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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Which Material Should Be Used for Mast Cell Evaluation in Gastric Cancer: Endoscopic Material or Resection Material?

Mide Kanserinde Mast Hücresi Değerlendirmesinde Hangi Material Kullanılmalı: Endoskopik Materyal mi, Rezeksiyon Materyali mi?

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ABSTRACT

Aim: *Histopathological examination has an important place in the evaluation of parameters that are important in the prognosis of gastric tumors. In addition to the prognostic data included in the guidelines, other observed findings that may be important for the tumor behavior are also evaluated in the histopathological examination. Mast cells, which are among the elements of the immune system, are among these findings. In this study, it is aimed to compare the endoscopic biopsy materials and resection materials, which have the potential to be used for the evaluation of mast cells.*

Material and Method: *Nineteen gastric tumor cases with endoscopic biopsy and resection material belonging to the same patient were included in the study. Toludine blue histochemistry was applied to the sections obtained from the paraffin blocks of the preparations representing the tumor. In the light microscopic evaluation, the area with the highest concentration of mast cells was selected at 100× magnification, and then 100 cells were counted inside and around the tumor at 400× magnification. Mast cells staining positively with toludine blue were noted in these 100 cells. Mann-Whitney-U was used in the analysis of the significance of mast cell number between groups, and Pearson's test was used in the correlation between groups.*

Results: *In the endoscopic biopsy material, the mean number of mast cells inside the tumor (MCIT) was 1.32±2.65, the mean number of mast cells around the tumor (MCAT) was 1.0±1.76; in the resection materials, the average number of MCIT was calculated as 4.84±4.86, and the average number of MCAT was calculated as 5.63±6.99. A statistically significant difference was observed between the number of MCIT (p=0.001) and the number of MCAT (p=0.000) between endoscopic biopsies and resection materials in the analyzes. When all the materials were included in analysis, it was determined that the number of MCIT and the number of MCAT showed a positive correlation. However, when endoscopic biopsies and resection materials were compared, it was noted that there was no correlation in terms of MCIT or MCAT.*

Conclusion: *Mast cells, which are an important element of the immune response, are evaluated with different aspects in gastric cancers as in various tumors. Considering the importance of tumor and tumor microenvironment analysis as well as the results of the presented study, it is thought that mast cells, which have the potential to be an important marker in gastric tumors in the future, should be evaluated in the resection material, and endoscopic material evaluations do not reflect the real picture.*

Key words: *gastric cancer; mast cell; endoscopic biopsy; resection material*

ÖZET

Amaç: *Mide tümörlerinin prognozunda önemli olan parametrelerin değerlendirilmesinde histopatolojik inceleme önemli bir yer tutmaktadır. Histopatolojik incelemede kılavuzlarda yer alan prognostik verilerin dışında gözlenen tümör davranışı için önemli olabilecek diğer veriler de değerlendirilmektedir. İmmun sistem elemanları arasında yer alan mast hücreleri bu veriler arasında yer almaktadır. Bu çalışmada mast hücrelerinin değerlendirilmesi için kullanılabilme potansiyeli olan endoskopik biyopsi materyalleri ile rezeksiyon materyallerinin karşılaştırılması amaçlanmaktadır.*

Materyal ve Metot: *Çalışmaya aynı hastaya ait endoskopik biyopsi ve rezeksiyon materyali bulunan 19 mide tümörü olgusu dâhil edilmiştir. Tümörü temsil eden preparatlara ait parafin bloklardan elde edilen kesitlere toludin blue histokimyası uygulanmıştır. Işık mikroskopik değerlendirmede mast hücrelerinin en yoğun olduğu alan 100× büyütmede seçilmiş ve sonrasında 400× büyütmede tümör içinde ve çevresinde 100 hücre sayılmıştır. Bu 100 hücrenin içinde yer alan toludin blue ile pozitif boyanan mast hücreleri not edilmiştir. Mast hücresi sayısının gruplar arası anlamlılığı analizlerinde Mann-Whitney U, gruplar arası korelasyonda Pearson testi kullanılmıştır.*

Bulgular: *Endoskopik biyopsi materyalinde tümör içinde yer alan mast hücre sayısı (TİMH) ortalama 1,32±2,65, tümör çevresi mast hücresi sayısı (TÇMH) ortalama 1,0±1,76; rezeksiyon materyallerinde TİMH sayısı ortalama 4,84±4,86, TÇMH sayısı ortalama 5,63±6,99 olarak hesaplanmıştır. Analizlerde endoskopik biyopsiler ve rezeksiyon materyalleri arasında TİMH sayısı (p=0,001) ve TÇMH sayısı (p=0,000) arasında istatistiksel anlamlı farklılık izlenmiştir. Tüm olgular incelendiğinde TİMH sayısı ile TÇMH sayısının pozitif korelasyon gösterdiği saptanmıştır. Ancak endoskopik biyopsiler ile rezeksiyon materyalleri kıyaslandığında TİMH veya TÇMH açısından herhangi bir korelsayon olmadığı dikkati çekmiştir.*

