$). In the post-hoc analysis, all groups differed significantly from each other. A linear association was observed between the degenerated neuron densities of trigeminal ganglions and atrophic hair follicles (r: 0.343, p: 0.007).

Conclusion: Trigeminal ganglion neurodegeneration may be an essential factor in hair follicles atrophy after SAH, which has not been mentioned in the literature so far.

Keywords: Denervation Injury, hair, ischemia, scalp, trigeminal ganglion

INTRODUCTION

The scalp is innervated by trigeminal, facial, glossopharyngeal, vagal and upper cervical nerves (1). The sensory nuclei of the trigeminal nerve (TN), which have somatomotor and somatosensitive fibers, are located in a wide area extending from the pons to the medulla spinalis. Motor and sensory roots pass through the subarachnoid space in separate bundles and enter the Meckel cave at the floor of the middle cranial fossa and together form the TN. Since the dermatome areas of the TN are intensely innervated, it has to get a richer network compared to other nerves. Efferent fibers extend from the motor nucleus in the pons, and afferents extend from the mesencephalon to the second cervical segment. The sensory fibers of the TN and the sensory fibers of the facial, glossopharyngeal, vagal and upper cervical nerves innervate the craniofacial superficial and deep regions (2-4). Sensory fibers emerge from the trigeminal ganglion (TGG) located between the two leaves of the dura in Meckel's cave. After leaving the ganglion, they proceed together with the motor fibers. They leave the cranium passing through the subarachnoid and subdural distance as three separate branches as ophthalmic, maxillary and mandibular roots. While these branches carry the sense of the whole face, especially the ophthalmic nerve carries the sense of the scalp up to the vertex. The other two branches carry the sense of the scalp, especially in the temporal region. Each branch carries the afferent impulses of pain, heat, pressure, touch, and chemosensitive sensations, including the pH of all structures, including

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Received: 26.04.2022 **Accepted:** 25.05.2022

the intracranial, intraorbital, and intranasal cavities that fall into its trace, as well as the mucosa in this area (4-7).

The temporal arteries of the scalp are innervated mainly by the TNs. A normal sensory innervation of the auriculotemporal nerve and normal vascular supply of the superficial temporal artery is required for the temporoparietal fascial flaps (8). So, we think that the TN also regulates the pH changes that occur in normal and pathological conditions in the areas it innervates. Actually, cervical dorsal root ganglia, which have vasodilator effects, have also been reported to prevent arterial vasospasm together with trigeminal-glossopharyngeal-vagal nerves (9). TN innervates ipsilateral craniofacial arteries and causes vasodilation in subarachnoid hemorrhage (SAH) (5, 9, 10).

Vasospasm and increased intracranial pressure are the most dangerous complications of SAH (10). Spasm of the arteries supplying the scalp threatens the prognosis of injured scalp tissue and scalp reconstruction. When SAH causes ischemia in the TN, the ischemic TN also causes a spasm in the scalp arteries, causing denervation and ischemia injuries in the entire scalp tissue together with its fibers.

Trigeminal ganglion ischemia results from vasospasm of the ipsilateral cerebral arteries supplying this nerve (11). We assumed that the temporal artery spasm of the scalp due to SAH might cause scalp ischemia. We aim to demonstrate this hypothesis.

MATERIAL AND METHOD

This study was approved by the Atatürk University Animal Experiments Local Ethics Committee (Date: 29.06.2010, Decision No: B.30.2.ATA.0.01.02/2798) and the care of the animals and the experiments were conducted according to the guidelines set forth by the same ethics committee. Because the study was designed as an animal experiment, no written informed consent form was required. All procedures were carried out in accordance with the ethical rules. We protect animal rights per the principles of the Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html).

Study Population and Design

Five normal (n=5), five Sham (n=5) and ten male rabbits (n=10) were chosen from formerly experimental SAH. Experimentally induced SAH was created by cisternal homologous blood injection (0.75cc) in the study group. Subjects were followed for three weeks. Stereological methods examined degenerated neuron densities of trigeminal ganglions and atrophic hair follicles numbers. Electrocardiographic data and blood pressures were recorded preoperative, intraoperative, and postoperatively.

Experimental protocol

Intracranial pressure, light reflexes, pupil diameters, electroencephalogram (EEG), and electrocardiogram (ECG) findings were recorded. Pupil diameters were measured in all animals in light and dark environments, and fundoscopic examinations were performed three times a day for two days prior to inducing SAH. Linear EEG and ECG were considered as brain and heart death. Five animals were used as the intact control group for the normal and pathoanatomical and histopathological examinations of the TN and ganglion. All animals were anesthetized by isoflurane, administered through a face mask, followed by a subcutaneous injection of 0.2 mL/kg of the anesthetic combination (ketamine HCl, 150 mg/1.5 mL; xylazine HCl, 30 mg/1.5 mL; and distilled water, 1 mL) before surgery. During the procedure, a dose of 0.1 mL/kg of the anesthetic combination was used when required; balanced, injectable anesthetics were used to reduce pain and mortality. Autologous blood (0.75 cc) was taken from the auricular artery and injected into the cisterna magna of the animals in the SAH group for 1 minute using a 22-gauge needle. In the sham-operated control group, 0.75 cc of physiological serum was injected into the cisterna magna. No injection was given to the control group. The animals were followed for three weeks to death without any medical treatment while their intracranial pressure values were recorded daily, and then the animals were sacrificed.

All animals' frontotemporoparietal scalp tissues, brain stems, TNs and trigeminal ganglions were examined for gross anatomopathological characteristics. Findings are summarized in the results section.

All deep temporal arteries with their neighbors, TNs and TGGs, including brain areas, were fixed in 10% formalin solution for five days. Then, all brain stems were horizontally sectioned at 2-mm distances from the origins of the oculomotor nerves, and oculomotor nerve roots sections were embedded in paraffin blocks. The tissues were stained with hematoxylin & eosin (H&E), van Gieson, Tunel, and Aldehyde Fuchscine methods to estimate the neuronal density of the TGG. The Stereological and Cavalieri method was used to evaluate the neuronal density of TGG.

As in our former study, the number of alive and degenerate neurons in TGG was evaluated using the physical dissector method (12). The Cavalieri volume estimation method was used to obtain the total number of neurons in each specimen, calculated by multiplying the volume (mm^3) by the numerical density of neurons in each ganglion. Histologically, cellular angulation, nuclear

shrinkage, cytoplasmic condensation, and cellular darkening were accepted for neuronal and follicular degeneration criteria.

Statistical Analysis

The differences between the degenerated neurons densities of trigeminal ganglion and degenerated hair follicles numbers were analyzed using a commercially available statistics software package (SPSS® for Windows v. 12.0, Chicago, USA). The Kruskal-Wallis and Mann-Whitney U tests were used for data analysis. Bonferroni correction was applied in post-hoc tests that determined significant differences between groups for physiological parameters, pupil diameter and density of degenerated neurons in TGG, and density of atrophic follicles. The correlation between the density of degenerated neurons in TGG and the density of atrophic follicles was analyzed by Spearman's correlation test. Differences were considered significant at a two-sided $p<0.05$.

RESULTS

Clinical Results

Two animals in the study group died during the experiment. Cardiorespiratory disturbances, stiff neck, convulsions, urinary retention, intestinal dysmotility and gait disturbances were recorded. Weakened corneal and light reflex pupillary enlargements were recorded in the study group. Significant electrocardiographic abnormalities such as prolonged QT intervals, ST depressions, and low voltage QRS were noticed in animals with myocardial necrosis. Central tendency measurements of heart and respiratory rates of animals in control, Sham, study-live and study-death groups are as follows: 265±27/min-19±4/min; 219±22/min-14±3/min; 129±11/min-10±2/min. Intracranial pressures of all animals were recorded via daily pupil examination.

Macroscobical Findings of Scalp, Brain, TN

Scalp softening, edema and hair loss were observed. Intracranial macroscopic examination with a surgical microscope revealed swollen brain with effaced sulci, thickening of the arachnoid membrane, pia-arachnoid adhesions, and edematous trigeminal ganglion in Meckel's cave.

Histopathological Results

In the microscopic analyzes of the trigeminal ganglion of the brain, thickening pia and arachnoid membranes, old or fragmented blood cells in the sulci, clot and spasm in the cortical vessels, neuronal angulation, cytoplasmic and nuclear condensation, halo formation and nuclear decentralization were observed in the trigeminal ganglion neurons.

Microscopic examination of the scalp revealed degenerative changes in glandular epithelial trigeminal ganglion cells, edema, vascular spasm, congestion, degenerative changes in hair follicles, necrosis, parafollicular destruction, loss of hair tissues and axonal pathologies in nerve fibers.

In **Figure 1**, the histological appearance of the trigeminal ganglion in the control group (**Figure 1A, B**), as well as the appearance of degenerated neurons in the Sham group and the study group with the SAH model (**Figure 1C and D**; respectively) were presented. While neuron degeneration was milder in the sham group, it was noticed that there were histopathological features, such as indicating significant degeneration in the study group. **Figure 2** represents the histological views of the normal and degenerated hair follicles. Degenerated and atrophic follicles were noted in the sham and study groups, and constructed-deformed follicular artery in the study group. In **Figure 3** and **Figure 4**, normal and variable degrees of degenerated hair follicles were demonstrated with aldehyde fuchsin and Von Gieson stains, respectively. In **Figure 5**, apoptotic hair follicles are seen in the subjects in the study group with Tunel staining.

Numerical Results

The mean degenerated neuron densities trigeminal ganglions (n/mm^3) and atrophic hair follicles (n/mm^2) were determined as $5±2/m^3$ and$12±4/mm^2$ in control; $12±3/m^3$ and $41±8/mm^2$ in Sham and, $168±23/m^3$ and $79±14/mm^2$ in the study group ($p>0.001$). In the post-hoc analysis, all groups differed significantly from each other. A linear association was observed between the degenerated neuron densities of trigeminal ganglions and atrophic hair follicles (r: 0.343, p: 0.007).

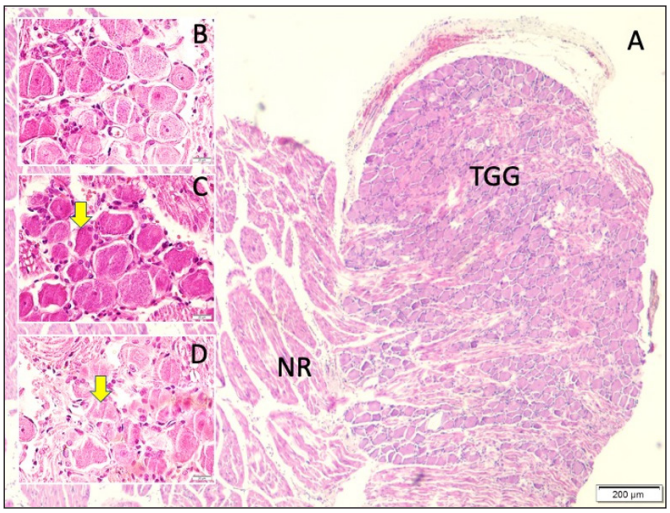

Figure 1. Histological appearances of trigeminal ganglion (TGG/A) (LM, H&E, x4/A; x10/B); histopathological appearances in with slightly degenerated neurons in Sham (Yellow arrow) (LM, H&E, x20/C), and significant degenerated neurons in study group (Yellow arrow) (LM, H&E, x10/D)
TGG: trigeminal ganglion, LM: Light microscope, H&E: Hematoxylin-eosin

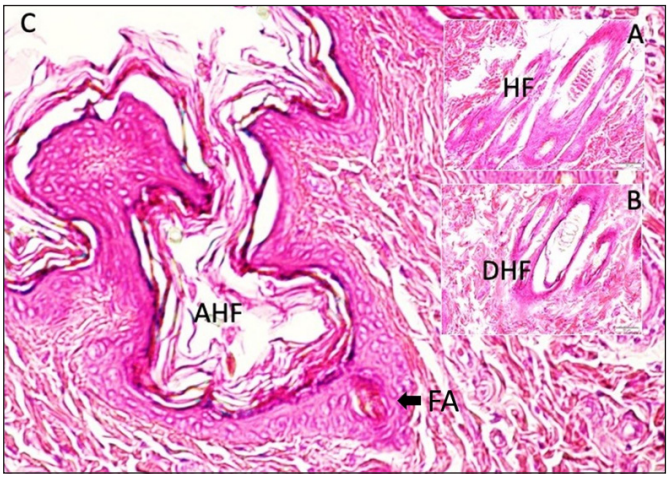

Figure 2. Histopathological appearances of normal hair follicle (HF) (LM, H&E, x20/A); slightly degenerated hair follicle (DHF) in SHAM (LM, H&E, x20/B), and significant degenerated, atrophic hair follicle (AHF) and constructed-deformed follicular artery (FA) (LM, H&E, x20/C) in study animal.
LM: Light microscope, H&E: Hematoxylin-eosin

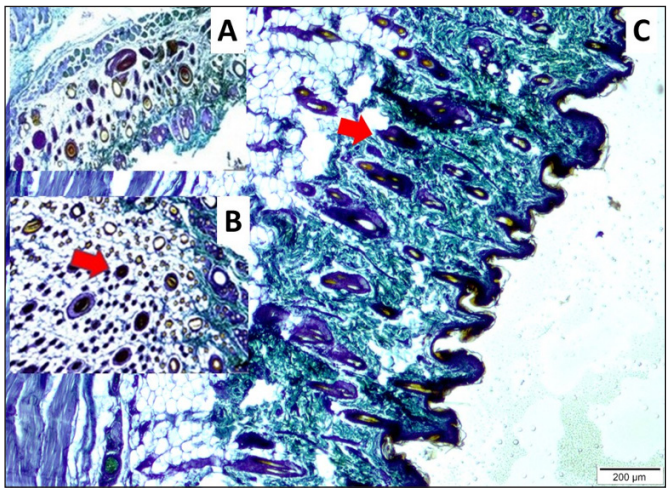

Figure 3. Histopathological appearances of the normal hair follicle (LM, Aldehyde fuchsine, x4/A); slightly degenerated hair follicle (Red arrow) in SHAM (LM, Aldehyde fuchsine, x4/B), and significant degenerated hair follicle (Red arrow) (LM, Aldehyde fuchsine, x4/C) in study animal.
LM: Light microscope

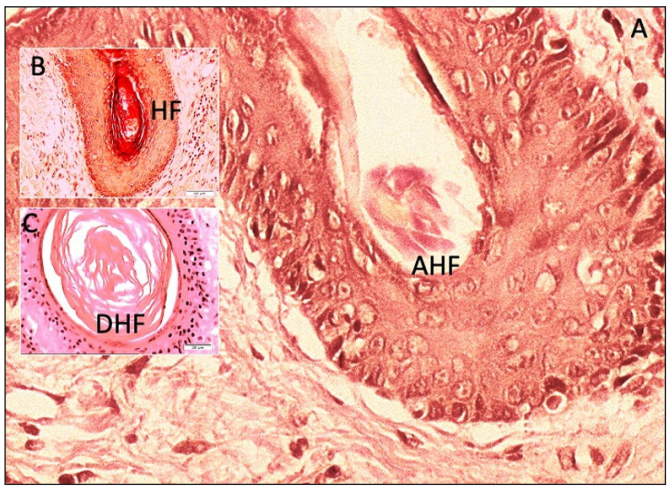

Figure 4. Histopathological appearances of normal hair follicle (LM, Van Gieson, x40/A); slightly degenerated hair follicle in SHAM (LM, Van Gieson, x40/B), and significant degenerated hair follicle (LM, Van Gieson, x40/C) in study animal.
LM: Light microscope

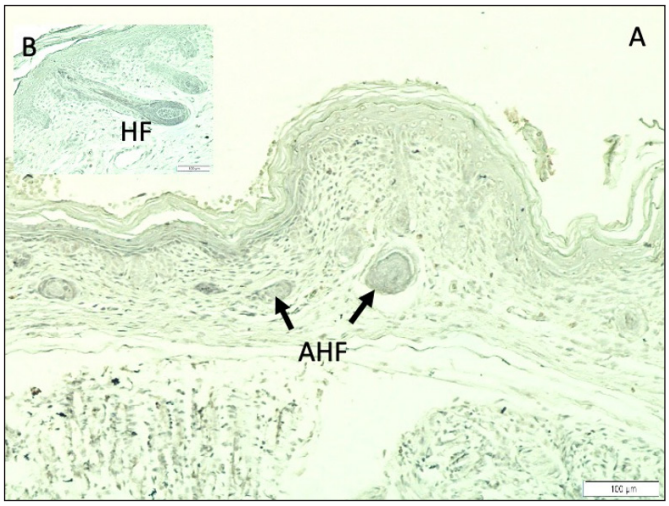

Figure 5. Histopathological appearances of the apoptotic hair follicles (AHF, Black arrow) (LM, Tunel, x10/A) in study animal and normal hair follicle in control group (LM, Tunel, x10/B).
LM: Light microscope

DISCUSSION

The craniofacial region's circulation is provided by supraorbital, supratrochlear, facial, maxillary artery, temporal and occipital arteries and their plexuses intracranial artery branches (13, 14). Cerebral vasospasm is the main cause of focal cerebral ischemia after SAH. Vasospasm is characterized by various degrees of narrowing of the vessel lumen, which develops early or late following arterial rupture. Cisternal blood injections mimicking SAH in animal models produce angiographically demonstrable vasospasm (9). In contrast to cerebral vasospasm, external carotid artery vasospasm has not been described much in the literature (10). In the case of cerebral vasospasm, the collateral system helps maintain the blood supply in the brain and allows for its self-treating process. Özdemir et al. (15) reported that this mechanism would be impaired in the case of external carotid spasm concurrent with cerebral vasospasm and, therefore, severe neurodegeneration developed in the temporal lobe fed by both the internal and external carotid systems. Özdemir et al. (9) theorized that decreased vasodilator functions of cervical dorsal root ganglia increased vasospastic effects of trigeminal-glossopharyngeal-vagal nerves and cervical sympathetic ganglia may be responsible for this phenomenon. Indeed, cerebral vessels also have a neural and humoral arrangement similar to the peripheral vascular system (15). Cerebrovascular sensory nerves are also mainly innervated from the trigeminocerebrovascular system. Trigeminal sensory nerves are distributed to the ipsilateral internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), rostral part of the basilar artery, posterior cerebral artery (PCA) and posterior communicating artery (5, 9, 10). Cranial arteries and

cephalic blood vessels, such as pial and dural vessels innervated by sensory fibers of trigeminal, facial and vagal ganglia (16, 17). Autonomic nerves reinnervated the grafts can contribute to the functional recovery of the transplanted tissues by their vessel diameters and blood flow (18). Adrenergic nerves cause vasospasm in cerebral and pia mater vessels, so desymmetrization prevents vasospasm (19). There is evidence that vasodilation of cranial vessels results from facial nerve stimulation (20). TNs have significant roles in the blood flow regulation of cerebral, dural, skull bone and scalp arteries (16). SAH is associated with craniocervical vessels vasospasm secondary to TN ischemia (21). Decreased trigeminal impulses cause facial artery spasms (22). If the vagal and facial nerve networks have a weak parasympathetic effect, adequate vasodilation will not occur in the arteries supplying TGG, and this will increase TGG ischemia.

Conversely, in those with weak external carotid artery spasms, the increased relative strength of the cervical sympathetic chain will also lead to vasoconstriction (1). While Gasser ganglion injury increases intracranial pressure with cerebral vasospasm, it can increase ischemic damage to scalp arteries and TN fibers distributed on the scalp surface (23). TN insufficiency may be responsible for weak scalp tissue and sunburns, infections, malignancies, and immune diseases usually involving the local lymph network or peripheral sensory nerves (24,25). Sensory neuropathies of the trigeminal, glossopharyngeal and vagal nerves may cause scalp and facial skin injuries (26). Trigeminal and upper cervical branches innervate the hair cells (27). Alopecia on the frontal area of the scalp may be originated from TN lesions (28,29). The mechanoreceptive innervation of the scalp has a major role in scalp life (30). Gasserian ganglion ablation may cause hair loss and craniofacial sensory-motor disabilities (31). In our study, the relationship between TGG ischemia secondary to SAH and significantly degenerated hair follicles points to denervation injury of the scalp.

The facial-scalp flap must be transferred as a single unit with a unilateral common carotid artery and external jugular vein (32). Trigeminofacial communicating fibers have important indicators for wound and flap healings (33). Supraorbital and supratrochlear nerve injuries may cause hair loss of the superciliary crescent (28). Facial allotransplantation in patients with facial injuries may be failed because of neurovascular injuries (33). We think that TN ischemia may be the crucial threatening factor in terms of scalp survival and surgery. Trigeminal ganglion stimulation has a vasodilatory effect in the acute phase of SAH (34). With this method, both denervation and hydropic degeneration of hair follicles can be prevented by vasodilation in the arteries involved. Therefore, electrophysiological recordings for the TN may help determine the prognosis of craniofacial surgery in patients with SAH. TN stimulation can be tried as a new treatment method.

CONCLUSION

This study showed that; ischemic damage of the TN, which has the richest network in the innervation of the head and neck region, may be the remarkable factor not mentioned in the prognosis of craniofacial trauma or surgery. Trigeminal stimulation may be a promising treatment method in such cases. We hope this study will inspire further studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Atatürk University Animal Experiments Local Ethics Committee (Date: 29.06.2010, Decision No: B.30.2.ATA.0.01.02/2798) and the care of the animals and the experiments were conducted according to the guidelines set forth by the same ethics committee.

Informed Consent: Because the study was designed as an animal experiment, no written informed consent form was required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study had received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1100294
J Health Sci Med 2022; 5(4): 1002-1008

Research of socioeconomic status and school-based health screening results of study with children after two years of COVID-19 pandemic

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Cite this article as: Ünlü U, Yıldız Çeltek N, Erdoğdu Ceylan E, Demir O. Research of socioeconomic status and school-based health screening results of study with children after two years of COVID-19 pandemic. J Health Sci Med 2022; 5(4): 1002-1008.

ABSTRACT

Aim: Schools are the most effective environments for health screenings for children and adolescents. The aim of school health screenings is to contribute to the protection and maintenance of children's health status by early diagnosis and treatment of diseases. We aimed to reveal the health screening findings of children whose lifestyles changed during the pandemic period, and to compare according to socioeconomic status.

Material and Method: Students from three different schools which were grouped as low, middle and high socioeconomic status were included. Hearing test, visual acuity examination, orthopedic examination, blood pressure measurements, height, weight and anthropometric measurements were performed. Descriptive statistical methods were used in the evaluation of the data.

Results: 1322 students with parental consent were included in our study. 667 (50.5%) of the students were female, mean age was 11.4±1.1, and mean body mass index score was 19.6±4.0. When body mass index scores were evaluated, 202 (15.3%) students were overweight and 189 (14.3%) were obese. Visual acuity defect was found in 257 (19.4%) of the students and hearing loss in 309 (23.4%). As a result of orthopedic examination and blood pressure measurements, 67 (5.1%) scoliosis and 131 (9.9%) high blood pressure were determined. The rate of hypertension was found to be significantly higher in school students with high socioeconomic status compared to the others ($p<0.001$).

Conclusion: The health problems detected at a high rate in our study emphasize the importance and necessity of school health screening practices. We would like to emphasize the importance of health screenings especially for children and adolescent age groups and the need for studies with broad participation and screening of many parameters.

Keywords: Child health, health, schools, socioeconomic factors

INTRODUCTION

Schools are the most effective environments for health screenings for children and adolescents. The aim of school health screenings is to contribute to the protection and maintenance of children's health status by early diagnosis and treatment of diseases. Regular health screenings for students and school personnel are very effective practices in order to protect and maintain the physical, mental and social health of all school-age children (1). The scope of school health screenings, vision, hearing, anthropometric measurements, scoliosis, oral-dental health and blood pressure screenings are recommended basic health screenings. Many researchers have contributed to the literature by conducting school health screening studies and emphasized the importance of the subject (2,3).

Strategies for the protection and improvement of child and adolescent health are implemented in Turkey, as in other countries in the world. The main purpose of these practices is to enable individuals aged 6-19 to acquire healthy attitudes and behavior models, as well as to detect and treat diseases at an early stage. In this rapid growth process, early recognition of growth and development problems and existing diseases is very important for the success of treatment and to prevent permanent damages (4). Visual and hearing acuity examinations are frequently performed in health screenings. Because vision and hearing problems that are not detected in the early period can cause permanent sensory loss over time. Early diagnosis and treatment of vision and hearing disorders are critical to prevent lifelong vision

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Received: 08.04.2022 **Accepted:** 30.05.2022

and hearing impairments. However, visual and hearing impairments are closely related to children's academic success and quality of life (5).

Childhood obesity is one of the most important public health problems of our time. For this reason, another target in health screenings is to determine the body mass index of children and adolescents. Its prevalence continues to increase in our country as it is in the whole world. Obesity is the main cause of many diseases, especially cardiovascular diseases. On the other hand, it is known that overweight and obesity cause mental problems in adolescents, cause problems with their families and close circles, and academic failure (6). Orthopedic examinations are also carried out with the aim of investigating scoliosis in health screenings. Scoliosis can be recognized by a simple examination, the Adam's forward bend test. Early diagnosis and treatment of scoliosis, which is characterized by asymmetry in the vertebrae, is important in terms of preventing deformities that will develop over time and solving the problem with exercise without the need for a surgical procedure (7).

Due to the COVID-19 pandemic, which is the most influential health problem in recent years, changes have occurred in the lifestyles and daily routines of individuals in the society. In our country, education was continued online and schools were closed for a while in order to prevent transmission. In addition, the curfews also caused a decrease in the physical activities of children and adolescents, as in all age groups. However, priority was given to COVID-19 disease in health centers and routine health checks and elective procedures were postponed. During the pandemic period, routine health checks of school-age children could not be done.

The health of individuals in adolescence, where a rapid physiological and psychological development is experienced, can be affected by many variable conditions such as family, school, social relations, and socioeconomic conditions. It is known that a low socioeconomic environment can negatively affect the health status of children (8). The evaluation of the health status of students from different socioeconomic environments has been studied by different researchers before. In a study examining obesity in children aged 7-14 from different socioeconomic status in Turkey, it was stated that the prevalence of obesity was higher in students from middle and high socioeconomic status (9). In a recent study conducted in the Netherlands, it was emphasized that the children of families with low socioeconomic status had more frequent hospital admissions due to chronic diseases and growth retardation and therefore more health expenditures (10).

In this period when the devastating effects of the pandemic began to diminish and we are in the process of transitioning to normal life, we carried out school health screenings with the aim of conducting health examinations of children in secondary school and directing the detected health problems to treatment. In our study, we aimed to reveal the health findings of children whose lifestyles changed during the pandemic period, as in the whole population, and to compare them according to socioeconomic status.

MATERIAL AND METHOD

The study was carried out with the permission of Clinical Researches Ethics Committee of Tokat Gaziosmanpasa University School of Medicine (Date: 18.01.2022, Decision No: 21-KAEK-281). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Students studying in three different schools were invited to the study. The schools are designated as a rural public school, a public school in the city center, and a private school in the city center. The public school in the rural area was considered to have a low socioeconomic status (SES), the public school in the city center was considered to have a medium SES, and the private school in the city center was considered to have a high SES.

Hearing test, visual acuity examination, orthopedic examination, blood pressure measurements, height, weight and waist-hip circumference measurements were made to the students as part of the health screening. Body mass index percentile values were determined by evaluating the height and weight values measured in the examination according to age and gender. According to these percentile values, students; they were grouped as underweight, normal weight, overweight and obese and recorded in the data form (11). Senti Desktop type SID 100433 model hearing aid was used for the hearing test. Beforehand, the children were told how the test was administered, and then their earphones were put on. In four different frequencies, 500, 1000, 2000, 4000 Hertz, separately for both ears; It was tested with a sound of 40-30-20 dB. Students were seated so that they could not see the screen and were asked to press the button in their hand each time they heard a sound. Inability to hear sound of 30 dB and above at any of the four frequencies was accepted as a failing criterion (12). Snellen chart was used for visual examination. Visual acuity deficits of 0.8 and below were defined as visual acuity defect. Appropriate blood pressure monitors with pediatric cuffs were used for blood pressure measurements. After the results were recorded by us, percentile calculations were made according to age and gender, and a data form was created. Students whose systolic or diastolic

blood pressure values were above the 95th percentile for age, gender, and height were considered to have hypertension (13). Height measurements were made with a tape measure hanging on the wall, without shoes, on a flat floor with the heels together, hips and shoulders against the wall. Care was taken to ensure that the line passing at eye-ear level was parallel to the ground. A digital scale sensitive to 100 grams was used for weight measurement and was checked before each measurement. Scoliosis examination was evaluated with the forward bending test. They were asked to bend forward 90 degrees from the waist without bending their knees and vertebral palpations were performed. After the results were recorded by us, percentile calculations were made according to age and gender, and a data form was created.

Descriptive statistical methods were used in the evaluation of the data. When comparing the means of quantitative variables between groups, the Significance of Difference between Two Means test and One-Way Analysis of Variance were used. Cross tables and chi-square tests were used to evaluate whether there was a relationship between qualitative variables. When p values were calculated less than 0.05, it was considered statistically significant. Ready-made statistical software was used in the calculations (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

RESULTS

A total of 1322 students with family consent for health screening practices were included in our study. Of the students, 667 (50.5%) were female and 655 (49.5%) were male. Their mean age was 11.4±1.1 years and their mean body mass index score was 19.6±4.0. When body mass index scores were evaluated, 122 (9.2%) students were underweight, 202 (15.3%) students were overweight, and 189 (14.3%) students were obese. In our study, quantitative variable data of students were compared according to gender. When the BMI percentile groups were evaluated, the obesity rate was 16.9% for male students and 11.7% for females. Obesity was observed more frequently in men than in women (p=0.017)

During the examinations, visual acuity defect was found in 257 (19.4%) of the students and hearing defect in 309 (23.4%) of the students. However, as a result of orthopedic examination and blood pressure measurements, 67 (5.1%) students had scoliosis and 131 (9.9%) students had high blood pressure. No statistically significant difference was found between the gender variable and the incidence of scoliosis (p=0.961), visual acuity defect (p=0.643), hearing impairment (p=0.887) and high blood pressure (p=0.277).

When the relationship between the quantitative variables and the SES of the schools was examined, a statistically significant difference was found between the waist-hip ratios of the students and the SES groups of the schools (p<0.001). No relationship was found between age, height, weight, BMI and SES groups (**Table 1**). In our study, in which the SES groups of the schools and the health problems detected in the examination findings were compared; hypertension detection rate was found to be significantly higher in students studying at a school with a high SES (p<0.001). Another finding is that a higher rate of scoliosis was detected in students studying at a school with a medium SES compared to the students in the other two schools (p<0.001). In addition, in the comparison of the incidence of hearing impairment, a statistically significantly higher rate of hearing impairment was found in the students in the low SES group than in the middle SES group (p=0.007). There was no statistical significance between the high SES group and the other groups in terms of hearing impairment (**Table 2**).

Table 1. Distribution of quantitative variables according to SES

Variables	Total	Socio-economic status (SES)			p
		Low SES	Middle SES	High SES	
		Mean±SD	Mean±SD	Mean±SD	
Age	11.45±1.07	11.34±0.86	11.5±1.15	11.48±1.11	0.080
Height	1.73±5.54	2.38±11.14	1.52±0.1	1.52±0.09	0.052
Weight	45.57±12.29	44.6±12.02	45.86±12.09	45.92±12.67	0.259
BMI	19.58±4.04	19.58±4.14	19.7±4.02	19.45±4.01	0.617
Hip-wrist ratio	0.82±0.07	0.85±0.09[a]	0.81±0.06[b]	0.83±0.08[c]	<0.001

One-way analysis of variance was used. (abc): Common letter as a line indicates statistical insignificance.

Table 2. Distribution of health problems identified by SES groups

Variables	Total n (%)	Socio-economic status (SES)			p
		Low SES	Middle SES	High SES	
		n (%)	n (%)	n (%)	
BMI percentile					0,206
Underweight	122 (9.2)	29 (8.9)	42 (8.1)	51 (10.6)	
Normal	809 (61.2)	212 (65)	307 (59.5)	290 (60.4)	
Overweight	202 (15.3)	43 (13.2)	94 (18.2)	65 (13.5)	
Obese	189 (14.3)	42 (12.9)	73 (14.1)	74 (15.4)	
Blood pressure percentile					<0.001
HT	131 (9.9)	26 (8)[a]	36 (7)[a]	69 (14.4)[b]	
Normal	1191 (90.1)	300 (92)[a]	480 (93)[a]	411 (85.6)[b]	
Scoliosis					<0.001
Positive	67 (5.1)	1 (0.3)[a]	61 (11.8)[b]	5 (1)[a]	
Negative	1255 (94.9)	325 (99.7)[a]	455 (88.2)[b]	475 (99)[a]	
Visual acuity defect					0.208
Positive	257 (19.4)	72 (22.1)	89 (17.2)	96 (20)	
Negative	1065 (80.6)	254 (77.9)	427 (82.8)	384 (80)	
Hearing loss					0.007
Positive	309 (23.4)	91 (27.9)[a]	98 (19)[b]	120 (25)[ab]	
Negative	1013 (76.6)	235 (72.1)[a]	418 (81)[b]	360 (75)[ab]	

Pearson chi-square test was used. (ab): A common letter as a line indicates statistical insignificance.

In our study in which students' anthropometric measurements were made; When the waist-hip ratio was compared with other variables, it was observed that the waist-hip ratio was higher in male students (p<0.001). At the same time, there is a significant relationship between the waist-hip ratio and the classification of BMI percentiles. A higher waist-hip ratio was found in those classified as overweight and obese (p<0.001). Waist-hip ratios of students with scoliosis were found to be significantly lower than those without scoliosis (p=0.011). No significant difference was found between the waist-hip ratio and other variables (p>0.005). (**Table 3**)

Table 3. Comparison of quantitative variables according to BMI

Variables		BMI Mean±SD	p
HT Percentile	HT	22.42±5.43	<0.001
	Normal	19.27±3.73	
Scoliosis	Positive	19.58±4.08	0.912
	Negative	19.53±3.38	
Visual acuity defect	Positive	19.47±4.05	0.049
	Negative	20.02±3.99	
Hearing loss	Positive	19.59±4.04	0.907
	Negative	19.56±4.06	

Significance test of the difference between two means or One-way analysis of variance was used. (abc): A common letter as a line indicates statistical insignificance.

In our study, the BMI scores of the students and the findings related to the health problems detected were also compared. In the comparison, it was seen that the BMI scores of the students with HT were statistically significantly higher than the normotensive ones. (p<0.001). In addition, the BMI scores of the students with visual impairment were found to be higher than the others (p=0.049).

DISCUSSION

According to the Turkish Statistical Institute (TUIK) 2020 data, approximately 19.9% of Turkey's population consists of school-age children aged 5-17 (14). Children's academic success is closely related to school health. School health covers all the processes done to evaluate, improve and maintain the health status of students and staff at the school. Screenings in schools provide early detection and treatment of students' health problems. In our study, we evaluated the data of health screenings we conducted in 3 different secondary schools. It was observed that 14.3% of 1322 children who underwent health screening were obese and 9.9% had high blood pressure. 19.4% of them had visual acuity defect and 23.4% of them had hearing defect. In addition, scoliosis was found in 5.1% of them. A significant relationship was found between the SES of the schools where the children were educated and the presence of hypertension, hearing impairment and scoliosis.

Obesity in children is related psychological disorders, asthma, obstructive sleep apnea, orthopedic and cardiovascular problems, and metabolic syndrome (15). Due to high prevalence, obesity among children and adolescent is crucial public health problem globally. The German Children and Adolescents Health Survey (KIGGS) announced that up to 6.3% of children and adolescents were obese and up to 15% were overweight (16). Obesity in school-age children draws attention as an important public health problem due to its increasing incidence in Turkey also. Unhealthy diet and decreased physical activity are among the main reasons for increasing obesity (17). It is thought that the current COVID-19 pandemic process has increased the frequency of obesity for different reasons. When studies on the prevalence of obesity in school-age children in Turkey were evaluated, it was seen that the prevalence of obesity was 0.7% between 1990-1995, while it increased to 7.1% between 2011-2015 (18). Regarding current studies, Uyar et al.'s (19) study with primary school students in 2019 revealed that 12.4% were overweight and 15.8% were obese. In our study, it was shown that 15.3% of the students were overweight and 14.3% were obese. Compared to similar studies, the obesity rate in our study was higher. This can be explained by the rapid increase in obesity rates all over the world. In addition, the decrease in the rate of physical activity may have been caused by the transition to online education, curfews and home quarantines in the current COVID-19 pandemic. Possible negative effects of pandemic on nutrition of children were studied by various researchers. In a study conducted with 397 children and their parents in Greece during the early stages of the COVID-19 pandemic, it is reported that body weight increased in 35% of children/adolescents (20). Considering the relationship between gender and obesity in school-age children, it was reported that although the prevalence of obesity increased in both genders, the prevalence of obesity was higher in the male gender (3). In our study, no significant relationship was found between gender and obesity (p=0.223). Data on underweight children are also presented in related studies. In the study conducted by Çalışır et al. (21) in Aydın, it was stated that there was 2.8% of underweight children. In our study, the percentage of children who were evaluated as underweight according to percentile values was determined as 9.2%. The similarity of our results with the findings in similar studies shows that the treatment is as important as the detection of underweight children.

Childhood hypertension is thought to be a precursor to hypertension diagnosed in adulthood (22). In a study conducted to determine the prevalence of hypertension in school-age children in our country, the rates of

prevalence were determined as 23.8% by Akdağ et al. (23). In our study, this rate was determined as 9.9%. In school-based blood pressure screening program study conducted with 22224 children in USA, it is found that prevalence of hypertension among children is 16.3 %. It is noteworthy that there are different prevalence of hypertension in different studies (24). It was thought that this situation may be caused by differences in the etiology of hypertension such as nutrition, sleep duration, obesity, and SES. Studies have found that as obesity increases, hypertension increases significantly (23,25) Similarly, in our study, the incidence of hypertension increases as BMI increases ($p<0.001$).

Visual defects, which are easy to detect and treat in school-age children, are one of the important health problems that affect school success. Therefore, it has an important place in school screenings. Common eye problems in school-age children are refractive errors, amblyopia, strabismus, and color blindness (26). Shrestha et al. (27) reported that the rate of visual acuity defect due to various reasons was 21.4 % in a study conducted with 2412 children in Nepal. Kalyoncu et al. (5) reported that visual acuity defect was 16.7% in school-age children in the examination performed with Snellen chart. In our scan, visual acuity deficits were found at a rate of 19.9%. This rate is consistent with the existing literature. In this case, it shows that the visual acuity defect detected in school age scans has not decreased over the years and reveals the importance of school scans.

Hearing loss has a very important place in speech and language development. Even mild hearing loss affects the social, mental and emotional development of the child. It can lead to learning difficulties and related academic failures. Early detection is very important in terms of preventing all these negativities. Various studies on the subject have been put forward by many researchers. In a study conducted with children aged 6-14 years in Kyrgyzstan, it was reported that 27.2% of the children had hearing impairment (28). Osei et al.'s (29) study of hearing screening for children aged 5-17 years in Ghana showed that 21% of participants failed the audiometric screening test. In our study, it was observed that 23.4% of the students failed the hearing test. Studies conducted in different countries have similarly reported a high rate of hearing loss among children and adolescents. These results point out the importance and necessity of hearing screenings.

Scoliosis is a vertebral column deformity that can lead to serious cardiopulmonary complications when diagnosed late. When the patient is diagnosed early, it can be treated with simple and inexpensive exercises without the need for surgical methods. Since the age range of the risk group is 9-15, it is very important to be screened in school-age children (7). Scaturro et al.'s (30) study emphasis that school-based screening protocol had a very high specificity in early diagnosis of adolescent idiopathic scoliosis. In Italy, 2.01% of students were found to have scoliosis in school scoliosis screening for children aged 9-14 (31). In related studies, the rate of scoliosis detection in school scoliosis screenings was reported as 26.1% in Kosovo, 14.2% in Mexico, and 24.3% in Brazil (32-34). In a study conducted by Dığrak et al. (1) in Turkey with 1421 primary school students, the incidence of scoliosis was expressed as 5.1%. In our study, this rate was also stated. It was found to be 5.1%. The variations in prevalence between studies could be attributed to the different methods used to detect scoliosis. However, results of all studies indicate that routine scoliosis screening programmes are necessary.

In our study, when schools were classified according to their SES, there was no difference between genders, making comparison easier. No significant relationship was found between the SES of the schools and the classification of students according to their BMI percentiles ($p=0.207$). On the other hand, the rate of obesity was found to be 12.9% in a school with a low SES, 14.1% in a school with a medium SES, and 15.4% in a school with a high SES. However, this proportional increase is not statistically significant ($p=0.206$). In Ireland study conducted by Keane and colleagues (35), it was showed that an inverse relationship between SES and the prevalence of child overweight and obese. Patrick et al.'s (36) study conducted with 14842 children age 6–19 years that has found that lower family SES was associated with higher risk in childhood obesity and hypertension. Unlike the results of this study we found that the prevalence of hypertension was found to be higher in students from schools with high SES compared to those in schools with low and medium SES ($p<0.001$). In our comparisons made according to school SES groups, the frequency of HT and obesity seem to be incompatible with each other. High HT rate inconsistently with BMI rates in high SES group participants reminds that various factors may be effective in blood pressure control. Therefore, we would like to emphasize the importance of blood pressure measurements in all children, regardless of BMI. When the students with scoliosis were evaluated according to the SES of their schools, scoliosis was found less frequently in the students at the school with a medium SES ($p<0.001$). This result may be related to many factors such as the homework intensity of the students, the weight of the bags, and the carrying times of the bags. As far as we know, there is no other study investigating SES and scoliosis data.

CONCLUSION

The importance of school health screenings, the effectiveness of which has been demonstrated by many researchers in the literature, remains up-to-date. In our study, similar to the studies conducted in previous years, high rates of health problems were detected. This result highlights the necessity of school health screening practices and their importance in maintaining and protecting children's health. We think that the need for these screenings has increased much more as routine health checks have been disrupted due to many restrictions and lifestyle changes that we have to experience during the COVID-19 pandemic process we are in. As a result, we would like to emphasize the importance of health screenings especially for children and adolescent age and SES groups, and the need for studies with broad participation and screening of many parameters.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Clinical Researches Ethics Committee of Tokat Gaziosmanpasa University School of Medicine (Date: 18.01.2022, Decision No: 21-KAEK-281).

Informed Consent: Parents of all participants signed the free and informed consent form because the participants were children

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1114475
J Health Sci Med 2022; 5(4): 1009-1014

Radiological comparison of the Wuhan and B.1.1.7 variant COVID-19 infection; are there any differences in chest CT scans?

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Cite this article as: Demircioğlu Ö, Kocakaya D, Cimşit C, Sarınoğlu RC, Ülger N, Çimşit NÇ. Radiological comparison of the WUHAN and B.1.1.7 variant COVID-19 infection; are there any differences in chest CT scans? J Health Sci Med 2022; 5(4): 1009-1014.

ABSTRACT

Aim: In September 2020, a variant of the SARS-CoV-2 virus was detected in England and it became the dominant type in most of the countries. The clinical behavior of the B.1.1.7 variant COVID-19 infectionis different from the Wuhan type.So we aimed to investigate whether there are any differences in computed tomography (CT) imaging findings of pneumonia caused by COVID-19 variants.

Material and Method: 340 patients who admitted to the emergency departmentwith symptoms of dyspnea and chest pain suspecting COVID-19 pneumonia and pulmonary embolism were included in the study. Oncology (n:12) and pediatric (n:8) patients, patients with negative PCR test (n:56), and patients infected with different variant (n:6) were excluded leaving 258 patients grouped into two (B.1.1.7 and Wuhan type) for evaluation of CT findings such as pleural thickening,pleural and pericardial effusion, consolidation, GGO presence and distribution, upper lobe involvement, pulmonary embolism, tree in bud pattern, centrilobuler nodule, revers halo sign, and hepatosteatosis.

Results: A statistically significant difference was obtained between the two groups in terms of pleural thickening (p=0.020), upper lobe involvement (p=0.037), localization of GGO (p=0.001), presence of pleural effusion (p=0.025), embolism (p=0.011) and presence of consolidation (p=0.042). However, no significant difference was found for the development of hepatosteatosis (p=0.520).

Conclusion: There aredifferences in radiological findings between B.1.1.7 variant and Wuhan type. In our study atypical radiological findings are more common in B.1.1.7 type. In addition, radiological findings that seen in severe COVID-19 pneumonia are more common in B.1.1.7.

Keywords: COVID-19, Wuhan type, B.1.1.7 variant, tomographic differences, tomography

INTRODUCTION

In September 2020, a variant of the SARS-CoV-2 virus was detected in South East England. It was named B.1.1.7 and became the dominant lineage in just a few months (1). Despite the restrictions of travel from the UK, this variant was seen for the first time in January 2021 in our country. Also, it has spread to at least 114 countries worldwide since that time (2).

B.1.1.7 variant has 17 mutations, including eight in the spike protein. Mutations affect the binding affinity to human angiotensin-converting enzyme 2 (ACE2) and entry into human cells which increase the infectivity (2-4) and changed the clinical presentation, morbidity and mortality of the disease (2,5,6). Due to the worse clinical presentation, we think that there may be differences in the radiological findings of the B.1.1.7 variant induced pneumonia compared to the Wuhan type. Therefore we investigate the literature, but we did not find a study about the radiological differences in pneumonia caused by COVID-19 variants.

As is known, typical CT findings of COVID-19 pneumonia are bilateral lower lobe and peripherally predominant ground glass opacities (GGO) whereas

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Received: 10.05.2022 **Accepted:** 30.05.2022

pleural effusion, pulmonary embolia, centrally located GGO and consolidations, upper lobe involvement are reported to be atypical CT findings (7-9). Consequently we aimed to compare CT findings of Wuhan type and B.1.1.7 variant induced pneumonia.

MATERIAL AND METHOD

The study was approved by the Marmara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 07.06.2021, Decision No: 09.2021.734). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

The study was conducted at our hospital in Turkey between February and April 2021. 340 patients who admitted to the emergency department with symptoms of dyspnea and chest pain suspecting COVID-19 pneumonia and pulmonary embolism were included in the study. Oncology (n:12) and pediatric (n:8) patients, patients with negative polymerase chain reaction(PCR) test (n:56), and patients infected with South Africa-Brazil variant (n:6) were excluded leaving 258 patients grouped into two (B.1.1.7 variant and Wuhan type) for evaluation of CT findings.Since the radiological imaging of the patients included in the study was evaluated retrospectively, informed consent could not be obtained from them.

Pulmonary CT Angiography Protocol

All examinations were performed on a 128-slice scanner (Ingenuity Core 128, Philips Healthcare) with the following scan parameters: tube voltage 120 kV and effective tube current 50 mAs, slices acquired with 128×0.6 mm setting in the caudocranial direction, 0.5 pitch, and 0.28-second rotation time. Field of view was adjusted to patient size, 512×512 matrix was used, and mean scan time was 4.2 s. Bolus tracking software was used with ROI cursor placed on RV with a setting of 50 HU and delay time of 3 s, using 0.8 ml/kg contrast (350 mg I/ml) with 5 ml/s delivery rate via antecubital line, followed by 20 cm^3 saline injection. The patient was instructed to hold her breath for 5 seconds just before starting the scan. The resulting images were reconstructed with 0.75 mm and 5 mm collimation.

Chest CT evaluation

The tomographic findings of the patients were evaluated by a radiologists experienced in chest radiology. The radiologist was blind to the PCR findings.

Pleural thickening, pleural and pericardial effusion were evaluated in mediastinal window. Consolidation (**Figure 1**), distribution of paranchymal changes like upper lobe involvement (**Figure 2**), presence and distribution of GGO (**Figure 3**), reverse halo sign, centrilobular nodule, tree-in-bud pattern and cavitation were evaluated in the lung window. Presence of pulmonary emboli was evaluated in pulmonary CT angiogram (PCTA) slides. GGO located in the subpleural area was accepted as peripheral, and those located adjacent to the bronchovascular tree as central distribution. Liver parenchyma density included in the non-contrast chest CT was measured. If liver attenuation was less than 10 HU that of spleen, it was accepted as fatty liver (**Figure 4**).

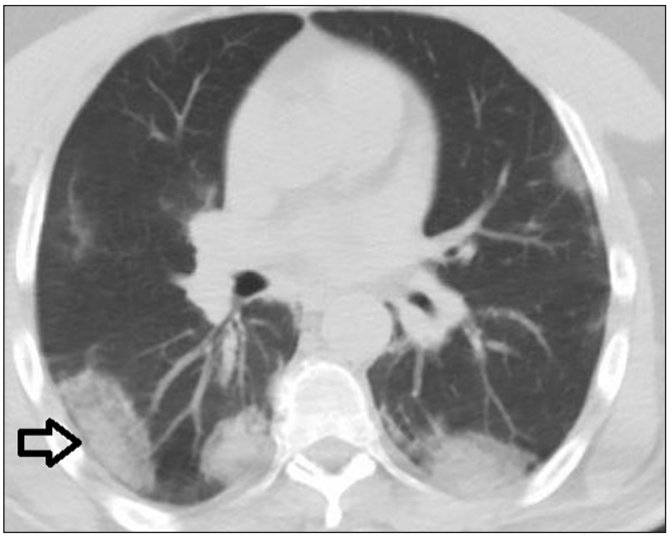

Figure 1. CT image shows round peripheral consolidation with GGOs in the bilateral lower lobe

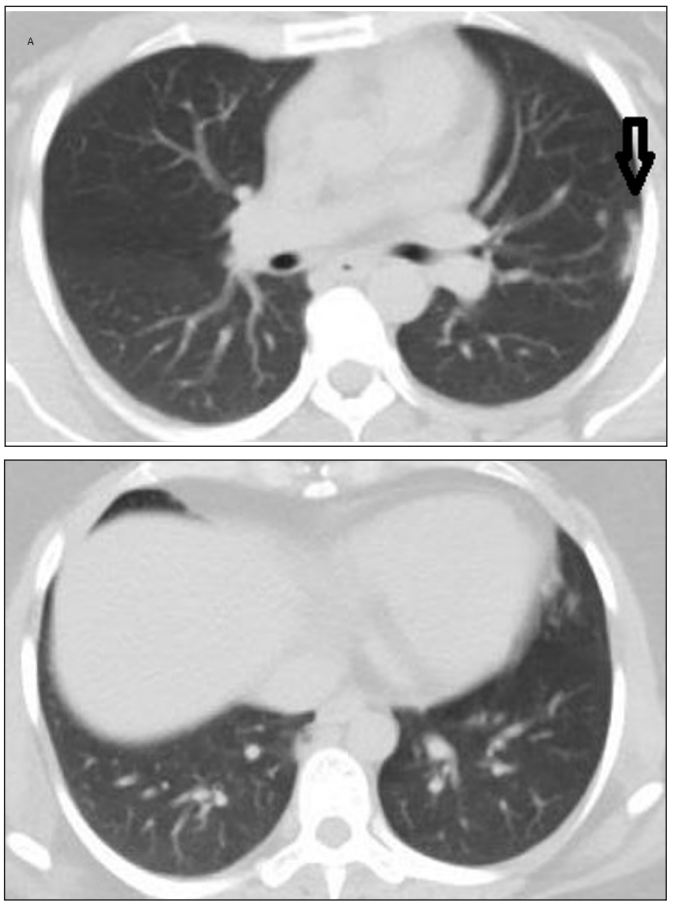

Figure 2. Isolated upper lobe involvement. **a.** Unenhanced chest CT shows ground glass opacities in the left upper lobe. **b.** Bilateral lower lobes appear protected

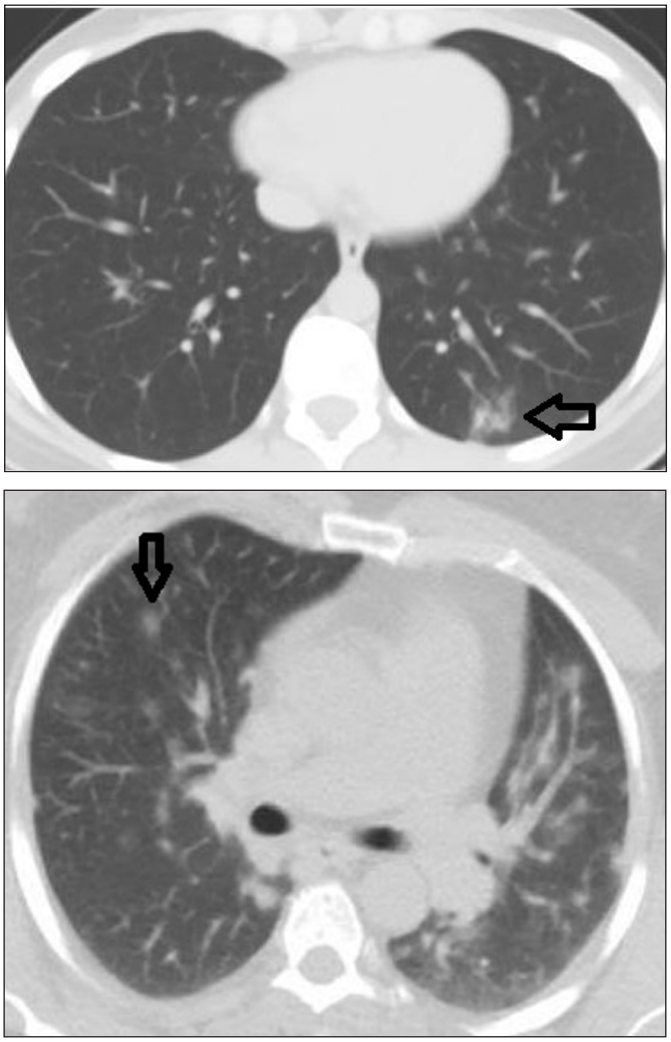

Figure 3. a. Axial unenhanced chest CT image of 35 year old patiet with Wuhan Type COVID-19 pneumonia shows peripheral GGOs **b.** Axial unenhanced chest CT image of patient with infected with B.1.1.7 variant shows noduler and patcy GGOs in central peribroncovascular area.

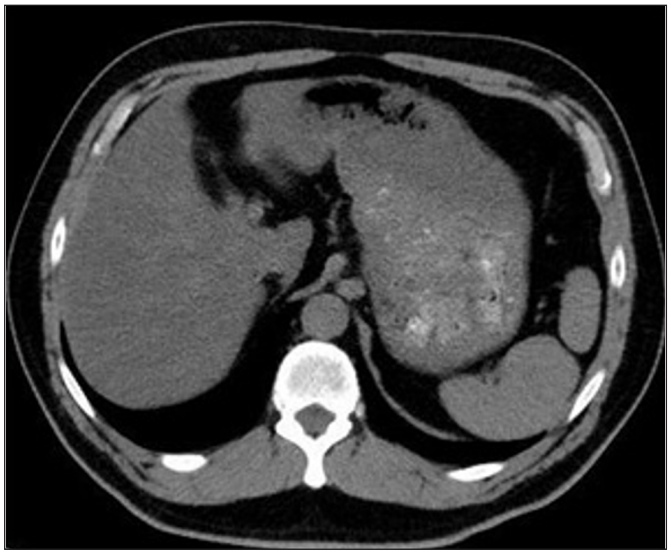

Figure 4. Axial chest CT image demonstrates hepatosteatosis (mediastinal window). Mean liver attenuation is 13 HU and mean splenic attenuation is 46 HU

Reticulation, subpleural band and architectural distortion, which are late findings of COVID pneumonia, could not be evaluated because the CT scans at the time of admission were examined in the study.

PCR

Combined nasopharyngeal and oropharyngeal swab samples were collected from individuals suspected of COVID-19. Viral RNA was extracted by using Bio-speedy® viral nucleic acid buffer (Bioexen LTD, Istanbul, Turkey). Specific kits were used for screening Wuhan, British, and South Africa Brazilian variants.

Statistical analysis

Descriptive statistics were made in the form of mean and standard deviation for age in both between two variants and gender differences. Then, all patients were divided into two groups as the Wuhan and B.1.1.7 variants. The data of presence of pleural involvement, upper lobe involvement, presence of pleural effusion, pulmonary embolism, consolidation and hepatosteatosis were recorded in categorical form. After that, chi-square test was used to determine the relationship of these independent samples in terms of variants. Since the minimum expected count was greater than 5 in the analyzes, the p values of the pearson chi-square value were recorded. A <0.05 p value indicated a statistically significant difference between the groups in terms of the relevant parameters.The IBM SPSS version 21.0 (IBM, Armonk, NY, USA) statistical package was used for the analysis of the study.

RESULTS

There were 113 patients in Wuhan type and 145 patients in B.1.1.7 variant group.Wuhan type group consisted of 61 male and 52 female patients andB.1.1.7 variant group consisted of 85 male and 60 female patients. The age of patients ranged from 28 years to 82 years in the group infected with the B.1.1.7 variant (mean 52.8±SD: 12.4 years) and ranged from 22 years to 90 years in the group infected with the Wuhan type (mean 53.1±SD: 14.2 years).

Out of 113 patients in Wuhan type group, 67% had consolidation, 70% peripheral GGO, 30% central GGO, 91% upper lobe involvement, 42% pleural thickening, 6% pleural effusion, 3% pulmonary emboli, 56% hepatosteatosis. One patient had pericardial effusion, and one showed tree in bud pattern (**Table**).

Out of 145 patients in B.1.1.7 variant group, 74% had consolidation, 19% peripheral GGO, 81% central GGO, 86% upper lobe involvement, 52% pleural thickening, 10% pleural effusion, 11% pulmonary emboli, 52% hepatosteatosis, 1% centrilobuler nodule. One patient had reverse halo sign (**Table**).

Table. The statistical comparison and the ratios of radiological findings according to Wuhan type and B.1.1.7 variant

	Mutation		P value	Value (Pearson Chi-Square)	df
	Wuhan n=113	B.1.1.7 n=145			
Pleural thickening					
Count	42	75			
% within mutation	37.2%	51.7%	0.020	5.429	1
% of Total	16.3%	29.1%			
Pleural effusion					
Count	6	14			
% within mutation	5.3%	9.7%	0.025	4.992	1
% of Total	2.3%	5.4%			
Pulmonary embolism					
Count	3	16			
% within mutation	2.7%	11.0%	0.011	6.537	1
% of Total	1.2%	6.2%			
Consolidation					
Count	76	107			
% within mutation	67.3%	73.8%	0.042	4.138	1
% of Total	29.5%	41.5%			
Upper lobe involvement					
Count	91	125			
% within mutation	80.5%	86.2%	0.037	4.349	1
% of Total	35.3%	48.4%			
Central ground glass opacity					
Count	34	118			
% within mutation	30.1%	81.4%	0.001	69.023	1
% of Total	13.2%	45.7%			
Peripheral ground glass opacity					
Count	79	27			
% within mutation	69.9%	18.6%	0.001	69.023	1
% of Total	30.6%	10.5%			
Hepatosteatosis					
Count	63	75			
% within mutation	55.8%	51.7%	0.520	0.414	1
% of Total	24.4%	29.1%			
Revers halo					
Count	0	1			
% within mutation	0%	0.69%	–	–	–
% of Total	0%	0.39%			
Centrilobuler nodule					
Count	0	2			
% within mutation	0%	1.38%	–	–	–
% of Total	0%	0.78%			
Pericardial effusion					
Count	1	0			
% within mutation	0.88%	0%	–	–	–
% of Total	0.39%	0%			
Tree in bud					
Count	1	0			
% within mutation	0.88%	0%	–	–	–
% of Total	0.39%	0%			

Pleural thickening, pleural effusion, pulmoner embolism, consolidation, upper lobe involment, central GGO were more common in patients infected with B.1.1.7 variant; hepatosteatosis, peripheral GGO were more common in patients infected with Wuhan type.

A statistically significant difference was obtained in chi-square test between the two groups in terms of pleural involvement (p=0.020), upper lobe involvement (p=0.037), localization of GGO (p=0.001), presence of pleural effusion (p=0.025), embolism (p=0.011) and presence of consolidation (p=0.042). However,no significant difference was found for the development of hepatosteatosis (p=0.520). The data of the statistical analysis are given in **Table**.

DISCUSSION

To our knowledge, this is the first study that suggests comparing tomographic findings of Wuhan type and B.1.1.7 variant induced COVID-19 pneumonias. As more information was started to share about this new type of virus, it was stated that the clinical course of pneumonia caused by the variant virus was much severe (2). For example one of our patients was infected with COVID-19 pneumonia with Wuhan type and B.1.1.7 variat virus at different times. In Wuhan type she did not hospitalized and the chest CT finding was only patchy GGO in inferior lingular segment. However in B.1.1.7 variant infection, she was hospitalized for 10 days and her CT finding was widespread GGO in both lung, distributed in the subpleural and central areas (**Figure 5**).

However, there is no information about the differences of radiological findings of the two type of virus. Chest CT findings of Wuhan type COVID-19 pneumonia have been described in many publications (10-13). Our experience from chest CTin our clinic was that atypical radiological findings are more common in the B.1.1.7 variant than Wuhan type COVID-19 pneumonia. In Wuhan type COVİD-19 pneumonia, peripheral-predominant GGO and consolidation are reported as the most common findings (14). Previously, Ceylan et al. (9) described centrally located GGO as atypical radiological findings in COVID-19 pneumonia before the definition of this variant in our country. In our clinic, we started to observe central or peribronchovascular located GGOs more frequently in COVID-19 pneumonia infected with B.1.1.7 variant compared to patients infected with Wuhan type. We found a significant statistical difference for the localization of GGO in the group of infected with B.1.1.7 variant in our study. This pattern can be confused with parenchymal involvement of diseases that may have peribronchovascular involvement, such as organized pneumonia. Due to this distribution pattern, we started to be more indecisive in the radiological differential diagnosis of patients infected with B.1.1.7 variant while comparing Wuhan type COVID-19 pneumonia. In addition, the difficulty we faces to obtain information about the PCR results of many patients and often their clinics during daily reporting made this differential diagnosis even more difficult.

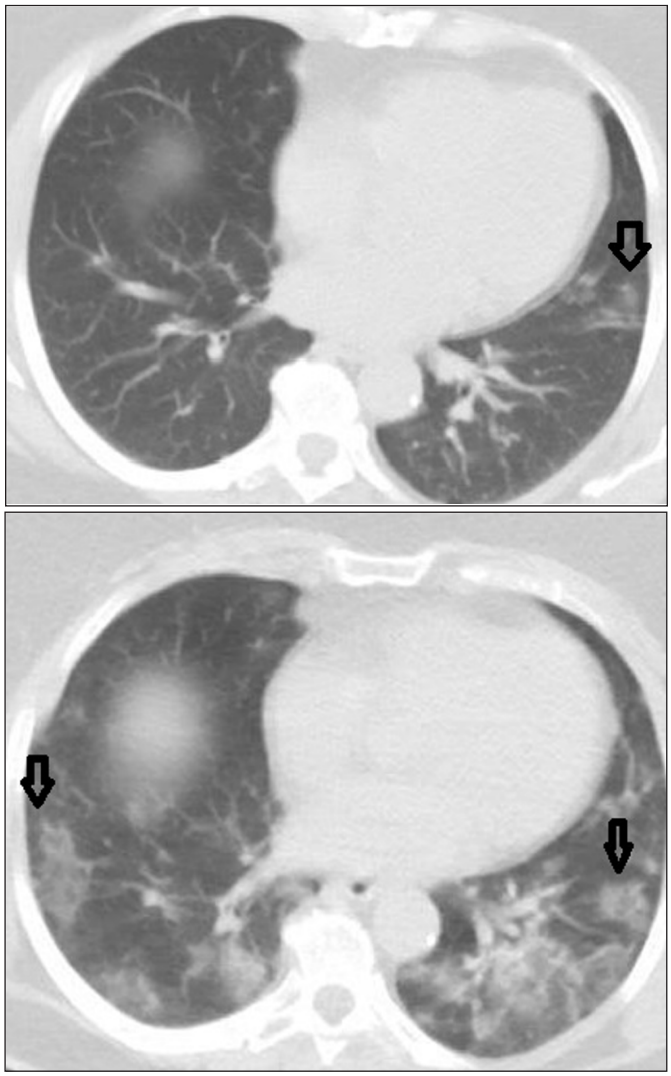

Figure 5. a. Chest CT image of a 61-year-old woman, who was infected with Wuhan Type COVID-19 virus in April 2020, shows patcy GGO only in the inferior linguler segment. **b.** Same patient was infected with B.1.1.7 variant in April 2021 again and her CT image shows widespread GGO in both lung, distributed in the subpleural and central areas

In the comparative evaluation of patch-style or lobar consolidated areas which are the other radiological findings can be detected in COVID-19 pneumonia; we found a significantly more in B.1.1.7 variant group.

In general, lower lobe predominant involvement has been reported in the COVID-19 pneumonia (15). On the other hand, Ceylan et al. (9) reported that; isolated upper lobe involvement can also be seen in Wuhan type COVID-19 pneumonia as an atypical sign. In our study, upper lobe involvement in infected group with B.1.1.7 variant wasstatistically significant higher than Wuhan type.

Pleural effusion, thickening and sometimes pericardial effusion may accompany parenchymal findings in COVID-19 pneumonia. Kunhua et al. (15) reported that; severe-critical patients showed higher incidences of pericardial effusion, and pleural effusion than ordinary patients. In our study, the incidence of pleural effusion was statistically higher in B.1.1.7 variant. Pleural thickening was also significantly more common in B.1.1.7 variant. Pericardial effusion was detected in only 1 patient infected with Wuhan type, and was not detected in the group infected with B.1.1.7 variant, that is because, statistical comparison could not be made.

Pulmonary embolism is relatively common complication in COVID-19 pneumonia and associated with increased mortality risk (16). All of our patients admitted to the ED with symptoms of dyspnea and chest pain suspecting COVID-19 pneumonia and pulmonary embolism. Also patients have high D-dimer levels. They underwent PCTA. In our study while pulmonary embolism was detected in only 3 patients in the Wuhan type, it was observed in 16 patients in the B.1.1.7 variant, and a statistically significant difference was obtained.

Finally, the prevalence of steatosis was high in COVID-19 patients (17) and fatty liver is an important sign for a poor prognosis (18) and can easily be detected on chest CT scans.In our study, although hepatosteatosis was more common in the B.1.1.7 variant than the Wuhan type, no statistical significant difference was found.

There were some limitations to the present study. The sample size was relatively smallbecause in patients with suspected COVID-19, chest radiograph is primarily preferred radiological examination and in addition, the patients included in the study had both chest CT and CT angiography. Second, this study used a retrospective approach. Studies conducted by including other variants and increasing the number of patients will contribute to literature in future.

In conclusion, similar to the differences in the clinical course and infectivity of B.1.1.7 variant and Wuhan type, this study showed differences in CT findings between these groups as well. Reported radiological findings that seen in severe COVID-pneumonia like consolidation, pleural effusion, pulmonary embolism, and atypical CT findings such as pleural effusion, central GGO, and upper lobe involvement which were more commonly seen in B.1.1.7could give the clinician an idea about the course of the disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Marmara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 07.06.2021, Decision No: 09.2021.734).

Informed Consent: No written informed consent form was obtained from patients because the study was designed retrospectively.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors declerate that there were no conflicts of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have read and approved the final versionof the manuscript.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1106106
J Health Sci Med 2022; 5(4): 1015-1022

The relationship of laboratory parameters and mortality of patients followed in intensive care units with COVID-19

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Cite this article as: Karacan Gölen M, Yılmaz Okuyan D, İlban Ö, Tutar MS, Işık ŞM. The relationship of laboratory parameters and mortality of paients followed in intensive care units wıth COVID-19. J Health Sci Med 2022; 5(4): 1015-1022.

ABSTRACT

Aim: We aimed to evaluate the parameters associated with mortality in COVID-19 patients followed up in the intensive care unit.

Material and Method: Three hundred twenty-one patients followed up with the diagnosis of COVID-19 were included in the study. Demographic characteristics, laboratory and clinical parameters were compared in patients with and without mortality.

Results: A higher intubation rate (98.6% vs. 10.9%) and longer hospitalization (10.0 vs. 8.0 days) were detected in the non-survivor group ($p<0.001$). The neutrophil count, ferritin, troponin I, INR, PT, LDH, urea, creatinine, procalcitonin, WBC, CRP, AST, neutrophil/lymphocyte ratio, and CRP/albumin ratio were significantly higher in the non-survivor group, whereas the lymphocyte count, albumin, monocyte, and platelet counts were significantly lower. A multivariate logistic regression model identified endotracheal intubation, high platelet count, low LDH, low albumin, and decreased CRP/albumin ratio as risk factors associated with intensive care unit mortality. Albumin had the highest prognostic accuracy with an AUC of 0.681 (95% CI: 0.621-0.742) and the highest sensitivity (84.5%), and the platelet count had the highest specificity (69.2%).

Conclusion: Advanced age, intubation status, and duration of intubation were associated with mortality, and it was thought that an increase in LDH levels and CRP/albumin ratio and a decrease in albumin levels and platelet counts had predictive value in predicting mortality

Keywords: COVID-19, intensive care, mortality, laboratory parameters

INTRODUCTION

Coronavirus disease (COVID-19) emerged in the city of Wuhan in December 2019 and affected the whole world, causing a pandemic. SARS-CoV-2 can cause asymptomatic infection or severe pneumonia and respiratory failure, which can result in death. It can affect all body areas (especially the respiratory system, lymphoid tissue, arterial venous system endothelial cells, urinary tract, glial cells in the brain, intestines, nasal mucosa, skin, heart, bone, spleen and muscle tissue) because it causes disease through the angiotensin-converting enzyme (ACE-2) receptor (1-2).

The most common symptoms of COVID-19 are fever, cough, and shortness of breath, which can progress to organ failure. In respiratory failure, which occurs with clinical worsening in the later stages of the disease, follow-up in the intensive care unit (ICU) is required according to the need for respiratory support (3).

The mortality rate is high in patients with COVID-19, and among the factors affecting mortality, especially advanced age, male sex, hypertension, immunodeficiency due to chronic diseases, and a history of cancer come to the fore. Supporting this, a study from China reported that advanced age, increased D-dimer, and high sequential organ failure assessment (SOFA) scores were associated with mortality in patients with COVID-19 (4). Apart from this, it has been reported that there is a relationship between mortality and male sex, hypertension, cardiovascular diseases and type-2 diabetes in different studies (5-8).

Although the need for mechanical ventilation in patients admitted to the ICU with the diagnosis of acute respiratory distress syndrome (ARDS) differs in case series, it has been reported to be associated with high mortality.

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Received: 19.04.2022 **Accepted:** 01.06.2022

In this study, we evaluated the laboratory parameters, recorded co-morbid diseases, treatments received during the follow-up in the ICU, intubation status, length of stay in the ICU, and discharge status from the ICU of patients we followed up with the diagnosis of COVID-19 and respiratory failure in the ICU.

MATERIAL AND METHOD

The study was initiated with the approval of the KTO Karatay University Non-Pharmaceutical and Non-Medical Device Researches Ethics Committee (Date: 11.03.2021, Decision No: 2021/002). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was a single-center, retrospective study, and patients with a probable and definite diagnosis of COVID-19 who were followed up in the ICU between July 2020 and January 2021 were included in the study. The probable or definitive diagnosis of COVID-19 was determined according to the diagnostic criteria of the European Centre for Disease Prevention and Control (ECDC). Patients were determined as possible, probable or confirmed cases according to the ECDC criteria. The case definitions are as follows: (1) possible case, any person meeting the clinical criteria; (2) probable case, any person meeting the clinical criteria with an epidemiologic link or any person meeting the diagnostic criteria, including radiologic evidence for COVID-19; (3) confirmed case, any person meeting the laboratory criteria (9).

This study included 321/398 patients with severe pneumonia followed in the intensive care unıt. Seventy-seven patients were excluded because they did not meet the inclusion criteria. The pneumonia severity of all patients with COVID-19 in this study was classified according to the World Health Organization (WHO) guidelines (10) and the inclusion criteria were as follows: age over 18 years, positive SARS-CoV-2 real-time transcription-polymerase chain reaction (RT-PCR) in nasopharyngeal swab and/or lung tomography compatible with COVID-19 viral pneumonia, and requiring follow-up in the ICU. Patients aged under 18 years, patients in whom COVID-19 was excluded or with missing file records were excluded from the study. Demographic characteristics, medical history, comorbid diseases, clinical findings, intubation status, intubation duration, laboratory findings, drug treatments, and discharge status from the ICU were evaluated retrospectively from the electronic medical records of hospitalized patients.

The relationship of age, sex, and comorbid diseases (hypertension, diabetes mellitus, pulmonary diseases, heart diseases and other comorbidities) with mortality was evaluated.

The treatments administered during the hospitalization period of the patients were evaluated. The contribution of tocilizumab, favipiravir, plasma therapy, and corticosteroid therapy to the patient's survival and their relationship with mortality were evaluated.

In terms of standardization of the data, the blood laboratory parameters of the patients at the first admission to the emergency department were examined. The normal ranges of the investigated parameters were as follows: white blood cell (WBC) count (4.49-12.68 $\times 10^9$/L), lymphocyte count (1.26-3.35 $\times 10^3$/mL), neutrophil count (2.1-8.89 $\times 10^3$/mL), monocyte count (0.25-0.84 $\times 10^3$/mL), platelet count (173-390 $\times 10^3$/mL), troponin (0-19.8 ng/L), D-dimer (0-0.5 µg/mL), lactate dehydrogenase (LDH) (25-248) IU/L), C-reactive protein (CRP) (0-8 mg/L), procalcitonin (0-0.5 µg/L), ferritin (23.9- 336.2 µg/L), albumin (35-52 g/L), aspartate aminotransferase (AST) (3-50 IU/L), alanine aminotransferase (ALT) (3-50 IU/L), urea (17-43 mg/dL), creatinine (0.67-1.17 mg/dL), prothrombin time (8.40-10.6 sec), and activated partial thromboplastin time (APTT) (23.9-33.2 sec). To evaluate the relationship of these parameters with mortality, a comparison was made between the two groups according to the patients' discharge status from the ICU.

Statistical Analysis

Statistical analyses were performed using the SPSS version 21.0 software. Data are presented as median and interquartile range (IQR) for continuous variables, and as numbers and percentages (%) for categorical variables. The normality of data distribution was determined using the Kolmogorov-Smirnov test. Categorical variables were compared using the Chi-square ($\chi 2$) or Fisher's exact test according to their suitability. Continuous variables with normal distribution were analyzed using the independent samples t-test, and those that did not fit were analyzed using the Mann-Whitney U test. A logistic regression model was used to evaluate risk factors associated with mortality. The significance of the relationship was indicated by the odds ratio (OR) and 95% confidence interval (CI). Based on the results of the logistic regression, the prognostic value of the parameters found to be significant was evaluated using receiver operating characteristic (ROC) curve analysis. The best discriminatory cut-off values were calculated using Youden's criteria. A value of $p<0.05$ was considered significant in all tests.

RESULTS

This study included 321 patients with a confirmed diagnosis of COVID-19 who were followed in the ICU. One hundred ten (34%) patients were in the survivor group, and 211 (66%) patients were in the non-survivor group. The mean age of all patients included in the

study was 71.0 (range, 65.0-80.0) years, the mean age in the survivor group was 69.0 (range, 61.0-77.0) years, and in the non-survivor group, it was 72.0 (range, 66.0-82.0) years. Of the included patients, 143 (44.5%) were female and 178 (55.5%) were male. In the survivor group, 42 (38.2%) patients were female and 68 (61.8%) were male. In the non-survivor group, 101 (47.9%) were female and 110 (52.1%) were male. When the survivor and non-survivor groups were compared in terms of age, the mean age was found to be significantly higher in the non-survivor group than in the survivor group (p<0.001). There was no significant difference between the groups in terms of sex. RT-PCR was negative in 44 (13.7%) of all patients and positive in 277 (86.3%). In the survivor group, 18 (16.4%) were negative, 92 (83.6%) were positive, and in the non-survivor group, 26 (12.3%) were negative and 185 (87.7%) were positive in terms of RT-PCR tests.

When the risk factors and accompanying comorbidities of the patients were examined, hypertension (the most common) was found in 144 (44.9%), diabetes mellitus in 83 (25.9%), pulmonary disease in 71 (22.1%), heart diseases in 78 (24.3%), and other additional diseases (e.g. kidney disease, malignancy, rheumatologic diseases) in 133 (41.4%) of 321 patients. There was no significant difference between the survivor and non-survivor groups in terms of co-morbid diseases.

When the medical treatment administered to the patients was evaluated, 304/321 (94.7%) received favipiravir, 252/321 (78.5%) corticosteroids, 181/321 (56.4%) convalescent plasma, and 42/321 (13.1%) had tocilizumab. There was no significant difference between the survivor and non-survivor groups in terms of medical treatment.

A higher intubation rate (98.6% vs. 10.9%) was found in the non-survivor group compared with the survivor group (p<0.001). Also, longer hospital stay (10.0 vs. 8.0 days) was observed. The characteristics of the patients are listed in **Table 1**.

When the laboratory parameters were evaluated, the neutrophil count (p<0.001), ferritin (p<0.001), troponin I (p<0.001), INR, PT (p<0.001), LDH (p<0.001), urea (p<0.001), creatine (p<0.001), procalcitonin (p<0.001), WBC, CRP (p<0.001), AST, neutrophil/lymphocyte ratio (p<0.001), and CRP/albumin ratio (p<0.001) were significantly higher in the non-survivor group, while the lymphocyte count (p<0.001), albumin (p<0.001), monocyte and platelet count were significantly lower (**Table 2**).

Table 1. Baseline characteristics of COVID-19 patients in ICU

Characteristics		All patients n=321	Survivor patients n=110	Non-survivor patients n=211	P value
Age (years) (Median)		71.0 (65.0-80.0)	69.0 (61.0-77.0)	72.0 (66.0-82.0)	0.001
Sex, n (%)	Female	143 (44.5%)	42 (38.2%)	101 (47.9%)	0.098
	Male	178 (55.5%)	68 (61.8%)	110 (52.1%)	
RT-PCR, n (%)	Negative	44 (13.7%)	18 (16.4%)	26 (12.3%)	0.318
	Positive	277 (86.3%)	92 (83.6%)	185 (87.7%)	
Hypertension, n (%)	No	177 (55.1%)	63 (57.3%)	114 (54.0%)	0.579
	Yes	144 (44.9%)	47 (42.7%)	97 (46.0%)	
Diabetes mellitus, n (%)	No	238 (74.1%)	80 (72.7%)	158 (74.9%)	0.676
	Yes	83 (25.9%)	30 (27.3%)	53 (25.1%)	
Pulmonary disease, n (%)	No	250 (77.9%)	87 (79.1%)	163 (77.3%)	0.706
	Yes	71 (22.1%)	23 (20.9%)	48 (22.7%)	
Heart disease, n (%)	No	243 (75.7%)	88 (80.0%)	155 (73.5%)	0.195
	Yes	78 (24.3%)	22 (20.0%)	56 (26.5%)	
Additional disease, n (%)	No	188 (58.6%)	70 (63.6%)	118 (55.9%)	0.183
	Yes	133 (41.4%)	40 (36.4%)	93 (44.1%)	
Tocilizumab therapy, n (%)	No	279 (86.9%)	94 (85.5%)	185 (87.7%)	0.575
	Yes	42 (13.1%)	16 (14.5%)	26 (12.3%)	
Favipiravir therapy, n (%)	No	17 (5.3%)	5 (4.5%)	12 (5.7%)	0.665
	Yes	304 (94.7%)	105 (95.5%)	199 (94.3%)	
Plasma therapy, n (%)	No	140 (43.6%)	45 (40.9%)	95 (45.0%)	0.480
	Yes	181 (56.4%)	65 (59.1%)	116 (55.0%)	
Corticosteroids, n (%)	No	69 (21.5%)	20 (18.2%)	49 (23.2%)	0.297
	Yes	252 (78.5%)	90 (81.8%)	162 (76.8%)	
Intubation, n (%)	No	101 (31.5%)	98(89.1%)	3 (1.4%)	<0.001
	Yes	220 (68.5%)	12 (10.9%)	208 (98.6%)	
Length of ICU (day)		9.0 (5.0-16.0)	8.0 (5.0-14.0)	10.0 (4.0-18.0)	0.218
Length of IMV (day)		3.0 (0.0-9.0)	0.0 (0.0-0.0)	6.0 (2.0-12.0)	<0.001

* Significant at 0.05 level; Chi-square test for categorical variables, Mann whitney u test for numerical variables. Median (25%-75%). Abbreviations: RT-PCR-Reverse Transcriptase-Polymerase Chain Reaction ICU-Intensıve Care Unıt, IMV- Invasiv mechanic ventilatore

Table 2. Laboratory parameters of COVID-19 patients in ICU

Laboratory parameter	All patients (n=321)	Survivor patients (n=110) (Median)	Non-survivor patients (n=211) (Median)	P value
Neutrophil count (10^3/mL)	8.72 (5.71-13.03)	7.11 (5.03-9.72)	9.97 (6.32-15.09)	<0.001
Lymphocyte count (10^3/mL)	0.80 (0.52-1.17)	0.94 (0.66-1.32)	0.69 (0.46-1.10)	<0.001
Ferritin (µg/mL)	380.0 (191.4-704.0)	272.50 (126.8-531.0)	438.5(235.0-853.0)	<0.001
D-dimer (µg/mL)	1.89 (0.7-9.34)	1.37 (0.55-8.80)	2.49 (0.75-9.41)	0.059
Troponin I (ng/mL)	22.80 (10.5-90.9)	15.35 (7.1-46.6)	33.0 (12.6-140.0)	<0.001
International normalized ratio (INR)	1.14 (1.05-1.3)	1.11 (1.03-1.25)	1.16 (1.07-1.32)	0.006
Prothrombin time (PT) (Second)	13.2 (12.1-15.0)	12.7 (11.9-14.1)	13.5 (12.3-15.4)	<0.001
Partial Thromboplastin Time (APTT) (Second)	29.4 (25.6-34.6)	28.95 (25.30-33.90)	29.4 (25.9-35.0)	0.192
Lactate Dehydrogenase (LDH), U/L	396.0 (293.0-561.0)	354.0 (266.0-456.0)	445.0 (323.0-658.0)	<0.001
Urea (mg/dL)	56.0 (39.0-90.0)	44.5 (32.0-63.0)	64.00 (43.0-110.0)	<0.001
Creatinine (mg/dL)	0.97 (0.72-1.44)	0.82 (0.66-1.08)	1.10 (0.78-1.67)	<0.001
Procalcitonin (U/L)	0.27 (0.11-1.47)	0.14 (0.07-0.39)	0.59 (0.16-2.30)	<0.001
Albumin (g/L)	2.71 (2.26-3.07)	2.91 (2.57-3.40)	2.56 (2.13-2.94)	<0.001
Monocyte (10^3/mL)	0.46 (0.31-0.71)	0.56 (0.39-0.80)	0.44 (0.28-0.68)	0.004
White blood cell count (10^9/L)	9.84 (7.00-14.34)	8.9 (6.19-11.65)	10.78 (7.32-16.37)	0.002
Platelet count (10^3 µ/L)	209.0 (157.0-287.0)	229.0 (163.0-310.0)	200.0 (153.0-271.0)	0.032
C reactive protein (CRP) mg/L)	108.0 (63.6-189.0)	91.65 (33.0-145.0)	118.0 (77.10-227.0)	<0.001
Aspartate aminotransferase (U/L)	40.0 (27.0-66.0)	36.0 (23.0-56.0)	43.0 (28.0-72.0)	0.017
Alanine aminotransferase (U/L)	26.0 (17.0-52.0)	24.5 (17.0-48.0)	27.0 (17.0-59.0)	0.715
Neutrophil/lymphocyte	10.89 (5.57-19.69)	7.45 (4.65-12.33)	13.89 (7.16-24.09)	<0.001
CRP/albumin (10^{-3})	41.17 (23.34-72.68)	30.42 (11.09-51.92)	46.78 (28.14-86.31)	<0.001
Monocyte/albumin (g)	0.18 (0.11-0.27)	0.19 (0.11-0.31)	0.18 (0.11-0.25)	0.295

*Significant at 0.05 level; Mann whitney u test for numerical variables. Median (25%-75%)

Based on the above observations, potential risk factors for mortality were examined using logistic regression. Predictors with p values <0.05 in the univariate analysis were included in the multivariate analysis. The multivariate logistic regression model identified endotracheal intubation, high platelet count, low LDH, low albumin, and decreased CRP/albumin ratios as risk factors associated with ICU mortality (T**able 3 and Figure 1**).

Table 3. Risk factors for mortality of COVID-19 patients in ICU

	OR (95% CI)	P value
Age (Year)	0.980 (0.931-1.031)	0.430
Intubation (yes)	4284.786 (303.303-60,531.5)	<0.001
Length of IMV (days)	1.013 (0.970-1.057)	0.560
Neutrophil count (10^3/mL)	0.754 (0.505-1.126)	0.168
Lyphocyte count (10^3/mL)	0.570 (0.146-2.219)	0.418
Ferritin (µg/mL)	1.000 (0.999-1.001)	0.752
Troponin (ng/mL)	1.000 (0.999-1.001)	0.947
International normalized ratio (INR)	5.951 (0.078-452.43)	0.420
Prothrombin time (PT) (Second)	0.918 (0.640-1.317)	0.642
Lactate Dehydrogenase (LDH) (U/L)	0.996 (0.991-1.000)	0.049
Urea (mg/dL)	1.010 (0.993-1.027)	0.239
Creatinine (mg/dL)	0.611 (0.301-1.239)	0.172
Procalcitonin (U/L)	0.992 (0.949-1.037)	0.726
Albumin (g/L)	0.122 (0.015-1.023)	0.049
Monocyte (10^3/mL)	0.419 (0.067-2.632)	0.353
White blood cell count (10^9/L)	1.238 (0.880-1.742)	0.221
Platelet count (10^3µ/L)	1.011 (1.004-1.019)	0.004
C reactive protein (CRP) mg/L)	1.035 (0.997-1.074)	0.068
Aspartate aminotransferase (IU/L)	0.997 (0.986-1.009)	0.641
Neutrophil/lymphocyte	0.932 (0.822-1.057)	0.270
C reactive protein (CRP)/albumin (10^{-3})	0.909 (0.827-0.999)	0.047

*Significant at 0.05 level

ROC curve analysis was performed to evaluate the overall prognostic accuracy of statistically significant parameters in discriminating between survivors and non-survivors. Of all the laboratory parameters, albumin had the highest prognostic accuracy with an area under the ROC curve (AUC) of 0.681 (95% CI: 0.621-0.742) and the highest sensitivity (84.5%), and the platelet count had the highest specificity (69.2%). Details of the ROC analysis are given in **Table 4 and Figure 2**.

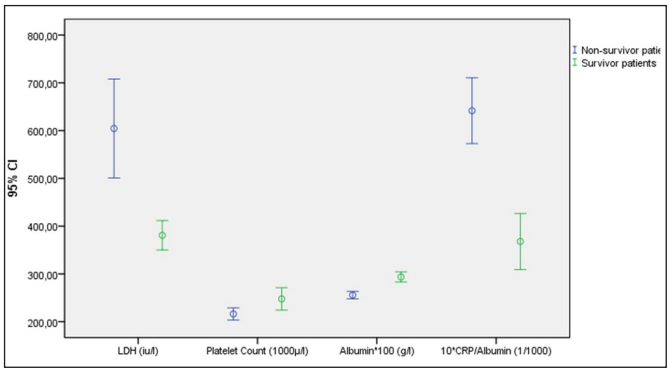

Figure 1. Comparison of significant parameters between survivors and non-survivors.
CI: confidence interval. LDH: lactate dehydrogenase, CRP: C-reactive protein

Table 4. Cut-off, sensitivity, specificity, and area under the curve levels of age, intubation day, LDH, and platelet count of COVID-19 patients in ICU

Characteristic	Cut-off	Specificity (%)	Sensitivity (%)	AUC (95% CI)	P value
LDH (IU/L)	392.5	66.4%	59.2%	0.655 (0.595-0.716)	<0.001
Platelet count (103µ/L)	247	69.2%	45.5%	0.573 (0.506-0.640)	0.032
Albumin (g/L)	2.44	46%	84.5 %	0.681 (0.621-0.742)	<0.001
CRP/albumin (10-3)	31.02	51.8%	70.1 %	0.676 (0.615-0.736)	<0.001

*Abbreviations: CRP- C Reactive Protein, LDH- Lactate Dehydrogenase

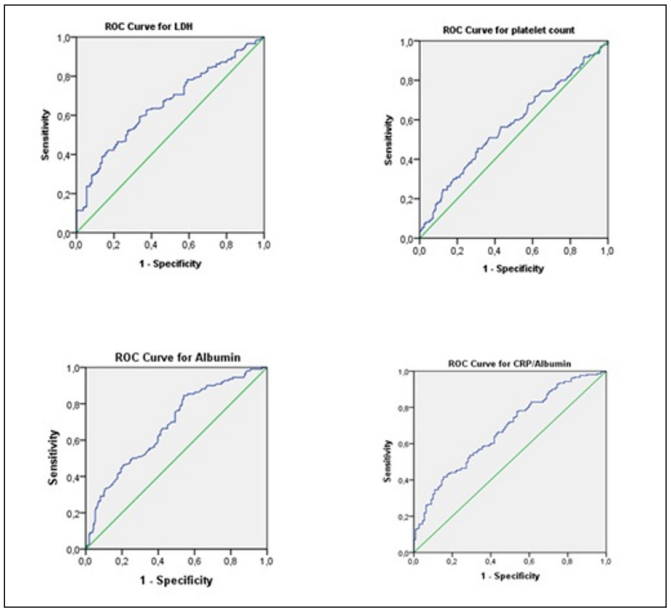

Figure 2. ROC curve of LDH, platelet count, albumin, and CRP/albumin in patients

DISCUSSION

According to our clinical experience, it was observed that conditions such as delay in admission to the hospital, delaying or rejecting treatment, comorbid diseases, old age, and immunodeficiency were the determining factors of ICU need.

Older age as a risk factor, which is thought to be related to mortality in patients followed up in the ICU due to COVID-19, is a common finding of many studies. In a multicenter study conducted to reveal the relationship of age with mortality, higher mortality in older adults compared with healthy older adults was associated with co-morbid conditions. It was argued that advanced age was an independent risk factor for COVID-19 mortality (11-12). In our study, it was noted that the patients in the non-survivor group were older than the patients in the survivor group [72.0 (66.0-82.0) vs. 69.0 (61.0-77.0)], and advanced age was found to be associated with mortality (p=0.001).

Another striking situation in the literature is that mortality is higher in males than in females. Biologic-based differences between the two sexes, hormonal changes, and sexual dimorphism in the expression of the ACE receptor responsible for the pathophysiology of the disease are thought to contribute to this situation. In our study, no association was found between sex and mortality (13-14).

It was suggested that there was a relationship between comorbid diseases, especially hypertension, pulmonary disease history, diabetes mellitus, and mortality. However, in our study, no relationship was found between comorbid diseases and mortality. This finding indicated that the effect of comorbid diseases on mortality might be masked by the effect of age. Similarly, in a study conducted in Wuhan, patients were classified according to disease severity and comorbid diseases were not found to be associated with disease severity (15-17).

Although no treatment has been found with proven effectiveness and safety for SARS-CoV-2 in scientific studies, no statistically significant relationship was found in terms of mortality with the treatment options received by our patients. During the hospitalization period in the ICU, favipiravir, convalescent plasma therapy, tocilizumab, and pulse steroid treatment were administered according to the recommendations of the Turkish Ministry of Health, the COVID-19 Adult Patient Treatment guideline, and according to their clinical status (18).

The efficacy of corticosteroid treatment is controversial; previous studies have shown that it does not contribute to reducing mortality, delay viral clearance, and increases secondary infections in SARS-CoV and MERS-CoV outbreaks. In a meta-analysis in which 10 studies were systematically evaluated in 2019, it was shown that systemic corticosteroids increased the length of hospital stay and increased the incidence of secondary bacterial or fungal infections in patients with influenza (19). When convalescent plasma therapy is used within 7 days at the latest after diagnosis and before intubation is required, it provides a reduction in the risk of disease progression. However, there is insufficient evidence for efficacy and safety in patients with severe pneumonia. It is suggested that late in the course of the disease, in intubated individuals, and during the cytokine storm period, it may do more harm than good (20-21).

It is known that SARS-CoV-2 causes an increase in plasma interleukin (IL)-6 levels during the active period of the disease. Tocilizumab stops the emergence of cytokine effects by preventing the virus from binding to IL-6 receptors. In a study evaluating 21 patients who were given tocilizumab, it was suggested that treatment given during severe disease with clinical worsening reduced

mortality and accelerated recovery (22-23). However, in our study, no positive contribution was observed in patients who were administered tocilizumab, which suggested that there might have been a delay in starting treatment due to the procedures for initiating treatment.

Intubation has become mandatory in patients whose hypoxia continues with non-invasive mechanical ventilation and high-flow nasal cannula oxygenation (HFNC) during a stay in the ICU. Of our patients, 71.4% (257/321) were intubated, and 98.6% of the non-survivor patients were intubated (208/211). The relationship between mechanical ventilation and mortality was found to be statistically significant in patients followed up as intubated (OR: 4284.79 (303.303-60531.46) (p<0.001) (**Table1-Table 3**) (p<0.001). In a study in which the observational experiences of patients with COVID-19 in Italy were reported, it was reported that most of the critically ill patients admitted to the ICU needed mechanical ventilation (>80%) and the mortality rate was high (~50%) (17,24). In different case series it was reported, respectively, that the need for intubation in critical patients were (75%), (71%) and the mortality rate of patients in the ICU was 67% (25-26).

In addition to demographic data, changes in laboratory parameters, clinical worsening, and predicting mortality have a very important role in terms of treatment plans. In our study, in the comparative evaluation made among survivors in the ICU, an increase in the neutrophil count (p<0.001), and a decrease in the lymphocyte count (lymphopenia) (p<0.001) were found to be statistically associated with mortality. In a study evaluating the effects of hematologic parameters on admission to the ICU, supporting our study, it was reported that severe lymphopenia was one of the markers indicating early admission to the ICU (27). Guan et al.'s (28) study concluded that severe lymphopenia was associated with the development of ARDS. However, in a retrospective study of 108 patients, increased D-dimer levels and severe lymphopenia were reported to predict mortality (29). Apart from this, increased levels of troponin (p<0.001), urea (p<0.001), creatinine (p<0.001), AST (p=0.017), procalcitonin (p<0.001), ferritin (p<0.001), and prolongation of prothrombin time (p<0.001) were found to be statistically associated with mortality in our study. In an Italian cohort study similar to our study, an increased neutrophil count, increased serum creatinine levels, increased C-reactive protein (CRP) and lactate dehydrogenase levels, and decreased platelet and lymphocyte levels were reported to predict mortality (30-32). In our study, we observed that the neutrophil/lymphocyte ratio was also statistically significant in predicting mortality (p<0.001). Similarly, it was illustrated that the neutrophil/lymphocyte ratio could be an indicator of disease severity, and in the same study, it was reported that renal markers were associated with hospital mortality, similar to our study (32).

In a retrospective study evaluating survivor patients of COVID-19 via thrombocyte values, one of the hematologic parameters, it was observed that thrombocytopenia was an independent risk factor for mortality in Cox proportional hazard regression analysis. They also reported that a 50 ×109/L decrease in platelet counts increased mortality by 40% (HR: 0.60, 95% CI: 0.43-0.84). In a multicenter study, low platelet levels were also reported to increase the risk of mortality (32-34).

LDH, which plays a role in the glucose metabolism pathway in cell metabolism, is known to be released when necrosis due to lung damage develops in COVID-19 pneumonia and is a marker showing cell damage and disease severity. However, in an observational study evaluating whether LDH values were an independent risk factor in patients with severe COVID-19, it was shown that LDH levels had a strong predictive value in detecting early lung injury and that they were positively correlated with the P/F ratio and computed tomography scores (17,28,32,35). In our study, LDH levels were found to be associated with mortality in patients with COVID-19. According to the ROC curve analysis, the value of 392.5 IU/L was determined as the best cut-off point for LDH. The sensitivity was 59.2% for people with LDH levels above 392.5 IU/L and the specificity was 66.4% for people with ≤392.5 IU/L. In a study evaluating 123 patients in Italy, it was reported that LDH (r=0.62, r2=0.38; p<0.001) and CRP (r=0.55, r2=0.31; p<0.001) levels were strongly correlated with respiratory performance (PaO2/FiO2), and it was emphasized that LDH and CRP had a strong predictive value in detecting respiratory failure . CRP values above 130 mg/L were found to be associated with mortality. In our study, a statistically significant increase in CRP levels was found in the non-survivor group compared with the survivor group (p<0.001) (36-37)

In our study, a relationship between a decrease in albumin levels and mortality was shown. In addition, when clinically important variable logistic regression analysis was performed, it was observed that the albumin ratio was AUC 0.681 (95% CI: [0.621-0.742]; p<0.001), and albumin had high sensitivity in predicting mortality (84.5%). Albumin is a harbinger of nutritional disorders in prolonged hospitalizations due to liver and kidney effects. In a retrospective study in which 427 patients with COVID-19 were evaluated comparatively in two groups (survivors or non-survivors), albumin levels were found to be associated with mortality (38). In a different study conducted in Wuhan, increased CRP and decreased albumin were reported to be correlated with disease progression (39). In our study, when a

statistically significant and clinically significant variable logistic regression analysis was performed in patients with COVID-19, it was found that the CRP/albumin ratio had a statistically significant predictive value in predicting mortality. According to the ROC curve analysis, 31.02 was determined as the best cut-off point for the CRP/albumin ratio, with a sensitivity of 70.1% for individuals with a CRP/albumin ratio above 31.02 and a specificity of 51.8% for individuals with ≤31.02. They defended the importance of CRP/albumin (CAR) ratio in predicting mortality in a retrospective cohort study evaluating mortality-related parameters of 875 patients in the ICU (40).

There were some limitations to our study, such as being a single-center study ,small sample size ,not having a placebo group, being a retrospective study, evaluating the blood tests at the first admission to the emergency department, and not evaluating the follow-up blood test values during the clinical worsening or recovery period of the patients. In the study the number of patients with mild and moderate pneumonia was insufficent and statitical evaluation could not be made between the groups. In addition, due to the fact that vaccition studies had not started in Turkey at the time the study was planned ande case were collected, no evaluotion was made regarding the vaccine.

CONCLUSION

In conclusion, demographic characteristics, especially advanced age, intubation status, and duration of intubation were associated with mortality in patients in our study. Neutrophilia, lymphopenia, thrombocytopenia; increased neutrophil/lymphocyte ratio; increased ferritin, troponin and CRP levels; decreased albumin levels; increased CRP/albumin ratio; prolongation of prothrombin time; increased renal function tests, and increased AST levels were observed. It was thought that an increase in the CRP/albumin ratio, a decrease in the albumin level, and a decrease in the platelet count had predictive value in predicting mortality. To determine parameters that affect mortality in patients with COVID-19 followed in the ICU, and to support our findings, multicenter prospective clinical studies with large numbers of patients are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the KTO Karatay University Non-Pharmaceutical and Non-Medical Device Researches Ethics Committee (Date: 1.03.2021, Decision No: 2021/002).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1120364
J Health Sci Med 2022; 5(4): 1023-1029

Algorithms for perforator-based flaps in different anatomical locations

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Cite this article as: Can B, Ekinci C. Algorithms for perforator-based flaps in different anatomical locations. J Health Sci Med 2022; 5(4): 1023-1029.

ABSTRACT

Introduction: Perforator-based flaps can be planned in any anatomic location in the body when there is a detectable perforator. Although preoperative perforator mapping ensures safety and versatility of these flaps, there is no consensus yet about flap planning in different anatomical locations.

Material and Method: 28 patients underwent perforator-based flap surgery for different anatomical locations as face (5), sternum (3), back (5), lomber (4), sacral (4) and scrotal (4) areas, leg (2) and foot (1). 19 of the patients were male while 9 were female. The mean age was 58.1±13.5 (22-80 years).

Perforator-based flaps were planned as V-Y design in face, sacral and scrotal areas while as perforator plus transposition flaps for lomber area, leg and sternum. On the other hand, for foot the flap was planned as subcutaneous-pedicled turnover flap.

Results: The mean follow-up time was 10 months (3-36 months). Partial flap necrosis is seen in all 3 patients who had underwent flap surgery on the lower extremity. There were no other complications seen in short- or long-term follow-ups. Comorbid diseases were not statistically significant on complications rates (P>0.05).

Conclusion: V-Y flap for the face and the sacral area; and perforator plus transposition flap for back ,lomber area and sternum are suggested as the ideal flap modifications for these anatomical locations. On the other hand, perforator-based flaps should not be used as a first choice in reconstruction of lower extremity defects.

Keywords: Perforator-based, versatility, flap modification, planning

INTRODUCTION

Perforator flap concept introduced security and versatility in the area of reconstructive surgery. Today, it is enough to plan a perforator flap for any anatomical location on the body if there is a perforator detected. The rules about mobility and design of the conventional flaps has been outdated with the emergence of perforator flap concept.

Conventional perforator flaps indicates dissection of the perforator from distal to proximal up to the source artery (1). Therefore, conventional perforator flap operations are microsurgical operations requiring expertise and sophisticated surgical instruments. Kim et al. (2) suggested that in perforator rich areas flaps can be transferred to the defect without perforator dissection. Flaps transferred to the defect without perforator dissection are called as "perforator-based flap". Perforator based flaps can also ensure similar advantages like security and versatility which were provided by conventional perforator flaps. Furthermore, they do not necessitate microsurgical expertise or sophisticated surgical tools reducing operating time is another advantage escipecially for co morbid patients who can not endure long operations.

Yıldırım et al. (3) suggested that as in the conventional perforator flaps, perforator-based flaps can also be planned in any anatomic location when there is detectable perforator present by a hand-held Doppler ultrasound. Concordantly, studies have showed that different perforator-based flaps can be planned in different designs for different anatomical locations as lower extremity (4), upper extremity (5), trunk (6), face (7) or scrotal area (8).

In all these studies, perforator-based flaps were defined for one anatomical location or single movement pattern and the authors suggested that the detection of the perforator is the only rule for planning perforator based flaps. In this study, we aim to define the important points that we consider when planning the flaps in different anatomical locations and present an algorithm.

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Received: 23.05.2022 **Accepted:** 06.06.2022

MATERIAL AND METHOD

The study was carried out with the permission of Balıkesir University Hospital, Noninvasive Clinical Researches Ethics Committee (Date: 23.02.2022, Decision No: 2022/34). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Records of 28 patients who had underwent reconstruction with perforator-based flaps were retrospectively investigated. Cause of the injury, anatomical location, movement pattern of the flap, comorbidities, complications and follow-up durations are obtained and listed in **Table 1**. Relationships of complications with comorbidities were investigated .

Data analysis was performed using IBM SPSS Statistics version 25.0 software (IBM Corporation, Armonk, NY, US). Shapiro-Wilk test was used to investigate whether the normal distribution assumption was met. Categorical data were expressed as numbers (n) and percentage (%) while quantitative data were given as mean ± SD and median (min-max). The mean differences between groups were compared Student's t test. Categorical data were evaluated Fisher's exact test. A p value less than 0.05 was considered statistically significant.

It was seen that perforator-based flaps were used in various anatomical areas such as face (5), sternum (3), back (5), lomber (4), sacral (4) scrotal (4) , leg (2) and foot (1). The flaps were planned as V-Y design in face, sacral and scrotal areas while as perforator plus transposition flaps for back ,lomber area, leg and the sternum. On the other hand, subcutaneous-pedicled turnover flap design

Table 1: Patient and flap demographics

Patient no	Age (year)/Sex	Comorbidity	Cause of defect	Defect Location	Defect size (cmxcm)	Pattern of flap	Flap size (cm)	Complications	Follow-up (months)
1	49/F	None	Trauma	Leg	4x3	Transposition-plus	15x5	partial necrosis	6
2	50/M	HT	Tumor	Back	5x1.5	Transposition-plus	6x3	None	12
3	58/M	DM	Fournier	Scrotum	15x8	V-Y	16x9&17x9	None	10
4	72/M	CAD-HT-DM	Postop dehiscence	Sternum	6x3	Transposition-plus	10x4	None	9
5	70/F	CAD	Postop dehiscence	Sternum	15x4	Transposition-plus	18x5	None	8
6	58/F	HT	Tumor	Back	4x3	Transposition-plus	6x3	None	16
7	67/M	HT-DM	Tumor	Face	3x2	V-Y	6x3	None	3
8	22/M	None	Trauma	Foot	4x2	Turnover	4x2	Partial necrosis	3
9	52/M	None	Tumor	Leg	4.5x2	Transposition-plus	9x3	Partial necrosis	10
10	45/F	None	Tumor	Back	5x3	Transposition-plus	8x4	None	18
11	62/M	None	Tumor	Back	6x4	Transposition-plus	10x4	None	22
12	65/M	None	Tumor	Face	3.5x1.5	V-Y	6x2	None	18
13	50/F	None	Tumor	Face	4x3	V-Y	6x3	None	5
14	79/M	CAD-PAD-DM	Decubitis ulcer	Sacral	15x10	V-Y	12x10 & 13x9	None	24
15	53/M	DM	Postop dehiscence	Lomber	8x4	Transposition-plus	13x4	None	28
16	41/M	None	Postop dehiscence	Lomber	12x8	Transposition-plus	14x7	None	36
17	41/M	DM	Fournier	Scrotum	15x10	V-Y	18x7&15x6	None	22
18	59/F	DM	Fournier	Scrotum	12x10	V-Y	10x8&14x8	None	24
19	58/M	ANAL FISSURE	Fournier	Scrotum	12x10	V-Y	14x9&12x8	None	3
20	57/M	None	Tumor	Face	3x2	V-Y	5x2	None	6
21	58/M	None	Tumor	Back	8x3	Transposition-plus	12x4	None	8
22	80/M	HT-DM	Decubitis ulcer	Sacral	15x9	V-Y	19x8&15x8	None	7
23	79/F	DM	Postop dehiscence	Sternum	14x5.5	Transposition-plus	19x5	None	9
24	58/M	DM	Postop dehiscence	Lomber	8x4	Transposition-plus	12x4	None	21
25	78/F	CAD-DM	Decubitis ulcer	Sacral	10x10	V-Y	14x4&15x6	None	24
26	71/F	CAD	Decubitis ulcer	Sacral	12x11	V-Y	10x3&16x4	None	10
27	49/M	None	Tumor	Face	3x2	V-Y	5x3	None	3
28	46/M	None	Postop dehiscence	Lomber	6x4.5	Transposition-plus	10x4	None	3

F: Female, M: Male, CAD: Coronary artery disease, HT: Hypertension, DM: Diabetes mellitus, PAD: Peripheral artery disease

was preferred for the foot .

RESULTS

36 flaps were performed in 28 patients who were included in this study. 19 of the patients were male (67,9%) while 9 were female (32.1%) and the mean age was 58.1±13.5 years (20-80 years) (**Table 2**) . 3 patients who perforator-based flaps used for lower extremity (2 leg, 1 foot) had partial necrosis .In one patient with partial necrosis who had reconstruction with perforator plus transposition flap on the leg, the defect after debridment of necrotic flap has left for secondary wound healing; while the other patient with partial necrosis on the leg, the defect skin grafted . For the partial necrosis developed after perforator-based turnover flap on the foot, the patient was referred to a higher center due to the necessity for a free-flap since vital structures were exposed.

Table 2. Demographic and clinical characteristics of cases

	n=28
Age (year) *	58.1±13.5
Range of ages (year)	22-80
Gender	
Female	9 (32.1%)
Male	19 (67.9%)
Comorbidity	
None	12 (42.9%)
DM	11 (39.3%)
HT	5 (17.9%)
CAD	5 (17.9%)
Other	2 (7.1%)
Cause of defect	
Tumor	11 (39.3%)
Postop dehiscence	7 (25.0%)
Decubitis ulcer	4 (14.3%)
Fournier	4 (14.3%)
Trauma	2 (7.1%)
Defect Location	
Back	5 (17.9%)
Face	5 (17.9%)
Lomber	4 (14.3%)
Sacral	4 (14.3%)
Scrotum	4 (14.3%)
Sternum	3 (10.7%)
Leg	2 (7.1%)
Foot	1 (3.6%)
Defect size (cm) **	7 (3-15)
Pattern of flap	
Transposition	16 (57.1%)
V-Y	11 (39.3%)
Turnover	1 (3.6%)
Lateralization	
Unilateral	8 (28.6%)
Bilateral	20 (71.4%)
Flap size (cm) **	12 (4-19)
Complications	
None	25 (89.3%)
Partial necrosis	3 (10.7%)
Follow-up (months) **	10 (3-36)

Descriptive statistics were shown as * mean ± SD or ** median (min-max). DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease

The mean follow-up time was 10 months (3-36 months). There were no complications seen except of the lower extremity during the follow-ups .There were no relationship between complications and comorbidities (**Table 3**).

Table 3. Gender and comorbidity distributions in terms of complication status

	Patients without complication (n=25)	Patients with complication (n=3)	p-value
Gender			>0.999‡
Female	8 (32.0%)	1 (33.3%)	
Male	17 (68.0%)	2 (66.7%)	
Comorbidity			0.067‡
None	9 (36.0%)	3 (100.0%)	
Exist	16 (64.0%)	0 (0.0%)	

† Student's t test, ‡ Fisher's exact test

CASE REPORTS

Case no.5

A 70 year old woman was consulted from cardiothoracic surgeon for sternal wound dehiscence after 6 days from coronary artery by pass surgery .The wound was prepared for reconstruction with serial debridements and negative pressure wound therapy performed at 3 days intervals. After the third debridement 15x4 cm defect on the sternum was covered with perforator plus transposition flap which was raised on the internal mamarian artery perforator. The flap survived completely without any complication (**Figure 1 a,b,c**)

Case no.7

67 year old man referred with a biopsy proven basall cell carcinoma on the left nasal ala. The lesion was removed with 4 mm margin and 3x2 cm defect was left. The defect was covered with perforator based V-Y advancement flap which was planned parallel to the nasolabial fold. The patient healed uneventfully and scar was aesthetically pleasing (**Figure 2 a,b,c**).

Case no. 24

58 year old man referred for lomber defect developed after spinal surgery due to surgical site infection.After serial debridements and negative pressure wound therapy ,the wound was covered with perforator plus transposition flap (**Figure 3 a,b,c**).

Case no.26

A 71 year old man was referred with grade 4 sacral dekubitis .He has been paraplegic due to cerebrovascular event for nine years . The wound was debrided and 12x11 cm defect

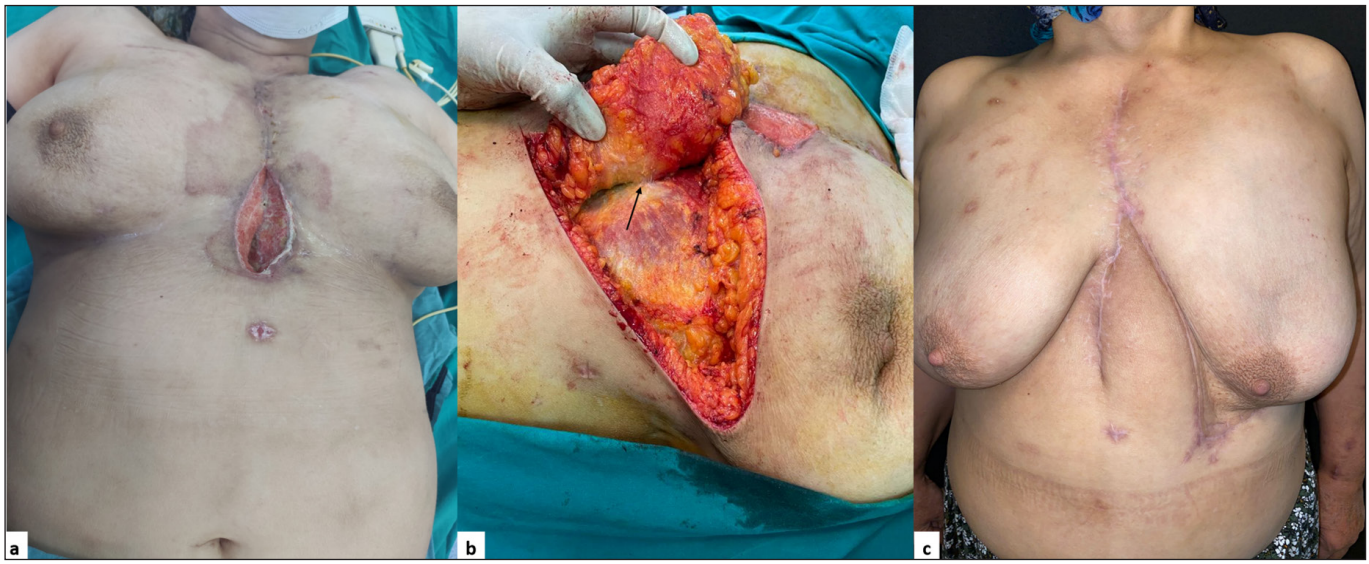

Figure 1a. Sternal wound dehcicence after coronary artery bypass surgery **b.** Perforator based transposition plus flap, arrow shows perforator from internal mamarian artery, which is visualised but not dissected intramusculary. **c.** Postoperative 4 months

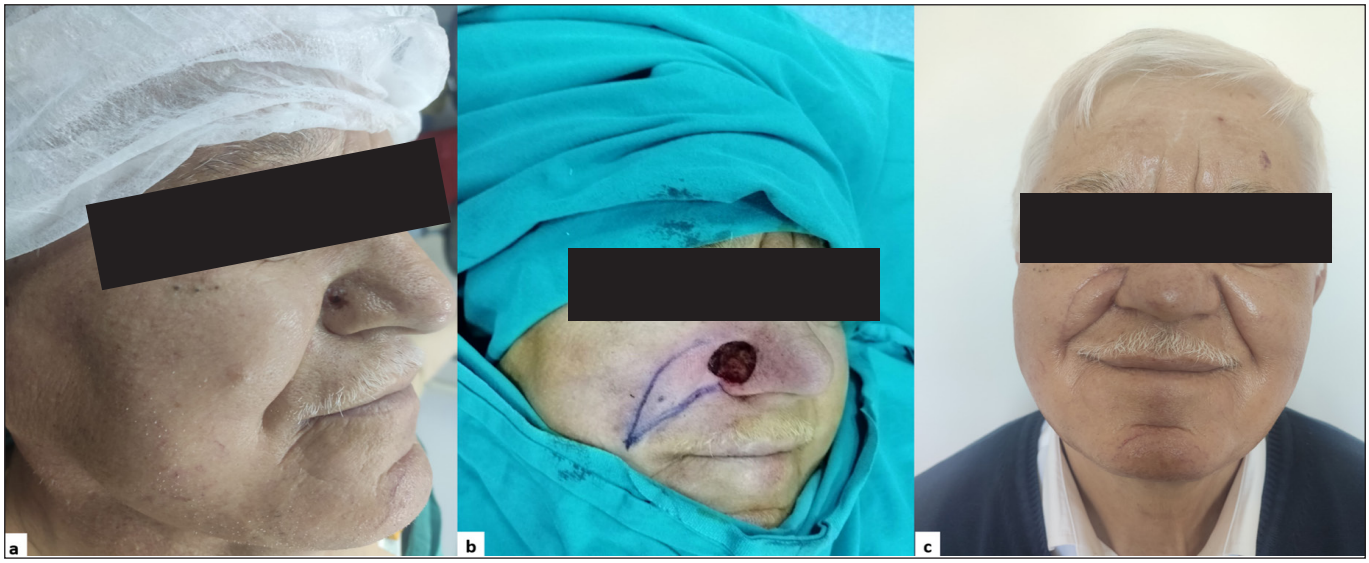

Figure 2 a. Biopsi proven basal cell carsinoma on the nasal ala **b.** 3x2 cm defect on the nasal ala was planned to cover with perforator based V-Y advancement flap **c.** Postoperative results after 2 months

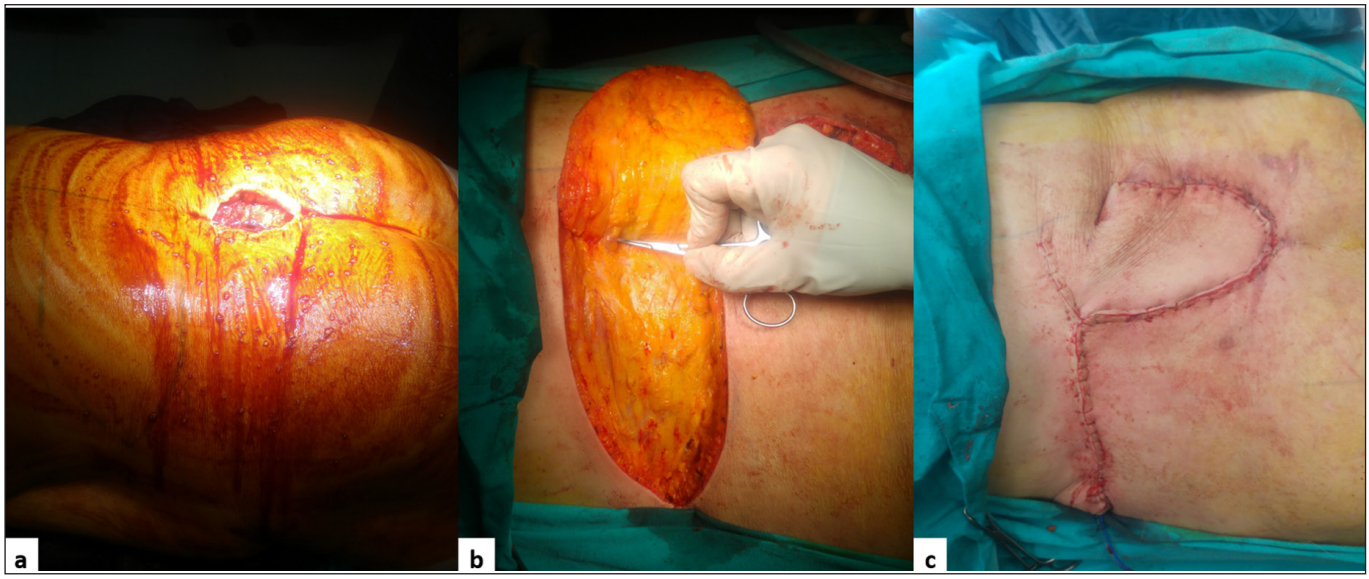

Figure 3 a. Lomber defect after neurosurgical procedure **b.** Flap elevated on one perforator shown at the tip of the clamp **c.** After closure

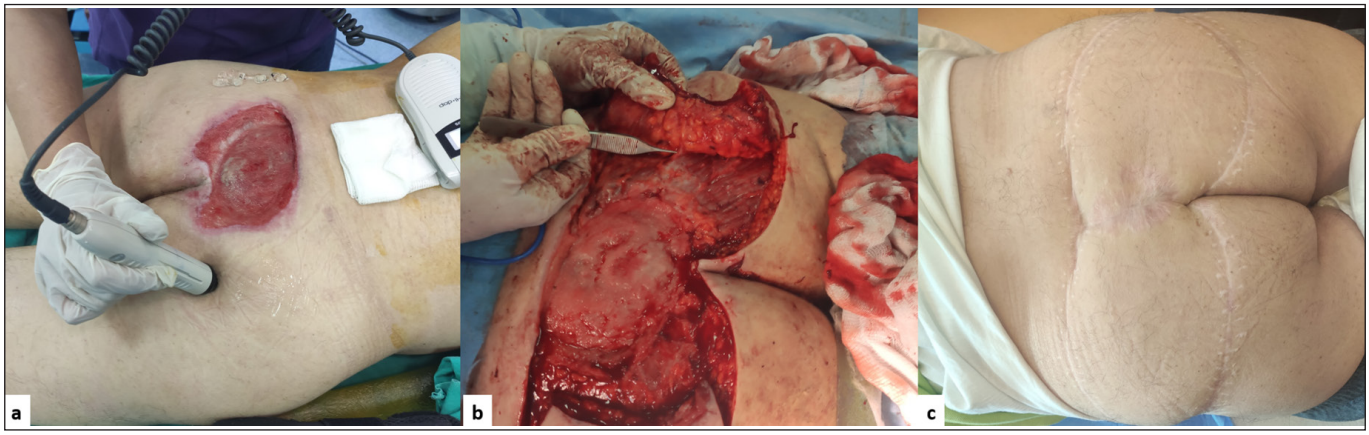

Figure 4 a. Sacral pressure sore , perforators are mapping with the handheld doppler **b.** Bilateral flaps were raised on a single perforator in each side, the perforator on the left side shown at the tip of the penset **c.** Postoperative 10 months

was left. Perforator vessels were detected with a handheld Doppler bilaterally in the gluteal regions and perforator based V-Y advancement flaps were raised on a single perforator ,bilaterally . The donor sites were closed primarly .Postoperative course was uneventful (**Figure 4 a,b,c**).

DISCUSSION

With the emergence of perforator flap concept, restrictions arising from conventional flap flap planning have been eliminated ; such as the length/width ratio for random flaps is no longer required for perforator flaps baceuse a perforator flap size can be planned according to the defect size (1,9,10). There is no need for inclusion of subfascial plexus in order to increase the perforator flap viability; and the flap thinning can be performed as wanted while preserving functional structures. Location-specific flap design is no longer necessary since a perforator flap can be harvested anywhere in the body when there is a detectable perforator.

Perforator flap means by definition that the perforator which nourishes the flap needs to be dissected until the source artery . Therefore, conventional perforator flap operations are sophisticated and long lasting operations. Perforator-based flaps, on the other hand, does not necessitate dissection of the perforator artery up until the source artery but only requires identification and preservation of the perforator artery (2-8). Since there is not a pedicle dissection, it does not require sophisticated microsurgery tools and take a shorter time to perform. Yıldırım et al (3) suggested that suprafascial dissection of the perforator vessels could be enough for the mobilization in the areas with adequate laxity. Furthermore, Kim et al. (2) propounded that in perforator rich areas these flaps could be harvested just by visualizing the perforator vessels without any dissection.

All these advantages of perforator-based flaps put them forward in the clinical practice and many studies are published in respect of their use in different anatomical locations on the body. However, in these studies only the liberty in flap planning that perforator flaps provide us was depicted and a detectable perforator was presented as the only entailment for the surgery (2-8). In this study, we aim to suggest the important points in flap planning apart from presence of detectable perforator; and present the algorithm that we established in the flap planning .

In this study, perforator-based flaps for the face were planned as V-Y advancement flaps; therefore, trapdoor deformity seen in transposition flaps were avoided. Furthermore, we suggest in keeping with literature (11) that V-Y advancement flaps adapt better with relaxed skin tension lines (RSTL) and dynamic skin tension lines (DSTL) providing better esthetic outcomes.

For the sternal and lomber defects, we used perforator-plus transposition flaps. Perforator-plus transposition flap is harvested by preserving skin paddle on the flap base. Preserving skin paddle is suggested to contribute arterial and venous circulation of the flap (12,13). We suggest using perforator-plus transposition flaps on the trunk is quite easy and convenient; also, preserving skin paddle does not interfere with the flap transposition. Dog-ear deformity is not seen as in traditional transposition flaps since dissection at the basis of the perforator is possible providing better mobility. Furthermore, there is not an obligation to follow the rule that length-to-width ratios are not to exceed 3:1 as in random flaps. Literature also shows that perforator-based flaps on the trunk with ratios of 1:4 or 1:5 are totally viable (14,15). This advantage of perforator-based flaps is quite important especially for long defects seen after coronary artery bypass complication since it enables to use a single flap to reconstruct the defect while causing less donor site morbidity.

We come up with partial flap necrosis in all patients reconstructed with perforator-based flaps for their lower extremities. In a study showing 400 the perforators identified in the body it was suggested that 93 of these

perforators are found in the lower extremity (16). On the other hand, necrosis ratio on the lower extremity has been shown higher than the ratios on the other areas of the body in several studies (3,4,17). Our results were also in rapport with these studies. We claim that worse tissue laxity in the lower extremity cause poor flap mobility. Although preserving the perforator ensures better security, too much tension can cause arterial or venous insufficiency endangering the perforator flap viability. Therefore, we suggest not to use perforator-based flaps as the first choice in reconstruction of lower extremity, or at least avoid dissections that can endanger harvesting conventional flaps as backup plan after perforator-based flaps.

Perforator-based V-Y advancement flaps from medial thigh were used for scrotal reconstruction. As regards to large defect size, usually bilateral flaps were planned and used. Although V-Y advancement flaps requires larger incisions compared to transposition flaps, V-Y advancement flaps were preferred since they constitute more natural inguinoscrotal fold which is constantly exposed to friction during walking. Although there are studies showing large linear incisions taking longer time to heal and causing scar contractures (18), we did not encounter any similar problems in our patients.

Perforator-based flaps are especially preferred in patients with pressure ulcers and comorbid diseases since they are harvested quickly decreasing anesthesia duration and side effects. Detection of the perforator provides us to dissect the flap base more extensively allowing increased flap mobility (19,20). Furthermore, Bonomi et al. (21),suggested that perforator bsed V-Y advancement flap can be designed with Pacman modification to enhance soft tissue coverage for the defect. We preferred perforator based flap in a V-Y advancement design essipecially for cachectic patients and when the donor site laxity did not allow primary closure. (Which is checked with pinch test.) Since flap dissection can be made more extensively than the conventional random V-Y advancement flap, these flaps have great mobility thus enabling bigger defects can be covered with smaller flaps. Besides their donor sites can be closed primarily.

In our study, we also showed that comorbidities do not have a significant effect on flap survival (P>0.05). Although number of cases in this study were small to evaluate the effect of patients spesifics on complications , this result conforms with literature. Chih-Hsun et al. (22) showed that local factors have a more significant effect on flap survival than systemic factors. They suggested that perforator vessel size detected during the dissection, its pulsatility, twisting or tension during flap adaptation are the most significant factors affecting flap survival.

This study has some limitations. The small number of cases prevented statistical comparisons. For example there are only three patients who developed complications. All complications were in the lower extremity which is a well defined anatomic localization for complications. It was hard to compare patients' spesifics which can be related with the complications because of the small number.

CONCLUSION

Perforator-based flaps can be designed in any location on the body if there is a detectable perforator present. Since better suits with facial lines, V-Y advancement flaps are preferred on the face; while perforator-plus transposition flaps yield better results on the anterior and posterior trunk. For the lower extremity, flap necrosis rates higher than the other anatomic localisations of the body therefore, perforator-based flaps should not be the first choice for the lower extremity. Nevertheless, if perforator-based flaps are planned to be used anyway, then avoid dissections that can endanger harvesting conventional flaps as backup plan.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Balıkesir University Hospital, Noninvasive Clinical Researches Ethics Committee (Date: 23.02.2022, Decision No: 2022/34).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1114579
J Health Sci Med 2022; 5(4): 1030-1035

The effect of coronavirus disease-2019 (COVID-19) according to gender on health-related quality of life

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Cite this article as: Çiftçi B. The effect of coronavirus disease-2019 (COVID-19) according to gender on health-related quality of life. J Health Sci Med 2022; 5(4): 1030-1035.

ABSTRACT

Aim: The purpose of this study was to evaluate the changes in health-related quality of life of hospitalized patients with the diagnosis of coronavirus disease-2019 (COVID-19) according to gender.

Material and Method: The medical records of 77 patients (37 females and 40 males) who were hospitalized for COVID-19 were examined. Sociodemographic features including age, gender, marital status, comorbid diseases, duration of hospitalization, the period after discharge, symptoms of COVID-19 disease were analyzed. Short Form 36 (SF-36) was applied to all patients for evaluating the health-related quality of life pre and post COVID-19.

Results: The median scores of physical function, bodily pain, vitality, social functioning and general health perceptions before COVID-19 were statistically significantly higher than the scores after COVID-19 in both gender. Social functioning and the scores were lower in females than males for pre and post COVID-19 period and the differences were statistically significant.

Conclusions: The findings of this study revealed that health-related quality of life is affected by COVID-19 for both genders, mostly females.

Keywords: Coronavirus, COVID-19, health-related quality of life, quality of life

INTRODUCTION

Coronavirus disease-19 (COVID-19) was first seen in December 2019 in Wuhan, China. After the rapid spread of disease all over the world, it was defined as a pandemic by the World Health Organization on March 11, 2020 (1). Until January 7, 2022, 298.915.721 confirmed cases of COVID-19, and 5.469.303 deaths were detected globally (2). Fever, productive cough, headache, exhaustion, loss of smell, and taste are the most common acute respiratory symptoms in COVID 19 patients. Most of patients have mild diseases, but in some patients the disease can be cause serious illness and result death (3,4). The exact pathophysiological mechanism of COVID-19 is unknown. Many studies are ongoing regarding the treatment and long – term effects of COVID-19 disease (5).

In Turkey, as many countries, various restrictions including closing the schools, staying at home especially over the age of 65, working from home as much as possible have been taken to prevent the spread of disease (6). During the pandemic period, psychological problems such as anxiety, sleep problems, and increased sense of loneliness due to social isolation had been seen in many people (7). As past outbreaks of infectious diseases, COVID- 19 had negative effects on physical, social and psychological functions of individuals and many studies showed that there are deteriorations in health-related quality of life due to COVID-19 (8,9).

There are many studies about COVID-19 and health-related quality of life. However, in the literature studies about health-related quality of life before and after COVID-19 and its relationship with gender are limited. The purpose of this study to investigate the alterations in health-related quality of life in hospitalized patients with the diagnosis of COVID-19 disease according to gender.

MATERIAL AND METHOD

The study was carried out with the permission of Tekirdağ Namık Kemal University Non-interventional Clinical Researches Ethics Committee (Date: 29/06/2021, Decision No: 2021.180.06.10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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Received: 10.05.2022 **Accepted:** 07.06.2022

Study Design and Setting

In addition, since the study protocol is related with the COVID-19 outbreak, approval was obtained from the Ministry of Health of the Republic of Turkey. The participants were informed about the aim of the study before applying the study, all participants were asked whether they accepted to complete the study and thus all participants have declared voluntary for the study.

Participants

The hospital records were examined and it was determined that there were ninety patients who were hospitalized for COVID-19 disease between April 2021 and November 2021. All patients were planned to be included to study but four patients were died because of COVID-19 in other hospitals or other reasons. Nine patients could not be reached by phone. Remaining seventy-seven patients were enrolled to the study. All patients were contacted by phone and the information about the study was obtained to all patients. All patients were asked ıf they want to accept study.

Sociodemographic features including age, gender, marital status, comorbid diseases, duration of hospitalization, the period after the discharge, symptoms of COVİD-19 were analyzed. Short Form 36 (SF-36) was applied to all patients for evaluation the health-related quality of life pre and post COVID-19. SF-36 has eight sections that include general health (5 items), vitality (4 items), physical functioning (10 items), bodily pain (2 items), physical role functioning (4 items); emotional role functioning (3 items); mental health (5 items); and social functioning (2 items). The total score was obtained the combination of the eight sections. And a higher score is associated to a higher quality of life. The SF-36 was adapted into Turkısh in1999 by Koçyiğit H et al. (10) and the study results suggest it is useful for clinical studies.

Statistical analysis

Continuous variables were declared as mean±standard deviation and median (minimum–maximum), whereas categorical data were numbers and percentages. The Kolmogorov-Smirnov goodness-of-fit test was used to perform normality analyses in the cross-group analysis of continuous variables. The groups with normal distribution of continuous variables were evaluated with the independent samples t-test. Cross-group comparisons of variables not eligible for normal distribution were analyzed with the Mann-Whitney U test. The chi-square test (Fisher's exact test when necessary) was used in the comparison of categorical data. To verify the behavior of the numerical variables within groups the Wilcoxon test was used. The analyses were performed with the Statistical Package for the Social Sciences (SPSS) software program version 22.0 (IBM Corporation, Armonk, NY, USA). The statistical significance level was set at $p<0.05$.

RESULTS

A total of 77 patients, including 37 females and 40 males, were enrolled in the study. The mean age of the female and male patients were 48.86±16.12 and 45.82±14.44, respectively. The patients were grouped based on gender. The differences between groups were statistically significant ($p=0.02$). However, there were no statistically significant differences between the two groups in terms of duration of hospitalization, duration after discharge, marital status, comorbidities, smoke ($p>0.05$). Also there were no statistically significant differences between groups according to the symptoms of COVID-19 including fever, cough and sputum, dry cough, fatigue, wheezing, headache, nasal congestion, nausea and vomiting, tiredness, dyspnea, flank pain, backache, loss of smell, myalgia, sore throat, chest pain and the diagnostic findings of COVID-19 as the PCR test and the findings of thorax CT ($p>0.05$). Comparisons of the demographic and some clinical features of the patients by groups are presented in **Table 1**.

Comparison of the mean values of SF-36 subscales between females and males and within females and males are shown in **Table 2**. The median scores of physical function, bodily pain, vitality, social functioning mental health scores and general health perceptions in before COVID-19 were statistically significantly higher than the scores after COVID-19 in females ($p=0.019$, $p=0.002$, $p=0.005$, $p<0.001$, $p=0.007$, and $p=0.012$ respectively). Similarly, the median scores of physical function, bodily pain, vitality, social functioning and general health perceptions in before COVID-19 were statistically significantly higher than the scores after COVID-19 in males ($p=0.001$, $p=0.001$, $p=0.005$, $p<0.001$, and $p=0.005$ respectively).

When the subscales score of females and males before COVID-19 were compared, there were statistically significant differences between the groups in terms of bodily pain, social functioning and the scores were lower in females than males ($p=0.003$ and $p=0.001$ respectively). The bodily pain and social functioning scores of female were lower than the scores of males after COVID-19 disease, the differences were statistically significant ($p=0.11$ and $p<0.001$ respectively).

Table 1. Demographic and clinical characteristics of the study group

		Females (n=37)	Males (n=40)	P
Age (years)		48.86± 16.12	45.82 ±14.44	0.386*
Duration of hospitalization		5.24±0.46	5.4±0.48	0.959**
Duration after discharge		121.27±11.81	138.5±11.42	0.076**
Marital status	Married Single	30 (81.1%) 7 (18.9%)	34 (87.5%) 5 (12.5%)	0.53***
Comorbidity	No Hypertension DM Cardiovascular disease Fibromyalgia COPD RA Cancer Hypothyroid	22 (59.5%) 6 (16.2%) 6 (16.2%) 1 (2.7%) 0 1 (2.7%) 0 0 1 (2.7%)	26 (65%) 3 (7.5%) 5 (12.5%) 3 (7.5%) 1 (2.5%) 0 1 (2.5%) 1 (2.5%) 0	0.5***
Smoke	Yes No	5 (13.5%) 32 (86.5%)	10 (25%) 30 (75%)	0.20**
Working status	Yes No	16 (43.2%) 21 (56.8%)	30 (75%) 10 (25%)	0.02**
Fever	<37.3 37.3-38.0 38.1-39.0	28 (75.7%) 9 (24.3%) 0	23 (57.5%) 15 (37.5%) 2 (5%)	0.14**
Cough and sputum	Yes No	18 (48.6%) 19 (51.4%)	23 (57.5%) 17 (42.5%)	0.44**
Dry Cough	Yes No	21 (56.8%) 16 (43.2%)	21 (52.5%) 19 (47.5%)	0.71**
Fatigue	Yes No	18 (48.6%) 19 (51.4%)	22 (55%) 18 (45%)	0.58**
Wheezing	Yes No	21 (56.8%) 16 43.2%)	16 (40%) 24 (60%)	0.14**
Headache	Yes No	16 (43.2%) 21 (56.8%)	15 (37.5%) 25 (62.5%)	0.61**
Nasal congestion	Yes No	8 (21.6%) 29 (78.4%)	9 (22.5%) 31 (77.5%)	0.92**
Nausea and Vomiting	Yes No	2 (5.4%) 35 (94.6%)	1 (2.5%) 39 (97.5%)	0.51**
Tiredness	Yes No	33 (89.2%) 4 (10.8%)	30 (75%) 10 (25%)	0.10**
Dyspnea	Yes No	12 (32.4%) 25 (67.6%)	16 (40%) 24 (60%)	0.49**
Flank pain	Yes No	0 37 (100%)	1 (2.5%) 39 (97.5%)	0.33**
Backache	Yes No	29 (78.4%) 8 (21.6%)	35 (87.5%) 5 (12.5%)	0.28**
Loss of Smell	Yes No	8 (21.6%9 29 (78.4%)	9 (22.5%) 31 (77.5%)	0.92**
Myalgia	Yes No	15 (40.5%) 22 (59.5%)	11 (27.5%) 29 (72.5%)	0.23**
Sore throat	Yes No	4 (10.8%) 33 (89.2%)	10 (25%) 30 (75%)	0.10**
Chest pain	Yes No	4 (10.8%) 33 (89.2%)	3 (7.5%) 37 (92.5%)	0.61**
Thorax CT	Normal Single lobe Multıple lobe	8 (21.6%) 15 (40.5%) 14 (37.4%)	7 (17.5%) 16 (40%) 17 (42.5%)	0.87***
PCR	Positive Negative	22 (59.5%) 15 (40.5%)	24 (60%) 16 (40%)	1***

*T test, ** Mann Whitney u test, *** Chi-square Test (aFisher's exact test), DM, Diabetes Mellitus; COPT, chronic obstructive pulmonary disease; RA, Rheumatoid arthritis; , CT, computerized tomography;PCR, Polymerase chain reaction

Table 2. Comparison of the Short Form 36 subscale scores features among groups

Variables	Females (n=37)			Males (n=40)			Pre COVID-19 Two groups	Post COVID-19 Two groups
	Pre COVID-19	Post COVID-19	p	Pre COVID-19	Post COVID-19	p	p	p
Physical function	90.94±3.11	87.43±2.82	0.019**	96.0±1.60	90.81±2.42	0.001**	0,569*	0,259*
Role-physical	95.54±2.33	93.24±3.16	0.109**	99.37±0.62	97.5±1.74	0,180**	0,136*	0,198*
Bodily pain	83.78±2.20	76.14±2.81	0.002**	92.12±1.82	85.37±2.54	0.001**	0,003*	0,011*
Vitality	73.58±1.52	69.66±2.15	0.005**	76.87±1.33	73.22±1.48	0.005**	0,133*	0,449*
Social functioning	77.9±2.93	63.51±3.62	<0.001**	90.81±2.06	79.87±3.22	<0.001**	0,001*	<0.001*
Role-emotional	97.29±1.99	96.39±2.15	0.317**	100±0.0	100±0.0	1**	0,139*	0,068*
Mental health	75.89±1.29	72.75±1.78	0.007**	76.1±1.29	74.66±1.32	0,071**	0,978*	0,739*
General health perceptions	66.40±2.50	63.02±2.45	0.012**	72.72±2.25	69.47±2.38	0.005**	0,083*	0,069*

*Mann Whitney u
** Wilcoxon signed-rank test

DISCUSSION

The effect of COVID-19 on the health-related quality life at patients hospitalized for COVID-19 and discharged was investigated in this study. The findings of this study may be considered that COVID-19 affects the health-related quality of life especially on physical function, bodily pain, vitality, social functioning, mental health and general health perceptions ın both genders but especially females had lower bodily pain and social functioning scores after COVID-19.

COVID-19 is a respiratory disease that affects not only the lungs but also the kidney, heart, musculoskeletal system, and other systems (11). Studies on the process of the disease and the treatment continue. Studies conducted so far have determined that many risk factors such as obesity, comorbidities such as cardiovascular diseases, diabetes mellitus, immune deficiencies, and age are associated with the severity of the disease and the delayed recovery period after the disease (12). Severe acute lung injury may be important factor associated with delayed recovery period. A study revealed that the degree of acute lung injury is associated with the measures of pulmonary and physical function at 6 months. However, the same study showed that persistent physical and mental ill health and cognitive impairment are not directly related to severity of acute lung injury (13). Also there can be other unknown factors that create differences in patients' recovery period. In the literature, it has been shown that female gender is a risk factor that delays the COVID-19 recovery process and on the other hand male gender is a risk factor to have more severe acute illness (13,14). It is showed with many studies that there is a relationship between COVID-19, autoimmunity, inflammation and preexisting autoantibodies (15). In addition, it is known that many autoimmune diseases, especially in middle aged women (16), ant-cytokine and tissue – specific autoantibodies and many others have been had a relationship with post COVID-19 syndromes (17,18). Thus the difference of COVID-19 recovery period for genders may be impact of health-related quality of life.

As it is known health –related quality of life is defined as a combination of the patient's physical, mental, emotional and social well-being at the perceptual level (19). Since COVID-19 is a multisystem disease, it affects health-related quality of life. A meta-analysis supported that 58% of the post-COVID-19 patients had poor quality of life (20). Another study that enrolled with 101 COVID-19 patients underwent pulmonary function and SF-36 showed that especially impairment was detected on scores of physical role limitation, physical function and vitality. Also, the study conducted that all domains of health-related quality of life except bodily pain is associated with low lung capacity (21).

Another important issue to be considered is post-acute COVID-19 syndrome may be impact physical and cognitive function, health-related quality of life, and participation in society (22). Many studies explained that post-acute COVID-19 syndrome which is associated with post-traumatic distress syndrome (PTSD) may be the potential reason for poor quality of life (23-27). PTSD after COVID-19 depends on fear, worry, being far away from relatives and also PTSD may be seen at higher incidence in people with comorbidities (28). Also it's known that females are prone to psychological problems such as depression, anxiety and PTSD more than males (29).

The disease itself, as well as the various restrictions taken by the states to prevent the spread of the disease, have also affected the recovery process of patients, especially their mental and physical functions (30). The current study

shows that health-related quality of life subscales scores are statistically significant lower in females than in males in the pre and post COVID-19 period. In addition, it was determined that the distribution within the group in terms of gender was lower in females. Hospitalization with COVID-19 can cause mental problems such as depression and anxiety (31). The social isolation and quarantine process that occurred with the COVİD-19 affected all individuals, especially women. The impact of working from home, childcare, shopping and housework may have been felt more in women and may have caused anxiety and depression (32). Most of the women in the current study are not working. This is an important factor that reduces social functionality. A study with 409 COVID-19 patients supported the current study as males had the scores of quality of life higher than females and also the same study showed that the employed patients had higher quality of life scores than unemployed patients (23).

There are some study limitations to consider: First, the small size of the study group and the inability to deal with COVID 19 risk factors and disease parameters in detail. Second; the effects of social isolation and the restrictions on physical and mental health were not assessed. Lastly, physical activities and exercise habits were not evaluated. Thus, the relationship between physical activities and health-related quality of life could not be reviewed.

CONCLUSION

Health-related quality of life may be affected on average after 4 months in people who had COVID-19 disease and complete the treatment process in the hospital, and especially the female gender carries a greater risk. In this process, where COVID-19 continues with it is new variants, studies with large samples are needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Tekirdağ Namık Kemal University Non-interventional Clinical Researches Ethics Committee (Date: 29/06/2021, Decision No: 2021.180.06.10).

Informed Consent: Informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declare that she has all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1093776
J Health Sci Med 2022; 5(4): 1036-1043

Atrial electromechanical delay is impaired in patients with COVID-19

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Cite this article as: Yılmaz Y, Keleşoğlu Ş, Sulaiman J, Elcik D. Atrial electromechanical delay is impaired in patients with COVID-19. J Health Sci Med 2022; 5(4): 1036-1043.

ABSTRACT

Background: COVID-19 infection has the potential to affect the cardiovascular system. Intra/ interatrial electromechanical delay (EMD) demonstrated by P wave dispersion (PD) and tissue doppler echocardiography (TDE) is related to the development of atrial fibrillation. This study aimed to investigate atrial conduction time by PD and TDE in patients with COVID-19.

Material and Method: A total of 143 participants were selected in the current study. The COVID-19 group included 90 subjects and the control group included 53 individuals. Two groups were compared with each other, in terms of electrocardiographic P wave measurements, and atrial electromechanical coupling (AEC) parameters by TDE.

Results: Maximum P-wave duration (Pmax) and PD were significantly higher in COVID-19 patients compared to the control group ($p<0.001$, for both). Interatrial and intraatrial EMD were also longer in the COVID-19 patients compared to control group ($p<0.001$, for both). Correlation analysis revealed a significant and positive correlation between CRP with Pmax, PD, interatrial and intraatrial EMD ($r=0.608$, $p<0.001$; $r=0.708$, $p<0.001$; $r=0.692$, $p<0.001$; $r=0.697$, $p<0.001$, respectively). Besides, a positive and significant relationship was also found between the interatrial and intraatrial EMD with PD and Pmax ($p<0.001$, for all).

Conclusion: Atrial EMD parameters were prolonged in patients with COVID-19. The measurement of atrial EMD parameters might be used to determine the risk of AF development in patients with COVID-19.

Keywords: Atrial fibrillation, COVID-19, atrial electromechanical delay

INTRODUCTION

Although COVID-19 primarily presents with acute pneumonia and severe respiratory distress syndrome, cardiovascular involvement including new onset atrial fibrillation (NOAF) has also been reported extensively. Acute cardiovascular events such as arrhythmias that complicate the clinical course of SARS-CoV-2 may be one of the causes of poor survival (1-3).

The most common rhythm disorder in clinical practice, atrial fibrillation (AF), is critical owing to the associated hemodynamic disorders and thromboembolic events (4). Even though the exact mechanisms that cause AF are not fully understood, several risk factors including age, hypertension (HT), coronary artery disease (CAD), cerebrovascular disease, and diabetes are supposed to play roles in the development of AF (5). Moreover, accumulating evidence has shown that inflammation and inflammatory factors, the autonomic nervous system, and oxidative stress play a significant role in AF pathogenesis (6,7).

COVID-19 infection can cause direct myocardial cell injury, myocardial oxygen supply/demand mismatch, hypoxia, enhanced systemic inflammation and catecholamine surge, increased thrombosis, and oxidative stress imbalance, which may all be related to the occurrence of AF (8-10). Therefore, the risk of NOAF due to all these mentioned mechanisms may increase in COVID-19.

The atrial conduction time (ACT) represents the interval between sinus impulses and atrial mechanical contraction. A noninvasive alternative to invasive electrophysiological measurements is tissue Doppler echocardiography (TDI) (11). Prolonged intraatrial and interatrial conduction time, called atrial electromechanical delay (EMD), is associated with a higher risk of AF (12). It has also been shown that P wave dispersion (PD) and maximum P wave duration (Pmax) can be electrocardiographically (ECG) noninvasive determinants of atrial fibrillation (13).

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Received: 26.03.2022 **Accepted:** 08.06.2022

To our knowledge, there is no study evaluating atrial conduction abnormalities in COVID-19 using noninvasive tests such as TDI and ECG. This study aimed to determine atrial conduction abnormalities and factors affecting atrial conduction time in COVID-19 patients.

MATERIAL AND METHOD

Approval for the study was granted by Kayseri City Hospital Clinical Researches Ethics Committee (Date: 25.06.2020, Decision No: 134). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. All patients signed the free and informed consent form.

The present study is a prospective single-center study conducted in an institute that accepts patients diagnosed with COVID-19 with polymerase chain reaction (PCR) tests and designated as a 'COVID-19 Hospital' by the Turkish Ministry of Health.

According to the definitions in the "COVID-19 Diagnosis and Treatment Guide" printed by the Turkish Ministry of Health (14), the clinical definition of patients was as follows: Mild illness presents with features such as fever, muscle/joint pain, cough, sore throat, and nasal congestion without pneumonia. Severe illness is defined as widespread findings of pneumonia in computed tomography (CT). Critical illness defines the requirement of the Intensive Care Unit (ICU). The routine criteria for ICU admission at our center were as follows (according to Ministry of Health guidelines); Signs conclusive for severe respiratory failure, including having an SpO_2 of ≤ 90% in ambient air, need for ≥ 6 L O_2/min, need for non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV).

The first electrocardiogram (ECG) recording of patients at the time of hospital admission were analyzed and conventional echocardiographies were performed. At that time, no patient was receiving any medical treatment. The patients in our study group consisted of patients with severe illness, older than 18 years of age, and having sinus rhythm at admission according to 12-lead electrocardiogram (ECG). We excluded patients with mild illnesses and patients in requirement of ICU on admission. Patients were also excluded from the study if any of the following criteria applied: a history of coronary artery disease (CAD), heart failure, arterial hypertension (HT) and diabetes mellitus (DM), LV ejection fraction (EF) less than 50%, primary cardiomyopathy, valvular heart disease, a history of AF, dysrhythmia, bundle branch block, atrioventricular conduction abnormalities on ECG, thyroid dysfunction, anemia, electrolyte imbalance, renal failure, who have previously tested positive for covid-19 pcr and/or have a history of severe flu symptoms, who have positive troponin results during hospitalization and poor quality echocardiographic and ECG imaging. A total of 199 hospitalized patients with COVID-19 diagnosis between september and december 2020 in our hospital were evaluated. One hundred nine patients who met the exclusion criteria were excluded from the study. The remaining 90 patients were included in the study. Fifty-three age- and sex-matched healthy volunteers with no previous positive covid-19 pcr test and/or no history of severe flu symptoms were randomized for comparison.

In order to show the poor statistical power of arrhythmias in covid-19 studies, a number of studies were selected for post hoc testing on the sample size in order to determine the achieved power. Gpower 3.1.9.4 program was used for calculation (3). Significance level and statistical power were set at 0.05 and 0.80 respectively. In the power analysis, it was concluded that a total of 119 participants (study and control groups) were sufficient.

On admission, a detailed medical history, 12-lead electrocardiography, complete blood count, serum biochemistry and detailed transthoracic echocardiographic examination were obtained from all patients before starting medical treatment. Blood pressure and oxygen saturation values during the echocardiographic examination were recorded. The presence of pneumonia was confirmed by computerized tomography imaging (CTI) within 24 h of hospital admission for all patients. The radiological appearance on CTI of the patients was diffuse infiltration.

The standard SARS-CoV-2 infection treatment protocol recommended by the Science Advisory Board of the Turkish Ministry of Health, including Oseltamivir phosphate 75 mg twice daily, and azithromycin 250 mg once daily (following a 500 mg loading dose), were administered to all patients.

Electrocardiography

ECG recordings were performed simultaneously by a Philips brand machine electrocardiography (ECG) device, including at least 3 QRS complexes for each derivation, at 25 mm / sec speed, 1 mV amplitude, and standard 12 leads. P wave duration in all derivations was measured manually with calipers and magnifying lenses to reduce error in measurements. P wave origin was taken as the point where the P wave crosses the isoelectric line. The endpoint was taken as the intersection of the isoelectric line and the end point of the P wave. The maximum P wave duration was accepted as the longest P wave and the longest atrial conduction time. The difference between the longest p wave (Pmax) and the shortest p wave (Pmin) was considered as P wave dispersion (PD=Pmax-Pmin) (15,16). All calculations were evaluated separately by two different cardiologists, who were unaware of the patients' clinical characteristics, in a single-blind fashion. The average of these two values was accepted as P wave dispersion and maximum P wave duration.

Echocardiography

Conventional echocardiography was performed with 2-dimensional, M-mode, pulsed wave, continuous color Doppler and tissue Doppler imaging using a Vivid 7 pro ultrasound system (Vivid 7 pro, GE, Horten, Norway, 2-4 MHz phased array transducer ultrasound system). Simultaneous ECG recording was done. All patients were in sinus rhythm at the time of examination. Conventional echocardiographic images were obtained from the parasternal and apical views according to the guidelines of the American Society of Echocardiography (17). Left ventricular (LV) diameters and wall thickness were measured from the para- sternal views by M-mode echocardiography. The Simpson's method was used for the calculation of LV ejection fraction. Right ventricular (RV) systolic function was determined by measuring tricuspid annular plane systolic excursion (TAPSE) using the M-mode technique. While the left atrial area (LAA) was measured from the apical 4-chamber view at the end-ventricular systole, LA diameter was measured from the parasternal long axis view. While the maximal LA volume was performed by applying Simpson's rule from apical 4 chamber imaging, the maximal right atrial (RA) volume was calculated by apical 4-chamber views using the area -length method. LV end-systolic and diastolic volumes were also calculated by 4-chamber views using the area - length method. Mitral inflow velocities were measured from apical views.

Atrial Electromechanical Time Measurement

TDI was performed using transducer frequencies of 3.5–4.0 MHz. The spectral pulsed Doppler signal filters were adjusted until a Nyquist limit of 15–20 cm/s was obtained. The minimal optimal gain was used. Myocardial TDI velocities [peak systolic (S'), early diastolic (E'), and late diastolic velocities (A')] were measured with a spectral pulsed Doppler from the apical 4-chamber view. The PW Doppler measurements were evaluated separately from the LV lateral mitral and LV septal mitral, RV tricuspid annulus.

The ultrasound beam slope did not exceed 15% in acquiring the optimal angle of imaging. The monitor sweep speed was adjusted at 50–100 mm/s to optimize myocardial velocities' spectral display. Atrial EMD was defined as the time interval from the onset of atrial electrical activity (P wave on surface ECG) to the beginning of mechanical atrial contraction (late diastolic A wave) (**Figure 1**). All values were averaged over three consecutive beats. Atrial EMD was measured from the lateral mitral annulus called 'PA lateral,' from the septal mitral annulus, called 'PA septal,' and from the right ventricle tricuspid annulus, called 'PA tricuspid.' Interatrial EMD was calculated as the difference between PA lateral and PA tricuspid, right intraatrial EMD was calculated as the difference between PA septum and PA tricuspid and left intraatrial EMD was calculated as the difference between PA lateral and PA septum (11).

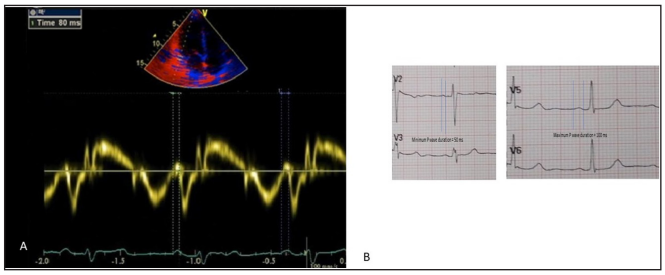

Figure 1. Operational duration according to the groups

A total of 20 participants, 10 from the patient group and 10 from the control group, were randomly selected to evaluate the intra-observational variability. Measurements were repeated under the same baseline conditions. Intra-observer variability was 3.2% for lateral PA, 3.6% for septal PA, and 4.3% for tricuspid PA, respectively.

Statistical Analysis

Statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) software for Windows. The distribution of quantitative variables was checked with the Kolmogorov-Smirnov test. Descriptive data were given as mean ± standard deviation, depending on the normality of distribution. Median and interquartile ranges were given when the variable did not follow a normal distribution. The independent sample t-test was used to compare normally distributed quantitative variables, and the Mann-Whitney U test was used to compare non-normally distributed quantitative variables. Categorical variables were compared with the chi-square test. The relationship between the variables was analyzed by Spearman correlation analysis. A P-value less than 0.05 was considered significant.

RESULTS

A total of 143 participants were selected in the current study. The COVID-19 group consisted of 90 subjects (63 male), and the control group included 53 individuals (34 male).

Baseline laboratory measurements and demographic features of the study groups are presented in **Table 1**. The study population was similar regarding sex distribution and age and there were no significant differences between the patients and the control group ($p > 0.05$).

Table 1. Baseline clinical and laboratory measurements of the study groups

Variables	Control Group (n=53)	Covid Group (n=90)	p value
Age (years)	54 (41-62)	52 (44-66)	0.568
Male/female	34 (64%)	63 (70%)	0.470
Glucose (mg/dL)	94 (83-116)	100 (88-113)	0.312
Creatinine (mg/dL)	0.82±0.16	0.87±0.25	0.200
AST (U/L)	22.5±5.7	21.4±7.8	0.119
ALT (U/L)	22.3±10	23.1±8.1	0.748
Total Bilirubin (mg/dL)	0.60±0.3	0.59±0.3	0.867
White Blood Cell (10^3/uL)	8.7 (7.14-9.83)	14.5 (9.3-19)	<0.001
Hemoglobin (g/l)	14.8±1.4	14.7±1.4	0.598
Platelet (/mm^3)	256 (199-300)	240 (215-295)	0.736
C-Reactive Protein (CRP)	3.2 (1.6-5.4)	16.6 (6.9-55.9)	<0.001
Neutrophils/Lymphocytes ratio (NLR)	1.9 (1.3-3.1)	4.7 (2.9-8.0)	<0.001
Systolic blood pressure	120.1±11.8	123.8±11.7	0.157
Diastolic blood presure	75.2±6.9	76±7.6	0.556
Oxygen saturation	97±0.9	92.4±1.2	<0.001

Serum C-reactive protein (CRP), white blood cell (WBC) levels and neutrophils/lymphocytes ratio (NLR) were significantly higher in COVID-19 patients (CRP; 16.6 (6.9-55.9) vs. 3.2 (1.6-5.4), p<0.001, WBC; 14.5 (9.3-19) vs. 8.7 (7.1-9.8), p<0.001, NLR; 4.7 (2.9-8.0) vs 1.9 (1.3-3.1), p< 0.001, respectively). Other blood parameters were similar between groups. Troponin values in COVID-19 patients were within the normal range. There were no differences between the groups.

The electrocardiographic parameters of the groups are shown in **Table 2**. Pmax and PD were significantly higher in COVID-19 patients when compared to the control groups (Pmax ;106.3±10 ms vs. 98.8±10 ms, p<0.001, PD; 46±10 ms vs. 39±11 ms, p<0.001) (**Figure 2**). Pmin was similar between the groups (p=0.596).

Table 2. Electrocardiographic Characteristics of the study population

Variables	Control group (N=53)	COVID group (n=90)	value
Heart Rate (min)	76.7±9.3	77.3±8	0.657
P Max (ms)	98.8±10	106.3±10	<0.001
P Min (ms)	60.4±5.3	60.9±7.2	0.596
PD (ms)	39±11	46±10	<0.001

Min: Minute, ms=millisecond, Pmax=maximum P-wave duration, Pmin=minimum P-wave duration, PD=P-wave dispersion

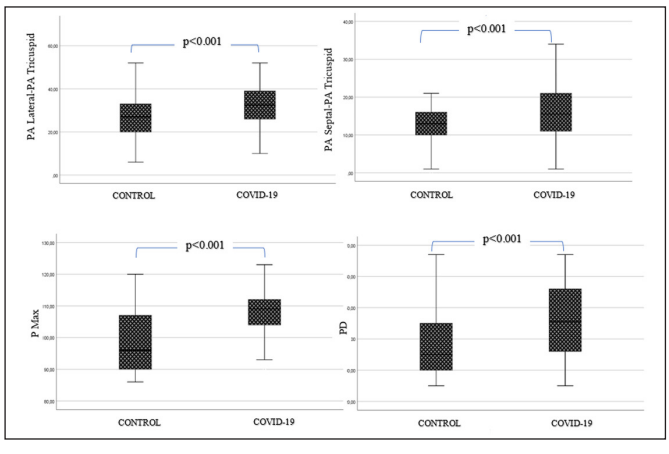

Figure 2. Change of PD, P max, PA Lateral -PA Tricuspid and PA Septal-PA Tricuspid between study groups

Echocardiographic and atrial electromechanical time parameters are shown in **Table 3**.

Table 3. Echocardiography Characteristics of the study population

Variables	Control group (N=53)	COVID group (n=90)	p value
LA Diameter, cm	3.37±0.28	3.43±0.29	0.230
LA area	21.8±2.1	22±2.2	0.729
LA volume, ml	36.4±3	37±3.1	0.230
LVED volume, ml	102.9±5.7	101.2±5.5	0.077
LVES volume, ml	34.4±4.5	35±5.4	0.519
LVEDD, cm	4.73±0.39	4.67±0.40	0.391
LVESD, cm	3.05±0.4	3.08±0.3	0.641
IVSD, cm	1.06±0.12	1.07±0.13	0.768
PWD, cm	1.03±0.9	1.04±0.1	0.598
LVEF, %	67.9±5.7	66.2±5.5	0.077
RA volume, ml	32.8±3.1	33±3.4	0.726
TAPSE, mm	23.4±2.1	23.5±2.2	0.729
PA Lateral, ms	61.4±9.3	64.6±12.3	0.110
PA Septum, ms	48.4±8.3	50.3±9.3	0.219
PA Tricuspid, ms	36.3±8.7	35.3±7.5	0.448
PA Lateral-PA Tricuspid (Interatrial delay)	26.6±10.3	32.3±11.5	<0.001
PA Septal-PA Tricuspid (Right intraatrial delay)	12.5±7.6	16.5±8.0	<0.001
PA Lateral-PA Septal (Left intraatrial delay)	13.2±9.1	14.4±9.3	0.448
E velocity	72±10	73±13	0.611
A velocity	56±16	60±16	0.249
DT,ms	182.6±37.1	183.8±33.1	0.851
Lateral (s') cm/s	11.5±3.3	11.5±2.7	0.997
Lateral (e') cm/s	13.8±3.3	13±2.7	0.109
Lateral (a') cm/s	9.8±2.3	10.2±2.3	0.410
Septal (s') cm/s	7.1±1.8	7.1±1.3	0.950
Septal (e') cm/s	7.9±3.4	8.2±2.2	0.546
Septal (a') cm/s	7.4±3.4	7.7±2.2	0.539
Tricuspid (s') cm/s	14.5±3.3	14±3.5	0.403
Tricuspid (e') cm/s	16.3±3.3	15.5±2.7	0.098
Tricuspid (a') cm/s	13.7±2	13.4±3.1	0.534

LA=Left atrium; LVEDD=LV end-diastolic dimension; LVESD=LV end-systolic dimension; IVSD=interventricular septum thickness; PWD=posterior wall thickness; LVEF=LV ejection fraction; RA=right atrium, TAPSE= tricuspid annular plane systolic excursion, DT=deceleration time. S': systolic myocardial flow; E': early myocardial diastolic flow; A': late myocardial diastolic flow. Interatrial delay: PA lateral – PA tricuspid. Right Intraatrial delay: PA septum – PA tricuspid. Left intraatrial delay: PA lateral – PA septum.

LV systolic and diastolic diameters, interventricular septum, LV posterior wall thickness, and LV ejection fraction were similar in all groups (p= 0.641, p=0.391, p=0.768, p=0.598, and p=0.077, respectively). No significant difference was observed between the groups between the left atrium diameters, and DT, one of the parameters showing left ventricular diastolic functions (p=0.230 vs. p=0.851, respectively). Moreover, other echocardiographic parameters were similar between groups (**Table 3**).

In tissue Doppler examination (TDI) and atrial electromechanical delay (AEMD) parameters (PA lateral, PA septum, and PA tricuspid) were similar between groups (PA lateral; 64.6±12.3 ms vs. 61.4±9.3 ms, p=0.110, PA septum; 50.3±9.3 ms vs. 48.4±8.3 ms, p=0.219, PA tricuspid; 35.3±7.5 vs. 36.3±8.7, p=0.448).

Interatrial EMD (PA Lateral–PA Tricuspid) and right intraatrial EMD (PA Septum–PA Tricuspid) were longer in the COVID-19 patients when compared to the control group (interatrial: 32.3±11.5 ms vs. 26.6±10.3 ms, p<0.001; right intraatrial: 16.5±8.0 ms vs 12.5±7.6 ms, p<0.001) (**Figure 2**). Left intraatrial EMD time was similar between groups (p=0.448). Correlation analysis revealed a significant and positive correlation between CRP with Pmax, PD, interatrial and right intraatrial EMD (r=0.608, p <0.001; r=0.708, p<0.001; r=0.692, p<0.001; r=0.697, p<0.001, respectively) (**Figure 3**). A similar relationship was also observed between NLR and Pmax, PD, and interatrial and intraatrial EMD (r=0.567, p<0.001; r=0.676, p<0.001; r=0.687, p<0.001; r=0.681, p<0.001, respectively).

In addition, a positive and significant relationship was found between the interatrial EMD with PD and Pmax (r=0.660, p<0.001 vs. r=0.623, p<0.001, respectively). A similar relationship was also observed between intraatrial EMD with PD and Pmax (r=0.706, p<0.001 vs. r=0.574, p<0.001, respectively) (**Figure 4**) .

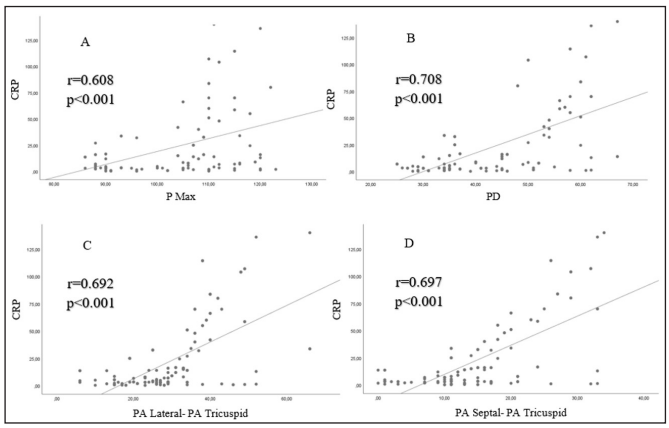

Figure 3. (A) Correlation between P max and CRP count. (B) Correlation between CRP and PD. (C) Correlation between CRP and PA Lateral- PA Tricuspid, (D) Correlation between CRP and PA Septal- PA Tricuspid

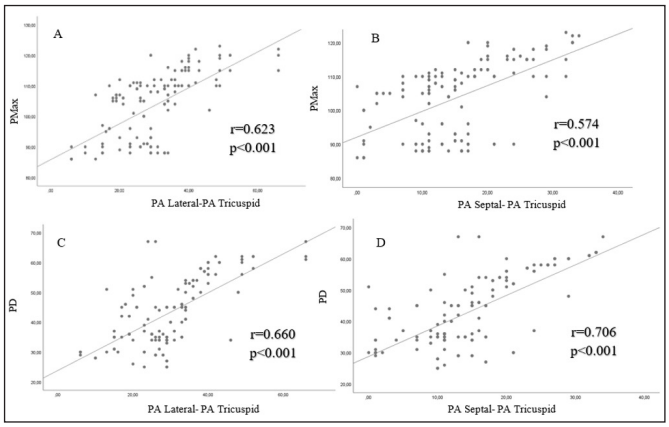

Figure 4. (A) Correlation between P max and PA lateral-PA Tricuspid (B) Correlation between P max and PA Septal- PA Tricuspid (C) Correlation between PD and PA Lateral- PA Tricuspid, (D) Correlation between PD and PA Septal- PA Tricuspid

In eight of the patients included in the study, the need for ICU developed during the follow-up. In six of these patients, non-invasive mechanical ventilation was required due to decreased oxygen saturation during follow-up. Two patients were also intubated because of ARDS and multiple organ failure. These two patients died during follow-up. However, none of these patients developed cardiac complications, including NOAF.

NOAF was observed in five COVID-19 patients with pneumonia during hospitalization. Three of these patients were male, and two were female, and their mean age was 60.4 (53, 58, 61, 64, 66 respectively). NOAF developed in these patients in the first three days of hospitalization. In these patients, initial ECG had present prolonged Pmax (128 ms, 126 ms, 120 ms, 119 ms, 115 ms respectively), PD (68 ms, 66 ms, 60 ms, 56 ms, 58 ms, respectively), interatrial EMD (43 ms, 39 ms, 40 ms, 36 ms, 34 ms, respectively) and intraatrial EMD (25 ms, 23 ms, 27 ms, 21 ms, 18 ms, respectively). All of these patients returned to sinus rhythm when discharged from the hospital.

DISCUSSION

In this study, the four crucial findings detected in COVID-19 patients can be listed as follows: (1) Pmax and PD on the 12-lead superficial ECG were significantly higher in COVID-19 patients. (2) Both interatrial and intraatrial EMD detected by TDI were longer in COVID-19 patients. (3) Pmax and PD times were significantly positively correlated with both interatrial and intraatrial EMD. (4) PD and Pmax durations and interatrial and intraatrial EMD were significantly positively correlated with C-Reactive Protein (CRP).

Even though COVID-19 is an infection that predominantly affects the lungs, cardiovascular involvement has also been reported extensively (1). Indeed, in Covid-19, after the respiratory system,

the most affected is the cardiovascular system. Many processes that affect the cardiovascular system directly and indirectly, work together. Direct myocardial cell injury, myocardial oxygen supply/demand mismatch, acute plaque rupture leading to the acute coronary syndrome as a part of systemic inflammation and catecholamine surge, increased thrombosis, and potential side effects of the current medications used for the treatment of COVID-19 have been considered to play a role in the presentation of cardiac manifestations (8, 18). For this reason, some authors accept the disease as "Acute Covid-19 Cardiovascular Syndrome" because of the frequent occurrence of acute myocarditis, acute coronary syndrome, and increased thromboembolic events in the course of the disease (19).

Atrial fibrillation is the most common arrhythmia in the population that causes increased cardiovascular mortality and morbidity (20). One of the most common rhythm disturbances encountered by clinicians, especially in patients with severe medical illnesses such as pneumonia, is AF. COVID-19 is a novel coronavirus infection, which predominantly affects the lungs, and pneumonia findings have become prominent and determinant in the disease's clinical course (21). The risk of NOAF in patients hospitalized for pneumonia has been investigated in several studies (22,23). A recent study performed by Pieralli et al. (22) showed that 10.3% of hospitalized patients for community-acquired pneumonia (CAP) experienced NOAF during hospitalization. Similarly, Cangemi et al. (23) found an increase in the incidence of NOAF within three days after hospitalization in patients hospitalized for community-acquired pneumonia. In our very recent study, we showed a significant increase in the incidence of NOAF in patients hospitalized for COVID-19 pneumonia (3). These findings suggest that patients hospitalized for pneumonia, regardless of the cause, may have a higher risk of developing new-onset AF. In particular, the development of AF has been shown to have a five-fold risk of stroke, a three-fold increased risk of heart failure, and a two-fold increased risk of death (24). Because of these undesirable effects, it is essential to determine in advance the risk of developing AF in patients. Therefore, some non-invasive methods have been described to predict the development and recurrence of AF.

Electromechanical delay (EMD), which can be easily measured non-invasively by TDI, is defined as the time interval between the onset of cardiac electrical activity and myocardial contraction. Prior studies have found that delays in interatrial and intraatrial conduction times, are significantly associated with new or recurrent AF (25,26). Also, it has been shown in previous studies that atrial EMD is also prolonged in several inflammatory clinical disorders such as psoriasis, and Inflammatory Bowel Disease (27, 28). Besides, the incidence of AF in these diseases has increased significantly compared to the normal population. In conclusion, atrial EMD is prolonged in paroxysmal AF and is considered a predictor of new-onset AF. P Max and PD are non-invasive markers showing the heterogeneous and unstable distribution of impulses from the sinus node in the atrial wall on standard ECG. Pmax and PD have been used as non-invasive markers to estimate AF's risk in various diseases, just like atrial EMD parameters (29-31). Especially, PD≥40 ms is associated with paroxysmal AF development (16).

In present study, we found that Pmax, PD, intraatrial and interatrial EMD, which are values that the noninvasive techniques TDI and ECG can easily measure, is significantly longer in patients with COVID-19. In other words, we have shown that the risk of developing AF increased in COVID-19 patients. Possible mechanisms between COVID-19 infection and increased risk of AF observed in this study can be listed as here.

Increased inflammation and serum inflammatory cytokines, have played an essential role in the initiation and persistence of AF independent of traditional risk factors, including HT and CAD (32-34). In particular, inflammatory mediators including CRP, interleukin-6, and tumor necrosis factor-alpha secreted during the inflammatory process have been demonstrated to trigger AF development in patients (35-37). Extensive data reveal that an inflammatory state and cytokine storm accompanies pneumonia in a subset of patients with COVID-19. In addition to the increased serum CRP levels, circulating TNF-alfa, IL-6, and IL-1β have been shown to increase in patients with COVID-19 infection (38). Serum CRP and NLR levels were high in our patient group, as in many inflammatory diseases. Moreover, we found that PD and Pmax durations and atrial EMD (interatrial and intraatrial) parameters were significantly positively correlated with CRP and NLR levels. These findings confirm previous studies' results, which underline the role of inflammation in AF' pathogenesis.

Apart from the increased inflammatory condition, increase in endogenous catecholamine release and hemodynamic breakdown might also form AF. In addition to those, widespread lung infiltration may cause ventilation / perfusion imbalance that precipitate hypoxemia, which could be another explanation for the development risk of NOAF in COVID-19 patients. Indeed, Radiological findings on CTI of the COVID-19 patients with pneumonia were diffuse infiltration in our study. As aresult, this study suggested that COVID-19 patients should be monitored for AF. The measurement of atrial EMD can be used to determine the high-risk population for AF development in COVID-19.

To the best of our knowledge, this study is the first in the literature to investigate intraatrial and interatrial EMD, Pmax, and PD in patients with COVID-19. We found that atrial conduction times were prolonged in COVID -19 patients. In light of the findings mentioned above, an increase in inflammatory load or inflammatory markers in COVID-19 patients seems to be a risk factor for AF occurrence. Indeed, recent research from Kelesoglu et al. (3) demonstrating that COVID-19 is independently associated with new-onset AF supports our findings. Moreover, extensive data have shown that COVID-19 patients have an increased risk of ischemic stroke. According to the findings presented here, the probability of NOAF should be kept in mind when COVID-19 patients complain of palpitations or suffer an ischemic stroke. Further research is needed to clarify the predictive role of atrial EMD, Pmax, and PD in evaluating AF's development in COVID-19 patients. Recent studies claim that the electromechanical delays measured on echocardiography differ from those measured in the electrophysiology study (39). Nevertheless, since echocardiographic electromechanical delay parameters represent the atrium's electromechanical integrity, we speculate that it can still be used non-invasively in determining the risk of AF.

CONCLUSION

COVID-19 disease has had an effect on cardiac functions by triggering arrhythmias and atrial fibrillation as the most important side effect. However, it is not clear in which patients it does this. In this study, we showed that this situation can be predicted in advance by evaluating the p wave, with the analyzes we performed on the p wave that best evaluates the atrial findings.

Limitations

This study's main limitations are the relatively small number of patients in the study group, to see if prolonged atrial EMD, Pmax, and PD develop AF in COVID-19 patients and the lack of follow-up in terms of possible future NOAF. Moreover, Because a follow-up study is required in these patients to show whether these changes are permanent or transient, we can never tell whether these parameters change over time. Unfortunately, we could not call these patients back for a follow-up, due to the COVID-19 pandemic. Therefore, Large-scale long-term follow-up is needed to evaluate the relationship between atrial EMD and AF occurrence accurately. Parameters with potential role in the pathophysiology, such as TNF-alfa, IL-6, and IL-1β levels were not measured, and these measurements might have been beneficial in finding the relationship between atrial EMD and COVID-19. Another limiting factor is the evaluation of CRP and NLR levels with only one measurement. We did not evaluate follow-up period. Also, since the echocardiographic examination was not performed again during the follow-up, we cannot speculate how the drugs used affect these parameters.

We looked at atrial EMD, a good marker for AF development, but the AF development has not been directly investigated. Although we found NOAF in five patients, lack of Holter monitoring or long-term ECG monitoring for all patients is also one of the study's main limitations and, silent AF may likely have been undetected.

ETHICAL DECLARATIONS

Ethics Committee Approval: Approval for the study was granted by Kayseri City Hospital Clinical Researches Ethics Committee (Date: 25.06.2020, Decision No: 134).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1099367
J Health Sci Med 2022; 5(4): 1044-1050

Can phosphatidylcholine increase the efficacy of bioactive glass graft when used as a carrier? an experimental study

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Cite this article as: Kaya M, Karahan N, Pepele Kurdal D, Yılmaz B, Midi A, Özpıçak B. Can phosphatidylcholine increase the efficacy of bioactive glass graft when used as a carrier? an experimental study. J Health Sci Med 2022; 5(4): 1044-1050.

ABSTRACT

Aim: Bioactive glass (Bioglass) is a substance causing strong mechanical bondings at the interface of soft tissue-biomaterial-bone through a series of biochemical and biophysical reactions, commonly used to restore developing bone defects due to surgery. On the other hand, phosphatidylcholine is a lipid substance increasing antibiotics' efficiency as a carrier. Since we met no study using the combination of Bioglass and phosphatidylcholine for bone defects, we aimed to investigate whether the bioglass-phosphatidylcholine combination would be more effective.

Material and Method: Thirty Sprague-Dawley 3-6-months-old female rats with a mean weight of 400 gr were divided into five subgroups (six in each group). A 5-mm critical defect was created in the middle of the condyle throughout the burr's diameter bilaterally. The phosphatidylcholine-bioglass graft was placed at one side, and Bioglass contralaterally to fill the defect. The rats were sacrificed at 24 hours, 72 hours, first, third, and sixth weeks postoperatively. The right and left rat femurs were removed and examined histopathologically.

Results: There was no statistically significant difference between the groups regarding filling volume, newly formed and necrotic bone, fibrous tissue, residual graft material, integration, foreign body reaction, and defect organization, indicating that Bioglass served efficiently for filling the defect. In addition, phosphatidylcholine neither augmented nor impaired the healing process.

Conclusion: These results indicated that Bioglass served efficiently for filling the defect, and the presence of phosphatidylcholine neither augmented nor impaired the healing process. However, further experimental studies are required until its clinical application is implemented.

Keywords: Phosphatidylcholine-bioglass, mechanical bondings, foreign body reaction, 5-mm critical defect, residual graft material

INTRODUCTION

Bioactive materials are substances causing strong mechanical bondings at the interface of tissue and material (soft tissue-biomaterial-bone) by a particular biological response through a series of biochemical and biophysical reactions (1). Bioactive materials may be either osteoconductive or osteoproductive, depending on their chemical and biological behaviors at the interface.

Such a promising biomaterial is bioactive glass (BAG), also known as bioglass (2). It is an osteoconductive biomaterial commonly used to restore developing bone defects during surgeries to treat trauma, tumors, implant revisions, osteomyelitis, and regenerate the region (3,4).

BAG involves a group of synthetic, silicate-based ceramics. When it was developed in the 1970s, it was formed using a combination of silicon dioxide (SiO_2), sodium oxide (Na_2O), calcium oxide (CaO), and phosphorus pentoxide (P_2O_5) (5). 45S5 (45% SiO_2, 24.5% CaO, 24.5% Na_2O, 6% P_2O_5, and hydroxy-carbon-apatite (HCA), in a form similar to in vivo bone and creating bioactivity on its surface) is one of the commonly utilized bioactive glass grafts (6). When exposed to body fluids after implantation, BAG causes the accumulation of a calcium phosphate layer through surface reactions. As a result, sodium, silica, calcium, and phosphate ions are released from the surface, increasing the local pH and osmotic pressure. Subsequently, a silica gel layer is

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Received: 06.04.2022 **Accepted:** 08.06.2022

formed on the surface of the glass, and amorph calcium phosphate precipitates on this layer. Such amorph structures are crystallized to natural hydroxyapatite that initiates the activation of osteoblasts for new bone formation. The glass is eventually resorbed and replaced by newly formed bone due to continuing reactions and layer formation. However, rapid BAG degradation seems to create a high pH microenvironment during the entire process, endangering ionic-level bone growth and not favored by the cells (7).

Phosphatidylcholine is a lipid substance with a high affinity for calcium ions and has a controlled release effect on the dissolution profile when it contacts body fluids. It has been shown in studies investigating antibiotic efficiency that, when added as a carrier, phosphatidylcholine increases the antibiotic efficiency by creating differences regarding the biofilm layer's inhibition, decomposition rate, and elongation profile (8,9). However, our literature review revealed no study investigating the effect of using phosphatidylcholine as a carrier substance for bioactive glass. Therefore, we aimed to investigate whether BAG would be more effective in filling the critical defects in the presence of phosphatidylcholine.

MATERIAL AND METHOD

The study was carried out with the permission of The Animal Experiments Local Ethics Committee in Acıbadem University approved the study protocols with the report (Date: 14.02.2019, Decision No: ACU-HAYDEK 2019/16). All procedures were carried out in accordance with the ethical rules and the principles.

Materials

The implant materials were Bioglass 45S5 (80% w/w) and Phospholipon 90 G (20% w/w) paste form (BIOMOLD paste; İDEA Ltd., Pendik, İSTANBUL). The study materials were separately packed and autoclaved as stated in the Animal Care and Use Statement.

Experimental Design

Thirty Sprague-Dawley 3-6 months old female rats with a mean weight of 400 gr were randomly divided into five subgroups according to the sacrification day. On the basis of results of comparable studies in rats with femoral defects, sample size estimation was performed. To detect significant differences in bone formation between the groups, a group size of at least 6 animals is reported to be required (10). The rats in Subgroup 1 were planned to be sacrificed at 24 hours, Subgroup 2 at 72 hours, Subgroup 3 at the end of the first week, Subgroup 4 at the end of the third week, and Subgroup 5 at the end of the sixth week postoperatively.

Surgical Procedures

The surgical procedure was performed under general anesthesia with the mixture of fentanyl citrate/fluanisone (Hypnorm, Janssen Pharmaceutica, Inc., Beerse, Belgium) 80 mg/kg/ 2.5 mg/kg, and midazolam (Dormicum, Roche, Basel, Switzerland) 1.25 mg/kg. In addition, cefuroxime (Zinacef, GlaxoSmithKline Manufacturing S.p.A., Verona, Italy) 20 mg/kg was subcutaneously administered to the animals preoperatively. Finally, lateral sites of rats' bilateral thighs were shaved, prepared using a Betadine scrub, and rinsed with 70% ethanol.

Skin, fascia, and muscle tissue were incised and dissected until the left femur's distal condyle was exposed. With a burr, a 5-mm diameter and 6-mm depth critical defect was created in the middle of the condyle throughout the burr's diameter (11). The phosphatidylcholine-carrying bioglass graft [FOS (+)] was placed to fill the defect entirely using micro forceps. The layers were appropriately closed.

The same procedure was performed on the right side. The skin, fascia, and muscle tissue were incised and passed until the right femur's distal condyle was exposed. A 5-mm critical defect was created in the middle of the condyle throughout the burr's diameter using a stainless steel burr. The wound was rinsed with saline. The bioglass graft with no carrier [FOS (-)] was placed to fill the defect completely using micro forceps. The muscles and skin were closed in two layers using absorbable 4.0 sutures (Dexon, Covidien, Mansfield, MA, USA). Buprenorphine (Temgesic, Reckitt & Colman Pharmaceuticals, Inc, Richmond, England) was administered subcutaneously with a dose of 0.01-0.05 mg/kg for postoperative pain relief. Total animal activity was permitted within the cages postoperatively.

The animals in five groups were sacrificed according to their predetermined days of sacrification. Subgroup 1 was sacrificed at 24 hours, Subgroup 2 at 72 hours, Subgroup 3 at the end of the first week, Subgroup 4 at the end of the third week, and Subgroup 5 at the end of the sixth week postoperatively. Necessary precautions to minimize pain and discomfort were taken during the sacrification process.

The right and left femurs of the sacrificed rats were disarticulated from their hip and knee joints and placed in 10% neutral buffered formalin after removing the soft tissues.

Histopathological Examination

In the histopathological examination of the defect area, filling volume (FV), newly formed bone (NFB), necrotic bone (NB), fibrous tissue (FT), and residual graft material (RG) were subjectively evaluated under the light microscope (Leica® DM 4000, Germany). The evaluation was performed according to the instructions in the literature(12). In addition, the parameters of integration

(Int), foreign body reaction (FBR), new bone formation at the defect's edge (DNB), and organization (Org) on the defect's surface were evaluated.

The investigated parameters and their evaluation criteria were as follows:

1. Filling volume (%)=Filling volume of the defect/Total defect area×100
2. Newly formed bone (%)=New bone area/Total defect area×100
3. Necrotic bone (%)=Necrotic bone area/Total defect area×100
4. Fibrous tissue, coagulum, granulation tissue (%)=Fibrous tissue area/Total defect area×100
5. Residual graft material (%)=Residual graft material are/Total defect area×100
6. Integration (%)=Integrated section/Defect area circumference×100
7. Foreign body reaction: Absent – 0; present – 1
8. New bone formation at the defect's edge: Absent – 0; present – 1
9. Organization on the defec's surface: Absent – 0; less than 50% - 1; more than 50% - 3;complete (thin-layered, less than 100 microns) – 4; complete (thick-layered, more than 100 microns) – 5.