Sonuç: *İmmun yanıtın önemli bir unsuru olan mast hücreleri çeşitli tümörlerde olduğu gibi mide kanserlerinde de farklı yönleri ile değerlendirilmektedir. Sunulan çalışma sonuçları yanısıra tümör ve tümör mikroçevre incelemesinin önemi göz önünde bulundurulduğunda gelecekte mide tümörlerinde önemli bir belirteç olma potansiyeli bulunan mast hücrelerinin rezeksiyon materyalinde değerlendirilmesi gerektiği, endoskopik materyal değerlendirmelerinin gerçek tabloyu yansıtmadığı düşünülmektedir.*

Anahtar kelimeler: *mide kanseri; mast hücresi; endoskopik biyopsi; rezeksiyon materyali*

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Introduction

Gastric cancer is the fifth most commonly diagnosed cancer worldwide in both gender, responsible for more than 1,000,000 new cases and an estimated 783,000 deaths in 2018[1]. Although survival rates have increased in the last few decades due to current treatment protocols, managing the disease still poses significant challenges[2]. As the stage of stomach cancer increases, the survival rate decreases significantly. Although the 5-year survival rate of non-metastatic gastric cancer cases is over 50%, the 5-year survival rate decreases to 30% because most of the diagnoses are made in advanced stages[3,4].

One of the most important risk factors for gastric cancer is *Helicobacter pylori* infection among the modifiable factors. Other modifiable risk factors include tobacco history, socioeconomic status, and salty meat consumption, and non-modifiable risk factors include age, gender, race, and genetics[5,6].

Histopathological examination has an important place in the evaluation of parameters that are important in the prognosis of gastric tumors. Histopathologically, tumor localization, histological type, histological grade, tumor depth (pT stage), condition of surgical margins, treatment effect in the presence of neoadjuvant therapy, lymphovascular and perineural invasion, regional lymph node metastases (pN stage), presence of distant metastases (pM stage), presence of intestinal metaplasia, presence of low/high grade dysplasia, presence of *Helicobacter pylori gastritis*, presence of autoimmune chronic atrophic gastritis, presence of polyps are evaluated[7].

The immune system is vital in controlling tumor growth and progression[8]. Gastric cancer cells have the ability to modulate the immune system and evade detection[9]. Mast cells are a group of innate immune cells that have immunomodulatory effects on tumor progression, such as angiogenesis, tumor microenvironment reconstruction, and interaction with other immune cells[10–13]. However, many unexplained areas remain regarding the phenotype, functional regulation and clinical correlation of mast cells in the human gastric cancer microenvironment. Studies investigating the effect of mast cells on prognosis in gastric cancer have shown that the presence and amount of mast cells, tryptase activity, and various parameters of the tumor and survival are related[14–17]. This raises the question of "how to evaluate mast cells, which can be used as a biomarker?" in gastric cancer. In this context, the current study evaluated the correlation between the number of mast cells observed inside and/or around the tumor, and between endoscopic biopsies and resection materials.

Materials and Methods

The study is approved by the Kafkas University Faculty of Medicine Ethical Committee (11.03.2021-02). 19 gastric tumor cases with endoscopic biopsy and resection material belonging to the same patient diagnosed in Kafkas University Health Research and Application Center between 01.06.2014 and 01.06.2016 were included in the study. Cases without pathology archive material were not included in the study. Hematoxylin&eosin stained slides of the cases were obtained from the pathology archive and the diagnosis was confirmed. Then, the slides representing the tumor were selected, sections of 4 micron thickness were taken from the blocks of these slides, and histochemical staining was performed with toludine blue (Sigma-Aldrich, St Louis, USA) in accordance with the kit's instruction manual.

Toludine blue stained slides were evaluated by a light microscope (Olympus BX46, Japan). During the evaluation, the area with the highest concentration of mast cells was selected at 100× magnification, and then 100 cells were counted in and around the tumor at 400× magnification. Mast cells staining positively with toludine blue were noted in these 100 cells.

Statistical Package for Social Sciences (SPSS) program version 15.0 package program (Released 2006. SPSS program for Windows, Version 15.0, SPSS Inc. Chicago, USA) was used for statistical analysis. Mann Whitney-U test was used to analyze the significance of mast cell number between groups, and the Pearson test was used for intergroup correlation. Values with $p<0.05$ were considered statistically significant in the 95% confidence interval analyses.

Results

In the evaluation of endoscopic biopsy material of 19 gastric tumor cases, the mean number of mast cells in the tumor was 1.32 ± 2.65 (minimum 0, maximum 10), and the mean number of mast cells around the tumor was 1.0 ± 1.76 (minimum 0, maximum 7). When the resection materials were evaluated, the mean number of mast cells in the tumor was 4.84 ± 4.86 (minimum