Statistical Analysis

The R ver.2.15.3 software (R Core Team, 2013) was used for statistical analysis. Median, first quartile, third quartile, frequency, and percentage were used to report the study data. In addition, the Kruskal-Wallis and Dunn-Bonferroni tests were used to make comparisons of the quantitative variables among the time subgroups. The Wilcoxon signed-ranks test made the intergroup comparisons regarding the quantitative variables. The Fisher-Freeman-Halton exact test compared qualitative variables among the time subgroups. The McNemar and McNemar-Bowker tests were used to make two-group comparisons of qualitative variables. A p-value less than 0.05 was considered statistically significant.

RESULTS

Summary of Histopathological Examination Results According to the Time Subgroups in Groups FOS (+) and FOS (-)

Subgroup 1 (24 hours): Newly formed bone, necrotic bone, integration, foreign body reaction, new bone formation at the defect's edge, and organization on the defect surface were not observed. However, <5% amounts of residual graft material and filling volume were identified in the groups with and without phosphatidylcholine (**Figure 1 and 2**).

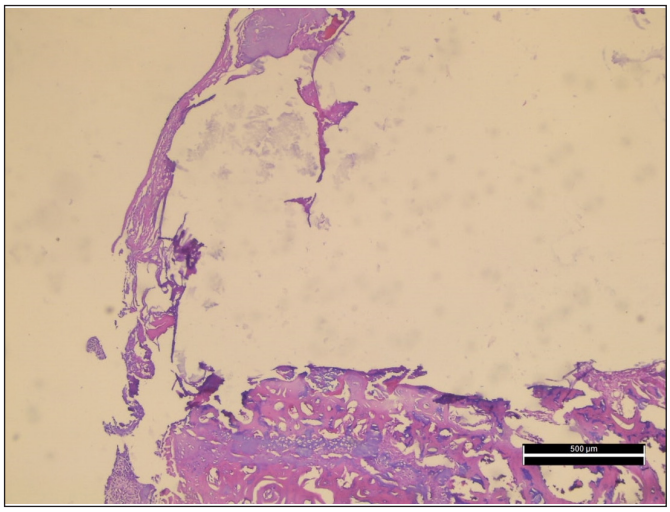

Figure 1. Group FOS (+) – Subgroup 3: granulation tissue forming a full-thickness layer on the surface, fibrinopurulent exudate around the graft particles in the defect area, the appearance of an early organization [7 days–With phosphatidylcholine (H&E, x40 magnification)]

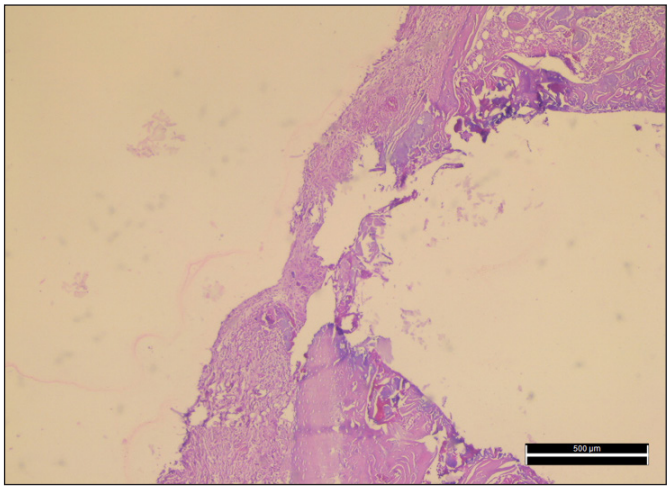

Figure 2. Group FOS (-) – Subgroup 3: granulation tissue forming a full-thickness layer on the surface, fibrinopurulent exudate around the graft particles in the defect area, the appearance of an early organization [7 days–Without phosphatidylcholine (H&E, x40 magnification)]

Subgroup 2 (72 hours): Newly formed bone, necrotic bone, integration, foreign body reaction, new bone formation at the defect's edge were not present. The organization on the defect's surface mainly was a complete (thick layered).

Subgroup 3 (7th day): Newly formed bone and new bone formation at the defect's edge were not observed. The organization on the defect's surface was mainly in a thick layer in both groups. In some samples, necrotic bone was observed together with a surrounding foreign body granulation tissue. Integration was present to a certain degree in all samples. <%5 amounts of residual graft material were observed.

Subgroup 4 (3rd week): In some cases, newly formed bone and new bone formation at the defect's edge were present. The organization on the defect's surface was mainly a

thick layer in both groups. In some samples, necrotic bone was observed together with a surrounding foreign body granulation tissue. Full integration was present in all samples. The filling volume was 100% in both groups. Residual graft material was observed, constituting most of the filling volume in all samples.

Subgroup 5 (6th week): Both groups' filling volume percentages were 100%. Newly formed bone was observed in varying degrees in all samples. In both groups, organization on the defect's surface was present as a thick layer. In some samples, necrotic bone was observed, together with surrounding foreign body reactions. Full integration and residual graft material were present in all cases. Because of the difficulty of histopathological evaluation due to the full integration of the newly formed bone and the old bone, the parameter of new bone formation at the defect's edge could not be evaluated in the sixth week (**Figures 3 and 4**).

The histopathological examination results for investigated parameters in Subgroups 1-5, together with the comparisons of Groups FOS (+) and FOS (-) to each other according to time subgroups and the comparisons of time subgroups within Groups FOS (+) and FOS (-), were presented in **Table 1.**

Table 1. The histopathological examination results for investigated parameters, together with the comparisons of Groups FOS (+) and FOS (-) to each other according to time subgroups and the comparisons of time subgroups within Groups FOS (+) and FOS (-)

	Subgroup 1	Subgroup 2	Subgroup 3	Subgroup 4	Subgroup 5	p
FV%						
FOS (+)	0.5 (0-2)	3.5 (0-5)	20 (12-30)	100 (100-100)	100 (100-100)	a<0.001*
FOS (-)	3.5 (1-15)	2.5 (0-5)	30 (20-40)	100 (100-100)	100 (100-100)	a<0.001*
bp	0.168	0.496	0.293	0.999	0.999	
NFB%						
FOS (+)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	35 (30-40)	a<0.001*
FOS (-)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-5)	30 (30-40)	a<0.001*
bp	0.999	0.999	0.999	0.180	0.655	
NB%						
FOS (+)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-0)	a0.271
FOS (-)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)	0 (0-0)	a0.153
bp	0.999	0.999	0.564	0.999	0.999	
FT%						
FOS (+)	0 (0-0)	0 (0-0)	9 (5-20)	40 (30-50)	62.5 (30-67.5)	a0.001*
FOS (-)	0 (0-0)	0 (0-0)	17.5 (15-35)	50 (40-50)	35 (0-70)	a<0.001*
bp	0.999	0.999	0.248	0.096	0.655	
RG%						
FOS (+)	0.5 (0-2)	3 (0-4)	5 (5-10)	60 (50-70)	0 (0-0)	a<0.001*
FOS (-)	3.5 (1-10)	2.5 (0-3)	5 (5-5)	50 (40-50)	0 (0-0)	a<0.001*
bp	0.168	0.581	0.655	0.072	0.999	
Int						
FOS (+)	0 (0-0)	0 (0-0)	30 (20-45)	100 (100-100)	100 (100-100)	a<0.001*
FOS (-)	0 (0-0)	0 (0-0)	45 (25-60)	100 (100-100)	100 (100-100)	a<0.001*
bp	0.999	0.999	0.168	0.999	0.999	
FBR						
FOS (+)	0 (0)	0 (0)	2 (33.3)	1 (16.7)	1 (16.7)	c0.767
FOS (-)	0 (0)	0 (0)	3 (50)	1 (16.7)	2 (33.3)	c0.222
cp	‡-	‡-	0.999	0.999	0.999	
DNB						
FOS (+)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	c0.999
FOS (-)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	c0.999
cp	‡-	‡-	‡-	0.999	‡-	
Org						
FOS (+)						c<0.001*
Absent	6 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Complete-thin	0 (0)	3 (50)	4 (66.7)	0 (0)	0 (0)	
Complete-thick	0 (0)	3 (50)	2 (33.3)	6 (100)	6 (100)	
FOS (-)						c<0.001*
Absent	6 (100)	0 (0)	0 (0)	0 (0)	0 (0)	
Complete-thin	0 (0)	3 (50)	1 (16.7)	0 (0)	0 (0)	
Complete-thick	0 (0)	3 (50)	5 (83.3)	6 (100)	6 (100)	
ep	‡-	0.999	0.250	‡-	‡-	

FV: filling volume; NFB: newly formed bone; NB: necrotic bone; FT: fibrous tissue; RG: residual graft material; Int: integration; FBR: foreign body reaction; DNB: new bone formation at the defect's edge; Org: organization, The results for FV%, NFB%, NB%, FT%, RG%, and Int are presented as median (first quartile, third quartile), and those for FBR, DNB, and Org as frequency (percentage)., a Kruskal-Wallis test; b Wilcoxon signed-ranks test; c Fisher-Freeman-Halton exact test; d McNemar test; e McNemar Bowker test; ‡ Because the number of observations was insufficient, related analyzes could not be performed.

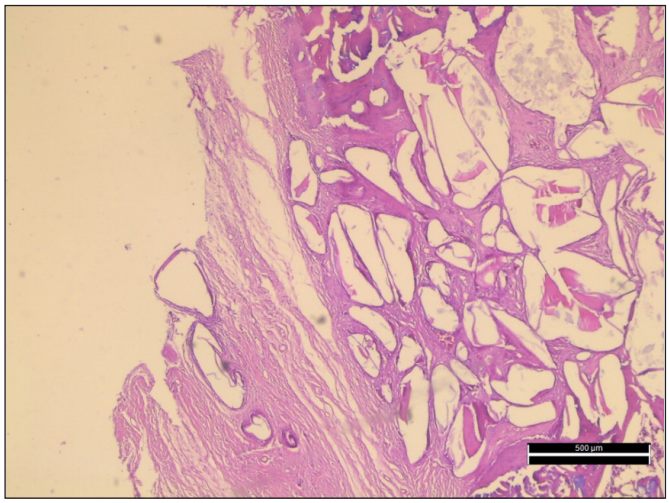

Figure 3. Group FOS (+) - Subgroup 5–In addition to thin fibrous bands, thin trabecular bone formation was observed, together with spaces of graft material pushed outward on the surface [6th week–With phosphatidylcholine (H&E, x40 magnification)]

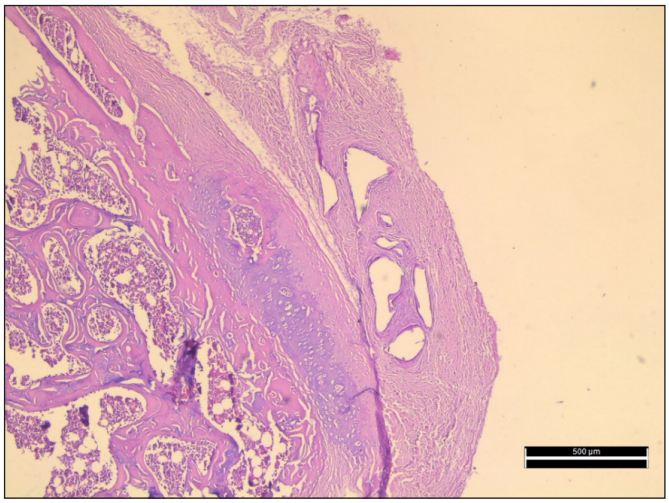

Figure 4. Group FOS (-) - Subgroup 5 –In addition to fibrous bands, trabecular bone formation and mature bone development from the hyaline cartilage were observed, together with spaces of residual graft material pushed outward on the surface [6th week–Without phosphatidylcholine (H&E, x40 magnification)]

DISCUSSION

This study aimed to histopathologically investigate whether BAG would be more effective in filling the critical defects with its osteoconductive effect in the presence of phosphatidylcholine. Femur defects were created bilaterally. BAG without any carrier was grafted to the created femur defect on one side, and BAG with phosphatidylcholine was grafted to the other side. The histopathological evaluation involved parameters of filling volume, newly formed bone, necrotic bone, fibrous tissue, residual graft material, graft integration, foreign body reaction, new bone formation at the defect's edge, and organization in time subgroups of 24 hours, 72 hours, seven days, three weeks, and six weeks. Statistical analysis of histopathological examination results revealed no difference between the group in which BAG was grafted together with phosphatidylcholine and the group that BAG was grafted alone. The defect was repaired similarly with BAG regardless of the presence of phosphatidylcholine as a carrier.

This study was the first study combining the use of BAG with phosphatidylcholine. It showed for the first time that using phosphatidylcholine as a carrier during BAG application neither augmented nor adversely affected bone healing promoted by BAG in a rat femur model. The histopathological examination revealed that bone formation occurred progressively. BAG with/without phosphatidylcholine degraded over time, was biocompatible, attracted osteoblasts, and permitted the new bone formation within the defect.

Various materials have been in clinical use for orthobiologics, either autologous such as bone and cartilage, heterologous such as animal-origin hydroxyapatite, or synthetics such as synthetic hydroxyapatite, calcium phosphate ceramic, and bioglass (13). For example, silicate bioglass particles have been tested for their porosity as microspheres or their non-porous features in bone grafting (14). Moreover, Bioglass and its composites (particularly with polymers to facilitate the degradation process) are commonly applied because of their osteoinductive/conductive capabilities (15).

A very recent study by Zhang et al. (16) reported that BAG could facilitate wound healing, collagen deposition, and angiogenesis through inhibition of pyroptosis – a newly defined type of programmed cell death when used alone. On the other hand, various BAG composites have been investigated for use in specialties dealing with bone graftings/tissue engineering, such as orthopedics and dentistry. For example, Shi et al. (17) combined the recombinant human bone morphogenetic protein-9 (rhBMP-9) with carriers such as BAG and collagen membranes (BioGide) to utilize in the preservation of tooth extraction site in a very recently published study, and they found a dramatic difference between BAG and BioGide regarding absorption and slow/steady release of rhBMP-9. Another composite of BAG is prepared with chitosan-alginate. A very recently published study reported that, with the increasing amount of sodium alginate in the composite, the mineralization ability of Bioglass was enhanced, and the composite's mechanical strength significantly increased (18). In addition, endogenous bone regeneration was determined by Zheng et al. (19) to be promoted by 3D bioglass-nanoclay scaffolds mimicking hypoxia. A comparative experimental study conducted by Camargo et al. (20) in rabbits demonstrated that BAG was similarly effective regarding bone neoformation when compared to autografting. A recent review article by Karadjian et al. (21) concluded that BAG appeared to be useful for osteogenic differentiation supported the integration of

composites into the bone, enhancing bone formation. In summary, Bioglass has been numerously reported to be useful experimentally and clinically when used alone or combined.

On the other hand, although numerous studies have been conducted with substances added to BAG, we have met no study conducted using BAG in combination with phosphatidylcholine. Phosphatidylcholine has been used as a carrier for various substances, particularly antibiotics (22). Regarding bone induction, studies conducted with phosphatidylcholine are few. For example, in their study evaluating the combined effects of phosphatidylcholine and demineralized bone matrix on bone induction, Han et al. (23) reported that phosphatidylcholine boosted the material's osteoconductivity features besides its enhanced handling properties. Furthermore, a recent study by Harahaliloglu and Kilicay (24) investigated the bone cement impregnated with selenium nanoparticles stabilized by phosphatidylcholine to apply in bone and concluded that it was an effective graft material. However, since we have met no publication using BAG and phosphatidylcholine in combination, we cannot make a detailed comparison with the literature.

CONCLUSION

Our study found no difference between the bioglass groups with and without phosphatidylcholine regarding the evaluated histological parameters. Furthermore, healing proceeded flawlessly and was accomplished regardless of the presence of phosphatidylcholine in the material. These results indicated that Bioglass served efficiently for filling the defect, and the presence of phosphatidylcholine neither augmented nor impaired the healing process, suggesting that when various materials, such as antibiotics, are needed to be added to the grafting process with Bioglass, phosphatidylcholine can be used as a carrier. However, such a suggestion should be tested with further experimental studies until its clinical application is implemented.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of The Animal Experiments Local Ethics Committee in Acıbadem University approved the study protocols with the report (Date: 14.02.2019, Decision No: ACU-HAYDEK 2019/16).

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgements: I would like to express my sincere thanks to Prof. Dr. Mustafa Harun Gürsoy for her practical suggestions and constructive criticisms during the creation of the article.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1122437
J Health Sci Med 2022; 5(4): 1051-1061

Research trends and global productivity on mechanical ventilation with the impact of COVID-19: a bibliometric analysis in the period 1980-2021

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Cite this article as: Zengin EN. Research trends and global productivity on mechanical ventilation with the impact of COVID-19: a bibliometric analysis in the period 1980-2021. J Health Sci Med 2022; 5(4): 1051-1061.

ABSTRACT

Aim: Although the number of global studies on mechanical ventilation (MV) therapy, which plays an important role in the life process of patients in the intensive care unit, has increased, there is still no bibliometric research on this subject in the literature. This study, it was aimed to determine trend topics and global productivity by holistically analyzing scientific articles on MV published between 1980 and 2021 using various statistical methods and bibliometric approaches.

Material and Method: Articles on MV published between 1980 and 2021 were downloaded from the Web of Science (WoS) database and analyzed using various statistical methods. Spearman's correlation coefficient was used for correlation studies. Network visualization maps were used to identify the most effective studies with global collaborations, trend topics, and citation analysis.

Results: The study, which was in the category of 5323 articles out of a total of 10135 publications, was analyzed. The first 3 countries that contributed the most to the literature were the USA (n=1740), France (448), and Canada (386). The most active author was Laurent Brochard (n=50). The top 3 most active institutions were Assistance Publique Hopitaux Paris (224), University of Toronto (216), and League of European Research Universities (169). The top 3 journals that published the most articles were Critical Care Medicine (289), Chest (204), and Intensive Care Medicine (166). Gross Domestic Product (GDP) was highly effective in article productivity ($r=0.719$, $p<0.001$).

Conclusion: In this study on MV, it was shared the statistical analysis information of 5323 articles published since 1980. With the developing technology, the usage area of MV is increasing and this situation is also reflected in the publications in the literature. It was also observed that the number of studies on MV increased with the COVID-19 (SARS CoV-2) pandemic. This study, which includes the bibliometric analysis of MV by summarizing the literature, will guide the authors who want to study in this area.

Keywords: Bibliography, COVID-19, intensive care unit, mechanical ventilation, respiratory failure

INTRODUCTION

Mechanical ventilation (MV) is the process of providing respiratory function artificially with the help of a device called a 'mechanical ventilator'. The primary purpose of MV is to normalize and/or stabilize the patient's gas exchange by increasing ventilation and oxygenation in patients with respiratory failure (1). MV plays a very important role in the management of patients with acute respiratory distress syndrome (ARDS), chronic obstructive pulmonary disease (COPD), acute severe asthma, sepsis, hypoxemia, COVID-19, and newborn babies with respiratory problems (2-4). If MV is performed through an instrument such as an endotracheal tube or a tracheostomy tube, it is called "invasive ventilation" (1). Pulmonary barotrauma, volutrauma, atelectotrauma, biotrauma, ventilator-induced lung injury, and ventilator-associated pneumonia are the main complications of invasive mechanical ventilation (IMV) (5). In medically fit patients, face or nasal masks are used for non-invasive mechanical ventilation (NIMV). Due to the complications of MV, NIMV is increasingly being used in clinical practice in order to avoid the use of endotracheal intubation or tracheostomy (6).

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Received: 27.05.2022 **Accepted:** 08.06.2022

Separating patients from MV is a major challenge in intensive care units (ICUs). The best methods to separate patients from MV in patients recovering from respiratory failure have been tried to be defined for years. With increasing recognition of the risks and economic consequences of long-term ventilation, research continues to identify strategies based on clinical experience to reduce MV duration. However, ongoing clinical uncertainty regarding the optimal separation strategy still continues (7). It has been suggested to switch from simple maneuvers to more complex methods such as multivariate scoring systems and computerized decision support models to identify patients ready for extubation (4,7). The search for an accurate way of predicting success in weaning a patient from MV continues (8). Various clinical scores have been developed to predict the weaning success of MV in different samples (4,8-10).

Successful weaning and recovery from IMV are important to improve outcomes in critically ill patients. Current international guidelines recommend daily assessment of readiness for extubation with a spontaneous breathing trial, regular breaks in sedation, early mobilization, and protocoled rehabilitation to aid weaning (11,12). Yeung et al. (6) as a result of a meta-analysis of twenty-five studies involving 1609 patients, it was reported that the use of NIMV to differentiate from MV reduces hospital mortality, the incidence of ventilator-associated pneumonia, and length of stay in the ICU. It has also been reported that NIMV as a weaning strategy seems to be most beneficial in patients with COPD.

MV is used to treat 30-40% of patients admitted to ICU (12). Esteban et al. (12) determined that in a cohort of 15757 consecutive adult patients admitted to 361 ICUs who underwent MV for more than 12 hours, 5183 patients (33%) received MV for a mean duration of 5.9±7.2 days. The mean (SD) length of stay in the ICU was 11.2±13.7 days. The overall mortality rate in the ICU was 30.7% (1590 patients) for the entire population, 52% (120) for patients ventilated for ARDS, and 22% (115) for patients ventilated for exacerbation of COPD. The survival rate of patients who received MV for more than 12 hours was 69% (12). Lim et al. (13) as a result of the meta-analysis of 69 studies describing 57420 adult COVID-19 patients undergoing IMV, the reported case fatality rates (CFRs) were estimated to be 45% (95% confidence interval [CI], 39-52%). Among studies in which age-stratified CFR was available, pooled CFR estimates ranged from 47.9% (95% CI, 46.4–49.4%) in younger patients (age ≤40 yr) to 84.4% (95% CI, 83.3–85.4%) in older patients (age >80 yr) (13).

Chang et al. (14), as a result of the meta-analysis of 28 studies including 12437 COVID-19 ICU admissions from 7 countries between December 2019 and 1 May 2020, found that the pooled ICU admission rate was 21% [95% CI 0.12-0.34] and reported the need for IMV in 69% of these cases [95% CI 0.61-0.75]. ICU and IMV mortality was 28.3% [95% CI 0.25-0.32], 43% [95% CI 0.29-0.58]. In addition, ICU and IMV duration 7.78 [95% CI 6.99-8.63] and 10.12 [95% CI 7.08-13.16] determined as days (14).

Bibliometrics is the analysis of scientific publications using various statistical methods (15-17). Thanks to the studies revealed as a result of the statistical and bibliometric analysis of the information obtained from thousands of articles in the literature, the most active countries, institutions, journals, and authors, international collaborations are revealed, and trend topics that have been studied in recent years can be determined (18-21).

Although the number of global studies on MV therapy, which plays an important role in the life process of patients in the ICU, has increased, there is still no bibliometric research on this subject in the literature. It was aimed to identify trend topics and global productivity by holistically analyzing scientific articles published on MV between 1980 and 2021 using various statistical methods and bibliometric approaches in this study.

MATERIAL AND METHOD

Since our research article is a bibliometric study, there is no need for an ethics committee approval.

Search Strategy

Web of Science Core Collection (WoS by Clarivate Analytics) database was used for the literature review. The search process was determined as 1980-2021 (publishes before 1980 are not available in WoS). All publications with MV in their titles were found. In order for researchers to access similar documents (search findings may vary according to different access dates, access date: April 1, 2022), repeatability codes are: (Title ("mechanical ventilation") Timespan: 1980-2021). As a result of cluster analysis, citation analysis, and trend topic determination analysis VOSviewer (Version 1.6.16, Leiden University's Center for Science and Technology Studies, Netherlands) package program was used to create bibliometric network visualizations (22).

Statistical Analysis

The website (https://app.datawrapper.de) was used to create the world map showing the distribution of articles by country. The Exponential Smoothing estimator using seasonal smoothing was used in Microsoft Office Excel to estimate the number of articles that could be published in the next 5 years based on past publication trends. Statistical analyzes were performed with SPSS (Version 22.0, SPSS Inc., Chicago, IL, USA) package program. The normal distribution test of the data was analyzed with the Shapiro-Wilks test. Correlation analyzes were performed

to determine whether some economic development indicators (Gross Domestic Product (GDP), Gross Domestic Product per capita (GDP per capita), Human Development Index (HDI)) of countries have an effect on MV (data were obtained from the world bank (23). Correlation analyzes were analyzed using the Spearman correlation coefficient as the data were not normally distributed. For a statistically significant relationship, $p<0.05$ was accepted.

RESULTS

As a result of the literature review, there were a total of 10135 publications on MV published in all research areas in the WoS database between 1980 and 2021. Of these publications, 52.5% (n=5323) were articles, 25.5% (n=2593) were meeting abstracts, 7.1% (n=723) were letters, 5.8% (n=595) were review articles, 4.1% (n=419) were proceedings papers and the remainders were in other publication types (editorial materials, book chapters, corrections, notes, early access, news items, books, book reviews, discussions, biographical items, retracted publications, bibliographies, data papers) (**Figure 1**). Bibliometric analyzes were carried out with 5323 articles published in the article category out of a total of 10135 publications. 92.1% (n=4902) of these articles were in English and the remainders were in other languages (Spanish (129), German (113), French (n=110), Turkish (30), Portuguese (23), Korean (7), Italian (4), Polish (2), Serbian (2), Norwegian (1)) were published. The h-index of 5323 articles was 155, the average citations per article were 26.99, and the sum of times cited was 143,660 (without self-citations: 127,185) (**Table 1**). Most of the articles were scanned in SCI-Expanded (n=4688, 88%) and Emerging Sources Citation Index (ESCI) (n=528, 9.9%). Few articles were indexed in the Social Sciences Citation Index (SSCI).

Table 1. Language distribution and citations

Language	Number of articles			
English	4902	Total 5323 articles	h- index	155
Spanish	129			
German	113		Average citations per article	26.99
French	110			
Turkish	30			
Portuguese	23		Sum of times cited	143660
Korean	7			
Italian	4			
Polish	2		Without self-citations	127185
Serbian	2			
Norwegian	1			

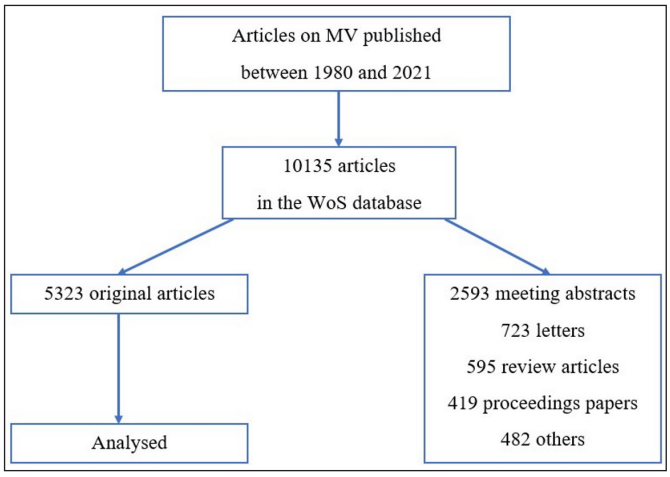

Figure 1. Diagram of Articles. Others: Editorial materials, book chapters, corrections, notes, early access, news items, books, book reviews, discussions, biographical items, retracted publications, bibliographies, and data papers

Active Research Areas

The top 10 research areas with the most research on MV were Critical Care Medicine (1557, 29.2%), Respiratory System (1271, 23.8%), Medicine General Internal (585, 10.9%), Anesthesiology (463, 8.6%), Pediatrics (433, 8.1%), Nursing (256, 4.8%), Surgery (219, 4.1%), Cardiac Cardiovascular Systems (215, 4%), Physiology (151, 2.8%), and Medicine Research Experimental (138, 2.5%).

Development of Publications

The distribution of the number of articles published on MV by year is shown in **Figure 2**. The values related to the results of the Exponential Smoothing estimation model, which takes into account the seasonal correction used to estimate the number of articles that would be published in the next 5 years, were shown in **Figure 2**. According to the estimation model results, it was estimated that 362 (CI %: 294-431) articles on MV would be published in 2022 and 477 (CI %: 392-562) articles will be published in 2026 (**Figure 2**).

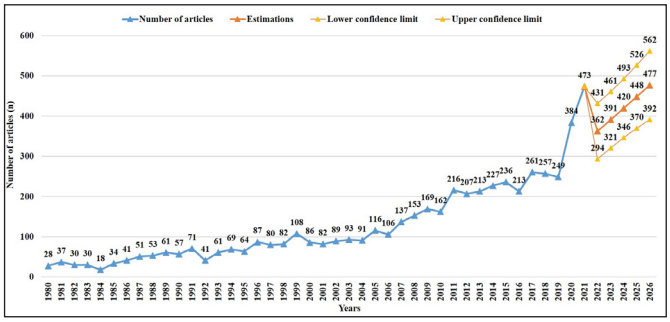

Figure 2. Bar chart showing the distribution of articles published in the mechanical ventilation by years and estimations for the number of articles for the next five years

Active Countries

The distribution of the number of articles by world countries was shown in **Figure 3**. The first 17 countries that contributed the most to the literature by publishing

more than 100 articles were found as follows; USA (number of articles, n=1740), France (448), Canada (386), Germany (384), China (343), Spain (329), Italy (291), United Kingdom (274), Brazil (214), Netherlands (179), Australia (153), Japan (149), Turkey (143), Switzerland (141), Taiwan (136), Sweden (124), and South Korea (104) (**Figure 3**).

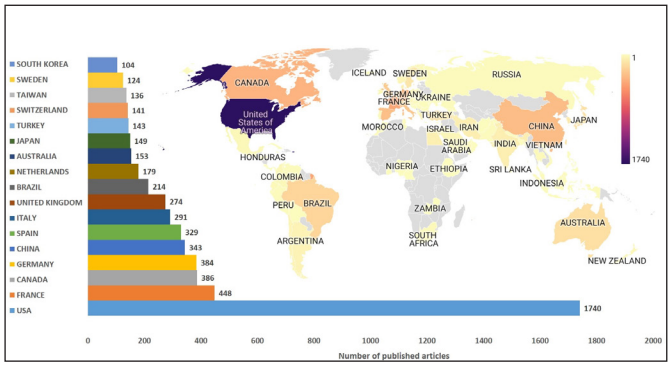

Figure 3. Global productivity world map showing the distribution of published articles on mechanical ventilation by country and bar chart showing the top 17 most active countries

Cluster analysis was performed among 60 countries that have published at least 5 articles from 99 countries that have published articles on MV, and whose authors have international cooperation, and it was shown in **Figure 4.a**. According to the results of the clustering analysis, 7 different clusters related to international cooperation were formed (Colors for Cluster 1: red, Cluster 2: green, Cluster 3: blue, Cluster 4: yellow, Cluster 5: purple, Cluster 6: turquoise, Cluster 7: orange). In addition, the total link strength (international cooperation score) scores showing the cooperation power of 60 countries were calculated and the international cooperation density map created according to these scores was shown in **Figure 4.b** (The first 15 countries with the highest score: USA=636, Canada=461, Germany =357, Spain=343, Italy=335, France=299, England (in United Kingdom)=267, Netherlands=194, Brazil=186, Australia=164, Argentina=144, Greece=135, Switzerland=134, China= 133, Belgium=125).

Correlation Analysis

A positive moderate statistically significant correlation was found between the number of articles produced by countries on MV and GDP, GDP per capita, and HDI values (respectively, r=0.719, p<0.001; r=0.688, p<0.001, r=0.657, p< 0.001).

Active Authors

The top 10 most active authors on MV were Brochard L. (50), Powers SK. (39), Rose L. (37), Esteban A. (36), Schultz MJ. (33) Slutsky AS. (33), Pelosi P. (32), Schonhofer B. (26), Nava S. (25), and Tobin MJ. (25).

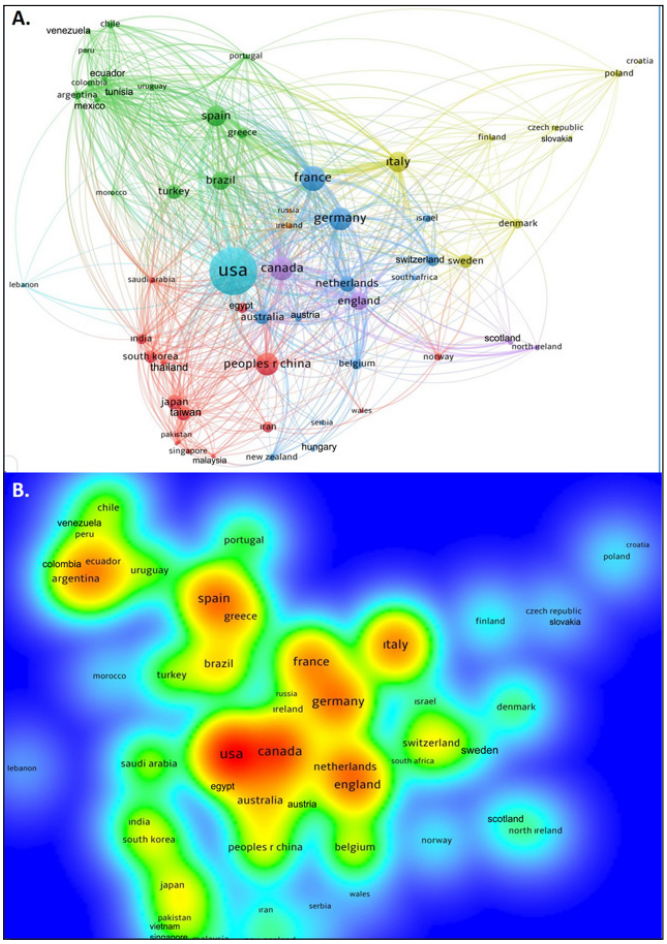

Figure 4. a. Network visualization map of results of cluster analysis showing international cooperation between countries on mechanical ventilation. Footnote: Each color represents a different Cluster. As the number of articles published by the countries increases, the size of the circles representing the countries also increases. The lines show the countries with which they cooperate. b. Density map showing the intensity of international cooperation of countries on mechanical ventilation. Footnote: The strength of the international cooperation score increases from blue to red (blue-green-yellow-red)

Active Institutions

The top 15 most active institutions in MV were; Assistance Publique Hopitaux Paris (224), University of Toronto (216), League of European Research Universities (169), Harvard University (166), Institut National De La Sante Et De La Recherche Medicale (163), University of California System (129), University De Paris (114), US Department of Veterans Affairs (114), Veterans Health Administration (113), Pennsylvania Commonwealth System of Higher Education (111), State University System of Florida (88), University of Texas System (86)), Saint Michaels Hospital Toronto (85), Massachusetts General Hospital (81) and Sorbonne University (79).

Active Journals

5323 articles on MV were published in 1250 different journals. The first 60 journals that contributed the most to the literature by publishing 15 or more articles from these journals, the total number of citations received by the journals and the average number of citations per article were presented in **Table 2**.

Table 2. The 60 most active journals that have published 15 or more articles on mechanical ventilation

Journals	RC	C	AC	Journals	RC	C	AC
Critical Care Medicine	289	16909	58.5	Journal of Trauma-Injury Infection and Critical Care	24	886	36.9
Chest	204	12052	59.1	Medizinische Klinik	24	66	2.8
Intensive Care Medicine	166	8064	48.6	Scientific Reports	24	140	5.8
Respiratory Care	136	2416	17.8	Anaesthesia and Intensive Care	23	325	14.1
American Journal of Respiratory and Critical Care Medicine	112	15027	134.2	BMC Pulmonary Medicine	23	207	9.0
Critical Care	99	3700	37.4	Thorax	23	1352	58.8
Journal of Critical Care	98	1473	15.0	Journal of Intensive Care Medicine	22	135	6.1
Plos One	62	805	13.0	Minerva Anestesiologica	22	344	15.6
Anesthesiology	60	3412	56.9	Pediatric Research	22	340	15.5
Pediatric Pulmonology	59	1116	18.9	Respiration	22	337	15.3
American Journal of Critical Care	58	1272	21.9	Annales Francaises D Anesthesie et de Reanimation	21	78	3.7
American Review of Respiratory Disease	50	7420	148.4	Schweizerische Medizinische Wochenschrift	21	66	3.1
Journal of Applied Physiology	48	2250	46.9	Egyptian Journal of Chest Diseases and Tuberculosis	20	52	2.6
Journal of Pediatrics	46	2043	44.4	Building and Environment	19	363	19.1
European Respiratory Journal	45	2670	59.3	Journal of Clinical Monitoring and Computing	19	108	5.7
Pediatric Critical Care Medicine	45	1099	24.4	Indian Journal of Critical Care Medicine	19	86	4.5
Acta Anaesthesiologica Scandinavica	39	494	12.7	Anaesthesist	18	68	3.8
Anesthesia and Analgesia	39	1238	31.7	Annals of the American Thoracic Society	18	198	11.0
Critical Care Clinics	34	621	18.3	Respiratory Physiology & Neurobiology	18	205	11.4
Respiratory Medicine	33	962	29.2	Energy and Buildings	17	268	15.8
Medicina Intensiva	30	180	6.0	Journal of Cardiothoracic and Vascular Anesthesia	17	251	14.8
JAMA-Journal of The American Medical Association	29	5332	183.9	Journal of Veterinary Emergency and Critical Care	17	123	7.2
American Journal of Physiology-Lung Cellular and Molecular Physiology	28	1164	41.6	Reanimation	17	6	0.4
Annals of Intensive Care	28	382	13.6	Acta Paediatrica	16	188	11.8
British Journal of Anaesthesia	28	749	26.8	American Journal of Emergency Medicine	16	227	14.2
Heart & Lung	28	450	16.1	Anaesthesia	16	191	11.9
Revue Des Maladies Respiratoires	28	87	3.1	Journal of Thoracic Disease	16	95	5.9
Medicine	26	138	5.3	Tuberculosis and Respiratory Diseases	16	56	3.5
Archivos de Bronconeumologia	24	280	11.7	Chinese Medical Journal	15	148	9.9
Clinics in Chest Medicine	24	278	11.6	Jornal Brasileiro de Pneumologia	15	119	7.9

C: Record count, C: Number of citation, AC: Average citation per document

Citation Analysis

Among the 5323 articles published on MV, the first 25 articles with the highest number of citations (with more than 450 citations) according to the total number of citations were presented in **Table 3**. In the last column of **Table 3**, the average number of citations the articles received per year was given.

Co-citation Analysis

There were 86393 studies in the references section of 5323 articles published on MV. Among these studies, the studies with more than 150 citations and the highest number of co-citations were respectively Brower et al. (2000) (Number of co-citation: NC=389), Boles et al. (2007) (NC=240), Knaus et al. (1985) (NC=213), Esteban et al. (2002) (NC=202), Esteban et al. (1995) (NC=189), Yang and Tobin (1991) (NC=187), Amato et al. (1998) (NC=175) and Ely et al. (1996) (NC=161) (24-27,12,8,28,7).

Keyword Analysis and Trend Topics

In all of the 5323 articles published on MV, 6990 different keywords were used. Among these keywords, 100 different keywords used in at least 16 different articles were shown in **Table 4**. The cluster network visualization map showing the results of the clustering analysis performed between these keywords was shown in **Figure 5**. As a result of the cluster analysis, it was determined that MV subjects formed 7 different clusters (Colors for Cluster 1: red, Cluster 2: green, Cluster 3: blue, Cluster 4: yellow, Cluster 5: purple, Cluster 6: turquoise, Cluster 7: orange). A trend network visualization map performed to identify trend topics was shown in **Figure 6**. The citation network visualization map performed to reveal the most cited topics was shown in **Figure 7**.

Table 3. The top 25 most cited articles with more than 450 citations on mechanical ventilation

No	Article	Author	Journal	PY	TC	AC
1	Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation	Kress JP. et al.	New England Journal of Medicine	2000	1736	75.48
2	Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome - A randomized controlled trial	Ranieri VM. et al.	JAMA-Journal of the American Medical Association	1999	1242	51.75
3	Characteristics and outcomes in adult patients receiving mechanical ventilation - A 28-day international study	Esteban A. et al.	JAMA-Journal of the American Medical Association	2002	1032	49.14
4	High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation	Simonnet A. et al.	Obesity	2020	942	314
5	Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously	Ely EW. et al.	New England Journal of Medicine	1996	878	32.52
6	A comparison of 4 methods of weaning patients from mechanical ventilation	Esteban A. et al.	New England Journal of Medicine	1995	792	28.29
7	A prospective-study of indexes predicting the outcome of trials of weaning from mechanical ventilation	Yang KL. And Tobin MJ.	New England Journal of Medicine	1991	772	24.13
8	Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation	Brook AD. et al.	Critical Care Medicine	1999	643	26.79
9	Mechanical ventilation guided by esophageal pressure in acute lung injury	Talmor D. et al.	New England Journal of Medicine	2008	631	42.07
10	Risk-factors for pneumonia and fatality in patients receiving continuous mechanical ventilation	Craven DE. et al.	American Review of Respiratory Disease	1986	628	16.97
11	Nosocomial pneumonia in patients receiving continuous mechanical ventilation - prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques	Fagon JY. et al.	American Review of Respiratory Disease	1989	620	18.24
12	A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure	Antonelli M. et al.	New England Journal of Medicine	1998	606	24.24
13	Comparison of 3 methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation	Brochard L. et al.	American Journal of Respiratory and Critical Care Medicine	1994	576	19.86
14	An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine Clinical Practice Guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome	Fan E. et al.	American Journal of Respiratory and Critical Care Medicine	2017	571	95.17
15	The use of continuous IV sedation is associated with prolongation of mechanical ventilation	Kollef MH. et al.	Chest	1998	551	22.04
16	A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial	Strom T. et al.	Lancet	2010	541	41.62
17	Daily cost of an intensive care unit day: The contribution of mechanical ventilation	Dasta JF. et al.	Critical Care Medicine	2005	522	29
18	Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation two randomized controlled trials	Jakob SM. et al.	JAMA-Journal of The American Medical Association	2012	515	46.82
19	Multiple system organ failure - Is mechanical ventilation a contributing factor?	Slutsky AS; Tremblay LN	American Journal of Respiratory and Critical Care Medicine	1998	515	20.6
20	Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation	Gajic O. et al.	Critical Care Medicine	2004	504	26.53
21	Severe impairment in lung-function induced by high peak airway pressure during mechanical ventilation - an experimental-study	Kolobow T. et al.	American Review of Respiratory Disease	1987	499	13.86
22	Patient-ventilator asynchrony during assisted mechanical ventilation	Thille AW. et al.	Intensive Care Medicine	2006	497	29.24
23	How is mechanical ventilation employed in the intensive care unit? An international utilization review	Esteban A. et al.	American Journal of Respiratory and Critical Care Medicine	2000	480	20.87
24	A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation	Cook D. et al.	New England Journal of Medicine	1998	475	19
25	Effect of failed extubation on the outcome of mechanical ventilation	Epstein SK. et al.	Chest	1997	465	17.88

PY: Publication year, TC: Total citation, AC: Average citations per year

Table 4. The 100 most frequently used keywords in articles on mechanical ventilation

Keywords	Number of uses	Keywords	Number of uses	Keywords	Number of uses
mechanical ventilation	1557	positive end-expiratory pressure	49	continuous positive airway pressure	21
intensive care unit (s)	252	prognosis	49	respiratory muscles	21
weaning	247	critical illness	45	weaning from mechanical ventilation	21
noninvasive (or non-invasive) ventilation, noninvasive (or non-invasive) mechanical ventilation	216	chronic respiratory failure	44	asthma	20
respiratory failure	183	extubation	44	mechanical ventilators	20
critical care	169	tidal volume	43	length of stay	19
mortality	153	diaphragm	42	monitoring	19
intensive care	124	survival	42	newborn	19
prolonged mechanical ventilation	119	lung injury	41	obesity	19
outcome (s)	118	bronchopulmonary dysplasia	38	complications	18
ventilation	115	sepsis	37	endotracheal intubation	18
tracheostomy	112	ICU	36	inflammation	18
acute respiratory distress syndrome	105	quality of life	36	pneumothorax	18
COVID-19	105	risk factors	36	spontaneous breathing trial	18
acute respiratory failure	91	cardiac surgery	35	atelectasis	17
ventilator weaning	87	respiratory distress syndrome	33	barotrauma	17
home mechanical ventilation	86	respiratory mechanics	33	cancer	17
sedation	78	epidemiology	32	controlled mechanical ventilation	17
respiration	77	mechanical	31	delirium	17
chronic obstructive pulmonary disease	75	dexmedetomidine	29	endotracheal tube	17
ventilator-induced lung injury	75	ventilator	28	Guillain-Barre syndrome	17
pneumonia	74	child	27	midazolam	17
acute lung injury	72	lung	27	neonate	17
pediatric (s)	70	nursing	27	positive-pressure respiration	17
artificial	67	Sars-CoV-2	27	pulmonary hypertension	17
ARDS	63	oxidative stress	25	surfactant	17
artificial respiration	63	propofol	25	ultrasonography	17
invasive mechanical ventilation	62	amyotrophic lateral sclerosis	24	ultrasound	17
children	60	extracorporeal membrane oxygenation	24	infant	16
COPD	56	hemodynamics	24	lung mechanics	16
respiration, artificial	55	ventilators	24	nitric oxide	16
respiratory insufficiency	55	hypercapnia	23	spontaneous breathing	16
ventilator-associated pneumonia	53	PEEP	23		
intubation	50	critically ill	22		

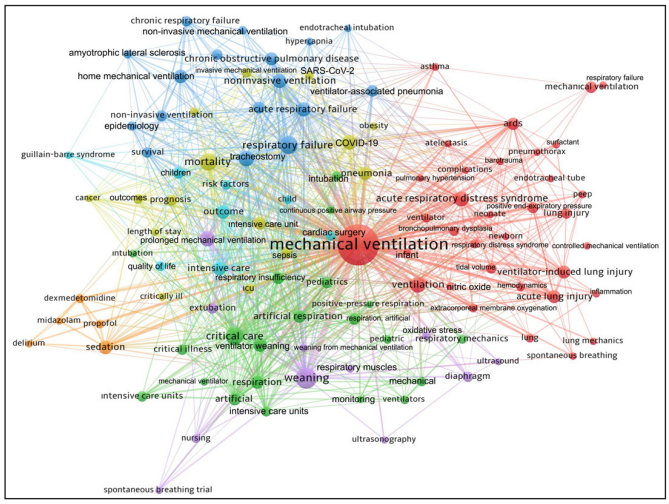

Figure 5. Network visualization map for cluster analysis based on keyword analysis performed to identify clustering of mechanical ventilation. Footnote: Each color represents a different cluster. Keywords in the same cluster are of the same color. The larger the number of times the keyword is used in articles, the larger the circle it represents

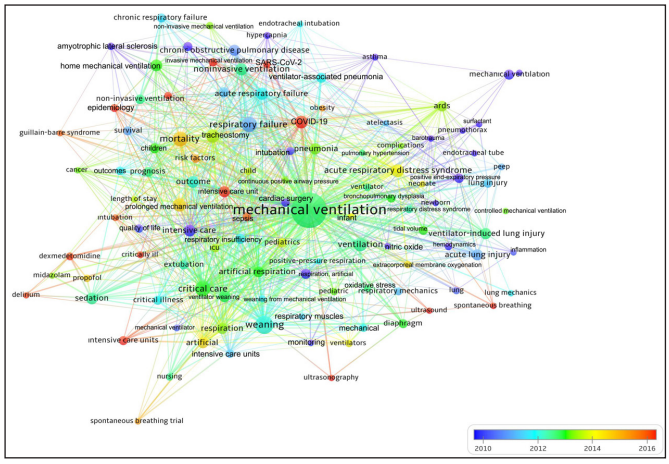

Figure 6. Network visualization map based on keyword analysis to identify past and current trends on mechanical ventilation. Footnote: In the indicator given in the lower right corner of the figure, the topicality of the article increases from blue to red (blue-green-yellow-red). The larger the number of times the keyword is used in articles, the larger the circle it represents

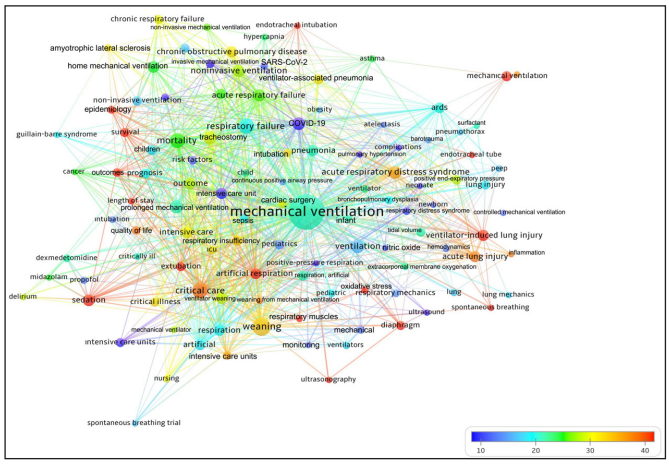

Figure 7. Network visualization map based on keyword analysis performed to identify the most cited topics on mechanical ventilation. Footnote: In the indicator given in the lower right corner of the figure, the number of citations received by the subject increases from blue to red (blue-green-yellow-red). The larger the number of times the keyword is used in articles, the larger the circle it represents

DISCUSSION

MV has accelerated the development of modern ICUs and has become a life-saving treatment (29). The history of MVs is around 200 years. MVs in the form of negative pressure ventilation first appeared in the early 1800s, while positive pressure devices began to be used in the 1900s. On the other hand, Today's typical ICU ventilator started being developed in the 1940s (30). Today, with the development of technology, ventilators can be used invasively and non-invasively. In addition, patient-specific settings can be made to provide ventilation support to patients. The COVID-19 pandemic, caused by SARS-CoV-2, emerged in late 2019 and has negatively affected all humanity as a global health problem as of 29 November 2021 (31-35). With the COVID-19 pandemic, the importance of MV has emerged once again due to respiratory support, which is one of the most important parts of the treatment for respiratory failure in patients with COVID-19 pneumonia (14,36,37). This situation was seen with the increase of publications on MV during the pandemic period.

When the number of articles published on MV by years was evaluated, 4 different trend periods were determined. The first period was the period 1980–2004. During this period, an average of 62 articles (between 18-108) were published annually. The second period was the 2005–2010 period. During this period, an average of 141 articles (between 106-169) were published annually. The third period was the period 2011–2019. In this process, an average of 231 articles (between 207-261) were published annually. The fourth period was the period 2020–2021. 384 articles were published in 2020 and 473 articles in 2021. The fact that there is an increasing publication trend over the years can be explained by the increase in the number of intensive care beds all over the world and the parallel increase in MV applications. The remarkable increase in the number of articles published in the last 2 years can be explained by the serious increase in MV application due to the COVID-19 pandemic. When the number of articles that can be published in the next five years obtained with the exponential smoothing estimator, which takes into account seasonal correction, is evaluated, it has been determined that the number of articles to be published on MV will continue with an increasing trend. This situation also shows that there may be a faster increase due to COVID-19 and similar pandemics that primarily affect the respiratory system.

When the publication distributions of the countries are examined, 14 of the first 17 active countries that contribute the most to the literature on MV article productivity are developed countries (USA, France, Canada, Germany, Spain, Italy, United Kingdom, Netherlands, Australia, Japan, Switzerland, Taiwan, Sweden, and South Korea) were determined. 3 of the 17 active countries (China,

Brazil, and Turkey) were developing countries. However, these countries have large economies, too. When the results of the correlation analysis were evaluated, a high level of correlation was found between article productivity and GDP, and a moderately significant correlation was found between GDP per capita and HDI values. This situation, in line with the literature, showed that the economic size and level of development of countries are effective factors in article productivity (16-18). In addition, the fact that these countries have more intensive care beds and have a significant share in the production of MV devices can explain more studies have been conducted in these countries.

When the density map created according to the total cooperation score between the countries was evaluated, it was determined that the first 15 countries with the most intensive cooperation were USA, Canada, Germany, Spain, Italy, France, England (in the United Kingdom), Netherlands, Brazil, Australia, Argentina, Greece, Switzerland, China, and Belgium, respectively. When the co-authorship cooperation of countries on MV is examined, it is seen that regional international collaborations based on the geographical neighborhood are common in article production (Countries in similar regions in the same cluster: (Austria, Belgium, Germany, France, Hungary, Netherlands, Serbia, Switzerland) (England, North Ireland, Scotland), (Croatia, Czech Republic, Denmark, Finland, Italy, Poland, Slovakia, Sweden), (Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, Peru, Uruguay, Venezuela), (China, Japan, South Korea, Malaysia, Singapore, Taiwan, Thailand, Indonesia) (Saudi Arabia, Egypt, Iran, Pakistan, India)).

The journals that publish the most articles on MV were Critical Care Medicine, Chest, Intensive Care Medicine, Respiratory Care, American Journal of Respiratory and Critical Care Medicine, Critical Care, Journal of Critical Care, Plos One, Anesthesiology, Pediatric Pulmonology, American Journal of Critical Care ve American Review of Respiratory Disease. We can recommend that authors who are in the research process of MV and want to publish on MV should consider the journals presented in **Table 2**. When the citation analyses of the journals that have published at least 5 articles on this subject are evaluated, the most effective journals according to the average number of citations per article they publish were New England Journal of Medicine (Average Citation Per Article, AC=534), Annals of Internal Medicine (AC=206), JAMA-Journal of the American Medical Association (AC=184), Lancet (AC=181), American Review of Respiratory Disease (AC=148), American Journal of Respiratory and Critical Care Medicine (AC=134), BMJ-British Medical Journal (AC=119), and Lancet Respiratory Medicine (AC=107). We can recommend that researchers who want to see more impact on their work to be published should primarily consider these journals.

When the analyzed articles were evaluated according to the total number of citations they received, it was determined that the most cited study was the study by Kress et al. (38) titled "Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation" published in the New England Journal of Medicine. The second study was the study by Ranieri et al. (39) titled "Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome-A randomized controlled trial" published in the JAMA-Journal of the American Medical Association. The third study was Esteban et al. (27)'s study titled "Characteristics and outcomes in adult patients receiving mechanical ventilation - a 28-day international study" published in the JAMA-Journal of the American Medical Association. When the analyzed articles were evaluated according to the average number of citations they received per year, it was determined that the most effective study was the article titled "High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation" by Simonnet et al. (40). The second study was the article titled "Elevated levels of IL-6 and CRP predict the need for mechanical ventilation in COVID-19" by Herold et al. (41). The third study was Fan et al. (3)'s Guideline on Mechanical Ventilation in Adult Patients with ARDS. The studies that received the highest number of co-citations from all analyzed articles were Brower et al. (24), Boles et al. (25), Knaus et al. (26), Esteban et al. (27), Esteban et al. (12), Yang and Tobin (8), Amato et al. (28), Ely et al. (7). We can recommend researchers interested in this subject read these publications first. It can be explained by the fact that the number of citations received per year in a very short period of time is in studies containing COVID 19 cases, the clinical uncertainties associated with the COVID 19 disease still contain question marks, and there are not enough data on effective MV strategies.

When the keyword analysis findings were evaluated, it was seen that MV subjects formed 7 different main clusters as a result of the cluster analysis. The most studied subjects from past to present were intensive care unit, weaning, non-invasive mechanical ventilation, respiratory failure, critical care, mortality, outcome (s), prolonged mechanical ventilation tracheostomy, acute respiratory distress syndrome, COVID-19, home mechanical ventilation, sedation, respiration, chronic obstructive pulmonary disease, ventilator-induced lung injury. The most cited keywords were sedation, artificial respiration, ventilator-induced lung injury, epidemiology, outcomes, survival, extubation, diaphragm, oxidative stress, ultrasonography, respiratory muscles, length of stay, quality of life,

endotracheal intubation, endotracheal tube, spontaneous It was determined that he had breathing, acute lung injury, inflammation, weaning from mechanical ventilation, acute respiratory distress syndrome. According to the results of the analysis made to determine the trend topics, the trend keywords studied in recent years were COVID-19 (SARS CoV-2), intensive care unit, dexmedetomidine, epidemiology, delirium, invasive mechanical ventilation, spontaneous breathing, ultrasound/ultrasonography, critically ill, sepsis, intubation, risk factors, Guillain-Barre syndrome, and obesity. Based on these findings, subjects such as sedation, inflammatory process, lung injury, and the outcome can be evaluated as topics that are still up-to-date and can be research topics. In addition, it should not be a surprise that point-of-care USG, which has been widely used in recent years on MV effects and follow-up, is included in the keywords.

As a result of our literature review on MV, we could not find any bibliometric study on this subject. It can be said that this study is the first bibliometric study on this subject. In addition, the use of many statistical approaches such as trend keyword analysis, international cooperation analysis, and correlation analysis, apart from citation analysis, can be said to be the superior aspects of this study.

As a limitation of this study, it can be said that we only used the WoS database to obtain the analyzed articles. However, in many bibliometric studies carried out in the literature, only the WoS database was preferred. According to the Scopus database, WoS indexes the articles published in more influential journals (Only journals scanned in SCI-expanded, ESCI, and SSCI indexes). On the other hand, citation analyzes cannot be performed in the PubMed database (16-19).

CONCLUSION

In this comprehensive bibliometric research we conducted on MV, we shared the statistical analysis information of 5323 articles published since 1980. It has been determined that the most studied trend topics in recent years are COVID-19 (SARS CoV-2), intensive care unit, dexmedetomidine, epidemiology, delirium, invasive mechanical ventilation, spontaneous breathing, ultrasound/ultrasonography, critically ill, sepsis, intubation, risk factors, Guillain-Barre syndrome, and obesity. With the developing technology, the usage area of MV is increasing and this situation is also reflected in the publications in the literature. It was also observed that the number of studies on MV increased with the COVID-19 (SARS CoV-2) pandemic. This study, which includes the bibliometric analysis of MV by summarizing the literature, will guide the authors who want to study in this area.

ETHICAL DECLARATIONS

Ethics Committee Approval: Since our research article is a bibliometric study, there is no need for an ethics committee approval.

Informed consent: For this type of study, formal consent is not required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declares that she has all participated in the design, execution, and analysis of the paper and that have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1118861
J Health Sci Med 2022; 5(4): 1062-1067

Treatment outcomes in high-risk prostate cancer: a single-centre experience

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Cite this article as: Kekilli E, Güzle Adaş Y. Treatment outcomes in high-risk prostate cancer: a single-centre experience. J Health Sci Med 2022; 5(4): 1062-1067.

ABSTRACT

Aim: The aim of that study was to evaluate the treatment results of patients with high-risk prostate cancer who received image-guided intensity-modulated radiotherapy with curative intent.

Material and Method: Patients who underwent curative radiotherapy (RT) for high-risk prostate cancer were evaluated retrospectively in our clinic from April 2010 to April 2021. Demographics, prostate specific antigen (PSA) levels, gleason score (GS), the TNM stage of the tumor, and the success of treatment and complications were noted.

Results: Eighty-two patients were evaluated. The mean follow-up time was 39.1 months. The mean age was 71.2±6.2 (range 50-84 years) years. The mean PSA levels of the patients was 41.1±33.8, and the median was 27 ng/ml (range 8-129 ng/ml). The mean GS of the patients was 8.3±0.6, and the median was 8 (range 7-10). The mean overall survival (OS) rate was 75.6%; survival rates for 24 months and 36 months were 91.1% and 80.4% respectively. The progression-free survival (PFS) was found to be 62.8%. Moreover, the PFS time was found to be 66,6 months. Twenty-four months and 36 months PFS rates were 83.6% and 65.4%, respectively.

Conclusion: Intensity-modulated radiotherapy (IMRT) combined with androgen deprivation therapy is a safe and effective treatment modality for elderly patients with high-risk prostate cancer.

Keywords: Prostate cancer, IMRT, high risk, treatment

INTRODUCTION

With a projected 1 414 259 new cancer cases and 375 304 deaths in 2020, prostate cancer is the second most commonly diagnosed cancer and the sixth leading cause of cancer mortality among men globally (1). Prostate cancer is categorized as very low risk, low risk, intermediate-risk, high risk, and very high risk according to PSA levels, GS, and TNM stage. Most patients with low-risk diseases can safely prefer active surveillance, while RT or radical prostatectomy (RP) is curative for patients with intermediate-risk prostate cancer (2). Radical prostatectomy or external beam radiotherapy with androgen deprivation treatment (ADT) should be considered for high-risk prostate cancer patients with PSA levels greater than 20 ng/ml, Gleason grade group 4 or 5, and/or clinical stage T3 or higher. Patients with high-risk prostate cancer are at an increased risk of oncological progression, so a multidisciplinary treatment approach is recommended for the ideal treatment of high-risk prostate cancer. Whether surgery or RT, treatment-related side effects, such as urinary, bowel, and sexual dysfunction, should be considered regardless of the treatment method chosen. In a systematic review that analysed the benefits and risks of surgery and RT in high-risk patients with localized and locally advanced prostate cancer, quality of life data mainly found that surgery was associated with genitourinary toxicity and sexual dysfunction, and radiotherapy was associated with bowel problems (3). Past studies have compared RP with RT applied to conventional RT techniques; modern RT techniques can deliver high doses to the tumor while minimizing toxicity to healthy tissues. So, RT-related side effects decreased with technological advances in radiotherapy. Intensity-modulated radiotherapy is associated with a substantial reduction in acute grade 2 gastrointestinal system (GIS) toxicity with decreasing trend in late grade 2 GIS toxicity (4,5). Pasalic et al. (6) showed that dose escalation from 70 Gray (Gy) to 78 Gy improved biochemical, clinical failure, and prostate cancer-specific mortality. In a study evaluating the efficacy of dose escalation in patients with localized and very high-risk localized prostate cancer: the external beam radiotherapy (EBRT) group treated with 70-72 Gy, the high

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Received: 19.05.2022 **Accepted:** 10.06.2022

dose EBRT(HDEBRT) group treated with 74-80 Gy, and the high-dose-rate brachytherapy (HDR)+EBRT(HDR boost) groups were compared using multi-institutional retrospective data. In the results of this study, the actuarial 5-year biochemical disease-free survival (bDFS) rate, prostate cancer-specific survival (PSS) rate, and overall survival rate were 75.8%, 96.8%, and 93.5%. Group HDEBRT showed superior 5-year bDFS rate (81.2%) as compared to the group EBRT (66.5%) (p<0.0001) with a hazard ratio of 0.397. Equivocal 5-year PSS (98.3% and 94.8% in group HDEBRT and group EBRT) and OS (93.7%) were found. When the three groups were compared in terms of late grade ≥2 toxicities in gastrointestinal and genitourinary system, the results were found to be similar. Therefore, both HDEBRT and HDR boost could be good options for improving the bDFS rate in cT3-T4 localized prostate cancer without affecting PSS and OS (7).

IMRT with Image Guided Radiotherapy (IGRT) dose-escalated irradiation of prostate cancer has been applied as a standard in our clinic. This study evaluated our institutional experience with high-risk prostate cancer patients treated by definitive high dose IMRT with IGRT.

MATERIAL AND METHOD

The study was initiated with the approval of the University of Health and Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Studies Ethics Committee (Date: 11/12/2021, Decision No:2021-11/3). All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

We retrospectively reviewed the clinical data of 82 patients treated between April 2010 and April 2021 with IMRT for high-risk prostate cancer. All patients had RT combined with ADT or orchiectomy.In addition to a bone scan, all patients had pelvic computed tomography or magnetic resonance imaging. Prostate-specific membrane antigen positron emission tomography was used on certain patients. Prostate cancer had been histologically verified in men above the age of 18. The inclusion criteria were high-risk prostate cancer according to D'Amico's risk classification criteria (≥T2c or a GS 8-10 or PSA level >20 ng/dl). Patients with clinical pelvic lymph node involvement were not included in the study.All of the patients received IMRT with daily imaging guidance.All treatment plans were generated by using inverse planning and the IMRT technique. The planning CT scan was performed with 3-mm slices in the supine position. RT was delivered in 2 Gy daily fractions with 6 MV photon beams five days a week. In some patients, pelvic lymph nodes were also selectively irradiated. Partin nomograms are used to decide elective pelvic lymph node RT, Pelvic RT applied to patients with pelvic lymph node involvement risk over 20% (8). Prostate and entire seminal vesicles were included in the CTV. The planning treatment volume (PTV) was generated by adding an 8-mm isotropic expansion to the CTV, excepting 6 mm posteriorly. According to the International Commission of Radiation Units and Measurements recommendations, the dose was prescribed at the isocentre. For treatment planning, the dose-volume constraints for the bladder were V65 Gy<50%; for the small bowel V45≤195 cc; for the rectum: V50 Gy≤50%, V60 Gy≤35%, and V70 Gy≤ 20%. Dose constraints for the organs at risk (OAR) were selected based upon Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) data (9). All patients were treated using bowel- and bladder-filling protocols. KV images and a cone beam-CT (CBCT) scan were taken prior to each delivery. Shifts were performed by aligning finally to soft tissue on CBCT.

The information about post-treatment follow-up of the patients was obtained from the hospital files. The treatment outcomes were assessed in biochemical failure, progression free survival (PFS) rates, and OS rates. BF was defined by a nadir PSA level+2 ng/ml. The final status of the patients was checked from the national death notification system.

Statistical analysis

Analyses were evaluated in 22 package programs of SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL).The study shows descriptive data as n and % values in categorical data and mean±standard deviation (Mean±SD) values in continuous data. The Chi-square analysis (Pearson Chi-square) test was used to compare categorical variables between groups. Conformity of continuous variables to normal distribution was evaluated with the Kolmogorov Smirnov test. Kruskal-Wallis test was used in the measurement comparison of more than two groups. Log Rank (Mantel-Cox) analysis was performed to compare overall survivals between categories. The statistical significance level was accepted as p<0.05

RESULTS

The study included 82 patients with high-risk prostate cancer who received IMRT in our radiation oncology department between April 2010 and April 2021. The mean follow-up time was 39,1 months. The mean age was 71.2±6.2 (range 50-84 years) years. The mean PSA value of the patients was 41.1±33.8, and the median was 27 ng/ml (range 8 -129 ng/ml). While 71 (86.6%) of the patients had a PSA level<100 ng/ml, 11 (13.4%) had a PSA level≥ 100 ng/ml. The mean GS of the patients was 8.3±0.6, and the median was 8 (range 7-10). While 52 patients (63.4%) had a GS≤8, 30 (36.6%) had a GS>8.

The TNM stage of 31 (37.8%) patients were T2N0M0, and 51 (62.2%) were T3N0M0 and T4N0M0. The mean RT dose of the patients was 76.4±1.7 Gray (Gy), and the median was 78 Gy (range 74-78 Gy). Twenty-four patients

(29.3%) received 74 Gy RT, 17 patients (20.7%) received 76 Gy RT and 41 patients (50%) received 78 GyRT. Thirty-four (41.5%) patients received pelvic radiotherapy, while the others received only local (including seminal vesicles and prostate) RT. When the last status of the patients was analysed, 49 (59.8%) complete responses, 13 (15.9%) local recurrence, and 16 (19.5%) distant metastasis was observed. There was no follow-up in 4 (4.9%) patients. Twenty (24.4%) deaths were observed during the follow-up time. Fifteen of these deaths (78.9%) were caused by cancer. The OS rate was 75.6%; survival rates for 24 months and 36 months were 91.1% and 80.4% (**Figure 1**).

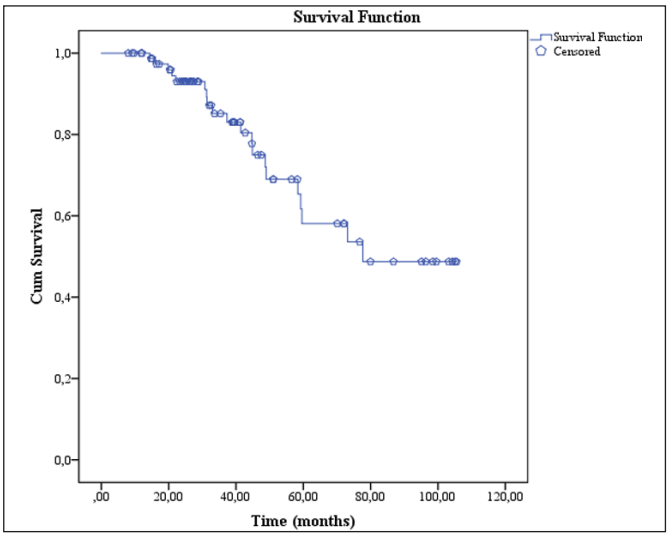

Figure 1. Overall Survival

GIS and genitourinary system (GUS) side effects due to RT were also evaluated according to RTOG toxicity criteria (10). While 52 of the patients (63.4%) had no GIS side effects, 18 (22%) of them had grade 1(increased frequency of bowel habits), and two of them (14.6%) had grade 2 GIS (diarrhea requiring drugs) side effects. While 38 (46.3%) of the patients had no GUS side effects, 33 (40.2%) of them had grade 1 (frequency of urination, urgency not requiring medication) and 11 (13.4%) had grade 2 (dysuria, urgency, bladder spasm) GUS side effects. Patients' characteristics and the results are summarized in **Table 1**.

Table 1. Patients' characteristics and results

		n	%
Age (years) , Mean±SD		71.2±6.2	
PSA (ng/ml)	<100	71	86.6
	≥100	11	13.4
Gleason score	≤8	52	63.4
	>8	30	36.6
TNM stage	II	31	37.8
	III-IVA	51	62.2
RT dose Gy, Mean±SD		76.4±1.7	
Pelvic RT	Yes	34	41.5
	No	48	58.5
GIS side effects	No	52	63.4
	Grade 1	18	22.0
	Grade 2	12	14.6
GUS side effects	No	38	46.3
	Grade 1	33	40.2
	Grade 2	11	13.4
Status at last control date	Complete response	49	59.8
	Local recurrence	13	15.9
	Distant metastasis	16	19.5
	No follow-up	4	4.9
Death	yes	20	24.4
	no	62	75.6
Cause of death	cancer	15	78.9
	Non-cancerous	4	21.1

Abbreviations; SD=standard deviation; RT=Radiotherapy; PSA=Prostate specific antigen GIS=gastrointestinal; GUS=genitourinary

The effects of PSA level, Gleason score, pelvic RT, treatment response, and TNM stage on OS were evaluated. The mean survival rate of those with a PSA value below 100 ng/ml was significantly higher than the mean survival time of those with a PSA value of 100 ng/ml and above (81.7% vs. 36.4%; p<0.001). The OS rate was significantly higher in the complete responder group than in the local recurrences and metastatic group (91.8% vs. 69.2% vs. 25%; p<0.001). There was no significant effect of GS, TNM stage, and pelvic RT on OS (p=0.931, p=0.810, p=0.137). Results of OS and comparison by various parameters are summarized in **Table 2**.

Table 2. Overall survival and comparison by various parameters

		OS rate	Mean	Standard Deviation	95% CI	p*
PSA (ng/ml)	<100	81.7	81.486	5.273	71.152-91.821	<0.001
	≥100	36.4	40.633	5.898	29.074-52.193	
Gleason score	≤8	76.9	79.256	5.882	67.727-90.785	0.283
	>8	73.3	66.191	7.934	50.639-81.742	
TNM stage	T2N0M0	77.4	74.834	7.915	59.321-90.347	0.810
	T3N0M0-T4N0M0	74.5	75.658	6.470	62.977-88.338	
Pelvic RT	Yes	61.8	66.278	6.015	54.488-78.068	0.137
	No	85.4	84.020	7.045	70.211-97.829	
Status at last control date	Complete response	91.8[a]	95.015	4.724	85.755-104.274	<0.001
	Local recurrence	69.2[b]	60.075	11.329	37.871-82.279	
	Distant metastasis	25.0[b]	40.789	4.482	32.006-49.573	

*Log Rank (Mantel-Cox) analysis was performed. Abbreviations: PSA=Prostate specific antigen, RT= Radiotherapy, OS=Overall survival

Local recurrence was observed in 13 patients, and distant metastasis was observed in 15 patients. The PFS rate was found to be 62.8%. The PFS time was found to be 66.6 months. 24-month and 36-month PFS rates were 83.6% and 65.4%, respectively. (**Figure 2**)

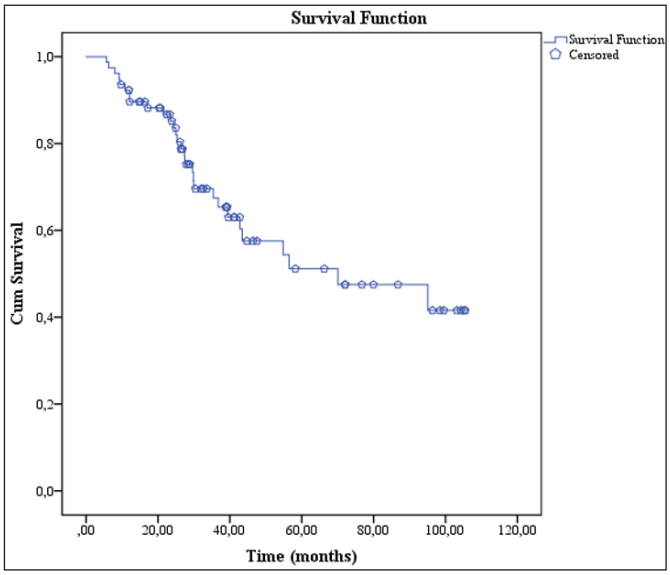

Figure 2. Progression-free Survival

The mean PFS of those with a PSA level<100 ng/ml was significantly higher than the mean survival of those with a PSA level≥100 ng/ml (70.6% vs. 10%; p<0.001). The mean PFS of those with a GS≤8 was significantly higher than the mean of survival of those with aGS> 8 (68.8% vs. 53.3%; p=0.042). There was no significant TNM stage and pelvic RT effect on PFS. Results of PFS and its comparison according to various parameters are summarized in **Table 3**.

For ADT only three patients had orchiectomy before RT, and all other patients received gonadotropin-releasing hormone agonist for 24 months.

Table 3. Progression-free survival and its comparison according to various parameters

	PFS rate	mean	Standard deviation	%95 Confidence Interval	p*
PSA ng/ml					<0.001
<100	70.6	74.110	5.616	63.103-85.117	
≥100	10.0	30.227	6.057	18.354-42.099	
Gleason score					0.042
≤8	68.8	72.223	6.487	59.509-84.936	
>8	53.3	55.848	7.983	40.201-71.495	
TNM stage					0.592
II	69.0	71.034	8.851	53.686-88.382	
III-IVA	59.2	64.311	6.500	51.572-77.051	
Pelvic RT					0.593
Yes	63.6	65.503	6.957	51.868-79.139	
No	62.2	67.984	6.949	54.365-81.603	

*Log Rank (Mantel-Cox) analysis was performed. Abbreviations: PSA= Prostate specific antigen, RT= Radiotherapy, PFS=Progression-free survival

DISCUSSION

IMRT with long-term ADT is a standard treatment option for localized high-risk prostate cancer patients. The effect of RT with ADT on cancer-specific survival and OS has been demonstrated by studies (11,12). In the EORTC 22863, the 10-year disease-free survival (48% vs. 23%) and OS (58% vs. 40%) were improved with a combination therapy compared with RT alone. Also, prostate cancer mortality was decreased from 30% to 10% with combination therapy (11). Clinical studies have been conducted to compare short-term and long-term ADT to investigate the toxicity associated with long-term ADT. RTOG 92-02 has investigated four months versus 28 months of ADT, and EORTC 22961 investigated six months versus 36 months of ADT. Both studies demonstrated improvements in OS with prolonged ADT. There was no statistically significant difference in ADT toxicity between long-term and short-term ADT (13,14). Nabid et al. (15) compared long-term (36 months) and short-term (18 months) ADT with RT; they showed no significant difference in survival between the two groups. ADT toxicity was high for hot flushes, sore or enlarged nipples or breasts, and sexual activity in the 36-month group. When evaluated with both the treatment results and toxicity, 18 months of ADT seems to be an attractive alternative for patients not tolerating the ADT. In this study, all patients had RT combined with ADT or orchiectomy. The Duration of ADT was 24 months in all patients who received ADT. No significant side effects were observed due to ADT. In this study, when evaluated together with our survival and disease-free survival results, it was found that 24-month ADT use is a safe treatment period in terms of both treatment results and side-effect profile.

Pelvic lymph node irradiation is controversial in patients with high-risk prostate cancer without lymph node involvement. Based on Partin tables or other tools, whole-pelvis radiation therapy (WPRT) can be considered in men with an estimated risk of nodal involvement exceeding 20%. WPRT for high-risk and very high-risk prostate cancer resulted in significantly improved biochemical failure-free survival (95.0% vs. 81.2% p<0.0001) and disease-free survival (89.5% vs. 77.2% p=0.002) as compared with only prostate RT, but did not impact OS (92.5% vs. 90.8% p=.83) (16). A randomized trial evaluated the role of WPRT and did not demonstrate a clear benefit of WPRT compared with prostate-only radiation therapy; 5-year PFS rates were 66% and 65.3% for the pelvis+prostate and prostate alone arms, respectively (p=.34) (17). In our study, thirty-four (41.5%) patients received pelvic radiotherapy. In contrast, the others received only local (including seminal vesicles and prostate) RT; there was no significant pelvic RT effect on OS and PFS.

In a study evaluating the results of hypo-fractionated IMRT for localized prostate cancer for patients with high-risk disease, the 10-year biochemical relapse-free survival(b-RFS) rate was 42% (p<0.0001), and the 10-year clinical relapse-free survival was 72% (p<0.0001) (18). Our biochemical outcomes are consistent with other trials reported in the literature, despite petite sample sizes. According to a risk assessment study, the probability of 5-year relapse-free after RP ranges from 49%-80% (19). In our study, the PFS rate was 62.8%. Twenty-four-month and 36-months PFS rates were 83.6% and 65.4%, respectively. These results are comparable with the RP results in Yossepowitch et al.'s (19) study.

A metaanalysis by Petrelli et al. (20) included trials that compared the outcomes of high-risk prostate cancer patients treated with RT or RP and showed that surgery was associated with better OS and prostate cancer-specific mortality than RT. However, RT was associated with a slightly better b-RFS than RP alone. Moreover, their study showed that most older RT patients had comorbidities and had adverse clinical features (e.g., higher rate of Gleason score ≥8, higher median PSA values) than RP patients. Also, in this study, RT techniques were old, and the RT doses were lower than the suggested current RT doses. There were 82 patients with high-risk prostate cancer who received definitive RT in this study, and their mean age was 71.2±6.2 (range 50-84 years) years. While 71 (86.6%) of the patients had a PSA<100 ng/ml, 11 (13.4%) had a PSA≥100 ng/ml. The mean PSA level of the patients was 41.1±33.8, and the median was 27 ng/ml (range 8 -129 ng/ml). While 52 patients (63.4%) had a GS ≤8, 30 (36.6%) had a GS > 8. The mean GS of the patients was 8.3±0.6, and the median was 8 (range 7-10). IMRT and IGRT are the standard of RT for prostate cancer. Dutch Trial compared conventional fractionation(39 fractions of 2 Gy) and hypofractionation (19 fractions of 3.4 Gy); there was no difference in 5-year relapse-free survival; gastrointestinal toxicity was more common in the hypofractionation group (21). In our study, the mean RT dose of the patients was 76.4±1.7 Gy, and the median was 78 Gy (range 74-78 Gy). Twenty-four patients (29.3%) received 74 Gy RT, 17 patients (20.7%) received 76 Gy RT and 41 patients (50%) received 78 GyRT. Thirty-four (41.5%) patients received pelvic RT, while the others received only local (including seminal vesicles and prostate) RT.

Gleason scores 8-10 are typically considered one grade category within the literature (22). GS 9-10 tumors have almost twice the risk of progression compared to GS 8, as demonstrated in the study by Pierorazio et al. (23), biochemical recurrence was not seen at 2 years in 70.9%, and 73.7% of men with GS 8 on biopsy and RP, respectively. For men with GS 9 and 10 on biopsy and RP, 66.7% and 58.5%, respectively, had no biochemical recurrence at 2 years. In our findings, the mean PFS of those with a GS≤8 was significantly higher than the mean survival of those with aGS 9-10 (68.8% vs. 53.3%; p=0.042).

In a study by Ang et al. (24) evaluating the effect of PSA level at the time of diagnosis on OS and prostate cancer-specific mortality; patients with a PSA >100 ng/ml at the time of diagnosis had significantly worse survival outcomes than those with PSA≤20 or 20-≤100 (p<0.001). Five-years survivals for each group (≤20; 20-≤100; >100) were: 87%, 62.5% and 29.1% respectively. The ten-year survivals for each group were 70.7%, 36.7%, and 18.2%, respectively. We obtained similar results in our study; the mean PFS of those with a PSA<100 ng/ml was found to be significantly higher than the mean of survival of those with a PSA≥100 ng/ml (70.6% vs. 10%; p<0.001).

The toxicity of RT is related to the dose of radiation delivered to surrounding healthy organs. Most related trials related to radiation toxicity included patients treated with older radiation techniques. Today IMRT is the mainly used technique for prostate cancer. When we evaluated the toxicities in our study, in the literature in which the patients treated using the dose and technique as in our clinic were evaluated, the toxicity rates were found as follows: 38.1% of patients experienced ≤ grade 2 GIS toxicity (grade1 12.4%, grade 2 25.6%). There was no grade 3 GIS toxicity. GUS late toxicity was reported at 4.1%: grade 1 0.8%, grade 2 3%, grade 3 only in 1. Only 21 patients (5.3%) developed chronic proctitis (25). In our findings, While 52 of the patients (63.4%) had no GIS side effects, 18 (22%) of them had grade 1, and 2 (14.6%) had grade 2 GIS side effects. While 38 (46.3%) of the patients had no GUS side effects, 33 (40.2%) of them had grade 1, and 11 (13.4%) had grade 2 GUS side effects.

CONCLUSION

As a result of our study, treatment decision in high-risk prostate cancer remains unclear; we think that RT combined with ADT may be the preferred treatment modality, especially in well-selected elderly patients with tolerable risk of side effects. In the elderly patient group with high-risk patient groups, starting treatment with a single modality may be recommended instead of burdening the patient with two significant treatment stresses. In some high-risk prostate cancer groups, it may be necessary to have adjuvant radiotherapy after surgery.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the University of Health and Sciences, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Clinical Studies Ethics Committee (Date: 11/12/2021, Decision No:2021-11/3).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: Both of authors declare that they have all participated in the design, data collection, analysis and interpretation of the data for the work and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1110424
J Health Sci Med 2022; 5(4): 1068-1072

Rate and reasons of missed screening mammography in the COVID-19 pandemic from Turkey

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Cite this article as: Akın ME. Rate and reasons of missed screening mammography in the COVID-19 pandemic from Turkey. J Health Sci Med 2022; 5(4): 1068-1072.

ABSTRACT

Aim: While screening mammography has been interrupted in many countries during the coronavirus disease (COVID-19) pandemic lockdowns, less is known about missed mammography screening and its reasons in the later periods of pandemic. In this study it was aimed to find out the rate and the reasons for missed mammography screening, and the associated factors in Turkey during the COVID-19 pandemic.

Material and Method: In this single center, cross-sectional observational study women who underwent mammography screening between September 1st to October 1st 2021 (15 months after the start of the COVID-19 pandemic) were recruited. A questionnaire developed for the purpose of this study was used to assess the participant characteristics, whether a screening mammography has been missed during pandemic and its reasons.

Results: The sample comprised of 144 women with a mean age of 50.2±8.0. Most of the sample were married and had children, 34.0% had chronic diseases. Ninety women (62.5%) misssed a screening mammography in the pandemic. Having equal or less than primary school education was associated with higher delay in mammography screening when compared to being having higher education (OR=2.26, 95%CI= 1.09- 4.69, p=0.027). Fear of COVID-19 transmission (92.2%) was the most common reason for missed mammography screening.

Conclusion: This study firstly demonstrated that most of the women delayed their screening mammography after the lockdown periods in the COVID-19 pandemic in Turkey and having equal or less than primary school education was associated with higher missed screening rates than having higher education levels. Effective solutions are needed to address the reasons for missed mammography screening to reduce breast cancer related morbidity and mortality both for this pandemic and for regular times.

Keywords: Mammography, cancer screening, breast cancer, missed mammography screening, COVID-19 pandemic

INTRODUCTION

Screening mammography is crucial in early diagnosis and prevention of advanced breast cancer and cancer related mortality (1). The World Health Organization announced that Coronavirus disease 2019 (COVID-19) outbreak had reached pandemic status on March 11, 2020 (2) and non-urgent cancer screening has become questionable and has been interrupted in many countries. The American College of Radiology recommended postponement of screening mammography as a form of non-urgent care (3).

As interruptions in cancer screening will lead to additional advanced diagnosed cancers and increase breast cancer related mortality (4); in different studies delay in breast imaging ranged between 87- 99% during the early stage of the pandemic (5-7). A study from Canada demonstrated that without adequate strategies to accommodate individuals who missed their screening, a six-month interruption would lead to 40,000 life-years lost (8). Therefore, it is important to know the rates and reasons for postponing screening mammography. Nationwide data from Taiwan showed that the total number of mammography screenings decreased significantly in the later stages of the pandemic (9). It was reported that the impact of the pandemic for mammography screening should be assessed in different populations (10).

In Turkey, breast cancer screening mammography has been started on July 2004 by the organization of screening centers by the Turkish Ministry of Health. However, like many countries, screening mammography have

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Received: 26.04.2022 **Accepted:** 10.06.2022

been temporarily suspended in the lockdown period during first months of the pandemic (11). After the first lockdown period, June 1st 2020, screening services were not shut down in Turkey while empirical knowledge shows that women still delay or postpone their screening mammography. However, the rates and reasons for missed mammography screening and its reasons in the later periods of pandemic is not reported in Turkey. This information is crucial to address the reasons and prevent late stage breast cancer and related death.

This study aimed to find out the rate and the reasons for missed mammography screening in Turkey during the late stages of the COVID-19 pandemic. It was hypothesized that the having low education would be associated with lower adherence to mammography screening program.

MATERIAL AND METHOD

The study was carried out with the permission of Yıldırım Beyazıt University Clinical Researches Ethics Committee (Date: 18.08.2021, Decision No: E-2021-46). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Patients

In this single center, cross-sectional observational study patients who will undergo mammography at the Yıldırım Beyazıt University Yenimahalle Training and Research Hospital Radiology Department between September 1st to October 1st 2021 (15 months after the lockdown period in Turkey) were included to this study. Inclusion criteria were being female, being≥40 years, able to write and speak in Turkish and providing written informed consent for this study.

Procedures

In the mammography waiting room, the researcher provided information about the study to the participants. After obtaining the informed consent form, the participants were given the written study form to fill in the waiting room. The study form was a questionnaire and included information on sociodemographic data and reasons for delays in screening mammography examinations. The reasons were asked as close ended questions and with yes or no checking boxes where participants were able to choose more than one reason. The reasons in the study form to check yes or no were: fear of COVID-19 transmission in the hospital, during the public transport, fear of pain in mammography, fear of radiation in the mammography, not being able to take leave from work, having COVID-19 infection at the time of screening in self or other family members, lack of knowledge on repeating mammography screening every year and being ashamed of mammography screening. There was also an open ended question at the end of the close ended questions for any other reasons that the participants want to express. The women were able to check multiple reasons in the study questionnaire. A missed mammography screening was defined as a delay in mammography screening after the lockdown period during the pandemic.

Data Analysis

Statistical analyses were done using IBM SPSS 20.0 (SPSS Inc., Chicago, IL, USA) package program. The Shapiro-Wilk test was used to determine whether the data were normally distributed. Numerical values were expressed as mean and standard deviation (SD) if distributed normally; median and interquartile range (IQR) values if not distributed normally. Categorical variables were given as numbers and percentages. The association between having chronic disease and not having any chronic disease, working versus not working (retired or housewife), having lower education (≤primary school) versus higher education (>primary school) (12) and missed mammography screening was done using the Chi-Square Test. These hypotheses were based on previous research of barriers to mammography screening and empirical knowledge of the author (13). The difference between ages of women who delayed and not delayed their screening mammography was tested with Student-t test if distributed normally, with Mann Whitney-U test if the distribution was not normal. The results were considered statistically significant using Odd's Ratios (OR), 95% Confidence Intervals (CI) and $p < 0.05$.

RESULTS

Totally, 188 patients were considered for eligibility in the study period. Of these, 39 (20.7%) did not provide consent for the study and 5 (2.7%) could not write in Turkish. Remaining 144 (76.6% of the recruited sample) patients comprised the study sample. The mean age of the sample was 50.2±8.0 years. All participants were women.

Sociodemographic and medical characteristics of the sample are summarized in **Table 1**. Most of the sample were married and had children. Median number of children was 2 (IQR: 2-3). Most women (70.1%) had more than primary school education. Forty-nine women (34.0%) had chronic disease including hypertension, diabetes mellitus, thyroid disease, asthma, cardiac disease, larynx cancer, thyroid cancer, Crohn's disease, chronic hepatitis and familial Mediterranean fever. Twenty-nine (20.1%) women had breast cancer family history and 54 (37.5%) had other cancers in the family history. Forty-one (28.5%) women had a friend with breast cancer.

Table 1. Sociodemographic and clinical characteristics of the sample (N= 144)

Sociodemographic characteristics	
Marital status (n, %)	
Married	122 (84.7)
Single	22 (15.3)
Have at least one child	136 (94.4)
Education (n, %)	
No education	3 (2.1)
Primary school	40 (27.8)
Secondary school	12 (8.3)
High school	45 (31.3)
University	39 (27.1)
Higher than university	5 (3.5)
Working status (n, %)	
Not working (housewife)	82 (56.9)
Working on a job	44 (30.6)
Retired	18 (12.5)
Clinical characteristics	
Chronic disease (any)	49 (34.0)
Hypertension	19 (13.2)
Diabetus mellitus	13 (9.0)
Thyroid disease	9 (6.3)
Asthma	4 (2.8)
Cardiac disease	5 (3.5)
Cancer	3 (2.1)
Other	6 (4.2)

Ninety women (62.5%) missed a screening mammography in the pandemic after the lockdown period. There was no difference in terms of having chronic disease versus not having any chronic disease (p=0.749), working versus not working (p=0.852) and mean age in women who delayed and have not delayed their screening mammography (50.8±7.8 vs 49.2±8.2 respectively, p=0.245). Having≤ primary school education was associated with higher delay in mammography screening when compared to being having higher education (OR=2.26, 95%CI=1.09- 4.69, p=0.027).

The reasons for delay in screening mammography during the pandemic that the women provided information for this study is given in **Table 2**. Fear of COVID-19 transmission (in the hospital (92.2%) and during public transport (35.6%)) was the most common reason for missed mammography screening. Five women provided other reasons to the open-ended questions including self-neglect, general dislike in being in hospitals, lack of permission by husband for the screening mammography, having more important life events, and having no health insurance.

Table 2. The reasons provided by the participants with delay in screening mammography during the pandemic (N=90)

The reasons of delay in mammography	**n**	**%**
Fear of COVID-19 transmission in the hospital	83	92.2
Fear of COVID-19 transmission during the public transport	32	35.6
Due to the fear of pain in mammography	18	20.0
Not being able to take leave from work	14	15.6
I had COVID-19 infection at the time of my screening	13	14.4
One of my family members had COVID-19 infection at the time of screening	11	12.2
I did not know that I have to repeat mammography screening every year	11	12.2
I believe that the radiation in the mammography has harmful effects	10	11.1
I do regular self physical exams so I do not need mammography screening	9	10.0
I am ashamed of mammography	4	4.4
Other	5	5.6

DISCUSSION

As the rate and reasons for missed mammography screening and its reasons in the later periods of pandemic has not been reported from Turkey, this study demonstrated the rate and reasons for missed screening mammography. Most of the women delayed their screening mammography and having equal or less than primary school education was associated with higher missed screening rates than having higher education levels. This information is crucial to address the reasons and prevent late stage breast cancer and related death. This research conducted in Turkey, firstly provided evidence for the reasons for delayed mammography screening during the pandemic. These reasons may be applicable for COVID-19 pandemic and possible future crises.