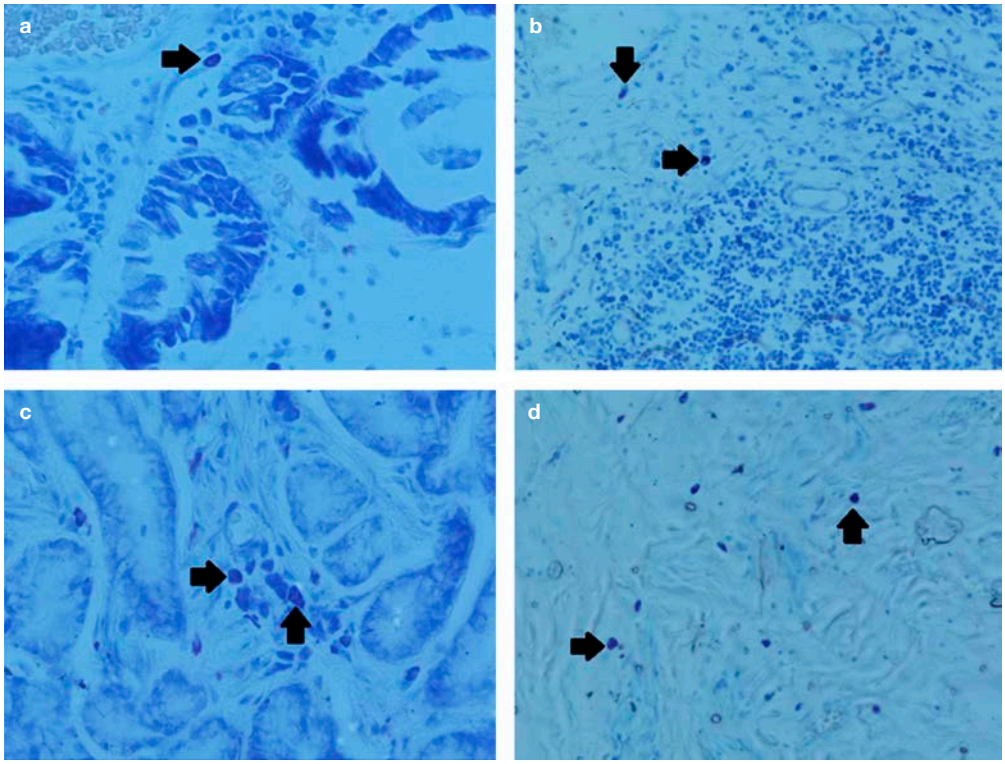

Figure 1. *a–d. Intra-tumoral mast cells (black arrow) in endoscopic biopsy material, Toludine blue, 400× (a); peri-tumoral mast cells (black arrow) in endoscopic biopsy material, Toludine blue, 200× (b); intra-tumoral mast cells (black arrow) in resection material, Toludine blue, 400× (c); peri-tumoral mast cells (black arrow) in resection material, Toludine blue, 200× (d).*

0, maximum 17), and the mean number of mast cells around the tumor was 5.63±6.99 (min 0, max 30). Intratumoral and peritumoral mast cells of endoscopic biopsy and resection materials were demonstrated in Fig. 1.

In the statistical analyzes performed, a statistically significant difference was observed between the endoscopic biopsies and resection materials in the number of mast cells within the tumor (p=0.001) and the number of mast cells around the tumor (p=0.000). When all cases were examined, it was found that the number of mast cells in the tumor and the number of mast cells around the tumor showed a positive correlation with the Pearson test (p=0.000, correlation coefficient 0.704). Similarly, when endoscopic cases and resection materials were examined separately, it was observed that the number of intra-tumor mast cells in the endoscopic material (p=0.003, correlation coefficient 0.643) and the resection material were positively correlated with the number of mast cells around the tumor (p=0.002, correlation coefficient 0.660). However, when endoscopic biopsies and resection materials were compared, it was noted that there was no correlation in terms of intra-tumoral mast cells (p=0.074, correlation coefficient -0.419). In addition, no correlation was observed between the endoscopic biopsies and the resection material when the mast cells around the tumor were compared (p=0.325, correlation coefficient -0.239).

Discussion

Gastric cancer is among the leading causes of death from cancer in the world[1]. In gastric cancer, in which the incidence and mortality rates increase with age 18, histopathological examination remains at a key point. A significant portion of the data proven to be of prognostic importance on the tumor is obtained through histopathological examination. These data are presented in standard pathology reports according to current guidelines[7]. However, apart from the known prognostic important data, observationally different findings form the basis for studies that will affect the behavior of the tumor, and therefore, the treatment and prognosis. Inflammatory response to tumors and tumor immunology are frequently encountered as one of these issues.

The immune system is critical in tumorigenesis and the control of tumor growth and progression[8]. In a healthy immune system, under normal conditions, tumor cells with abnormal genetic structure and behavior are detected and eliminated before they turn into detectable malignancies. However, as in many cancer types, malignant cells in gastric cancer can modulate the immune system and evade detection[9].

Mast cells exert their immunomodulatory effects on tumor progression mainly through angiogenesis, tumor microenvironment reconstruction, and interaction with other immune cells[10–12]. This system, which plays a critical role in maintaining normal microenvironment tissue homeostasis, is an obstacle to tumorigenesis. However, an abnormal microenvironment alters homeostasis and creates the necessary environment for tumorigenesis. The inflammatory microenvironment containing mast cells, macrophages, lymphocytes, neutrophils, and natural killer cells may form the basis for tumorigenesis[19]. This raises the question of whether mast cells are a factor or an inhibitor in tumor development. Mast cells are long-lived cells and have the potential to respond quickly to changes in their microenvironment. By degranulation, they can release large amounts of immunomodulatory compounds and cause a massive proinflammatory response in and around the tumor, which may be detrimental to cell survival[20]. However, as tumor proliferation with critical granules containing trophic or mitogenic factors, the medium can also lead to the formation of an enriching microenvironment[21].

A study evaluating the relationship between gastric cancer and mast cells reported that the percentage of mast cells increased significantly in the advanced stages of the tumor, and mast cells might induce tumor progression. In the same study, it is suggested that the increase in the percentage of mast cells is positively correlated with the overall survival of gastric cancer patients[22]. Similarly, another study stated that there is a significant positive correlation between the number of infiltrating mast cells in gastric cancers and clinical features such as tumor size. In addition, it has been reported that the overall survival rate of the patient is lower independently in patients with increased intratumoral mast cell count, and disease-free survival is inversely correlated with intratumoral mast cell levels[21]. Tryptase is considered an indicator of mast cell activity. It has been reported that tryptase-positive mast cells are correlated with new vessel formation in gastric cancers[22]. In a study published in 2017, it was reported that tryptase expression is an independent predictor of overall survival and recurrence-free survival in gastric cancer cases; It has been suggested that the combination of tryptase expression and tumor-node-metastasis (TNM) stage has higher prognostic power than each of these markers alone in predicting survival[16]. A study that included both gastric and colorectal cancers found that tryptase-positive mast cells in the primary tumor tissue showed a positive correlation with the number of metastatic lymph nodes, regardless of tumor staging or location[17].

As seen in the studies, mast cells infiltrating the tumor, whether they have positive or negative effects on tumorigenesis, have the potential to be used as a useful clinical prognostic marker in the future. Future targeted treatment protocols may include blocking the protumorigenic effects of tumor-infiltrating mast cells and/or increasing their proinflammatory activity. In this context, the detection of the mast cell gains importance. In our technical study on which pathological material would be more appropriate to detect the mast cell, the mean number of intra-tumoral mast cells in all materials was 3.08±4.25, and the mean number of mast cells around the tumor was 3.32±5.55. When endoscopic biopsy and resection materials were evaluated, it was noted that the mean of intra-tumoral ($p=0.001$) and peri-tumoral ($p=0.000$) mast cells in endoscopic materials was statistically significantly lower than that of resection material. Endoscopic biopsies are thought to contain a more limited area for selection, although the same amount and quality of areas are selected.

When the number of intra-tumoral mast cells and the number of peri-tumoral mast cells were evaluated individually in endoscopic cases ($p=0.003$, correlation coefficient 0.643) and resection materials ($p=0.002$, correlation coefficient 0.660), it was observed that there was a statistical correlation in both material types. This indicates that the tumor microenvironment shows a similar distribution of mast cells in the tumor area. However, no correlation was found when the endoscopic and resection materials were compared with intra-tumoral (Pearson correlation coefficient -0.419, $p=0.074$) and peri-tumoral (Pearson correlation coefficient -0.239, $p=0.325$) mast cells. This indicates that intra- and peri-tumor mast cells in endoscopic materials are not representative of those in resection materials. The statistically significant difference in the mean of mast cell numbers also confirms this proposition.

As a result of our study, the necessity of using resection material that better represents the tumor and tumor microenvironment has been demonstrated in the evaluation of mast cells, which can potentially be an important marker in gastric tumors in the future. In addition, it is thought that endoscopic biopsy materials should not be used in the evaluation of mast cells because they cannot adequately express the tumor and its microenvironment, and the adequacy of endoscopic biopsies should be questioned in studies to be conducted in terms of other possible different markers.

Statement of Ethics

The study is approved by the Kafkas University Faculty of Medicine Ethical Committee (11.03.2021-02).

Conflict of Interest Statement

All the authors declare no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Determination of Mental Health Status of Nurses Caring for Patients With COVID-19

COVID-19'lu Hastalara Bakım Veren Hemşirelerin Ruhsal Etkilenme Durumlarının Belirlenmesi

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ABSTRACT

Aim: *The present study aims to determine the effects of COVID-19 on the psychological well-being of nurses caring for diagnosed or suspected cases of COVID-19.*

Material and Method: *The population of the descriptive study consists of nurses (n: 149) working at theEge University Hospital COVID-19 Units who voluntarily agreed to participate in the study. Data were collected through Socio-demographic questionnaire form, Fear of Coronavirus Scale, and Brief Symptom Inventory (BSI) from nurses who voluntarily agreed to participate in the study.*

Results: *Nurses caring for patients with COVID-19; Gender, weekly working hours, previous psychiatric diagnosis history, being educated about COVID-19 and needing personal and professional help during the pandemic were found to be statistically significant with the somatization sub-dimension of BSI. It was seen that the nurses who lived with BSI were statistically significant with the depression sub-dimension. The state of being educated about COVID-19 and needing personal and professional help during the pandemic were found to be related to the anxiety and depression sub-dimensions of BSI. Among nurses caring for patients with COVID-19, gender, marital status, number of children, household members, household members over 65 years of age, receiving education about COVID-19, frequency of following the news about COVID-19, and need for personal and professional help during the pandemic were found to be statistically significantly correlated with the Fear of Coronavirus Scale.*

Conclusion: *The study's results exhibit consistency with the literature and demonstrate that nurses are psychologically affected during this pandemic. Repetitive studies are required in larger hospital patient groups to organize necessary interventions with the Consultation-Liaison Psychiatry Nursing.*