Tsai et al. (9) from Taiwan showed that although breast cancer screening program has continued during the COVID-19 pandemic, total number of screenings decreased by 22% . In our study the delay in screening mammography rate was much higher. It may be explained by higher accessibility to mammography screening in Taiwan where most of the women do not have to go the hospital and community services also provided screening. While the authors did not investigate the reasons, they discussed possible reasons such as restriction on hospital visits, triage of patients with COVID-19 infection risks, and fear of going to the hospital (9). In the United States of America where health insurance does not cover screening mammography for every citizen; poverty, lack of health insurance and being minority were key barriers to breast cancer screening different from our study (14,15). The most common reason for missed mammography screening in our study was fear of COVID 19 transmission in the hospital. It is important that one fifth of the study sample provided reasons for missed screening which were not related to the COVID-19 pandemic. These reasons included lack of information or misinformation of yearly screening mammography and

misinformation on radiation hazards. Three studies before the COVID-19 pandemic investigated the barriers and reasons for missed mammography screening (13,16). Two studies of Ozmen et al. (13, 16) investigated the rates and associates of mammography screening from a rural and an urban area of Turkey. Mammography screening rate was only 35% (16) similar to our study (37.5%). Widowhood, being illiterate, not reading newspapers regularly, unemployment, a monthly income lower than the hunger threshold, limited insurance were associated with missed mammography screening (13,16). Supporting our findings; women who had knowledge on regular mammography screening program and about little to none harmful effects of radiation during mammograms, screening rates were higher (16). Another study from Turkey found lack of mammography screening in 5 years as 37% in an urban population (17). It seems that missed screening rate has not been changed before and after the pandemic while fear of COVID-19 transmission was added to other reasons that were present before the pandemic.

Another aspect of this study is that 4 women were ashamed of their mammography screening, and 1 woman delayed the screening because her husband did not allow the screening. While these causes seem rare in this example from the Turkish capital, they can be much higher in rural areas. These reasons should be seen as preventable etiology of breast cancer mortality and morbidity, and should be addressed as soon as possible by the health care system.

This study has important implications for practice. United Nations Sustainable Development Goals and the World Health Organization's Global Monitoring Framework commits to reduce the burden of breast cancer in low- and middle-income countries (18). Turkey as a middle income country needs effective interventions based on an education model for increasing regular mammography screening rates (19).

The main strength of this study is the low refusal rate by the participants which lessens bias. The urban, single center setting is an important limitation of the study. Further research, therefore, is needed to investigate the rates and reasons of missed mammography screening in multiple, preferably international settings, including women with different education levels.

CONCLUSION

The results of this study showed that the missed screening mammography rate is high from the capital of Turkey. Studies are needed to investigate breast cancer outcomes after the COVID-19 pandemic. Effective solutions are needed to address the reasons for missed mammography screening to reduce breast cancer related morbidity and mortality both for this pandemic and for regular times.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Yıldırım Beyazıt University Clinical Researches Ethics Committee (Date: 18.08.2021, Decision No: E-2021-46).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1124163
J Health Sci Med 2022; 5(4): 1073-1080

Three years of interventional pediatric cardiology experience in a newly built city hospital

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Cite this article as: Sunkak S, Argun M. Three years of interventional pediatric cardiology experience in a newly built city hospital. J Health Sci Med 2022; 5(4): 1073-1080.

ABSTRACT

Aim: The importance of interventional methods in the treatment of congenital heart disease (CHD) is increasing. In this article, we retrospectively evaluated our angiography experience for the diagnosis and treatment of congenital heart diseases in the newly built Kayseri City Hospital for 3 years.

Material and Method: The demographic data of the patients, their diagnoses and information about interventions were evaluated retrospectively.

Results: In our center, 291 interventional procedures were performed in a 36-month period. 71 (24%) procedures were for diagnostic evaluation and 220 (76%) procedures were for treatment. 74 (25%) atrial septal defect (ASD) closure procedures, 9 (3%) ventricular septal defect (VSD) closure procedures and 62 (21.3%) patent ductus arteriosus (PDA) closure procedures were performed via percutaneous technique. Eleven of the patients who underwent PDA closure were <2500 g infants who hospitalized in the neonatal intensive care unit. Balloon valvuloplasty was performed for 17 (5.8%) pulmonary valvular stenosis and 9 (3%) aortic valvular stenosis. Balloon angioplasty was performed to aortic coarctation in 21 (7.2%) patients and stent angioplasty was performed in 4 (1.3%) patients. As rare procedures, stent angioplasty to ductus arteriosus in 4 (1.3%) patients, pericardiocentesis in 5 (1.7%) patients, and temporary pacemaker implantation in 1 patients were performed. Major complications occurred in 2 procedure for ASD closure, 1 procedure for stent implantation to the ductus arteriosus, and 1 procedure for aortic balloon valvuloplasty (1.3 %). Two patients died due to major complications related to angiographic procedures (0.68%).

Conclusion: Treatment of CHD with interventional methods should be preferred instead of surgery if anatomically appropriate, due to the lower rate of major complications, not requiring sternotomy, and shorter hospital stay. More experience is needed in pediatric cardiology teams who are new to these procedures.

Keywords: Congenital heart diseases, interventional treatments, city hospitals

INTRODUCTION

CHDs are the most common diseases among congenital anomalies, affecting 0.8% to 1.2% of live births all over the World (1). The incidence varies between 5-7.7% in the studies reported in Turkey (2). Mortality has decreased and survival rate has increased with easier access to health services, improvements in treatment methods and intensive care practice.

In recent years, many CHDs treated with surgery have become treatable with interventional methods. After the first balloon septostomy procedure was applied in 1966 as an interventional treatment, there have been many developments so far. Now, procedures such as balloon dilatations, device closure, stenting, transcatheter valve implantation have taken their place in interventional treatment in CHDs.

With the opening of the city hospital in Kayseri city in June 2018, interventional treatments for pediatric cardiac patients were started. In the new center, congenital heart defects such as ASD, VSD, and PDA are closed with the transcatheter method, and valve stenosis and coarctation are treated with balloon and stent applications. In this article, we retrospectively evaluated our experience in the interventional diagnosis and treatment of CHDs during the first 3 years.

MATERIAL AND METHOD

The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 17.06.2021, Decision No: 409). All procedures were performed in accordance with ethical rules and the principles of the Declaration of Helsinki.

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Received: 31.05.2022 **Accepted:** 12.06.2022

Diagnostic and therapeutic angiography procedures performed in the pediatric cardiology clinic of Kayseri City Hospital between 1 August 2018 and 1 August 2021 were evaluated retrospectively.

Before the angiography procedures, written consent inform was obtained from the parents. Before the procedure, complete blood count, liver and kidney function tests, HIV and hepatitis markers and chest X-ray were performed. All procedures were performed under general anesthesia. After the procedure, the patients were followed up in the pediatric cardiology service, if necessary, in the neonatal intensive care unit and in the pediatric intensive care unit.

The procedures were performed in the angiography unit of Kayseri City Hospital with Siemens Artis Icono® monoplane angiography device and GE Vivid7® transthoracic echocardiography device. Transesophageal echocardiography examination could not be performed during the procedure, unfortunately, due to the absence of a pediatric transesophageal echocardiography probe.

Demographic data of the patients and information about the procedures were obtained retrospectively from the hospital registry system and the archive of the angiography unit.

RESULTS

Between August 2018 and August 2021, a total of 301 angiography procedures (71 diagnostic and 230 therapeutic, 24% vs 76%) were performed. The age was 6.85 years (min: 1day-max: 17.9 years), body weight was 18.7 kg (min: 1.3-max: 85 kg). 46 patients were neonates who followed in the neonatal unit.

Atrial Septal Defect Closure

Transcatheter ASD closure was performed in 74 (25%) patients. 72 Amplatzer septal occluder® devices and 2 Occlutech ASD ocluder® devices were used. The largest device was 34 mm, the smallest device was 8 mm.

Complications

1. Device was removed surgically one day after the procedure because of the variable compression of the ascending aorta with the heartbeat (**Figure 1**).
2. Device embolized into the descending aorta and was removed with snare catheter. In this case, there was only one defect in all axis in TTE examination, and the device was implanted in this defect. However, after the device was released, it embolized into the aorta. This patient was evaluated with TEE in another center and a second posterior located defect was detected in the interatrial septum. The second larger defect was closed in the other center with the help of TEE, and the discs of the device also closed the adjacent small defect.

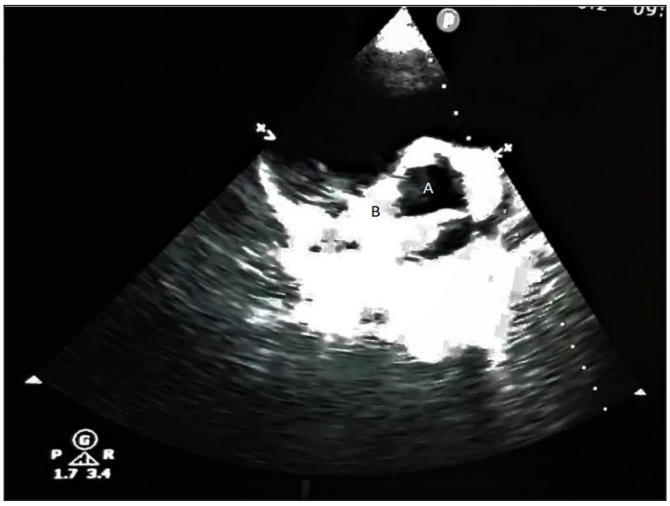

Figure 1. Compression of the aorta by the Amplatzer septal occluder device®

3. A 15-year-old girl admitted to the emergency clinic with headache and dizziness 3 days after the defect closure with a 34 mm ASO device. The ECG revealed first degree AV block. AV block resolved gradually after 2mg/kg/day prednisolone treatment. Steroid treatment was continued for 15 days. AV block did not recur in further follow-ups (**Figure 2**).

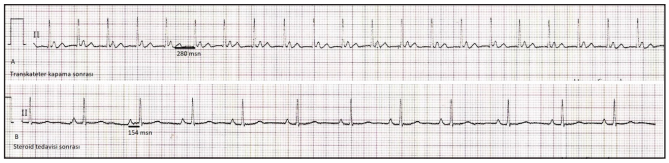

Figure 2. 1st degree AV block after transcatheter ASD closure

Complications such as cardiac perforation, peripheral vascular injury or cardiac erosion, which can be seen due to ASD closure, did not occur.

Pulmonary balloon valvuloplasty was performed in 2 patients during the ASD closure procedure. Jugular vein intervention was planned and the procedure was delayed for 8 years old girl because of interrupted inferior vena cava.

Patent Ductus Arteriosus Closure

PDA closure procedure was performed to 62 (21.3%) patients. 11 (3.7%) patients were hospitalized in the neonatal unit under 2500 grams and the lowest body weight was 900 grams. 18 procedures were closed antegradely, and the other 44 procedures were closed retrogradely. Seven of the premature PDAs were closed antegradely and 4 of them were closed retrogradely. 6 ADO I,® 11 ADO II,® 17 ADO II AS,® 25 Piccolo duct occluder®, 3 Cook coil® were used.

The largest device used was the 8x6 ADO I® device. In this procedure, the device (6x6 ADO I) embolized to the right pulmonary artery, was catched and removed with snare, and the PDA was closed with 8x6 ADO I® device.

In 2 procedures, the device could not be implanted, one of these patients was referred to surgery and the other to another more experienced center. No other complications occured during or after the procedure. The residual shunts seen in the control injection after implantation disappeared in the follow-up 1 month later.

Ventricular Septal Defect Closure

The procedure was performed to 9 (3%) patients. ADO I® was used in 2 case, ADO II® in 6 cases, and Amplatzer muscular VSD occluder® in 1 case. Since the defect was large and perimembranous aneurysm in one patient, the device could not be implantated in the defect and was referred to surgery. In a patient with 2 muscular (4 mm and 3 mm) VSDs, the large defect was closed retrogradely with a 6 mm Amplatzer muscular VSD occluder® device. After closure, a residual shunt was observed from the adjacent small defect. The residual shunt decreased in the follow-up, but persisted. No other complications occurred (**Figure 3**).

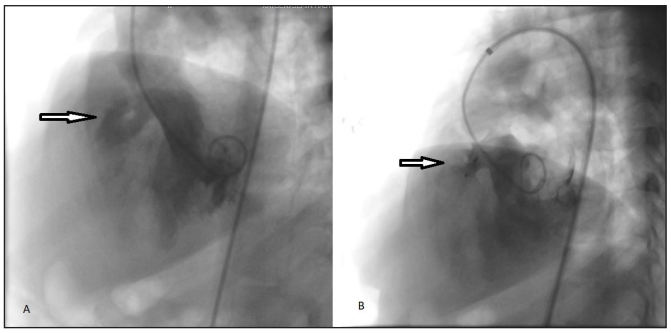

Figure 3. Closure of the VSD with the Amplatzer muscular VSD occluder device®

Pulmonary Balloon Valvuloplasty Procedure:

The procedure was applied to 17 (5.8%) patients. One procedure was performed with ASD closure. Osypka VACS II® balloons were used in one procedure and Numed Tyshak II® balloons were used in the other procedures.

6 patients were newborn patients with ductus-dependent critical pulmonary stenosis followed in the neonatal unit. Two of the critical pulmonary stenosis procedures failed. 1 patient was referred to surgery, and 1 patient was referred to another more experienced center. Except for 2 failed procedures, restenosis or re-balloon valvuloplasty were not needed for the other cases.

Two procedures were performed for palliation of residual pulmonary stenosis in a patient followed up with Tetralogy of Fallot. However, in one case, the procedure was insufficient due to hypoplasia of the annulus and PDA stent implantation was performed in the follow-up.

No complications occurred during or after the procedure. In the follow-up, no severe right heart failure or pulmonary insufficiency was observed to require valve replacement.

Aortic Balloon Valvuloplasty

Aortic balloon valvuloplasty was performed in 9 (3%) patients. Numed Tyshak II® balloons were used in the all procedures. Three patients had ductus arteriosus-dependent critical aortic stenosis in the neonatal period. Two procedures were performed with rapid pacing. Two patients had aortic coarctation at the same time, and balloon angioplasty was performed on the coarctation of aorta at the same procedure.

Left ventricular rupture developed in a newborn baby with endocardial fibroelastosis, borderline left ventricular cavity and mitral orifice. Emergency pericardiocentesis was performed and although the rupture was surgically repaired, the patient died. In one patient, the ascending aorta was hypoplasic and also had coarctation. Coarctation and valve stenosis recurred 1 month after balloon angioplasty and valvuloplasty, and surgical valvulotomy and coarctation repair were performed in another center.

Except for 1 major complication, no complication developed.

Other Procedures

Ductus arteriosus stent implantation was performed successfully in 4 (1.3%) patients (1 Tetralogy of Fallot, 1 interrupted aortic arch, 2 pulmonary atresia) and they were referred to elective surgery in the follow-up.

However, the procedure failed in a procedure, because the procedural wire could not be placed due to the vertical ductus arteriosus originating from the aortic arch (**Figure 4**), and a surgical central shunt was performed between the aorta and the pulmonary artery. In 1 patient, the stent embolized into the descending aorta and when it could not be removed by the transcatheter method, it was removed surgically, but the patient died in the follow-up.

Balloon angioplasty procedure for aortic coarctation was performed in 21 (7.2%) patients. 17 patients were diagnosed in the neonatal period. Numed Tyshak II® balloons were used as in other procedures. 9 patients in the neonatal period were recoarctated. Balloon angioplasty procedure was not repeated in patients who developed recoarctation. All recoarctation patients were surgically repaired. Femoral artery was used in all procedures, axillary artery or carotid artery were not used in any case. Complications did not occured. Middle aortic syndrome was diagnosed in a patient who was followed up with neurofibromatosis and hypertension. Angioplasty was performed with a Z-med balloon®. Middle aortic syndrome was resolved partially and the gradient decreased. Hypertension regressed in the follow-up (**Figure 5**).

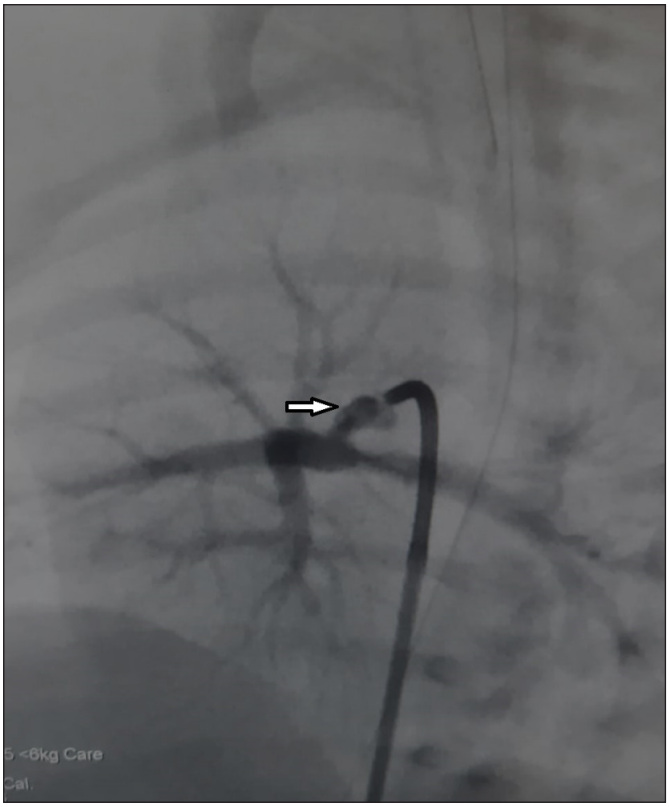

Figure 4. Vertical ductus arteriosus originating from the aortic arch, Arrow: Ductus arteriosus

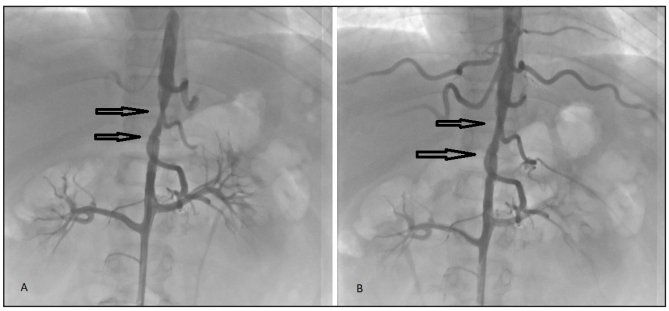

Figure 5. Treatment of middle aortic syndrome with balloon angioplasty

Stent implantation for aortic coarctation was performed in 4 (1.3%) patients. Numed CP stent® and Numed BIB® balloon were used in these cases. Numed bare CP stent® was used in one procedure due to its proximity to the subcalvian artery, and Numed covered CP stent® was used in the other 3 patients (**Figure 6**). No complications developed in the follow-up.

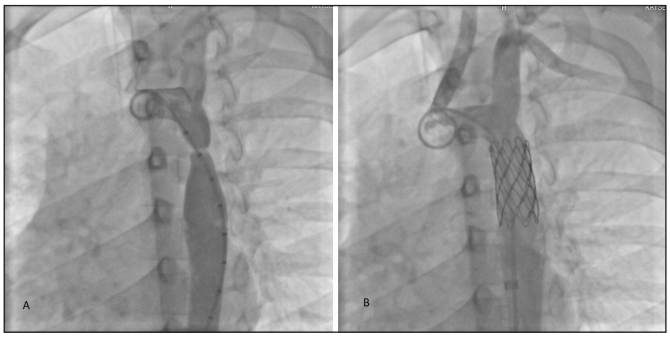

Figure 6. Treatment of aortic coarctation with Numed® covered stent

Pericardiocentesis was performed in 5 (1.7%) patients. 4 patients were diagnosed with viral myopericarditis. One patient was a 700-gram premature neonate who developed cardiac tamponade due to a central venous catheter. The procedure was performed with a 20G (pink) intraket, and minimal pericardial effusion remained at the end of the procedure. Any complications occurred during or after the procedure.

Temporary transvenous pacemaker was implanted to an infant who presented with syncope and was diagnosed with congenital complete AV block. Permanent pacemaker or ICD was not implanted in any patient, patients with indications were referred to another center.

71 diagnostic angiography procedures were performed for diagnostic and preoperative evaluation in cyanotic and acyanotic CHD. No complications developed during or after the procedure.

Table 1. Procedures and demographic data of patients. Values are expressed as median, 25th and 50th percentiles.

Procedures	Patient number	Body weight	Age
ASD closure	74 (25%)	25.5 (16.25-48.75)	7.29 (4.58-13.77) years
PDA closure	62 (21.3%)	12.5 (6.5-18.4)	1.6 (0.7-9.8) years
PDA closure (prematuer neonate)	11 (3.7%)	1.85 (1.52-2.2)	10.5 (8.25-23) day
VSD closure	9 (3.0%)	26.5 (16.5-39.5)	8.61 (3.66-11.31) years
Aortic balloon valvuloplasty	9 (3.0%)	6.2 (3.2-26.0)	2.0 (0.18-80.45) months
Pulmonary balloon valvuloplasty	17 (5.8%)	6.5 (3.7-12.7)	3.73 (0.02-33.09) months
Balloon atrial septostomy	14 (4.8%)	3.45 (2.97-3.82)	2.0 (1.0-6.25) days
Aortic balloon angioplasty	21(7.2%)	4.2 (3.6-6.95)	29.5 (13.5-170) days
Stent implantation in ductus arteriosus	4 (1.3%)	6.2 (3.2-26)	2, 8 days
Stent implantation in aortic coarctation	4 (1.3%)	38. 45. 57	12, 14, 15 years
Pericardiocentesis	5 (1.7%)	Min: 10 days, max: 15 years	700 g, 64 kg
Temporary transvenous pacemaker implantation	1 (0.3%)	4 months	7 kg
Diagnostic angiography	71 (24%)	6.3 (3.87-12.0)	4.7 (0.1-20.11) months
Total	291		

Statistical Analysis

The data were recorded in the IBM SPSS version 22.0 statistical package program. The distribution of demographic data of the patients was evaluated using the Shapiro-Wilks test. As descriptive statistics, mean ± standard deviation, median, and minimum maximum values were used for quantitative data, and numbers and percentages were given for qualitative data.

DISCUSSION

CHDs are the most common congenital anomalies. Its incidence varies between 1000/5-7.7 in studies conducted in our country (2). The treatment of CHDs is mainly surgical. However, the importance of interventional treatment methods is increasing with the developing technology and experience. After balloon atrial septostomy was performed for the first time by Rashkind and Miller in 1966, many advances were made in pediatric cardiology (3). Interventional treatments have now become the gold standard treatment for many congenital heart defects.

ASD is a common congenital heart defect seen in 1 in 1000 live births (4). Transcatheter closure has become the gold standard for secundum ASDs due to shorter hospital stay, no need for thoracotomy, and lower complication rate. Jalal et al. (4) experienced only 24 (1.8%) cases with major complications in 1326 transcatheter closure procedures. In our case series, major complication developed in 2 patients (device embolization and 1st degree AV block). The risk of AV block is <1% after transcatheter ASD closure.

TEE examination is widely used in ASD closure. The use of TEE allows better assessment of rims and defect size. However, it has been reported that ASD closure procedures can be performed safely with TTE in experienced centers (6). Performing the closure with TTE allows to avoid the complications of TEE itself and also saves time for the team. Although TEE is preferred for defects with insufficient rims, lower major and minor complication rates have been reported with TTE compared to TEE (6). Due to the absence of a pediatric TEE probe in our hospital, ASD closure procedures were performed only with TTE. If the correct evaluation with TEE could be made in the procedure where the device is embolized into the aorta, this major complication could have been prevented. However, in other cases, ASD closure with TTE was successfully performed. The absence of a TEE probe is a major shortcoming for a team with little experience. However, a careful TTE review partially corrected this shortcoming. Complications such as femoral vein or artery injuries, residual shunt, or cardiac erosion were not experienced (7).

Transcatheter closure is now the first choice in the treatment of PDA and the success rate is over 95% (8). With the newly developed devices, PDA can be closed both antegradely and retrogradely, and the use of smaller carrier systems has increased the success rate and reduced complications. However, complications such as device embolization, residual shunt, stenosis in the pulmonary arteries or descending aorta, and peripheral vascular injuries have been reported (9). In our center, transcatheter closure was not performed in 2 cases due to the large size of the defect, and the defects were surgically ligated.

With the increase in the frequency of application of assisted reproductive techniques, the frequency of PDA seen in premature babies has increased. The presence of PDA in premature infants prolongs the need for oxygen, length of hospital stay, and increases the rate of diseases such as retinopathy of prematurity (ROP) and necrotizing enterocolitis. Transcatheter or surgical closure of PDA becomes obligatory in premature babies who do not respond to medical treatment. Although surgical ligation was the only option in the first years, the transcatheter closure method is now successfully performed in experienced centers. In selected cases, transcatheter closure saves these neonates from thoracotomy. Hazeem et al. (10) reported that transcatheter closure of PDA in premature infants resulted in a shorter return to previous respiratory conditions when compared to surgical ligation. Narin et al. (11) found any difference between surgical ligation and transcatheter closure in terms of hospital stay in premature babies weighing <2 kg. Major complications such as peripheral vascular injury, stenosis in the left pulmonary artery or aort coarctation due to the device have been reported (10,11). Although complications such as stenosis and residual shunt occurred in the left pulmonary artery in our series, these conditions improved in the follow-up. Surgical ligation was performed in 2 cases and no complications developed in these patients. However, larger case series and longer follow-up times are needed to compare surgical ligation and transcatheter closure in premature infants. Inexperienced centers should be careful in terms of complications during and after PDA closure in extremely low birth weight babies.

First generation devices allowed only antegrade closure of the PDA. Passing from the pulmonary artery to the aorta for antegrade closure is technically difficult and prolongs the procedure time, especially in small-medium PDAs. Also, first generation devices need thicker delivery systems and the use of the femoral artery in small patients is risky. Today, devices such as ADO II® and Amplatzer Piccolo duct occluder® can be used both retrogradely and antegradely with thinner delivery systems. However,

the widest diameter of the ADO II® is 6 mm, and the Amplatzer Piccolo duct occluder® is 5 mm. Therefore, it is not possible to use these devices in PDAs with a narrowest diameter larger than 4 mm. Another necessity is premature babies. Although there is no definite body weight limit in the literature for the use of the femoral artery should be avoided, especially under 1000 grams. In our experience, the retrograde method was used in the majority of patients. However, there were also patients for whom we preferred the antegrade method according to the size of the defect and the patient's body weight.

VSD is the most common congenital heart disease with a rate of 20%. Surgical or transcatheter closure is recommended for cases with significant left to right shunts (12). Experience in closure of VSDs with the transcatheter method has been increasing over the years. Although transcatheter closure is not possible in all types of VSD, a significant proportion of defects can be closed with the transcatheter method. However, major complications such as device embolization, injury of the tricuspid and aortic valves, residual shunt, and AV block should not be ignored. Senaidi et al. (13) reported a 4.7% major complication rate in their transcatheter closure experience of 118 cases, and they stated device embolization as the most common major complication. Pamukçu et al. (12) reported one major complication (complete AV block that developed after 6 months) in 49 pediatric patients who were closed with the ADO II® device. Another problem in VSD closures is the residual shunt. The reason for the residual shunt is the mutiple defect or the use of a small device compared to the defect. In the series of 412 cases reported by Walavalkar et al. (14) residual shunt was observed in 34 patients (9.5%) in the first 24 hours, while it was observed in only 4 patients (3%) during the follow-up. In our series of 9 cases, no major complications were observed. One patient had 2 muscular VSDs, and the largest of these defects was closed with the Amplatzer muscular VSD occluder device and a residual shunt was observed from the adjacent defect. Transcatheter VSD closure can be performed in appropriate defect size and type in the presence of indication.

Congenital valvular aortic stenosis can be different clinical severity, from asymptomatic cases to ductus arteriosus-dependent critical aortic stenosis. Although bicuspid aortic valve is reported at a rate of 1.3% in autopsy reports, symptomatic aortic stenosis is less common (15). In many centers, balloon valvuloplasty for moderate and severe aortic stenosis has replaced surgical valvulotomy. Emergency balloon valvuloplasty is life-saving especially in cases if left ventricular systolic function is impaired in the neonatal period and prostaglandin E1 infusion is needed to maintain systemic blood flow. The most common complication of balloon valvuloplasty is aortic valve insufficiency. Varan et al. (16) reported moderate and severe valve insufficiency in 17 patients (26.2%) after valvuloplasty in their series of 65 cases. In order to reduce postprocedural valve regurgitation, the postoperative pressure gradient should be reduced to 30-35 mmHg, and the balloon diameter should be chosen to be 0.8-0.9 times the aortic annulus (16). In the follow-up of our patients, it was observed that aortic valve regurgitation ranged from minimal to first degree. Aortic regurgitation did not develop enough to require valve replacement. However, an important complication is left ventricular rupture. Ewer et al. (17) reported 3 myocardial perforations in 1004 cases in a multicenter study. In our series, in a case with borderline mitral orifice and left ventricular volume and accompanied by endocardial fibroelastosis, left ventricular perforation developed during the procedure and the patient died after surgery.

Pulmonary valvular stenosis is the most common right ventricular outflow tract stenosis and the first choice in treatment is transcatheter balloon valvuloplasty. Balloon valvuloplasty is life-saving especially in ductus arteriosus-dependent critical stenosis in the neonatal period. Isolated valvular pulmonary stenosis rarely requires surgery and balloon valvuloplasty is highly effective. In the series of 1200 cases by El-Saeidi et al. (18) the success rate of the procedure was reported as 78.7% in the neonatal period, 82.9% in the infant period and 84.5% in the childhood. In our series, the procedure failed because the valve could not be passed in one patient with critical stenosis in the neonatal period. Other procedures were successful. Complications of the procedure are cardiac perforation, arrhythmia, cardiac arrest and pulmonary valve insufficiency in the long term (18). Cardiac arrest developed during the procedure in 2 newborns with critical stenosis who required prostaglandin E1 infusion and CPR was performed, but the procedures of these patients were completed successfully. Cardiac perforation did not develop. Pulmonary insufficiency, the most common complication, was mild and moderate. Pulmonary insufficiency that was severe enough to develop right ventricular failure was not observed. In the series of 53 cases by Merino-Ingelmo et al. (19) it was reported that pulmonary failure developed in all patients in the long-term, 58.2% of them were grade 2 and 31.2% were grade 3. Pulmonary valve insufficiency may seem innocent in the early period after the procedure, but careful follow-up is required in the long term.

The incidence of aortic coarctation is 5-7% of all congenital heart diseases (20). Emergency balloon angioplasty can be life-saving in neonatal coarctations with cardiovascular collapse (20). Surgery is recommended primarily in the neonatal period due to the high rate of recoarctation

after balloon angioplasty and the accompanying isthmus hypoplasia in most cases (20). Although not as high as stated in the literature, recoarctation developed in 9 of 17 patients in our center. These patients were referred to surgery instead of repeated balloon angioplasty. Considering the low rate of recoarctation in centers with an experienced pediatric cardiovascular surgery team, surgery should be preferred instead of angioplasty, balloon angioplasty should be preferred only in patients who are not suitable for surgery and who have developed cardiogenic shock. After the neonatal period, the success rate of balloon angioplasty and stenting is higher and the risk of recoarctation is low (21). In our center, after the newborn period, balloon angioplasty was applied to 4 children, one of them was middle aortic syndrome, and stenting was applied to 4 patients. Stenting to coarctation can be applied in native coarctations, recoarctations, as well as complications such as aneurysm developing after surgery or balloon angioplasty (21). However, the requirement for the patient to be over 20 kg for stenting is an important limitation. It should be kept in mind that the success rate of balloon angioplasty alone is high in pediatric patients (22).

Balloon atrial septostomy provides a mixture of systemic and pulmonary blood flow in cyanotic congenital heart diseases, thus saving time until surgery. The success rate of the procedure is high and the complication rate is low. Complications such as balloon rupture and embolization of its parts, stroke or cardiac rupture may occur during the procedure (23). We did not encounter any complications in balloon septostomy procedures performed in our center, but the procedure was unsuccessful in one hypoplastic left heart patient because the balloon could not be passed into the left atrium. The success rate of the procedure is lower in hypoplastic left heart syndrome. This is because the left atrium is also hypoplasic and the interatrial septum has an unusual configuration (24).

Ductus arteriosus stenting is an alternative to shunt operations in CHDs. It can be applied to provide pulmonary blood flow in diseases such as pulmonary atresia, as well as to provide systemic blood flow in diseases such as hypoplastic left heart, interrupted aortic arch. It has advantages such as lower complication rate, not requiring thoracotomy and cardiopulmonary bypass compared to shunt operations (25). McMullan et al. (25) reported a lower complication rate and peripheral pulmonary artery stenosis in the stent group in their study comparing 42 shunt operations and 13 ductal stent applications. In our center, ductus arteriosus stent implantation was successfully performed in 4 patients. In 1 patient, the stent embolized into the descending aorta and died after surgery. In 1 patient, the duct could not be located and the procedure was unsuccessful. We could not reach the number of cases to compare with surgical shunt operation.

Cardiac tamponade is the decrement of diastolic and systolic functions of the heart due to increased fluid in the pericardium, and it is a condition that requires urgent intervention. Pericardiocentesis can be performed under the guidance of fluoroscopy and transthoracic echocardiography. The procedure has a high success rate and a low complication rate (26). Pericardial tamponade may develop due to percutaneous central long catheter in premature neonates and pericardiocentesis should be performed carefully in these cases (27). Pericardiocentesis was performed with a 20-gauge (pink) intraket in a premature baby weighing 700 grams. The short, plastic tip of the intraket helped prevent myocardial damage (28).

With the advancement in the technology of the devices and the increase in the experience of the physicians in transthoracic echocardiography examination, diagnostic angiography is no longer needed in the diagnosis of many CHDs. Computed tomography angiography and cardiac magnetic resonance examination also play a role in reducing this need (29). However, conventional diagnostic angiography is still needed, especially in the surgical decision-making of patients with left-right shunts or in the identification of complex cardiac pathologies. Although angiography is mostly performed for therapeutic purposes in our center, it has also been applied for diagnostic purposes.

CONCLUSION

The rate of interventional methods in the treatment of CHDs has been increasing over the years. Compared to surgery, less length of hospital stay, less complication rate, and the absence of the need for thoracotomy make interventional methods more preferable. In addition, considering the birth rate and the incidence of these diseases in Turkey, more pediatric heart centers are needed. However, the missing equipment should be completed and the team should gain more experience in this field, especially in the newly opened centers that have just started to make these interventions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 17.06.2021, Decision No: 409).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients for the study. However, written informed consent was obtained from the parents before the all procedures.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1112460
J Health Sci Med 2022; 5(4): 1081-1085

Mental status of healthcare professionals according to the level of exposure to COVID-19 patient during the pandemic

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Cite this article as: Kaya MN. Mental status of healthcare professionals according to the level of exposure to COVID-19 patient during the pandemic. J Health Sci Med 2022; 5(4): 1081-1085.

ABSTRACT

Introduction: The frontline healthcare workers during the coronavirus outbreak work under intense pressure while working in close contact with COVID-19 patients, and can subsequently develop mental health-related problems. This study aimed to evaluate the mental impact of COVID-19 on healthcare workers according to exposure level.

Material and Method: This cross-sectional study included a total of 282 participants. Healthcare workers were divided into two groups as low-risk contact and high-risk contact according to the degree of contact with the coronavirus. Anxiety, depression, and insomnia were evaluated among the groups using the Insomnia Severity Index (ISI), General Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9) scales.

Results: One hundred seventy eight (62.4%) women and 104 (36.8%) men, with a mean age of 24.59 years were included in this study. The number of low-risk patients was 180 (63.8%), while the number of high-risk patients was 102 (36.1%). In addition, according to the multivariate analysis, staff working in the department with high-risk contact had significantly lower high to suffer anxiety (OR 1.283, 95% CI 1.109-1.483, p=0.001), depression (OR 1.052, 95% CI 1.019-1.088, p=0.001) and insomnia (OR 3.460, 95% CI 2.506-4.784, p<0.001).

Conclusion: Our results show that healthcare workers working in high-risk contact units for exposure to COVID-19 have high levels of anxiety, depression, and insomnia than healthcare workers working in low-risk contact units.

Keywords: COVID-19, medical staff, anxiety, depression, insomnia

INTRODUCTION

In December 2019, a new coronavirus quickly spread as the cause of pneumonia cases in the Chinese city of Wuhan, causing an epidemic throughout China. Afterwards, it caused a worldwide pandemic with cases that were found positive as a result of tests performed on nearly two million people (1). In February 2020, the International health organizations named this disease coronavirus disease 2019 (COVID-19) and the virus causing this disease severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Severe COVID-19 can affect healthy individuals of all ages but has been found to predominantly occur in adults of advanced age and those with underlying medical conditions (2). After initial reports of COVID-19, the number of cases rapidly increased, and the disease was reported among healthcare workers, indicating person-to-person transmission (3). The frontline healthcare workers during the coronavirus outbreak work under intense pressure while working in close contact with COVID-19 patients during diagnosis, taking nasopharyngeal swabs, and providing treatment and patient care in hospital wards or intensive care units (ICU), and can subsequently develop mental health-related problems (4). The continuous increase in the number of suspected and confirmed cases, heavy workload, shortages in personal protective equipment, widespread media coverage, shortage in certain medications, and inadequate access to mental support accumulate to cause the deterioration of mental status among health workers (5). Previous studies have shown that healthcare workers developed psychological symptoms in response to the severe acute respiratory syndrome (SARS) epidemic in 2003 (6). Recent studies concerning the SARS-CoV-2 epidemic report that healthcare workers express anxiety due to fear of transmitting COVID-19 to their families and friends. For these reasons, healthcare professionals may suffer long-term psychological consequences such as unwillingness to work, intent to resign, and high levels

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Received: 04.05.2022 **Accepted:** 14.06.2022

of stress, anxiety, depression, and insomnia (7). This study aimed to evaluate the mental impact of COVID-19 on health care workers according to exposure level.

MATERIAL AND METHOD

The study was carried out with the permission of Harran University Clinical Researches Ethics Committee (Date: 31.08.2020, Decision No: 20/15/22). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki

Participants

This study was carried out in a total of three months between June 2020 and September 2020 at the Health Sciences University Şanlıurfa Training and Research Hospital. Our hospital is among the largest and most prominent hospitals of the region in terms of the number of wards, intensive care unit (ICU) beds, equipment and healthcare professionals, and plays an important role in the prevention and control of the COVID-19 epidemic. A questionnaire was prepared to investigate the impact of the COVID-19 epidemic on the healthcare professionals of our hospital and distributed to the medical staff to assess insomnia, anxiety, and depression. Demographic information of healthcare professionals was recorded with a standard form. Insomnia was evaluated with The Insomnia Severity Index (ISI) questionnaire, anxiety was evaluated with the General Anxiety Disorder-7 (GAD-7) questionnaire, and depression was evaluated with The Patient health questionnaire-9 (PHQ-9). Sample size calculation was performed via Roasoft sample size calculator. Using the total number of healthcare workers as 670, %5 margin of error and %95 confidence level, and the anxiety level of healthcare workers in the study of Lai et al. (8), the minimum number of sample size was calculated to be 245. Healthcare workers included in the study are doctors, nurses, medical secretaries and cleaning staff. Incomplete questionnaires and participants with a history of mental illness and cognitive impairment were excluded from the study. Participants were divided into low-risk contact group and high-risk contact group according to their departments. As high-risk contact health workers working in COVID-19-related units (respiratory diseases department, infectious diseases department, emergency department, intensive care), as low-risk contact health workers, not working in COVID-19-related units and working in non-clinical units (administrative unit, cleaning unit, technical operation) (7). The questionnaires were filled in by the healthcare professionals, giving them sufficient time. No interviewer was used.

The Questionnaire Measurement of Anxiety, Insomnia and Depression

General Anxiety Disorder-7 is a well-established, satisfactorily reliable and valid scale that has been widely used to evaluate anxiety. It consists of 7 items and is scored over a total of 21 points. The results are evaluated as follows: 0-5 minimal anxiety, 6-10 mild anxiety, 11-15 moderate anxiety, 16-21 severe anxiety (8). The Insomnia Severity Index is a well-recognized index with confirmed reliability, sensitivity, and validity. It consists of 7 items and is scored over a total of 28 points. The total score is used to determine the degree of insomnia. Total scores are evaluated as follows: 0-7 no clinically significant insomnia, 8-14 subthreshold insomnia, 15-21 moderate clinical insomnia, 22-28 severe clinical insomnia (9). The Patient health questionnaire-9 is a 9-item scale scored over 27 points that measures depression. It is a well-established and reliable scale that is used to evaluate depression. The results are evaluated as follows: 0-4 no depression, 5-9 mild depression, 10-14 moderate depression, 15-19 moderately severe depression, 20-27 severe depression (10).

Statistical Analysis

Written informed consent was obtained from the participants in the study. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software package version 26. Visual and analytical methods were used to determine whether the variables were normally distributed. Normally distributed continuous variables are expressed as mean±SD, non-normally distributed parameters as median values with minimum and maximum values and categorical variables as numbers and percentages. Normally distributed data were compared with the Student's t-test, and non-normally distributed data were compared with Mann-Whitney U test. $p < 0.05$ was accepted as statistically significant. The variables were dichotomized for the presence of depression, anxiety, and insomnia and multivariate binary logistic regression models were performed identify variables with predictive capacity for the presence of these conditions.

RESULTS

A total of 292 questionnaires were filled out in the scope of this cross-sectional study. Ten questionnaires were excluded due to being incomplete. Hence, 282 questionnaires were included in the study. The overall response rate of healthcare professionals was 96.57%. A total of 282 patients, 178 (62.4%) women and 104 (36.8%) men were included in this study. The number of low-risk patients was 180 (63.8%), while the number of high-risk patients was 102 (36.1%). The majority of the participants were under 30 years old. 74.5% of the low-

risk contact group and 71.7% of the high-risk contact group were aged below 30 years (p=0.073). In both groups, the majority of the participants had worked for less than 5 years: 93.1% of the low-risk contact group and 82.2% of the high-risk group (p=0.002). The number of marriages in high-risk contact workers was statistically higher than in low-risk contact workers (p=0.004). The level of exposure was not significantly associated with other parameters such as education and occupation (p>0.05) (**Table 1**).

Table 1. Baseline characteristics of the 282 enrolled participants in the study

Variables	Low-risk contact n (%)	High-risk contact n (%)	χ^2	p
Sex			18.219	<0.001
Male	83 (46.1)	21 (20.6)		
Female	97 (53.9)	81 (79.4)		
Age (years)			5.223	0.073
<30	129 (71.7)	81 (74.5)		
31-40	39 (21.7)	20 (20.9)		
>40	12 (6.7)	1 (4.6)		
Working years			12.493	0.002
0-5	148 (82.2)	95 (93.1)		
6-10	27 (15)	2 (2)		
>10	5 (2.8)	5 (4.9)		
Education			4.42	0.110
Below university	13 (7.2)	9 (8.8)		
College	7 (3.9)	10 (9.8)		
Master's degree or above	160 (88.9)	83 (81.4)		
Marriage			8.517	0.004
Married	61 (33.9)	18 (17.6)		
Unmarried	119 (66.1)	84 (82.4)		
Profession			2.784	0.084
Doctor	33 (18.3)	12 (11.8)		
Nurse	125 (69.4)	77 (75.5)		
Cleaning staff	8 (4.4)	3 (2.9)		
Medical secretary	14 (7.8)	10 (9.8)		

According to the ISI, participants in the high-risk contact group had moderately severe and severe insomnia indexes than those in the low-risk contact group. (20 vs 38.3%, respectively) (p<0.001). According to the GAD-7 scale, participants in the high-risk contact group had moderately severe and severe anxiety indexes compared to the participants in the low-risk contact group. (45% vs. 16.7% vs. 32.2%) (p<0.001). According to the PHQ-9, participants in the high-risk contact group had moderately severe and severe depression indexes (25% vs. 35%) compared to the participants in the low-risk contact group (p<0.001) (**Table 2**). We compared the mean insomnia, anxiety, and depression scores of the low-risk and high-risk contact groups obtained by the questionnaire, as presented in **Table 3**. The Insomnia Severity Index and PHQ-9 scores were significantly different between the two groups (p<0.001). Also, the GAD-7 scores of the two groups were significantly different (p=0.017) (**Table 3**).

Table 2. The different severity of insomnia, anxiety, depression among 282 enrolled participants in the study

Variables	Low-risk contact n (%)	High-risk contact n (%)	χ^2	p
ISI			29.273	<0.001
0-7=No clinically	1 (0.6)	11 (10.8)		
8-14=Subthreshold	74 (41.1)	91 (89.2)		
15-21=Moderate severity	69 (38.3)	0 (0)		
22-28=Severe	36 (20)	0 (0)		
GAD-7			27.721	<0.001
0-5=Mild	11 (6.1)	0 (0)		
6-10=Moderate	81 (45)	54 (52.9)		
11-15=Moderately severe	30 (16.7)	36 (35.3)		
16-21=Severe	58 (32.2)	12 (11.8)		
PHQ-9			24.561	<0.001
0-4=None	0 (0)	0 (0)		
5-9=Mild	29 (16.1)	23 (22.5)		
10-14=Moderate	43 (23.9)	43 (42.2)		
15-19=Moderately severe	45 (25)	26 (25.5)		
20-27=Severe	63 (35)	10 (9.8)		

ISI=Insomnia Severity Index; GAD-7= General anxiety disorder-7; PHQ-9= Patient health questionnaire-9.

Table 3. Comparison of the average level of insomnia, anxiety and depression between low-risk contact and high-risk contact groups

Variables	Low-risk contact	High-risk contact	p*
ISI	10.0 (6.0-12.0)	15 (13.0-28.0)	< 0.001
GAD-7	8.0 (6.0-15.0)	10 (4.0-24.0)	0.017
PHQ-9	12.0 (6.0-21.0)	18.0 (8.0-27.0)	< 0.001

*p value for two independent samples Mann–Whitney U tests; ISI=Insomnia Severity Index; GAD-7= General anxiety disorder-7; PHQ-9= Patient health questionnaire-9

In addition, according to the multivariate analysis, staff working in the department with high-risk contact had significantly high risk to suffer anxiety (OR 1.283, 95% CI 1.109-1.483, p=0.001), depression (OR 1.052, 95% CI 1.019-1.088, p=0.001) and insomnia (OR 3.460, 95% CI 2.506-4.784, p<0.001) (**Table 4**).

Table 4. Multivariate analysis of insomnia, anxiety and depression between low-risk contact and high-risk contact

Variables	OR	CI (95%)	p
ISI			< 0.001
High-risk contact	3.460	2.506-4.784	
Low-risk contact	1 (Reference)	NA	
PHQ-9			0.002
High-risk contact	1.052	1.019-1.088	
Low-risk contact	1 (Reference)	NA	
GAD-7			0.001
High-risk contact	1.283	1.109-1.483	
Low-risk contact	1 (Reference)	NA	

ISI= Insomnia Severity Index; GAD-7= General anxiety disorder-7; PHQ-9= Patient health questionnaire-9; NA= Not applicable. *Gender, Age, Working years, Education, Marriage, Profession were included as covariates in ordinal logistic regression model.

DISCUSSION

This study was conducted to evaluate the mental impact of COVID-19 exposure levels on healthcare workers. Our results demonstrate that anxiety, depression, and insomnia are higher in medical staff who work in hospital units at high-risk for COVID-19 exposure than low-risk units. To the best of our knowledge, there are a limited number of studies concerning the healthcare workers involved in the 2003 SARS epidemic, and very few investigated the mental status of healthcare professionals. SARS-CoV-2 is a virus known to be highly contagious that can spread rapidly. Frontline healthcare workers suffer from a significantly increased workload. Confirmed and suspected cases, lack of protective equipment, and suspected patients concealing their medical history can all increase the risk of infection for healthcare workers. Health workers feared that if they themselves were infected, they could spread the virus to their families, friends, and relatives (11). Our results showed that healthcare workers working in units at high-risk for COVID-19 exposure were at higher risk for anxiety, depression, and insomnia compared to their colleagues working in lower-risk units. With the increasing number of COVID-19 infections in China, frontline healthcare professionals were required to wear protective masks and equipment to reduce the burden of stress (12). A combination of anxiety, stress, and self-esteem determines the sleep quality of healthcare professionals. Anxiety affects sleep quality because anxious people often have trouble falling asleep and frequently wake up during sleep (13). Anxiety has been shown to result in impaired sleep, and poor sleep quality has been shown to increase anxiety. The combination of anxiety with sleep disorders can make it difficult to fall asleep (14,15). Therefore, as in the COVID-19 outbreak in Wuhan, China, cohort studies with larger samples are needed to investigate the effects of increased stress and workload on healthcare professionals' sleep quality and function (16).

As a result of the increasing demands related to COVID-19, taking measures to increase social support for healthcare professionals may increase their productivity related to their work. For example, professional psychotherapy teams and other supportive practices must take responsibility and provide individually targeted interventions to support the mental health of healthcare professionals. Logistics assistance should be provided and support groups should be established for the directors of the relevant health institutions and health personnel (17).

A previous study reported that high-risk exposure during the SARS epidemic caused psychological symptoms in 89% of healthcare workers (18). A study investigating the impact of the COVID-19 pandemic on healthcare workers reported a significant correlation with age, region, education status, and work experience, and COVID-19 exposure. We found similar results in terms of age and years of working in our study. However, distinctively, we also found a significant relationship with gender and marital status. Despite using different anxiety and depression assessment scales, the same study indicated increased anxiety and depression among healthcare workers working in high-risk units for COVID-19 exposure, similar to our results (19,20).

A Chinese study by Xiao et al. (21) found that anxiety and depression were higher in healthcare workers dealing with COVID-19, similar to our study, and also self-esteem and sleep quality disorders were found to be more common compared to the normal population. Lai et al. (8) described a high prevalence of depression, anxiety, insomnia, and stress symptoms among healthcare workers dealing with COVID-19. We similarly found high levels of depression, anxiety and insomnia. The limitation of our study is that it is a single-centered study with a limited number of subjects.

CONCLUSION

Our results show that healthcare workers working in high-risk contact units for exposure to COVID-19 have high levels of anxiety, depression, and insomnia than healthcare workers working in low-risk contact units. Protecting healthcare workers is an important component of public health measures that address the COVID-19 outbreak. Healthcare workers, especially those exposed to COVID-19, should be provided with psychological support to promote mental well-being. Future studies, including cohort studies with large samples that investigate objective indicators of stress along with questionnaires, such as serum cortisol levels, are needed (22).

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Harran University Clinical Researches Ethics Committee (Date: 31.08.2020, Decision No: 20/15/22).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.
Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1106023
J Health Sci Med 2022; 5(4): 1086-1091

Systemic inflammation indices predict mortality in patients with COVID-19

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Cite this article as: Işık ŞM. Systemic inflammation indices predict mortality in patients with COVID-19. J Health Sci Med 2022; 5(4): 1086-1091.

ABSTRACT

Aim: In recent years, inflammation-based indices obtained from hematologic parameters have been shown to have prognostic value in various inflammatory diseases and cancer types. In this study, we aimed to investigate whether inflammation indices could be used to predict mortality in patients with COVID-19.

Material and Method: A total of 295 patients with a proven diagnosis of COVID-19 who were followed up in the intensive care unit were included in this retrospective, cross-sectional study. The patients were divided into two groups, survivors and non-survivors.

Results: D-dimer (HR:1.001, 95% CI:1-1.001) and troponin (HR: 1.001 95% CI: 1-1.001) levels of non-survivors were significantly higher in univariate analyses ($p<0.05$). Procalcitonin levels of whom were found to be high in univariate (HR: 1.018 95% CI: 1.003 – 1.034) and multivariate (HR:1.02 95% CI: 1.004-1.037) analyses ($p<0.05$). There was no significant difference between the groups in terms of median values of PLR, SIRI, and AISI indices ($p>0.05$). The median NLR value of the survivors was 7.45, while it was 11.39 in the non-survivors, and this difference was statistically significant ($p<0.001$). The median value of the SII index of the non-survivors was found as 2421.02, which was significantly higher than the survivors ($p<0.001$). The value of NLR and SII indices in predicting mortality in COVID-19 was evaluated using ROC analysis (NLR: AUC=0.644, 95%CI: 0.581-0.708, $p<0.001$; SII: AUC=0.584, 95%CI: 0.517-0.651, $p=0.017$). When the cut-off value for NLR was accepted as 9.574, the sensitivity was 59.3% and the specificity was 67% in predicting mortality. When the cut-off value for SII was accepted as 2285,846, it was found that it could predict mortality with a sensitivity of 52.38% and specificity of 66.04%.

Conclusion: SII and NLR indices can predict mortality in patients with COVID-19 followed up in the intensive care unit.

Keywords: COVID-19, inflammatory index, SII, NLR

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a global pandemic that emerged in the Wuhan province of China in December 2019 and still threatens humanity. It infected more than 386 million people and killed approximately 6 million people worldwide (1). The virus can cause a wide variety of symptoms with the involvement of multiple organs, especially the respiratory tract. It is well known that COVID-19–related organ dysfunction and mortality are associated with an increased inflammatory response (2). Studies conducted in this context have shown that inflammatory parameters can be used as a biomarker to predict prognosis in patients with COVID-19 (3-5).

The complete blood count is an easy and inexpensive test used in clinical practice. It can provide the physician with extensive information about the cell types involved in the immune response and their number and morphology. In addition, it is also possible to obtain ratios such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic inflammation index (SII), systemic inflammation response index (SIRI), aggregate index of systemic inflammation (AISI), which are defined as inflammation indices, from these parameters. NLR and PLR reflect systemic inflammation with neutrophil and platelet activation. It has been associated with increased mortality in cardiovascular diseases and with poor prognosis in various cancers (6). It has been proven that SII and SIRI reflect the inflammatory response and can predict prognosis in many inflammatory diseases and cancer types (7-9). It has been shown that these indices can also have diagnostic value in COVID-19

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Received: 19.04.2022 **Accepted:** 15.06.2022

and can be used to determine the severity of the disease (10,11). Based on these findings, we aimed to investigate whether these indices could be used to predict mortality in patients with COVID-19 followed up in the intensive care unit (ICU).

MATERIAL AND METHOD

The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-Pharmaceutical and Non-Medical Device Researches Ethics Committee (Date: 14.01.2022, Decision No: 2022/022). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who were admitted to Konya Numune Hospital between March 2020 and January 2021 and were followed up in the ICU were included in this study. It was designed as a single-center, retrospective, cross-sectional study.

Clinical, demographic, and laboratory data of the patients were extracted from electronic medical records (Karmed) using a standardized data collection form. The records of a total of 312 patients aged over 18 years were analyzed for the study. Among these patients, a total of 295 patients were included in the analysis after the diagnosis of COVID-19 was eliminated during their follow-up. Those with a history of head trauma, malignancy, or cerebrovascular disease, and those who were pregnant were excluded.

The diagnosis of COVID-19 was made through respiratory tract swab samples (throat swabs) using real-time qualitative polymerase chain reaction (RT-qPCR). Data on the main comorbidities included diabetes mellitus (DM), hypertension (HT), pulmonary disease, and history of cardiac disease. The results of complete blood count and serum biochemical tests (D-dimer, myocardial enzymes [troponin], urea, creatinine, procalcitonin, albumin, lactate dehydrogenase [LDH], and ferritin levels) were recorded.

Systemic inflammation indices were determined from the first complete blood count using the following formulae:NLR: neutrophil count/lymphocyte count; PLR: platelet count/lymphocyte count; SII: neutrophil count x platelet/lymphocyte count; SIRI: neutrophil x monocytes/lymphocyte; AISI: neutrophil x platelet x monocytes/lymphocytes.

Statistical analysis

The data were analyzed using the IBM SPSS V 23 software package. Conformity to normal distribution was evaluated using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare indices according to mortality status. Cut-off values of indices for mortality were analyzed using receiver operating characteristics (ROC) analysis. Cox regression analysis was used to examine the risk factors affecting the survival time in the ICU. Analysis results are presented as mean±standard deviation and median (Q1 – Q3) for quantitative data, and frequency (percent) for categorical variables. The significance level was accepted as $p<0.05$.

RESULTS

A total of 295 patients who were diagnosed as having COVID-19 were included in the study and followed up during their stay in the ICU. All patients were divided into survivors and non-survivors. Of the patients,45.8% were female and no significant difference was observed between the groups in terms of sex distribution ($p>0.05$). Risk factors affecting survival time in the ICU were analyzed using univariate and multivariate models. As a result of the univariate analysis, it was determined that age was an independent risk factor that affected the mortality status (hazard ratio [HR]: 1.017, 95% confidence intervals [CI]: 1.004-1.03). The mean age of the patients who died (72.51±12.58) was significantly older than the patients who survived (67.58±13.37) ($p=0.009$). (**Table 1**)

No significant difference was observed in terms of white blood cell count (normal range: 4.49-12.68 10^9/L), neutrophil count (normal range: 2.1-8.89 10^9/L), lymphocyte count (normal range: 1.26-3.35 10^9/L), platelet count (normal range: 173-390 10^9/L), monocyte count (normal range: 0.25-0.84 10^9/L), ferritin level (normal range 23.9-336.2 ng/mL), albumin level (normal range: 35-52 g/L), C-reactive protein (CRP) (normal range: 0-8 mg/L), and alanine aminotransferase(ALT) and aspartate transaminase(AST) values (normal range: 3-50 IU/L)between the groups (**Table 1**).

D-dimer (normal range: 0-0.5 µg/mL) (HR:1.001, 95% CI:1-1.001) and troponin (normal range: 0-19.8 ng/L)(HR: 1.001, 95% CI: 1-1.001)levels of non-survivors were significantly higher in univariate analyses($p<0.05$). Procalcitonin level (normal range: 0-0.55 µg/L) (HR:1.02, 95% CI: 1.004-1.037) was found to be high in multivariate analyses.

When the patients (n=256) who did not receive Tocilizumab treatment were taken as a reference, the mortality risk of patients who received treatment (n=39) was found 0.458 times less ($p=0.004$). When patients who were not treated with plasmapheresis were taken as reference, the mortality of patients who underwent plasmapheresis was found to be significantly lower ($p=0.005$). (**Table 2**).

Table 1.

	Mortality		Univariate		Multivariate	
	Survivors	Non-survivors	HR (95% CI)	p	HR (95% CI)	p
Sex[a]						
Female	45 (42.5)	90 (47.6)	0.921 (0.691 – 1.228)	0.575	0.964 (0.703 – 1.321)	0.819
Male	61 (57.5)	99 (52.4)	Reference			
Age[b]	67.58±13.37	72.51±12.58	1.017 (1.004 – 1.03)	0.009	1.011 (0.995 – 1.027)	0.197
Neutrophil count[b]	7.64±3.51	9.30±4.00	1.016 (0.98 – 1.054)	0.391	1.03 (0.971 – 1.093)	0.322
Lymphocyte count[b]	1.02±0.42	0.95±0.70	1.09 (0.83 – 1.432)	0.534	1.136 (0.835 – 1.545)	0.417
Platelet count[b]	263.88±115.66	234.28±93.86	0.999 (0.998 – 1.001)	0.267	0.999 (0.998 – 1.001)	0.356
Ferritin[b]	417.99±429.95	656.66±808.85	1 (1 - 1)	0.166	1 (1 - 1)	0.485
D-Dimer[b]	244.09±918.36	834.87±3639.95	1.001 (1 – 1.001)	0.004	1 (1 - 1)	0.201
Troponin[b]	167.59±928.58	556.38±2692.98	1.001 (1 – 1.001)	<0.001	1 (1 - 1)	0.081
Lactate dehydrogenase[b]	381.25±165.38	607.60±801.69	1.002 (1 – 1.003)	0.033	1 (1 - 1)	0.188
Urea[b]	50.55±26.83	80.46±58.98	1.004 (1.002 – 1.006)	0.001	1.001 (0.997 – 1.004)	0.715
Creatine[b]	1.03±0.84	1.50±1.29	1.198 (1.084 – 1.323)	<0.001	1.184 (1.009 – 1.39)	0.039
Procalcitonin[b]	1.74±9.55	3.31±8.80	1.018 (1.003 – 1.034)	0.018	1.02 (1.004 – 1.037)	0.016
Albumin[b]	2.94±0.56	2.57±0.58	1.113 (0.869 – 1.425)	0.396	1.124 (0.807 –1.564)	0.489
Monocyte count[b]	0.63±0.34	0.56±0.42	0.715 (0.487 – 1.049)	0.086	0.627 (0.393 – 0.999)	0.049
White blood cell count[b]	9.71±4.84	11.43±5.78	1.011 (0.986 – 1.037)	0.381	1.003 (0.962 – 1.047)	0.881
C-reactive protein[b]	101.91±81.21	146.20±100.80	1.001 (1 – 1.003)	0.040	1.001 (0.999 – 1.002)	0.378
Aspartate aminotransferase[b]	54.20±65.39	84.69±157.69	1 (1 – 1.001)	0.271	1 (0.998 – 1.003)	0.724
Alanine aminotransferase[b]	48.61±81.27	61.43±122.19	1 (0.999 – 1.001)	0.547	0.999 (0.996 – 1.002)	0.668
Duration of mechanical ventilation[b]	1.63±7.04	9.60±12.23	0.95 (0.935 – 0.964)	<0.001	0.929 (0.911 – 0.949)	<0.001
Length of stay at intensive care unit[b]	10.33±8.42	13.64±13.61		---		---

[a]n (%); [b]Mean±StandardDeviation

Table 2. Comparison of treatments according to mortality status

	Mortality		Univariate		Multivariate	
	Survivors	Non-survivors	HR (95% CI)	p	HR (95% CI)	p
Tocilizumab[a]						
No	91 (85.8)	165 (87.3)	Reference			
Yes	15 (14.2)	24 (12.7)	0.564 (0.366 – 0.868)	0.009	0.458 (0.27 – 0.776)	0.004
Favipiravir[a]						
No	5 (4.7)	11 (5.8)	Reference			
Yes	101 (95.3)	178 (94.2)	0.609 (0.33 – 1.124)	0.113	1.314 (0.553 – 3.123)	0.536
Plasmapheresis[a]						
No	44 (41.5)	85 (45)	Reference			
Yes	62 (58.5)	104 (55)	0.551 (0.411 – 0.738)	<0.001	0.583 (0.4 – 0.849)	0.005
Steroid[a]						
No	19 (17.9)	45 (23.8)	Reference			
Yes	87 (82.1)	144 (76.2)	0.414 (0.293 – 0.584)	<0.001	0.596 (0.371 – 0.956)	0.032

[a]n (%)

When the inflammation indices were examined to evaluate the mortality risk, there was no significant difference between the groups in terms of median values of PLR, SIRI, and AISI indices (p>0.05). The median NLR value of the survivors was 7.45, whereas the median NLR value of the non-survivors was 11.39, which was statistically significantly different (p<0.001). When the cut-off value of NLR was accepted as 9.574, it was found that it could predict mortality with 59.3% sensitivity and 67% specificity. (**Figure 1**).

The median value of the SII index of non-survivors was found as 2421.02, which was significantly higher than in survivors (p<0.001) (**Table 3**). The cut-off value of the SII was found as 2285,846. The area under the ROC curve (AUC) cut-off value was 0.584,which was statistically significant (p=0.017). It was observed that the sensitivity was 52.38% and the specificity was 66.04%. (**Figure 2**).

The mean length of stay in the ICU was 10.33±8.42 days in survivors and 13.64±13.61 days in non-survivors. The duration of invasive mechanical ventilation was 1,63±7,04 days in survivors and 9.60±12.23 days in non-survivors, which was higher than in survivors (p<0.001).

Table 3. Comparison of index values according to mortality status

	Survivors, n=106	Non-survivors, n=189	Total, n=295	Test statistics	pb
NLR[a]	7.45 (4.75 – 11.64)	11.39 (6.01 – 17.9)	9.55 (5.32 – 15.78)	7129.00	<0.001
AISI[a]	902.22 (423.69 – 1831.61)	1137.67 (454.24 – 2062.23)	1081.93 (434.47 – 1942.72)	9500.00	0.462
SII[a]	1703.73 (1036.19 – 3126.15)	2421.02 (1166.47 – 4071.58)	2072.27 (1081.65 – 3733.53)	8332.00	<0.001
SIRI[a]	3.79 (1.99 – 7.2)	4.96 (2.61 – 8.84)	4.52 (2.2 – 8.42)	8846.00	0.096
PLR[a]	237.08 (176.58 – 363.64)	286.27 (182.65 – 409.09)	260.8 (180.56 – 392.77)	9217.00	0.255

[a]Median (Q1 – Q3); [b]Mann-Whitney U test

Table 4. Examining the cut-off values of the indices for mortality status using ROC analysis

	Cut-off value	AUC (%95CI)	p	Sensitivity	Specificity	PPV	NPV	Accuracy
NLR	≥9.574	0.644 (0.581 - 0.708)	<0.001	59.3%	67.0%	76.2%	48.0%	62.0%
AISI	---	0.526 (0.458 – 0.594)	0.462	---	---	---	---	---
SII	≥2285.846	0.584 (0.517 – 0.651)	0.017	52.38%	66.04%	73.33%	43.75%	57.3%
SIRI	---	0.558 (0.491 – 0.626)	0.096	---	---	---	---	---
PLR	---	0.540 (0.472 – 0.608)	0.255	---	---	---	---	---

---:Cut-off values were not calculated because the AUC value was not significant.

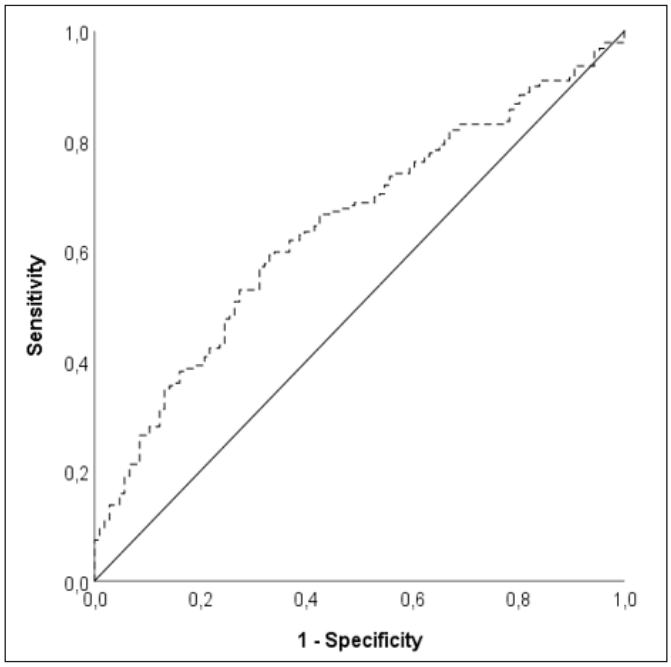

Figure 1. ROC curve of NLR according to the groups

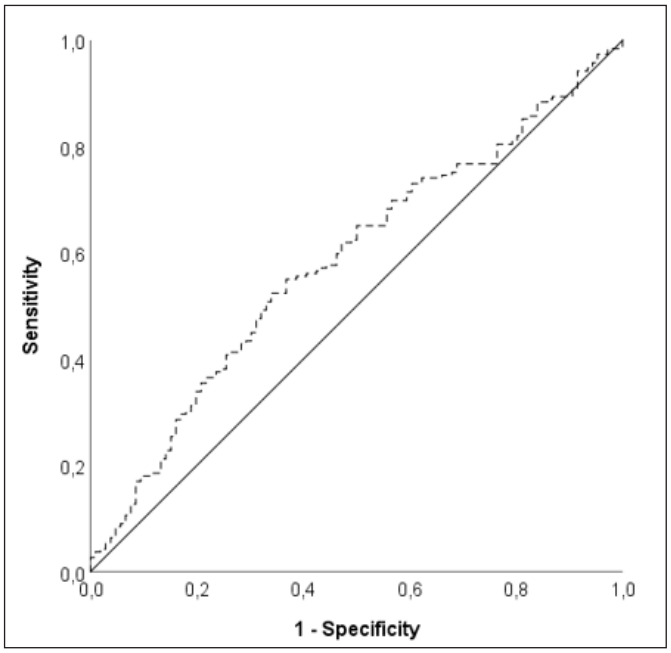

Figure 2. ROC curve of SII

DISCUSSION

The COVID-19 pandemic has caused many deaths and severe economic consequences around the world. These results have led the scientific community to search for inexpensive and easily obtainable biomarkers that can be used to predict mortality. Thus, it will be possible to reduce mortality with an early and appropriate therapeutic approach. In this study, we investigated whether the inflammation indices obtained from the complete blood count could be used to predict mortality in patients with COVID-19.

Age-related defects in T-cell and B-cell function and overproduction of type 2 cytokines may lead to a defect in the control of viral replication and longer-lasting proinflammatory responses, resulting in poor outcomes (13). In various studies conducted on patients with COVID-19, age alone has emerged as a significant risk factor for mortality (14-16). Our study supports the literature by revealing a significant relationship between increasing age and mortality.

It has been shown that high D-dimer levels are one of the most common laboratory findings observed in hospitalized patients with COVID-19. Zhang et al. (17) found that in-hospital mortality was higher in patients with COVID-19 with D-dimer levels higher than 2.0 µg/mL at the time of admission. This situation has been associated with an increased pro-inflammatory response due to virus infection and excessive thrombin production due to endothelial damage triggered by the insufficient anti-inflammatory response, increased blood viscosity secondary to hypoxia, and prolonged bed rest (17). High D-dimer levels were found to be associated with mortality in two studies examining patients with stroke who were

COVID-19 positive, which might be explained by an increased susceptibility to thrombosis (18, 19). In our study, it was determined that the risk of mortality increased as the D-dimer value increased (HR: 1,001 %95 CI: 1 – 1,001).

It is known that COVID-19-related organ dysfunction and mortality are associated with the inflammatory response (20). In addition to high inflammatory cytokine levels in patients with COVID-19 (3), serologic inflammation parameters such as CRP, LDH, and procalcitonin also increased (5). Our study revealed that these serologic inflammatory parameters could also predict mortality in patients with COVID-19.

The NLR can be defined as the ratio of the neutrophil count to the lymphocyte count. Previous studies revealed that NLR was elevated in chronic conditions with low-grade inflammatory nature, such as obesity, HT, DM, metabolic syndrome, atherosclerotic events of the heart and brain, and various cancers (21-23). After the pandemic started, studies focused on patients with COVID-19 and it was reported that increased NLR predicted poor prognosis, mortality, the possibility of intubation, risk of serious disease in intubated patients, and longer admission to the ICU in these patients (24-29). In our study, when compared according to mortality status, the median NLR value of the survivors was 7.45, whereas the median value of the non-survivors was 11.39, and this difference was found to be statistically significant.

In studies related to COVID-19, SII was found to be a reliable biomarker. When Xue et al. (30) examined the relationship between various markers and disease severity, they found that SII could significantly predict disease severity in univariate analyses. In a study of 397 patients, Doğancı et al. (31) showed that SII was significantly lower in surviving patients. Another study showed that SII was the only significant marker superior to NLR in predicting mortality in multivariate analyses (32). In our study, the median value of SII was 2421.02 (1166.47-4071.58) in the non-survivors, which was significantly higher than the survivors.

The most important limitation of our study is that it is a retrospective study. The relatively small number of patients and the inability to specify the severity of illness during hospitalization are other limitations of our study.

CONCLUSION

Our study showed that NLR and SII could predict mortality in patients with COVID-19, albeit with low specificity and sensitivity. The most important advantage of these indices is that they are obtained from very cheap and easily accessible hematologic parameters, regardless of the level of development of countries and ICUs. Our study is a guide for more comprehensive and detailed studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of KTO Karatay University Faculty of Medicine Non-Pharmaceutical and Non-Medical Device Researches Ethics Committee (Date: 14.01.2022, Decision No: 2022/022).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author have no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1109355
J Health Sci Med 2022; 5(4): 1092-1096

Association of IgE elevation with blood group in COVID-19 patients

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Cite this article as: Şenol FF, Bahçeci İ, Babacan A, Akgül S. Association of IgE elevation with blood group in COVID-19 patients. J Health Sci Med 2022; 5(4): 1092-1096.

ABSTRACT

Aim : All parameters that are thought to be efficient in getting sick and follow-up of the disease should be investigated because of COVID-19 disease has serious consequences. The aim of this study was to investigate whether there is a relationship between the AB0 blood group with Rh factor systems and the frequency of catching COVID-19 infection and between IgE elevation according to blood groups and COVID-19 positivity.

Material and Method: Blood groups and IgE levels of the control group (2690 patients) were compared retrospectively with 7300 patients who were admitted to our hospital between March 10, 2020, and March 31, 2021, and confirmed as COVID-19 positive with viral ribonucleic acid reverse transcriptase-polymerase chain reaction (RT-PCR).

Results: It was found that among the blood groups, the highest COVID-19 positivity belonged to the A blood group (46.17%) and the lowest belonged to the AB blood group (9.04%). The increase in IgE elevation was found statistically significant in COVID-19 positive patients (P<0.001) when compared to the control group(P<0.001). All blood groups, except AB Rh (-), had a statistically significant increase in IgE level when blood groups were evaluated together with Rh factors (P<0.001).

AB Rh (-) blood group had an increase in IgE level that is not statistically significant (P=0.171).

Conclusion: The results of this study showed that the risk of COVID -19 disease may be associated with the AB0 blood group and Rh factor systems, and high IgE level may be observed in patients during the disease. Therefore, investigation of IgE levels may be beneficial in the follow-up of COVID-19 patients

Keywords: COVID-19, blood group, IgE

INTRODUCTION

Before the emergence of severe acute respiratory syndrome (SARS), the human coronaviruses were responsible for causing 15-30% of common cold cases. Coronaviruses are a family of RNA (ribonucleic acid) viruses that can cause infection in humans and a wide variety of animal species (1). In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 infections, named coronavirus disease 2019 (COVID-19), was reported in Wuhan, China. COVID-19 virus has rapidly spread worldwide and has been accepted as a pandemic by the World Health Organization (WHO) (2). Clinical courses of COVID-19 were divided into three categories: asymptomatic cases, moderate cases, and severe cases. It has been reported that the mortality rate is 2-3 percent in patients with severe clinical symptoms. However, this is not seen in every patient and it varies according to the clinical presentation of the patient (mild or asymptomatic) and geographical location (3,4). Male sex, age over 60 years, diabetes, high blood pressure, lung diseases, cancer, immune system weakness are risk factors for severe COVID-19 (4,5).

The blood group is determined by the AB0 gene located on the long arm of chromosome 9 (9q34). Blood groups designate according to the presence or absence of A and B antigens produced by A and B variant alleles (6). Many studies have explored the association between AB0 and Rh blood groups and cardiovascular diseases, malignancies, and paralysis. In these studies, it has been found that the risk of disease increased in some blood groups (7,8). It has

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Received: 26.04.2022 **Accepted:** 15.06.2022

been suggested that the blood group have been correlated with COVID-19 disease susceptibility and the severity of the clinical course. Previous studies have shown various and contradictory results (9, 10)

Immunoglobulins (Ig) are specific molecules that bind to antigens. The IgE like other Ig (IgG, IgA, IgM, and IgD) is composed of two light chains and two heavy chains. Compared to other immunoglobulins, the IgE monomer is consists of four constant regions. The weight of IgE is 190 kDa, correspondingly, which is higher than IgG (150 kDa). The heavy chain is epsilon. Receptors are found on mast and basophil cells in the Epsilon chain. Serum concentrations of IgE are lower compared with IgG concentrations. The half-life of free IgE in the serum is approximately 2 days while IgE bound to mast cells can last for around two weeks (11). IgE is also called "allergic antibody"; plays a major role in the pathogenesis of allergic diseases and it is an important initiator of the humoral response. High IgE serum level is not always related to allergy. There are many clinical conditions associated with an increased IgE serum level (12). IgE has an important role in response to parasitic diseases (protozoa and helminths) and antitumor immunity (13). IgE serum level increases from birth, ranged up to 200 IU/mL until the age of 15 years and then decreases rapidly. IgE serum level is lower than 100 IU/mL for adults (12]). Humoral and cellular immune responses work together against viral infections but the humoral response is easier to determine under laboratory conditions than the cellular response (14). With this approach, humoral immunity investigates for the rapid diagnosis of diseases most virology laboratories (15). RT-PCR analysis is the gold standard for detecting infection in the diagnosis of COVID-19. Among the laboratory findings, lymphopenia occurred most frequently while thrombocytopenia, leukopenia and elevated levels of C-reactive protein (CRP) can also be observed. It has been reported that elevations of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and D-dimer are less commonly observed. Laboratory abnormalities are more obvious in severe patients in comparison to non-severe patients (16,17).

MATERIAL AND METHOD

For this study, permission was obtained from the Presidency of the Non-interventional Researches Ethics Committee of Fırat University Faculty of Medicine (Date: 18.11.2021, Decision No: 2021//12-21). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Nose and throat swabs were collected from 7300 patients who were admitted to the emergency department with clinical complaints or COVID-19 contacts between March 2020, and March 2021, and they were confirmed as COVID-19 positive by RT-PCR BİORAD (Qiagen, Germany). The blood group and Rh factor of these patients were determined by a gel card system (Grifols Eflexis Diana, Spain). IgE levels were quantified with the nephelometry method by using the IMMAGE 800 (Beckman Coulter) and levels of 165 IU/ml or above were considered high. In this study, 2690 patients with known blood groups and levels of IgE who were admitted to our hospital were identified as a control group. The IgE levels according to blood group and Rh factor of the COVID-19 positive patients were compared with the control group. Data were analyzed using IBM SPSS version 20.0. The chi-square test was used to compare the IgE elevation in terms of blood types and Rh positivity among COVID-19 positive and negative groups. Results of the study were analyzed using frequency distributions and percentages. Chi-square results were shown in table format with the p-value.

RESULTS

Blood types and IgE levels of 7300 patients who were diagnosed with COVID-19 and the control group were compared retrospectively. Of the 7300 COVID-19 positive patients, 63,01% (4600) were men and 36.98% (2700) were women. In the control group of 2690 patients, 1360(50.55%) were men and 1330(49.44%) were women. The positivity of COVID-19 was found statistically significant in male patients compared to the control group (P<0.001). It was observed that the highest blood group was A with 46.17% and the lowest was AB blood group with 9.04%. It was found that the increase in IgE level according to Rh (+) blood factors was statistically significant among COVID-19 positive patients with IgE elevation compared to the control group(P<0.001). The increase in IgE elevation was found statistically significant in COVID-19 positive patients (P<0.001) when compared to the control group according to Rh (-) blood factor. No statistically significant increase in IgE level was observed difference between Rh factor groups (P=0,621). In **Table 1**, the distribution of IgE level of COVID-19 positive patients according to blood group and Rh factor was shown.

Blood groups according to Rh (+) and Rh (-) factors compared to the control group, all blood groups except AB Rh (-) had a statistically significant increase in IgE level(P<0.001). COVID-19 patients with AB Rh (-) blood group had an increase in IgE level compared to the control group that is not statistically significant (P=0,117). In **Table 2**, elevations of IgE level compared with all blood groups according to Rh(+) factor and Rh(-) factors.

Table 1. Distribution of IgE elevations according to blood group, Rh factors

	Patient		IgE		Control		IgE		Total		p
	n	%	n	%	n	%	n	%	n	p	
A	3400	46.57	850	25	1280	47.54	210	16.40	1060	<0.001	<0.001
0	1970	26.98	660	33.50	640	23.79	120	18.75	780	<0.001	
B	1270	17.39	520	40.94	550	20.44	140	25.45	660	<0.001	
AB	660	9.04	160	24.24	220	8.17	30	13.63	190	0.001	
Rh+	6530	89.45	1910	29.24	2320	86.24	480	20.68	2390	<0.001	0.621
Rh-	770	10.54	280	36.36	370	13.75	20	5.40	300	<0.001	

Table 2. Comparison of IgE elevations with blood groups according to Rh (+) and Rh(-) factor

	Patient		IgE		Control		IgE		Total		p
	n	%	n	%	n	%	n	%	n	p	
A Rh +	3030	41.50	730	24.09	1080	40.14	210	19.44	940	0.002	<0.001
0 Rh +	1800	24.65	600	33.33	570	21.18	120	21.05	720	<0.001	
B Rh +	1120	15.34	450	40.17	490	18.21	130	26.53	580	<0.001	
AB Rh +	580	7.94	130	22.41	180	6.69	20	11.11	150	0.001	
A Rh -	370	5.06	120	32.43	200	7.43	0	0	120	<0.001	<0.001
0 Rh -	170	2.32	60	35.29	70	2.60	0	0	60	<0.001	
B Rh -	150	2.05	70	46.66	60	2.23	10	16.66	80	<0.001	
AB Rh -	80	1.09	30	37.5	40	1.48	10	25	40	0.171	

DISCUSSION

Several research has been done on the susceptibility to infection between the pathogenesis of COVID-19 disease and blood groups. AB0 blood groups have been reported to be associated with many diseases such as type 1 diabetes, autoimmune diseases, rheumatic diseases, dengue fever, multiple sclerosis, hepatitis B and psoriasis (18,19). It has been shown that SARS-CoV infects individuals according to AB0 blood groups and can synthesize AB0 antigens in pneumocytes, the enterocytes of the small intestine, and kidney distal tubular epithelial cells (20). Antibodies of the AB0 system were suggested to hinder the interaction between SARS CoV spike protein and angiotensin-converting enzyme 2 (ACE 2) (21). There is no study on the use of biological markers to predict susceptibility to COVID-19. SARS CoV has surface proteins that bind to sugars. It has been postulated that individuals with blood group A are more susceptible to COVID-19 infection due to N-acetyl galactosamine, on the surface of blood group A cells (22). AB0 blood groups of 265 patients infected with COVID-19 were retrospectively analyzed, and the blood groups of the patients were group as follows: A in 39.3%, group B in 25.3%, group AB in 9.8%, and group 0 in 25.7%. Compared to the control group, the rate of those with blood group A was reported to be significantly higher (39.3% vs. 32.3%, P=0.017) while those with blood group 0 was significantly lower (25.7% vs. 33.8%, P<0.001) (23). Wu et al. (24). reported that the risk of getting infected by COVID-19 in a blood group A individual was significantly higher than that in other blood groups while in a 0 blood group individual had a much lower risk of getting infected by COVID-19 Arac et al. (25) reported that blood group A was dominant compared to other blood groups especially blood group 0 among COVID-19 patients,their results indicated that no statistically significant difference exists between COVID-19 patients and healthy individuals in terms of the AB0 blood group system. Gur et al. (26) found that the ratio of blood group A was higher 48.6% vs. 42.8% and blood group 0 28.2% vs. 33.7% had a lower ratio compared to Turkey's average in COVID-19 patients. In addition, they stated that the percentages of patients with A Rh+ and A Rh- blood groups were significantly higher than Turkey's average 42.1% vs. 37.8%, and 6.5% vs. 5% . In the study, the blood group A (46.57%) is highly frequent among COVID-19 patients, while blood group AB(9.04%) is the lowest. Abdollahi et al. (27) and Bhandari et al. (28) have not determined any correlation between Rh positivity and susceptibility to COVID-19. Latz et al. (29). and Zietz et al. (30) found that individuals in Rh (+) blood type had a higher risk for COVID-19 infection. Although the rates of Rh-positive patients were higher than the rates of Rh-negative patients among COVID-19 patients (89,45%,10,54%) compared to the control group (%86,24,%13,75), we observed no statistically significant difference between Rh type and risk of COVID-19 infection (P=0,612). Kirisci et al. (31) indicate that the COVID-19 disease affected men more than women (OR= 2.091) (p=0.0001) . Similarly, in our study, we detected a statistically significant association between gender and the prognosis of COVID-19, and men had a higher risk than women.

The increase in IgE level is generally observed with allergic diseases. However, the elevation of IgE level is also seen in some diseases such as malignancies,

immunodeficiency syndromes, skin diseases, inflammatory diseases, and infections. Parasitic infections are a primary cause of raised IgE levels among infectious diseases. IgE elevation can be seen with some parasitic infections such as Entamoeba, Giardia, Ascaris. IgE elevation can also be seen with viral diseases. Infectious mononucleosis due to Epstein-Barr virus (EBV) infection presents fever, pharyngitis, cervical lymph node enlargement, and fatigue. Increased IgE levels may take weeks or months to normalize after infection (32). A multicenter study has demonstrated that cytomegalovirus (CMV) and EBV seropositivity are much higher in allergic individuals compared with nonallergic individuals (33). Another study determined a high total IgE in Human Immunodeficiency Virus (HIV) infected children, independent of the activation and aggravation of HIV infection (34). It has been hypothesized that IgE serum level elevation in HIV infection results from increased polyclonal stimulation of B lymphocytes. Due to the fact that COVID-19 is a viral infection, our study demonstrated a statistically significant increase in IgE level among all blood groups compared to control groups (P<0.001). Blood groups according to Rh factors compared to control group, all blood groups except AB Rh (-) had a statistically significant increase in IgE level(P<0.001). There was no statistically significant increase in AB Rh(-) blood group with IgE level compared to the control group (P=0,117).

CONCLUSION

In our study, we investigate if there is an association between the AB0 blood group according to Rh factors and IgE elevation in COVID-19 patients confirmed with PCR. Our study demonstrated that total IgE level, except for AB Rh (-) patients, increased significantly in COVID-19 patients. All parameters of COVID-19 infected patients in the general population worldwide should be evaluated and examined with serological approaches.

ETHICAL DECLARATIONS

Ethics Committee Approval: For this study, permission was obtained from the Presidency of the Non-interventional Researches Ethics Committee of Fırat University Faculty of Medicine (Date: 18.11.2021, Decision No: 2021//12-21).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest: The authors have declared that no conflict interests exist.

Financial Disclosure: The authors declared that this study had received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1128102
J Health Sci Med 2022; 5(4): 1097-1102

Evaluation of pediatric rheumatologists' knowledge, attitudes, and behavior regarding vaccination in pediatric rheumatic diseases

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Cite this article as: Karagöl C, Ekici Tekin Z, Coşkun S, et al. Evaluation of pediatric rheumatologists' knowledge, attitudes, and behavior regarding vaccination in pediatric rheumatic diseases. J Health Sci Med 2022; 5(4): 1097-1102.

ABSTRACT

Aim: Developments in diagnostic methods and advances in the treatment of pediatric rheumatic diseases (PRDs) have improved the quality of life in this patient group. However, vaccine-preventable infectious diseases are still outstanding causes of morbidity and mortality in immunocompromised patients more than in healthy population. Pediatric rheumatologists play a critical role in increasing vaccination rates since they have ample opportunity to administer vaccinations. The aim of this study is to determine the knowledge, attitudes, and behaviors of pediatric rheumatologists about vaccination in rheumatic diseases.

Material and Method: Between March 2022-May 2022, an online questionnaire of 20 items was used to evaluate the knowledge, attitudes, and behaviors of pediatric rheumatologists in Turkey with respect to vaccination.

Results: A total of 81 participants answered all survey questions completely. The ages of the study group ranged from 30 to 48 years, at a mean of 37.5±3.8 years. Most of the pediatric rheumatologists (n:76, 93.8%) were working in a tertiary pediatric hospital; 27.2% did not consider themselves primarily responsible for the vaccination of children with PRDs, and 30.9% did not refer their patients to the department that administers the vaccine either before or during immunosuppressive therapy. In addition, it was found that only 14.8% regularly questioned the vaccination history of patients at each outpatient visit. One-third of study group recommended the implementation of non-scheduled vaccines and the most recommended non-scheduled vaccine was seasonal influenza (n:48, 59.3%). The comparative analysis between pediatric rheumatology residents and staff physicians showed no statistically significant difference in the level of knowledge except in the question concerning live vaccines.

Conclusion: This study revealed that there are still serious problems in clinical practice about the vaccination of PRDs patients. For this purpose, pediatric rhematologists' awareness and knowledge about vaccination should be increased with a special education program.

Keywords: Vaccination, pediatric rheumatic diseases, awareness, knowledge

INTRODUCTION

Developments in PRDs diagnostic methods and advances in treatment, especially the discovery of new generation biological agents, have increased survival and quality of life in this patient group. This results in being more exposed to infectious agents, and consequently these patients are more prone to contracting severe infectious disease (1,2). Vaccination is the most effective, reliable, and affordable way to prevent infectious diseases. The immune system may be suppressed due to drugs used in the treatment of PRDs. In addition, immune dysregulation is common in the etiology of PRDs. Infections are therefore a major cause of hospitalizations and increased disease activity in these patients (1). Although the protective antibody level provided by a vaccine in this patient group is lower than in healthy people, it is essential to vaccinate children with chronic inflammatory diseases. Serious side effects from the vaccine or active infection due to live-attenuated vaccines may also be seen in these patients whose immune system is affected (3). In addition, vaccination effects may differ from healthy children due to the fact that

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Received: 08.06.2022 **Accepted:** 16.06.2022

PRDs progress with exacerbation attacks and remission. Pediatric rheumatologists are the physicians primarily responsible for regularly following up on these children and thus have a significant window of opportunity to vaccinate patients with PRDs. Since the studies on the efficacy and safety of vaccines in children with PRDs are limited in the literature, pediatric rheumatologists may have concerns about this issue (1, 4).

The aim of this study is to determine the knowledge, attitudes, and behaviors of pediatric rheumatologists about vaccination in rheumatic diseases and concerning patients using immunosuppressive drugs. The data to be obtained in this regard will be important in determining and solving the problems experienced in the vaccination of this patient group.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No 2 Non-interventional Clinical Researches Ethics Committee (Date: 16.03.2022, Decision No: E2-22-1498). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This current study was conducted as a multicenter, cross-sectional, and descriptive questionnaire study. The sample size was calculated on the basis of the number of pediatric rheumatologists working in our country (n=92) with a 95% confidence interval and using the simple random "haphazard sampling" method. The questionnaire, consisting of three different parts and containing a total of 20 questions, was applied to pediatric rheumatologists on an online platform.

The first section comprises 6 questions about demographic characteristics. This section includes questions about age, gender, academic position, number of years worked in the field of pediatric rheumatology, the institution worked at, and the department that administers vaccines in this institution.

The second section of the questionnaire, devoted to the attitudes and behaviors of the participants towards vaccination in patients with PRDs (including COVID-19 vaccines), was evaluated with 7 questions. Finally, in the third section, 7 multiple-choice questions were asked to discern the knowledge level of the participants. This last section pertained to the evaluation of knowledge levels regarding all vaccines administered to pediatric rheumatology patients (both those included in the national immunization schedule as well as non-scheduled vaccines). The accuracy of the data was determined according to the recommendations of the European Alliance of Associations for Rheumatology (EULAR) (5).

All data obtained from the study were evaluated for the entire study group. Afterwards, the participants were categorized into 2 different groups according to their academic positions (residents and staff physicians) and a comparison was made as to whether there was a difference between the groups. Those who had worked in the pediatric rheumatology department for less than 6 months were excluded from the study.

Statistical analysis was performed using IBM SPSS Statistics for Windows Version 21.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Qualitative data were presented in terms of frequency (n) and percentage (%). Categorical variables are shown in numbers (n), percentages (%) and continuous variables are shown in terms of mean (±) standard deviation (SD). The chi-square ($\chi 2$) test was used to compare categorical data. Statistical significance was accepted as $p < 0.05$.

RESULTS

A total of 81 participants completely answered all survey questions. The ages of the study group ranged from 30 to 48 years, at a mean of 37.5±3.8 years. Most of the pediatric rheumatologists (n:76, 93.8%) were working in a tertiary pediatric hospital, and it was found that only 13 (16%) were working in a hospital where vaccinations are not administered. Other demographic data for the study group are given in **Table 1**.

Table 1. Demographic characteristics of the pediatric rheumatologists participating in the survey (n=81), SD, Standard deviation

Characteristic	Total n, (%)
Gender	
Female	65, (80.2)
Male	16, (19.8)
Age, Mean±SD	37.5±3.8
Years of professional experience	
0-3 Years	39, (48.1)
3-6 Years	17, (21.0)
>6 Years	25, (30.9)
In which hospital do you work?	
University Hospital	44, (54.3)
Training and Research Hospital	32, (39.5)
State Hospital	3, (3.7)
Private Hospital	2, (2.5)
What is your academic title?	
Associate professor	17, (21)
Specialist	21, (25.9)
Resident	43, (53.1)
Which department administers the vaccine in your institution?	
Vaccine not administered	13, (16.0)
Pediatric rheumatology department	0, (0)
Pediatric infectious diseases department	4, (4.9)
Social pediatrics department	68, (84.0)

It was determined that 27.2% of the pediatric rheumatologists did not consider themselves primarily responsible for the vaccination of children with PRDs, and 30.9% did not refer their patients to the department that administers vaccines either before or during immunosuppressive therapy. In addition, it was found that only 14.8% regularly questioned the vaccination history of patients at each outpatient visit. The rest inquired into this rarely or only at the first admission. The study group believed that the most important problem regarding vaccination was related to inadequate antibody response to the vaccine. This was followed by a concern for active infection caused by the vaccine strain and an increase in vaccine-related disease activity. The responses of the participants revealing their attitudes and behaviors regarding vaccination are given in **Table 2**.

Table 2. Pediatric rheumatologists attitudes towards vaccination (n=81)

Questions	n, (%)
Which physician is primarily responsible for the vaccination of pediatric rheumatology patients?	
Pediatric rheumatologists	59, (72.8)
Family physicians	32, (39.5)
Social pediatricians	44, (54.3)
Pediatric infectious diseases specialists	18, (22.2)
Do you refer your patients who will be receiving immunosuppressive therapy to the department that administers the vaccine?	
No, I don't.	25, (30.9)
Yes, before the initial treatment	44, (54.3)
Yes, after the initial treatment.	26, (32.1)
Yes, at the end of the treatment	5, (6.2)
What is the biggest problem in pediatric rheumatology practice regarding vaccination?	
Vaccine-related increase in disease activity or severity	17, (21.0)
Serious vaccine-related side effects	9, (11.1)
Active infection caused by the vaccine strain	18, (22.2)
Inadequate antibody and immune response to vaccine	64, (79.0)
No idea	5, (6.2)
Do you question the vaccination history of a patient with a rheumatological disease in daily practice?	
Regularly at every visit	12, (14.8)
Only on the first admission	27, (33.3)
Rarely	36, (44.4)
No, I don't.	6, (7.4)
Do you recommend the COVID-19 vaccine to your rheumatology patients receiving immunosuppressive therapy?	
Yes, I do	81, (100)
No, I don't	0, (0)
If you are recommending the COVID-19 vaccine, is there a vaccine you specifically recommend?	
Coronovac-inactivated vaccine	0, (0)
Biontech-mRNA vaccine	43, (53.1)
I leave it to the patient's choice	38, (46.9)

While almost all of the pediatric rheumatologists thought the implementation of the national vaccination schedule was enough for PRD patients, only one-third recommended the administration of non-scheduled vaccines as well. The most recommended non-scheduled vaccine was seasonal influenza (n:48, 59.3%), and the least recommended was Human Papilloma Virus vaccine (21.4%). In addition, it was seen that the entire study group recommended the COVID-19 vaccine to their patients. While all of the participants recommended the Biontec-mRNA vaccine, none recommended the Coronovac inactivated vaccine. Data on vaccines recommended by the pediatric rheumatologists are given in **Table 3**.

Table 3. Vaccines recommended by pediatric rheumatologists HPV, human papilloma virus, Men, meningococcal bacteria, HIB, haemophilus influenza type B, BCG, Bacillus Calmette–Guérin

Vaccines	Which vaccine(s) would you recommend for the rheumatology patient? n, (%)
Vaccines in the national schedule	81, (100)
Seasonal influenza	48, (59.3)
HPV	17, (21.4)
Men ACWY	25, (30.9)
Men B	25, (30.9)
HIB	25, (30.9)
Conjugated Pneumococcus	25, (30.9)
Polysaccharide Pneumococcus	22, (27.2)
BCG	34, (42.0)
All scheduled and non-scheduled vaccinations	8, (9.8)

It was found that the entire study group answered the question about inactivated vaccines correctly. However, the rate of those who answered the question about live vaccines correctly was only 60.5%. It was also found that one-third of the participants incorrectly thought that vaccines could increase the severity of rheumatic diseases or cause more serious side effects in patients with PRDs. The lowest correct response rate (18.5%) was found in the question about administering live vaccines to the infant of a pregnant woman using biological agents. The levels of knowledge of the entire group of participants are given in **Table 4**.

In the comparative analysis of the groups, the mean age of the pediatric rheumatology residents (n:43, 53.1%) and staff physicians (n:38, 46.9%), was found to be 37.4±3.7 and 38.5±3.4 respectively. There was no significant difference between the groups in terms of demographic data. The comparison was made to evaluate levels of knowlege based on the correct answers given by both groups to the questions. The number of staff physicians (n:28, 73.7%) who correctly answered the question about administering only live vaccines in line with the national vaccination schedule to children with PRDs was significantly higher than among the residents (n:21, 48.8%) ($p. <0.05$). The other responses given to the questions that evaluated the level of knowledge were found to show no statistically significant difference between the groups in terms of knowledge levels. Comparative analysis was not performed for the attitude and behavior questions since it was considered that the residents in the group had not as yet attained full competence in daily rheumatology practice.

Table 4. Pediatric rheumatologists' level of knowledge about vaccination (n=81)

Questions	Answered correctly n, (%)	Answered incorrectly n, (%)	No idea n, (%)
In all rheumatology patients with stable disease, regardless of treatment, inactivated vaccines can be administered on time, following the national vaccination schedule.	81, (100)	0, (0)	0, (0)
In all rheumatology patients with stable disease, regardless of treatment, live-attenuated vaccines can be administered on time, following the national vaccination schedule.	49, (60.5)	32, (39.5)	0, (0)
In children with active rheumatic disease, the appropriate timing of vaccination should be determined on a case-by-case basis by evaluating the risks and benefits of immunization.	55, (67.9)	26, (32.1)	1, (1.2)
Administered vaccines do not increase the severity of the underlying rheumatological disease.	48, (59.3)	31, (38.3)	2, (2.5)
All administered vaccines do not cause serious side effects in rheumatology patients compared to healthy children.	50, (61.7)	28, (34.6)	3, (3.7)
Treatment of a newly diagnosed rheumatology patient should be initiated after completing the missing vaccines unless the initiation of immunosuppressive therapy is not urgent.	65, (80.2)	11, (13.6)	5, (6.2)
Live vaccines of the infant of a mother using biological agents during pregnancy should be delayed for at least 6 months.	15, (18.5)	16, (19.8)	50, (61.7)

DISCUSSION

Despite increasing evidence supporting vaccine safety and efficacy in children with PRDs, vaccination coverage for these children is still lower than in the healthy population across the world (6, 7). Pediatric rheumatologists play a critical role in increasing vaccination rates since they have ample opportunity to administer vaccinations. To the best of our knowledge, our study is the first study in the literature in our country to evaluate the knowledge, attitudes, and behaviors of pediatric rheumatologists about the vaccinating children with PRDs. Although there is a wide variation among them, pediatric rheumatologists seem to have adequate knowledge regarding vaccination. However, this study revealed that there are still serious problems in this respect in daily clinical practice. The most important problems are that approximately one-third of the pediatric rheumatologists did not regard themselves as responsible for vaccinations and only a very few actually questioned vaccination histories at each visit.

Pediatric romatologists treat a wide spectrum of autoimmune and autoinflammatory diseases. The majority of pediatric rheumatology patients are juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), vasculitides, and autoinflammatory disorders etc. Immunosuppressive medications such as steroid, cyclophosphamide, methotrexate, and biological agents are commonly utilized in treatment. Some children with PRDs have a higher risk of developing infectious diseases compared to healthy children, due to both the immunosuppressive drugs used in treatment and underlying immune dysfunction (1,3). Therefore, effective and safe vaccination is crucial for these patients, but it has been reported that vaccination coverage is inadequate in 1/3 of children with PRDs (6, 7). In a recent cohort that evaluated the vaccination status of 187 children with PRDs, 35% of the children were found to be incompletely vaccinated. In addition, it was emphasized that the leading reason for vaccination dropout is the advice of the treating rheumatologist (6). In a Canadian study (8) conducted with 200 children with JIA the rate of complete vaccination of patients at the last clinic visit was found to be 61%. In a German study (9) with 715 children with JIA, one-third of the patients were incompletely vaccinated. Moreover, the incomplete vaccination rate was found to be 43.5% in 207 children with PRDs in a Brazil cohort (10). The concerns about vaccines both in parents and patients and an emphasis on contraindications by rheumatologists are seen as the greatest obstacles to vaccination (6, 10). Despite growing evidence, concerns still remain about the safety and efficacy of vaccination. Pediatric rheumatologists should have adequate knowledge about vaccines, especially about their immunogenicity and side effects.

We found in our study that the greatest concern of pediatric rheumatologists about vaccination is inadequate antibody and immune response to the vaccines. The efficacy of vaccines in patients with PRDs is difficult to evaluate. Many factors such as the underlying primary disease, the activity of the disease, the dose and type of immunosuppressive drugs, the type of vaccine administered, and the time of administration, affect the immunogenicity of vaccines (4). Vaccine efficacy studies in the literature have studied protective antibody levels, indicators of immunogenicity, rather than real-life data. These studies have not evaluated all diseases, drugs and vaccines. Nevertheless, the 2011 EULAR recommendations for vaccination in pediatric patients with rheumatic diseases (5) emphasized that the evidence for the efficacy of vaccines is reassuring.

Another concern of rheumatologists and families regarding vaccination is about vaccine safety. Vazhappilly et al. (11), in a survey study evaluating 82 children with PRDs, reported that the most important factor decreasing vaccination rates was the concerns of families

about vaccine safety. It was also found that informing families about vaccine safety and contraindications through rheumatologists increases vaccination rates. Our study shows that half of pediatric rheumatologists have concerns about vaccine safety. In addition, vaccine-related active infection and increased disease activity were found to be the most frequent safety concerns. Many studies have shown that vaccines do not cause serious side effects in children with PRDs compared to healthy children (4), and this is also stated in EULAR recommendations (5). However, it is still debated whether vaccines cause autoimmune disease or increase disease activity. It has been shown in studies performed with measles, mumps, and rubella-MMR vaccine in JIA patients (12) and varicella-zoster virüs-VZV vaccine in juvenile SLE patients (13) that disease activity is not affected by the vaccine in most patients. Data on the use of live attenuated vaccines in patients receiving high-dose immunosuppressive therapy are increasing day by day. The Centers for Disease Control and Prevention (CDC) have defined high-dose immunosuppressive therapy , and it is stated that there is no inconvenience in administering live vaccines in patients receiving low-dose immunosuppressive therapy. However, there is a consensus that live vaccines should be avoided in patients using high-dose immunosuppressive and biologic agents (14,15). In the EULAR guidelines published in 2019 (16), it was emphasized that more research is needed on this issue. In these patients, it seems more appropriate to make a decision on a case-by-case basis, taking into account the risk-benefit ratio. Due to these ongoing discussions in the literature, it is not surprising that pediatric rheumatologists were more concerned about live attenuated vaccines than inactivated vaccines in our study. To address these concerns, it is obvious that well-planned controlled studies are needed to examine rare serious adverse events, particularly in patients using high-dose immunosuppressive drugs, steroids and biologics.

We observed in our study that all of the pediatric rheumatologists considered the implementation of the national vaccination schedule in children with PRDs to be enough. It was not surprising that seasonal influenza was the most recommended vaccine among the special vaccines that are not included in the national vaccination schedule. Seasonal influenza is the most common infection in children with PRDs and poses a risk for lower respiratory tract infection in these patients. The safety and efficacy of influenza and other non-funded vaccines have been proven in these patients (4, 14, 17). The awareness of pediatric rheumatologists about non-funded vaccines will increase the recommendation of these vaccines.

No significant difference was found in our study between resident rheumatologists and staff physicians, except in the matter of the administration of live vaccines. This revealed that the level of knowledge about vaccination is not related to professional experience. In other words, it was observed that the level of knowledge about vaccination did not increase during an individual's rheumatology residency, which is an indication that more education should be provided on vaccinating children with PRDs during the rheumatology education program.

There are some limitations in our study. First of all, the study did not include all pediatric rheumatologists in Turkey because they did not want to participate voluntarily. However, a significant number of participants has been reached. Secondly, the survey questions were designed generically for all PRDs therefore specific diseases and treatment agents were not evaluated. Future researchs may focus on vaccination in specific PRDs like JİA and specific immunomodulatory drugs. However, our study is the first study in our country to evaluate the knowledge, attitudes, and behaviors of pediatric rheumatologists about the vaccinating and contributed to the literature with its significant results.

CONCLUSION

Some patients with PRDs are at a higher risk of infection than healthy children. The most effective way to prevent infections is vaccination, but vaccination coverage for this patient group is not at the desired level due to safety and efficacy concerns. Awareness should be raised and more knowledge should be provided about vaccination during the course of the pediatric rheumatology residency program. Additionally, there is a need for carefully planned randomized controlled studies that will address concerns about vaccination.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No 2 Non-interventional Clinical Researches Ethics Committee (Date: 16.03.2022, Decision No: E2-22-1498).

Informed Consent: Online informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1110150
J Health Sci Med 2022; 5(4): 1103-1109

The protective role of low-dose acetylsalicylic acid use and relation with inflammatory and thrombotic parameters on radial artery occlusion in patients undergoing elective transradial coronary angiography

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Cite this article as: Özbeyaz NB, Açıkel S, Algül E, et al. The protective role of low-dose acetylsalicylic acid use and relation with inflammatory and thrombotic parameters on radial artery occlusion in patients undergoing elective transradial coronary angiography. J Health Sci Med 2022; 5(4): 1103-1109.

ABSTRACT

Aim: Transradial angiography (TRA) is recommended in clinical practice; it is better than the transfemoral route to prevent site-related complications. Radial artery occlusion is one of the most seen significant complications after TRA. In the present study, the protective effect of low dose acetylsalicylic acid (ASA) use against the radial artery occlusion (RAO) and the predictive ability of some thrombotic and inflammatory factors for the development of RAO were investigated.

Material and Method: One thousand two hundred fifty-four patients who planned for elective coronary angiography were screened to include transradial coronary angiography. The patients have grouped group I, who took ASA (100 mg) (n= 56), and group II (n= 51), who did not. Blood samples were taken immediately after sheath insertion and after the six hours of the sheath removal. The D-dimer and C-reactive protein values were analyzed between groups. In the first 24 hours after the procedure, the radial Doppler ultrasonography assessment was performed to detect RAO. Multivariable regression analysis was used to evaluate the independent risk factors for the TRA.

Results: Eligible one hundred seven stable patients were included in the study. The demographic, laboratory and procedural characteristics were similar between the two groups (Table 2). TRA was statistically lower in Group I compared to Group II. (n=3 vs. n=22, p=.001). Multivariable regression analysis demonstrated that postprocedural higher D-dimer levels and non-ASA status were found to be the independent risk factors for RAO (OR (95% CI=1.235(1.014-1.582) p=.001, 5.534 (3.376-9.252), p <.001). ROC analysis demonstrated the cut-off value of the D-dimer level was 144 ng/ml for predicting RAO (AUC =0.658, sensitivity 62.4%, specificity 89.2%, p=.016). Preprocedural and postprocedural CRP values did not differ between groups (p>.05).

Conclusion: Preprocedural ASA use may have a protective role against the RAO. Pre- and post-procedural D-dimer levels can predict the thrombotic process in the early phase of the RAO.

Keywords: Acetylsalicylic acid, radial artery occlusion, D-dimer, C-reactive protein, protection

INTRODUCTION

Transfemoral and transradial access are the most commonly used entry routes for coronary angiography (CAG). The operators nowadays prefer transradial access (TRA) since it has proven safer than transfemoral access (TFA) to diagnose and treat cardiovascular atherosclerotic disease (1,2). Radial artery occlusion is one of the procedural complications after transradial procedures. Impaired local endothelial functions and the development of thrombotic processes are shown as the leading cause of radial artery occlusion. The development of this complication is mainly minimized by applying routine intraradial anticoagulation, administering vasodilator drugs via the sheath, and patent homeostasis, besides using contralateral ulnar compression and selecting small-caliber sheaths, catheters, etc. (2-7).

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Received: 27.04.2022 **Accepted:** 18.06.2022

D-dimer is a blood parameter obtained from a complete blood count measurement, showing fibrin formation and degradation. It usually is present in a low amount in serum in healthy individuals, but it shows a severe increase in serum in individuals who develop any thrombotic events. D-dimer is routinely used to diagnose and follow up venous thromboembolism (VTE) and pulmonary thromboembolism (PR). And also; It is used for the diagnosis of disseminated intravascular coagulopathy (DIC), to determine the risk of stroke in patients with atrial fibrillation, to predict the development of cardiovascular events in patients with coronary artery disease (CAD) and HIV infection, or to exclude acute aortic dissection (8).

Acetylsalicylic acid (ASA) is a widely used agent with proven efficacy in treating broad atherothrombotic vascular diseases. It exerts its antithrombotic effect by suppressing platelet activation by inhibiting the cyclooxygenase (COX) pathway. It is a protective effect over arterial and venous thromboembolic events is well known (9-11). However, ASA's clinical effectiveness for preventing radial artery occlusion (RAO) is not well defined. This study aimed to assess the protective role of low-dose ASA use before the transradial CAG and a relationship between RAO and hematologic, inflammatory parameters such as CRP and D-dimer.

MATERIAL AND METHOD

The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.09.2019, Decision No:72/02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

This study is a single-center, prospective, observational study. That included the patients who underwent coronary angiography from the right radial route between July 2018 and August 2020. The patients' data were obtained from the hospital automation system, and the anamnesis was taken from the patient themself.

1254 patients who underwent transradial coronary angiography were analyzed for the study. After excluding the patients with an exclusion, then the patients in the aspirin-taking (100mg) and non-aspirin (100mg) groups were matched according to their demographic, laboratory, and procedural characteristics. The appropriate patient groups to be included in the study were determined. Finally, 107 patients, aged between 32 and 85 years, who underwent right radial route CAG for the first time by their physician, and who had no abnormality in Allen and Barbeau tests were included. The patients involved in the study underwent planned elective coronary angiography and had aortic root width and configuration within normal limits, no coronary outflow anomaly, stable hemodynamics, and no common pathology on the radial artery side where the sheath was placed. Blood samples for D-dimer were obtained from blood taken from the radial sheath after coronary angiography, and upper extremity Doppler was performed within 24-48 hours after the procedure. Those who had emergency coronary angiography indication (STEMI, NSTEMI, USAP, Shock, Cardiac arrest), peripheral artery disease, active infection/inflammatory disease, decompensated heart failure, severe valvular disease, chronic kidney disease, malignancy, acute pulmonary thromboembolism, myocarditis/pericarditis, who used anticoagulant or non-aspirin antiplatelet and immunosuppressive therapy, and whose treatment changed after undergoing the procedure were also excluded from the study.

Coronary Angiography

Repa brand 5F-6F radial sheaths (Repa Group Health Products Co, Ltd., Turkey) were placed in the patient's right radial artery. Single-wall anterior puncture with micropuncture needle method was used. All patients were routinely given 5000 Units of heparin and a varying amount of nitroglycerin via transradial route at 50-1000 mcg doses to prevent the development of radial occlusion according to their hemodynamic status. The procedure was performed using a Judkins 4 left catheter at the left coronary artery and a Judkins 4 right catheter at the right coronary system. Following coronary angiography, the sheath was immediately removed from the artery; a manual homeostasis control was performed to provide radial homeostasis, as typically used by many operators (12). No other homeostasis method was used in the patients.

Doppler Ultrasonography

In the first 24 hours after the procedure, the radial doppler ultrasonography (USG) assessment was performed by the experienced physicians working in the radiology outpatient clinic's doppler USG laboratory using the Aplio 500 Tokyo device with the linear 7.5 MHz high-resolution probe (Toshiba, Japan).

Laboratory Analysis

Blood samples were taken immediately after the procedure (basal blood samples) from the radial sheath and at the 6th hour after sheath removal from the peripheral venous route. The D-dimer value was measured using the ACL TOP 700 coagulation analyzer (Instrumentation Laboratory Company, Germany). Using Fab fragments, the detection of the D-dimer

value was achieved more precisely, and the interference of some endogenous factors such as the rheumatoid factor was prevented. The D-dimer reference value was 0-243 ng/ml. Automatic hematology analyzers (Symex XN-550 analyzer, Symex, Kobe, Japan) were used to measure whole blood parameters; biochemistry devices carried out biochemical analyses (Beckman Coulter Inc., Brea, New York, USA).

Statistical Analysis

Categorical data were presented as numbers and percentages. The chi-square test was used in the analysis of non-parametric data. All the variables obtained were examined with the Kolmogorov-Smirnov test for normality and the Levene test for homogeneity of variances before the significance tests were made. An independent t-test was used for homogeneous data showing normal distribution in evaluating the differences. The Mann-Whitney U test was used for the parameters not showing normal distribution. The receiver operating characteristic (ROC) analysis was used to estimate the optimal cut-off value of D-dimer in RAO patients. Sensitivity, specificity, and area under the curve (AUC) values were calculated. The data were analyzed before multivariate logistic regression analysis with the Shapiro Wilk test for normality and Levene test for homogeneity of variances. Afterward, the significance tests were performed in terms of all variables. The univariate logistic regression analysis was first applied to all variables, and the variables related to the presence of RAO were detected. These variables were then used as candidate variables to enter the multivariate logistic regression model to determine the risk factors for the disease. The backward subtraction method was employed in the multivariate logistic regression model, and the Wald statistics tested the significance of the variables. The variables that were not significant in the multivariate model were excluded from the regression model, and odds ratios were used to interpret the final model. The ROC analysis was performed with Medcalc 9.2.0.1 software, while other statistical analyses were conducted with IBM SPSS 23.0 (IBM Corp., Armonk, NY, USA) statistical software package. The significance level was considered 2-sided p <.05 for all statistical analyses.

RESULTS

A total of 107 patients were included in the study. The mean age of the patients was 56.5±11.9. 51 (47.6%) patients were male. A total of 25 (23.4%) patients had RAO. The patients' baseline demographic and laboratory characteristics are summarized in **Table 1.**

Table 1. Baseline characteristics of all patients included in the study.

Demographic Characteristics	**N=107**
Age, year	56.5±11.9
Male, n (%)	51 (47.6)
Diabetes mellitus, n (%)	50 (46.7)
Hypertension, n (%)	71 (66.4)
Hyperlipidemia, n (%)	43 (40.2)
Smoking, n (%)	48 (44.9)
Coronary artery disease, n (%)	28 (26.2)
CAG Story, n (%)	8 (7.5)
Height, cm	169.1±9.4
Weight, kg	84.3±15.8
Radial occlusion, n (%)	25 (23.4)
Medications	
Use of beta-blockers, n (%)	35 (32.7)
Use of ACE-I, n (%)	34 (32.8)
Statin use, n (%)	33 (30.8)
Use of Aspirin, n (%)	56 (52.3)
Procedural characteristics	
Amount of nitrate given, mcg	248.5±152.6
Amount of heparin given, Unit	4816±737
Sheath size (f)	5.28±0.45
Laboratory Characteristics	
Hemoglobin, g/dL	13.5±1.4
WBC, cells/mL	8.6±2.9
Creatinine, mg/dl	0.83±0.25
Platelet, cells/mL	266.8±69.8
APTT, sec.	29.2±3.4
INR	1.33±0.39
LDL, mg/dL	122.8±38.3
HDL, mg/dL	43.69±9.8
TG, mg/dL	186.31±104.8
HBA1C, mmol/ml	6.7±1.5
TSH, mIU/l	1.86±1.2
CRP (Basal), mg/l	4.39±2.49
CRP (at 6.hr.), mg/l	5.27±2.36
Δ-CRP, mg/l	0.87±0.41
D-dimer (Basal), ng/ml	105.3±58.8
D-dimer (at 6.hr), ng/ml	126.14±65.55
Δ-D-dimer, ng/ml	20.85±16.48

CAG: Coronary Angiography, ACE-I: Angiotensin-converting enzyme-inhibitors, APTT: activated partial thromboplastin time, WBC: White blood cell, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: Triglycerides, HBA1c: glycosylated hemoglobin, TSH: Thyroid-stimulating hormone, CRP: C-Reactive protein, Δ: Delta

Patients were divided into two groups according to their ASA use status. Patients using ASA were classified as group 1, and patients not using ASA were classified as group 2. Radial occlusion was significantly higher in patients not using ASA (22 (43.1%) vs. 3 (5.4%), p=<.001). No difference was found between these patients' procedural features and laboratory data. In demographic data, only CAD and statin use were higher in patients using aspirin, and other findings were similar (**Table 2**).

Table 2. Essential characteristics of patients according to their aspirin use status

Demographic characteristics	Group I, n=56	Group 2, n=51	p value
Age, year	56.75±12.78	56.27±11.16	.83
Male, n (%)	26 (46.4)	25 (49)	.47
Diabetes mellitus, n (%)	30 (53.6)	20 (39.2)	.09
Hypertension, n (%)	37 (66.1)	34 (66.7)	.55
Hyperlipidemia, n (%)	27 (48.2)	16 (31.4)	0.11
Smoking, n (%)	25 (44.6)	23 (45.1)	.55
Coronary artery disease, n (%)	21 (37.5)	7 (13.7)	.008
Height, cm	168.73±8.56	169.61±10.42	.63
Weight, kg	83.04±14.46	85.69±17.18	.38
Radial occlusion, n (%)	3 (5.4)	22 (43.1)	<.001
Medications			
Use of beta-blockers, n (%)	20 (35.7)	15 (29.4)	.31
Use of ACE-I, n (%)	17 (30.4)	17 (33.3)	.45
Statin use, n (%)	22 (39.3)	11 (21.6)	.038
Procedural characteristics			
Amount of nitrate given, mcg	255.46±170.69	241.18±131.79	.63
Amount of heparin given, unit	4700±649.78	4941±810.22	.09
Sheath size (f)	5.28±0.45	5.29±0.46	.92
Laboratory characteristics			
Hemoglobin, g/dl	13.38±1.46	13.71±1.38	.23
WBC, cells/mL	8.69±3.07	8.58±2.91	.85
Creatinine, mg/dl	0.83±0.26	0.82±0.24	.75
Platelet, cells/mL	256.86±65.40	277.75±73.56	.12
MPV, fl	8.09±0.80	8.38±0.85	.07
APTT, sec.	29.94±3.18	29.71±3.74	.72
INR	1.33±0.42	1.35±0.51	.61
LDL, mg/dL	123.73±40.32	121.86±36.34	.79
HDL, mg/dL	43.26±10.04	44.45±9.74	.45
TG, mg/dL	187.88±98.21	184.60±112.63	.87
HBA1C, mmol/ml	6.94±1.73	6.43±1.45	.13
TSH, mIU/l	1.83±1.15	1.91±1.31	.73
CRP, mg/l	4.22±2.31	4.58±2.69	.45
CRP (at 6.hr.), mg/l	5.13±2.31	5.43±2.68	.53
Δ-CRP, mg/l	0.90±0.34	0.84±0.06	.42
D-Dimer, ng/ml	100.18±61.19	110.92±56.27	.34
D-dimer (at 6.hr), ng/ml	118.25±63.82	134.82±66.95	.19
Δ- D-dimer, ng/ml	23.90±19.34	18.07±12.91	.07

CAG: Coronary Angiography, ACE-I: Angiotensin-converting enzyme-inhibitors, APTT: activated partial thromboplastin time, WBC: White blood cell, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: Triglycerides, HBA1c: glycosylated hemoglobin, TSH: Thyroid-stimulating hormone, CRP: C-Reactive protein, Δ: Delta

When the patients are evaluated according to the development of radial occlusion; in patients with radial occlusion; basal D-dimer (135.20±66.58 ng/ml vs. 96.18±53.49 ng/ml, p=.003), D-dimer at 6 hours post-procedure (172.16±81.34 ng/ml vs. 112.12±53.01 ng/ml, p=.002), and post and the pre-procedure difference between the D-dimer values (Δ- D-dimer) (36.96±26.12 ng/ml vs. 15.93±6.98 ng/ml, p=.001) was found to be significantly higher. Again, basal MPV values were higher in the group with radial occlusion (8.34±0.82 fl vs. 7.92±0.81 fl, p=.028). Other findings do not show any difference between the two groups (**Table 3**).

Table 3. Essential characteristics of patients according to radial occlusion status.

Demographic Characteristics	Radial occlusion n=25	No radial occlusion n=82	p value
Age, year	54.84±10.06	57.04±12.51	.42
Male, n (%)	14 (56)	37 (45.1)	.23
Diabetes mellitus, n (%)	8 (32)	42 (51.2)	.11
Hypertension, n (%)	18 (72)	53 (64.6)	.63
Hyperlipidemia, n (%)	6 (24)	37 (45.1)	.06
Smoking, n (%)	14 (56)	34 (41.5)	.25
Coronary artery disease, n (%)	3 (12)	25 (30.5)	.07
Height, cm	170.36±10.75	168.78±9.07	.46
Weight, kg	87.44±19.61	83.34±14.44	.51
Aspirin use n	3 (12)	53 (64.6)	<.001
Medications			
Use of beta-blockers, n (%)	8 (32)	27 (32.9)	.56
Use of ACE-I, n (%)	8 (32)	26 (31.7)	.58
Statin Use, n (%)	6 (24)	27 (32.9)	.27
Procedural characteristics			
Amount of nitrate given, mcg	271.05±140.74	241.36±156.28	.35
Amount of heparin given, unit	5040±1098.48	4796±576.21	.21
Sheath size (f)	5.16±037	5.32±0.47	.11
Laboratory characteristics			
Hemoglobin, g/dL	13.65±1.58	13.56±1.38	.66
WBC, cells/mL	8.65±3.17	8.63±2.93	.97
Creatinine, mg/dl	0.76±0.24	0.85±0.25	.15
Platelet, cells/mL	277.72±77.02	263.49±67.70	.41
MPV, fl	8.34±0.82	7.92±0.81	.028
APTT, sec.	29.57±3.13	29.90±3.54	.67
INR	1.32±0.32	1.34±0.43	.53
LDL, mg/dL	116.96±37.84	124.60±38.49	.38
HDL, mg/dL	42.12±10.11	44.17±9.82	.37
TG, mg/dL	206.31±109.06	180.22±103.43	.29
HBA1C, mmol/ml	6.57±1.87	6.74±1.51	.69
TSH, mIU/l	1.92±1.41	1.85±1.17	.78
CRP, mg/l	3.92±2.08	4.53±2.60	.23
CRP (at 6.hr.), mg/l	4.91±2.18	5.38±2.57	.37
Δ-CRP, mg/l	0.98±0.51	0.84±0.38	.13
D-Dimer, ng/ml	135.20±66.58	96.18±53.49	.003
D-dimer (at 6.hr), ng/ml	172.16±81.34	112.12±53.01	.002
Δ- D-dimer, ng/ml	36.96±26.12	15.93±6.98	.001

CAG: Coronary Angiography, ACE-I: Angiotensin-converting enzyme-inhibitors, APTT: activated partial thromboplastin time, WBC: White blood cell, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TG: Triglycerides, HBA1c: glycosylated hemoglobin, TSH: Thyroid-stimulating hormone, CRP: C-Reactive protein, Δ: Delta

As a result of the regression analyses performed to determine the risk factors indicating the development of radial occlusion, according to univariate regression analysis, MPV, basal D-dimer, 6th-hour D-dimer, and not using ASA were found to be predictive factors for the RAO. Multivariable regression analysis results also showed that; not using AS, high basal, and 6th-hour D-dimer values are independent risk factors for RAO development (**Table 4**).

Table 4. Factors of predicting the development of radial artery occlusion after transradial angiography.

Risk Factor	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
MPV	1.005 (1.002-1.011)	.029	0.607 (0.299-1.236)	.16
D-dimer (basal)	1.011 (1.003-1.018)	.008	1.235 (1.014-1.582)	.001
D-dimer (at 6. Hr.)	1.013 (1.006-1.021)	<.001	1.232 (1.097-1.384)	<.001
Not taking aspirin	5.402 (3.695-9.611)	<.001	5.534 (3.376-9.252)	<.001

MPV: Mean Platelet Volume

Table 5. ROC analysis results of D-Dimer values.

	Cut- off	Sensitivity	95% CI	Specificity	95% CI	AUC	p
D-Dimer	>144*	62.4*	41.3–82.2	89.2*	80.2-94.8	0.658	0.016*

ROC: Receiver operating characteristics, CI: Confidence interval, AUC: Area under the curve

Regarding the significance of D-dimer in predicting RAO as a result of ROC analysis, the AUC was 0.658 (95%CI: 0.612-0.738, p= .016), and the optimal cut-off value was 144 (62.4% sensitivity, 89.2% specificity) (**Figure 1**).

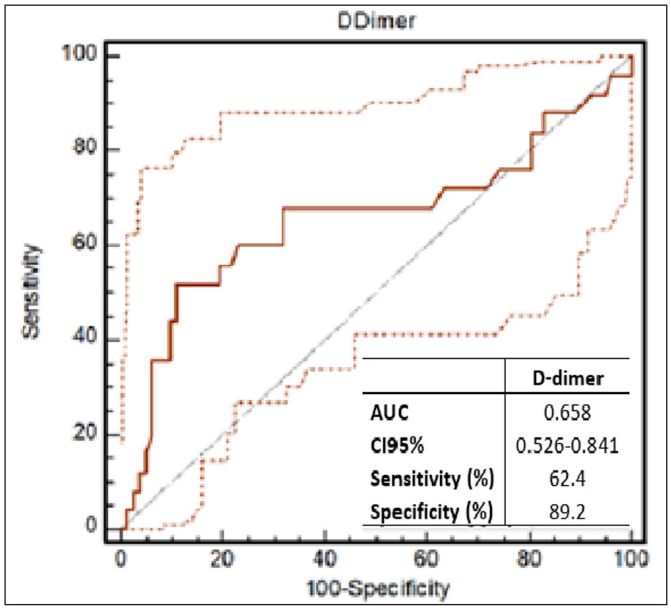

Figure 1. Receiver operating characteristics (ROC) analysis curve of D-dimer values

DISCUSSION

When the current literature is examined, our study is the first and only study evaluating the relationship between RAO and ASA use and the relationship between RAO, CRP, and D-dimer. In this study, D-dimer values obtained immediately after the procedure (basal D-dimer) were compared, and the RAO group values were higher than the non-RAO group (135.2 ng/ml ± 66.5 vs. 96.1 ng/ml ± 53.4 p=.017). As a result of multivariable logistic regression analysis, the basal D-dimer value was an independent risk factor for RAO development. Since patients with thromboembolic and active infectious/inflammatory diseases were excluded from the study, high basal D-Dimer values in these patients without a dynamic, active thrombotic process showed that fibrin production and destruction were higher in the basal state of the body and that the coagulation cascade, which will become much more active after an intravascular intervention such as angiography, suggests that it triggers thrombus development much faster and more (13). The D-dimer results indicated that choosing the vascular access route according to the basal D-Dimer value might be beneficial in preventing RAO in patients. For this purpose, the D-dimer value of 144 ng/ml can be considered a practical and easily applicable cut-off value for radial or femoral route selection before the CAG procedure. One study revealed that pre-operative D-dimer values predicted post-operative graft thrombosis in patients who had previously undergone coronary artery bypass grafting (CABG) and received arterial grafts supports our research (14). On the other hand, in the study of Kleinegris et al. (15) in peripheral arterial patients, it was determined that increased D-dimer values increase coronary and arterial thrombotic events, which supports that radial occlusion may result in increased thrombosis in patients with high D-dimer values. In addition to all this, the increase in D-dimer at the 6th hour is higher in patients with RAO (172.16±81.34 ng/ml vs. 112.12±53.01 ng/ml, p=.002). The result of the ROC analysis also supports this; although the sensitivity is low (62.4%), it has a high specificity (89.2%) because it is not in a situation to explain anything else. There is no other condition to explain this D-dimer elevation in the patient group in our study. This result may enable us to predict RAO development in patients who underwent TRA, even if they are asymptomatic in the post-procedure follow-up.

It has been known for a long time that the use of ASA has a protective effect against many thrombotic vascular diseases (16). It is also widely used in coronary syndromes, venous thromboembolism, prevention and treatment of stroke, as demonstrated in the guidelines (17,18). Although prophylactic use has been evaluated to protect

some arterial access routes in previous studies, no study shows that it is protective against RAO in TRA, which is becoming increasingly common today. In our research, RAO was found to be significantly lower in patients using low-dose ASA before TRA (22 (43.1%) vs. 3 (5.4%), p=<.001). Here, it is thought that ASA reduces endothelial damage by regulating local endothelial functions and inhibits the COX pathway, reducing platelet efficiency and reducing the possible microthrombi, reducing gross thrombosis that will develop over these microthrombi, and reducing RAO (19).

While evaluating the safety of TRA, it was compared with TFA in general, and major complications were assessed both in themselves and in comparison, with TFA. The development of RAO was low and was not subjected to a direct evaluation in all essential and extensive studies such as; RIVAL, MATRIX, ARTEMIS, RIFLE-STEACS, SAFARI-STEMI (20-24). At the same time, most of the patients in these studies were acute coronary syndromes (ACS) patients and had multiple systemic thrombotic complications, making it challenging to evaluate only RAO. On the other hand, it was not possible to assess the efficacy of ASA alone since these patients used multiple drugs (clopidogrel, ticagrelor, prasugrel, etc.). For this reason, those studies may help predict the safety and efficacy of the TRA, especially in patients who will undergo elective CAG; however, they do not provide reliable and direct information on the prevention of complications that may develop in the radial artery in the elective procedures. The rates of ASA use in our study were correlated with previous studies. Still, the incidence of RAO detected in these studies was lower than that obtained in our study. RAO was seen in 25 (23.4%) patients in our study. Post-procedure RAO has been observed at 1 to 38% in large-center, multi-participant studies (25). Our study's high rate of radial occlusion (23.4%) may have been due to the operators' lack of experience in CAG procedures performed using the transradial artery and a manual compression method with a classical radial bandage homeostasis control. Due to not using transradial bands for homeostasis, complete homeostasis control based on manual compression with the applied plaster may have caused more stasis in the radial artery. These situations caused thrombosis to elevate, thus increasing the occlusion of the radial artery in the patients. This finding seems consistent with studies comparing homeostasis methods in the literature (26). On the other hand, a few studies detected no difference between manual and mechanical compression in RAO; however, in that study, the duration of manual compression was kept very short compared to mechanical compression (27,28). The absence of multiple antiaggregant uses and standard-dose heparin and providing complete homeostasis with manual compression can be shown as the reason for this outcome (20,21,23,29).

RAO is less common in patients with hyperlipidemia in this study; this may be because these patients are currently using statins. In the study of Charles Hsu et al. (30), statins in patients with deep venous thrombosis increased thrombus resolution support our results. At the same time, stabilizing endothelial functions due to the pleiotropic effects of statins may have contributed to less occlusion by reducing catheter-based endothelial damage, independently of atherosclerotic load and cholesterol level (30,31).

The study's limitations are that it was observational, modern homeostasis methods were not used, and a limited number of patients participated. The findings need to be confirmed in a large-scale randomized controlled trial.

CONCLUSION

The D-dimer values measured before CAG provide information about the probability of RAO development after the procedure and may be a guide for selecting the vascular access route.. There is a direct relationship between RAO and ASA use, which reduces RAO's development. For this reason, in patients with high D-dimer values, avoiding the radial route and using prophylactic ASA before the procedure may prevent the development of this complication and reduce patient suffering. Prospective studies comparing different antiaggregant and anticoagulant regimens may be planned to determine the importance of ASA and D-dimer's clinical role in developing RAO.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.09.2019, Decision No:72/02).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1094124
J Health Sci Med 2022; 5(4): 1110-1113

The effect of lactose intolerance on plasma glucose levels and related biochemical parameters

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Cite this article as: Yalçın KS, Karapoğlu B, Alanlı R, et al. The effect of lactose intolerance on plasma glucose levels and related biochemical parameters. J Health Sci Med 2022; 5(4): 1110-1113.

ABSTRACT

Aim: To determine the effect of lactose intolerance on serum glucose levels and related biochemical parameters in the adult population who refrain from consuming milk and milk products.

Material and Method: This retrospective, observational study was conducted in a tertiary care hospital between January 2016 and December 2019 with 296 participants. Plasma glucose, calcium, 25-hydroxyvitamin D3, folate, vitamin B12, thyroid-stimulating hormone (TSH), and ferritin levels were controlled. Patients with positive lactose intolerance test results were accepted as the study group and negative results were accepted as the control group, and data of two groups were compared.

Results: Of the total 296 participants 212 (71.7%) were found to have lactose intolerance and 84 (28.3%) were found to be normal. In the lactose intolerant group, blood glucose levels were significantly lower than the control group (5.14±0.53 mmol/L versus 5.47±0.54 mmol/L, p<0.001). In the lactose intolerant group, 29 (13.7%) patients, and in the control group 18 (21.4%) patients were having type 2 diabetes mellitus. In diabetic patients, both fasting blood glucose (5.68±0.49 mmol/L versus 6.30±0.59 mmol/L, p<0.001) and glycated hemoglobin levels were also significantly lower than the control group in the study group (6.78±1.08 versus 7.62±0.96, p<0.001).

Conclusions: In this study, based upon the findings of people with insufficient milk consumption, any decrease in blood calcium or vitamin D levels was not observed. Lactose intolerant people may have lower blood glucose levels compared to lactase persistent people. Larger-scale and long-term studies are needed to demonstrate that persistence of lactase is an independent risk factor for the development of diabetes.

Keywords: Lactose intolerance, plasma glucose, biochemical parameters

INTRODUCTION

Lactose is a disaccharide, found in milk and milk products, composed of simple sugars; glucose and galactose. Lactase enzyme is needed in the degradation process. Decreasing enzyme activity during the lifetime may lead to less diabetes risk during adulthood theoretically. Enzyme activity of lactase decrease as time passes and in adulthood, the enzyme capacity decreases down to 30% (1). Intestinal epithelial lactase enzyme deficiency causes insufficient degradation of lactose into glucose and galactose and results in lactose intolerance (2,3). Due to flatulence and dyspepsia experienced after ingesting dairy products, many people presume that they have lactase deficiency and refrain from consuming lactose-containing foods, such as milk and milk products, although they, have no lactase enzyme deficiency (4).

According to statistical data of the year 2017, diabetes is an epidemic condition affecting 451 million people (5). Treating diabetes is very important in many aspects of community health. The majority (over 90%) of diabetic patients are having type 2 diabetes mellitus (6). Protective measures such as regular physical exercise and losing excess weight, and diet are key points in the treatment of type 2 diabetes mellitus. According to different trials; maltase, sucrase, and lactase enzyme activities are shown to be increased in diabetic patients and treatment of diabetes results in decreases in the activity of those

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Received: 27.03.2022 **Accepted:** 19.06.2022

enzymes (7,8). In addition, high plasma glucose levels cause decreased intestinal motility (9). Hyperglycemic patients have low duodenojejunal motility index and have longer intestinal transit time, which allows more time for intestinal bacteria to process available nutrients (10,11), which may result in remarkable dyspeptic complaints in case of concomitant lactose intolerance. Milk and milk products are shown to be protective against the progression of diabetes (12-14). People who do not have lactose intolerance but refrain from milk and milk products because of dyspeptic symptoms, are at increased risk to develop diabetes and hypertension (15).

This study was designed to observe the effects of lactose intolerance on glycemic control and related biochemical parameters, among lactose intolerance positive and negative patients refraining from milk and milk products.

MATERIAL AND METHOD

The study was carried out with the permission of the Lokman Hekim University Noninvasive Clinical Researches Ethics Committee (Date: 15.10.2019, Decision No: 2019/47). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Setting, Design, Duration, Population

This single-center, retrospective study was conducted in a tertiary care hospital, in the department of internal medicine clinic between January 2018 to February 2020.

A total of 296 patients, 176 (59.5%) female, and 120 (40.5%) male; who suffered from abdominal pain, dyspepsia, and diarrhea were included. The ages of participants were between 18 to 77 (mean 35.61±13.9). Patients who become symptomatic after ingesting milk and milk products were tested for lactose intolerance, and positive results were accepted as the study group and negative results were accepted as the control group. Participants, who had >126 mg/dl fasting glucose, glycated hemoglobin (HbA1c) levels above % 6.5, or who were taking anti-diabetic medications were accepted to have diabetes mellitus. Plasma glucose, calcium, 25-hydroxyvitamin D3, folate, vitamin B12, thyroid-stimulating hormone (TSH), and ferritin levels were controlled in all patients included in this study. All tests were performed at the time of admission. Patients who were under 18 years, who had additional diseases other than diabetes mellitus and hypertension, who were using other drugs other than anti-diabetics and anti-hypertensives (such as drugs for inflammatory bowel diseases, any antibiotic and probiotic usage), who had unregulated diabetes (HbA1c > 8, Type 1 diabetes mellitus or Brittle diabetes), who had hypothyroidism or hyperthyroidism were excluded.

Lactose Tolerance Test

All patients enrolled in this study were tested for lactose intolerance. After 12 hours of fasting, patients ingested a solution containing 50 gr of lactose. Plasma glucose levels were checked at the beginning, 30th, 45th, 60th, and 90th minutes. An increase, lower than 20 mg/dL in plasma glucose level from the baseline, during the test, was accepted as lactose intolerance. The standard lactose tolerance test, which measures blood glucose, may be unreliable in insulin-dependent diabetics, but it can be reliable in non-insulin-dependent diabetics. Thus standard lactose tolerance test can be used in Type 2 diabetic patients under oral anti-diabetic treatments whose blood sugar is regulated.

Statistical Analysis

All data were analyzed by the computer software program SPSS, version 20 (SPSS Inc., Chicago, Illinois, USA, 2016). Results were reported as means±standard deviation. Group analyses were made with Pearson's chi-square test. Within and between-group differences were analyzed by students' paired and unpaired t-tests. A p-value <0.05 was considered statistically significant.

RESULTS

All patients were tested for lactose intolerance and 212 (71.7%) patients were found to have lactose intolerance, whereas 84 (28.3%) patients were found to be normal. There was no statistical difference between the study group and control group in age, gender, calcium, 25-hydroxyvitamin D3, folate, vitamin B12, TSH, ferritin levels, and duration of diabetes and hypertension. Both groups were distributed homogeneously according to demographic and some biochemical and hormonal levels (**Table 1**).

Table 1. Demographic characteristics and laboratory results of study participants

	Lactose intolerance group (n=212)	Control group (n=84)	p value
Age	35.40±13.20	37.20±13.60	0.308
Gender (Female/Male)	133/79	43/41	0.880
Glucose (mmol/L) (4.0-6.0)	5.14±0.53	5.47±0.54	<0.001
Calcium (mmol/L) (2.12-2.62)	2.35±0.12	2.35±0.07	0.655
25-Hydroxyvitamin D3 (nmol/L)(30-100)	44.68±22.96	54.66±29.20	0.227
Folate (nmol/L) (6.12-38.52)	13.63±6.14	14.55±5.90	0.589
Vitamin B12 (pmol/L) (160-950)	256.83±112.22	293.13±128.23	0.191
TSH* (mIU/L) (0.5-4.5)	2.10±1.10	2.40±1.30	0.251
Ferritin (pmol/L) (24-336)	147.42±113.26	190.79±152.14	0.248
Hypertension (%)	19 (9.0%)	12 (14.3%)	0.255
Diabetes Mellitus (%)	29 (13.7%)	18 (21.4%)	0.001

*Thyroid stimulating hormone

In the lactose intolerant group, blood glucose levels were significantly lower than in the control group (5.14±0.53 mmol/L versus 5.47±0.54 mmol/L, p<0.001). Among study participants, 47 patients were having type 2 diabetes mellitus. In the lactose intolerant group, 29 (13.7%) patients, and in the control group 18 (21.4%) patients were having type 2 diabetes mellitus. In diabetic patients, both fasting blood glucose (5.68±0.49 mmol/L versus 6.30±0.59 mmol/L, p<0.001) and glycated hemoglobin levels were also significantly lower than the control group in the study group (6.78±1.08 versus 7.62±0.96, p<0.001). However the was no significant difference in the frequency of hypertension between the lactose intolerant (9%) and control group (14.3%) (p=0.255) (**Table 2**).

Table 2. Fasting blood glucose and glycated hemoglobin levels of participants who have diabetes mellitus

	Lactose Intolerance Group (n: 29)	Control Group (n:18)	p Value
Fasting blood glucose (mmol/L)	5.68±0.49	6.30±0.59	<0.001
Glycated hemoglobin (%)	6.78±1.08	7.62±0.96	<0.001

DISCUSSION

To the best of our knowledge, for the first time in literature, the results of this study demonstrate that; diabetes was less common in lactose-intolerant patients and diabetic lactose-intolerant patients had lower blood glucose and glycated hemoglobin levels compared to the diabetic participants who do not have lactose intolerance.

In this presented study, 296 patients expressed symptoms after consuming milk, and for this reason; they were refraining from consuming milk. But, 84 of them (28.4%) had no lactose intolerance. This finding guided us to conclude that nearly 25% of people getting symptomatic after milk consumption were suffering from dyspeptic conditions in the absence of lactose intolerance. In this study, based upon the findings of people with insufficient milk consumption, any decrease in blood calcium or vitamin D levels was not observed. It should be taken into consideration that some of the patients examined at outpatient clinics might consume vitamin D supplements when needed. Some vitamin D supplements also contain calcium; this may be the reason that patients included in the study had no vitamin D or calcium deficiency.

Some previous studies stated that higher amounts of milk consumption, especially in infants, were correlated with an increased risk of developing diabetes (16-18). A French study made by Lambri et al. (19) proposed that people having a genetic polymorphism causing lactase enzyme persistency had higher rates of impaired fasting glucose and diabetes. Low consumption of milk and milk sugar may lead to a decrease in plasma glucose levels compared to milk-consuming people. Controversially, in some of the previous studies it was demonstrated that among the adult patients, lactose intolerance was found more frequently than the non-diabetic people (20).

A study with a large number of participants reported from Denmark showed that there was no significant difference between low and high amounts of milk consumption, in an aspect of diabetes incidence (21). Similarly, in a Finnish study, designed by Enettah et al, lactase enzyme persistence was not found to be associated with diabetes (22). In contrast to these studies, the present study showed that blood glucose levels were significantly lower in the lactose intolerant group. However, this does not mean that lactose intolerance alone is a protective factor from diabetes. Larger-scale and long-term studies are needed to demonstrate the persistence of lactase is an independent risk factor for the development of diabetes.

Some previous studies proposed that lactose intolerance is correlated with hypertension. A Brazilian study showed that hypertension was more frequently diagnosed among lactose-intolerant patients than normal population (23). No significant association between lactose intolerance and diabetes or hypertension was documented in this presented study. This may be caused by restrictive diets followed by patients having dyspepsia and flatulence problems and also because they refrained from consuming milk products. Many of the participants included in this study were relatively young since both diseases are rarely reported to be diagnosed in younger people; this may be why no association with diabetes mellitus or hypertension was documented in this study.

In this study, those people who refrained from consuming milk and milk products were not found to have vitamin D and calcium deficiency. Vitamin D deficiency, usually, is considered; diagnosed and treated in our country; mainly by family physicians. Because of this, although they had low milk consumption, calcium and vitamin D deficiency might not be demonstrated in participants.

There are some limitations of this study that should be mentioned. Firstly, no comparison was performed based on body mass index data. The number of diabetic patients was low since the mean age of our study population was relatively young. Also, this study had no genetic analysis of lactase gene constitution, which would give a more clear idea about the presence of lactose intolerance. And lastly, body mass index, duration of diabetes, and medications of the diabetic patients, which may affect the HbA1c values were not recorded and analyzed in this study.

CONCLUSION

Lactose intolerant people may have lower blood glucose levels compared to lactase persistent people. But, assuming to have lactose intolerance and refraining from consuming milk and milk products without testing for lactose intolerance, would not be the right behavior for any person because milk products are necessary for better bone health. Long-term follow-up of lactose intolerant patients may help us understand whether this condition is protective against diabetes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Lokman Hekim University Noninvasive Clinical Researches Ethics Committee (Date: 15.10.2019, Decision No: 2019/47).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1109130
J Health Sci Med 2022; 5(4): 1114-1118

The association between diabetes mellitus and functionality in knee osteoarthritis: a cross-sectional study

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Cite this article as: Kaymaz S, Aykan SA. The association between diabetes mellitus and functionality in knee osteoarthritis: a cross-sectional study. J Health Sci Med 2022; 5(4): 1114-1118.

ABSTRACT

Objective: The aim of this study was to determine the roles of diabetes mellitus (DM) on quality of life, function of knee, and muscle strength in patients with knee osteoarthritis (OA).

Material and Method: This single-center, case-control study prospectively enrolled outpatients with knee OA visiting a physical therapy and rehabilitation clinic. The patients were grouped according to the presence of DM diagnosis. Demographic data, disease duration, and medical treatments of patients were recorded. Clinical parameters, radiographic grading (Kellgren-Lawrence grades), functional scales of the knee and quality of life were evaluated.

Results: The study included 82 participants [age: 61.3±6.7 years; female: 76.8%]. The mean Western Ontario and McMaster Universities Osteoarthritis Index of OA patients with (n=37) and without DM (n=45) were 45.79±18.04 vs. 65.94±16.23, respectively (p=0.003). The Hb A1c levels showed a negative correlation with Knee Injury and Osteoarthritis Outcome Score components (pain, quality of life, sports, daily activities, symptom duration) (p<0.001, r:-0.440; p<0.001, r:-0.393; p<0.001, r:-0.396; p<0.001, r:-0.336; p:0.002, r:-0.342, respectively) and also, a negative correlation with knee flexion degree (p<0.001, r:-0.401).

Conclusion: DM has a negative effect on quality of life and activities of life in knee OA.

Keywords: Osteoarthritis, diabetes, functionality, quality of life

INTRODUCTION

Diabetes mellitus (DM) is the ninth causes of death worldwide and causes many defined complications that attract the attention of the patient and physician (1). The musculoskeletal system, which constitutes 60-70% of the body weight, consists mainly of muscles, joints, bones, and soft tissues surrounding these structures (2) Even though the relationship of DM with musculoskeletal system has not been fully defined (3,4), a large number of diabetic patients suffer from musculoskeletal system complications that cause significant morbidity in their lives (3,4).

There are many studies in the literature compiling the relationship between DM and musculoskeletal complications. Hoff et al. (6) reported that the relative risk (RR) for musculoskeletal system complication is 1.6 in diabetic patients. Mathew et al. (7) reported that the most commonly described were diabetic solid hand syndrome, dupuytren contracture, adhesive capsulitis, carpal tunnel syndrome, charcot neuropathic osteoarthropathy, diabetic amyotrophy, muscle infarction, diffuse idiopathic skeletal hyperostosis (DISH), reflex sympathetic dystrophy and septic arthritis. Even though, the relationship between osteoarthritis and DM on proven medical basis is questionable, DM can negatively affect joint cartilage and accompany of OA is inevitable (8). Hyperglycemia causes oxidative and osmotic stress causing lesions in the eyes, kidneys and other tissues (9). Moreover, previous studies have determined that hyperglycemia is a risk factor for OA (10,11), It was also found that the proteoglycan ratio and molecular weight were lower compared to diabetic cartilage than normal cartilage (12).

In this present study, we analyzed the effect of DM on knee OA patients in terms of knee functionality, quality of life, pain level, and muscle strength. We also aimed to determine any potential relationship between the DM duration, glycemic control, and knee OA to able to define diabetes metabolic impact on OA rather than mechanic.

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Received: 26.04.2022 **Accepted:** 20.06.2022

MATERIAL AND METHOD

Study Design and Participants

This observational and case-control study was conducted in Ankara Training and Research Hospital and approved by Noninvasive Clinical Researches Ethics Committee (Date: 02.22.2017, Decision No:46). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The data were collected from Ankara Training and Research Hospital outpatient clinic between February and June 2017 who applied to our hospital physical therapy outpatient clinics for knee pain and diagnosed with primary / idiopathic knee OA according to the American Rheumatology Criteria (ACR) were included in the study (13). Inclusion criteria were; (i) patient age between 45 and 90 years, (ii) knee OA diagnosis based on the American Society of Rheumatology (10), and (iii) ability to cooperate and read and write in Turkish. Exclusion criteria were the presence of any inflammatory or rheumatological disease such as rheumatoid arthritis, chondrocalcinosis, psoriatic arthritis and hemochromatosis that may lead to secondary OA. The participants were grouped as with or without DM (Type 2). The diagnosis of DM was self-reported and confirmed by the national health database.

Clinical and demographic features of all participants patients were recorded. Height and weight of all patients included in the study were questioned and body mass index (BMI) was calculated. The Hba1c levels of diabetic patients and auxiliary devices (wheelchair, walker, walking stick, tripod) used by patients during ambulation were recorded.

Clinical Parameters

1. Range of Motion: Extension (0-10 degrees) and flexion (130-140 degrees) supine lying, the angle between the distal femur tip and the proximal tibial tip was measured by goniometry.
2. Manual muscle strength: Patients' quadriceps muscle strength was tested with manual muscle strength.
3. Functional Ambulation Categories (FAC): It is rated between 0 and 5. It is divided into six categories. It is a scale that evaluates ambulation skills of patients (14).

Functional Scales of Knee OA

1. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): This scale consists of 24 items. It is a scale that examines the pain, stiffness, and physical function of OA. It can measure changes in the patient's condition after both surgical and pharmacological interventions. Tüzün et al. (15) determined the reliability and validity of this index in Turkish in 2005.
2. Lequesne Index: It consists of 3 main sections: pain / discomfort, daily life activities and maximum walking distance. It consists of 10 items (16).
3. Knee Injury and Osteoarthritis Outcome Score (KOOS): It consists of 42 questions. It has 5 subgroups: pain, sports, daily life activities, quality of life, other symptoms, and functional status in leisure time activities. Each subgroup is scored between 0-100 (0 indicates that there are serious problems and 100 indicates no problems). Peker et al. (17) showed the reliability and validity of the Turkish version in 2007.

Evaluation of quality of life

The quality of life was evaluated with a scale consisting of 8 subgroups with 36 items (SF-36). These subgroups are vitality, physical function, general health, pain, social function, role limitation in physical and emotional aspects and mental health. Koçyiğit et al. (18) demonstrated the reliability and validity of SF-36 in our community in a study conducted in 1999.

Radiography

In order to evaluate knee osteoarthritis, knee radiographs were taken in the anterior-posterior and lateral positions with the foot 20-30 degrees flexed and 10 degrees internal rotated. Ratings were made according to Kellgren-Lawrence radiological evaluation criteria (19).

Statistical Analysis

The Statistical Package for the Social Sciences for Windows (version 20.0, IBM.Corp., Armonk, NY, 2011) was used for data analysis, and normal distribution was determined using the Kolmogorov-Smirnov test. Data are expressed as mean±standard deviation or percentage values. Where appropriate, case-control comparisons were performed by Student t, Mann-Whitney U, or Chi-squared test. Pearson and Spearman's coefficients determined the correlation. Statistical significance was set at $p<0.05$.

RESULTS

The mean age of the study population was 61.33±6.7 years, and 63 patients (76.8%) were female. The mean age of patients with DM (n=50) was 61.38 ±9.89 years, and those without DM (n=47) was 59.32±9.98 years. The frequency of females in the patients with DM and without the diabetic group were 76.4% and 78.4%. No significant difference was found between the groups regarding sex, age, BMI, and dominant hand ($p>0.05$). The mean duration of DM was 11.76±6.89 years, and Hemoglobin A1c (HbA1c) averaged was 8.35±2.02

in patients with DM. There was no statistically significant difference between the two groups in terms of demographic characteristics. But a statistically significant difference was found between the case and the control group in terms of knee function scales, daily life activities, range of motion, FAC, manuel muscle strength and KLS stage. The demographic and clinical features of the patients are shown in **Table 1**.

Table 1. Clinical, demographic, and pain characteristics of knee osteoarthritis patients with and without DM

	Without DM (n=45)	With DM (n=37)	p value
Age, year (mean± SD)	59.32 ± 9.98	61.38 ±9.89	0.354
BMI, kg/m² (mean±SD)	30.41±6.29	33.03±5.63	0.051
Diagnosis duration of DM, years (mean± SD)	-	11.76 ± 6.89	-
HbA1c, (mean± SD)	-	8.35 ± 2.02	-
Sex n(%)			0.763
Male	8 (21.6)	11 (24.4)	
Female	29 (78.4)	34 (76.4)	
Muscle strength, n (%)			**<0.001**
3/5	8 (17.8)	3 (8.1)	
4/5	28 (62.8)	7 (18.9)	
5/5	9 (20)	27 (73)	
Auxiliary device use, n (%)	13 (28.9)	6 (16.2)	0.176
Existence of polyneuropathy, n (%)	31 (68.1)	0	**<0.001**
Functional ambulation score, n (%)			**0.001**
3	22 (48.9)	5 (13.5)	
4	10 (22.2)	7 (18.9)	
5	13 (28.9)	25 (67.6)	
Kellgren-Lawrence scale			**<0.001**
Grade 1-2	7 (15.6)	23 (62.2)	
Grade 3	33 (73.3)	13 (35.1)	
Grade 4	5 (11.1)	1 (2.7)	
WOMAC	65.94±16.23	45.79±18.04	**0.003**
Lequesne	16.62±4.22	10.19±4.45	**<0.001**
Knee injury and osteoarthritis outcome score			
Quality of Life	45.49±23.42	22.8±19.51	**0.049**
Pain	56.81±18.12	35.98±14.5	**<0.001**
Symptoms	62.37±19.09	43.01±17.57	**0.008**
Sports	37.03±25.99	15.56±16.49	**0.002**
Activities of Daily Living	55.72±20.87	35.1±16.51	**0.002**
Short Form of 36			
Function	16.33±14.48	32.32±25.81	**0.031**
Pain	28.94±15.04	45.14±19.93	**0.035**
Range of Motion			
Flexion (mean±SD)	120.22±13.6	132.43±7.87	**<0.001**
Extension (mean±SD)	-0.35±1.6	1.98±2.51	**<0.001**

DM: diabetes mellitus, SD: standard deviation, BMI: body mass index, HbA1c: hemoglobin A1c, VAS: visual analog scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. Chi-square test, Mann Whitney-U test, Fisher Exact test and Student's t test were used in comparisons according to the distribution characteristics of data. Statistically significant variables are shown in bold.

The correlation of the knee functional indexes of the diabetic patients and SF-36 components with DM diagnosis and Hb A1c were calculated. While there was a weak negative correlation between Hb A1c and KOOS components (pain, quality of life, sports, daily activities, symptom duration), but there was a moderate negative correlation between knee flexion restriction and Hb A1c (r = -0.401) (**Table 2**).

Table 2. Correlation of length of DM and hemoglobin A1c level with clinical findings

	Diagnosis duration of DM		HBA1C	
	p	r	P	r
Knee injury and osteoarthritis outcome score				
Pain	**<0.001**	0.513	**<0.001**	-0.440
Symptom	**0.001**	0.485	**0.001**	-0.343
Activities of daily living	**<0.001**	0.654	**<0.001**	-0.396
Quality of life	**<0.001**	0.683	**0.001**	-0.336
Sports	**0.001**	0.495	**0.002**	-0.342
WOMAC	**<0.001**	-0.561	**<0.001**	0.410
Lequesne	**<0.001**	-0.666	0.275	0.462
Short form of 36				
Pain	0.373	-1	**0.013**	-0.273
Function	0.226	-0.135	0.073	-0.199
Range of motion				
Flexion degree	0.056	0.287	**<0.001**	-0.401
Extension degree	0.038	-0.310	**0.001**	0.347

DM: diabetes mellitus, SD: standard deviation, BMI: body mass index, HbA1c: hemoglobin A1c, VAS: visual analog scale, WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index. Spearman`s correlation test was used in comparisons according to the distribution characteristics of data. Statistically significant variables are shown in bold.

DISCUSSION

Although it is common in diabetic patients, the relationship between DM and OA development has not been established definitively on evidence-based medicine. However, studies at the molecular level showed that adipokine hormone has a potential contribution to the development of OA (20). In our study, it was found that knee functional indices, joint range of motion, radiographic grading and quality of life were worse in diabetic patients compared to non-diabetic patients with gonarthrosis. It was observed that the diagnosis duration of DM and Hb A1c level were correlated with knee functional indices, quality of life scales and joint range of motion limitation, respectively.

Although the number of studies that compile the relationship between radiography and DM in the literature is limited. Eymard et al. (21) investigated the effect of diabetes on joint space narrowing in the medial tibiofemoral joint (EAD) in 559 patients. However, radiographic changes may be related to the treatment of diabetic patients. Khaled El Jarallah et al. (22) included 99 type 2 diabetic patients who did not receive insulin therapy, 112 diabetic patients receiving insulin therapy and 100 patients with non-diabetic gonarthrosis and compared

the radiographs. In the radiographs of the group receiving insulin therapy, less osteophyte formation was detected. Horn et al. (23) also compared radiographs of 25 diabetic female patients and 48 non-diabetic gonarthrosis patients. In this study, lesser osteophyte formation was detected in diabetic group radiography. In our study, while 38 (84.4%) patients in the diabetic group had grade 3-4 according to the Kellgren-Lawrence (KLS) classification, 14 (37.8%) patients in the control group had grade 3-4 gonarthrosis. Moreover, the detection of osteophyte formation more than the control group may be related to the patients who did not receive insulin therapy as a treatment. Because insulin has been shown to reduce chondrogenesis and osteogenesis required for osteophyte formation at the cellular level (24).

There are many studies compiling the relationship between knee OA and quadriceps muscle strength. Shigeru et al. (25) evaluated 976 knee muscle strength with a quadriceps training machine (QTM-05F, Alcare Co.). As a result, they determined that quadriceps muscle weakness was a risk factor in increasing the incidence of radiographic knee OA, but it was not effective in progression. In literature, patients diagnosed with OA radiographically had a lower quadriceps muscle strength compared to patients without OA. Another study reported that the quadriceps muscle strength of patients diagnosed as gonarthrosis radiographically was 22% lower compared to patients who were not diagnosed as OA radiographically (27). In our study, quadriceps muscle strength was evaluated with manual muscle strength. Muscle strength was less than 5/5 in 36 (80.6%) patients in the case group and 10 (27%) patients in the control group. However, unlike the two studies above, the control group was also diagnosed with gonarthrosis in our study. Therefore, the effect of radiographic OA on quadriceps muscle strength could not be determined. In addition, since the muscle strength measurement sensitivity was performed with low manual muscle strength, the difference in muscle strength or loss between the case and the control group could not be measured objectively. Therefore, the lack of quadriceps muscle strength with a sensitive device is one of the biggest limitations of our study.

There are studies evaluating knee function and quality of life in diabetic patients. Annet Eitner et al. (28) performed and compared the KOOS test in 23 diabetic and 47 non-diabetic patients. There was a statistically significant difference between the two groups. Moreover, a statistically significant relationship was detected between HbA1c and KOOS test (28). Baldwin et al. (29) on the other hand, the KOOS test was found to be correlated with the limitation of joint range of motion. Elena Zonova and colleagues (30) compared 52 patients with diabetic OA and 28 patients in terms of pain, quality of life, WOMAC total index and SF-36. As a result, a numerically significant difference was found between the indices between the two groups. Antje Miksch et al. (31) reported that diabetic patients with group OA had numerically low scores in the components of the SF-36 test when compared to diabetic patients with hypertension. In our study, the pain and function components of SF-36, WOMAC and KOOS, were different, similar to the results of the above study. In addition, it was observed in our study that Hb A1c and limitation of joint range of motion in the knee were correlated with the KOOS test.

Diabetic patients have limited activities of daily living compared to healthy controls. There are many studies on this subject (32). Eriksson et al. (33) reported that diabetic patients had 10% lower vital capacity with V02 max and 16% lower physical activity compared to healthy control. An important reason for the low capacity of life activities of diabetic patients may be that axonal loss causes muscle atrophy. Anderson et al. (34) found that a significant reduction in strength in tibialis anterior and quadriceps muscles due to axonal loss. In our study, the FAS was below 5 in 32 diabetic patients (71.1%). There was a statistically significant difference between the two groups in the comparison of the control group and FAS. In addition, 61% of our patients had polyneuropathy. Therefore, the loss of muscle strength in the quadriceps and tibialis anterior due to axonal loss, decreased physical function capacity, may explain the statistical difference in our study.

Although the relationship between DM and knee OA was shown in our study, prospective studies are needed to confirm this situation. Therefore, the cross-sectional nature of our study is an important limitation. But the biggest limitation of our study is to evaluate quadriceps muscle strength with low sensitivity and manual muscle strength. Because the loss of muscle strength in the case group could not be clarified.

CONCLUSION

DM has a negative effect on quality of life and activities of life in knee OA. It is critical to question DM in those diagnosed with OA in rehabilitation clinics.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Training and Research Hospital Noninvasive Clinical Ethics Committee (Date: 02.22.2017, Decision No:46).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1090756
J Health Sci Med 2022; 5(4): 1119-1123

Vaccination rates and the causes of vaccine hesitancy among patients with end stage renal disease

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Cite this article as: Karagöz Özen DS, Yavuz D, Demirağ MD. Vaccination rates and the causes of vaccine hesitancy among patients with end stage renal disease. J Health Sci Med 2022; 5(4): 1119-1123.

ABSTRACT

Aim: Chronic kidney disease creates a tendency to infections, and infections are the second most common reason for mortality following cardiovascular events in chronic kidney disease. Health authorities recommend vaccination against hepatitis B, annual influenza, pneumonia, zoster, tetanus, and new coronavirus disease for people with end-stage kidney disease. Vaccine-preventable diseases cause mortality in the adult population with chronic diseases.

The primary purpose of this study is to investigate vaccination rates and awareness about vaccination among end-stage renal disease patients who were on renal replacement therapies in a single tertiary center in Turkey.

Material and Method: 86 hemodialysis patients were included in this cross-sectional study. A questionnaire was used to investigate whether the patients were aware of the immunization schedule or not and whether they were vaccinated against hepatitis B virus, seasonal influenza virus, pneumonia, herpes zoster, tetanus, and SARS-CoV-2 or not.

Results: Fifty-eight (67.4%) patients were vaccinated against SARS CoV2. 48(55.8%) patients were vaccinated against the Hepatitis B virus. 31 (36%) patients were vaccinated against Pneumococcus pneumonia. 48 (55.8%) patients have been vaccinated against the influenza virus annually. Only 14 (16.3%) patients were vaccinated against tetanus during the previous 10 years, and only 1 (1.2%) patient was vaccinated against Herpes zoster. Influenza vaccination rates were found to be higher in patients with a longer duration of hemodialysis when compared to the other group(p=0.03). SARS-CoV 2 vaccination rates were higher in patients who were older than 59 years of age when compared to the younger patients(p=0.03).

Conclusion: Vaccination rates are far from the targets in patients with end-stage kidney disease. The most common reason to be unvaccinated is a lack of enough knowledge about the subject.

Keywords: End-stage kidney disease, adult vaccination, vaccine hesitancy

This study is presented as oral presentation in the "Sağlık Bilimleri Üniversitesi 4. Ulusal İç Hastalıkları Kongresi 24-28 kasım 2021, İstanbul" by the corresponding author.

INTRODUCTION

Chronic kidney disease (CKD) creates a tendency to infections, and infections are among the most important reasons for mortality following cardiovascular events in chronic kidney disease (1,2). Prevention from infections is easier, cheaper, and safer than their treatment. Active immunization is the key point of prevention from various bacterial and viral infectious diseases not only in the pediatric group but also in adults. Advisory Committee on Immunization Practice (ACIP) recommends immunization against influenza, hepatitis B, pneumococcal pneumonia, herpes zoster, varicella-zoster, tetanus, diphtheria, pertussis, measles-mumps-rubella, and human papillomavirus for chronic kidney disease patients (3). Unfortunately, vaccine-preventable disease-related deaths are not rare in the adult population, especially in patients with comorbidities (4). Furthermore, the vaccination coverage rate of patients with comorbidities is far from the target. For example, pneumococcal vaccination coverage for adults in the United States was 65.2% in people older than 65 years of age, while it was 20.1% for the high-risk group younger than 65 years of age (5).

The Adult Vaccination Campaign in Europe (ADVICE) was developed in 2012, to increase awareness about immunization in adults (6). This goal may be achieved in various ways, one of which is to define the properties of regions. According to ADVICE, major barriers against immunization are organizational, health care provider-related, health care system-related, and patient-related (6).

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Received: 25.03.2022 **Accepted:** 21.06.2022

We don't have enough knowledge either about vaccine hesitancy rates or vaccine awareness among adult CKD patients in Turkey. Because vaccine hesitancy rates are increasing day by day, it is important to find out the main reasons for this subject. Unvaccinated persons transmit infectious diseases easily to the main population (7).

The primary purpose of this study is to investigate immunization rates and awareness about vaccination among end-stage renal disease (ESRD) patients who were on renal replacement therapies in a single tertiary center in Turkey. The secondary purpose is to find out the vaccine hesitancy rates among this patient group and to define the reasons for vaccine hesitancy.

MATERIAL AND METHOD

The study was carried out with the permission of Samsun University Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 01.05.2021, Decision No: GOKA/2021/9/9) and all participants gave written informed consent. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This is a cross-sectional questionnaire-based study. The patients were selected among adult end-stage renal failure patients who were on a hemodialysis program in Samsun Training and Research Hospital. 86 hemodialysis patients who accepted to join the study were included.

Participants' Eligibility and Recruitment

Hemodialysis patients who were taking renal replacement therapy at our center were included in the study. All patients who were older than 18 years of age and who were willing to attend were included.

Questionnaire

A questionnaire was created to investigate whether the patients were aware of the immunization schedule or not and whether they were vaccinated against hepatitis B virus, seasonal influenza virus, pneumonia, herpes zoster, tetanus, and SARS-CoV-2 or not. A literature search was done for optimal question selection and the authors form the questionnaire based on the current literature (8-10). For each question there were three answers Likert scale including "yes", "no", and "I can't remember". For the answers indicating that the patient was not vaccinated against the specific microorganism, a new question was formed with eleven distinct answers. These answers were related to the reasons for vaccine refusal or deprivation. The patient could mark more than one reason. The questions and the summary of the questionnaire were shown in **Table 1**.

Table 1. The questionnaire form

Demographical properties		
Age		
Gender		
Educational status		
The duration of chronic kidney disease		
The duration of dialysis		
Vaccination status		
Have you ever been vaccinated against Hepatitis B?	Yes	No
If your answer is "No", please mark all the appropriate answers for you.		
a. I'm afraid of the side effects of the vaccines.		
b. I don't believe that the vaccines can prevent diseases.		
c. I have previous history of adverse vaccine reaction.		
d. I think that the alternative and complementary medicine has more effecive and less harming than vaccines.		
e. I don't think that I am in the risk group for this disease.		
f. I refuse vaccination because of my religious belief.		
g. I'm not vaccinated because of the news on media.		
h. I did not know that I should get vaccinated.		
i. I did not have enough knowledge about the vaccine.		
j. My practitioner did not recommend, if he/she would recomend I would.		
k. No idea		
Have you ever been vaccinated against Pnomococcus (pneumonia)?	Yes	No
If your answer is "No", please mark all the appropriate answers for you.	Same as the above 11 answers	
Are you vaccinated against seasonal influenza virus (flu)?	Yes	No
If your answer is "No", please mark all the appropriate answers for you.	Same as the above 11 answers	
Have you get vaccinated againts tetanus in the previous 10 years?	Yes	No
If your answer is "No", please mark all the appropriate answers for you.	Same as the above 11 answers	
Have you ever get vaccinated against herpes zoster?	Yes	No
If your answer is "No", please mark all the appropriate answers for you.	Same as the above 11 answers	
Are you vaccinated against new coronavirus disease (COVID 19)?	Yes	No
If your answer is "No", please mark all the appropriate answers for you.	Same as the above 11 answers	

Statistical analysis

Statistical Package for the Social Sciences (SPSS) Programme Version 22.0 was used for statistical analysis. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) whereas non-normal distributed continuous variables were expressed as median (min-max). Categorical variables were expressed as numbers and percentages (%). The Chi-square test was used for the comparison of categorical variables. The p-value < 0.05 was accepted as statistically significant.

RESULTS

86 patients, 52 (60.5%) male, and 34 (39.5%) female, with end-stage chronic kidney disease were included in this study. The mean age was 59.1 (23-81; SD 12.28). The median duration of hemodialysis was 41 months (2-291 months). The educational status of 78 (90.7%) patients was elementary school while 8 (9.3%) of them were high school.

Vaccination status against each recommended infection was summarized in **Table 2.** The hepatitis B status of the patients was also recorded. There were 38 people who were not vaccinated against hepatitis B. Of these 38 people, 34 either had chronic hepatitis B infection (positive hepatitis B surface antigen more than 6 months) or had positive antibody hepatitis B surface antigen. So only four patients were not vaccinated against Hepatitis B despite recommendation. For each vaccine, the patients without any vaccination history were asked to answer eleven questions, and these answers were analyzed separately for each vaccine. The results were shown in **Table 3**.

Table 2. Vaccination status against recommended vaccines

Type of vaccine	Vaccinated patients n (%)	Unvaccinated patients n (%)
Hepatitis B	48 (55.8)	4 (4.6)
Pneumonia	31 (36)	55 (64)
Influenza annually	48 (55.8)	8 (44.2)
Tetanus in the previous 10 years	14 (16.3)	72 (83.7)
Zoster	1 (1.2)	85 (98.8)
SARS CoV2	58 (67.4)	28 (32.6)

For hepatitis B vaccine, pneumococcal vaccine, tetanus vaccine, and herpes zoster vaccine we did not find any significant difference between the two groups according to age, gender, duration of hemodialysis, and educational status (p>0.05) (**Table 4**) . Influenza vaccination rates were found to be higher in patients with a longer duration of hemodialysis when compared to the other group (p=0.03). But there was no statistically significant difference between groups according to age, gender, or educational status for influenza vaccination (p>0.05). SARS-CoV 2 vaccination rates were higher in patients who were older than 59 years of age when compared to the younger patients (p=0.03).

A univariate analysis was performed to demonstrate whether age, gender, duration of hemodialysis, and educational status have an impact on overall the study population (**Table 4**).

Table 4. The evaluation of unvaccinated patients according to the demographical properties for each vaccine

	n (%)	n (%)	p value
Age	<59 years-old	≥59 years-old	
Hepatitis B	17 (45.9)	20 (54.1)	0.992
Pneumococcus	28 (51.9)	26 (48.1)	0.145
Tetanus	31 (43.7)	40 (56.3)	0.355
Herpes zoster	38 (45.2)	46 (54.6)	0.459
Influenza	20 (54.1)	17 (45.9)	0.184
SARS-CoV-2	17 (63.0)	10 (37.0)	0.031
Gender	Female	Male	
Hepatitis B	14 (36.8)	24 (63.2)	0.650
Pneumococcus	23 (41.8)	32 (58.2)	0.514
Tetanus	31 (43.1)	41 (56.9)	0.130
Herpes zoster	34 (40.0)	51 (60.0)	1.000
Influenza	13 (34.2)	25 (65.8)	0.369
SARS-CoV-2	11 (39.3)	17 (60.7)	0.974
Hemodialysis duration	< 41 months	≥ 41 months	
Hepatitis B	19 (50)	19 (50)	1.000
Pneumococcus	29 (52,7)	21 (47.3)	0.500
Tetanus	36 (50)	36 (50)	1.000
Herpes zoster	43 (50.6)	42 (49.4)	1.000
Influenza	24 (63.2)	14 (36.8)	0.030
SARS-CoV-2	13 (46.4)	15 (53.6)	0.645
Educational status	Primary and secondary school	High school and above	
Hepatitis B	36 (94.7)	2 (5.3)	0.293
Pneumococcus	51 (92.7)	4 (7.3)	0.451
Tetanus	67 (93.1)	5 (6.9)	0.118
Herpes zoster	77 (90.6)	8 (9.4)	1.000
Influenza	36 (94.7)	2 (5.3)	0.293
SARS-CoV-2	25 (89.3)	3 (10.7)	0.712

Table 3. The results for the vaccine refusal reasons

Causes of vaccine refusal	Type of vaccine				
	SARS CoV2	Pneumonia	Influenza	Tetanus	Zoster
a. I'm afraid of the side effects of the vaccines.	14 (50)	14 (25.5)	5 (13.2)	8 (11.1)	8 (9.4)
b. I don't believe that the vaccines can prevent diseases.	7 (25)	4 (7.3)	4 (10.5)	5 (6.9)	5 (5.9)
c. I have previous history of adverse vaccine reaction.	4 (14.3)	3 (5.5)	1 (2.6)	4 (5.6)	4 (4.7)
d. I think that the alternative and complementary medicine has more effecive and less harming than vaccines.	7 (25)	3 (5.5)	4 (10.5)	5 (6.9)	6 (7.1)
e. I don't think that I am in the risk group for this disease.	7 (25)	3 (5.5)	3 (7.9)	7 (9.7)	12 (14.1)
f. I refuse vaccination because of my religious belief.	2 (7.1)	1 (1.8)	2 (5.3)	5 (6.9)	3 (3.5)
g. I'm not vaccinated because of the news on media.	7 (25)	1 (1.8)	2 (5.3)	7 (9.7)	3 (3.5)
h. I did not know that I should get vaccinated.	7 (25)	12 (21.8)	13 (34.2)	30 (41.7)	30 (35.3)
i. I did not have enough knowledge about the vaccine.	12 (42.9)	26 (47.3)	16 (42.1)	37 (51.4)	47 (55.3)
j. My practitioner did not recommend, if he/she would recomend I would.	11 (39.3)	30 (54.5)	20 (52.6)	34 (47.2)	42 (49.4)
k. No idea	18 (64.3)	44 (80)	27 (71.1)	38 (52.8)	56 (65.9)

DISCUSSION

Chronic kidney disease patients are advised to be vaccinated against Hepatitis B virus, Pneumococcus pneumonia, influenza, Herpes zoster, tetanus, and SARS CoV2 according to the Turkey Health Ministry vaccination recommendations (11). Our study indicates that vaccination hesitancy is still common among hemodialysis patients .

Because hepatitis viruses can be transmitted between patients through hemodialysis systems, these viruses are well evaluated. Screening of hepatitis B virus in patients undergoing hemodialysis and providing immunization against this virus with vaccination are topics that have been studied for many years. It is recommended that all patients undergoing hemodialysis be vaccinated against hepatitis B (3,12-13). In a study evaluating the general immunization status of ESRD patients, the rate of hepatitis B vaccination within the first 3 years after starting dialysis was found to be 77% (14). In another study, the rate of vaccination against hepatitis B in ESRD patients was determined as 73% (15). Our results show that only 4 patients have not been vaccinated despite recommendation. We think that vaccination and immunization rates for hepatitis B virus in our study are compatible with the literature.

Our study showed that 55.8% of hemodialysis patients were vaccinated against the influenza virus in the previous year. There are different results in the literature about influenza vaccination rates among ESRD patients. A recent study showed that the influenza vaccination rate for the previous year was 24% among 95 hemodialysis patients (16). 62.5% of these patients thought that they were in the high-risk group for influenza infection (16). This result may be affected by various factors rather than the lack of awareness for immunization. Two other study results showed that the influenza vaccination rate was 71% and 73% in ESRD patients (14,15). The influenza vaccination rate of our patient group was lower than that of the literature. The most common reason for influenza vaccine hesitancy was lack of enough knowledge about the vaccine. Nearly half of the patients who did not get vaccinated answer "yes" to the question "My practitioner did not recommend if he/she would recommend I would." This ratio was found to be 54.5% for the pneumococcal vaccine.

Pneumococcal pneumonia has a higher mortality rate in hemodialysis patients when compared to the general population (17). There are conflicting data in the literature about the pneumococcal vaccination rates of ESRD patients. For example, in one study, the rate of pneumococcal vaccination within the first 3 years of starting hemodialysis was found to be 53% (14). In another study, the pneumococcal vaccination rate of ESRD patients was found to be 44% (15). In our study, the rate of pneumococcal vaccination in patients undergoing hemodialysis was 36%, and it was found to be lower than the aforementioned sources. However, compared to the study that found the pneumococcal vaccination rate of 25% in ESRD patients, it can be said that there was a higher vaccination rate in our study (18).

In a study in which half of the patients diagnosed with ESRD and had shingles were followed up for two years, 51% of the patients died and the mean time from the diagnosis of shingles to death was 8.1 months (19). However, we could not find data on zoster vaccination of ESRD patients in the literature. In our study, only one patient was vaccinated against zoster. The reasons for zoster vaccine hesitancy were similar to that of the other vaccines. But we think that another reason for the low vaccination rate against zoster is that vaccine is out of insurance. The lack of the question "I am not vaccinated because of payment." in the questionnaire is a limitation of our study.

We found that the second-highest vaccination rates were for SARS CoV-2 vaccines following hepatitis B. We think that this result is a consequence of the global pandemic. 28 patients refuse vaccination, but the vaccine hesitancy reason was different from the other vaccines. Half of the patients refuse vaccination because they were afraid of the side effects of SARS COV2 vaccines. This result is compatible with the literature (20).

The majority of the patients who were not vaccinated answered “yes” to the question “I have no idea”. In general, for each vaccine except SARS-CoV2, insufficient knowledge about vaccines was the most common real reason for vaccine hesitancy. It was shown in the previous studies that vaccine hesitancy increases when the educational status of the people improves (21). According to this study, the high educational status of the parents was correlated with the high levels of vaccine hesitancy. We did not find any significant difference between the groups according to educational status or gender.

We showed that the patients were more vaccinated against SARS COV2 by increasing age. The high mortality rates of new coronavirus disease among the elderly might direct the patients for vaccination in this group. We showed that the longer duration of dialysis is related to the higher levels of vaccination against influenza. This may be related to the accumulated experience of the patients. But this hypothesis may not be true because it was not get verified for the other vaccines.

Another key point is the awareness of healthcare professionals about adult vaccination. For example, nephrology practitioners were asked about adult vaccination awareness for patients with chronic kidney disease in a study (22). While all 32 consultants told that CKD patients should have a vaccine against the Hepatitis B virus, only 19 of them agree with this for the influenza

virus and only 22 of them agree with pneumococcus vaccination (22). However, we think that there is a need for more comprehensive studies on this subject.

The literature search showed that religious beliefs and some news on media may affect the vaccine refusal rates (23). But our study showed that these reasons for vaccine hesitancy were rarely seen in patients with end-stage renal failure disease. Most of the studies about vaccine hesitancy were done in pediatric patient groups by asking their parents. Unfortunately, evidence about adult vaccine hesitancy and its reasons is lacking. More epidemiological studies are needed to determine the rates and reasons for vaccine hesitancy among adults.

CONCLUSION

This study found out that vaccination rates for end-stage renal disease patients were low in our center. Study results showed that the most common reason for vaccine hesitancy is a lack of knowledge about the subject. Our study emphasizes the importance of the education of patients on adult vaccination. We think that our study elucidates methods to handle this public health problem.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Samsun University Training and Research Hospital, Non-interventional Clinical Researches Ethics Committee (Date: 01.05.2021, Decision No: GOKA/2021/9/9).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgments: We sincerely thank Asst. Prof. Özlem Terzi for evaluating the final version of the article. Special thanks to our hemodialysis team, nurses, and patients for their support.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1111517
J Health Sci Med 2022; 5(4): 1124-1127

Human papillomavirus prevalence in unexplained infertile women with chronic endometritis

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Cite this article as: Ağar M, Ayar Madenli A, Gürbüz T. Human papillomavirus prevalence in unexplained infertile women with chronic endometritis. J Health Sci Med 2022; 5(4): 1124-1127.

ABSTRACT

Introduction: This study investigates unexplained infertile women with or without chronic endometritis (CE) and examines the prevalence of the human papillomavirus (HPV) in this population.

Material and Method: This study was done with a cross-sectional and retrospective method. The prevalence of HPV infection and related cases in the participants were examined. In this study, 15 infertile women with CE and 64 infertile women without CE were and analyzed from four perspectives: negative HPV, low-risk HPV, probable high-risk HPV, and the presence of high-risk HPV.

Results: The participants have mean age of 32.89 years ±3.95. High-risk HPV infection was detected in 3 (20%) and 11 (17%) of the patients with and without CE, respectively (p>0.05). The negative HPV (2 (13%) and 17 (26%)), low-risk HPV (3 (20%) and 20 (31%)), and probable high-risk HPV (7 (46%) and 16 (25%)) in infertile women with CE and infertile women had no significantly different prevalence (p>0.05). The two studied groups had no significantly different mean age, body mass index (BMI), and Infertility duration were not in (P=0.08, P=0.932, and P=0.283, respectively).

Conclusion: HPV has no significantly different prevalence in unexplained infertile women with and without CE. It is recommended that this study be repeated with more unexplained infertile women with CE.

Keywords: Human papillomaviruses, chronic endometritis, infertility, the prevalence of HPV

INTRODUCTION

Cervical cancer causes mortality due to cancer in developing countries. Infection with high-risk groups of human papillomavirus (HPV) causes cervical cancer as the second most common malignancy in the world as the third leading cause of mortality in women (1,2). More than 95% of the cervical cancers caused by HPV are one of the most common sexually transmitted infections in the world (2). The prevalence of HPV has been studied in different countries (3). Some studies have indicated an association between HPV and other cancers, such as lung, breast, esophageal, colon and rectum, and prostate cancers; however, a recurrent causal relationship between these cancers and the virus has not been shown (4,5).

Infertility is an essential psychological stress factor for couples (6,7) and has high costs for the health systems of countries and couples. Between 15-30% of the couples face infertility problems globally (8). Different factors cause reproductive dysfunction in both men and women (9,10). Many couples also suffer from infertility for unexplained reasons one of which is chronic endometritis (CE) (11-12).

Monthly change of endometrium causes menstruation, proliferation, and decidualization affected by ovarian steroids. CE is caused by infiltration of lymphocytes, higher cell density of the stroma, and plasma cells in the stromal fibroblasts, endometrial stroma, superficial mucosal edema, and asynchronous maturation of epithelial cells (13).

CE chronically causes inflammation in the endometrium leading to infertility, mostly with or without symptoms such as dyspareunia, uterine bleeding, pelvic pain, and secretions (14). It also causes poor pregnancy outcomes such as abortion and labor preterm (15). Several studies show the important role of CE in abortion and recurrent

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Received: 30.04.2022 **Accepted:** 21.06.2022

implantation failure (16-18). Hysteroscopy with biopsy predicts intrauterine inflammation well (16). CE has the approximate prevalence rate of 10-11% based on biopsies of those undergoing hysterectomies under benign gynecologic conditions (12).

Therefore, this study aimed to study the prevalence of HPV infection in infertile women with and without CE. We can design preventive strategies and appropriate and novel treatment approaches by understanding the disease pathogenesis.

MATERIAL AND METHOD

The study was carried out with the permission of Clinical Research Ethics Committee of Beykoz University (Date: 16.04.2021, Decision No: 1). All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki. Seventy-nine participants in this study visited Medistate Hospital Gynecology and IVF Clinic for infertility treatment from January 2020 to January 2021. Participants ranged in age from 23 to 40 years.

Inclusion and Exclusion Criteria

Seventy-nine participants in this study visited our hospital for infertility treatment from January 2020 to January 2021. Participants ranged in age from 23 to 40 years. The inclusion criteria were: (1) the woman between the ages of 20 and 45. The exclusion criteria were: (1) pregnant women and women in the breastfeeding period; (2) women who did not receive infertility treatment; (3) absence of diabetes, thyroid dysfunction, and systemic diseases; (4) not smoking and not using alcohol.

The study participants were divided into two groups. The infertile women had CE in the first group, and the second group included infertile women without CE. The number of participants in the first and second groups was 15 and 64, respectively. All infertility cases were unexplained, and hysteroscopy was performed on all participants. Demographical and clinical characteristics, including age, body mass index (BMI), average menstrual cycle, infertility duration, menstruation time, abortus, infertility type, pap smear results, premenstrual spotting, intermenstrual bleeding, dysmenorrhea, and menorrhagia were similar.