Key words: *COVID-19; nursing; pandemic; mental health; mental trauma*

ÖZET

Amaç: *Çalışmada COVID-19 tanısı alan ya da şüpheli olan vakaların bakımını üstlenen hemşirelerin ruhsal yönden etkilenme durumlarını belirlemek amaçlanmıştır.*

Materyal ve Metot: *Tanımlayıcı tipte olan araştırmanın evreni, Ege Üniversitesi Hastanesi COVID-19 Birimlerinde görev yapan ve çalışmaya gönüllü olarak katılan hemşireler (n: 149) oluşturmaktadır. Araştırmanın yapılması için gönüllü olarak çalışmaya katılmayı kabul eden, hemşirelere Sosyodemografik anket formu, Koronavirüs (COVID-19) Korkusu Ölçeği ve Kısa Semptom Envanteri (KSE) veri toplama araşları olarak kullanılmıştır.*

Bulgular: *Covid-19'lu hastaları bakan hemşirelerin; cinsiyeti, haftalık çalışma saatleri, daha önceden konulmuş psikiyatrik tanı öyküsü, COVID-19 ile ilgili eğitim alma durumu ve pandemi döneminde kişisel ve mesleki yardıma ihtiyaç duyma halleri, KSE'nin somatizasyon alt boyutuyla istatistiksel olarak anlamlı bulunmuştur. Hemşirelerde birlikte yaşadıkları kişiler KSE'nin depresyon alt boyutuyla istatistiksel olarak anlamlı olduğu görülmüştür. COVID-19 ile ilgili eğitim alma durumu ile pandemi döneminde kişisel ve mesleki yardıma ihtiyaç duyma halleri ise KSE'nin anksiyete ve depresyon alt boyutlarıyla ilişkili bulunmuştur. COVID-19'lu hastalara bakan hemşirelerin; cinsiyet, medeni durumu, çocuk sayısı, birlikte yaşadıkları kişiler, birlikte yaşadığı kişilerde 65 yaş üstü birey olması, COVID-19 ile ilgili eğitim alma durumu, COVID-19 ile ilgili haberleri takip etme sıklıkları ve pandemi döneminde kişisel ve mesleki yardıma ihtiyaç duyma hali Koronavirüs Korkusu Ölçeği ile istatistiksel olarak anlamlı düzeyde ilişkili bulunmuştur. Yaş, Kısa Semptom Envanterinin alt boyutları ve Koronavirüs Korkusu Ölçeği ile istatistiksel olarak anlamlı bulunmamıştır.*

Sonuç: *Çalışma sonuçları, genel anlamda literatür ile uyumlu olup, hemşirelerin bu pandemi döneminde psikolojik olarak etkilendiğini göstermektedir. Araştırmanın daha büyük gruplarda ve farklı hastanelerde de tekrarlanması ve sonuçlara göre, Konsültasyon Liyezon Psikiyatrisi Hemşireliği ile birlikte uygun girişimler planlanması önerilir.*

Anahtar kelimeler: *COVID-19; hemşirelik; pandemi süreci; ruh sağlığı; ruhsal travma*

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Introduction

The COVID-19 pandemic, with the first cases emerging on December 1, 2019 in Wuhan, China, was reported to be the first "Wuhan pneumonia"[1]. On January 12, 2020, the World Health Organization described the virus as a new Coronavirus (2019-nCoV) named "SARS-CoV-2" on February 11, 2020[2–4]. COVID-19, or 2019-nCoV, is a new type of contagious viral disease caused by severe acute respiratory syndrome (SARS) coronavirus-2 (SARS CoV-2)[5–7]. The pandemic, starting in the Asian countries followed by China, has affected many countries and spread around the World[8]. COVID-19, which emerged in Wuhan, China at the end of 2019, affected 13 countries by January 24, 2020, and 118.000 people in 114 countries by March 11, 2020, becoming an epidemic. World Health Organization declared the COVID-19 epidemic on January 30, 2020, as "a public health emergency of international concern (PHEIC)", and with the number of cases doubling by 13 and countries affected by the virus tripling within 15 days, the World Health Organization declared it as a "pandemic" on March 11, 2020[3,9,10].

In Türkiye, the first COVID-19 case was detected on March 11, 2020[11–13], while the first COVID-19-related death occurred on March 17[5]. Initially, the strategies of neighboring countries were monitored to delay the entry of the infection into Türkiye and measures were taken accordingly[14]. In January, the Science Committee and COVID-19 Guidelines were established to fight the COVID-19 outbreak[11].

During a pandemic, healthcare workers are among the occupational group with the highest risk[15]. Nurses, who constitute the majority of healthcare workers, are most at risk of COVID-19 infection as they provide one-on-one nursing care to patients diagnosed with COVID-19 or suspected cases at a distance of less than one meter[13]. The International Union of Nurses (ICN) reported that thousands of nurses were infected with the virus, and many died due to COVID-19[16]. According to the data obtained from the National Nursing Association, a member of the International Union of Nurses (ICN), more than 90.000 healthcare workers worldwide have been infected with the virus and, at least 260 nurses died due to COVID-19[17].