Laboratory Parameters

After performing a cervical canal swab (Roche Molecular Systems, Cobas PCR collection media, Inc.) for all participants, samples were tested (Cobas 4800 HPV, Roche Diagnostics, GmbH, Mannheim, Germany) for HPV DNA diagnosis and analysis of samples. In this test, the target DNA was amplified using nucleic acid hybridization and polymerase chain reaction (PCR) to identify different types of HR HPV in cervical epithelial cells. The two types, HPV-18 and HPV-16 are the critical types. This analysis makes it possible to diagnose other types of HPV in infectivity clinically significant levels.

PCR is a very widely used test tube system developed for in-vitro replication of nucleic acids. The selective amplification allows for target DNA. At the end of PCR amplification, the target DNA increases logarithmically, and more than 1 million target DNAs are generated after 30 cycles. PCR assays commonly employed in epidemiologic investigations target genetically conserved areas in the L1 gene.

Statistical Analysis

Data were analyzed, tabulated, and subjected to using the SPSS.

(version 26). The continuous data were displayed as mean±SD. At the same time, categorical data were illustrated as percentages and numbers. The Kolmogorov-Smirnov test of normality was utilized to test the normality hypothesis. The test results used proper parametric (Independent t-test) and nonparametric tests (Man Whitney and Chi-square test). A p-value of < 0.05 was regarded as statistically significant.

RESULTS

This study sample included 79 participants (15 cases and 64 control) with unexplained infertility. The participants' BMI and mean age were 23.29±2.92 and 32.89 years ±3.95, respectively. The mean duration of infertility is 3.46±1.38 years. The mean average menstrual cycle is 26.20±3.03. The mean number of menstruation time oocytes is 5.02±0.98. The HPV findings showed that low-risk HPV was found in 23 (29.1%), probable high-risk HPV was detected in 23 (29.1%), and high-risk HPV was found in 14 (17.7%). 19 (24.1%) patients detected negative HPV. **Table 1** shows the explanatory information of the variables. Descriptive characteristics of other variables omit for brevity.

Table 1. Explanatory information on the variables

Variable	N	Min	Max	Mean	SD
Age(yr)	79	23.00	40.00	32.89	3.95
BMI	79	18.20	34.00	23.29	2.92
Infertility duration (yr)	79	1.00	7.00	3.46	1.38
Average Menstrual Cycle (days)	79	2.00	29.00	26.20	3.03
Menstruation time (yr)	79	3.00	8.00	5.02	0.98
HPV		**Frequency**		**Percent**	
HPV Negative		19		24.1	
Low-Risk HPV +		23		29.1	
Probable High Risk HPV +		23		29.1	
High-Risk HPV +		14		17.7	

Min: Minimum, Max: maximum

Table 2 shows the comparison of laboratory findings of the two groups. The patients with CE as a case group and control group in terms of age had no statistically significant difference(p-value=080). The control group had higher age (33.29) than the case group (31.20). There was no statistically significant difference between the case group and controls in terms of BMI, average menstrual cycle, infertility duration, menstruation time, and abortus (p-value>0.05).

Table 2. The distinction between laboratory results of two groups

Variable	Categories	Patients with CE (n=15) (Mean±SD) or n(%)	Control (n=64) (Mean±SD) or n(%)	P value
Age(yr)		31.20±4.53	33.29±3.72	0.080**
BMI		23.72±2.89	23.19±2.94	0.932*
Average menstrual cycle (days)		25±6.45	26.48±1.32	0.990**
Infertility duration (yr)		3.13±0.99	3.54±1.45	0.283**
Menstruation time (yr)		5±1.25	5.03±0.92	0.720**
Abortus		0.06±0.25	0.12±0.37	0.616**
Infertility type				0.912**
	Primer	12 (80.0)	52 (81.3)	
	Secondary	3 (20.0)	12 (18.8)	
Pap smear results				0.922***
	Normal	10 (66.7)	45 (70.3)	
	ASCUS	2 (13.3)	10 (15.6)	
	HGSIL	1 (6.7)	4 (6.3)	
	LGSIL	2 (13.3)	5 (7.8)	
Premenstrual Spotting				0.399***
	Yes	4 (26.7)	11 (17.2)	
	No	11 (73.3)	53 (82.8)	
Intermenstrual Bleeding				0.108***
	Yes	8 (53.3)	20 (31.3)	
	No	7 (46.7)	44 (68.8)	
Dysmenorrhea				0.368***
	Yes	6 (40.0)	18 (28.1)	
	No	9 (60.0)	46 (71.9)	
Menorrhagia				0.391***
	Yes	2 (13.3)	15 (23.4)	
	No	13 (86.7)	49 (76.6)	

* Independent-Samples t-test ** Mann–Whitney U test ***Pearson Chi-Square Test

The case group and controls had no statistically significant difference infertility type, pap smear results, premenstrual spotting, intermenstrual bleeding, dysmenorrhea, and menorrhagia (P-value>0.05). **Table 3** compares HPV prevalence in two groups. The prevalence of HPV types in the two groups is not significantly different.

Table 3. Comparison of HPV prevalence in two groups

Variable	Categories	Patients with CE (n=15) n(%)	Control (n=64) n(%)	P value
HPV				0.330*
	HPV Negative	2 (13.3)	17 (26.6)	
	Low-Risk HPV+	3 (20.0)	20 (31.3)	
	Probable High Risk HPV+	7 (46.7)	16 (25.0)	
	High-Risk HPV+	3 (20.0)	11 (17.2)	

*Pearson Chi-Square Test

The **Figure** shows the tissue samples studied by the two groups and the prevalence of negative HPV, low-risk HPV, probable high-risk HPV, and high-risk HPV infection. The most prevalent in patients with CE was probable high-risk HPV +. HPV negative had the lowest prevalence in patients with CE. The most prevalent in the control group was low-risk HPV +. High-risk HPV + had the lowest prevalence in control group.

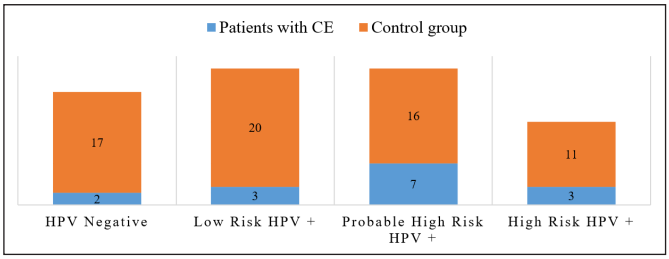

Figure. HPV infection prevalence in patients with CE and control group

DISCUSSION

The present study investigates to what extent HPV is prevalent in unexplained infertile women with and without CE. Our study showed no significantly different incidence of HPV infection between the two groups with CE and without CE. Also, it was not associated with age, BMI, average menstrual cycle, infertility duration, menstruation time, abortus, infertility type, pap smear results, premenstrual spotting, intermenstrual bleeding, dysmenorrhea, and menorrhagia.

Due to the role of HPV infection in cervical cancer, the low-risk, probable high-risk, and high-risk HPV prevalence in women in general and infertile women was studied in many research (3,6,19,20). Investigation revealed that the HPV prevalence in infertile women (21) and women with ovarian endometriosis (22). The HPV prevalence in women with CE was not studied.

In this study, 13% of women with CE had no HPV infection. This infection was not detected in 26% of women in the control group. This finding showed that the number of the infertile woman without disease in the control group was twice as much as in the case group. Low-risk HPV was detected in 20% and 31% of case and control groups, respectively. 46% and 25% in case and control groups had probable high-risk HPV, respectively. Prevalence of probable high-risk HPV was almost twice as common in infertile women with CE. 20% and 17% had high-risk HPV in the case and control groups, respectively. The prevalence of low-risk HPV and high-risk HPV was similar in both groups.

In many studies on HPV, high-risk HPV prevalence is considered the primary measure of majority (22).

According to the study's findings, the high-risk HPV prevalence in the two groups of infertile women with CE and infertile women is not significantly different.

The HPV prevalence in unexplained infertile women with and without CE for the first time was investigated. It is not possible to compare the prevalence of this infection with other studies. It is recommended that this study be conducted with a larger sample to gain more reliable results. This study's limitation is that the piece is small, and there is no access to more detailed information from the participants. The limitation of this study is that the number of patients group (the infertile women had CE) and control groups (infertile women without CE) are not enough.

CONCLUSION

The HPV prevalence in infertile women with CE and infertile women is not significantly different. The findings of this study can be used as the baseline for future studies to study the HPV prevalence in CE infertile women. It is recommended that this study be repeated with more case-patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Clinical Research Ethics Committee of Beykoz University (Date:16.04.2021, Decision No: 1).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study had received no financial support.

Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1129291
J Health Sci Med 2022; 5(4): 1128-1132

Three-year results of combined pars plana vitrectomy and phacoemulsification in diabetic vitreous hemorrhage

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Cite this article as: Karadağ MF. Three-year results of combined pars plana vitrectomy and phacoemulsification in diabetic vitreous hemorrhage. J Health Sci Med 2022; 5(4): 1128-1132.

ABSTRACT

Aim: The purpose of this study was to evaluate the efficacy and safety of complications following combined pars plana vitrectomy and phacoemulsification surgery of the eyes for the management of vitreous hemorrhage due to proliferative diabetic retinopathy as well as pronounced cataracts.

Material and Method: Phacoemulsification and 23G pars plana vitrectomy procedures were performed for the management of vitreous hemorrhage and cataracts. Age, gender, best-corrected visual acuity before and after surgery, and intra- and post-operative complications were recorded in patients with cataracts who underwent surgery due to vitreous hemorrhage.

Results: A total of 40 eyes of 40 patients, 22 females (55%) and 18 males, were included in the study. The mean age was 58.7±7.1 (44–76) years. Logmar visual acuity changed from a mean of 2.82±0.5 preoperatively to a mean of 0.7±0.6 postoperatively. Visual acuity increased in 38 eyes (95%) postoperatively. No reduction in visual acuity was observed in any eye. Complications associated with surgery included transient intraocular pressure increase (12 eyes), hyphema (2 eyes), posterior capsule rupture (1 eye), anterior chamber fibrin exudation (4 eyes), neovascular glaucoma (1 eye), vitreous hemorrhage (4 eyes), retinal detachment (1 eye), and posterior capsule opacification (2 eyes).

Conclusion: It was found that combined phacoemulsification and PPV surgery was safe and effective in patients with proliferative diabetic retinopathy. Combined phaco-vitrectomy is a reliable method with a minimum complication profile and prevents the need for subsequent cataract surgery.

Keywords: Diabetic retinopathy, cataract, phacoemulsification, vitrectomy

INTRODUCTION

Cataract and vitreoretinal diseases can coexist, especially in the elderly population. In combined cases, when vitreoretinal surgery is performed first, the presence of a cataract may make it difficult to visualize the fundus during vitreoretinal surgery, and contact with the lens during the surgical procedure is a potential risk for cataract progression. Especially in cases that require extensive cleaning of the vitreous floor, such as proliferative vitreoretinopathy, the possibility of contact with the thickened lens due to aging increases (1). In the two-year period after pars plana vitrectomy (PPV) surgery, cataract development has been reported at rates as high as 17%-80% (2-3). When silicone oil is used as a buffer, this rate rises to 100% (4). In addition, the risk of zonular dialysis, excessively mobile posterior capsule, and posterior capsule rupture increase in cataract surgery performed in vitrectomized eyes because there is no vitreous support (5-6).

The simultaneous removal of the lens with vitreoretinal surgery allows rapid visual recovery in cases with the coexistence of cataract and vitreoretinopathy but also increases cost-effectiveness (7-9). Although the prevalence of combined phacoemulsification and pars plana vitrectomy surgery in the treatment of cataract-related vitreoretinal disorders has been shown in many studies (10-16), there are few studies in the literature reporting the long-term results of combined therapy (17-18).

In this study, we presented the three-year results of patients who underwent combined pars plana vitrectomy and phacoemulsification surgery with the diagnosis of diabetic vitreous hemorrhage.

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Received: 11.06.2022 **Accepted:** 21.06.2022

MATERIAL AND METHOD

The study was initiated with the approval of the Gaziantep Islam Science and Technology University Non-interventional Clinical Researches Ethics Committee (Date: 07.06.2022, Decision No: 113.17.02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Medical records of patients who underwent PPV with phacoemulsification for vitreous hemorrhage due to proliferative diabetic retinopathy (PDR) and accompanying cataract between May 2018 and January 2019 were retrospectively reviewed. Before surgery, patients were informed about possible complications. Informed written consent was obtained from all patients. All surgeries were performed by the same surgeon (MFK).

The charts of the patients were evaluated. Patients with incomplete records and less than 3 years of follow-up were excluded. Preoperative and postoperative visual acuity, slit-lamp biomicroscopy, intraocular pressure (IOP) measurements, and indirect ophthalmoscopy findings were recorded. When the fundus could not be visualized, ultrasonography was performed to evaluate the vitreous and retina. Visual acuity was assessed using Snellen visual acuity and converted to the logarithm of the minimum resolution angle value (logMAR) for statistical analysis.

Oculus SDI Inverter 2 (OCULUS Surgical, Inc. Port St. Lucie, USA), in conjunction with Oculus BIOM 2, was used for retinal imaging. Surgical procedures were performed under general anesthesia. PPV was applied first after phacoemulsification. In all patients, triple accesses were performed with the transconjunctival 23 G vitrectomy technique before phaco. In phakic eyes, an inferior temporal sclerotomy was made with an MVR blade at a distance of 4 mm from the limbus, and in pseudophakic and aphakic eyes, 3.5 mm from the limbus, and two sclerotomies from the superior nasal and superior temporal regions, one for the light source and the other for the vitrectomy probe. All phaco accesses were made with a 2.8 mm clear corneal incision. Core and peripheral vitrectomy were performed according to the needs of the cases. Additional surgical interventions such as endolaser photocoagulation, endocautery application, peeling of epiretinal membranes, tractional membranes, and application of intravitreal steroid or antivascular endothelial growth factor were performed according to indications. Silicone oil, air, or gas (C3F8) was used as a buffer. An intraocular lens (IOL) was placed. At the end of the surgery, tightness control was performed, and when necessary, the port entrances were closed with 8.0 vicryl.

Statistical analyzes were performed using the SPSS 16.0 package program (SPSS Inc, Chicago, IL, USA). All numerical data were expressed as median (minimum-maximum) or mean±standard deviation. All categorical variables were expressed as numbers and percentages (n, %). Wilcoxon test was used to compare variables. A value of $P < 0.05$ was accepted as the statistical significance level.

RESULTS

Forty eyes of 40 patients were recorded. The mean age of the patients was 58.7±7.1 (44-76) years. There were 22 women (55%) and 18 men (45%). All patients had diabetes mellitus. Other than diabetes, 22 patients had hypertension as a systemic disease. Laser endophotocoagulation was performed in all eyes. For tamponade, silicone oil was injected in 16 eyes (40%), C3F8 gas was injected in 12 eyes (30%), and the air was injected in 2 eyes (5%).

Preoperative best corrected visual acuity (BCVA) was between 20/40 and 20/400 in five (12.5%) eyes and between 20/400 and light perception in 35 (87.5%) eyes. The mean preoperative logMAR visual acuity changed from 2.82±0.5 to 0.7±0.6 postoperatively. This difference was statistically significant (p= 0.002). BCVA increased in 38 eyes (95%) postoperatively. At 3 years postoperatively, BCVA was 20/200 or better in 28 eyes (70%) and 20/40 or better in 8 eyes (20%). It was 10/200 in both eyes. Visual acuity in both eyes was at the level of hand movements and remained unchanged after surgery (**Table 1**). Optic nerve atrophy was present in both of these two cases, one of which was secondary to neovascular glaucoma. No decrease in visual acuity was observed in any eye.

Table 1. BCVA distribution before and after surgery

BCVA (logMAR)	Preoperative	Postoperative
0-1	5 (12.5%)	36 (90%)
2-3	35 (87.5%)	4 (10%)

BCVA: Best corrected visual acuity; logMAR: logarithm of the minimum resolution angle value

Posterior capsule rupture (2.5%) was observed in only one eye as an intraoperative complication. Postoperative complications are given in **Table 2**. Postoperative transient intraocular pressure (IOP) increase (< 24 mmHg) was observed in 12 eyes (30%), but all were medically controlled with topical antiglaucomatous drugs. Moderate transient vitreous hemorrhage (10%) was observed in 4 eyes. All resolved within an average of two weeks without surgery. Retinal detachment requiring reoperation developed in one patient (2.5%) three months after primary surgery. Fibrin exudation (10%) in the anterior chamber (AC) was observed in four eyes and hyphema in two eyes (5%). These findings also regressed with appropriate treatment. No complications related to endophthalmitis or intraocular lens (IOL) were observed in any of the patients.

Table 2. Intraoperative and postoperative complications

Complications	Patients, n (%)
Posterior capsule tear	1 (2.5%)
Transient increase in IOP	12 (30%)
Hyphema	2 (5%)
Neovascular glaucoma	1 (2.5%)
Vitreous hemorrhage	4 (10%)
Fibrin exudation in the AC	4 (10%)
Retinal detachment	1 (2.5%)
Posterior capsule density	2 (5%)

IOP: Intraocular pressure, AC: Anterior chamber

DISCUSSION

In this study, it was found that combined pars plana vitrectomy and phacoemulsification surgery provided a significant improvement in visual acuity in diabetic vitreous hemorrhage, and acceptable complications were observed in the 3-year follow-up, consistent with the literature.

Cataract is a common condition in eyes with PDR. In addition to changing the visual acuity of the patients, it also causes the surgeon to distort the vision during vitreoretinal surgery. Although it is reported in the literature that combined surgery is mostly more advantageous and preferable, there is no consensus yet on leaving the patient phakic during pars plana vitrectomy or performing combined surgery (7-8, 16).

Many advantages of combined surgery have been reported. The visibility of the posterior pole is better during vitrectomy. It provides early visual rehabilitation after surgery. It is more comfortable for the patient and also offers advantages such as cost-effectiveness. This method also allows for a detailed vitreous floor cleaning surgery (19). Pars plana vitrectomy with cataract surgery is especially important in cases where cataracts and vitreoretinal disorders are seen together. There are studies showing that combined PPV and phaco surgery are safe and effective. (20-22). In addition, no significant difference was observed in the studies when combined and sequential procedures were compared in terms of postoperative visual outcome (23, 24).

In addition to the above-mentioned advantages of combined surgery, some disadvantages are also known. Capsulorhexis may be difficult to do because the red reflex is weak. Difficulties in visualization may increase the risk of posterior capsule rupture, increasing the risk of postoperative neovascular glaucoma. Manipulations during posterior segment surgery may cause corneal wound leakage and anterior chamber loss, which may result in prolonged surgical time. Miosis, bleeding from anterior segment structures, folds in Descemet's membrane, and corneal edema after cataract extraction, intraocular lens-related prismatic effects, and unwanted light reflections during vitreoretinal surgery, iris capture in patients with tamponade, postoperative anterior chamber inflammation and diffuse fibrin formation are potential limitations of combined surgery. (20-21, 24-29).

Yang et al. (30) in a study in which they compared the results of combined and sequential phacoemulsification and PPV surgeries in patients with PDR, it was found that BCVA improved in 18 (62.1%) eyes, remained the same in 8 (27.6%) eyes, and decreased in 3 (10.3%) eyes in the combined surgery group. , on the other hand, reported improvement in 7 eyes (58.3%), remained the same in 4 (33.3%) eyes and decreased in 1 (8.3%) eye in patients who underwent sequential surgery. In another study, in which the results of 91 eyes that underwent pars plana vitrectomy with phacoemulsification and intraocular lens implantation were shared, it was shown that postoperative BCVA improved significantly compared to preoperatively ($p<0.001$). The authors reported that BCVA increased by 61%, remained stable at 24%, and decreased by 15% (18). In another study reporting the results of combined PPV and phacoemulsification in the treatment of vitreous hemorrhage in patients with proliferative diabetic retinopathy, Canan et al. (31) reported that postoperative BCVA improved in 79 (92.9%) eyes, remained unchanged in 6 (7.1%) eyes, and no decrease in visual acuity was observed in any eye. In our study, similar to the literature, postoperative BCVA increased in 38 (95%) eyes and remained unchanged in only two (5%) eyes. No decrease in visual acuity was observed in any eye.

Intraoperative and postoperative complications of combined surgery have generally been reported at acceptable levels. Canan et al. (31) reported intraoperative posterior capsule rupture in one eye and transient corneal edema in 5 eyes in combined surgery. Similarly, posterior capsule rupture developed in only one eye (2.5%) in our study. Transient increase in IOP, corneal epithelial defects, hyphema, vitreous hemorrhage, retinal tears, and retinal detachment are generally reported among the postoperative complications of combined surgery (30-32).

The rate of recurrent bleeding in patients with posterior capsular opacity diabetic vitreous hemorrhage has been reported to be between 12% and 63% in publications (33-37). In our study, moderate vitreous hemorrhage was observed in 4 eyes (10%). All resolved within an average of two weeks without surgery. Neovascularization of the iris is a well-known complication of PDR. In this study, one patient had preoperative neovascular glaucoma that did not improve after surgery.

A transient increase in IOP may occur after combined surgery. The rate of transient IOP increase has been reported between 9.7-25% in various publications

(28,38). We observed a transient increase in IOP in 30% (12 eyes) of the patients. IOP returned to normal levels in all patients with antiglaucomatous therapy. We speculate that this transient increase in IOP may be due to viscoelastic that was not completely aspirated at the end of surgery.

Güven et al. (18) In their 3-year follow-up, 57 eyes with combined surgery required additional treatment, of which 17.6% had antiglaucomatous treatment, 16.5% had silicone oil removal and/or PPV repeated, 16.5% had intravitreal drug injection and 1.1% had IOL reposition. They have stated. In our study, retinal detachment requiring reoperation developed in only one patient (2.5%) three months after primary surgery.

There are some limitations of our study. First, due to the retrospective design, we only included patients with complete charts, which may have created a partial selection bias. Secondly, our sample size was relatively small since we were the only center. Despite these limitations, to our knowledge, there are few studies in the literature reporting long-term results of combined therapy. In addition, we think that it would be beneficial for the centers to present their own experiences in reaching a certain level of scientific evidence and would be valuable in the preparation of treatment algorithms.

CONCLUSION

Combined pars plana vitrectomy and phacoemulsification surgery seem safe and effective in diabetic vitreous hemorrhage. Eliminating the need for a second surgery for cataract extraction also provides benefits in terms of both complication risk and cost. Given the advantages of the procedure, we believe that combined surgery can be safely performed in suitable patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Gaziantep Islam Science and Technology University Non-interventional Clinical Researches Ethics Committee (Date: 07.06.2022, Decision No: 113.17.02).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version..

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1126149
J Health Sci Med 2022; 5(4): 1133-1138

The utilization of BMI in patients with high WHtR as to cardiovascular risk

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Cite this article as: Uygur MM. The utilization of BMI in patients with high WHtR as to cardiovascular risk. J Health Sci Med 2022; 5(4): 1133-1138.

ABSTRACT

Introduction: A waist to height ratio (WHtR) greater than 0.5 may be a global screening tool for cardiovascular disease (CVD) and diabetes. However, it is unclear whether WHtR could be used instead of BMI. This study aimed to evaluate the role of BMI regarding CVD and diabetes in a subset of Turkish adults with WHtR greater than 0.5.

Material and Method: The cross-sectional study involved 118 participants with WHtR>0.5, 18 years and older who applied to the endocrinology and metabolism disease outpatient clinic between September 2019 and February 2020. WHtR and BMI were calculated.

Results: The prevalence of hypertension and hyperlipidemia increased with BMI. WHtR was correlated with FBG. BMI was significantly associated with TG, HDL-c, SBP, and DBP in linear regression analysis, but not with FBG. On the other hand, there was a significant association between WHtR and FBG.

Conclusion: This study confirmed that the simple value of '0.5' for WHtR was associated with diabetes risk. The cut-off value of 35 for BMI was effective categorizing participants with high blood pressure and lipid levels in paticipants with high WHtR. Further population-based studies in Turkish adults are needed to evaluate whether WHtR could be used independent from BMI as an early warning of cardiovascular risks for preventive interventions.

Keywords: Body mass index, waist to height ratio, obesity, cardiovascular risk

INTRODUCTION

The prevalence and incidence of obesity have increased and tripled since 1975. In 2016, 39% of adults were overweight, and 13% were obese. Turkey had the highest prevalence of obesity in Europe in 2016, according to the World Health Organization (WHO) (1). Compared with TURDEP-I, the prevalence of obesity increased by 40% in TURDEP-II among Turkish adults within twelve years and reached to 32% (2,3). Obesity is defined as an excessive fat collection that might damage health and is diagnosed at a body mass index (BMI) ≥30 kg/m^2 (4). Increased BMI is a significant risk factor for cardiovascular diseases, diabetes, musculoskeletal disorders, and cancers (5-7). The World Obesity Federation has stated obesity as a chronic progressive disease, instead of a significant risk factor for other non-communicable diseases (8).

BMI has been used for the diagnosis of obesity. However, recently marks of abdominal obesity (waist-hip ratio [WHR] and waist circumference [WC]) have increasingly been related to higher cardiometabolic risk than BMI. In the mid-1990s, the waist to height ratio (WHtR) was first proposed for detecting abdominal obesity and associated health risks (9-11). It has been suggested that WHtR greater than 0.5 may be a global screening tool for cardiovascular disease and diabetes (12). In 73% of the studies, WHtR revealed a significant correlation between anthropometric indexes and cardiometabolic risk. That was greater than that for BMI (66%) and WC (64%) (12). So, the health message 'keep your WC to less than half your height' is disclosed (13). This boundary value is useful in many populations, and WHtR is supported as a simple and effective anthropometric index for identifying health risks (6,14,15). In recent guidance of The National Institute for Health and Care Excellence (NICE), waist circumference has been advised to be used in addition to BMI in people with a BMI less than 35 kg/m^2 (16). The UK National Diet and Nutrition Survey data show

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Received: 04.06.2022 **Accepted:** 23.06.2022

that a simple boundary value for WHtR (0·5) is more beneficial to identify more people at 'early health risk' than the combination of BMI and WC within the adult UK population (17). So, a new section was published as 'Identification and classification of overweight and obesity' by NICE (18). Related to its previous clinical guidance on obesity (CG189), this remarks new evidence and expert feedback showing the superior discriminatory benefit of WHtR as an alternate measure of adiposity (18).

It is unclear whether WHtR could be used instead of BMI, especially in different populations. A cut-off point of '0.5' was recommended for categorizing WHtR to predict people at high cardiovascular risk for preventive actions in Turkish adults (19).

This study aimed to evaluate the role of BMI regarding cardiovascular disease (CVD) and diabetes in a subset of Turkish adults with WHtR greater than 0.5.

MATERIAL AND METHOD

The study protocol was approved by the Clinical Researches Ethics Committee of the Marmara University Medical School (Date: 07.05.2021, Decision No: 09.2021.580). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

Data on 118 adult subjects, 82 (69.5%) women and 36 (30.5%) men who applied to the endocrinology and metabolism disease outpatient clinic were evaluated between September 2019 and February 2020. Subjects under 18-year-old, pregnant, or with a chronic disease that might alter the body composition or metabolic condition (e.g., hypothalamic disease, chronic hepatitis, and cirrhosis) were eliminated from the analysis. All the subjects had central obesity with WHtR ≥0.5, as it was suggested as a universal cut-off (17). Participants were divided into two groups; BMI less than 35 kg/m^2 and BMI more than 35 kg/m^2.

Anthropometric Measurements

Height was measured as stood erect, barefoot, with feet together, while looking forward. Weight was measured with an automatic scale as subjects wore light clothes. BMI was calculated by dividing weight in kg by height in meters squared (kg/m^2). WC was measured at the midpoint between the rib cage's lower border and the iliac crest at the end of expiration (20). WHtR was calculated by dividing WC by height, and the cut-off of 0.5 was used for WHtR (13). Blood pressure (BP) was measured after 10-min of rest as seated using a standard sphygmomanometer placed on the subject's right arm.

Blood samples were taken in the morning after at least 8 hours fasting. Fasting blood glucose (FBG), total cholesterol, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-c) levels were measured enzymatically. Serum insulin was measured using chemiluminescent immunoassays. Hemoglobin A1C (HbA1c) was determined by an ion-exchange HPLC method. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated. Hypertension was described as systolic BP (SBP) ≥130 mmHg or diastolic BP (DBP) ≥85 mmHg. Hyperglycemia was described as fasting glucose ≥100 mg/dL, and hypertriglyceridemia was described by fasting triglyceride level ≥150 mg/dL. Decreased HDL-c was described by a level of < 40 mg/ dL for man and and of < 50 mg/dL for woman (21,22).

Statistical Analyses

All analyses were performed using commercial statistical software (version 22.0; IBM SPSS). Descriptive statistics were given as mean and standard deviation for continuous data , and percentages and frequency for categorical data. Continuous variables were analyzed for homogeneity of variance using the Kolmogorov-Smirnov test, and those with normal distribution were analyzed with the t-test. In contrast, those with uneven distribution were analyzed with the Mann-Whitney U test. The Chi-square test or Fisher's exact test analyzed categorical data. The correlation between anthropometric indices and cardiometabolic risk factors analyzed with Pearson's correlation coefficients. The determinants of BMI and WHtR were evaluated by performing a sex-and age-adjusted linear regression analysis.

RESULTS

The characteristics of the patients and the prevalence of cardiovascular risk factors, according to gender, are shown in **Table 1**. The mean age was 43.4 years in both men and women, and the mean BMI was 35.7±5.8 kg/m² in women and 35.5±6.7 kg/m² in men (p: 0.90). The mean WC was 107.9±11.3 cm in women and 115.1±13.1 cm in men (p:0.003), and the mean WHtR was 0.67±0.07 in women and 0.65±0.07 in men (p:0.29). The percentage of diabetes mellitus (p:0.29), hypertension (p:0.66) , hyperlipidemia (p:0.15), and coronary heart disease (CHD) (p:0.27), did not differ according to gender. Triglyceride levels were higher in men than women but were not statistically significant (p:0.07). The percentage of hypothyroidism is significantly higher in women than men (p:0.04).

Table 2 summarizes the clinical characteristics of patients grouped by BMI. In patients with BMI>35, the

prevalence of hypertension and hyperlipidemia were higher than patients with BMI<35 (p:0.001; p:0.04, respectively). Also, SBP and DBP were higher in this group (p:0.001, p:0.02, respectively). FBG, insulin, and HbA1c did not differ according to BMI, and HOMA-IR was also similar between the groups. FBG, insulin, HbA1c, and HOMA-IR were high in both BMI groups, indicating the association between WHtR and diabetes risk independent from BMI.

Table 1. Clinical and cardiometabolic characteristics of the patients according to gender

	WOMEN (n=82)	MEN (n=36)	P Value
Age (years)	43.4±12.5	43.2±12.1	0.94
BMI (kg/m^2)	35.7±5.8	35.5±6.7	0.90
WC (cm)	107.9±11.3	115.1±13.1	0.003
WHtR	0.67±0.07	0.65±0.07	0.29
SBP (mmHg)	129.7±18.8	131.8±13.8	0.55
DBP (mmHg)	79.1±13.4	83.1± 8.7	0.10
FBG (mg/dl)	130.06±67.85	129.65±52.06	0.97
Insulin (mg/dl)	17.67±7.01	19.02±8.25	0.36
HOMA-IR	5.03±3.08	5.81±3.08	0.20
HbA1c	6.4±1.7	6.6±1.6	0.54
TC (mg/dl)	204.85±48.38	218.7±54.7	0.17
TG (mg/dl)	170.7±183.1	263.4±382.4	0.07
HDL-C (mg/dl)	49.6±11.4	48.7±25.3	0.80
LDL-C (mg/dl)	124.2±40.2	126.5±45.7	0.78
Diabetes mellitus, n (%)	27 (32.9%)	16 (44.4%)	0.29
Hypertension, n (%)	24 (29.3%)	12 (33.3%)	0.66
Hyperlipidemia, n (%)	28 (34.1%)	18 (50%)	0.15
CHD, n (%)	6 (7.3%)	5 (13.0%)	0.27
Hypothyroidism, n (%)	19 (23.8%)	3 (8.3%)	0.04

Values are means±SD or n (%). P values are from t-tests or chi-square tests for analysis of variance for continuous variables and categorical variables.
BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; FBG, fasting blood glucose; HOMA-IR, Homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low- density lipoprotein cholesterol. CHD, coronary heart disease

The correlation coefficients between BMI and TG, SBP, and DBP were statistically significant. The correlation between BMI and HDL-c was also significant but represented minor magnitude (**Table 3**). WHtR was correlated with FBG, and WHtR was also significantly correlated with SBP with a lesser degree than BMI (**Table 4**).

On linear regression analysis adjusted for age and gender, BMI was significantly associated with TG (p:0.004), HDL-c (p:0.014), SBP (p:0.003), DBP (p:0.007) but not with FBG (p:0.07) (**Table 5**). On the other hand, there was a significant association betweeen WHtR and FBG (p:<0.001) on linear regression analysis adjusted for age and gender. WHtR was also associated with TG, HDL-c, SBP, DBP (p:<0.001) (**Table 6**).

Table 2. Clinical and cardiometabolic characteristics of the patients according to BMI

BMI	>35 (n=59)	<35 (n=59)	P Value
AGE	44.4±13.2	42.2±11.4	0.34
No. of male/female	17/42	19/40	0.6
BMI (kg/m^2)	40.4±4.7	30.9±2.6	<0.001
WC (cm)	117.9±10.8	102.3±8.2	<0.001
WHtR	0.72±0.65	0.61±0.04	<0.001
SBP (mmHg)	135.4±18.5	125.3±14.7	0.001
DBP (mmHg)	82.8±14.1	77.8±9.6	0.02
FBG (mg/dl)	129.6±68.5	130.2±58	0.95
İnsulin (mg/dl)	19.5±7.5	16.6±6.9	0.03
HOMA-IR	5.3±2.9	5.2±3.2	0.86
HbA1c	6.5±1.6	6.4±1.7	0.88
TC (mg/dl)	211.7±56.7	206.4±43.9	0.57
TG (mg/dl)	234.5±345.3	163.5±130.2	0.14
HDL-C (mg/dl)	47.9±16.6	50.7±16.9	0.35
LDL-C (mg/dl)	124.7±40.6	125.1±43.3	0.96
TSH	2.3±1	2.6±1.9	0.36
Diabetes mellitus, n (%)	23 (39%)	20 (33.9.%)	0.56
Hypertension, n (%)	26 (44.1%)	10 (16.9%)	0.001
Hyperlipidemia, n (%)	28 (47.5%)	18 (30.5%)	0.04
CHD, n (%)	5 (8.5%)	6 (10.2%)	0.50
Hypothyroidism, n (%)	14 (24.1%)	8 (13.8%)	0.11

Values are means±SD or n (%). P values are from t-tests or chi-square tests for analysis of variance for continuous variables and categorical variables.
BMI, body mass index; WC, waist circumference; WHtR, waist-to-height ratio; FBG, fasting blood glucose; HOMA-IR, Homeostasis model assessment of insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low- density lipoprotein cholesterol; CHD, coronary heart disease

Table 3. Correlation coefficients between BMI and cardiovascular risk factors

	Correlation coefficient	P Value
FBG	0.049	0.50
TG	0.231	0.007
HDL-C	-0.191	0.028
SBP	0.287	0.001
DBP	0.231	0.007

FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index

Table 4. Correlation coefficients between WHtR and cardiovascular risk factors

	Correlation coefficient	P Value
FBG	0.190	0.029
TG	0.088	0.316
HDL-C	-0.118	0.175
SBP	0.272	0.002
DBP	0.170	0.05

FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index

Table 5. Independent determinants of BMI on linear regression analysis adjusted for age and gender

	Adjusted R^2	P Value
FBG	0.030	0.074
TG	0.076	0.004
HDL-C	0.057	0.014
SBP	0.080	0.003
DBP	0.068	0.007

FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index

Table 6. Independent determinants of WHtR on linear regression analysis adjusted for age and gender:

	Adjusted R^2	P Value
FBG	0.120	<0.001
TG	0.121	<0.001
HDL-C	0.120	<0.001
SBP	0.137	<0.001
DBP	0.129	<0.001

FBG, fasting blood glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; BMI, body mass index

DISCUSSION

WHtR, an indicator of abdominal obesity, is accepted as a superior tool for establishing obesity-related cardiovascular risk than BMI. However, alterations in measurement levels (23), different cut-off values among gender and between various ethnic groups (24) and the possibility of wrong measurements by physicians may limit its effectiveness (10). The present study used the simple value of 0.5 for WHtR as a cut-off point associated with diabetes risk. The cut-off value of 35 for BMI was effective categorizing participants with high blood pressure and lipid levels in paticipants with high WHtR.

Many studies confirm the superiority of WHtR compared to other indices; nevertheless, the optimal cut-off point is controversial (19). One study showed that 0.55 was the optimal cut-off point for both sexes (19). Another study from Turkey recommended the optimal cut-off point for Turkish adults as 0.59 (25). Some studies from different populations that recommend 0.5 as the optimal cut-off point. In two different studies on Chinese adults, 0.5 was the optimal cut-off point (26,27), similar to a study performed in Iran (28). A review that considers anthropometric indices across fourteen countries, 0.5 as an optimal boundary was recommended (12).

Among Turkish adults, a cut-off point of '0·5' for WHtR can be useful to categorize people at high cardiovascular risk for preventive actions. WHtR persisted significantly associated with the risk of CHD even after adjusting for age, sex, and BMI (19). The interaction between BMI and WHtR was also evaluated in this study. The odds ratios of high WHtR in assessing cardiovascular risk were classified according to BMI. High WHtR was significantly correlated to cardiovascular risk in each BMI category. There was no interaction between BMI and WHtR (19). In contrast, we found a positive correlation between BMI and high blood pressure.

Two extensive prospective studies from the USA have shown that WHtR is better than BMI in predicting diabetes risk (29) in all adult age groups. Similar results have been found in Korea (30).

In Japan, 6141 men and 2137 women took part in a study in which hypertension, elevated blood glucose, elevated TG, and reduced HDL-c were evaluated as coronary risk factors. Participants with two or more risk factors were classified as high risk. WHtR showed the highest correlation, and BMI showed the lowest correlation with coronary risk factors for both genders. Additionally, WHtR showed larger area under a receiver operating characteristic (ROC) curve (31) for identifying any coronary risk factors in this study. Furthermore, because of the balance between sensitivity and specificity in the discovery of coronary risk factors and the importance of assessing people with higher via simple measurements, WHtR > 0.5 may be the most effective anthropometric index for Japanese adults for determination of public health action (32).

In a study from Turkey, 571 men (34 %) and 1121 women (66 %) participated in which the best anthropometric index for predicting cardiometabolic risk factors in Turkish adults was investigated. It was found that WHtR was the best indicator for predicting most of the cardiometabolic risk factors. The study confirmed WHtR as a better anthropometric index to predict most cardiometabolic risk factors. Although a little difference was found between BMI, WC and WHtR considering CVD risk factors in correlation analyses, AUC in ROC curve analyses indicated that WHtR was superior to predict hypertension, diabetes and metabolic syndrome than other indices (33). The present study showed that the correlation between WHtR and FBG was superior to BMI and FBG. Furthermore, WHtR was significantly associated with FBG and, BMI was related to high blood pressure and lipid levels, vice versa.

A meta-analysis that aimed to compare the performance of BMI against waist circumference, WHR, and WHtR in the discrimination of hypertension in ethnically diverse populations concluded that 'no anthropometric index was systematically better than others at the discrimination of hypertension' (34). Bell et al. (35) showed a stronger association between BMI and hypertension in Chinese than Caucasians and non-Hispanic Blacks than Caucasians and Mexican-Americans. Caucasian populations demonstrated a positive association between BMI and blood pressure in both cross-sectional and prospective studies (36-38). Another large, population based study from Italy also showed the relation between BMI and hypertension (39). There was also a positive association between BMI and blood pressure on the basis of our results, suggesting a causative relation according to ethnic differences.

Strengths and Limitations of the Study

A significant limitation of the present study is its cross-sectional design, which prevents determining a cause-and-effect relationship between anthropometric

measurements and CVD risk. Another limitation is the small sample size from a population of well-educated, white-collar workers, leading to a selection bias. On the other hand, evaluating participants with high WHtR for BMI cut-off for the first time might be counted as the study's strength, leading to further studies with larger sample sizes.

CONCLUSION

This study confirmed that the simple value of '0.5' for WHtR was associated with diabetes risk. BMI classification was practical to recognize participants with high blood pressure and lipid levels. Further population-based studies in Turkish adults are needed to evaluate whether WHtR could be used independent from BMI as an early warning of over-all cardiovascular risks for preventive interventions.

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; CHD, coronary heart disease; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, Homeostasis model assessment of insulin resistance; LDL-C, low- density lipoprotein cholesterol; NICE, The National Institute for Health and Care Excellence; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WHO, World Health Organization; WC, waist circumference; WHtR, waist-to-height ratio; WHR,waist-hip ratio

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Marmara University Medical School Noninvasive Clinical Ethics Committee (Date: 07.05.2021, Decision No: 09.2021.580).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

Financial Disclosure: The author declared that this study has received no financial support.

Author Contributions: The author declared that she has participated in the design, execution, and analysis of the paper and that has approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1102111
J Health Sci Med 2022; 5(4): 1139-1144

The predictors of mortality in patients with methyl alcohol intoxication

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Cite this article as: Büberci R, Karahisar Şirali S, Duranay M. The predictors of mortality in patients with methyl alcohol intoxication. J Health Sci Med 2022; 5(4): 1139-1144.

ABSTRACT

Aim: Methanol intoxication is a worldwide public health problem. Mortality rates are quite high unless there is early intervention and diagnosis. The aim of this study was to investigate the predictors of mortality in patients with methyl alcohol intoxication.

Material and Method: The study included 18 patients admitted to emergency department of our hospital in 2019-2020, who were diagnosed with methanol intoxication. Laboratory parameters and basic features of the patients were recorded. According to the criteria of 2012 Clinical Practice Guideline for Acute Kidney Injury (AKI), patients were diagnosed with AKI.

Results: The mean age of the patients was 45.7±15.21 years and 72.2% of those were male. The mortality and AKI rate were 38.9% and 44.4%, respectively. In regression analyses, delay in admission to hospital, low Glasgow coma scale score, AKI development and high lactate level were independent predictors of mortality. According to ROC analyses when lactate level was more than 5.75 mmol/L, mortality rate increased more rapidly.

Conclusion: Mortality rate is very high in methanol intoxication. Patients with AKI and high lactate levels should be intervened faster.

Keywords: Acute kidney injury, methyl alcohol intoxication, mortality

INTRODUCTION

Methanol is a substance that has industrial use and is liquid at room temperature. Rarely, cases of methanol poisoning occur due to illegal alcohol consumption, accidental, or suicidal exposure. Methanol is not a toxic substance; however, methanol is converted into formaldehyde by the enzyme alcohol dehydrogenase and subsequently, converted into formic acid by a reaction with the enzyme aldehyde dehydrogenase. The metabolites create toxic effects such as high anion gap metabolic acidosis, and damage to many cells particularly the basal ganglia and the optic nerve. If intervention is not relatively quick, the clinical picture proceeds to coma and death (1). The aim of this study was to investigate the predictors of mortality in patients with methyl alcohol intoxication.

MATERIAL AND METHOD

The study was approved by the Clinical Resarches Ethics Committee of the Ankara Training and Research Hospital (Date: 17.09.2020, Decision No: 14.08.2020/E-20/393). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study included 18 patients admitted to emergency department of our hospital in 2019-2020, who were diagnosed with methanol intoxication. Since the level of methanol was not screened in our hospital, the diagnosis was performed with the presence of metabolic acidosis (pH<7.25) with increased anion gap (AG>20), in which other causes were excluded and anamnesis from patients and their relatives and clinical findings. Patients' clinical and demographic features (age, gender, chronic diseases, chronic alcohol users, alcohol type (handmade or not), complaints, time from alcohol exposure to admission to hospital, interventions in hospital (iv. hydration, iv. ethanol, hemodialysis, intubation), acute kidney injury (AKI) development, hospitalization duration, survival status), and laboratory data (blood pH, PCO_2, bicarbonate, lactate, sodium, potassium, chlorine, serum creatinine at admission and basal creatinine,

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Received: 12.04.2022 **Accepted:** 24.06.2022

albumin, urea, white blood cell, hemoglobin, platelets at admission) were recorded. Hospitalization duration, whether it is the intensive care unit or the service, is the time from the moment of admission to the hospital until leaving the hospital. AKI was defined as an increase in known within 48 hours baseline creatinine greater than 0.3 mg/dl or a baseline creatinine increase of more than 1.5 times, according to the criteria of 2012 Clinical Practice Guideline for AKI.

Statistical Analysis

IBM Statistical Package for the Social Sciences 22.0 version (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analyses. All data were checked for normality of distribution using the Kolmogrov-Smirnov and Shapirov-Wilk test. Normally distributed data are presented as the mean± standard deviation. Non-normally distributed data are represented as the median (inter-quartile range). Independent samples T test,was used to compare parametric continuous variables between groups. Mann Whitney U was employed for the comparison of non-parametric variables. Pearson's X^2 or Fisher's exact were used for categorical variables. Univariate binary logistic regression analyses were performed to detect the factors affecting mortality and AKI. Multivariate regression analyses were not performed due to small sample size. ROC analyses was used to find the cut-off value of parameters found to be significant in binary logistic regression analyses. Survival data were analysed with Kaplan-Meier method and tested for significance using the long rank test.

RESULTS

Eighteen patients were included in the study. The mean age of the patients was 45.7±15.21 years, and 72.2 % of those were male. 94.4% of the patients were chronic alcohol users and 94.4% of the patients used handmade alcohol. Time from alcohol exposure to admission to hospital was 39.3±14.7 hours. The most frequent symptoms were loss of consciousness (33.3%), nausea-vomiting (16.7 %) loss of vision (16.7 %), and their combination (33.3%). The patients were found to be hypovolemic on physical examination. 83.3% of the patients underwent hemodialysis. All of the patients who received hemodialysis underwent hemodialysis at the time of admission to the hospital. All of these patients had bicarbonate below 10 meq/L and had severe metabolic acidosis. IV ethanol was administered in 88.8% of patients. Ethanol (10% solution) infusion was given at a load-ing dose of 7.5-8.0 mL/kg for over 1 hour; followed by infusion of 1.0-2.0 mL/kg during follow-up or 2.5-3.0 mL/kg during HD. The ethanol infusion was set to maintain a serum ethanol level above 100 mg/dL. No patient received oral ethanol therapy. 44.4% of the patients were intubated. Hospitalization duration was 5.72±4.61 days. 38.9% of patients died (**Table 1**). Demographic characteristics and laboratory data of each patient were shown in **Table 2**.

The patients were divided into two groups as survivor and non-survivor. In the non-survivor group, the rates of AKI development and intubation, and the delay in admission to the hospital were higher. In addition, pH and Glasgow coma scale scores were lower, and PCO_2, lactate and creatinine values were higher in the non-survivor group (**Table 3**). In binary logistic regression analyses, delay in admission to hospital (OR:1.11, 95%CI: 1.008-1.224, P:0.035), low Glasgow coma scale score (OR:0.638, 95%CI: 0.432-0.943, P:0.024), AKI development (OR:0.037, 95%CI:0.03-0.505, P:0.013) and high lactate level (OR:2.11, 95%CI:1.094-4.073, P:0.026) were independent predictors of mortality

Table 1. Patients' clinical and demographic features and laboratory data

Gender (Male)(%)	%72.2
Age (years)	45.7±15.21
Complaints(%)	
Loss of consciousness	%33.3
Nausea-vomiting	%16.7
Loss of vision	%16.7
Both loss of vision and vomiting	%33.3
Chronic alcohol users(%)	%94.4
Alcohol type(%)	
Handmade	%94.4
Commercial	%5.6
Time from alcohol exposure to admission to hospital (hour)	39.3±14.7
Hospital Interventions (%)	
iv. hydration	%100
iv. etanol	%88.8
Hemodialysis	%83.3
Intubation	%44.4
AKI development (%)	%44.4
Hospitalization duration (day)	5.72±4.61
GCSS	10.9±3.9
Mortality rate (%)	%38.9
At admission blood pH	7.02±0.21
At admission PCO_2 (mmHg)	32.55±17.96
At admission bicarbonate (mmol/L)	7.98±4.78
At admission lactate (mmol/L)	6.23±4.6
At admission creatinine (mg/dL)	1.16±0.42
At admission urea (mg/dL)	27.16±14.05
At admission sodium (mmol/L)	137.6±4.34
At admission potassium (mmol/L)	5.05±0.87
At admission chlorine (mmol/L)	102.05±4.03
At admission albumin (g/dL)	4.68±0.37
At admission WBC (10^6/L)	17622±5868
At admission hemoglobin (g/dL)	15.77±1.88
At admission platelets (10^6/L)	288064±124080
At admission Glasgow coma scale score	10.94±3.93
At admission anion gap	29.86±5.57
Basal creatinine (mg/dL)	1.11±1.22

AKI: Acute kidney injury, GCS: Glasgow coma scale score

Table 2. Demographic and laboratory data of each patient

No	Gender	Age	Outcome	Complaints	Hospital Interventions	Time*	AKI	Time**	ph	PCO_2	HCO3	Lactate	Anion Gap	Creatinine admission	Basal creatinine	GCS
1	F	42	R	Loss of vision, Nausea,vomiting	Hydration, HD	24	-	12.00	7.06	15.20	4.10	3.90	33.10	.92	.90	13
2	M	46	D	Loss of vision, Nausea,vomiting	Hydration, HD Intubation	48	+	9.00	6.94	69.00	3.90	8.20	38.10	1.10	.70	14
3	M	33	R	Loss of vision, Nausea,vomiting	Hydration, HD iv.Ethanol	24	-	4.00	7.13	17.20	5.50	2.40	32.30	1.01	.95	13
4	M	43	R	Loss of vision, Nausea,vomiting	Hydration, HD iv.Ethanol	24	+	4.00	7.18	17.20	6.20	6.20	34.60	1.18	.73	14
5	M	47	R	Nausea,vomiting	Hydration	24	-	1.00	7.23	34.00	17.00	1.90	28.10	.87	.91	13
6	M	19	R	Nausea,vomiting	Hydration	24	-	1.00	7.25	18.80	18.00	1.70	20.00	.90	.94	14
7	M	39	R	Nausea,vomiting	Hydration	24	-	1.00	7.25	33.90	18.10	2.20	23.30	.88	.89	13
8	F	23	R	Loss of vision, Nausea,vomiting	Hydration, HD iv.Ethanol	24	-	4.00	7.13	15.00	5.20	1.30	29.00	.72	.85	14
9	F	41	D	Loss of consciousness	Hydration, HD iv.Ethanol, Intubation	48	+	1.00	6.58	53.40	4.70	14.00	37.40	1.80	.90	8
10	F	33	D	Loss of vision, Nausea,vomiting	Hydration, HD iv.Ethanol, Intubation	24	+	13.00	6.71	48.20	5.70	11.80	38.30	1.36	.80	13
11	F	38	R	Loss of consciousness	Hydration, HD iv.Ethanol, Intubation	48	+	14.00	6.95	24.10	5.10	4.00	34.70	.90	.53	7
12	M	68	D	Loss of consciousness	Hydration, HD iv.Ethanol, Intubation	60	+	1.00	7.00	62.30	11.00	10.00	27.00	1.04	6.00	7
13	M	60	D	Loss of consciousness	Hydration, HD iv.Ethanol, Intubation	60	+	4.00	6.95	29.50	6.70	5.30	24.30	1.17	.60	7
14	M	71	R	Loss of vision	Hydration, HD iv.Ethanol	48	-	10.00	7.19	22.40	8.30	1.70	22.70	.82	.92	14
15	M	39	D	Loss of consciousness	Hydration,HD iv.Ethanol, Intubation	48	+	4.00	6.72	29.00	4.50	11.50	32.50	1.58	.82	3
16	M	58	R	Loss of vision	Hydration, HD iv.Ethanol	48	-	4.00	7.25	15.40	7.30	8.60	26.70	.85	.88	13
17	M	42	D	Loss of consciousness	Hydration, HD iv.Ethanol, Intubation	60	+	12.00	6.71	59.40	5.00	15.00	30.00	1.36	.79	3
18	M	71	R	Loss of vision	Hydration, HD iv.Ethanol	48	+	4.00	7.16	22.00	7.50	2.60	25.50	2.42	.93	14.

F: Female, M:Male, R:Recovery, D:Death, HD: Hemodialysis, Time* (day): Time from alcohol exposure to admission to hospital, AKI: Acute kidney injury Time** (hour): Time from the moment of admission to the hospital until leaving the hospital, GCS: Glasgow coma scale score

Table 3. The comparison of demographic and laboratory data between survivor and non-survivor group

	Survivor group (n:11)	Non-survivor group (n:7)	p
Gender (female) (%)	27.3	28.6	0.676
Age (year)	42 (25)	42 (21)	0.791
Chronic alcohol users (%)	100	85.7	0.389
Alcohol type (Handmade) (%)	90.9	100	0.611
AKI (%)	27.3	100	0.004
Hemodialysis (%)	72.7	100	0.202
Intubation (%)	9.1	100	<0.001
Time* (hour)	24 (24)	48 (12)	0.002
Blood ph	7.18 (0.12)	6.72 (0.24)	<0.001
Bicarbonate (mmol/L)	7.3 (11.8)	5 (2.2)	0.104
Anion gap	28.1 (9.8)	32.5 (11.1)	0.126
PCO_2 (mmHg)	18.8 (8.7)	53.4 (32.8)	<0.001
Lactate (mmol/L)	2.4 (2.3)	11.5 (5.8)	<0.001
Creatinine (mg/dL)	0.9 (0.16)	1.36 (0.48)	0.008
Basal Creatinine (mg/dL)	09 (0.08)	0.8 (0.2)	0.211
WBC (10^6/L)	9260 (7220)	19090 (9970)	0.008
Hemoglobin (g/dL)	14.3 (1.9)	17.4 (3.7)	0.049
Hospitalization duration (day)	4 (9)	4 (11)	0.791
GCSS	13 (1)	7 (10)	0.027

Time* Time from alcohol exposure to admission to hospital, AKI: Acute kidney injury, WBC: White blood cell, GCS Glasgow coma scale score

Table 4. Binary logistic regression analysis of risk factors affecting mortality

Parameters	β	OR	95% CI	P
Gender	0.065	1.067	0.129-8.793	0.952
Age	0.010	1.010	0.947-1.077	0.770
Complaint	-2.303	0.1	0.006-1.544	0.09
Time*	0.105	1.111	1.008-1.224	0.035
AKI development	-3.296	0.037	0.003-0.505	0.013
Hospitalization time	0.046	1.047	0.848-1.292	0.671
Glasgow coma scale score	-0.449	0.638	0.432-0.943	0.024
Blood pH	-28.45	0.00	0.00-1740	0.120
Bicarbonate	-0.124	0.807	0.560-1.163	0.251
PCO_2	0.216	1.241	0.986-1.562	0.06
Lactate	0.747	2.111	1.094-4.073	0.026
WBC	0.001	1	1-1	0.051
Hemoglobin	0.596	1.815	0.956-3.446	0.069
Platelets	0.001	1	1-1	0.086

* time from alcohol exposure to admission to hospital, WBC: White blood cell

(**Table 4**). The Kaplan-Meier analyses disclosed that AKI patients suffered lower cumulative survival than non-AKI patients (**Figure 1**). In ROC analyses it was found that mortality increased significantly when lactate level exceeded 5,75mmol/L (**Figure 2**). Regression analyses revealed that intubation (OR:12, 95 CI%:1.294-111.32, P:0,029), high lactate (OR:1,445, 95%CI:1.045-1.998, P:0,026) and hemoglobin levels (OR:2,527,95%CI:1.108-5.766, P:0,028) were independent risk factors for the development of AKI, (**Table 5**). According to ROC analyses if hemoglobin and lactate levels were more than 15,6g/dL and 5,75mmol/L, respectively AKI developed more rapidly (**Figure 3,4**).

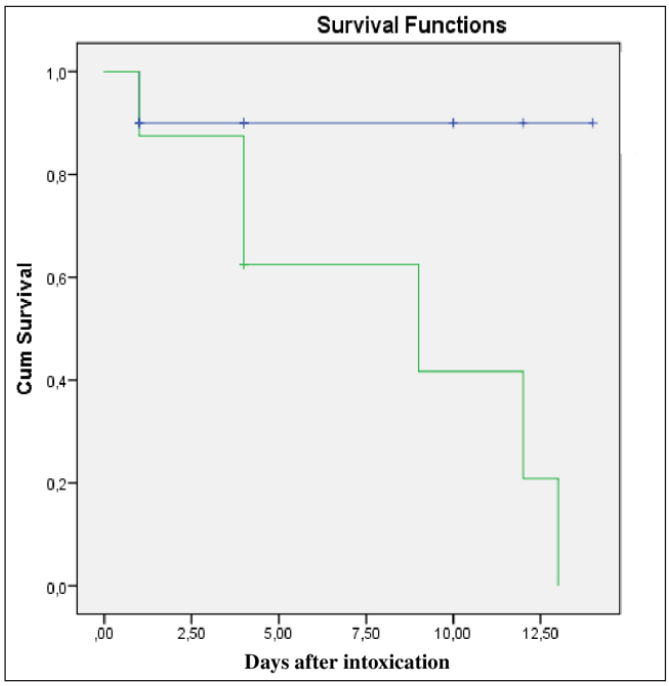

Figure 1. Kaplan-Meier analysis. Acute kidney injury patients (green line) suffered from lower cumulative survival than non-acute kidney injury patients (blue line) (log rank test, chi-square:3.845 p:0.048)

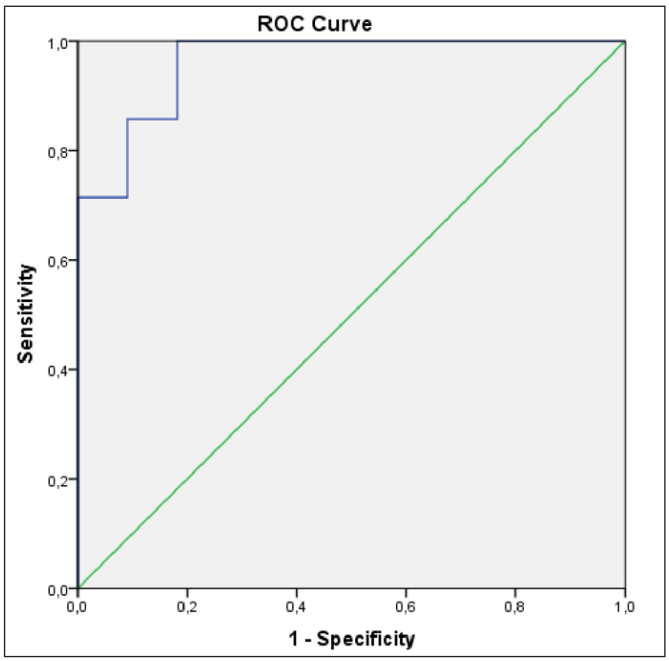

Figure 2. ROC (Receiver operating characteristic) curve analysis of lactate level affecting mortality in patients with methanol intoxication. Area under the ROC curve:0,961, %95CI (Confidence interval):0,881-1, P:0,001 sensitivity:81.8%, specifity:85.7%)

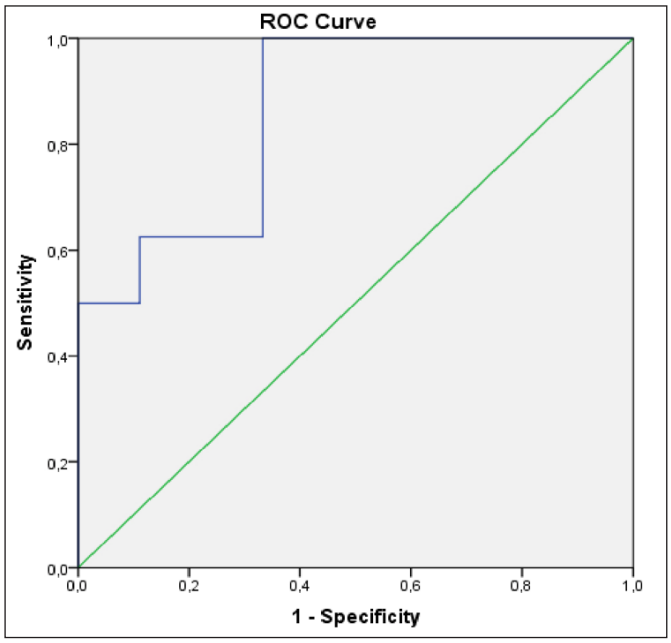

Figure 3. ROC (Receiver operating characteristic) curve analysis of hemoglobin level affecting acute kidney injury development in patients with methanol intoxication. Area under the ROC curve:0,861, %95 CI (Confidence interval):0,684-1,P:0,012 sensitivity:66.6%, specifity:62.5%

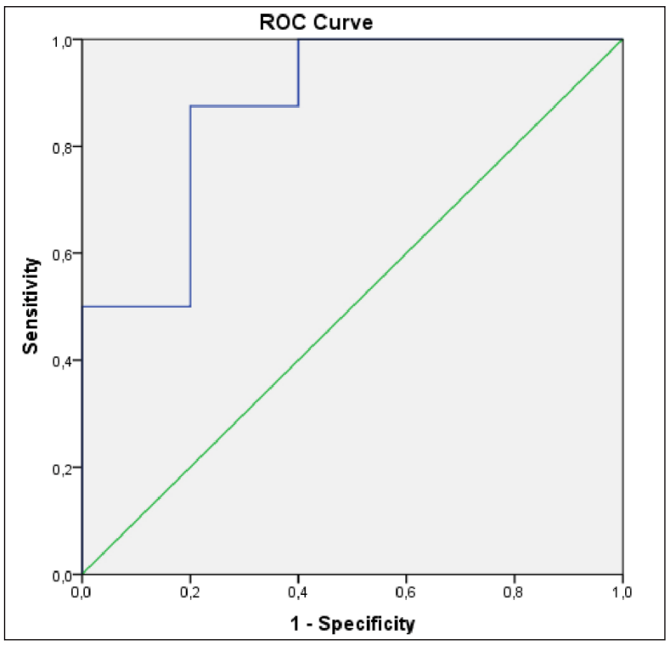

Figure 4. ROC (Receiver operating characteristic) curve analysis of lactate level affecting acute kidney injury development in patients with methanol intoxication. Area under the ROC curve:0,875, %95 CI(Confidence interval):0,713-1, P:0,008 sensitivity:80%, specifity:75%)

DISCUSSION

There is a latent period in methanol intoxication until the formation of metabolites and the manifestation of their toxic effects. The amount of methanol taken, the route of intake, and whether or not ethanol is taken

concomitantly causes this period to extend from 12 to 72 hours (1). In the current study, patients were admitted to the hospital after a mean of 39 hours due to nausea, vomiting, or loss of vision. Six patients were brought to the hospital with loss of consciousness. Since these patients had severe metabolic acidosis, they were immediately underwent hemodialysis. Hemodialysis is a method that enables the rapid removal of both methanol and its metabolites from the body. In a study by Lachance et al. (2), using the formula of 3.390 x (Ln(initial methanol concentration(MCI)/4)) for women and 3.534 x (Ln (MCI/4)) for men, the safe level of 4 mmol/L methanol was found to be achieved in 141 minutes and 147 minutes in women and men, respectively. Since methanol levels could not be monitored in our hospital, a standard 240-minutes hemodialysis program was applied to the patients. In the blood tests taken after hemodialysis, the metabolic picture was observed to be recovered.

Another treatment method in methanol intoxication is the intravenous application of fomepizole or ethanol; both of which inhibit the alcohol dehydrogenase enzyme and prevent the formation of its metabolites (1). The enzyme affinity of fomepizole is 500-1000 times higher than ethanol. However, it is considered an expensive treatment, and ethanol is also known to have 10 times more enzyme affinity than methanol. Since there was no fomepizole in our hospital, intravenous ethanol was applied.

In methanol intoxication, the mortality rates are quite high if the patients are not intervened early. In a case series, the mortality was observed to range from 0 to 48% (3-17). In the current study, the mortality rate was determined as 38.9 % and it was observed that delay in admission to hospital, lower Glasgow coma scale score, high lactate level, and AKI development were independent predictors of mortality. Similar to our study, Chang et al. (17), reported that a significant relationship was found between mortality and AKI in patients with methanol intoxication. In the comparison of the two groups with and without AKI, it was emphasized that mortality and intubation rates were high in the AKI group. In this study, where it was stated that the patients did not have hemoglobinuria or myohlobinuria, it was stated that intubation may play a role in the development of AKI by triggering the release of cytokines (17). There have been publications suggesting that cytokines released during intubation affect kidney function (18,19). In various past studies, AKI rate was shown to range from 15.4 to 66% (17,20,21). In current study, we found that 44.4% of patients developed AKI and a significant relationship between AKI development and intubation, high lactate and hemoglobin levels. The high hemoglobin level was interpreted as an indicator of the volume deficiency caused by vomiting of the patients. When lactate level exceeded 5,75 mmol/L, both AKI and mortality rates increased rapidly. In methanol intoxication, methanol metabolites may have a direct effect on the tubule in the development of AKI, and they may also damage the kidney by triggering hemoglobinuria and myoglobinuria. In a study by Velvet et al. (21) hydropic changes in the proximal tubule were demonstrated in kidney biopsies of patients who died due to methanol intoxication. In addition, in this study, hemoglobinuria and myoglobinuria were detected in the patients living and it was stated that this may play a role in the development of AKI.

CONCLUSION

Delay in admission to hospital, lower Glasgow coma scale score, high lactate level, and AKI development were independent predictors of mortality. Intubation, high lactate, and hemoglobin levels were risk factors of AKI development. Therefore, patients should be recognized early and aggressively treated to avoid mortality. Nevertheless, the retrospective nature of the study, small sample size, and absence of urine output, urinalysis, creatinine kinase and methanol measurements limit the certainty of our conclusions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Clinical Resarches Ethics Committee of the Ankara Training and Research Hospital (Date: 17.09.2020, Decision No: 14.08.2020/E-20/393).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: All authors declare no conflict of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1118677
J Health Sci Med 2022; 5(4): 1145-1150

The relationship between colorectal cancer and gastric histopathology: case-control study

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Cite this article as: Yalınbaş Kaya B, Tuğrul F. The relationship between colorectal cancer and gastric histopathology: case-control study. J Health Sci Med 2022; 5(4): 1145-1150.

ABSTRACT

Aim: The aim of this study was to investigate the gastric histopathological findings (*Helicobacter pylori* (*H. pylori*), intestinal metaplasia (IM), atrophic gastritis (AG), and dysplasia) in the patients with and without colorectal cancer (CRC).

Material and Method: Two hundred ninety five patients (160 CRC patients and 135 control individuals) were included in the study. Gastric histopathological findings of the patients who underwent upper gastrointestinal (GI) endoscopy were analyzed retrospectively.

Results: *H. pylori* positivity and IM rates in the CRC patient group were significantly higher than the control group (58.8%&27.8% and 33.1%&19.5%, p<0.001 and p<0.012, respectively). In addition, AG, lymphoplasmocytic infiltration, and dysplasia rates were also higher in the CRC patients compared to the control group. But, they were not statistically significant (p=0.462, p=0.103, and p=0.195, respectively).

Conclusion: In our study, the frequency of *H. pylori* and IM in patients with CRC was higher than in the control group. Since the prevalence of *H. pylori* infection is high in Turkey and *H. pylori*-related gastric diseases may be potential risk factors for colorectal neoplasia, it is recommended that individuals in the high-risk group to be screened for colonoscopy. Also, upper GI endoscopic examination should be performed to screen for gastric premaling lesions in patients with CRC.

Keywords: *Helicobacter pylori*, colorectal cancer, intestinal metaplasia

INTRODUCTION

Colorectal cancer (CRC) has a prevalence of 4-5% worldwide and is the leading cause of cancer related deaths. Many factors cause the development of carcinogenesis in the colon(1). Diet, obesity, lack of physical activity, tobacco and alcohol use, age, familial history of colorectal polyp or CRC, Lynch syndrome, inflammatory bowel disease, type 2 diabetes, cholecystectomy, exposure of abdominal radiation, older age are risk factors (2-4). The loss of genomic and epigenomic stability leads to the accumulation of mutations that occurs in oncogenes, tumor suppressor genes, and genes related to DNA repair mechanisms, and may lead to the development of CRC. As a result of mutations, CRC is classified as sporadic, hereditary, and familial. Studies have shown that the gut microbiota induces the formation of reactive metabolites and carcinogens. This may induce the formation of colorectal malignancy by causing changes in carbohydrate expression and chronic mucosal inflammation (5).

Helicobacter pylori (*H. pylori*) is a spiral-shaped, microaerophilic, gram-negative bacterium that infects more than half of the world's population (6,7). Its prevalence in the adult population in Turkey is 82.5% and varies according to age, gender and educational status (8). *H. pylori* is the most common chronic bacterial infection in humans and causes chronic gastritis, atrophic gastritis, intestinal metaplasia, dysplasia, and invasive gastric cancer (6-8). Many studies have proven that AG and IM are precancerous lesions of gastric cancer. More than 90% of gastric cancer patients have been or are still infected with *H. pylori* (7,9).

H. pylori may cause hypergastrinemia, hypochlorhydria and damage to the colorectal epithelium via IL-8. It is thought that hypergastrinemia is associated with cell proliferation in the rectum and may stimulate colon adenoma and the development of the adenoma-cancer sequence (10,11). In our study, we aimed to investigate

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Received: 19.05.2022 **Accepted:** 26.06.2022

the relationship between histopathologies (*H. pylori* gastritis, IM, AG, dysplasia), which are risk factors for gastric cancer, and colorectal cancer.

MATERIAL AND METHOD

The study was approved by the Non-interventional Clinical Resarches Ethics Committee of the Eskişehir Osmangazi University (Date: 23.02.2022, Decision No: 2021-320). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Our study included 295 patients who have been followed between years 2018 and 2021. The data of 160 patients who were diagnosed with colorectal cancer radiologically, histologically and endoscopically and who underwent upper gastrointestinal endoscopy (GIS) were analyzed retrospectively. The control group consisted of 135 individuals without malignancy in endoscopy and colonoscopy. Colorectal cancer localization (cecum, ascending colon, hepatic flexure, transverse colon, descending colon, splenic flexure, sigmoid colon and rectum), histology and staging were performed. Tumor staging of CRCs were performed using the TNM classification established and updated by the American Cancer Committee (AJCC) and the International Association for Cancer Control (UICC). Demographic and laboratory data of the patients and control groups included age, gender, co-morbid diseases, glucose, ferritin, vitamin B12, carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA 19-9), alpha-fetoprotein(AFP), carcinoma antigen 15-3 (CA 15-3). Upper GI endoscopy histopathological data were analyzed for *H. pylori*, intestinal metaplasia, dysplasia, lymphoplasmocytic infiltration, and atrophy. Multiple biopsies were taken from the antrum, incisura angularis, and/or corpus. IM with Alcian blue+PAS mixed and *H. pylori* positivity with Giemsa were detected. All individuals included in the study were divided into Hp(+) Hp(-) group, AG(+) AG(-) group, IM(+) IM(-) group, dysplasia(+) dysplasia(-) group, lymphoplasmacytic infiltration(+) lymphoplasmacytic infiltration(-) group.

Statistical Analysis

The data were evaluated using SPSS 24 program. First of all, the suitability of the quantitative data to the normal distribution was tested with the Kolmogorov - Smirnov test. For the analysis, Mann Whitney U test was used for non-normally distributed data and t-test was used for normally distributed data. In statistical analysis, $p<0.05$ values were considered significant. Chi-square analysis was performed for categorical data. For cases where the expected frequency is less than 5, P values were calculated with the Fisher Exact test. The results were interpreted according to these test results.

RESULTS

Demographic and clinicopathological features of CRC patients and control subjects are shown in (**Table 1**). The mean age of 160 colorectal cancer patients and control groups was 64.4±10.31 and 60.48±10.66, respectively. In CRC patients, tumor localization was most common in rectosigmoid colon 99(55.6%)(sigmoid colon 27.5%; rectum 28.1%) ($p<0.001$). There was no statistical significance between glucose, AFP, CEA and CA 15-3 in laboratory results of CRC patients and control group, but a significant difference was determined for CA 19-9.

Table 1. Demographic and clinicopathological features

	Colorectal cancer group	Control group	P value
Age (year, mean ±SD)	64.4± 10.31	60.48± 10.66	<0.002
Sex			<0.001
Females	61 (38.1%)	82 (61.7%)	
Males	99 (61.9%)	51 (38.3%)	
Tumor localization (%)			<0.001
1. Cecum	25 (15.6%)		
2.Ascending colon	25 (15.6%)		
3.Transverse colon	9 (5.6%)		
4.Descending colon	12 (7.5%)		
5.Colon	44 (27.5%)		
6. Rectum	45 (28.1%)		
łTNM Stage			<0.001
Stage 1	40 (25.0%)		
Stage 2	56 (35..0%)		
Stage 3	26 (16.3%)		
Stage 4	36 (22.5%)		
Differentiation(%)			
Well	41 (13.9%)		
Moderate	95 (32.3%)		
Poor	22 (7.5%)		
*Laboratory Data			
Glucose (mg/dl)	119.63±39.71	115.77 ±36.11	0.313
ǂAFP (ng/ml))	337.67±1056.37	237.47±278.02	0.525
ǂCEA (ng/mL)	430±1320.10	356.65 ±601.80	0.170
ǂCA 19-9 (U/mL)	466.17±1372.21	1398±2718.06	<0.004
ǂCA 15-3 (U/ml)	16.06±10.43	34.27±68.81	0.271
Vitamin B12 (pg/ml)	280.72±173.05	440.89±374.65	<0.001
Ferritin(ng/ml)	219.77±617.80	121.53±561.03	<0.001
The site of the biopsy in the stomach			
1.Antrum	150 (93.8)	98 (73.7)	<0.001
2.Antrum-corpus	10 (6.3)	35 (26.3)	
Co-morbid diseases			0.966
Hypertension	13 (19.4%)	5 (20%)	
Diabetes mellitus	18 (26.9%)	5 (20%)	
Ischemic heart disease	3 (4.5%)	1 (4.0%)	
Other	3 (4.5%)	1 (4.0%)	
No disease	30 (44.8%)	13 (52%)	

* (Mean ±SD)
ǂ Alpha-fetoprotein(AFP); Carcinoembryonic antigen (CEA); Carbohydrate antigen 19-9(CA 19-9); Carcinoma antigen 15-3 (CA 15-3)
Ł Stage 1(T1-2,N0,M0), Stage 2(T3-4,N0,M0), Stage 3(T1-4,N1-2,M0), Stage 4(T1-4,N1-2,M1)

H. pylori positivity in the CRC patient group was higher compared to the control group (94 (58.8%), 37 (27.8%), p<0.001). CRC in intestinal metaplasia was higher and statistically significant in patients compared to the control group (53(33.1%), 26(19.5%), p<0.012). Although atrophy, lymphoplasmocytic infiltration and dysplasia were higher in gastric biopsy histopathologies of CRC patients compared to the control group, they were not statistically significant (p=0.462, p=0.103, p=0.195) (**Table 2**).

Table 2. Gastric histopathology in patients with colon cancer and control group

	Colorectal Cancer Group	Control Group	P value
H. pylori			<0.001
No	66 (41.3%)	96 (72.2%)	
Yes	94 (58.8%)	37 (27.8%)	
Intestinal metaplasia			<0.012
No	107 (66.9%)	107 (80.5%)	
Yes	53 (33.1%)	26 (19.5%)	
Atrophy			0.462
No	155 (96.9%)	131 (98.5%)	
Yes	5 (3.1%)	2(1.5%)	
Lymphoplasmocytic infiltration			0.103
No	123 (76.9%)	113(85.0%)	
Yes	37 (23.1%)	20 (15.0%)	
Dysplasia			0.195
No	150 (93.8%)	131 (97.0%)	
Yes	10 (6.3%)	4 (2.96%)	

There was no significant age difference between *H. pylori* positive and *H. pylori* negative groups in CRC patients. *H. pylori* positivity was significantly higher in male CRC patients(64(68.8%), p<0.046). *H. pylori* positivity in CRC patients was higher in Stage 2,3,4 group according to TNM staging, but it was not statistically significant (p=0.080). According to tumor localization, *H. pylori* was positive at a higher rate in tumors located in the left colon and rectum, but it was not statistically significant (p=0.489).

H. pylori positivity was higher in the moderately differentiated group than in the mildly and poorly differentiated group (55(59.1%)), 25(26.9%), 13(14%), but it was not statistically significant (p=0.945)(**Table 3**). Those with intestinal metaplasia in CRC patients were higher in TNM Stage 2 and moderately differentiated groups, but it was not statistically significant (p=0.413, p=0.399). Cancer localization, age and gender groups were not significant in CRC patients with intestinal metaplasia (p=0.335, p=0.432, p=0.825) (**Table 4**).

Table 3. Association with *H. pylori* tumor characteristics in patients with colorectal cancer

	Colorectal cancer *H. pylori* negative	Colorectal cancer *H. pylori* positive	P value
*TNM Stage			0.080
Stage 1	23 (35.4%)	17 (18.3%)	
Stage 2	18 (27.7%)	38 (40.9%)	
Stage 3	9 (13.8%)	17 (18.3%)	
Stage 4	15(23.1%)	21 (22.6%)	
Differentiation			0.945
Well	16 (24.6%)	25 (26.9%)	
Moderate	40 (61.5%)	55 (59.1%)	
Poor	9 (13.8%)	13 (14%)	
**Tumor localization			0.489
1. Right colon	24 (36.9%)	26 (28.0%)	
2. Left colon	23 (35.4%)	37 (39.8%)	
3. Rectum	18 (27.7%)	30 (32.3%)	
Sex			0.046
Females	31 (47.7%)	29 (31.2%)	
Males	34 (52.3%)	64 (68.8%)	
Age(year, mean ±SD)	64.35±11.40	64.25±9.49	0.738

*Stage 1(T1-2,N0,M0), Stage 2(T3-4,N0,M0), Stage 3(T1-4,N1-2,M0), Stage 4(T1-4,N1-2,M1), ** Right colon (cecum, ascending colon,transverse colon proximal), Left colon (transverse colon distal,descending colon, sigmoid colon)

Table 4. The relationship of intestinal metaplasia with tumor characteristics in patients with colorectal cancer.

	Colorectal cancer intestinal metaplasia No	Colorectal cancer intestinal metaplasia Yes	p value
TNM Stage			0.413
Stage 1	31 (29.2)	9 (17.3)	
Stage 2	35 (33.0)	21 (40.4)	
Stage 3	16 (15.1)	10 (19.2)	
Stage 4	24 (22.6)	12 (23.1)	
Differentiation			0.399
Well	28 (26.4%)	13 (25.0%)	
Moderate	66 (62.3%)	29 (55.8%)	
Poor	12 (11.3%)	10 (19.2%)	
Tumor localization			0.335
1. Right colon	33 (31.1%)	17 (32.7%)	
2. Left colon	37 (34.9%)	23 (44.2%)	
3. Rectum	36 (34.0%)	12 (23.1%)	
Sex			0.432
Females	38 (35.8%)	22 (42.3%)	
Males	68 (64.2%)	30 (57.7%)	
Age (year, mean ±SD)	64.16±10.55	64.55±9.82	0.825

Hp(-) İM(+) group was significantly higher in the control group than in the CRC patient group (79(59.4%), p< 0.001). Hp(+) IM(-) group and Hp(+) IM(+) group were higher and statistically significant in CRC patients compared to the control group (p< 0.001)(**Table 5**).

Table 5. Comparison of *H. pylori* and intestinal metaplasia in patient and control groups

	Colorectal cancer group	Control group	P value
Hp-, İM-	46 (28.7%)	79 (59.4%)	<0.001
Hp+,İM-	61 (38.1%)	28 (21.1%)	
Hp-,İM+	20 (12.5%)	18 (13.5%)	
Hp+,İM+	33 (20.6%)	8 (6.0%)	

DISCUSSION

Many factors affect the process of colonic carcinogenesis. In our study, we investigated the relationship between the gastritis-atrophy-metaplasia-dysplasia-cancer process triggered by *H. pylori* in the gastric mucosa and colon cancer patients. *H. pylori* infection is the type 1 carcinogen and is considered as an important cause of gastric cancer. In our study, the prevalence of *H. pylori* was higher in patients with colorectal cancer compared to the control group (58.8%, 27.8%, p<0.001). Wu Q, et al. (14), Hong SN, et al. (15), Zuo Y. et al. (16) in their meta-analysis of different subgroup populations, including Asian, American, and European populations, and Choi DS, et al. (17) in their meta-analysis of 48 studies including 171,045 patients showed positive correlations in HP infection and CRC risk. Mechanisms that may cause *H. pylori* colorectal cancer development are hypergastrinemia, CagA-positive *H. pylori*, systemic inflammatory response triggered by chronic inflammation induced by *H. pylori*, the effects of chronic *H. pylori* infection and proton pump inhibitor use on gut microbiota. In CRC carcinogenesis, hypergastrinemia due to *H. pylori* causes cell proliferation (18-20). There are studies showing that gastrin and cholecystokinin type B/gastrin receptor (CCKBR) are expressed in colorectal adenocarcinoma and colon polyps (12,20). *H. pylori* was not detected in CRC cancerous tissue in many studies. However, Grahn N, et al. (21) detected *H. pylori* DNA in 27% of cancerous tissue histopathology of patients with CRC (21,22,27). As a result of colonization of Helicobacter organisms in the intestine, *H. pylori* may have a direct carcinogenic effect. Although Fujimori S, et al. (23) showed that *H. pylori* infection induces a significantly higher risk in female patients with CRC in the Japanese population in their study, *H. pylori* positivity was significantly higher in male CRC patients in our study (64 (68.8%), p< 0.046). In the meta-analysis of De Martel C, et al. (24) they investigated the relationship between *H. pylori* infection and gender, and in the study of Wang C, et al. (25) in a large population, *H. pylori* positivity was high in male individuals. In this study, *H. pylori* was at a higher frequency in male patients and was consistent with the literature. In our study, according to tumor localization, *H. pylori* was positive at a higher rate in tumors located in the left colon and rectum, but it was not statistically significant (p=0.489). Although Wang C, et al. (25) found the risk of CRC associated with *H. pylori* infection to be high in the left colon and rectum, Fujimori S, et al. (23), Sonnenberg A, et al. (26) and a few studies found no differences in location (26-28). There was no significant relationship between *H. pylori* positivity, CRC differentiation (poor, moderate, well) and TNM stages.

AG is characterized by chronic inflammation of the gastric mucosa with loss of gastric glandular cells and their replacement by intestinal type epithelium, pyloric type glands and fibrous tissue. The relationship of gastric precancerous lesions (chronic atrophic gastritis, gastric intestinal metaplasia, dysplasia) with the risk of colon carcinogenesis is unknown(29-31). Hypochlorhydria that develops after AG controls not only the colonization and growth of oropharyngeal bacteria, but also changes in the distal intestinal microflora, leading to a significant increase in intestinal bacteria, including Bacteroides fragilis and E. feacalis group (32,33). Strains of the enterotoxigenic Bacteroides fragilis (ETBF) bft gene have been shown to contribute to colon carcinogenesis. In the studies of Wang C, et al. (25) and Lee JY, et al. (34) it increased the risk of CRC when *H. pylori* infection and AG were positive together. In the Montani A. et al. (31) study, although chronic *H. pylori* infection and atrophic gastritis might increase the risk of rectal cancer, they did not increase the risk of CRC. In our study (5 (3.1%), p=0.462) and in the studies of Laiyemo AO, et al. (29) and Lahner E, et al. (36), atrophic gastritis was not found to be associated with the risk of colorectal cancer (35).

IM is the advanced stage of atrophy. It is defined as the replacement of surface in the oxyntic or antral mucosa, foveolar and glandular epithelium with intestinal epithelium. IM has been classified into two types: the small bowel or complete type and the colonic or incomplete type. The development of IM is a long process and the most important risk factor for its development is *H. pylori* infection (6,38). IM causes decreased gastric acid secretion and this causes hypergastrinemia. Hypochlorhydria caused by *H. pylori* positive IM results in bacterial overgrowth and impaired protein absorption. Impairment of protein absorption causes the release of some metabolites (eg H2S, phenols, NH3) arising out of bacterial fermentation of proteins. These metabolites are accepted as risk factors in the development of colon cancer(38,39). In our study, while IM was 53 (33.1%) in the CRC group, it was 26 (19.5%) in the control group and it was statistically significant (p<0.012) (**Table 2**). IM associated with *H. pylori* was higher in the patient group than in the control group (33 (20.6%); 8(6.0%)) (**Table 5**). In the *H. pylori* negative IM group, there was no difference between the patient

and control groups (20 (12.5%); 18(13.5%) (**Table 5**). In several studies including this study, the risk of colorectal carcinogenesis was increased in individuals with IM in gastric histopathology. However, only a few studies and small sample sizes are insufficient to determine the risk of colorectal neoplasia (13,26,40).

Our study has several limitations. First, the serum gastrin level, which is thought to be important in the progression of colorectal carcinogenesis, was not included in our analysis. Second, study data were obtained from two centers but one region. The strengths of our study are that the individuals included in the study (CRC group and control group) were patients who had both endoscopy and colonoscopy scans, *H. pylori* was detected through multiple gastric biopsies, and it was case-controlled.

CONCLUSION

Our study showed that the frequency of *H. pylori* and IM is higher in patients with CRC than in the control group. The relationship between the risk of colon neoplasia and premaling gastric lesions due to *H. pylori* is still unknown, and the results of the few studies on this subject are inconsistent. Because of the high prevalence of *H. pylori* infection in Turkey and because *H. pylori*-related gastric diseases may be potential risk factors for colorectal neoplasia, it is recommended that people in high-risk groups to be screened for colonoscopy. Also, upper GI endoscopic examination should be performed to screen for gastric premaling lesions in patients with CRC. However, multicenter studies in the Turkish population are needed to clarify further this relationship and to understand the underlying pathophysiological mechanism.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Non-interventional Clinical Resarches Ethics Committee of the Eskişehir Osmangazi University (Date: 23.02.2022, Decision No: 2021-320).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1100231
J Health Sci Med 2022; 5(4): 1151-1155

The comparison of chest X-ray and CT visibility according to size and lesion types in the patients with COVID-19

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Cite this article as: Doğan E, Gürsoy C, Oral Tapan Ö, Elibol C, Togan T, Demirbilek S. The comparison of chest X-ray and CT visibility according to size and lesion types in the patients with COVID-19. J Health Sci Med 2022; 5(4): 1151-1155.

ABSTRACT

Introduction: Chest X-ray (CXR) is one of the routinely used radiological examinations in COVID-19. However, the lesion detectability level of CXR is low. To date, to the best of our knowledge, the visualization quality of X-ray in COVID-19 has not been specifically evaluated in different lesions. Our study aims to determine the visualization quality of CXR in COVID-19 patients according to elementary lesions.

Material and Method: 52 COVID-positive patients (26 Males and 26 Females); 69,6346±15,14250 (32-89) years [mean±SD age (range)] were included in the study. 98 different elementary lesions of lung detected on CT were evaluated in six different groups (consolidation, indeterminate ground-glass opacity (IGGO), dense GGO (DGGO), reversed halo, parenchymal band and curvilinear band). Lesions were compared with CXR taken on the same day. The detectability rates of the lesions on CXR were evaluated.

Results: The mean sizes of CXR negative and CXR positive lesions for every group (consolidations, IGGO, DGGO, reversed halo sign, parenchymal band, curvilinear band) were respectively 1.36 cm -5.75 cm, 3.44 cm -5.50 cm, 2.25 cm -5.06 cm, 2.5cm -4.09 cm, N/A -3.14 cm and 1 cm -4.5 cm. According to Mann-Whitney U analysis, p values were found as (respectively in consolidations, IGGO, DGGO, reversed halo sign, and curvilinear band) 0.0001p, 0.145, 0.0001 p, 0.143 and 0.286. Given consolidation and DGGO groups, there was a statistically significant difference between non-visualized and visualized groups. According to ROC analysis, cut-off values were respectively 3 cm and 3.5 cm for consolidation and DGGO.

Conclusion: Our study showed that consolidations smaller than 3 cm and DGGO smaller than 3.5 cm are difficult to visualize with CXR. Although there is no definite cut-off value in other elementary lesions, the visualization ratio of parenchymal bands and curvilinear bants on chest X-rays is quite high. IGGOs may not be detected even at higher dimensions. Reversed halos less than 3 cm can rarely be detected on CXR.

Keywords: COVID-19, Chest X-Ray, computed tomography, thorax radiology

INTRODUCTION

A novel highly contagious respiratory pathogen in the corona virus (CV) group was first reported in December 2019 in Wuhan, China. This virus is named severe acute respiratory syndrome coronavirus-2-(SARS-coV-2) and the disease of this virus was called officially COVID-19 by World Health Organization (1-3). The first official case was reported in March 2020 in Turkey (4).

COVID-19 is a disease that may be led to various levels of pneumonia, necrotizing encephalopathy, systemic and pulmonary thromboembolism, acute respiratory distress syndrome, respiratory failure, systemic inflammatory response and sepsis. Chest computed tomography (CT) is a key diagnostic method coupled with Polymerase Chain Reaction (PCR) as the primary evaluation and follow-up method in COVID-19 (5,6). CT can show the progression of the disease, its severity, and the effectiveness of the treatment. Especially in the early phase, when the viral load is low, CT can be

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Received: 07.04.2022 **Accepted:** 27.06.2022

positive (7). CT was used as a screening test almost as widely as PCR in our country at the beginning of the pandemic (8). However, the use of CT decreased with the increase in experience about the disease in the forthcoming days and clinical findings and the use of Chest X-rays (CXR) became more prominent (9,10). The effectiveness of CRX in detecting COVID-19's radiological findings is quite low compared to CT. So far, many studies have been conducted on the use of CRX in patients with COVID-19 (11,12). However, to the best of our knowledge, there is no lesion-specific study on this subject in the literature. In addition, there is also no study on the lesions that can be detected over which cut-off value. Our study is the first study with these aspects. In this paper, the detection rates of elementary lesions due to COVID-19 with CRX are discussed. Our study aims to determine the visualization quality of CXR according to elementary lesions in COVID-19.

MATERIAL AND METHOD

Study Design and Patient Population

Our retrospective study was approved by Muğla Sıtkı Koçman University Human Research Ethics Committee (Date: 04.06.2020, Decision No: 200140). The Republic of Turkey Ministry of Health Scientific Research Council approved this study before applying to the ethics committee. Also, the pandemic board approved to study. All procedures were performed adhered to the ethical rules and principles of the Helsinki Declaration.

52 patients with both PCR and CT positivity and having CXR (26 Males and 26 Females); 69,6346±15,14250 (32-89) years [mean± SD age, (range)] were included in the study. All of the patients' CT findings were also compatible with COVID-19 pneumonia [In the typical group according to Radiological society of North America (RSNA) classification].

Real-time PCR (RT-PCR Charite, Berlin, Germany) test was performed from the nasopharyngeal and oropharyngeal swabs obtained at a time interval of 24 hours. Two consecutive negative RT-PCR results were considered negative. The demographic characteristics, clinical findings, and laboratory results of the patients were collected from PACS and hospital data systems.

CT Technique

All CT scans were performed without the contrast agent, during deep inspiration, and in the supine position. CT images were obtained using a 256-slice multi-detector CT scanner (Somatom, Siemens Healthcare, Erlangen, Germany) or 4 slices of Toshiba-TCT-60 AX (Toshiba Medical system Corporation, Yokohama, Japan) devices. The following technical parameters were used; tube voltage, 100–120 kV; tube current–exposure time product, 200–300 mAs; pitch, 0.9125-1.375 and; and section thickness after reconstruction, 1-1.25 mm. The room was decontaminated with 62-71% ethanol or 0.1% sodium hypochlorite. Passive air exchange was applied for 40-60 minutes after the thorax CT examination.