Infectious diseases have a deep and wide range of psychosocial effects at the individual, social, and international level[18]. Pandemics create fear and anxiety both in society and among healthcare professionals due to the infectious nature of the disease and its danger, invisibility, and gradually narrowing areas of influence[19]. Healthcare workers are exposed to social shifts and psychological stress at a higher level than the general population[20]. In China, a study conducted on 1257 healthcare workers during the COVID-19 pandemic reported distress among more than 70% of the participants, depression among 50%, and insomnia at 34%[21]. In Singapore, the study of Tan et al.[22] reported higher levels of psychological distress among non-physician healthcare workers during the COVID-19 pandemic. A study conducted on 325 nurses in the Philippines reported that 123 nurses (37.8%) had dysfunctional levels of anxiety[23]. In Türkiye, a study conducted by Hacimusalar et al.[24] showed that healthcare workers' hopelessness and anxiety levels were higher than those who were not healthcare workers while reporting higher hopelessness and anxiety levels among nurses compared to doctors and other healthcare professionals. On the other hand, in Türkiye, the study of Kilincel et al.[25] found that 48.5% of healthcare workers experienced increased health-related anxiety and 54.3% experienced decreased desire to work.

Material and Method

Study Type

The study was designed as a cross-sectional, descriptive study.

Ethical Permissions

Ethical approval was obtained from T. C. Ege University Medical Research Ethics Committee (TAEK) (number E-99166796–050.06.04–43828) and the Ministry of Health. In addition, separate institutional permissions were obtained from the heads of departments of these units to carry out the study in the COVID-19 Units of the Ege University Medical Faculty Hospital. Permission was obtained from Prof. Dr. Nesrin Hisli Sahin, developer of the scale, for the "Brief Symptom Inventory (BSI)" scale to be used in the study via e-mail. For the "Fear of Coronavirus (COVID-19) Scale", permission was obtained from Ozan Korkmaz, one of the colleagues of Bakioglu who translated the scale into Turkish, via e-mail.

Research Questions

How are the mental effects of nurses who care for patients with COVID-19?

Nurses who care for patients with COVID-19 have an effect on their psychological impact.

What are the factors?

Research Hypothesis

Hypothesis of the Study: Nurses who care for patients with COVID-19 are affected.

Sampling and Sampling Method

The population of this study consists of nurses (n: 223) working in the COVID-19 units of Ege University Medical Faculty Hospital, with the sample consisting of 149 nurses, 118 (79.2) women and 31 (20.8) men, who agreed to participate in the study voluntarily. In this study, 69% of the population were reached.

Data Collection Tools

Research data were collected using the following tools:

1) Socio-demographic Questionnaire prepared by the researchers
2) Brief Symptom Inventory (BSI)
3) Fear of Coronavirus (COVID-19) Scale

Socio-demographic Questionnaire Form

The researchers prepared the form to investigate participants' sosyodemographic characteristics. These are; age, gender, marital status, number of children, whom they live with, number of years in the profession, work schedule, weekly work hours, past psychiatric history, presence of chronic disease posing a risk in case of infection with COVID-19, presence of chronic disease in household members posing a risk in case of infection with COVID-19, presence of a household member over 65 years of age, whether they care for patients diagnosed with COVID-19, training by the relevant institution about COVID-19, the frequency of following the news about COVID-19, need any professional help, and whether they knew where they could get this help.

Brief Symptom Inventory (BSI)

Brief Symptom Inventory (BSI) was developed by Derogatis in 1992. The BSI is the short form of the 90-item Symptom Checklist known as the SCL-90, which can be completed in approximately 5–10 minutes. Brief Symptom Inventory is a Likert-type scale consisting of 53 items in which items are scored from 0 to 4, corresponding to the statements "Not at all", "Somewhat", "Moderately", "Quite a Lot", and "Extremely". The scale consists of depression (14 questions), anxiety (17 questions), negative self-perception (9 questions), somatization (7 questions), hostility (4 questions) subscales, and two questions (32nd and 15th) as additional items. Each subscale was studied separately in the reliability study conducted by Şahin et al.[26] in 2002 where the Cronbach's Alpha coefficient was calculated as 0.88 for depression, 0.84 for anxiety, 0.74 for negative self-perception, 0.70 for somatization, and 0.73 for hostility. The reliability of the scale was calculated as a Cronbach's Alpha coefficient of 0.94 for the sum of all items. In our study, the Cronbach Alpha coefficient, the reliability of which was obtained from the sum of all items, was 0.96.

Fear of Coronavirus (COVID-19) Scale

The scale was developed by Ahorsu et al.[27] and translated into Turkish by Bakioglu et al.[28]. The Turkish reliability and validity study of the scale was carried out by Ladikli et al.[29]. The Cronbach's alpha internal consistency coefficient was found as 0.86 for the reliability of the scale[29]. The scale consists of one subscale and seven items, with no reverse items, in which items are scored from 0 to 4, corresponding to the statements "strongly disagree", "disagree", "neither agree nor disagree", "agree" and "strongly agree", with the total scale score indicating the level of fear of Coronavirus (COVID-19) experienced by the individual. The scores that can be obtained from the scale range between 7 and 35, with higher scores indicating a high level of fear of Coronavirus[28]. In our study, the reliability of the scale's Cronbach's alpha coefficient was 0.88.

Research Process

Research data were collected between 01.04.2021 and 15.05.2021 in the burn unit, emergency service, infectious diseases service, chest diseases service, and dialysis unit of Ege University Medical Faculty Hospital where COVID-19 patients received care. The COVID-19 units were visited during working hours to meet the nurses working therein. Detailed information was conveyed about the study. Nurses who agreed to participate in the study were asked to complete the Socio-demographic questionnaire form, Brief Symptom Inventory (BSI) and Fear of Coronavirus (COVID-19) Scale.

Table 1. *Distribution of the participants by socio-demographic characteristics*

Socio-demographic features	n	%
Age group		
23–30 years old	101	67.8
31–40 years old	35	23.5
41–50 years old	13	8.7
Gender		
Woman	118	79.2
Man	31	20.8
Marital status		
Married	51	34.2
Single	98	65.8
How many children do you have?		
0	115	77.2
1	17	11.4
2 + 3	17	11.4
Whom do you live with in your house?		
Family	77	51.7
Friends	21	14.1
Alone	51	34.2
What year are you in the profession?		
1–5 years	83	55.7
6–10 years	36	24.2
11–15 years	18	12.0
16- >16 years	12	8.1
How long do you work a day?		
8-hour shift	9	6.0
12-hour shift	15	10.1
16-hour shift	48	32.2
8–16 hour shift	77	51.7
How many hours a week do you work?		
Less than 40 hours	6	4.0
40–48 moments	126	84.6
More than 48 hours	17	11.4
Do you have any previous diagnosed history of psychiatric disorders?		
Yes	9	6.0
No	140	94.0
Does anyone have a chronic disease that can be considered risky in case of covid-19 infection?		
Yes	16	10.7
No	133	89.3
Does anyone you live with have a chronic disease that can be considered risky in case of covid-19 infection?		
Yes	36	24.2
No	113	75.8
Are there any individuals over 65 whom you live with?		
Yes	17	11.4
No	132	88.6
Have you been trained by your agency on how to protect yourself from COVID-19 infection?		
Yes	122	81.9
No	27	18.1
How often do you keep track of news about COVID-19?		
Every day	77	51.7
Weekly	38	25.5
Rarely	24	16.1
Never	10	6.7
Do you need help for your personal and professional needs during the pandemic period?		
Yes	78	52.3
No	71	47.7
From whom they get help when they need?		
– Family	12	8.1
– Friends	25	16.8
– Family and Friends	13	8.7
– Needs help but cannot ask	19	12.8
– Infection committee	2	1.3
– Psychologist	3	2.0
– Not needed	75	50.3
Total	149	100.0

n=149

Data Analysis

Obtained data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows (SPSS Inc., Chicago, IL) program version 25.0. Data were analyzed using descriptive statistics (number, percentage, mean, standard deviation). The distribution of the groups was assessed by the Kolmogorov-Smirnov test. The Mann-Whitney U test and ANOVA test were used to compare data, and $p<0.05$ was considered statistically significant.

Results

A total of 149 nurses working in COVID-19 units were recruited for the study. Evaluation of the sociodemographic data in Table 1 shows that 67.8% of the participants were between the ages of 23–30 and 79.2% were women. According to Table 1, 55.7% of the participants have been in the profession for 1–5 years, 51.7% worked in 8–16 hour shifts and 84.6% worked 40–48 hours a week. While 75.8% of the participants reported no household member with a history of chronic disease that could pose a risk in case of infection with COVID-19, 88.6% reported no household member over 65 years of age. According to Table 1, 81.9% of the participants received training on protection against COVID-19 by their institution. It was found that 51.7% of the participants follow the news about COVID-19 daily, and 52.3% need help for their personal and professional needs during the COVID-19 pandemic.

Table 2a and Table 2b shows a statistically significant difference between gender and somatization ($p=0.001$) and fear of coronavirus ($p=0.002$). The level of somatization ($X=0.69$) and fear of coronavirus ($X=2.32$) were higher among female nurses than the level of somatization ($X=0.44$) and fear of coronavirus ($X=1.80$) among male nurses. It was determined that gender differences affected the extent of somatization and the level of fear of coronavirus. A statistically significant difference was observed between the nurses' marital status ($p=0.008$), number of children ($p=0.012$) and fear of coronavirus. Married nurses had higher fear of coronavirus ($X=2.48$), whereas single nurses had less fear of coronavirus ($X=2.07$). While the fear of coronavirus ($X=2.79$) was higher in nurses with two or more children, those with a single child exhibited less fear of coronavirus ($X=2.14$). Whether the nurses lived with their families, friends, or alone caused a statistically significant difference in their levels of depression ($p=0.046$) and fear of coronavirus ($p=0.031$). A statistically significant difference was detected between the number of years in the profession and negative self-perception among the nurses ($p=0.037$). A statistically significant difference was observed between weekly working hours ($p=0.014$), psychiatric history ($p=0.011$), and somatization. The nurses with a past psychiatric history had higher somatization ($X=1.14$), while those with a past psychiatric history had lower somatization ($X=0.62$). A statistically significant difference was found between the nurses living with individuals over 65 years of age ($p=0.010$) and the fear of coronavirus. Higher fear of coronavirus ($X=2.76$) was found among the nurses who lived with individuals over 65 years of age than those who did not live with any individuals over 65 years of age ($X=2.15$).