CT image analysis: Two experienced radiologists evaluated CT images that belong to patients who were diagnosed to be COVID-19. The patients were re-evaluated together in case of discrepancy. The incidence of o lung elementary patterns seen on CT images was determined. The radiological features of GGO, consolidation, reversed halo sign, parenchymal band and the curvilinear band were evaluated.

CXR technique: All CXRs were taken using digital radiographs with DRGEM TOPAZ 100 ma X-ray machine. In accordance with the hospital isolation protocol, CXRs were taken in the anteroposterior (AP) plane for bed-ridden patients whereas in the posteroanterior (PA) plane for proper patients. Follow-up CXRs were obtained according to the same protocol.

CXR analysis: The visibility of the lesions detected on CT was evaluated by comparing the CT Scenogram separately for each lesion.

Statistical Analysis

All continuous variables were expressed as medians, intervals, counts, and percentages. The data were recorded (Excel 2010, Microsoft) and analysed using statistical software (SPSS, version 22.0, IBM). Continuous variables were expressed as mean±SD (Standard deviation) values. CT findings were compared with Mann Whitney-U test because the groups were inhomogeneous and independent. $P < 0.05$ values were considered statistically significant. Cut off values were determined with ROC analysis.

RESULTS

Six different elementary lung lesions in 52 patients (26 males, 26 females) were probed. Lesions in the form of consolidation, GGO, reversed halo sign, curvilinear and parenchymal bands were evaluated in CT. The mean sizes of consolidation, indeterminate GGO(IGGO) and dense GGO(DGGO) were altered in the range from 3.68 to 4.48 cm. Parenchymal and curvilinear bands' thicknesses were ranged from 0.31 to 0.58 mm. The number of lesions, minimum and maximum dimensions, mean values and standard deviation values are as follows (**Table 1**).

Table 1. Table shows the number of the elementary lesions, minimum sizes (cm), maximum sizes (cm), mean values (cm) and standard deviation (cm) of the lesions.

	N	Min	Max	Mean	Std. Deviation
Consolidation	38	1.00	13.00	4.4868	2.85810
IGGO	11	2.00	10.00	3.8182	2.43180
DGGO	26	1.00	10.00	3.9808	2.05173
Reversed Halo	8	2.00	6.00	3.6875	1.33463
Parenchymal B	8	0.400	0.800	0.57500	0.158114
Curvilinear B	7	0.200	0.400	0.31429	0.069007

Visualization rates of CRX were evaluated. While the visualization rates of fibrotic bands (in parenchymal band 100%, in curvilinear band 85.7%) are highest, reversed halo sign and consolidation are highly visualized with 75% and 71.1% ratios, respectively. DGGOs were detectable in 61.5% of the patients, while IGGOs were only detected in 18.2%. Detailed visualization rates of elementary lesions in CXR are as follows (**Table 2**).

Visible and non-visible groups were compared as two inhomogeneous independent groups with Mann Whitney-U and Wilcoxon Z tests. Out of consolidation and DGGO, there is a statistically significant difference between the visible and non-visible groups, which differs significantly in size ($p<0.05$). There was no significant difference in the findings of IGGO, reversed halo sign and curvilinear band. For this reason, although an exact cut-off value can be determined in terms of visibility value for these three findings, a definite value cannot be mentioned. Test values, Z values and two tailed and single tailed P values are given in the table (**Table 3**).

Test Statistics[a]

A cut-off value was determined by ROC test for elementary lesions with significant differences between values. According to ROC analysis; cut-off value was 3 cm for DGGOs whereas 3.5 cm for consolidations.

DISCUSSION

PCR test is accepted as the gold standard in the diagnosis of COVID-19 (13). However, radiological evaluations are frequently used for rapid diagnosis. It is recommended that CT should be preferred primarily in cases where there is clinical and PCR incompatibility, as well as in the presence of embolism, malignancy, and severe respiratory distress (14,10). CXR is the first preferred examination in the radiological algorithm. However, the false negativity of CXR is quite high. While the sensitivity and specificity of CT is 98-99%, in CXR this rate remains at 63% (The rates alter between 60% and 90%) (10). To date, many studies have been conducted to determine the specificity and sensitivity of CXR (10,12,15,16). However, to the best of our knowledge, there is no study on which lesions CXR is ineffective in diagnosis and in which size lesions it is more helpful.

Typical radiological presentation of COVID-19 pneumonia is characterized by consolidation and GGO involving the peripheral, basal, and posterior parts of lung (17). The prevalence of GGO and consolidation has been reported between 46% and 100% in previous studies (7). The term GGO refers to increased CT attenuation with preserving bronchial and vascular markings. GGO had different radiological characters in mild and prominent forms. Therefore, in our study, these two findings were called and evaluated as different entities as IGGO and DGGO (18, 19).

Table 2. Table shows visible and non-visible elementary lesions' number and percentage according to six different group. Abbreviations; RH: Reversed halo sign PB: Parenchymal band CLB: Curvilinear band

Elementary lesions	Consolidation Freq (N)	Consolidation Per (%)	IGGO Freq (N)	IGGO Per (%)	DGGO Freq(N)	DGGO Per (%)
Non-visible	11	28.9	9	81.8	10	38.5
Visible	27	71.1	2	18.2	16	61.5
Total	38	100.0	11	100.0	26	100.0
Elementary lesions	**RH Freq(N)**	**RH Per (%)**	**PB Freq (N)**	**PB Per (%)**	**CLB Freq (N)**	**CLB Per (%)**
Non-visible	2	25.0	0	0.00	1	14.3
Visible	6	75.0	8	100.0	6	85.7
Total	8	100.0	8	100.0	7	100.0

Table 3. The table shows statistical between analysis visible and nonvisible groups in the five different group. We didn't make a comparison for parenchymal band because there was no non-visible lesion in the sample group.

	Consolidation	IGGO	DGGO	Reversed Halo	CLB
Mann-Whitney U	.000	2.000	7.500	1.500	.000
Wilcoxon W	66.000	47.000	62.500	4.500	1.000
Z	-4.814	-1.673	-3.857	-1.518	-1.673
Asymp. Sig. (2-tailed)	0.0001	0.094	0.0001	0.129	0.094
Exact Sig. (2*(1-tailed Sig.))	0.0001	0.145	0.0001	0.143	0.286

a. Grouping Variable: visible-non visible ; Consolidation, IGGO, DGGO, reversed Halo, CLB, b. Not corrected for ties.

GGO without consolidation is a radiological finding that is seen mostly in the early stages of the COVID-19 (18). It often accompanies consolidations. The visibility of GGO is more difficult than consolidation since HU values and density of GGO are lower than in consolidation. If we sort the lesions according to density, the line is consolidation > DGGO > IGGO, respectively (20,21). According to the results of our study, DGGO over 3.5 cm and consolidations over 3 cm can be easily detected with CXR. The visualization rate in consolidation was 71.1%, whereas in DGGO was 61.5%. It is not possible to talk about such a size limit for IGGO. Considering the detection rate in CXR, no statistically significant difference was found between the groups when patients with and without IGGO were compared. Even, some IGGOs with gross sizes up to 10 cm could not be visualized with CXR in our study. The visualization rate was BGGO is quite low with 18.2%.

The reversed halo sign was a disease-specific finding normally used in the diagnosis of organizing pneumonia

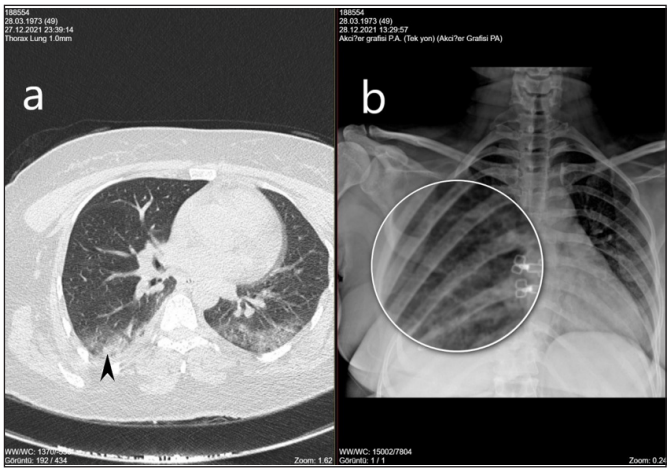

Figure 1a. In the CT sections passing through the inferior pulmonary vein level in the axial sections, the consolidation area with an anteroposterior thickness of 2 cm (cutted arrowhead) accompanied by GGO 1b. This consolidation is not seen in the magnified CRX image taken from the same area

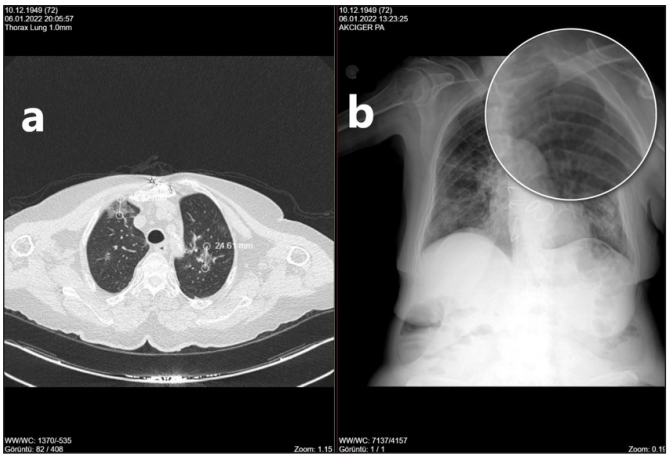

Figure 2a. A DGGO is present in the upper left quadrant. 2b. No lesion was detected in the same area on CRX.

(22). However, after the COVID-19 pandemic, it has been included in the literature in a different way as a radiological finding accompanying the novel disease with a high rate (23). Reversed halo's prevalence varies between 1.7% -15.1% (6). Therefore, the finding was added to the study. According to the results of our study, Reversed halo sign is visualized with CRX at a rate of 75%. A cut off value was not found with the ROC test. The size of the central clear area and the density of the peripheral ring (as consolidation, DGGO or IGGO) were thought to be effective in the visualisation. Notwithstanding, we can say that the detection rate of reversed halos over 3 cm is quite high.

In the late stages of COVID-19, however, parenchymal changes and curvilinear bands overlapping with old filtration areas are quite common (6). In our study, these findings were also evaluated. Parenchymal bands may occur late in the disease secondary to true fibrosis or sub-segmental bronchial plugs. Curvilinear bands are common in the late-covid and post-covid periods, especially in the posterior and basal areas where COVID-19 is more affected (24,25). The thickness of this band is measured in mm, unlike other lesions. Although the dimensions are small, their visibility is quite high compared to others. According to the results of our study, parenchymal bands could be detected at a rate of 100% and curvilinear bands at a rate of 85.7% with CRX.

Our results show that it is seen that the mean lesion size ranges between 3.68 and 4.48 cm for consolidation, GGO, and RHS. Considering that the mean visualization limit is 3-3.5 cm, it is seen that the majority of the lesions in the COVID-19 are visualized lesions. In this respect, the findings of our study support the previous study findings showing the sensitivity values of CRX at least 60%. However, considering that approximately 40% of the lesions are below 3 cm, visualization rates of up to 90% stated in some studies are too optimistic (10).

There are some limitations of our study. CTs and CXRs taken on the same day were compared, ignoring hourly differences. However, the reflection of this hourly clinical change on the radiological change is minimal. In addition, the number of patients is limited, since CRX and CT were not taken simultaneously in each patient at the desired time interval and the study was a single-center study. However, according to the G power test (51 patients), it is above sufficient sample sizes. In addition, hidden areas were not taken into account in the study. Only the visualization rate of localized lesions at the point that can be seen on both CRX and CT was evaluated. Lung tissue is not of the same thickness in the apical area and basally, and the magnification of the lesions located anteriorly and posteriorly is different. However, the effect of these technical physics rules on the routine is quite low.

CONCLUSION

In COVID-19 pneumonia, CXR can mostly detect curvilinear bands and parenchymal bands and DGGO, reversed halo sign and consolidations as long as greater than 3-3.5 cm. According to the results of our study, approximately 60% of COVID-19 lesions are over 3 cm. Therefore, CXR can detect most of the Covid lesions. The usefulness of CRX in detecting IGGO is greatly limited with %18,2 visualisation rate. Although CXR positive findings support the diagnosis, negative findings do not exclude the presence of a lesion.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Muğla Sıtkı Koçman University Human Researches Ethics Committee (Date: 04/06/2020, Decision No: 200140).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1118649
J Health Sci Med 2022; 5(4): 1156-1161

Radiomics analysis of pre-treatment F-18 FDG PET/CT for predicting response to transarterial radioembolization in liver tumors

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Cite this article as: Coşkun N, Yüksel AÖ, Canyiğit M, Özdemir E. Radiomics analysis of pre-treatment F-18 FDG PET/CT for predicting response to transarterial radioembolization in liver tumors. J Health Sci Med 2022; 5(4): 1156-1161.

ABSTRACT

Aim: To investigate the relationship between the textural features extracted from pre-treatment fluorine-18 fluorodeoxyglucose positron emission with computed tomography (F-18 FDG PET/CT) and the response to treatment in patients undergoing transarterial radioembolization (TARE) due to primary or metastatic liver tumors.

Material and Method: A total of 25 liver lesions from the pre-treatment F-18 PET/CT images of 14 patients were segmented manually. Standard uptake value (SUV) metrics and radiomics features were extracted for each lesion. Metabolic treatment response was determined according to PERCIST criteria in 18F-FDG PET/CT imaging performed 2 months after the treatment. Feature selection was done with recursive feature elimination (RFE). The association between selected features and treatment response was evaluated with logistic regression analysis.

Results: Eventually, 13 lesions responded to TARE, while 12 lesions remain stable or progressed. All standard uptake values and 27 out of 30 textural heterogeneity indicators were significantly higher in lesions that responded to treatment. SUVmax, kurtosis and dissimilarity features were selected by the RFE algorithm for the prediction of response to TARE. Logistic regression analysis revealed that all three parameters were significantly associated with treatment outcome.

Conclusion: Textural features extracted from pre-treatment F-18 FDG PET/CT in patients undergoing TARE due to liver tumors are promising biomarkers that can be potentially used to predict metabolic treatment response.

Keywords: PET/CT, radiomics, transarterial radioembolization, PERCIST

INTRODUCTION

Local treatments have been widely adopted into clinical practice for the treatment of primary and metastatic tumors of the liver that are not adequate for surgical resection. Transarterial radioembolization (TARE), one of these local treatment strategies, is an internal radiotherapy method performed by injecting beta-radiating radiolabeled microspheres into the tumor microcirculation through transarterial intervention of the hepatic artery branch. The rationale of this treatment is based on the fact that tumor cells are predominantly perfused through the arterial system and hepatocytes mostly from the portal venous system. By this means, radioactive microspheres can be selectively directed to the tumor and the tumor cells are exposed to high-dose radiation, while healthy liver parenchyma is minimally affected by radiation. TARE can be applied in all primary (hepatocellular cancer and cholangiocarcinoma) and metastatic (e.g., colorectal cancer and neuroendocrine tumors) malignancies of the liver that are not surgically resectable.

Tumor heterogeneity is a long-known phenomenon that determines treatment outcomes and prognosis in oncologic diseases (1). It is known that tumor biology varies between different regions in a lesion and between different lesions in a patient. Various molecular, genetic, epigenetic, and microenvironmental effects are thought to be among the causes of this entity (2). The biological nature of the liver malignancies was investigated in previous genotype studies and it was estimated that up to 60% of recurrent or metastatic tumors harbor

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Received: 19.05.2022 **Accepted:** 27.06.2022

subclones different from the primary tumor, and that up to 66% of single tumors demonstrate intratumoral heterogeneity (3).

Recent improvements in molecular imaging and medical informatics have promoted the weight of quantitative analyses and led to emergence of a novel research field called "radiomics". This approach is based on the extraction of quantitative characteristics of texture from medical images and originates on the premise that medical images hold quantitative data representing intratumoral heterogeneity. These relationships, which are otherwise invisible to the human eye, can be revealed with image analysis and may provide guidance for patient management (4-9). It has been previously reported that metabolic heterogeneity features extracted from fluorine-18-fluorodeoxyglucose positron emission with computed tomography (F-18 PET/CT) images can accurately predict prognosis in various malignancies (10,11). However, the number of studies investigating the role of radiomics analysis in PET imaging prior to TARE is limited.

In this context, we made radiomics analysis on the pre-treatment F-18 FDG PET/CT images of patients undergoing TARE due to liver tumors, and aimed to investigate the relationship between the PET textural features and response to treatment.

MATERIAL AND METHOD

The study was approved by the Ankara City Hospital No. 1 Clinical Researches Ethics Committee (Date: 14.10.2020, Decision No: E1-20-1180). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

This retrospective observational study included 14 patients that underwent baseline F-18 FDG PET/CT imaging and received Y-90 resin microsphere TARE due to primary or metastatic liver tumors. Exclusion criteria were having non-FDG avid lesions in the pre-treatment PET/CT and inaccessibility of follow-up data. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

PET/CT Imaging Protocol

PET/CT imaging was performed with a 6-slice CT-integrated PET scanner (GE Discovery IQ PET/CT, Milwaukee, WI, USA). After fasting for at least 4 hours, 444-629 MBq (12-17 mCi) 18F-FDG was injected intravenously while blood glucose level was below 150 mg/dL. Patients rested in a quiet room for 1 hour for adequate biodistribution of the radiopharmaceutical. Following the scout scan, CT (120 keV, 10-90 mA) and PET (3 minutes/bed) images from vertex to mid-thigh were acquired. Sagittal, coronal, and transverse slices and MIP images were obtained by iterative reconstruction (ordered subset expectation maximization, 14 subsets, 6 iterations), attenuation correction and model-based scatter correction on PET images.

Texture Analysis Protocol

The segmentation of lesions and extraction of radiomics features were performed using Local Image Features Extraction (LIFEx) software (12). Lesions with increased FDG uptake were manually segmented into a 3D volume of interest (VOI) by a nuclear medicine physician with 5 years of experience. Standard uptake values were discretized to 64 grey levels at a bin size of 0.3125. Multiple radiomics parameters (shape, histogram and textural features derived from gray-level co-occurrence matrix (GLCM), neighborhood gray-level different matrix NGLDM, gray-level run length matrix (GLRLM) and gray-level zone length matrix (GLZLM) were extracted for each lesion.

Assessment of Response to Therapy

Metabolic response was assessed on a lesion level using the PERCIST criteria (13). Accordingly, complete metabolic response was defined as normalization of SUV adjusted for lean body weight (SUL). Partial response and progression were defined as the decrease or increase of at least 30% in SULpeak, respectively. Lesions that neither responded partially nor progressed were interpreted as stable. Eventually, lesions with complete or partial response were classified as responsive, and those that remained stable or progressed were classified as non-responsive.

Statistical Analysis

Normally distributed numerical variables are presented as mean (standard deviation), and non-parametric variables were presented as median (min-max). Categorical variables are presented as numbers and percentages. The selection of the most discriminant features was made with recursive feature elimination (RFE), a feature selection method that fits a model and removes the weakest feature until the specified number of features is reached. Independent predictors of response to TARE were determined with multivariable regression models built on the selected features. Statistical analyses were performed using the R statistical package (R Foundation for Statistical Computing, Vienna, Austria) and Stata/MP 16 (Stata Corporation, College Station, Texas, USA) software. A p-value below 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

A total of 25 liver tumors from 14 consecutive patients were included in the final analyses. The mean (SD) age was 57 (17) years. Eight patients had one single lesion, whereas 7 patients had multiple lesions varying between 2 and 4. Twelve patients (48%) were diagnosed with primary hepatocellular carcinoma (HCC), and 12 patients had metastatic liver tumors (10 colorectal cancer, 2 neuroendocrine tumors and 1 cholangiocarcinoma). The mean time between pre-treatment PET and application of TARE was 32 (19) days, and the mean time between TARE and response assessment was 75 (31) days. Characteristics of the study population are presented in **Table 1**.

Table 1. Characteristics of the study population and analyzed lesions

	All Patients (n=14)
Gender	
Male	9 (64%)
Female	5 (36%)
Age, years	57 (17)
Time Between Baseline PET and TARE, days	32 (19)
Time Between TARE and Response Assessment, days	75 (31)
	All Lesions (n=25)
Pathology	
HCC	12 (%52)
Metastatic	13 (%48)
Tumor Volume, mL	570.46 (1001.11)
Tumor/Background Ratio	2.48 (1.75)
Administered Activity, GBq	1.19 (0.67)
Absorbed Tumor Dose, Gy	183.18 (113.70)
Response to TARE	
Complete response	7 (28%)
Partial response	6 (24%)
Stable	10 (40%)
Progression	2 (8%)

Data are presented as mean (SD) for continuous variables, and n (%) for categorical variables

Characteristics of Responsive and Non-Responsive Lesions

In total, 13 lesions metabolically responded to TARE (7 complete response, 6 partial response), while 12 lesions either remained stable or progressed. The mean values of SUV metrics and textural features according to responsive and non-responsive lesions are shown in **Table 2**. Most of the extracted features were significantly different between responsive and non-responsive lesions. Indicators of intratumoral heterogeneity (e.g., contrast, correlation, entropy dissimilarity) were significantly higher in responsive lesions. Accordingly, indicators of lower intratumoral heterogeneity (e.g. homogeneity and correlation) were significantly higher in non-responsive lesions. **Figure 1** shows the pre-treatment and post-treatment PET images of a lesion that responded partially and another lesion that remained stable.

Table 2. SUV metrics and textural features of lesions according to their respond to TARE

	Responsive (n=13)	Non-Responsive (n=12)	p-value
SUVmax	10.90 (4.64)	4.30 (1.59)	<0.001
Skewness	0.48 (0.36)	-0.05 (0.89)	0.059
Kurtosis	2.65 (0.75)	3.90 (0.92)	0.001
Sphericity	0.84 (0.07)	0.82 (0.09)	0.56
Surface Area (mm^2)	4276.14 (3270.22)	7406.02 (6072.16)	0.12
Compacity	4.34 (1.31)	5.54 (2.13)	0.10
Homogeneity	0.36 (0.17)	0.63 (0.11)	<0.001
Correlation	0.02 (0.03)	0.08 (0.04)	<0.001
Contrast	43.92 (40.93)	3.61 (6.11)	0.003
Correlation	0.44 (0.15)	0.54 (0.16)	0.12
Entropy	2.01 (0.41)	1.30 (0.28)	<0.001
Dissimilarity	4.60 (2.74)	1.12 (0.89)	<0.001

Data are presented as mean (SD)

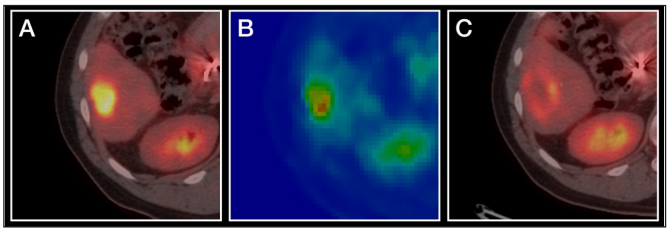

Figure 1. Example of a highly heterogeneous lesion with partial metabolic response to TARE (A) Pre-treatment PET/CT; SUVmax: 14.76, Entropy: 8.01, Kurtosis: 1.83 (B) Textural representation of the tumor (C) Post-treatment PET/CT.

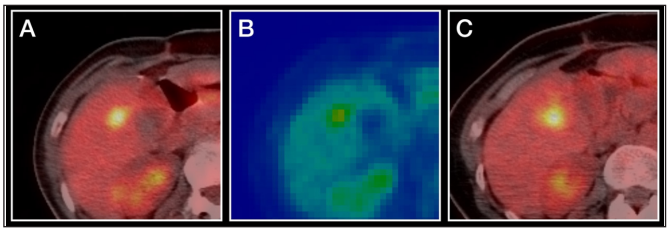

Figure 2. Example of a homogeneous lesion that was not responsive to TARE (A) Pre-treatment PET/CT; SUVmax: 7.34, Entropy: 5.75, Kurtosis: 5.78 (B) Textural representation of the tumor (C) Post-treatment PET/CT.

Predictors of Response to TARE

SUVmax, kurtosis and entropy were selected by the RFE method as highly discriminant features for predicting metabolic response to TARE. Association between these features and treatment response were confirmed with logistic regression analysis (**Table 3**). The odds ratio SUVmax, kurtosis and dissimilarity were 0.53 (0.33 – 0.86, p: 0.011), 10.71 (95% CI: 1.50 – 76.42, p: 0.018) and 0.35 (95% CI: 0.16 – 0.78, p: 0.010), respectively.

Table 3. Logistic regression analysis for predicting response to TARE

Variable	Odds Ratio	95% Confidence Interval	p-value
SUVmax	0.54	0.33 – 0.87	0.011
Kurtosis	6.53	1.52 – 28.13	0.012
Dissimilarity	0.35	0.16 – 0.78	0.010

DISCUSSION

The current study indicates that radiomics analysis in pre-treatment F-18 FDG PET/CT images could be a useful approach to predict treatment response in patients undergoing TARE. Textural features are known to be associated with response to therapy in various tumor types (14-20). However, to the best of our knowledge, this is the first study to investigate predictive potential of radiomics analysis on baseline F-18 FDG PET/CT for predicting metabolic tumor response after TARE. According to our results, multiple heterogeneity parameters were significantly higher in the lesions that responded to treatment. SUVmax, entropy and dissimilarity were the three prominent parameters for predicting the metabolic response.

SUVmax is the cornerstone parameter of oncologic PET imaging, and it is widely used for the objective assessment of metabolic activity. Considering that glucose is an essential molecule for cellular proliferation (21), PET imaging with F-18 FDG, a glucose analog, allows the identification of regions with increased proliferation, particularly malignant tumors (22,23). Lesions with a higher SUVmax on PET/CT are known to have an increased mitotic activity. This means that these lesions could demonstrate favorable response to radiation therapy when compared to lesions with lower SUV, since their exposure to radiation during cell division will be longer. This phenomenon was previously confirmed in several studies. Jo et al. (24) analyzed the pre-treatment F-18 FDG PET/CT images of 36 HCC patients and found that lesions with higher SUVmax demonstrated better response to radiotherapy. In a similar study including 35 HCC patients treated with RT, Kim et al. (25) analyzed the predictive value of baseline SUVs and found that the response of tumors with higher SUVmax was better than those in the lower SUVmax group. Pant et al. (26) reported that FDG-avid HCC lesions carry higher risk for metastasis than non-18F-FDG-avid primary tumors and HCC at higher stages was found more commonly in 18F-FDG-avid primary tumors. Tumors with a higher SUVmax will have a shorter doubling time. Thus, the response to radiation therapy is expected to be better in the lesions with higher SUV than those with lower. This finding is also in line with other studies (27-29) that investigated the relationship of SUV and treatment response in the tumors of the lung, esophagus, and nasopharynx, which reported that increased FDG uptake is an indicator of response to radiation therapy. Although the lesions with higher SUV are more radiosensitive to radiation therapy, they also tend to have more aggressive biological behavior. So in case of any residual tumor cells after TARE, lesions with higher SUVmax can potentially spread more rapidly.

An indicator of tumor aggressiveness other than SUVmax is the increased genotypic and phenotypic heterogeneity within the tumor, which can be non-invasively quantified with radiomics analysis. We have previously shown that there are strong correlations between the textural features extracted from PET images and the SUVmax values (30). Results of the current study indicate that two textural features, kurtosis and dissimilarity, were associated with treatment failure after TARE. Kurtosis is a relatively simple, histogram-based parameter that describes heterogeneity in a tumor. Lower values of kurtosis indicate a wider, flattened histogram. In other words, a decrease in kurtosis indicates a large spectrum of gray-levels and increased heterogeneity within the tumor. Kurtosis is reported to be a promising parameter for differentiating between cancer subtypes including renal cancer (31), gliomas (32), or discriminating pseudo-progression from tumor progression in glioblastomas (33). Dissimilarity, a textural feature derived from gray-level co-occurrence matrix, is an expression of intratumoral heterogeneity. Higher values of dissimilarity indicate increased inequality of intensity values between adjacent voxels. It has been previously reported for different patient groups that dissimilarity was significantly associated with response to treatment. Mosconi et al. (34) emphasized that the GLCM Dissimilarity feature extracted from CT images of intrahepatic cholangiocarcinoma patients undergoing transarterial radioembolization is a factor predicting treatment response. We previously found that increased dissimilarity in baseline F-18 FDG PET/CT images was associated with failure of first-line chemotherapy in diffuse large B-cell lymphoma (30). This feature was found to be associated with treatment response in non-small cell lung cancer as well (35). Dissimilarity was proposed as a prognostic biomarker for not only FDG PET, but also for PET imaging with other radiopharmaceuticals. Hotta et al. (36) conducted texture analysis on C-11 methionine PET and concluded that dissimilarity was the best feature to distinguish recurrent tumor from radiation necrosis in metastatic brain cancer patients.

Our findings should be interpreted in the context of several limitations. Firstly, this was a retrospective study that included a small population from a single center and imaged with the same PET/CT scanner. Lesions were

segmented manually, which could be prone to inter-observer variability. In future studies, segmentation methods can be compared to determine the preferred approach in this patient population. Lastly, considering the complex background of cancer biology, it should not be expected to get comprehensive outcomes based solely on textural analysis (37).

CONCLUSION

Radiomics features extracted from pre-treatment F-18 FDG PET/CT images in patients undergoing TARE are promising biomarkers that can be potentially used to for patient selection and predicting response to treatment. Future prospective multi-centric studies with larger cohort are needed to confirm these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Ankara City Hospital No. 1 Clinical Researches Ethics Committee (Date: 14.10.2020, Decision No: E1-20-1180).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1133659
J Health Sci Med 2022; 5(4): 1162-1169

A higher incidence of diabetic peripheral neuropathy may be associated with decreased sleep and increased depression in older adults

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Cite this article as: Selvi Öztorun H, Gözükara B, Bahsi R, et al. A higher incidence of diabetic peripheral neuropathy may be associated with decreased sleep and increased depression in older adults. J Health Sci Med 2022; 5(4): 1162-1169.

ABSTRACT

Aim: Diabetes mellitus (DM) tends to increase with aging. Nearly half of the patients with DM develop neuropathy (DPN). Despite its high burden and morbidity, the conditions that DPN may be associated with have not been adequately studied in older adults. We aimed to identify sleep duration and comprehensive geriatric assessment components that may be associated with DPN.

Material and Method: This is a cross-sectional retrospective study. DPN diagnosed with a medical history, neurologic examination, and electromyography (EMG). 125 diabetic older patients were included. All comprehensive geriatric assessment tests and questions about sleep quality and time were performed. We divided the patients into two groups those without neuropathy and with neuropathy and compared them.

Results: The median age of 125 patients was 72 (min-max; 64-94). 58.8% of them were women. The percentage of married people and living with their spouse and slept for 6 hours or more had a lower percentage in the DPN group. Polypharmacy and the percentage of heart failure were significantly higher in the DPN group. Lawton-Brody score, which shows instrumental daily living activities (IADL) and geriatric depression score (GDS) was higher in the DPN group. In logistic regression, we found that depression scores were higher and sleep duration was shorter in the DPN group (respectively, odd ratio:265 p:.012; odd ratio:.1.917 p:.045)

Conclusions: DPN in older adults may affect the functionality and be associated with fewer sleep hours and depression. Not only blood glucose regulation but also other factors such as sleep duration and depressed mood may be associated with DPN in older adults.

Keywords: Diabetic neuropathy, comprehensive geriatric assessment, older adults, sleep duration, depression

INTRODUCTION

The incidence of diabetes mellitus (DM), particularly type 2 DM, tends to increase with age. Moreover, it is estimated that the prevalence of DM in older adults will be around 20% in the future (1). Diabetic peripheral neuropathy (DPN) has been defined as a length-dependent, symmetrical sensorimotor polyneuropathy linked to metabolic and microvascular changes resulting from chronic high blood glucose exposure from DM, as well as cardiovascular changes (2). Complications of neuropathy develop in approximately half of the patients followed for DM (3). As a result, it is predicted that this painful condition will affect approximately 10% of older adults in the 2030s (4).

The etiology of diabetic neuropathy has not been fully elucidated, but the possible underlying cause is hyperglycemia and microangiopathy. The most common form is distal symmetric sensorimotor polyneuropathy, but most body systems can be effected through the involvement of autonomic nerves (5).

DPN causes not only pain but also loss of activity and decreased quality of life. In older adults, DPN causes

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Received: 21.06.2022 **Accepted:** 27.06.2022

decreased vibration, pressure, and sensory losses. This causes balance and coordination disorders in walking. As a result, older adults tend to lose muscle strength and fall (6,7). In addition, it can disrupt sleep and mood, decrease quality of life, and negatively affect their activities of daily living (ADLs). Geriatric syndromes can be defined as common health problems that result from the disruption of more than one system in older adults. These syndromes can be identified by comprehensive geriatric assessments (CGA). It is possible to say that DPN is more common in older adults with the increase in years of exposure to high blood glucose. Diabetes treatment in older adults is more difficult due to cognitive and physical problems. The presence of geriatric syndromes is thought to complicate adherence to diet and treatment for diabetes. Therefore, evaluating the relationship between geriatric syndromes and diabetes-related complications like DPN is important. The tests used in CGA evaluate the basic and instrumental daily activities, mental status, and nutritional status of older adults. DPN can cause walking difficulties, depression that may be associated with chronic disease, and pain. This situation may cause deterioration in the general mental and physical activities of the older adults evaluated by CGA(5,8,9).

Despite its high health burden and morbidity, the conditions with which DPN may be associated have not been adequately researched in older adults. At present, a few studies have investigated associations between diabetic neuropathy and sleep and comprehensive geriatric assessments in older adults. DPN was found in 28.2% of older diabetics. They found that DPN was associated with lower Mini-Mental Status Examination, Activities of Daily Living, Instrumental Activities of Daily Living, and higher Mini Geriatric Depression Scales (8,10,11). Older adults are excluded from most studies of complications of diabetes. Therefore, there is a need for more studies investigating interactions in older adults.

Thus, this study aimed to identify sleep duration and comprehensive geriatric assessment components that may be associated with diabetic peripheral neuropathy in older adults.

MATERIAL AND METHOD

The study was approved by the Clinical Resarches Ethics Committee of the Ankara University Medical Faculty (Date: 13.08.2018, Decision No: 13-878-18). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

125 patients admitted to geriatrics clinics were included in this cross-sectional, retrospective study. Individuals diagnosed with diabetes-related neuropathy based on medical history and peripheral neurologic examination and with electromyography (EMG) findings recorded in their files were included. Persons with incomplete demographic data and comprehensive geriatric assessment records were excluded from the study. The patients' sociodemographic data are shown in **Table 1**.

Table 1: Demographic, comprehensive geriatric assessment and laboratory values of the participants and comparisons by group

*Variables	Without neuropathy n=89 (71.2%)	With neuropathy n=36 (28.8%)	All n=125 (100%)	p-value
Sociodemographics				
Age, median (range)	71 (64–87) years	73 (64–94) years	72 (64–94) years	.260
Gender, n (%)				.921
Female	61 (48,8)	25 (10.0)	86 (58.8)	
Male	28 (22.4)	11 (8.8)	39 (41.2)	
Educational status, n (%)				.095
<5 years	40 (31.7)	24 (19.0)	64	
6–8 years	36 (28.6)	11 (8.7)	47	
>8 years	13 (10.3)	2 (1.6)	15	
Marital status, n (%)				<.005
Married	47 (42.0)	11 (9.8)	58 (51.8)	
Widowed or divorced	33 (29.5)	21 (18.8)	54 (48.2)	
Living situation, n (%)				<.005
Alone	22 (19.5)	12 (10.6)	34 (30.1)	
With partner	36 (31.9)	11 (9.7)	47 (41.6)	
With child/children	11 (9.7)	10 (8.8)	21 (18.6)	
With somebody else	11 (9.7)	0 (0)	11 (9.7)	
Living place, n (%)				.345
Nursing home	2 (1.8)	2 (1.8)	4 (3.5)	
Private home	79 (69.3)	31 (27.2)	110 (96.5)	
Sleep quality, n (%)				.122
Poor	19 (19.2)	13 (13.1)	32 (32.3)	
Good	50 (50.5)	17 (17.2)	67 (67.7)	
Sleep duration, n (%)				<.005
<6 hours	17 (18.5)	14 (15.2)	31 (33.7)	
≥6 hours	46 (50)	15 (16.3)	61 (66.3)	

(cont...)

Table 1: Demographic, comprehensive geriatric assessment and laboratory values of the participants and comparisons by group (cont...)

*Variables	Without neuropathy n=89 (71.2%)	With neuropathy n=36 (28.8%)	All n=125 (100%)	p-value
Diseases				
Hypertension, n (%)	68 (54.0)	31 (24.6)	99 (78.6)	.358
COPD, n (%)	13 (10.3)	5 (4.0)	18 (14.3)	.873
Heart failure, n (%)	3 (2.4)	8 (6.3)	11 (8.7)	**<.005**
Dementia, n (%)	4 (3.2)	5 (4.0)	9 (7.1)	.073
Cerebrovascular disease, n (%)	6 (4.8)	4 (3.2)	10 (7.9)	.442
Hypothyroidism, n (%)	13 (10.3)	3(2.4)	16 (12.7)	.318
Coronary artery disease, n (%)	19 (15.1)	10(7.9)	29 (23)	.490
Smoking, n (%)	19 (18.1)	7 (6.7)	26 (24.8)	.738
Nephropathy, n (%)	3 (2.4)	11 (8.7)	14 (11.1)	**<.001**
Retinopathy, n (%)	6 (4.8)	9 (7.1)	15 (11.9)	**<.001**
Comprehensive geriatric assessment				
Polypharmacy, n (%) (>5 drug use)	27 (21.4)	45 (35.7)	72 (57.1)	**<.005**
Number of drugs mean (range)	5 (1–9)	6 (0–13)	5 (0–13)	**<.005**
Number of falls mean (range)	0 (0–3)	0 (0–3)	0 (0–3)	.865
Katz ADL mean (range)	6 (4–6)	6 (4–6)	6 (4–6)	.366
Lawton–Brody IADL mean (range)	8 (2–8)	7 (2–8)	7 (2–7)	**<.005**
MMSE score mean (range)	24 (10–30)	25 (13–29)	24 (10–30)	.669
MNA-SF score mean (range)	13 (10–14)	13 (10–14)	13 (10–14)	.290
GDS score mean (range)	3 (0–8)	4 (0–9)	3 (0–10)	**<.005**
Depression score, n (%)				**<.001**
<5	71 (56.3)	17 (13.5)	88 (69.8)	
≥5	18 (14.3)	20 (15.9)	38 (30.2)	
Handgrip strength (kg) mean (range)	18.5 (0–41.7)	21.2 (5.10–39)	19.4 (0–41.70)	.400
Laboratory values The mean and standard deviation for the normally distributed variables and median and range for the non-normally distributed variables				
Fasting blood glucose (mg/dL)	131 (80–306)	126 (86–462)	131 (80–462)	.803
Creatinine (mg/dL)	0.81 (0.51–1.56)	0.85 (0.55–2.76)	0.84 (0.50–2.76)	.431
GFR (ml/min/1.73 m²)	81 (16–90)	71.5 (16–90)	78 (16–90)	.207
Sodium (mmol/L)	138 (127–142)	139.5 (131–143)	139 (127–143)	.077
Potassium (mmol/L)	4.5 (4–5.40)	4.6 (3.50–5.10)	4.6 (3.50–5.40)	.552
Calcium (mg/dL)	9.93±0.56	9.87±0.47	9.50±0.53	.062
Albumin (g/L)	4.2 (3–4.70)	4.10 (3.40–4.70)	4.10 (3–4.70)	**<.005**
Total cholesterol (mg/dL)	185.8 (122.1–375.2)	192.8 (117.2–315.4)	177.4 (117.2–375.2)	.963
LDL (mg/dL)	104.6 (64.3–253.3)	107.5 (56.7–246.4)	105.8 (56.7–253.3)	.917
Alanine aminotransferase (ALT) (U/L)	17 (9–122)	16 (8–44)	16 (8–122)	.754
Aspartate aminotransferase (AST) (U/L)	24 (11–88)	18 (8–57)	20 (8–88)	.290
Sedimentation (mm/h)	20 (4–60)	21 (3–13)	20 (3–60)	.466
Leukocyte (WBC) (×10⁹/L)	8.19 (3.03–13.0)	7.5(3.97–11.30)	7.75 (3.03–13.0)	.696
Hemoglobin (Hb) (g/dL)	13.5 (8.60–16.20)	12.5 (10–14.20)	13.0 (8.60–16.20)	**<.001**
Hematocrit (%)	40.7 (26.5–49.0)	38.80 (30.90–44.10)	40.10 (26.5–49.0)	**<.005**
Platelet Count ×10⁹/L	291.9±93.44	283.66±62.37	289.93±83.50	.319
HbA1c (with electrophoresis method) (%)	7.3 (5.40–11.50)	7.45 (5.70–17.02)	7.40 (5.40–17.02)	.835
Vitamin B12 (pg/mL)	243 (102–1500)	322 (151–1500)	301 (102–1500)	.217
TSH (μIU/mL)	1.75 (0.08–72.8)	1.57 (0.51–4.83)	1.72 (0.08–72.80)	.348
Folate (ng/mL)	9 (4–25)	8.2 (1.68–25)	8.98 (1.68–25)	.176
CRP (mg/L)	3 (0.30–76)	4.5 (0.6–210)	3.20 (0.30–210)	.331
25-hydroxy vitamin D (μg/L)	20.98±10.07	19.42±9.80	20.43±9.94	.494

* Percentages in cells show percentages in the total. Missing values are included in the calculation of the percentages. The results of the descriptive analyses were presented in mean and standard deviation for the normally distributed variables and in median and range for the non-normally distributed variables. The frequencies of the categorical variables were expressed as (%). The percentage comparison of categorical variables was performed with the Chi-squared test. An independent t-test was used for normally distributed variables for 2 groups to compare means, and the Mann–Whitney U test was used for 2 groups for comparison of non-normally distributed continuous variables. The correlations between normally distributed numerical variables were evaluated using the Pearson test, and the non-normally distributed variables were evaluated using the Spearman test. Statistical significance was accepted as p<0.05. Values in bold are significant.

Abbreviations: COPD: chronic obstructive pulmonary disease, Katz ADL: Katz index of activities of daily living; LB-IADL: Lawton–Brody instrumental activities of daily living scale; MMSE: mini-mental state exam; MNA-SF: mini nutritional assessment-short-form; GDS: geriatric depression scale; GFR: glomerular filtration rate; TSH: thyroid-stimulating hormone; CRP: C-reactive protein.

Comprehensive Geriatric Assessment

Comprehensive geriatric assessment tests include the Katz Activities of Daily Living Index (Katz ADL), Lawton-Brody Instrumental Activities of Daily Living Scale (LB-IADL), Geriatric Depression Scale (15-item short form) (GDS), Mini-Mental State Examination (MMSE), and Mini Nutrition Assessment-Short Form (MNA-SF).

ADLs were assessed using the Katz ADL, which assesses bathing, dressing, going to the toilet, transfer, feeding, and continence; 0 or 1 point is given for each activity for a total score of 0–6 points (12). Instrumental ADLs were evaluated with the LB-IADL on a total scale of 0–8 points; 0 or 1 point was given for each activity. This scale evaluates using the phone, shopping, preparing meals, cleaning the house, doing laundry, using modes of transportation, being able to control finances, and being responsible for one's medications (13). Cognitive functions were examined and recorded using the MMSE test, which is valid and reliable in a Turkish setting. It grades cognitive functions in a 30-point range, with low scores indicating cognitive function impairments. (14). The nutritional status of the patients was evaluated with the MNA-SF test, in which the maximum obtainable score is 14: 0–7 points indicate malnutrition, 8–11 points indicate pre-malnutrition and 12–14 points indicate normal nutrition statuses (15). Muscle strength was assessed using an electronic hand dynamometer (GRIP-D digital handgrip dynamometer; Takei, Tokyo, Japan). The number of falls experienced by the individual during the one year preceding the test was documented by asking the patients and/or their relatives. The sleep duration of each patient was recorded as either less than 6 hours or 6 hours or more. The cut-off time of 6 hours was determined by reviewing the results of similar previously published studies (16, 17).

Laboratory Assessment

These values were added to the study because they were related to the general health, nutrition, and inflammatory status of the patients. Biochemical parameters were studied using spectrophotometry. C-reactive protein (CRP) levels were determined by the turbidimetric method, hormonal levels were determined by the electrochemiluminescence immunoassay (ECLIA) method, and vitamin D levels were determined using the high-performance liquid chromatography (HPLC) method.

Fasting plasma glucose (FPG) and HbA1c values were used to determine a diagnosis of DM. Blood samples were taken by venipuncture after overnight 12-h fasting. FPG was measured using the glucose oxidase method. HbA1c levels were measured in the same laboratory by HPLC. Fasting plasma glucose levels of ≥126 mg/dl and HbA1c of ≥6.5% were considered diagnostic of DM.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) for Windows version 24.0 (IBM SPSS Inc., Chicago, IL) was used to perform statistical analyses. The conformity of the variables to the normal distribution was examined using visual (histograms and probability graphs) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. The results of the descriptive analyses were presented as mean and standard deviation (for normally distributed variables), median, and minimum-maximum range (for non-normally distributed variables). The frequency of the categorical variables was given as a percentage (%). An independent t-test was used to compare the means of the two groups. The Mann–Whitney U test was used to compare the two groups that did not fit the normal distribution. Multivariate logistic regression analysis was performed using the Enter method with independent variables (Model 1) that were significant in univariate linear regression analysis and independent variables that could be clinically significant (Model 2). The results were evaluated within the 95% confidence interval (CI), and a p-value <0.05 was considered statistically significant.

RESULTS

The median age of the 125 patients included in the study was 72 years (range: 64–94 years); 58.8% were women. Among the 125 patients, 89 (71.2%) had neuropathy (neuropathy group), whereas 36 (28.8%) had no neuropathy (non-neuropathy group). The number of married people was significantly lower in the neuropathy group. The percentage of those living with their spouses was lower. In the comparison of sleeping hours, those who slept for 6 hours or more had a lower percentage of neuropathy. The percentage of those with heart failure was significantly higher in the neuropathy group. The incidence of retinopathy and nephropathy was also higher in the neuropathy group. Moreover, the polypharmacy rate and the median number of drugs used were significantly higher in the neuropathy group.

The median of the Lawton–Brody score, which shows instrumental ADLs (IADLs), was found to 8(2-8) in without neuropathy group and 7(2-8) in with neuropathy group (p-value: <.005). The median geriatric depression score (GDS) was 3(0-8) in without neuropathy group and 4(0-9) in with neuropathy group (p-value: <.005). In the grouping of depression scores according to the cut-off used for depression, the percentage was found to be higher in the neuropathy group. In the comparison of laboratory results, albumin, hemoglobin, and hematocrit values were found to be significantly lower in the neuropathy group. Demographic, CGA, and laboratory values and comparisons by the group are shown in **Table 1**.

Models were used in the logistic regression analysis. DPN was taken as the independent variable. In Model 1, univariate analysis was performed with the variables found to be significant as shown by the comparisons in **Table 2**. In Model 2, factors that were found to be associated with neuropathy in previous studies were analyzed using univariate analysis. In Model 3, significant variables were analyzed in Models 1 and 2 and included in the multivariate analysis.

Table 2. Univariate linear and multivariate logistic regression analysis of factors associated with diabetic neuropathy

Variable	Univariate analysis		
	Odds ratio	p-value	95% CI
Model 1			
Heart failure	.126	.002	.031–.509
Polypharmacy	.379	.023	.164–.874
Sleep duration (≥ 6 h)	2.525	.048	1.010–6.315
Lawton-Brody IADL	.890	.067	.786–1.008
GDS groups (≥ 5 point)	1.179	.030	1.016–1.368
Hemoglobin (Hb)	.720	.011	.559–929
Model 2			
Age	1.043	.921	.451–2.413
HbA1c	1.042	.684	.852–1.277
Vitamin B12 (pg/mL)	1.004	.382	.987–1.009
Folate (ng/mL)	.964	.370	.88–1.045
Model 3			
Variable	**Multivariate analysis**		
	Odds ratio	**p-value**	**95% CI**
Heart failure	.177	.063	.029–1.096
Hemoglobin (Hb)	.356	.145	.259–.569
Sleep duration (<6 hours)	1.917	.045	.678–5.418
Polypharmacy	.428	.119	.147–1.244
GDS groups (≥5 point)	.265	.012	.094–5.417

DISCUSSION

To our knowledge, this is the first study in Türkiye to examine the relationship between diabetic neuropathy and CGA components in older adults. The main finding of this study is that diabetic neuropathy is a condition that may negatively affect the IADLs of older adults, and a higher incidence of diabetic neuropathy may be associated with depression and less (i.e., <6 hours a day) sleep. As a result of these analyses, we found that there may be a relationship between the geriatric depression score, sleep duration, and diabetic peripheral neuropathy in older adults. Moreover, we found that the risk of developing neuropathy increases 0.2 times when depression scores are high and 1.9 times with less than 6 hours of sleep a day.

Diabetic neuropathy is a complication that affects functionality and quality of life, especially among older adults. Previous studies have examined how complications can be prevented by DM regulation, especially in the middle-aged group. However, complications develop as an inevitable result of aging and long-term DM. We designed this study to draw attention to these inevitable results. In the current study, we observed that the rate of diabetic neuropathy was lower in married individuals; however, in some studies examining demographic data, no significant difference was found (8).

A population survey study of 33,663 people, in which demographic data but no comparisons were given, found that as the marriage rate decreased, more serious complications increased (18). This situation can be interpreted as married people being more motivated to care for their chronic illnesses, and their partners can help in their care. This interpretation is strengthened by the fact that diabetic neuropathy was less common in the married people we identified in this study.

One of the main targets of our study was sleep problems. As a result of this study, we also determined a relationship between diabetic neuropathy and sleep. The rate of diabetic neuropathy was significantly lower in those whose sleep duration was longer than 6 hours a day. In other words, we found that diabetic neuropathy was associated with decreased sleep duration. In logistic regression, less sleep was found to be significantly associated with DPN. Moreover, a systematic review of sleep problems and diabetic neuropathy found that diabetic neuropathy was more common in patients with sleep apnea-hypopnea syndrome (19). Moreover, it has been stated that diabetic neuropathy may worsen sleep quality by causing pain and nocturia (19). Furthermore, a meta-analysis showed that restless leg syndrome (related to sleep disorders) may also be associated with diabetic neuropathy (20).

A study on treatment with melatonin together with pregabalin for painful diabetic neuropathy is interesting. It has also been reported that sleep deprivation may lead to hyperalgesia and a decrease in pain thresholds, which can be attributed to variations in melatonin levels (21). Besides, it is well-known that apart from its effects on the regulation of circadian rhythms in general as well as sleep-wake rhythms, melatonin also has neuroprotective, antioxidant, anti-inflammatory, immunomodulatory, anti-nociceptive, anti-depressant, anxiolytic, locomotor activity regulator, pressure-lowering ring, and antitumor activity effects. Therefore, other studies support our hypothesis that insufficient sleep may cause neuropathy, as well as other diseases due to a lack of melatonin, which is protective, as mentioned above (21).

Regarding comorbidities, we found that the rate of heart failure was higher in the diabetic neuropathy group (the diagnosis of heart failure was confirmed by a cardiologist). Moreover, cardiovascular autonomic

neuropathy (affecting the cardiovascular system) is possible in these patients; indeed, this is one of the most common complications of diabetes.

There are several mechanisms by which clinical heart failure develops, particularly metabolic changes, such as oxidative stress-mediated by reactive oxygen species (ROS), decreased myocardial perfusion due to endothelial dysfunction, autonomic dysfunction, and impaired glucose levels caused by insulin resistance (22). Irregular neurohormonal activation, due to diabetic neuropathy, leads to many diabetes-related cardiovascular diseases. Many neuropeptides are involved in cardiac injury. For this reason, the co-occurrence of these two diseases (DM and cardiovascular disease) is common (23). In fact, in a study of 4095 DM participants without detected heart failure, at least one of nephropathy, retinopathy, and neuropathy was detected in 34.8% upon evaluation (24).

Indeed, DM is a major risk factor for heart failure. Thus, even in undiagnosed patients, heart failure should be considered. In the logistic regression analysis performed in the current study, statistical significance was lost with co-factor assets. However, the clinical risk is always present.

We also obtained interesting results regarding the relationships between comprehensive geriatric assessments and DPN, which is the main aim of our study. The polypharmacy rate was higher in the neuropathy group, and the mean number of drugs was also significantly higher in the neuropathy group.

Considering that there are complications in people with uncontrolled DM treatment, multiple diabetes medications may be useful. The most common and disturbing effect of DPN is pain. Indeed, patients with DPN may take many painkillers.

It is well known that older adults often have many comorbidities and therefore may suffer from the side effects of polypharmacy (25). In another study conducted in Türkiye, the relationship between foot ulcers, one of the worst complications of diabetic neuropathy, and polypharmacy was examined. Complaints of hypertension, ischemic heart disease, and diabetic retinopathy were found to be significantly higher in patients with diabetic foot ulcers and polypharmacy (26).

DPN is one of the main causes of low handgrip strength and falls in older adults. In addition to age and polypharmacy, diabetes-related loss of strength, sensory perception, and loss of balance and cognitive function due to peripheral neuropathy contribute to an increased risk of low handgrip strength and falls (27).

In many other studies, the incidence of falls due to loss of balance and sensory damage was higher in the neuropathy group, and neuropathy was considered one of the main causes of falls in older adults. However, no correlation between falls and DPN was found in the results we obtained, which may be due to the small number of patients in the DPN group in our study. This may also be because most participants in our study were outpatients.

The effect of DPN on functionality in older adults is commonly seen in geriatric practice. Indeed, previous studies have shown that DPN affects both quality of life and daily functions, not only in the older adults but also in the general population (28, 29). A study conducted on older adults found that DPN affects ADLs but not IADLs (8). In our study, unlike this result, we found that DPN was not associated with ADLs but could be negatively associated with IADL.

The effect of DPN on functionality may be due to both its metabolic effects and its negative effects on the mental states of patients. In addition, most people with DPN have difficulty walking transferred because it is painful. We know that walking affects many IADLs. Indeed, DPN seems likelier to affect patients' IADLs. In the logistic regression analysis, this correlation decreased in the presence of cofactors.

Depression is another common geriatric syndrome whose relationship with DPN was investigated in our study. In our study, both the mean depression scores and their grouping were found to be higher in the DPN group. Moreover, it has also been emphasized in previous studies that DPN is associated with depression (30). In all studies of complications caused by DM, it has been shown that patients with DPN are more prone to depression compared to other microvascular complications (30, 31). Given the high prevalence of depression and DPN in diabetes, it is hardly surprising that these two conditions are related. In two meta-analyses, depression was independently associated with DPN (32, 33). In addition, antidepressants are used effectively to treat depression (34). It has been determined that DPN patients with high depression screening test scores feel pain more (35).

In most of the studies mentioned above, people over the age of 65 years were not included. One of the aims of the current study was to highlight this bias. Our study showed that there are similar findings in the relationship between DPN and depression in the over-65 age group. In addition, one of the conditions independently associated with DPN is included in the analysis in Table 3.

Regarding the comparisons of the laboratory results, in the DPN group, albumin, hemoglobin, and hematocrit values were observed to be low, which (when combined) suggests possible nutritional disorders. These nutritional deficiencies may be the cause of (or contribute to)

neuropathy. Drugs (used in the treatment of DPN), absorption deficiencies, and autoimmune conditions (such as pernicious anemia) may be the cause of anemia (36, 37).

In our study, we found no significant difference (according to the MNA scores) between the groups in terms of nutritional deficiency. We also found that there was no significant difference between the groups in terms of vitamin B12, folate, and vitamin D levels, which may cause or affect neuropathy when in nutritional deficiencies. We would like to point out that we could not find a relationship between these nutrients at the end of the study, since the difference between the neuropathy groups in albumin and hemoglobin values disappeared in multivariate logistic regression analysis (Model 3).

Another remarkable result is that there was no difference in the Hba1c results between the two groups (with or without DPN). Previous studies have shown that DM patients complaining of neuropathic pain have DM for a long period and poor glycemic control(5, 38, 39).

In our study, there was no significant difference in HbA1c values between the groups. The average HbA1c percentage in the participants in our study was 7.40%. Hence, their control of DM was within good limits. Among older adults, the Hba1c value, which shows the regulation of diabetes in the previous 3 months, may not have a significant relationship with neuropathy, unlike the general adult population.

The main strength of this study is that it evaluates DPN in older adults together with a comprehensive geriatric assessment, including sleep duration and laboratory values. Additional diseases and nutritional conditions that may affect neuropathy were also included in the study. A clinical psychiatric evaluation was performed for depression. Diagnosis of DPN was made by clinical evaluation, and patients diagnosed by a neurologist were included in the study.

This study has some limitations. First, the study could not yield a causality result due to its retrospective cross-sectional structure; it only considered factors that may be related. Due to the same structure, the number heterogeneity between the groups could not be achieved. Since the study was conducted with patients who applied to a health institution due to their complaints, it cannot be said that the results fully reflected the epidemiological findings. Second, the duration of DM in each participant was not noted in the study, despite DM duration being closely related to the incidence and severity of complications. Finally, a sleep assessment was done by asking the patients to provide the required information. And there was no formal tool used for pain assessment (e.g., Visual Analog Scale) which is crucial for DNP and insomnia relation. However, it would be better to use more objective methods, such as sleepiness and visual analog scales, in further studies.

CONCLUSION

DPN in older adults may affect the functionality and be associated with fewer sleep hours and depression, independent of DM regulation. In addition to blood glucose regulation, other factors, such as sleep duration and depressed mood, may be associated with DPN in older adults.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by the Clinical Resarches Ethics Committee of the Ankara University Medical Faculty (Date: 13.08.2018, Decision No: 13-878-18).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1092191
J Health Sci Med 2022; 5(4): 1170-1175

The role of red cell distribution width in predicting the prognosis of patients with breast cancer

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Cite this article as: Özdemir DB, Karayiğit A, Dizen H, Ünal B. The role of red cell distribution width in predicting the prognosis of patients with breast cancer. J Health Sci Med 2022; 5(4): 1170-1175.

ABSTRACT

Objective: In this study, we aimed to assess the relationship between preoperative red cell distribution width (RDW) and the clinicopathological stage and prognosis of disease in patients operated for invasive epithelial breast cancer (BC).

Material and Method: This retrospective cross-sectional study was conducted between January 2010 and January 2015 at a tertiary hospital in Turkey. A total of 280 patients who underwent surgery for histologically diagnosed invasive epithelial BC were included in the study.

Results: The mean age of the patients was 53.31±12.58 years. The median follow-up time was 83 (IQR: 56.5–102) months. According to the results we found, there was a statistically significant positive correlation between progesterone receptor (PR) negativity and RDW values (p=0.015). In addition, the RDW values of patients with perineural invasion (PNI) were found to be significantly higher than those without (p=0.036).

Conclusion: When the results of our study are evaluated together with prior reports, it can be said that higher preoperative RDW is associated with poor prognosis. When RDW is evaluated together with other possible prognostic factors, such as PNI and PR status, it has the potential to be a new, easily applicable and accurate marker to assess prognosis in patients with invasive epithelial BC.

Keywords: Breast cancer, red cell distribution width (RDW), progesterone receptor, perineural invasion, overall survival

INTRODUCTION

Breast cancer (BC) is the most common cancer and the main cause of cancer-related death in women (1). Its mortality and morbidity are increasing gradually (2). In addition to frequent local relapses and distant metastases, about 20% of patients with BC are diagnosed at advanced stages and experience either recurrence or distant metastasis within 5 years (1). Recognition of prognostic features are of critical importance (3). Despite significant improvements in treatment with advances in surgical treatments, prognosis still needs to be improved (4). Early diagnosis of cancer and prediction of prognosis are important for decision-making both before and after surgery. This shows the importance of identifying simple, useful and sensitive biomarkers that can be utilized for diagnostic, clinical and prognostic evaluation of BC (2).

Red cell distribution width (RDW) is a laboratory parameter commonly used in the measurement of erythrocyte anisocytosis (variability of the volume of circulating erythrocytes), and can be easily acquired from routine blood tests (5). In addition to its usual roles in the diagnosis of iron deficiency anemia or thalassemia (6), RDW elevation has been associated with ischemic heart disease, heart failure, atherosclerosis, vascular occlusive disease, hypertension, inflammatory bowel disease, and rheumatoid arthritis (7-10). Today, RDW is also employed as an inflammatory biomarker which may be important for cancers, since cancer presence has been associated with chronic inflammation (10,11). For instance, recent studies have established that RDW levels are associated with carcinogenesis, tumor progression and cancer prognosis (12-14). More specifically, RDW is demonstrated to be associated with poor prognosis in various tumor types such as lung cancer, malignant mesothelioma, and multiple myeloma (15-17). There

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Received: 29.03.2022 **Accepted:** 28.06.2022

has been an increase in the number of studies examining possible relationships between the stage and prognosis of BC and RDW, and it has been suggested that RDW has a prognostic value in BC in the majority of these studies (2,18-20). However, considering that complete blood count parameters may demonstrate considerable variations based on measurement devices and demographic characteristics, it is clear that more studies are needed to assess the prognostic value of RDW in women with BC.

In this study, we aimed to assess the relationship between preoperative RDW values and the clinic-pathological stage and prognosis of disease in patients operated for invasive epithelial BC.

MATERIAL AND METHOD

Study Design

This cross-sectional study was conducted from January 2010 to January 2015 at the Department of General Surgery, Osmangazi University Faculty of Medicine, Eskişehir, Turkey. The study was initiated with the approval of the Ethics Committee of Osmangazi University Faculty of Medicine (Date: 15.06.2021, Decision No: 02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written informed consent for study participation was not deemed to be necessary by the Osmangazi University Medical Ethics Committee, since the study was retrospective. All data were recorded anonymously.

Study Population

A total of 280 patients who underwent surgery for histologically diagnosed invasive epithelial BC were included in the study. Male patients, subjects who had received neoadjuvant chemotherapy and/or radiotherapy, those with second primary cancers, subjects with autoimmune diseases, those with hematological malignancies, patients who used corticosteroids in the last 6 months, cases with active infection, patients who could not be followed, and subjects with incomplete data were excluded from the study.

Data Collection

The following information about each patient was obtained from hospital records: demographic characteristics, menopause status, tumor localization, biopsy method, type of surgery, axillary management, laboratory results, pathological and immunohistochemical results, whether adjuvant chemotherapy and/or adjuvant radiotherapy was received, use of hormonal therapy, presence of recurrence, follow-up time (months), final status (mortality).

Laboratory Analysis

Preoperative blood samples were drawn from the antecubital vein for measurement of complete blood count (CBC), cancer antigen 15-3 (CA15-3), carcinoembryonic antigen (CEA). CBC including neutrophil count ($\times 10^3$) lymphocyte count ($\times 10^3$), platelet count ($\times 10^3$) and RDW; CA15-3 and CEA values were measured using routine devices 2 weeks before surgery at the Clinical Biochemistry Department of Osmangazi University Faculty of Medicine.

Pathological and Immunohistochemical Analysis

All of the specimens acquired from fully resected tumors had been sent to the pathology unit of Osmangazi University Faculty of Medicine for pathological examinations. Pathological diagnosis, surgical margin, tumor grade, estrogen receptor (ER) status, progesterone receptor (PR) status, c-erbB-2 positivity, ki-67 score, presence/absence of perineural invasion (PNI), lymphovascular invasion (LVI), extracapsular invasion (ECI), multifocality, multicentricity, T and N stages, and clinical stage (reported according to the pathological classification criteria of the 8th Edition of the American Joint Committee on Cancer guidelines for BC), number of lymph nodes, number of metastatic lymph nodes were reported by qualified pathologists. Immunohistochemical evaluations were performed by the same pathologists using the same routine techniques and devices.

Statistical Analysis

All analyses, with a significance threshold of 0.05, were performed on SPSS v25 (SPSS Inc., Chicago, IL, USA). Q-Q and histogram plots were evaluated to determine presence/absence of normal distribution. Data are given as mean ± standard deviation or median (interquartile range; IQR) according to normality results, and as frequency (percentage) for categorical variables. Comparison of RDW levels were performed with the Mann-Whitney U or the Kruskal-Wallis test depending on the number of groups being compared. Spearman correlation coefficients were calculated to evaluate relationships between RDW and other continuous variables.

RESULTS

Two hundred and eighty female patients were included in our study, and the mean age of the patients was 53.31 ± 12.58 (range: 27–89) years. Median follow-up time was 83 months (IQR: 56.5–102). Clinic and demographic characteristics of the patients, surgical features, pathological results and laboratory findings are summarized in **Table 1**.

Table 1. Summary of patients and tumor characteristics	
Age	53.31 ± 12.58
Sex, female	280 (100.0%)
Menopause status	
Premenopausal	104 (37.1%)
Postmenopausal	176 (62.9%)
Side	
Right	143 (51.1%)
Left	137 (48.9%)
Bilateral	0 (0.0%)
Diagnosis	
Invasive ductal carcinoma	233 (83.2%)
Invasive lobular carcinoma	17 (6.1%)
Other invasive tumors	30 (10.7%)
Biopsy method	
Tru-cut	190 (67.9%)
Excisional	40 (14.3%)
Incisional	50 (17.9%)
Surgery	
Mastectomy	213 (76.1%)
Breast-conserving	67 (23.9%)
Surgical margin	
Negative	261 (93.2%)
Positive & Re-excision	5 (1.8%)
Positive & Mastectomy	14 (5.0%)
Axillary management	
SLNB (-)	114 (40.7%)
SLNB (+) & ALND	103 (36.8%)
ALND	63 (22.5%)
Grade	
Grade 1	75 (26.8%)
Grade 2	147 (52.5%)
Grade 3	58 (20.7%)
Estrogen receptor positivity	245 (87.5%)
Progesterone receptor positivity	216 (77.1%)
cerbB2 positivity	108 (38.6%)
ki-67 score	
0-15	131 (46.8%)
16-30	83 (29.6%)
>30	66 (23.6%)
Perineural invasion	65 (23.2%)
Lymphovascular invasion	86 (30.7%)
Extracapsular invasion	93 (33.2%)
Multifocal	59 (21.1%)
Multicentric	39 (13.9%)
T stage	
T1	77 (27.5%)
T2	169 (60.4%)
T3	25 (8.9%)
T4	9 (3.2%)
N stage	
N0	115 (41.1%)
N1	85 (30.4%)
N2	45 (16.1%)
N3	35 (12.5%)
M stage	
M0	278 (99.3%)
M1	2 (0.7%)
Stage	
Stage I	51 (18.2%)
Stage II	137 (48.9%)
Stage III	90 (32.1%)
Stage IV	2 (0.7%)
Number of lymph nodes	12 (3-21)
Number of metastatic lymph nodes	1 (0-4)
Adjuvant chemotherapy	255 (91.1%)
Adjuvant radiotherapy	183 (65.4%)
Hormonotherapy	253 (90.4%)
Recurrence	41 (14.6%)
Follow-up time, months	83 (56.5-102)
Final status	
Exitus	66 (23.6%)
Alive	214 (76.4%)
Neutrophil ($\times 10^3$)	4.45 (3.60-5.56)
Lymphocyte ($\times 10^3$)	2.0 (1.6-2.5)
Platelet ($\times 10^3$)	254 (218-296.5)
RDW	13.9 (13.1-15.0)
CA15-3	22.4 (15.7-30.76)
CEA	1.86 (1.18-2.86)

Data are given as mean ± standard deviation or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. SLNB: Sentinel lymph node biopsy, ALND: Axillary lymph node dissection

There was a significant positive correlation between PR negativity and RDW values (p=0.015). In addition, RDW values of cases with PNI were found to be significantly higher than those without PNI (p=0.036). When the relationship of RDW with continuous variables was examined, it was seen that there was a significant negative correlation only between CA15-3 and RDW, but the correlation coefficient was very weak (r=-0.135, p=0.024). There were no significant relationships between RDW value and age (p=0.455), menopause status (p=0.663), pathological diagnosis (p=0.943), tumor grade (p=0.783), ER positivity (p=0.141), c-erbB-2 (p=0.792), Ki-67 score (p=0.908), LVI (p=0.614), extracapsular invasion (p=0.810), tumor multifocality (p=0.091), tumor multicentricity (p=0.810), T stage (p=0.641), N stage (p=0.286), clinical stage (p=0.947), number of lymph nodes (p=0.831), number of metastatic lymph nodes (p=0.826), CEA (p=0.248), presence of recurrence (p=0.326), or death status (p=0.900) (**Table 2 and 3**).

DISCUSSION

Breast cancer currently accounts for almost 1 in 3 cancers and is considered the most common cancer worldwide. Most importantly, BC is currently the main cause of cancer-related death in women (18). Although the overall mortality rate from BC decreased by 36% from 1989 to 2012 due to advances in early detection and systemic treatments, to our current knowledge, about 20% of BC patients are diagnosed in advanced stages and experience recurrence or distant metastasis within 5 years (18,21) Therefore, outcome evaluation in patients with BC is very important because it influences treatment decisions.

Table 2. RDW levels with regard to patients and tumor characteristics		
	RDW	**p**
Menopause status		
Premenopausal	13.85 (12.95-15.5)	0.663
Postmenopausal	13.9 (13.1-14.8)	
Diagnosis		
Invasive ductal carcinoma	13.9 (13.1-14.9)	0.943
Others	13.9 (12.9-15.5)	
Grade		
Grade 1	13.8 (13.1-14.8)	
Grade 2	14.0 (13.0-15.3)	0.783
Grade 3	13.55 (13.2-14.9)	
Estrogen receptor		
Negative	14.5 (13.2-15.8)	0.141
Positive	13.8 (13.1-14.9)	
Progesterone receptor		
Negative	14.3 (13.25-15.75)	0.015
Positive	13.7 (13.05-14.8)	
cerbB2		
Negative	13.9 (13.1-15.0)	0.792
Positive	13.9 (13.2-14.9)	
ki-67 score		
0-15	14.0 (13.1-15.1)	
16-30	13.9 (13.1-14.9)	0.908
>30	13.75 (13.0-14.9)	
Perineural invasion		
No	13.7 (13.0-14.9)	0.036
Yes	14.2 (13.4-15.8)	
Lymphovascular invasion		
No	13.9 (13.1-15.0)	0.614
Yes	13.85 (13.2-15.1)	
Extracapsular invasion		
No	13.8 (13.1-15.0)	0.810
Yes	13.9 (13.1-14.9)	
Multifocal		
No	13.7 (13.0-14.9)	0.091
Yes	14.2 (13.3-15.1)	
Multicentric		
No	13.9 (13.1-14.9)	0.810
Yes	13.8 (13.1-15.1)	
T stage		
T1	13.9 (13.2-14.8)	
T2	13.9 (13.1-15.1)	0.641
T3 & T4	13.45 (13.0-14.8)	
N stage		
N0	13.7 (13.2-15.0)	
N1	14.0 (13.0-14.9)	0.286
N2	14.5 (13.1-15.6)	
N3	13.6 (13.1-14.2)	
Stage		
Stage I	13.7 (13.2-14.8)	
Stage II	14.0 (13.1-15.1)	0.947
Stage III & IV	13.9 (13.05-15.2)	
Recurrence		
No	13.9 (13.1-15.1)	0.326
Yes	13.6 (13.0-14.6)	
Final status		
Exitus	13.8 (13.1-14.8)	0.900
Alive	13.9 (13.1-15.0)	

Data are given as median (1st quartile-3rd quartile) according to normality of distribution.

Table 3. Correlations between RDW and other continuous variables

	r	**p**
Age	-0.045	0.455
Number of lymph nodes	-0.013	0.831
Number of metastatic lymph nodes	-0.013	0.826
CA15-3	-0.135	0.024
CEA	-0.069	0.248

Inflammation in the tumor microenvironment triggers tumor growth, invasion, angiogenesis, and metastasis (2). Cancer-related systemic inflammation has been shown to play an important role in the development and progression of many neoplastic diseases, including BC. In addition to clinicodemographic data, many new hematological prognostic markers have been discovered and defined (19). RDW describes the size variability of circulating red blood cells and has recently gained use as an inflammatory biomarker (18). It has been suggested that RDW is associated with the poor prognosis of different cancer types, such as non-small cell lung cancer, prostate cancer, colorectal cancer, and gastric cancer (22-25). The reason for the relationship between RDW and survival and prognosis of cancer has not been clearly explained. However, high RDW is thought to be associated with malnutrition, oxidative stress and age-related diseases as well as inflammation (26). In a retrospective cohort study including 825 patients, a significant positive correlation was found between RDW elevation and tumor size, lymph node metastasis number, and tumor stage in patients with BC. In the multivariable analysis of the same study, it was suggested that RDW was an independent predictor for local recurrence/distant metastasis. It was also found that the group with high RDW demonstrated poorer prognosis compared to patients with low RDW. Again in this study, no significant relationship was found between RDW and ER positivity, PR positivity and c-erbB-2 positivity (2). In a study of several preoperative routine laboratory markers that could be used to predict postoperative recurrence and death in patients with BC, RDW value demonstrated the highest predictive power

for postoperative mortality and survival (18). RDW elevation has also been shown to be an independent prognostic factor for both OS and disease-free survival (DFS). In this study, a significant correlation was found between RDW and peritumoral vascular invasion, ER status, PR status, c-erbB-2 status, and Ki-67 score (19). Another retrospective study showed that RDW is one of the most effective indicators in distinguishing BC from healthy individuals and, when combined with other tests, RDW can enable early detection of BC (20). In a pilot study focused on this topic, RDW was found to be significantly elevated in patients with BC and it was suggested that RDW could be helpful in differentiating benign or malignant tumors (27). An interesting result of the same study was that RDW was significantly correlated with primary tumor diameter and the number of infiltrating axillary lymph nodes. The study also emphasized that there was a close relationship between RDW elevation and c-erbB-2 overexpression. As a result, it has been said that RDW can be used to monitor response recipients of anti-c-erbB-2 agents (27). In the present study, we did not find a significant relationship between RDW and OS. However, RDW values were higher in BC patients with PR negativity. In addition, there was a significant relationship between RDW level and PNI presence.

In addition to being critical regulators of transcription, PRs also function to activate the signal transduction pathways of proliferation (28). The ER is a nuclear hormone receptor that acts as a transcription factor, and PR is involved in ER signaling. Both ER and PR are important triggers of BC development, and it is well known that positivity for ER and PR improve response to endocrine therapy but not cytotoxic chemotherapy. Consequently, the presence/absence of these receptors play an important role in disease recurrence and OS (29). Huang et al. (30) found positive PR status as an independent prognostic for OS and DFS. Similarly, multivariable analyses of another study confirmed the independent association between PR expression and survival (31), similar to other studies (32). Although RDW was not found to be associated with OS in our study, this indirect relationship between RDW and PR status and the fact that PR negativity was associated with poor OS in previous studies may suggest that RDW may be indirectly associated with OS.

Perineural invasion is a relatively rare histological feature that occurs 10 times less frequently than LVI in patients with invasive BC. It has been established that PNI may be associated with some tumor features, such as higher T stage, higher tumor grade, and LVI, but its role as an independent poor prognostic factor is controversial (33). In one study, vascular invasion, axillary lymph node and PR positivity ratios were found to be significantly higher in PNI-positive patients than in PNI-negative ones. In the same study, no difference was found between PNI-positive and PNI-negative patients in terms of DFS in patients with BC (1). Cox regression analysis of another study also found PNI to be significantly associated with DFS (34). These discrepancies between studies examining relationships between PNI and survival reveal the need for more comprehensive studies on this subject. To our knowledge, there is no other study examining the relationship between RDW and PNI in BC.

There are some limitations of our study. First, the current study is single-center which limits the generalizability. Secondly, the research was performed in a retrospective manner, so the data obtained should be supported by prospective studies due to possible biases. Third, we did not investigate the molecular mechanisms, and therefore, our results only show associations which may have emerged in relation with various other factors or parameters. Finally, imbalances in the distribution of the patient numbers in the subgroups of some factors may have adversely affected statistical evaluations. Therefore, there is a need for collaborative, multicenter, prospective studies with larger numbers of patients in which molecular mechanisms are also examined to confirm our results.

CONCLUSION

In this study in which we investigated the prognostic role of RDW in BC, we did not find a direct significant relationship between RDW and survival, contrary to most published literature. There was a positive correlation between RDW and PNI only, and a negative correlation only with PR positivity. When the results of our study and previous studies are evaluated together, it can be said that patients with relatively higher preoperative RDW may require closer follow-up. Also, if RDW is evaluated together with other possible prognostic factors (such as PNI and PR status), it may be more likely to obtain potential benefits with its assessment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Ethics Committee of Osmangazi University Faculty of Medicine (Date: 15.06.2021, Decision No: 02).

Informed Consent: Written informed consent for study participation was not deemed to be necessary by the Osmangazi University Medical Ethics Committee, since the study was retrospective. All data were recorded anonymously.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: The author declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1130930
J Health Sci Med 2022; 5(4): 1176-1182

The effect of COVID-19 fear on hygiene behaviors in hemodialysis patients during the COVID-19 pandemic

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Cite this article as: Kemeç Z, Aslan S. The effect of COVID-19 fear on hygiene behaviors in hemodialysis patients during the COVID-19 pandemic. J Health Sci Med 2022; 5(4): 1176-1182.

ABSTRACT

Aim: Current study aims to specify the fear levels and hygiene habits of hemodialysis (HD) patients infected or not infected with coronavirus disease 2019 (COVID-19) in the course of the COVID-19 pandemic.

Material and Method: This study was performed between 15-30 April 2021 as a case-control study whose population consisted of 124 dialysis patients treated in the dialysis unit of Batman Education and Research Hospital. In the dialysis unit, while 25 HD patients who were not present with COVID-19 were included in the control group, 25 dialysis patients were diagnosed with COVID-19 and agreed to participate in the study were included in the case group. "Patient Descriptive Form", "COVID-19 Hygiene Scale (CHS)" and "COVID-19 Fear Scale (CFS)" were used to collect the study data.

Results: While the mean score of the Changing Hygiene Behaviors sub-dimension of the HD patients in the case group was 23.72±4.90; the mean score of the same sub-dimension belonging to the HD patients in the control group was determined as 22.40±5.25, and there was no statistically meaningful difference between the two groups. The mean CFS score of the HD patients in the case group was 13.60±7.92; while the mean CFS score of the HD patients in the control group was found to be 17.72±7.43. No statistically meaningful difference was observed between the two groups.

Conclusion: The mean CFS and CHS scores of the HD patients in the control group were higher, but no statistically meaningful difference was observed between the two groups.

Keywords: Fear levels, hygiene habits, hemodialysis, coronavirus disease 2019

INTRODUCTION

Hemodialysis is an extracorporeal blood purification procedure resorted to filtering uremic substances in the blood in chronic kidney disease (CKD) (1). CKD is characterized by the progressive and irreversible loss of nephrons, and metabolic and also hormonal dysfunction is present in the kidneys, thus adversely affecting the balance of fluid, electrolytes, and other shaped elements in the urine (2). The principle behind HD is based on the displacement of molecules from high concentrations to low ones until the concentration of small molecules that can pass through the membranes equalizes on both membrane surfaces (3).

Today, the number of CKD patients in our country is over 83,000 and according to 2019 data, CKD treatment is provided with HD at a rate of 73.21% (1, 4). It is thought that the number of CKD patients undergoing HD has increased 2.5 times in the last 15 years, and it is known that the majority of patients are waiting for kidney transplantation. It is estimated that there are around 3.5 million CKD patients awaiting kidney transplantation worldwide and that approximately 10% of the world's population suffers from CKD, CKD ranks third among the causes of mortality (5).

Chronic kidney disease patients routinely come to hospitals or HD centers to receive HD treatment 3 times a week. Being an HD patient is an extremely stressful and tiring experience, which significantly threatens individual independence, weakens the workforce, as well as disrupts psychological state, while reducing comfort as well as the quality of life, and limit social life (1, 6). During the pandemic, the already difficult lives of HD patients may have become even more problematic (7).

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Received: 14.06.2022 **Accepted:** 29.06.2022

COVID-19, which causes viral pneumonia, is a coronavirus and was called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) because of its resemblance to the SARS virus (8, 9). COVID-19, which causes SARS, is a destructive disease that arises in Wuhan, China towards the end of 2019, the disease has given rise to a global pandemic and people still sense its devastating impacts. World Health Organization declared the epidemic caused by SARS-CoV-2 as a pandemic in March 2020, since it has influenced large human populations (10). The available studies in the literature have shown that HD patients are in the risk group in this process and that this group of patients is severely affected by the COVID-19 virus, just like in other chronic diseases. It has been stated in studies that those with at least one chronic disease are among the groups that increase the fatality rates in the COVID-19 pandemic anywhere in the world and in our country (8,9). In the literature, 23.7% of COVID-19 patients were found to be accompanied by at least one chronic disease (11), the COVID-19 virus was more common in individuals with chronic disease (51%), and the disease symptoms caused by the virus had a more severe course (12,13), and also that 48% of patients with COVID-19 virus were present with comorbidities (9).

Chronic kidney disease generally leaves significant effects on the lives of patients. It is known that the social performance of CKD patients decreases, they have difficulty in fulfilling their family roles and professional responsibilities, and their sexual life deteriorates due to the disease (14, 15). The pandemic process and the threat of COVID-19 may urge CKD patients to think about the fear of death. Fear and depression may cause loss of control in patients in general, coupled with inner withdrawal as well as the preconceived idea that the use of drugs may be unnecessary, weakening the immune system (16). The life motivation and adaptation of CKD patients who experience intense stress accompanied by fear may be weakened. HD patients, who are more exposed to infectious agents and virus threats than other individuals due to their frequent clinic visits, may become infected when hygiene is missing. HD patients who can easily become infected due to a lack of hygiene can also pass away. COVID-19 contamination can cause individuals to become infected more rapidly in the existence of the chronic disease or aggravate the course of the disease, even if there are hygiene and distance limits set between people. Therefore, COVID-19 may be riskier in the HD patient group, a chronic disease (17). It is thought that there is a relationship between the hygiene habits of HD patients and COVID-19 during the pandemic caused COVID-19 in this study. In this study, it was purposed to examine the relationship between fear of COVID-19 and hygiene habits of CKD patients.

Main Points

1. Hemodialysis patients who do not have COVID-19 have higher fear levels.
2. Hygiene behaviors of HD patients who do not have COVID-19 are higher.
3. The mean CFS and CHS scores of the HD patients in the control group were higher, but no statistically meaningful difference was observed between the two groups. The high fear of patients without Covid 19 disease may be due to their ignorance of the complications of the disease.

MATERIAL AND METHOD

This single-center, questionnaire study was designed in accordance with the Declaration of Helsinki, with the approval of the Batman University Ethics Committee (Date: 09.04.2021, Decision No: 2021/01-12). This study purposes to establish the fear levels and hygiene habits of HD patients infected or not infected with COVID-19 along with the COVID-19 pandemic.

Study Design and Participants

This study was conducted between 15-30 April 2021 as a case-control study whose population consisted of 124 dialysis patients treated in the Dialysis Unit of Batman Education and Research Hospital. In the dialysis unit, 35 dialysis patients were recognized with COVID-19. At the time of the study, 7 patients passed away, 2 patients were receiving treatment in the intensive care unit and 1 patient was excluded as we could not communicate with him (**Figure 1**). 25 HD patients who met the study criteria and were approved to participate in the study were included in the case group, while 25 HD patients who were not present with COVID-19 were included in the control group.

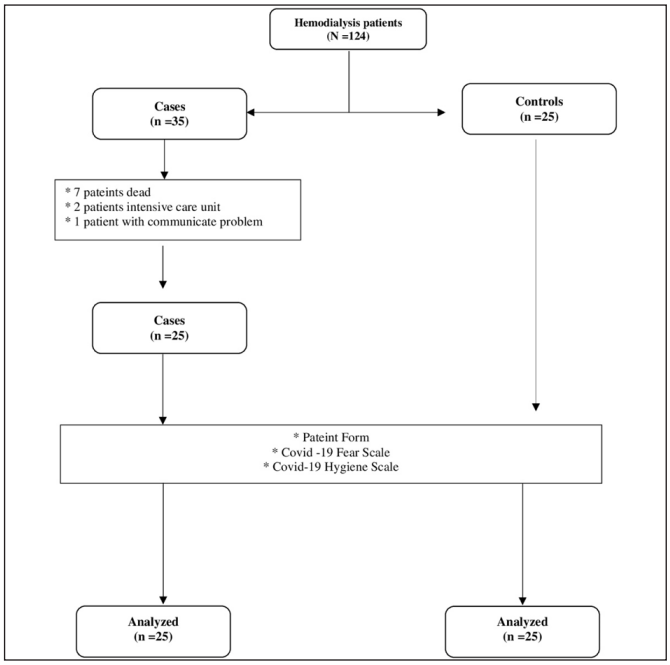

Figure 1. Study flow diagram

Inclusion Criteria

i. Not having any connection problems.
ii. Approving joining the study
iii. Hemodialysis patients with and without COVID-10 were included in the study.

Data Collection Tools

"Patient Descriptive Form", "COVID-19 Fear Scale (CFS)" and "COVID-19 Hygiene Scale (CHS)" were used to collect the study data. The Patient Descriptive form consists of 9 questions on the patient's demographic data such as education status, age, gender, family type, income status, presence of any chronic disease other than CKD, COVID-19 test status, COVID-19 and CKD status in relatives.

COVID-19 Fear Scale

Ahorsu et al. (18) developed a scale to quantify the fear levels of individuals arising from COVID-19. The substances of the scale originated derived from an exhaustive review of existent scales on fear, expert assessments, and participant interviews. While Turkish adaptation of the scale was carried out by Satici et al. (19) the Cronbach alpha internal consistency coefficient was observed to be 0.84.

The scale has a single factor system and comprises 7 items in a five-point Likert type (1 = I strongly disagree; 5 = I strongly agree). There is no test-oriented substance on the scale. The internal consistency of the scale and the test-retest credibility were calculated as 0.82 and 0.72, respectively. A high score on the scale indicates a high fear of COVID-19. In this study, the Cronbach Alpha value was determined as 0.91.

COVID-19 Hygiene Scale

COVID-19 Hygiene Scale which was created by Çiçek et al. (20) in order to determine the hygiene behaviors of individuals during the COVID-19 epidemic process consists of 6 sub-dimensions and 27 items. While the "Changing Hygiene Behaviors" sub-dimension consists of 6 items (7th, 11th, 12th, 14th, 21st, and 27th items), the Home Hygiene sub-dimension consists of 4 items (16th, 18th, 19th, and 20th items), Social Distance and Mask Wear sub-dimension consists of four items (1st, 2nd, 3rd, and 25th items), Shopping Hygiene sub-dimension consists of 5 items (15., 22., 23., 24. and 26. items), Hand Hygiene sub-dimension consists of five items (4th, 5th, 6th, 8th and 9th items) and lastly, Hygiene When Coming Home from Outside sub-dimension consists of three items (10^{th}, 13^{th}, and 17^{th} items). The scale is a 5-point Likert scale (1- never, 5- always). The highest and the lowest scores acquired from the scale were 135 and 27, respectively. The high score indicates that individuals have a high level of behavior related to personal and general hygiene in order to protect themselves from the epidemic and give importance to hygiene measures. The Cronbach alpha value obtained in the study was 0.90.

Data Analysis

After being coded by the researchers, the data were subjected to statistical analysis using SPSS (Statistical Packed for The Social Sciences) 25.0 IBM statistical software. The analysis of data was calculated on the basis of descriptive statistics. Since the data was suitable for normal distribution, ANOVA and t-tests were applied to independent groups from parametric tests. Pearson correlation analysis was executed to ascertain the relationship between descriptive features and scales. Scale Reliability Coefficient was identified in the form of Cronbach's Alpha. The evaluation of the procured outcomes, $p<0.05$ error level, and 95% confidence interval were taken into consideration.

Ethical Aspect of the Study

The aim of the study was expressed to the patients who were identified as suitable for inclusion in this study. They were also informed about patients are optional and that they can opt-out anytime they want. Patients participating in the survey were reassured that their personal information will not be disclosed to others, and their affidavits for confidentiality are signed.

RESULTS

The comparison of the descriptive characteristics of the control and case groups of HD patients is presented in Table 1. According to **Table 1**, there wasn't any statistical difference in terms of gender, age, marital status, income status, chronic disease status, or COVID-19 test status of the HD patients participating in the study ($p>0.05$). A statistically substantial difference was defined between the educational status of the patients in the case and control groups undergoing HD (In other words, high school graduate patients are more involved in the control group than in the case group.) ($p<0.05$), (**Table 1**). The comparison of CFS and CHS sub-dimension and total mean scores of the patients in the case-control group of HD patients is given in **Table 2**. While the mean CFS score of the HD patients in the control group 17.72±7.43; the mean CFS score of the HD patients in the case group was found to be 13.60±7.92. Any statistically significant difference wasn't detected between the two groups. However, the mean CRF scale scores of the HD patients in the control group were higher (**Table 2**).

Table 1. Comparison of the descriptive features of the case and control groups in hemodialysis patients

Variables	Case n (%)	Control n (%)	Sig. (2-tailed)	p
Gender			X^2= 1.299	0.254
Female	16 (32.0)	12 (24.0)		
Male	9 (18.0)	13 (26.0)		
Age (years)			X^2= 3.346	0.062
Below 64	17 (34.0)	21 (42.0)		
Above 65	9 (18.0)	3 (6.0)		
Marital status			X^2= 14.266	0.001
Married	24 (48.0)	12 (24.0)		
Single	1 (2.0)	13 (26.0)		
Education level			X^2= 7.714	0.06
Illiterate	15 (30.0)	6 (12.0)		
Primary school	8 (24.0)	13 (26.0)		
High school	1 (2.0)	5 (10.0)		
Universty	1 (2.0)	1 (2.0)		
Income level			X^2= 0.083	0.959
Poor	13 (26.0)	12(24.0)		
Middle	11 (22.0)	12 (24.0)		
High	1 (2.0)	1 (2.0)		
Presence of chronic illness			X^2= 1.299	0.254
Yes	16 (32.0)	12 (24.0)		
No	9 (18.0)	13 (26.0)		
Diabetes mellitus			X^2= 0.015	0.574
Yes	8 (16.0)	7 (14.0)		
No	18 (36.0)	17 (34.0)		
Hypertension			X^2= 2.039	0.126
Yes	15 (30.0)	9 (16.0)		
No	11 (22.0)	15 (30.0)		
Cardiovascular diseases			X^2= 0.952	0.329
Yes	2 (4.0)	4 (8.0)		
No	24 (48.0)	20 (40.0)		
The status of performing COVID-19 test			X^2= 0.397	0.754
Yes	19 (38.0)	17 (47.0)		
No	6 (12.0)	8 (16.0)		
The status of their relatives being diagnosed with COVID-19			X^2= 0.0001	0.999
Yes	7 (14.0)	7 (14.0)		
No	18 (36.0)	18 (36.0)		

The mean score of the Changing Hygiene Behaviors sub-dimension of the HD patients in the control group was 22.40±5.25; while the mean score of the Changing Hygiene Behaviors sub-dimension of the HD patients in the case group was determined as 23.72±4.90, and there was no statistically meaningful difference between the two groups. However, the mean scores of the Changing Hygiene Behaviors sub-dimension of the HD patients in the case group were found to be higher. Home Hygiene sub-dimension score of HD patients in the control group was 16.76±3.09; while the mean in the case group was found to be 16.36±3.60, and the difference between the two groups was not statistically meaningful (**Table 2**). On the other hand, the mean scores of the Home Hygiene sub-dimension of the HD patients in the control and case groups were almost equal to each other.

Table 2. Comparison of the COVID-19 fear scale and COVID-19 hygiene scale sub-dimensions and total mean score of hemodialysis patients in the case and control groups

Variables	n	X ±Sd	Sig. (2-tailed)	p
COVID-19 Fear Scale			U=380.000	0.186
Cases	25	13.60±7.92		
Control	25	17.72±7.43		
Changing hygiene behaviors in the pandemic			U=264.000	0.344
Cases	25	23.72±4.90		
Control	25	22.40±5.25		
Home hygiene			U=326.000	0.786
Cases	25	16.36±3.60		
Control	25	16.76±3.09		
Social distance and wear of masks			U=342.000	0.553
Cases	25	17.04±5.62		
Control	25	17.16±3.99		
Shopping hygiene			U=350.500	0.459
Cases	25	14.04±5.62		
Control	25	15.64±6.47		
Hand hygiene			U=363.000	0.321
Cases	25	19.40±5.08		
Control	25	21.04±4.01		
Hygiene when coming home from outside			U=319.000	0.899
Cases	25	10.44±3.41		
Control	25	10.68±3.33		
COVID-19 hygiene scale			U=334.000	0.676
Cases	25	101.00±20.24		
Control	25	103.68±19.83		

*p<0.05, U =Mann-Whitney U

Social Distance and Mask Wear sub-dimension mean scores of HD patients in the control group were 17.16±3.99; while the mean score of the Social Distance and Mask Wear sub-dimension of the HD patients in the case group was found to be 17.04±5.62, and there was no statistically meaningful difference between the two groups. Also, Social Distance and Mask Use sub-dimension mean scores of HD patients in the control and case groups were almost equal to each other. While the mean Shopping Hygiene sub-dimension score of HD patients in the case group was 14.04±5.62; the same mean score in the control group was found to be 15.64±6.47, and the difference between the two groups was not statistically meaningful. However, the Shopping Hygiene sub-dimension mean scores of HD patients in the control group were found to be higher. While the mean score of the Hand Hygiene sub-dimension of the HD patients in the case group was 19.40±5.08; the same in the control group was not found to be 21.04±4.01 and the difference between the two groups was not statistically meaningful. However, the Hand Hygiene sub-dimension mean scores of HD patients in the control group were observed to be higher.

The mean scores for the same in the control group were 10.68±3.33; while the mean score of the Hygiene When Coming Home from Outside sub-dimension of the HD

patients in the case group was determined as 10.44±3.41, and there was no statistically meaningful difference between the two groups. However, the mean scores of the Hygiene sub-dimension of the HD patients in the control and case groups were found to be almost equal to each other. The mean CHS score of the HD patients in the case group was 101.00±20.24; while the same for those in the control group was 103.68±19.83, and the difference between the two groups was not statistically meaningful. However, the mean CHS scale scores of the HD patients in the control group were found to be higher (**Table 2**, **Figure 2**).

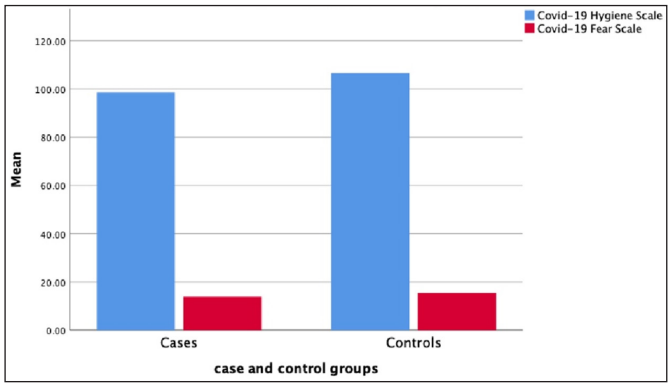

Figure 2. Comparison of the COVID 19 fear scale and COVID-19 hygiene scale total mean score of hemedialysis patients in the case and control groups

DISCUSSION

People undergoing HD feel the unfavorable impacts of the COVID-19 process at a higher grade. The infection risk of this patient group is high and they are in the chronic patient's category. In addition to advanced age and the presence of comorbidities, the immune system is significantly weakened in patients who experience COVID-19 complications (21). It has been reported in the literature that, 20.3% of the mortalities sourced by SARS-COV-1 are patients with more than one comorbidity (22). COVID-19 has been causing extremely important and frightening consequences around the world. High stress, weak immune system, and increased catabolism are the factors that give rise to COVID-19 to be riskier for patients receiving HD and the infection course can be mortal in these groups.

In the literature, it has been noted that total lymphocytes are depressed, the prothrombin time is prolonged and lactate dehydrogenase levels are increased due to COVID-19 (10). However, T and B cell dysfunctions are common in patients receiving HD (23, 24), and they may suffer from more advanced lymphopenia with COVID-19 infection (25). Nevertheless, pre-infectious lymphopenia and similarly elevated procalcitonin do not provide insight as a prognostic criterion in the COVID-19 diagnosis, which requires the use of advanced diagnostic methods (radiographic findings, and viral nucleic acid testing) in COVID-19 infected HD patients (25).

The knowledge and awareness of individuals about undesirable impacts of COVID-19 are augmenting daily, due to the increased effect of both social media and mass. Therefore, HD patients are as well conscious of that, vulnerability of COVID-19 can be mortal which can arouse fear in individuals. Experiencing high levels of stress and fear is an undesirable experience which suggests the possibility of death (26). As a matter of fact, COVID-19 fear level of control group with COVID-19 was higher than the patients in case group ($p<0.05$) in our study. It was emphasized that the risk of transmission arouses high fear due to the knowledge of the harmful impacts of COVID-19 in a study carried by Souse and coworkers with the participation of dialysis patients (27). Besides to this situation, the fact that patients receiving HD are generally older and have more than one such chronic diseases and comorbidities as hypertension (HT), diabetes mellitus (DM) and cardiovascular diseases (CVD) increase mortality (28).

In our study, the control and case groups had similar characteristics in terms of DM, cardiovascular diseases, HT and other comorbid diseases. COVID-19 has a mortality rate of 4.6% worldwide (29), and it has so far been determined that10.5% of these mortalities are owing to CVD (30). However; DM was the frequent comorbidity in patients with middle east respiratory syndrome (MERS) and SARS-CoV-1 previous to COVID-19. In SARS, the prevalence of DM was 11%, and the existence of DM was hypotheses to increase the risk of death 12-fold (31,32). HT and DM were found in 50% of MERS cases (33). It has also been determined that the risk of CVD development due to COVID-19 is high in patients with DM and HT, and deaths occur in more than 50% of these patients (34-36). In a prior study, it was reported that 5.7% of mild cases and 16% of severe COVID-19 cases are DM ones (11).

Compared to the normal population, the mortality rate among dialysis patients is 6.5-7.9 times higher (37). Also, infectious diseases were found to be the most prevalent reason of mortality in 240 patients with acute and CKD (38, 39). Good hygiene behaviors are a psychological response to minimize the risk of contracting COVID-19 (40). Practicing good hygiene behaviors makes the person psychologically feel better in order not to be exposed to the devastating effects of the pandemic. In other words, thanks to good hygiene behaviors, individuals' fear of contracting COVID-19 is alleviated. In our study, while the mean CHS score of the HD patients in the control group was 103.68±19.83, the mean CHS score of the HD patients in the case group was 101.00±20.24 ($p>0.05$). The mean CHS scale scores of the HD patients in the control group were defined to be higher. However, both groups had a good CHS score and in our study, a positive

correlation was found between good hygiene behaviors and fear of contracting COVID-19 in both groups. Therefore, as the fear of COVID-19 increases, hygiene behaviors also improve.

It has been reported in a study that fear of COVID-19 improves hygiene behaviors, but individuals with anxiety and depression remain weak in acquiring good hygiene behaviors because their self-perception is negatively affected (40). In our study, the high CHS scores of both groups may not give an insight into their psychological resilience since hygiene behaviors have social, moral, religious, and societal dimensions. Thus, wearing a mask during the pandemic process, using hand sanitizer at the entrances and exits of the HD unit under the supervision of healthcare professionals, and the distance between the dialysis stretchers have led HD patients to gain good hygiene behaviors.

Limitations

The article has several limitations. First of all, the study is single-centered and the number of patients is low. The number of patients we could reach was only this much. Secondly, only hemodialysis patients with and without COVID-19 were included in the study. Except for hemodialysis, other COVID-19 patients were not included in the study.

CONCLUSION

It is clear that the whole world is feeling the overwhelming effects of the pandemic, and in this process, the hygiene behaviors of individuals are affected by COVID-19 fear. It is possible to say that HD patients, a population with a high burden of disease and care, have a high risk for COVID-19. It is of big importance that this particular patient group is handled by health care professionals, encouraged, and provided with psychological and social support.

The findings obtained in our study confirm that the adverse effects of fear of COVID-19 in HD patients should not be ignored and that they are encountered at a high rate. The chronic long-term effects of COVID-19 are yet to be fully perceived. In addition, due to the pandemic, not all of the available evidence could be confirmed by advanced diagnostic methods due to financial problems and lack of workforce, which, therefore, calls for additional studies are needed. Clinicians should be aware of the hygiene behaviors of HD patients, deficiencies should be determined at an early stage, and patients should be supported and educated.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Batman University Ethics Committee (Date: 09.04.2021, Decision No: 2021/01-12).

Informed Consent: Verbal consent was obtained from all patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1129894
J Health Sci Med 2022; 5(4): 1183-1189

Identification of lymphocyte subgroups with flow cytometry in COVID-19 patients

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Cite this article as: Berber İ, Kırıcı Berber N, Sarıcı A, et al. Identification of lymphocyte subgroups with flow cytometry in COVID-19 patients. J Health Sci Med 2022; 5(4): 1183-1189.

ABSTRACT

Objective: We aimed to determine lymphocyte subgroups and activation status of flow cytometry in COVID-19 patients and examine their relationship with disease stage and length of hospital stay.

Material and Method: Forty patients were analyzed in this study and compared with the age and sex-matched 40 healthy controls. COVID-19 patients have split as early and advanced-stage diseases. Flow cytometry assay was performed to determine the counts of lymphocyte subsets and activation status. Total lymphocyte count was calculated and CD45 (cluster of differentiation), CD3, CD4, CD8, CD19, CD27, CD38, CD56, CD57, and IgD were studied on lymphocyte gate. T helper / T cytotoxic rates and length of hospital stay were recorded.

Results: The patients' CD3(+)CD4(+) (T helper) count and CD27 expression on T cells counts were significantly lower, and CD57 expression on CD3(+)CD8(+) T cytotoxic cells were significantly higher ($p<0.05$) than the control group. When the patients were divided into early and advanced stages, it was observed that CD38 expression on T cells was significantly lower in advanced-stage patients ($p< 0.05$) Total lymphocyte count and CD3(+) T lymphocyte count were negatively correlated with the duration of hospitalization as statistically significant ($p <0.05$).

Conclusion: Our data showed that the SARS-CoV-2 primarily affects T lymphocytes. It was thought that this effect occurred by impairment of development and activation of T lymphocytes. There are some discordances among the studies on T lymphocytes in the literature.

Keywords: COVID-19, flow cytometry, lymphocytes, SARS-CoV-2, T cells

INTRODUCTION

Coronaviruses (CoV) are a large family of viruses that cause a diversity of diseases varying from common gribal infections to more serious diseases. The new Coronavirus Disease was first identified in China (1,2). The disease caused by a 2019-new coronavirus (advanced acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) was officially named COVID-19 by the World Health Organization (WHO) (3). While most of the infected patients recovered, some patients experienced the infection at a serious and vital level (4,5).

The severity of the disease is related to many clinical features, such as age and the presence of co-morbidities, like diabetes, obesity, heart disease, and laboratory parameters such as elevated procalcitonin, lactate dehydrogenase, D-dimer, C-reactive protein, neutrophil, lymphocyte counts, and pro-inflammatory cytokines like interleukin-6, respectively (6,7,8). Both innate and adaptive immune responses are critical for the control of viral infections. Lymphocytes in the blood, which are an important part of the immune response, participate in

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Received: 13.06.2022 **Accepted:** 29.06.2022

various host defense mechanisms against viral infections. Although changes in major lymphocyte subsets (CD3, CD4, CD8, CD19, CD3(-)CD56(+)) and lymphocyte activation status have been observed in patients infected with SARS-CoV-2, the results of the studies differ from each other. Therefore, we aimed to determine lymphocyte subgroups and activation status in COVID-19 patients with flow cytometry and examined the effects of these changes on the disease stage and duration of hospital stay.

MATERIAL AND METHOD

The study was carried out with the permission of the İnönü University Faculty of Medicine Clinical Researches Ethics Committee (Date: 30.06.2020, Decision No: 101). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

The data of COVID-19 patients diagnosed with reverse transcriptase-polymerase chain reaction (PCR) at Malatya İnönü Training and Research Hospital between June 01, 2020, and July 01, 2020, were retrospectively evaluated. Informed consent from patients was provided. Forty COVID-19 patients and forty disease-free control groups were included in this study. Disease-free controls were selected from hospital staff of similar age and sex to the patient group. To assess the effect of infection on lymphocyte subgroups and activation status of each patient at a patient/control ratio of 1: 1. Patients were divided into as early and advanced stages, according to the severity of COVID 19. Age, gender, lymphocyte subgroups, and activation status of the patient and disease-free control groups were compared. The relationship between these findings of all patients and hospitalization was examined.

Patients were divided into 4 stages from early to advanced according to clinical severity. Stages 1 and 2 were considered as early-stage patients, and stages 3 and 4 were considered advanced-stage patients (9,10).

Flow Cytometry Analysis

We made the flow analyses in BD Diva software. Blood was collected in an Ethylenediaminetetraacetic acid (EDTA) tube early in the morning from all patients, and all tests were performed within 2 hours. Six-colour, three tube analyses were performed with the different fluorochromes labeled monoclonal antibodies (CD45, CD3, CD4, CD8, CD19, CD24, CD27, CD38, CD56, CD57, IgD). BNII fluorochromes were conjugated. CD3, CD4, CD8, CD19, CD27, CD38, CD45 were studied in the first tube, CD57, CD16, CD3, CD45, CD19 in the second tube, and CD24, CD19, CD45, and CD38 in the third tube. The lymphocyte gate was determined according to CD45 and side scatter intensity curve. The lymphocyte subtypes: CD3(+) (/microL), CD3(+)CD4(+) (/microL), CD3(+) CD8(+) (/microL), and CD3(+)CD4(+)/ CD3(+) CD8(+) ratio studied. Moreover, the expressions of CD27, CD57, CD38, and IgD were studied to demonstrate the activation status of T cells, and B cells. Markers indicating the activation status of the cells were expressed in percent.

Statistical Analysis

Statistical analyzes were performed using IBM SPSS v25 software. p-value ≤ 0.05 was contemplated statistically significant. Variables evaluated for normal distribution were analyzed with the Kolmogorov Smirnov test. Categorical variables were analyzed with the chi-square test. Numerical variables were compared with the Mann-Whitney U test.

Roc analysis was applied to find a cutoff point for the different morphological conditions between early and advanced patients. Spearman's rho correlation coefficient (rs) was used to investigate the relationships between quantitative variables.

RESULTS

The patients included in the study were compared with the age and sex-matched healthy controls (**Table 1**). The patients' CD3(+) CD4(+) (T helper) count (**Figure 1**) and CD27 expression on T cells counts were significantly lower (**Figure 2**), and CD57 expression on CD3(+) CD8(+) T cytotoxic (**Figure 3**) cells were significantly higher ($p<0.05$) than the control group. While the CD3(+) and CD8(+) counts of the patients were low, the difference was not statistically significant when compared control group. No statistically significant difference was found in the expression of IgD, CD27, and CD38 on CD19+ B cells, showing the activation status of B cells. Moreover, B cell count is not different between groups.

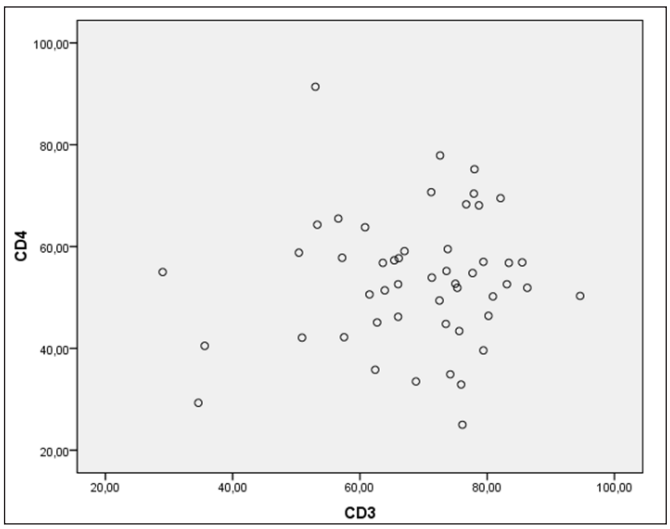

Figure 1. CD3(+)CD4(+) (T helper) count of the patient group

Table 1. Clinical features and laboratory values of all the patients.

Characteristics and laboratuvar values (Normal range)	All patients median (min-max)	Control median (min-max)	p
Total number of patients	40	40	
Median Age (year)	38 (12-88)	38.5 (21-47)	0.802
Gender			
Female (number/percent)	17 (42.5)	16 (40)	1.000
Male (number/percent)	23 (57.5)	24 (60)	
Total lymphocyte count (/microL)	1.42 (0.39-4.56)	1.83 (1.04-2.84)	0.125
CD3(+) (/microL)	0.98 (0.20-3.13)	1.34 (0.89-2.25)	0.087
CD3(+)CD4(+) (/microL)	0.58 (0.09-1.33)	0.77 (0.44-1.3)	0.039
CD3(+)CD8(+) (/microL)	0.43 (0.01-2.06)	0.52 (0.15-1.19)	0.264
Th/Ts (CD3(+)CD4(+)/ CD3(+)CD8(+))	1.19 (0.34-79)	1.34 (0.67-4)	0.264
CD3(+)CD27(+) (%)	45.5 (20.4-71.3)	59.1 (50.9-68.1)	0.001
CD3(+)CD57(+) (%)	15.35 (2.5-37.4)	11.15 (2.2-20)	0.144
CD3(+)CD38(+) (%)	29.8 (9.2-57.3)	25.75 (14.5-39.1)	0.827
CD3(+)CD8(+)CD57(+) (%)	40.8 (14.2-74.3)	30.6 (8.2-43.7)	0.030
CD3(-)CD56(+) (/microL)	0.22 (0.07-0.92)	0.26 (0.08-0.98)	0.126
CD19(+) (/microL)	0.16 (0.05-1.10)	0.25 (0.11-0.32)	0.144
CD19(+)IgD(+) (%)	8 (1.7-26.2)	7.8 (5-17)	0.765
CD19(+)CD24(+) (%)	10.3 (1.7-31.1)	10.25 (6.5-17.6)	0.896
CD19(+)CD27(+) (%)	4.05 (0.8-38.4)	4.85 (2.6-9.5)	0.369
CD19(+)CD38(+) (%)	7.8 (3-25.8)	7.35 (5.4-14.6)	0.693
Length of stay in Hospital (day)	6 (1-17)		

When the patients were divided into early and advanced stages, they were similar in terms of gender, while advanced stage patients were found to be significantly older. In lymphocyte subgroup analysis, it was observed that CD38 expression on T cells was significantly lower in advanced-stage patients ($p<0.05$) (**Table 2, Figure 4**).

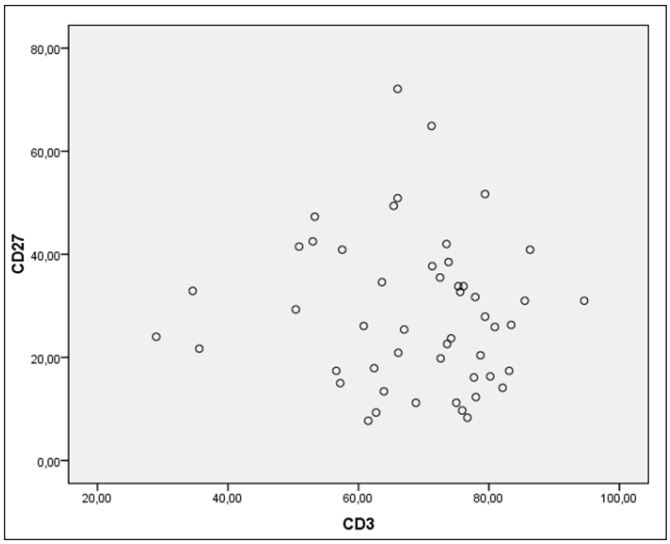

Figure 2. CD27 expression on T cells of the patient group

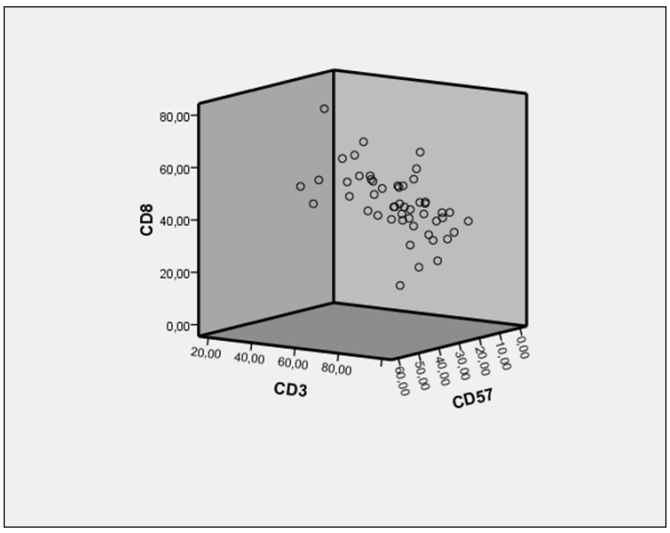

Figure 3. CD57 expression on CD3(+)CD8(+) T cytotoxic cells of the patient group

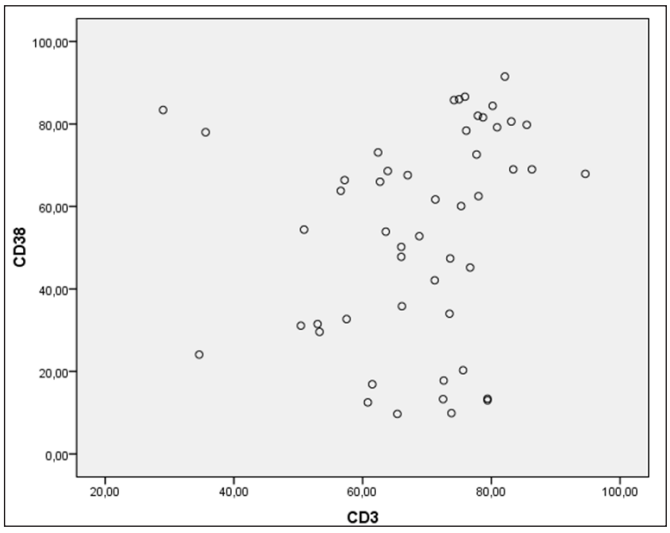

Figure 4: CD38 expression on T cells in advanced-stage patients

Table 2. Comparison of laboratory values and clinical features of mild and severe stage patients

Characteristics and laboratuvar values (Normal range)	Mild Stage Median (min-max)	Severe Stage Median (min-max)	p
Total number of patients	23	17	
Median Age (year)	28 (12-52)	58 (31-88)	<0.001
Gender			
Female (number/percent)	9 (39.1)	8 (47.1)	0.859
Male (number/percent)	14 (60.9)	9 (52.9)	
Stage (Number, (%)			
Mild			
Stage I	4 (17.4)		
Stage II	19 (82.6)		
Severe			
Stage III		15 (88.2)	
Stage IV		2 (11.8)	
Total lymphocyte count (/microL)	1.38 (0.79-4.56)	1.44 (0.39-2.32)	0.342
CD3(+) (/microL)	1.03 (0.26-3.13)	0.96 (0.20-1.74)	0.191
CD3(+)CD4(+) (/microL)	0.64 (0.14-1.33)	0.54 (0.09-1.19)	0.149
CD3(+)CD8(+)(/microL)	0.46 (0.10-2.06)	0.35 (0.01-0.81)	0.401
Th/Ts (CD3(+)CD4(+)/ CD3(+)CD8(+))	1.11 (0.34-2.43)	1.40 (0.36-79)	0.120
CD3(+)CD27(+) (%)	52.6 (20.4-71.3)	41.2 (25.5-67.6)	0.191
CD3(+)CD57(+) (%)	15.1 (5-37.4)	15.6 (2.5-35.7)	0.607
CD3(+)CD38(+) (%)	37.2 (10.2-57.3)	22.95 (9.2-40.4)	0.007
CD3(+)CD8(+)CD57(+) (%)	39 (15.7-74.3)	42.6 (14.2-72)	0.957
CD3(-)CD56(+) (/microL)	0.22 (0.07-0.92)	0.21 (0.09-0.45)	0.967
CD19(+) (/microL)	0.16 (0.05-1.10)	0.14 (0.05-0.55)	0.342
CD19(+)IgD(+) (%)	8 (3.3-18.9)	8 (1.7-26.2)	0.892
CD19(+)CD24(+) (%)	10.5 (5.3-28.2)	9.2 (1.7-31.1)	0.315
CD19(+)CD27(+) (%)	4.2 (0.8-27.2)	3.5 (1-38.4)	0.464
CD19(+)CD38(+) (%)	8.7 (4.6-24.2)	6.6 (3-25.8)	0.058

Total lymphocyte count and CD3(+) T lymphocyte count were negatively correlated with the length of hospital stay as statistically significant ($p<0.05$). The strength of the relationships between hospitalization days with lymphocyte count and CD3(+) T were found to be weak but close to moderate (**Table 3, Figure 5**).

Table 3. Relationship of patients' laboratory parameters with the length of stay

		All patients (n=40)
Lymphocyte	rs	-0.395
	p	0.012
CD3 (+) (/microL)	rs	-0.358
	p	0.023
CD3 (+) CD4 (+) (/microL)	rs	-0.305
	p	0.056
CD3 (+) CD8 (+) (/microL)	rs	-0.184
	p	0.255
Th / Ts	rs	-0.218
	p	0.176
CD3 (+) CD27 (+)	rs	-0.062
	p	0.706
CD3 (-) CD56 (+)	rs	-0.018
	p	0.936
CD3 (+) CD57 (+)	rs	0.096
	p	0.556
CD3 (+) CD38 (+)	rs	-0.226
	p	0.257
CD3 (+) CD8 (+) CD57(+)	rs	0.137
	p	0.399
CD19 (+) (/microL)	rs	-0.083
	p	0.611
CD19 (+) IgD (+)	rs	0.169
	p	0.297
CD19(+) IgM(+)	rs	-0.155
	p	0.490
CD19(+) CD24 (+)	rs	0.008
	p	0.960
CD19 (+) CD27 (+)	rs	0.095
	p	0.560
CD19 (+) CD38 (+)	rs	0.037
	p	0.821

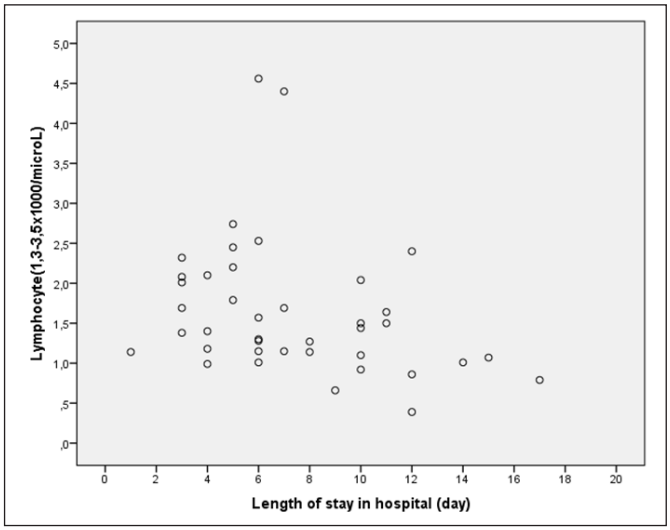

Figure 5A. Relationship between total lymphocyte count and length of hospital stay.

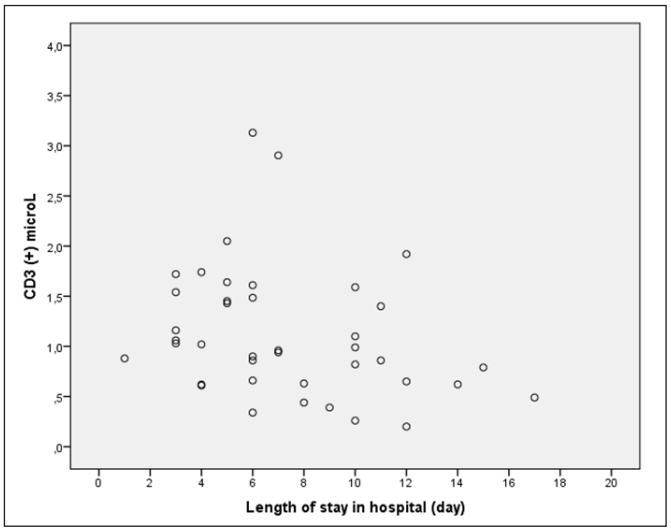

Figure 5B. Relationship between CD3 (+) lymphocyte count and length of hospital stay**.**

DISCUSSION

Our study showed that T helper count and CD27 expression on T cells are significantly decreased, and CD57 expression on cytotoxic T cells is significantly increased in COVID-19 patients at the time of diagnosis ($p < 0.05$).

T helper (CD3(+)CD4(+)) cells are the mediator cells in the immune response. They proliferate and release cytokines that regulate or assist effector lymphocyte function when activated. They are one of the targets of many viral infections and the reduction in CD4+ T cells facilitates the emergence of virus-related diseases (11). In our study, T helper counts were significantly decreased in the patient group. While CD27 was highly expressed in central memory and stem cell memory cells, its expression was decreased in effector T cells (12). In our study, it was observed that the CD27 expression on T cells was significantly decreased in the patient group. The CD57 antigen is routinely used to identify terminally differentiated 'senescent' cells with reduced proliferative capacity and altered functional properties (13). We also found that CD57 expression on cytotoxic T cells increased significantly in the patient group.

When the patients were divided into early and advanced stages, the CD38 on T cells was found to be significantly lower in an advanced stage. CD38 is expressed at a low rate in mature naive T lymphocytes, but CD38 expression in T lymphocytes is upregulated with mitogenic activation (14). This finding may suggest that T lymphocytes may lose their active state as the COVID-19 infection progresses. The total lymphocyte count and CD3(+) T cell count of the patients were negatively correlated with the length of hospital stay (15). When this result is evaluated together with the other results obtained from our study, it shows that the COVID-19 virus may change the number and activation status of T lymphocytes, especially in the advanced stage.

Jiang et al. (15) showed the count and immune status of lymphocytes by flow cytometry in 32 COVID-19 patients and 18 healthy individuals. They observed total T (CD3(+)), CD3(+)CD8(+) and NK (CD3(-) CD56(+)) cells in COVID-19 patients decreased significantly as compared with disease-free group. Similarly, we have observed that T cells decreased in patients. Jiang et al. (15) showed that a sustained decrease of total T and NK cells in the critical group was observed, and CD8+ T cell count in the critical group was significantly decreased as compared with healthy individuals and the early group. In our study, when compared with the early disease group, the total T and NK cell number was lower in patients with advanced disease, although it was not statistically significant. Nonetheless, no significant difference in CD3(+) CD4(+) and B cell (CD19(+)) count was observed between patients and disease-free individuals in the same study (15).

Kazancioglu et al. (16) reported that B, T lymphocytes, and NK and natural killer T (NKT) cells were found to be decreased in patients with advanced COVID-19. Wang et al. (17) showed that CD4+ and CD8+ T cells, B cells, and NK cells decreased in COVID-19 patients, and advanced cases had lower total lymphocytes than early cases. In our study, a significant decrease was not observed in the B lymphocyte count, but there was a statistically significant decrease in the CD4(+) T lymphocyte counts. Jiang et al. (15) found that circulating CD8(+) T cells from COVID-19 patients had higher expression of CD38 compared to healthy individuals, while the expression of CD38 in CD8(+) T cells was not significantly different among the severity of the disease. In our study, we studied CD38 on total T lymphocytes (CD3(+)). Although it was not statistically significant CD38 counts were higher in the patient group compared to the control group. In addition, the level of CD3(+) CD38(+) was interpreted as significantly higher in early patients.

Almeida et al. (18) reported that patients who received antiretroviral therapy, those with high CD 38 expression in CD8 and CD4 T lymphocytes measured from peripheral blood after 1-year treatment, had a better response to treatment. When evaluated together with the data of this study, the high mortality reported in the literature in advanced-stage patients can be explained by the low level of CD38 in T lymphocytes in these advanced-stage patients. Kang et al. (19) compared cell-mediated immune responses between advanced and early COVID-19 cases. They also examined frequencies of CD38 as makers of activated T cells. Although CD4(+) CD38(+) and CD8(+) CD38(+) tended to be higher in the patient groups than in the healthy control group, but not statistically significant. We could not find any significant difference in flow cytometry evaluations in early and advanced-stage patients,

except for lower CD3(+) CD38(+) levels in early patients at the time of diagnosis. Mazzoni et al. (20) reported that CD3(+), and CD19(+) cell counts were significantly lower in COVID-19 patients than in healthy subjects. In addition, among CD3(+) cells, they found a significant reduction of CD4(+), and CD8(+) cells in COVID-19 patients. In our study, the number of CD3(+), CD19(+), CD3(+)CD4(+), CD3(+) CD8(+) cells decreased compared to the healthy group, but this decrease was only observed significantly in CD3(+)CD4(+) cells. Also, they showed that the CD4(+)/ CD8(+) T cell ratio in COVID19 patients was significantly higher than in healthy subjects.

Kazancioglu et al. (16) observed that the CD4+/CD8+ ratio was not significantly different between patients with COVID-19 and healthy controls. Wang et al. (17) found that CD4+ /CD8+ ratio showed no significant association with the severity of the disease. No statistically significant difference was found between the patient and the healthy group in the CD4(+)/CD8(+) T cell ratio in our study. On the other side, in our study CD57(+) expression on cytotoxic T cells was significantly higher in COVID-19 patients when compared to healthy subjects. Huang et al. (21) reported that CD4(+) T cell, CD8(+) T cell, B cell, NK cell, and total lymphocyte cell counts statistically significant were lower in patients with advanced/critical COVID-19 than in early/moderate disease. Although it was not statistically significant in our study, the number of these cells was found to be low in advanced-stage patients.

Jiang et al. (17) reported that in receiver operator characteristics (ROC) curve analysis, total lymphocytes and CD3(+) lymphocytes also had good value in distinguishing critical COVID19 patients with a total area under the curve (AUC) of 0.865 and 0.826, respectively. Wang et al reported that CD8+ T cells tended to be an independent predictor for COVID-19 severity and treatment efficacy. In our study, there was a significant negative correlation between total lymphocyte and total T lymphocyte count and length of hospital stay by the data of this study. In some studies, multivariate analysis has shown that Th/Ts (CD3(+) CD4(+)/ CD3(+)CD8(+)) are independent predictors of patient outcomes (21). In our study, the Th / Ts ratio was not statistically significant when evaluated together with the length of hospital stay.

The strengths of our study are that at the time of diagnosis, blood samples of all patients were taken before any COVID-19 treatment and the flow cytometry study was performed by the same person. The limitations of our study are the small patient group included in the study, the inability to associate the data with disease mortality due to this small patient group, and the inability to monitor cell number and activation status with intermittent evaluations during patient follow-up.

CONCLUSION

The evaluated data showed that the SARS-CoV-2 primarily affects T lymphocytes. It was thought that this effect occurred by impairment of development and activation of T lymphocytes. There are some discordances among these studies on T lymphocytes in the literature. Studies with more patients are needed to make this information more reliable.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the İnönü University Faculty of Medicine Clinical Researches Ethics Committee (Date: 30.06.2020, Decision No: 101).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1116129
J Health Sci Med 2022; 5(4): 1190-1194

Fifth metacarpal neck fracture fixation: antegrade intramedullary pinning with two K-wires or percutaneous retrograde crossed pinning

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Cite this article as: Fidan F, Çetin MÜ. Fifth metacarpal neck fracture fixation: antegrade intramedullary pinning with two K-wires or percutaneous retrograde crossed pinning. J Health Sci Med 2022; 5(4): 1190-1194.

ABSTRACT

Objective: The present study aimed to compare clinical and radiological outcomes in patients with displaced fifth metacarpal neck fractures after treatment with antegrade intramedullary pinning with two K-wires or percutaneous retrograde crossed pinning.

Material Method: While seventeen patients were treated with antegrade intramedullary pinning (Group), 14 were treated with percutaneous retrograde crossed pinning (Group 2). Clinical and radiological outcomes included Quick Dash, active range of motion (ROM), VAS, and dorsal angulation loss at weeks four and twelve and in the final follow-up.

Results: The findings revealed that the groups had mean ages of 29.41±8.15 years and 27.78±7.42 years, res-pectively. While ROM was better in Group 2 at weeks four and twelve, we could not find a significant difference between the groups by active ROM in the final follow-up. Moreover, Group 1 had a better Dash score in the fourth week and twelth week , but both groups had similar Dash scores in the final follow-up. Finally, the groups had no preoperative and postoperative differences radiologically.

Conclusion: The present findings uncovered that treatment of a displaced fifth metacarpal neck fracture by anteg-rade intramedullary pinning yielded a better in the first three months improvement in active ROM and Quick Dash than percutaneous retrograde crossed pinning.

Keywords: Fifth metacarpal fracture, percutaneous retrograde crossed pinning, intramedullary anteg-rade pinning

INTRODUCTION

Fifth metacarpal neck fractures are among the most common injuries of the hand and account for about 20% of all hand fractures (1-3). These fractures are more common in males and young adults (4). Such fractures are often managed conservatively using an ulnar gutter splint or strapping; howev-er, shortening of the metacarpus by more than 3 mm, angulation by more than 30 degrees, and rota-tional deformities are indications for surgical fixation (1-5). Several techniques are currently available for the surgical treatment of the fifth metacarpal neck fracture, including crossed pinning with Kirschner (K)-wire, antegrade intramedullary K-wire, retrograde intramedullary K-wire, retrograde crossed pinning with K-wire, transverse pinning with K-wire, external fixation, and plate fixation (1-7). Nevertheless, a gold standard surgical technique has not been established yet. The decision of which surgical method to use all depends on the surgeon's preference, considering both the pros and cons of each method and the pathoanatomy of each case (1-5).

The goal of operative management is to ensure alignment and stability and initiate early mobilization (5-9). Antegrade intramedullary fixation methods are commonly used, and the application of ante-grade intramedullary pinning seems relatively uncomplicated and minimally invasive (6-10). Retro-grade crossed pinning can also result in good stability; however, it may cause more restrictions on met-acarpophalangeal joint motion due to scarred adhesions of the extensor structures (6).

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Received: 13.05.2022 **Accepted:** 01.07.2022

Ultimately, we hypothesize that the antegrade intramedullary Kirschner -wire technique does not involve joint penetration, thus leading to superior finger movements and clinical results in the early peri-od. Therefore, our study aimed to compare clinical and radiographic outcomes of antegrade intrame-dullary pinning with two Kirschner -wires and percutaneous retrograde crossed pinning in patients with fifth metacarpal neck fractures.

MATERIAL AND METHOD

The study was carried out with the permission of the Tekirdağ Namık Kemal University Noninvasive Clinical Researches Ethics Committee (Date: 28.09.2021, Decision No: 2021.223.09.09). All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients. We retrospectively collected data between January 2020 and January 2022 on 68 patients with metacarpal neck fractures. We set the inclusion criteria as 1) preoperative angulation of more than 40 degrees on initial presentation before manual reduction and 2) treatment with closed reduction via antegrade intramedullary two Kirschner-wires or retrograde crossed pinning 3) follow-up period of at least six months. However, we excluded 1) patients with open fractures, 2) patients undergoing a conservative treatment, 3) those undergoing an open reduction, 4) patients using plates and screws for fixation, and 5) those with accompanying hand and upper extremity injuries. Thirty-three patients satisfying the above-specified criteria were included in the study. Then, we divided the patients into two groups by surgical treatment performed. While Group 1 consisted of those with antegrade intramedullary fixation, Group 2 comprised the patients with retrograde cross-pinning fixation. We also recorded the demographic characteristics of both groups, including age, sex, injury side, and operation time.

Surgical treatments and postoperative management

Two orthopedic surgeons performed surgery under general or regional anesthesia for all patients. For Group 1, a short longitudinal incision was made on the dorsal-ulnar base of the fifth metacarpal. The metacarpal cortex was reached by blunt dissection. The proximal dorsoulnar cortex was opened with a 2.5 mm drill. The drill was tilted approximately 60 degrees to enter the intramedullary canal at as wide an angle as possible. After adjusting the entry point, 1.4 mm two K-wires were prepared by bending. The distal end was bent upwards by about 20 degrees with pliers. About 2 cm distal, the wire was bent again by no more than 10 degrees in the same direction. The K-wires to be applied were bent 90 deg-rees proximally so that they were longer than the metacarpal and in the same plane with the distal slo-pe from the proximal part for ease of insertion. These bent wires were manually inserted into the me-dullary canal and advanced into the diaphysis before reaching the fracture site. Following closed re-duction, the wires were advanced from the fracture site to the metacarpal head. The position was checked using fluoroscopy. The K-wires were then rotated so that the bent ends were dorsal. Finally, the ends of the K-wires were cut and bent to be outside the skin.

For group 2, a closed fracture reduction was achieved, and reduction was confirmed using fluoros-copy. Then, 1.4 mm two K-wires were pinned on the fifth metacarpal, radial, and ulnar sides, using a crossed-pin configuration. The fixation and position of the wires were confirmed by fluoroscopy. Fi-nally, the K-wires were cut and bent so that they were outside the skin.

Ulnar gutter splints were applied to all patients postoperatively along the ulnar side of the wrist with the wrist extension of 10-20 degrees, metacarpophalangeal (MCP) joints of the fourth and fifth finger at 70 to 90° flexion, and the proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints in slight flexion.

The same standard protocol was applied postoperatively to both groups. After using a splint for four weeks, the movement was initiated in the fourth week. After 4-6 weeks, the K-wires were removed.

Radiographic Evaluation

For both groups, radiologic evaluation was evaluated by one orthopedic surgeon on PA, lateral, and oblique X-rays on the preoperative-postoperative first day, in the fourth and twelfth weeks, and the final follow-up (**Figure 1 and 2**). The degree of angulation is assessed on the lateral radiograph, with lines drawn through the medullary canal.

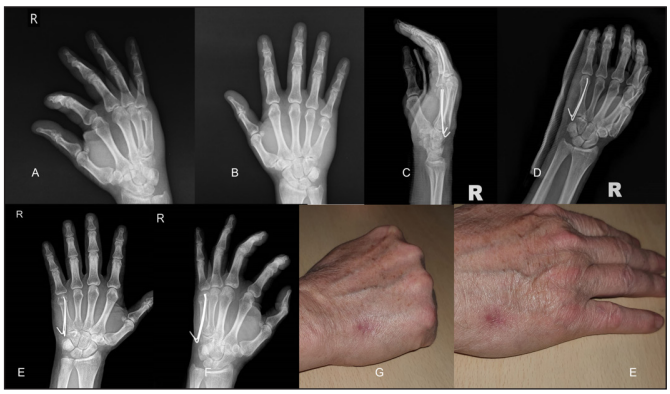

Figure 1. 52 years male patient treated with antegrad intramedullary pinning. Preoperative oblique view radiograph (A). Preoperative AP view radiograph (B). Postoperative radiographs showing a good reduction of the fracture on the lateral view (C) and oblique view (D). Radiograph in the 8th week after the surgery showing the union of the fracture on the anteroposterior view (E) and oblique view (F). ROM of the MCP in flexion (G) and extension (H) in the final follow-up.

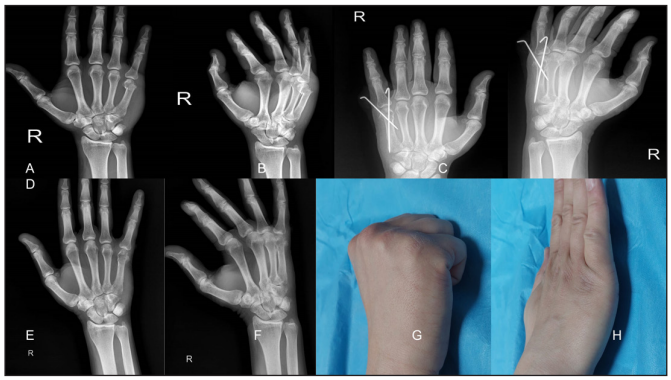

Figure 2. 35 years male patient treated with retrograde crossed pinning. Preoperative AP view radiograph (A). Preoperative oblique view radiograph (B). Postoperative radiographs showing a good reduction of the fracture on the anteroposterior view (C) and oblique view (D). Radiograph in the 6th month after the removal of the nails on the anteroposterior view (E) and oblique view (F). ROM of the MCP in flexion (G) and extension (H) in the final follow-up.

Functional Evaluation

Clinical evaluation included assessment of the range of movement at the MCP joint, visual analog sca-le (VAS), and Quick DASH scoring in the fourth and twelfth weeks and final follow-up. (11). Moreo-ver, the time of first return to work was recorded for both groups. A goniometer measured a joint's range of motion (ROM). The Quick-DASH scoring includes patients' difficulties in daily activities, working life, and social relationships. It consists of 11 items inquiring about restriction and pain; high scores indicate a poor result (12). Besides, the visual analog scale (VAS) is a valid, subjective measure of pain. The responses are scored on a scale ranging from 0 (no pain) to 10 (worst pain) (11). Finally, any complications were noted, including loss of reduction, pin tract infection, tendon irritation, skin irritation, and injury to the dorsal cutaneous branch of the ulnar nerve.

RESULTS

In this research, we studied 31 patients with displaced metacarpal neck fractures treated with the antegrade intramedullary technique (Group 1; n=17) and retrograde crossed pinning fixation (Group 2; n=14). We found the mean ages to be 29.41±8.15 years and 27.78±7.42 years, respectively. The findings also revealed that the cohort included only two female patients and five patients had fractures in their non-dominant hands. The mean time from injury to surgical intervention was 7.8 days in group 1 and 6.4 in group 2. There was no statistically significant difference between the groups (p=0.739). While the mean follow-up period was 9.8±2.8 months, the mean duration of operations was 32.2±10.3 minutes. The groups did not significantly differ by the parameters above (p=0.228). There were also no significant differences between the groups by pin removal time (M=6.03±0.6 weeks; p=0.769). Without differing significantly (p=0.184), the patients returned to work after an average of 7.6±1.6 weeks (**Table 1**).

Table 1. Participants' demographic characteristics

	Group 1	Group 2	p
Age	29.41±8.15	27.78±7.42	0.575
Sex (n) (female/male)	2/15	0/14	
Side (n) (right/left)	3/14	2/12	
Operation time (minute)	32.64±10.01	31.78±11.02	0.228
Follow-up (month)	9.64±2.95	9.07±2.78	0.584
Pin removal (week)	6.00±.70	6.07±.61	0.769
Time of first return to work (week)	7.29±1.57	8.07±1.59	0.184

Regarding their clinical characteristics in the fourth week, ROM of the fifth metacarpophalangeal joint was significantly greater in Group 1 than in Group 2 (p=0.002). Group 2 had a significantly higher mean Quick Dash score (M=63.47±7.65) than Group 1 (M=55.31±6.70) (p=0.004). Nevertheless, we concluded the mean VAS scores of the groups to be similar (p=0.227). (**Table 2**).

In the 12th week, the mean VAS scores of the groups were similar (p=0.856). Yet, we reached a significant difference between the groups by active ROM (p=0.009). While the mean ROM score was 85.35±3.01 in Group 1, it was 82.21±3.21 in Group 2. There was also a statistically significant difference between the groups by Quick Dash (p=0.016).

In the final follow-up, all clinical outcomes (VAS, Quick Dash, ROM) were similar in both groups (p=0.984, p=0.469, and p=0.944, respectively) (**Table2**).

Table 2. Functional outcomes

VAS			
	Week 4	**Week 12**	**Final follow-up**
Group 1	4.11±1.05	2.52±0.62	1.47±0.94
Group 2	3.64±1.08	2.57±0.66	1.42±0.75
p-value	0.227	0.856	0.984
ROM			
	Week 4	**Week 12**	**Final follow-up**
Group 1	73.82±2.53	85.35±3.01	90.29±3.68
Group 2	70.08±3.45	82.21±3.21	90.21±2.19
p-value	0.002	0.009	0.944
Quick Dash			
	Week 4	**Week 12**	**Final follow-up**
Group 1	55.31±6.70	29.74±6.76	3.07±1.76
Group 2	63.47±7.65	33.76±8.62	2.60±1.73
p-value	0.004	0.016	0.469

We also compared the radiological outcomes of the patients by angulation. Accordingly, we could not find significant differences between the groups by their radiological outcomes in the 4th and 12th weeks and the final follow-up (**Table 3**).

Table 3. Radiologic (angulation) outcomes

	Preoperative	Early Postoperative	Final follow-up
Group 1	42.76±6.85	6.9±2.63	8.2±2.76
Group 2	43.59±7.22	7.0±2.49	8.1±2.58
p	0.869	0.763	0.784

Thus, a union was achieved in all patients at follow-up. Although superficial infection developed in one patient undergoing an antegrade technique, he received antibioteraphy and wound care and needed no revision. Besides, five patients (2 in Group 1 and 3 in Group 2) developed skin irritation, which was healed with wound care follow-up without any additional procedure. No loss of reduction, non-union or malunion, or nerve injury in any patient in this study.

DISCUSSION

This present study demonstrated that the patients undergoing intramedullary K-wire fixation of displaced metacarpal neck fractures with low complication rates showed better functional outcome scores and ROM than those with retrograde crossed pinning in the first three months. However, similar func-tional results were achieved between the groups at final follow-up.

Various surgical techniques were previously described for fifth metacarpal neck fractures (1-9). Int-ramedullary techniques have recently become a commonly used method for such fractures and, fol-lowed by early mobilization, have been reported with good outcomes with low complication rates (3-10). In their study, Facca et al. (13) compared the results of locking plates and intramedullary K-wires. Accordingly, they reported that locking plates with immediate mobilization paradoxically provided poorer mobility at the end of follow-ups than intramedullary K-wires with six weeks' immobilization. Intramedullary nailing fixation can also provide adequate stability, and its success was attributed to the basic principle of three-point fixation (8). Intramedullary pinning can be done with one or more K-wires. A recent study compared clinical and radiological outcomes in patients with displaced metacar-pal neck fractures after treatment with single or dual antegrade elastic intramedullary nails (8). They reported that double fixation provided better MCP extension and radiological outcomes than single fixation (8). Theoretically, fixation with a single K-wire would allow rotational instability (14). In this study, we used two K-wires with the intramedullary fixation and showed that the functional outcomes in these patients were satisfactory and displayed acceptable, low-rate complications.

Retrograde fixation may lead to joint stiffness by causing restriction in the MCP joint and may also cause damage to the extensor structures during pinning (14). Kim et al. (3) concluded that antegrade intramedullary pinning results in better outcomes than retrograde pinning at three months postoperati-vely. In their nonrandomized retrospective study, Schädel-Höpfner et al. (6) compared the outcomes of antegrade intramedullary pinning, and percutaneous retrograde crossed pinning for fifth metacarpal neck fractures. As a result, antegrade splinting yielded a significantly better outcome for ROM restric-tion of the metacarpophalangeal joint. Similarly, we found that antegrade fixation of fifth metacarpal neck fractures, compared with retrograde crossed pinning, provided better ROM and DASH scores in the 4th and 12th weeks. However, we could not reach significant differences between the groups in the final follow-up. This may be explained by the idea that retrogradely applied K-wires may have caused stiffness in the MCP joint or damage to the extensor mechanism.

In the present study, fracture reduction with retrograde crossed pinning was similar to antegrade intra-medullary pinning in the early postoperative period and follow-up. Although radiologically similar results were obtained in both groups, in the retrograde group, K-wires are prone to complications, inc-luding restricted motion and stiffness. In addition, wire ends are left outside the skin, commonly resul-ting in problems such as loss of reduction, infection, and skin irritation (4,5,10). Regarding such complications, five patients experienced superficial infection and skin irritation. Yet, the group comp-lication rate was parallel to previous studies (3,5,15).

The limitations of this study include a small number of patients and a relatively short follow-up time.

CONCLUSION

In conclusion, although it is possible to obtain good results with both the antergard technique and the retrograde technique in displaced fifth metacarpal neck fractures ,our study results show that by antegrade intramedullary pinning produces better functional outcomes at 3 months postoperatively in terms of ROM and DASH score of the fifth metacarpophalangeal joint than percutaneous retrograde crossed pinning.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Tekirdağ Namık Kemal University Noninvasive Clinical Researches Ethics Committee (Date: 28.09.2021, Decision No: 2021.223.09.09).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execu-tion, and analysis of the paper and that they have approved the final version

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Review

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1054519
J Health Sci Med 2022; 5(4): 1195-1198

Anal canal cancers

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Cite this article as: Karabulut Gül Ş, Oruç AF. Anal canal cancers. J Health Sci Med 2022; 5(4): 1195-1198.

ABSTRACT

Although anal canal cancer is rare, its incidence has increased in the last 30 years, especially in young men. The most common pathological type is squamous cell carcinoma. Definitive histopathological diagnosis is made by biopsy. "American Joint Committee on Cancer" (AJCC) TNM staging is used for staging. The standard approach in treatment is radiochemotherapy, and surgery is applied in persistent or recurrent failure.

Keywords: Anal canal cancers, surgery, radiotherapy, chemotherapy

INTRODUCTION

Anal canal cancers are rare and constitute approximately 3% of all gastrointestinal malignancies. Human immunodeficiency virus is considered as the most important risk factor. Due to the increasing prevalence of (HIV) and Human papilloma virus, there is an increase in the diagnosis of anal canal cancer (1-3). Cervical dysplasia, transplant recipients, autoimmune disorders, number of sexual partners, anal intercourse status and smoking are also risk factors.

Male gender, T3-T4 and node positivity, HPV negativity, smoking, presence of anemia and HIV positivity are bad prognostic factors in anal canal cancers. As of 2019, the number of newly diagnosed patients is approximately 8300 annually (4). Its incidence is 1/100,000 for women, 0.5-0.8/100,000 for men, and it is usually seen between the ages of 60-65 (5).

Tumors from the anal verge to 2 cm beyond the linea dentata are defined as anal cancer, and tumors beyond 2 cm are defined as rectal cancer. The average length of the anal canal is 3.5-4 cm, and it is defined as surgical and anatomical anal canal. The anatomical anal canal is between the anal verge and the dentate line, and the surgical anal canal is the 3-4 cm section between the anal verge and the anorectal ring (6).

Anal canal cancers are mostly squamous cell cancers (60%), followed by transitional cell (25%) and adenocancers (7%). Malignant melanoma, small cell cancers and basoloid cell cancers, which have a high risk of metastasis, are also rarely encountered (7).

DIAGNOSIS

Patients with anal cancer often present with a variety of symptoms that can be hard to distinguish from benign anorectal disease, often hemorrhoids. Rectal bleeding, straining during defecation, pain and itching around the anus are the most common symptoms. In addition, they can occur as a mass, non-healing ulcer, discharge, fecal incontinence and fistula. Anal cancers usually give symptoms in the early period.

In general, the initial evaluation of a patient with suspected anal canal cancer requires a detailed history and physical examination, including anal verge inspection, digital rectal examination, inguinal lymph node palpation. The biopsy required for diagnosis is usually taken during a rectal examination under anesthesia and endoscopic evaluation of the colon. Computed tomography of the thorax, abdomen, and pelvis for clinical staging, magnetic resonance imaging of the pelvis to evaluate local invasion of the tumor and pelvic/inguinal lymph nodes are used fort he diagnosis. In recent years, fluodeoxyglucose-positron emission tomography is also used to evaluate treatment response in terms of better evaluation of nodal status and distant metastases.

STAGING

American Joint Committee on Cancer (AJCC) TNM staging is used for anal cancers. According to the 8th edition of AJCC, the definitions of N2 and N3 nodal stages were removed, and the N1 category was divided into three subcategories as N1a, N1b and N1c. Tis high, defined as

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Received: 07.01.2022 **Accepted:** 09.02.2022

carcinoma in situ, Bowen's disease, anal intraepithelial neoplasia II-III, high grade anal intraepithelial neoplasia Grade squamous was defined as squamous intraepithelial. In addition, with new staging, perianal skin cancers in the anoderm region between the anal inlet and the intersphincteric groove; the skin is staged and treated like anal canal cancers, not squamous cell cancer. Anal canal TNM staging is summarized in **Table 1** and anatomical staging is summarized in **Table 2** (7).

Table 1. TNM staging in anal cancer (AJCC 8th edition)

Primary tumor (T)	
T	T criteria
TX	Primary tumor unspecified
T0	No evidence of primary tumor
Tis	High grade squamous squamous intraepithelial lesion
T1	Tumor ≤2 cm
T2	Tumor >2 cm but ≤5 cm
T3	Tumor >5 cm
T4	Tumor of any size but adjacent organ or organs (such as vagina, urethra, bladder) invaded
Regional lymph nodes (N)	
N	N criteria
NX	Regional lymph nodes cannot be evaluated
N0	No regional lymph node metastases
N1	Metastasis to inguinal, mesorectal, internal iliac, or external iliac lymph nodes
N1a	Metastasis to inguinal, mesorectal, internal iliac lymph nodes
N1b	Metastasis to external iliac lymph nodes
N1c	Metastasis to external iliac lymph nodes + one N1a lymph node metastasis to the node
Distant metastasis (M)	
M	M criteria
M0	No distant metastases
M1	There is distant metastasis

Table 2. AJCC Anatomical staging

Anatomical Stage Groups			
T	N	M	Stage
Tis	N0	M0	Stage 0
T1	N0	M0	Stage 1
T2	N0	M0	Stage 2A
T3	N0	M0	Stage 2B
T1-2	N1	M0	Stage 3A
T4	N0	M0	Stage 3B
T3-T4	N1	M0	Stage 3C
Any T	Any N	M1	Stage 4

TREATMENT

The curative treatment of anal canal cancers was abdominoperineal resection (APR) before sphincter-sparing treatments. The rates of locoregional recurrence after APR were 27-50% and the 5-year overall survival (GSC) rate was 24-62%. Today, APR is used in cases where chemoradiotherapy cannot be performed or in relapses after chemoradiotherapy (8,9)

Although the number of patients suitable for curative local excision is small, local excision; it can be applied for curative purposes in stage 1, smaller than 2 cm in diameter, superficial, only submucosal, mobile and well-differentiated squamous anal cancers. Local recurrence after local excision is 20-78%, and 5-year GCI is 45-85% (10,11).

In a small number of case series in anal canal squamous cancers treated only with radiotherapy, 5-year local control was reported as 100% for tumors 2 cm and below. Local recurrence is 44-51% in these series, with tumor diameter over 2 cm (12,13).

For the first time in 1972, Nigro et al. (14) applied neoadjuvant chemoradiotherapy (5-Fluorouracil (5-FU) and combined RT with Mitomycin C) in the treatment of anal canal squamous cancers. When abdomino-perineal resection pieces were examined, it was found that complete response was obtained in most of the cases.

In the following years, curative radiochemotherapy has been accepted as the main treatment method for stage 1-3 anal canal squamous cancers, as a result of the detection of radiochemotherapy causing a significant increase in local regional control in studies including adjustments of radiation doses and chemotherapy doses (15).

In the results of prospective randomized studies comparing only radiotherapy and radiochemotherapy in anal canal cancer, it was determined that radiochemotherapy significantly increased local control of the locus(16). The most commonly used agents for chemotherapy are Mitomycin C and 5-Flurouracil (5-FU). Bleomycin, cisplatin and doxorubucin can also be given for the same purpose (17-19).

In concomitant therapy, Mitomycin C 12 mg/m² on day 1 of RT 5-FU 1000 mg/m² on days 1 to 4 and days 29 to 32 of RT, or Mitomycin C is administered on days 1 and 29 of 10mg/m² RT, and from days 1 to 4 and days 29 to 32 of 5-FU 1000 mg/m² RT.

As a result of studies investigating effective chemotherapy agents in concomitant chemotherapy, it was concluded that survival and local control without colostomy are better with Mitomycin C, Mitomycin C is more effective than cisplatin, and prolonged chemotherapy does not provide benefit (20,21).

Palliative radiotherapy, palliative chemotherapy, chemoradiotherapy are used in the treatment of stage IV anal cancer. If the patient has received palliative radiotherapy before, one of the abdominoperineal excision options can be applied (22).

Anal canal region radiotherapy is complex due to irregularity of target volumes and proximity to critical dose-sensitive structures such as the small intestine, femoral heads, perineum and external genitalia. Early complications of radiochemotherapy include dermatitis, diarrhea, cystitis, urgent need for defecation, fatigue, and bone marrow suppression. Late complications are proctitis, rectal bleeding, fecal incontinence, narrowing of the small intestine and malabsorption. Rarely, the need for colostomy arises due to worsening of rectal functions (23). In retrospective series, recurrences of 35-46% in the pelvic lymph nodes and 13-16% in the inguinal lymph nodes after surgery revealed the necessity of including the pelvic and inguinal lymph nodes in the radiotherapy area (24,25). After intensity modulated radiotherapy technique (IMRT) and volumetric arc therapy (VMAT), side effects were found to be less than after conventional radiotherapy technique, resulting in better quality of life and less treatment interruption rates. Reduction in gastrointestinal and skin toxicities and 2-year local regional control was reported as 80% after treatment, and IMRT/VMAT, which are more conformal techniques, is recommended in radiotherapy planning.

The optimal radiotherapy dose and scheme in the treatment of anal canal squamous cancer is still being investigated, and the recommended total radiation dose is usually 50-54 Gy. The results of using higher doses are uncertain and studies are ongoing.

In anal canal tumors, regression is slow after chemoradiotherapy and a response is observed in an average of 3 months, this period is 12 months for some patients. After simultaneous chemoradiotherapy, rectal examination and inguinal lymph node examination are performed 8-12 weeks after the completion of treatment. Since magnetic resonance imaging is not beneficial in the early period, it is not recommended. In patients with residual disease, examination should be continued once a month, and biopsy should not be performed if no progression is observed at 8-12 weeks. Biopsy should be postponed until progressive disease is detected by physical examination (26). After a complete response, patients are treated every 3 months for the first two years, and every 2 years for 5 years.

CONCLUSION

Anal canal cancer is a rare cancer, and the main goal in treatment is to maintain local regional disease control and to preserve anal functions to improve quality of life. Curative radiochemotherapy is the main treatment modality. Surgery is recommended in persistent or recurrent disease. Today, radiotherapy doses and schemes continue to achieve a more effective response.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1108174
J Health Sci Med 2022; 5(4): 1199-1206

Comprehensive approach to hemophilia

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Cite this article as: Gök V, Ünal E. Comprehensive approach to hemophilia. J Health Sci Med 2022; 5(4): 1199-1206.

ABSTRACT

Hemophilia A, B are X-linked recessive bleeding disorder that typically results from a deficiency of clotting factor VIII (FVIII) and factor IX (FIX). The severity of the disease is determined according to the FVIII and FIX levels. Hemophilia A and B have similar symptoms and are both characterized by bleeding, particularly in large joints such as ankles, knees, elbows. Recurrent bleeding in joints eventually causes progressive hemophilic arthropathy. Life-threatening hemorrhages may occur rarely. Treatment of hemophilia has improved significantly in recent years with clotting factor concentrates. The average life expectancy was <40 years until the 1960s, but with better accessing clotting factor concentrates and prophylactic replacement of the missing factor, today hemophilia patients can perform social activities like other healthy individuals and live with an almost normal life expectancy. The future of hemophilia seems bright with gene therapy and new non-replacement treatments.

Keywords: Bleeding, factor concentrates, factor VIII, factor IX, hemophilia

DEFINITION AND INHERITANCE OF HEMOPHILIA

Hemophilia is an X-linked recessive bleeding disorder that typically results from a deficiency of clotting factor VIII (hemophilia A) and factor IX (hemophilia B). Coagulation factor XI (FXI) deficiency was previously described as hemophilia C; however, currently only FVIII and FIX deficiencies are defined as hemophilia. The prevalence of hemophilia A and hemophilia B is reported to be almost 1 in 5,000 and 1 in 30,000, respectively, in the male population (1). The severity of the disease depends on the FVIII or FIX levels, determined by the type of mutation in the genes (F8 and F9) encoding the factors: severe (<1 international unit (IU)/dl), moderate (1-5 IU/dl), or mild (6 IU/dl to 40 IU/dl).

Since the disease is X-linked recessive inherited, women are usually carriers and men are affected. About 30-35% of patients with hemophilia A and B have a de novo mutation without a family history (2). The factor 8 (F8) encoding FVIII is located at the distal end of the long arm of the X chromosome (Xq28), consists of 26 exons and encodes the 2,332 amino acids. F8 mutations are numerous, but are largely categorized as deletions, nonsense mutations, intron 22 or intron 1 inversion, and missense mutations. Inversion of intron 22 is the most detected mutation in severe hemophilia A, occurring in approximately 40% of cases. Missense variants of the F8 are observed in about all non-severe cases of hemophilia A.

The factor 9 (F9) encoding FIX is located at the X chromosome (Xq27.1) with 8 exons. Hemophilia B is genetically heterogeneous and missense mutations are the most common in F9. Hemophilia B Leyden (HBL) is a subgroup of hemophilia B characterized by low levels of FIX during the first years of life, which then rises and potentially normalizes in adulthood. HBL accounts for approximately 3% of all hemophilia B cases. HBL is distinct from other forms of hemophilia because, while it is caused by very low levels of clotting FIX early in life, over time, patients begin to produce FIX. This is because mutations causing HBL occur in the promoter region of the gene for clotting FIX. The promoter region is an area in the DNA that controls when a certain gene is turned off or on. In HBL, one activator region is disrupted by mutations, but the promoter region that responds to activation by hormones (estrogen and testosterone) is unaffected (3).

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Received: 27.04.2022 **Accepted:** 06.06.2022

Hemophilia A and B is known as a male disease. In some cases, it can also be seen in women. Depending on the type of mutation, mild hemophilia may also be present in carrier women. Carrier women appear to have decreased levels of FVIII due to X inactivation. Although rare, a hemophilia woman can be born with a 25% probability from the marriage of a hemophilia male and a carrier woman. In addition, a severe hemophilia clinic can be seen in a woman with Turner syndrome with an X0 chromosome (4).

CLINIC FEATURES OF HEMOPHILIA

The severity of hemophilia is usually correlated with factor deficiency. According to the factor level, it is classified as severe (<1 IU/dl), moderate (1-5 IU/dl), and mild (6-40 IU/dl). Bleeding in patients with hemophilia can occur anywhere. All males in a family who inherit the familial mutation will have approximately the same degree of factor deficiency and similar disease severity, as they share the same genetic defect. Throughout life, age and disease severity affect the site of the bleeding. Common bleeding sites in infants and newborns include the central nervous system, circumcision, and areas of medical intervention. Approximately 3% of infants with severe hemophilia develop subgaleal or intracerebral hemorrhage in the perinatal period (5). Skin bruising, joint bleeding, and other musculoskeletal bleeding become more common as children begin to walk. Common bleeding sites in older children and adults are the joints, muscles, central nervous system, and gastrointestinal tract.

Generally, people with severe hemophilia are diagnosed before the age of two, but some people with mild hemophilia may only be diagnosed at the time of injury or when they show symptoms of bleeding associated with surgery. In a data collection study with 13,399 participants; The age at diagnosis for severe, moderate, and mild hemophilia was 1 month, 8 months, and 36 months, respectively (6). Some bleeding sites are mentioned below.

Intra-Articular Bleeding

Hemarthrosis (bleeding into the joint) is the most common site for bleeding in ambulatory patients and represents 80% of bleedings. Bleeding into the joint cavity originates from the synovial vessels. Bleeding episodes often affect various joints, particularly the knees and ankles, which are weight-bearing joints. The ankles are most affected in young children, while the knees and elbows are more commonly affected in adolescents and adults. Hemarthrosis is painful due to stretching of the synovial space and consequent muscle spasm causes increase in intrasynovial pressure. Clinical presentation varies with age; In infants, early signs of bleeding include agitation and reduced use of the affected limb. In older children and adults, it first presents with a characteristic feeling of warmth in a joint, followed by acute pain, swelling and stiffness. The diagnosis of hemarthrosis is clinically based on pain, limitation of movement, and/or physical examination findings. Imaging may be performed in complex situations where the target joint has developed, and it is more difficult to determine whether the findings are new. Target joint is a term used for a joint that has bled three or more times in the past six months. Joint aspiration is usually not performed in patients with hemophilia. With increased joint bleeding frequency, joint damage and inflammation may occur, and the joint may become a target joint with an increased susceptibility to further bleeding.

Hemophilic arthropathy is multifactorial. It is known that repetitive bleeding into synovial joints leads to degenerative articular cartilage damage, as well as severe joint destruction resembling the inflammatory processes (7). In the target joint due to recurrent bleeds, the synovium becomes hypertrophied and protrudes into the joint cavity. The detection of early changes in arthropathy are difficult. Studies show that joint damage in hemophilic arthropathy is induced by direct contact of blood with articular cartilage, interaction with the iron and inflammatory cytokines such as IL-1β and tumor necrosis factor (TNF). These inflammatory cytokines also activate other cytokines, causing progressive joint destruction.

Bleeding into the Muscle

Bleeding into muscles with hematoma formation is common. Often this affects large muscle groups, such as those in the leg (quadriceps), hip (iliopsoas), and arm. Muscle bleeding can be severe, widespread and compromise neurovascular structures. It can cause a compartment syndrome by compressing the vessels and nerve bundles, especially in the lower leg and forearm. In addition, untreated or inadequately treated intramuscular bleeding leads to the formation of a pseudotumor with a hematoma surrounded by a fibrous membrane. Except for iliopsoas, other intramuscular hemorrhages are visible and can be diagnosed and treated at an early stage. However, in the iliopsoas bleeding, a feeling of anesthesia in that leg begins, and then pain and limitation in extension of the hip develop. Usually, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) are needed for diagnosis. Since it may take a long time until the diagnosis, there may be much bleeding to impair hemodynamics. Therefore, prompt diagnosis and treatment are very important.

Intracranial Bleeding

Intracranial hemorrhage (ICH) is relatively rare compared to other bleeding sites, but it is one of the most dangerous and life-threatening events in patients with

hemophilia. It can occur spontaneously or after trauma in individuals of all ages. The overall incidence of ICH in patients with hemophilia is approximately 3-4% at birth. In a meta-analysis included over 54,000 people with hemophilia in 2021, the pooled ICH incidence was 0.23% per year, compared with a higher incidence of 0.74% per year in children and young adults (8). Risk factors for ICH include trauma (especially in births requiring instrumentation), severe factor deficiency, presence of inhibitors, over 50 years of age, hypertension (9). Prophylaxis was found to be the most effective factor in reducing the risk of ICH.

Nose Beeding, Intraoral and Gastrointestinal Bleeding

Bleeding may occur from multiple oropharyngeal sites such as the nose, oral mucosa, gingiva, and frenulum. This type of bleeding follows minor traumas or dental treatments. Also, bleeding from coughing or vomiting can spread to the neck, which can lead to airway obstruction. With or without various lesions in the gastrointestinal tract such as gastritis, polyps, diverticulum, it may present with blood in the stool or hematemesis.

Genitourinary System Bleeding

Hematuria is a common manifestation of severe hemophilia; It is usually benign and does not result in progressive loss of kidney function. Bleeding may originate from the kidneys or bladder. Fibrin clots can form throughout the urinary tract with bleeding. This causes severe colic pain and ureteral obstruction. Intravenous hydration, factor replacement therapy is initiated, and a urinary double J catheter can be inserted if necessary. Antifibrinolytic drugs are not recommended due to increase the fibrin clots in ureter.

Clinical Practice in Heterozygous Women

Female carriers of hemophilia are heterozygous for the associated genetic defect (having one normal allele and an allele with a pathogenic variant in the gene encoding the relevant factor). Therefore, they usually have enough factor activity (factor >50 IU/dl) not to cause bleeding. Since FVIII and FIX levels are normal in heterozygous women, carrier cannot be determined by factor level determination. Only 30% of carrier women have low factor level. Therefore, the causative variant should be performed in likely carrier women. Heterozygous women with low factor levels exhibit similar clinical manifestations to men with mild hemophilia. Causes of severe hemophilia in women include inheritance of pathogenic variants from both parents, X chromosome inactivation (lyonization), loss of the X chromosome containing the normal F8 or F9 allele (as in Turner syndrome) (4). Thus, a woman who is known as heterozygous or likely to be carrier should be monitored closely before any intervention such as surgery that may cause severe bleeding.

Obstetric Problems

Known as a carrier of hemophilia or potential carrier women should get genetic counseling and information about hemophilia. The information includes the risk of having an affected fetus, the timing of diagnosis (at birth and postpartum), the choice to terminate the pregnancy, and potential problems with delivery (such as potential risks from a vaginal delivery if the child has hemophilia). Carriers of hemophilia may have low factor levels as mentioned above. Therefore, if the factor activity level has not been determined before, it should be checked at least once during pregnancy and repeated if it is low (<40%). It should not be forgotten that the FVIII level is found higher than the basal value due to stress and hormones during pregnancy, whereas the FIX level remains more stable. Women with low factor activity levels may be at increased risk of bleeding during procedures, including neuraxial anesthesia, during pregnancy and/or delivery. In addition, even if factor levels are normal during pregnancy, a decrease is observed frequently after delivery, so it should be carefully monitored in terms of postpartum hemorrhage risk. If necessary, postpartum factor levels can be monitored.

Pregnant women should undergo fetal gender assessment using a non-invasive method such as ultrasound, as boys are potentially affected. There are also methods such as detecting Y chromosome sequences from maternal blood for sex determination. There are invasive diagnostic methods (amniocentesis or chorionic villus sampling) for the detection of affected male fetus. In some cases, these invasive methods are recommended if the family will consider terminating the pregnancy when an affected fetus is diagnosed. If prenatal diagnosis is not done, a diagnosis of hemophilia can be made by measuring FVIII or FIX levels in the cord blood of a newborn at birth. While it is reliable for FVIII, FIX level may result in low than expected due to decreased liver maturation and deficiency of vitamin K.

Fetal problems include the absence of a definitive diagnosis at the time of delivery in most cases, and the potential risks of bleeding during or after delivery, particularly intracranial hemorrhage and cephalohematoma (10). Although the best method of delivery (vaginal vs cesarean section) continues to be a matter of debate, most newborns with hemophilia can deliver safely with either method. There is a consensus that instrumental vaginal delivery (use of forceps, vacuum extraction) should be avoided because of the risk of cephalohematoma and ICH. A very large series of births (583,340 births of non-hemophiliacs) in the general population compared various risks with different methods of delivery (11). The risk of subdural or cerebral hemorrhage with spontaneous vaginal delivery, vacuum or forceps delivery was 2.9, 8.0,

or 9.8 per 10,000, respectively. With vacuum plus forceps, the risk was 21.3 per 10,000. The rate of assisted vaginal delivery-associated intracranial bleeding in patients with hemophilia is approximately 4.4% (5).

DIAGNOSIS IN HEMOPHILIA

Diagnostic evaluation in suspected cases of hemophilia begins with a thorough review of the individual's bleeding history and family history. Screening tests are then performed, and the diagnosis is confirmed by specific clotting factor measurements and/or genetic testing.

Laboratory tests are similar for most people with clotting factor deficiency. Initial tests include hemostasis screening tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT), and platelet count (**Figure 1**). If elongation is detected in the aPTT test, the mixing test is performed to distinguish the presence of a factor deficiency or inhibitor. The mixing test is performed by mixing patient plasma and normal plasma in equal proportions. Improvements in aPTT of less than 50% because of mixing suggest the presence of inhibitor, while improvement of more than 50% indicates factor deficiency. Especially coagulation factors (FVIII, FIX, FXI, FXII) that work in the intrinsic pathway are studied. In patients with factor VIII deficiency, it is important to exclude von Willebrand disease (VWD) with the von Willebrand factor (VWF) antigen test (VWF:Ag). Patients with mild hemophilia may have a normal aPTT because aPTT may result in normal with factor levels greater than 15%, especially in hemophilia B (12). Whatever the scenario leading to the suspicion of hemophilia, the definitive diagnosis is made by measurement of residual FVIII and FIX coagulation activity (FVIII:C and FIX:C). These measurements can be performed by using one-stage or chromogenic coagulation methods. The one-stage method is the most widely used due to its long-term use and less costly than the chromogenic assay (13).

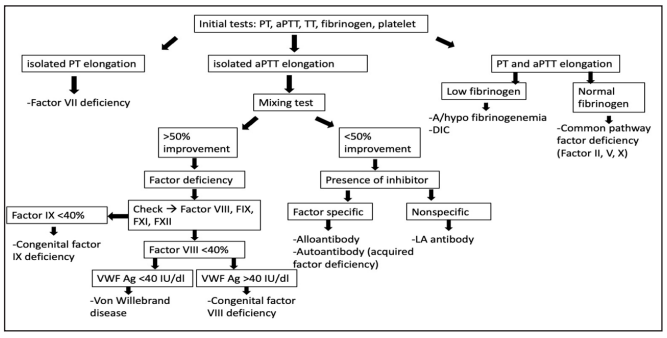

Figure 1. Laboratory differential diagnosis of hemophilia.

PT; prothrombin time, aPTT; activated partial thromboplastin time, TT; thrombin time, VWF; von Willebrand factor, LA; lupus anticoagulant, DIC; disseminate intravascular coagulopathy

Genetic testing (also called molecular testing) is appropriate for most patients. This information helps to estimate the risk of inhibitor formation in the patient and facilitates carrier identification in female family members. It should be done routinely for severe to moderate hemophilia but is less frequently needed for mild hemophilia. For hemophilia B, full gene sequencing is usually done for F9, whereas inversions of intron 22 (40% frequency) and intron 1 (1%) is initially studied for severe hemophilia A (14). Since hemophilia A families with mild to moderate disease are more likely (approximately 90%) to have a point mutation, whole gene sequencing is recommended in families with mild to moderate disease if genetic testing is indicated (15). About 30% of individuals with hemophilia do not have a family history.

Differential Diagnosis

The differential diagnosis of hemophilia includes other inherited bleeding disorders and other causes of aPTT isolated prolongation. Generally, these diseases can be easily distinguished by measuring the appropriate factor level. Like hemophilia, VWD is an inherited bleeding disorder that may be associated with a normal or long aPTT; Some patients with VWD will also have decreased FVIII levels. Most types of VWD show mucosal bleeding patterns clinically different from hemophilia, while some types of VWD (type 2N and type 3) have bleeding patterns similar to hemophilia.

Like hemophilia A and B, factor XI deficiency is characterized by a long aPTT. Unlike hemophilia A and B, patients with factor XI deficiency tend to exhibit provoked bleeding rather than spontaneous bleeding. Factor XI deficiency is more common in Ashkenazi Jews (Jews from Eastern Europe).

Someone may have combined FVIII and FV deficiency due to a defect in a gene that affects cellular transport (endoplasmic reticulum and Golgi apparatus) rather than a defect in the coagulation factor gene. These patients have a longer PT as well as aPTT. It shows autosomal recessive inheritance.

Acquired factor inhibitors are autoantibodies that disrupt the normal activity of clotting factors. Inhibitors of factors, particularly factor VIII, have been reported; they may develop during pregnancy in patients with an underlying systemic disorder such as rheumatoid arthritis, systemic lupus erythematosus, malignancy, or drug reaction. Like hemophilia, acquired inhibitors may present with bleeding and prolonged aPTT.

Antiphospholipid antibody syndrome (APS) results from autoantibody that prolongs aPTT in vitro but clinically creates a risk of thrombosis rather than bleeding. Thromboembolism and/or recurrent pregnancy loss may occur in patients with APS. The expected improvement in aPTT is not seen in the mixture test (16).

INFECTION IN HEMOPHILIA

Existing coagulation factor products from human plasma undergo a variety of procedures to reduce the risk of transmission of infectious organisms, including extensive pre-donation screening, viral reduction and inactivation processes, and other methods to eradicate human immunodeficiency (HIV). Patients treated with plasma-derived factor concentrates, which began to be produced in the late 1970s, were at increased risk for infection with HIV, HCV, and other hepatitis viruses (A, B, D [delta]). Prior to factor concentrates, patients had been treated with blood products such as whole blood and fresh frozen plasma (FFP) were at higher risk for hepatitis viruses. The risk of viral transmission has been greatly reduced by the use of viral inactivation procedures and recombinant factor products produced in cell culture. Co-infection with HCV and HIV is clinically important as it can cause refractory liver disease and poses a high risk for hepatocellular carcinoma. Other potentially infections are Parvovirus B19 and prion.

INHIBITOR IN HEMOPHILIA

Inhibitors are allo-antibodies in immunoglobulin G (IgG) structure that develop against exogenous coagulation factors (FVIII or FIX) in Hemophilia A and B and neutralize the activity of the factors. Peptides from exogenous FVIII (eFVIII) are presented on the surface of antigen-presenting cells via class II MHC proteins, stimulating a population of T helper (TH) cells. This causes the antibody-producing B cells to mature and produce allo-antibodies. The anti-eFVIII allo-antibodies formed recognize the infused eFVIII as a foreign antigen and inhibit eFVIII function; therefore, these antibodies are called inhibitors.

The risk of developing inhibitors in hemophilia with severe FVIII and FIX deficiency is approximately 30% and 5%, respectively. The risk of developing inhibitors varies with the level of deficiency, race/ethnicity, some genetic (complete deletions, nonsense mutations, etc.) and environmental factors, but not all contributing effects have been fully explained. Inhibitor determination is made with the Bethesda test, and the inhibitor titer that neutralizes 50% of 100% factor activity is called one Bethesda unit (BU/ml). A positive inhibitor is defined as ≥ 0.6 BU/mL for FVIII and ≥ 0.3 BU/mL for FIX. Detection of inhibitor titer of <5 BU/mL is called low titer inhibitor, and ≥5 BU/mL is called high titer inhibitor. High titer inhibitors tend to be persistent. When an inhibitor is suspected, a mixture test should be done first, and if it is positive, inhibitor measurements should be made with the Nijmegen-Bethesda test (NBT) to determine the exact inhibitor titer. NBT reduces false positive measurements in the range of 0.6-2 BU/mL as measured by the Bethesda test (17).

Although inhibitors can occur at any time during a patient's life, they occur most frequently within the first 50 exposure days. For this reason, while screening is recommended for inhibitors more frequently in the first applications, is recommended once a year after the first 100 exposure days. The SIPPET study pointed out that the inhibitor development was increased with the recombinant clotting factor concentrates compared to products derived from plasma in the first 50 exposure days (18). For this reason, plasma derived FVIII concentrates are recommended for the first 50 exposure days in many European countries as in Turkey. There is no such recommendation for FIX concentrates, since the inhibitory risk is low in hemophilia B.

THERAPY IN HEMOPHILIA

Although there are many treatment options in hemophilia, treatment is determined according to different geographical and economic conditions around the world. Effective and multidisciplinary approach to the hemophilia is major to prevent bleeding and ensure healthy life. Prophylactic or on-demand treatments are considered mainstay of the treatment in hemophilia. Patients with hemophilia should be treated in comprehensive care unites with a multidisciplinary team of specialists such as hematology, physical therapist, orthopedist, radiology, physiotherapists, nurses, and psychologists specialized in the hemophilia.

Factor Replacement Therapy

The main aim of hemophilia treatment is to increase plasma coagulation factor levels with exogenous factor replacement to stop or prevent bleeding. Whenever possible, only the missing factors should be replaced. Because products such as FFP and prothrombin complex concentrates may have thrombotic potential with high factor levels. Plasma-derived and recombinant products are available for patients with hemophilia. They have no superiority over each other in terms of their effects. What is only known is that recombinant FVIII products increase the inhibitory risk, especially in the first 50 exposure days (19). When FVIII is given 1 IU/kg, the plasma FVIII level increases by 2%, with a half-life of 8-12 hours. Plasma-derived FIX, when given 1 IU/kg, increases the plasma FIX level by 1%, and its half-life is 18-24 hours. Since the dose calculations of recombinant products of FIX may differ, the information of the product used should be checked. Factors should be administered as a slow intravenous bolus for at least 5 minutes (not to exceed 3 mL/minute in adults and 100 IU/minute in children).

There are two main approaches to replacement, prophylaxis or on-demand therapy.

Prophylaxis in Hemophilia

It is the continuous and regular use of clotting factor concentrates that aim to prevent heavy bleeding, especially joint bleeding, and damage, as well as increase the quality of life of patients and provide hemostasis. Prophylactic treatment targets a trough level of >1 IU/dl of the missing factor. However, higher factor VIII levels can be targeted depending on lifestyle and activity of a person in hemophilia.

Time-based prophylaxis classification is determined by the time of prophylaxis initiation (**Table 1**). Primary prophylaxis is the treatment that is started before the second joint bleeding and before the age of three, before physical examination and/or imaging methods reveal signs of joint damage. Secondary prophylaxis is the treatment that is started after two or more joint bleedings, but before "joint damage" occurs by physical examination and radiological imaging methods. Tertiary prophylaxis is the treatment applied after the onset of joint damage in the affected joints by physical examination and radiological imaging methods. It is the type of prophylaxis that is usually started in adult with hemophilia.

Table 1. Definitions of prophylaxis by onset time

Prophylaxis model	Description
Primary prophylaxis	The continuous and regular* treatment that is started before the second joint bleeding and before the age of three, is before the signs of joint damage are revealed by physical examination and/or imaging methods.
Secondary prophylaxis	The continuous and regular* treatment that is started after two or more joint bleedings but is before signs of joint damage are revealed by physical examination and/or imaging methods.
Tertiary prophylaxis	The continuous and regular* treatment is applied after the onset of signs of joint damage by physical examination and/or imaging methods. The initial prophylaxis in adulthood is usually of this type.
Intermittent prophylaxis	The short-term treatment that is applied <45 weeks in a one-year period to prevent bleeding.

*Application of the treatment is >45 weeks in a one-year period

On-demand Therapy

Although prophylaxis reduces the frequency of breakthrough bleeding, it may not prevent them completely, so additional factor doses are needed for bleedings. Treatment should be adjusted to achieve individual best results based on the location, extent, and severity of the bleeding. Immediate treatment is essential for all bleeding episodes. The targeted factor level and duration according to the bleeding site and severity are summarized in **Table 2**.

Inhibitor Therapy

Inhibitor therapy varies depending on the titer usually measured by NBT; however, non-specific coagulation inhibitors (lupus anticoagulants) may cause false positives in the in vitro test. As mentioned above, a titer of <5 BU/mL is called a low titer inhibitor, and a titer of ≥5 BU/mL is called a high titer inhibitor. In the presence of a low-titer inhibitor, it can be treated with high-dose factor concentrate to achieve hemostasis. However, in patients with an inhibitor titer of >5 BU/ml, bypassing agents (BPAs) are preferred to achieve hemostasis. However, such a strategy is not suitable for patients with inhibitor titers >5 BU/ml; instead, bypassing agents (BPAs) are used to achieve hemostasis. BPAs which are commonly used in the treatment or prophylaxis, are recombinant factor VIIa (rFVIIa) and activated prothrombin complex concentrates (aPCCs).

Table 2. WFH recommended dosage and duration of replacement therapy according to bleeding site and type of hemophilia[c]

Bleeding site	Hemophilia A		Hemophilia B	
	Target factor level[b] (IU/dl)	Duration of the treatment	Target factor level[b] (IU/dl)	Duration of the treatment
Joint bleeding	40-60	1-2 days, 1-3 doses[a], every 8-12 hours	40-60	1-2 days, 1-3 doses[a], every 18-24 hours
Intramuscular bleeding (Except iliopsoas)	40-60	2-3 days, longer if response is not sufficient	40-60	2-3 days, longer if response is not sufficient
Iliopsoas bleeding *Initial **Following	*80-100 **40-60	*1-2 days **7-10 days, longer if response is not sufficient	*60-80 **30-60	*1-2 days **7-10 days, longer if response is not sufficient
Intracranial bleeding *Initial **Following	*80-100 **50	*1-7 days **8-21 days, longer if response is not sufficient	*60-80 **30-60	*1-7 days **8-21 days, longer if response is not sufficient
Neck/throat *Initial **Following	*80-100 **50	*1-7 days **8-14 days, longer if response is not sufficient	*60-80 **30-60	*1-7 days **8-14 days, longer if response is not sufficient
Gastrointestinal tract *Initial **Following	*80-100 **50	*1-7 days **8-14 days, longer if response is not sufficient	*60-80 **30-60	*1-7 days **8-14 days, longer if response is not sufficient
Urinary system	40-60	3-5 days, longer if response is not sufficient	40-60	3-5 days, longer if response is not sufficient
Deep laceration	40-60	3-7 days, longer if response is not sufficient	40-60	3-7 days, longer if response is not sufficient
Surgery (major) *pre-surgery **post-surgery	*80-100 **60-80 **40-60	1-3 days 4-14 days (longer if needed)	*60-80 **40-60 **30-50	1-3 days 4-14 days (longer if needed)

WFH; World Federation of Hemophilia, [a]Discontinue if bleeding symptoms have resolved after the first dose, [b]for hemophilia A, dose of factor=(target level-current level)xkgx0.5 for hemophilia B, dose of factor=(target level-current level)xkgx1, [c]WFH recommended dosage and duration of replacement therapy in acute bleeding (27), *Initial doses are given as calculated above, followed by half of dose (every 8-12 hours for hemophilia A, 18-24 hours for hemophilia B).

In low responders, inhibitors may resolve spontaneously over time. Both low-responders and high-responders can be treated with immune tolerance induction (ITI). ITI is given in frequent doses of FVIII or FIX over time to increase tolerance. This practice can be intensive, long-term, and costly (20).

Non-replacement and Bypassing Therapy

A new agent, emicizumab is a biphenotypic antibody and mimics the role of FVIII as in the tenase complex (21). So, emicizumab cannot be used in patients with hemophilia B. Prophylactic use of emicizumab has been shown to be effective in patients with inhibitory hemophilia A. Clinical studies have shown a significant reduction in annual bleeding rate (ABR) as compared to bleeding or prophylactic BPA regimens. Emicizumab is not preferred in acute bleeding; FVIII should be given in patients without inhibitors and BPA should be given in patients with inhibitors. Instead of aPCC, rFVIIa is preferred as BPA for the treatment of acute bleeding in a patient receiving emicizumab prophylaxis treatment. aPCC is a mixture of plasma-derived activated coagulation factors acting by the presence of prothrombin and FXa and therefore the risk of thrombotic events is very high. No thrombotic events have been reported in the use of rFVIIa during emicizumab prophylaxis (22).

The Future of Hemophilia Treatment and Gene Therapy

There have been significant advances in the treatment of hemophilia in recent years. Despite this, there are important issues that continue to be lacking in treatment; establishing new treatment centers that every patient can easily reach and access to safe therapeutic agents. In addition, long-term and effective treatments are being developed. The important point to be considered in the treatment of hemophilia is that the pharmacokinetics, bleeding phenotype and lifestyle of each patient, so the treatment should be individualized. In personalized therapy, the pharmacokinetics and efficacy of the infused factor concentrate, the individual's bleeding phenotype, access to treatment, compliance, and societal perspectives should be considered. In the future, it is hoped that personalized therapy may replace weight-based, fixed-dose prophylaxis regimens, but difficulties in accessing drugs in different countries, cost and compliance limit the widespread use of this therapy. Newly developed treatments are entering the market and are promising for the near future. Several agents are currently under investigation, including fitusiran (23), Super FVa, factor Xa, APC inhibitors, and TFPI inhibitors (24).

Gene therapy trials using adeno-associated virus (AAV)-based vectors have now been reported in hemophilia A and B. In the interim evaluations of the studies, the almost complete elimination of bleeding episodes and the decreased need for factors seem promising. In non-insertional gene therapy products, the levels of the nascent factor may decrease over time; stable expression of coagulation factor transgenes should be provided to avoid the need for treatment. A recent hemophilia A gene therapy trial demonstrated sustained F8 expression for >2 years (25). It was observed to show sustained F9 expression over 8 years in a hemophilia B gene therapy trial (26). However, further studies and observations are required to achieve persistent factor 8 or factor 9 expression.

ETHICAL DECLARATIONS

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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