A statistically significant difference was observed between a previous training on COVID-19 provided by the institution they work, and the subscales of anxiety ($p=0.011$), depression ($p=0.004$), negative self-perception ($p=006$), somatization ($p=0.022$) and fear of coronavirus ($p=0.026$), revealing that previous training on COVID-19 affected anxiety, depression, negative self-perception, somatization, and fear of coronavirus. It is found that the fear of coronavirus was higher ($X=2.29$) among nurses who received training on COVID-19 from the institution they worked in. In contrast, the fear of coronavirus was lower among nurses who did not receive any training ($X=1.88$). Nurses who did not receive training on COVID-19 from the institution they worked in had higher levels of anxiety ($X=0.96$), depression ($X=1.28$), negative self-perception ($X=1.08$), and somatization ($X=0.86$)). In comparison, the levels of anxiety ($X=0.61$), depression ($X=0.79$), negative self-perception ($X=0.59$), and somatization ($X=0.60$) were lower among nurses who received training.

It was determined that the frequency of nurses following the news about COVID-19 affected the scores obtained from the subscales of depression ($p=0.001$), negative self-perception ($p=0.002$), and fear of coronavirus ($p=0.001$), with a statistically significant difference between them. The levels of depression ($X=1.55$) and negative self-perception ($X=1.20$) were higher among the nurses who never followed the news about COVID-19 compared to the levels of depression ($X=0.73$) and negative self-perception ($X=0.52$) of nurses who followed the news every day. Evaluation of the frequency of following the news about COVID-19

Table 2a. *Distribution of the correlations between socio-demographic characteristics, BSI subscales, and mean scores of the fear of coronavirus (COVID-19) scale*

Socio-demographic features	The extent of anxiety X ± SD	The extent of depression X ± SD	Negative self size X ± SD	The size of the somatization X ± SD	Hostility size X ± SD	Coronavirus fear scale X ± SD
Age	P: 0.729	P: 0.237	P: 0.158	P: 0.790	P: 0.566	P: 0.093
23–30 years old	0.70±0.61	0.94±0.69	0.74±0.66	0.65±0.55	0.94±0.62	2.11±0.84
31–40 years old	0.62±0.56	0.75±0.60	0.58±0.52	0.62±0.53	0.96±0.48	2.45±0.94
41–50 years old	0.60±0.47	0.75±0.56	0.46±0.43	0.74±0.57	0.77±0.61	2.40±0.73
Gender	P: 0.08	P: 0.71	P: 0.488	**P: 0.001**	P: 0.387	P: 0.002
Woman	0.69±0.56	0.92±0.66	0.70±0.64	**0.70±0.54**	0.93±0.55	**2.32±0.86**
Man	0.69±0.70	0.71±0.68	0.58±0.51	**0.44±0.56**	0.92±0.75	1.80±0.76
Marital status	P: 0.544	P: 0.055	P: 0.589	P: 0.625	P: 0.646	P: 0.008
Married	0.64±0.59	0.75±0.65	0.640.60	0.62±0.55	0.89±0.55	2.48±0.92
Single	0.69±0.59	0.95±0.67	0.69±0.63	0.66±0.56	0.95±0.61	2.07±0.80
Number of children	P: 0.291	P: 0.302	P: 0.619	P: 0.307	P: 0.229	P: 0.012
0	0.69±0.60	0.91±0.67	0.69±0.64	0.66±0.55	0.93±0.61	2.15±0.85
1	0.48±0.38	0.66±0.60	0.54±0.52	0.49±0.44	0.75±0.43	2.14±0.78
2+3	0.74±0.68	0.88±0.68	0.69±0.59	0.76±0.64	1.09± , 59	2.79±0.87
Cohabited person	P: 0.355	**P: 0.046**	P: 0.371	P: 0.675	P: 0.380	P: 0.031
Family	0.63±0.58	**0.77±0.64**	0.61±0.57	0.65±0.56	0.88±0.55	2.39±0.90
Friends	0.84±0.70	**1.14±0.78**	0.81±0.79	0.74±0.60	1.08±0.75	1.94±0.71
Alone	0.67±0.54	**0.95±0.62**	0.72±0.62	0.61±0.52	0.94±0.59	2.06±0.82
The year in the profession?	P: 0.127	P: 0.066	**P: 0.037**	P: 0.295	P: 0.182	P: 0.204
1–5 years	0.70±0.64	0.97±0.73	**0.76±0.68**	0.65±0.58	0.94±0.65	2.14±0.85
6–10 years	0.77±0.58	0.91±0.63	**0.73±0.59**	0.74±0.57	1.06±0.47	2.17±0.92
11–15 years	0.39±0.32	0.53±0.36	**0.35±0.38**	0.43±0.31	0.69±0.35	2.40±0.86
16- >16 years	0.59±0.46	0.72±0.49	**0.46±0.37**	0.66±0.57	0.84±0.66	2.61±0.72

Table 2b. *Distribution of the correlations between socio-demographic characteristics, BSI subscales, and mean scores of the fear of coronavirus (COVID-19) scale*

Socio-demographic Features	The extent of anxiety X ± SD	The extent of depression X ± SD	Negative Self size X ± SD	The size of the somatization X ± SD	Hostility size X ± SD	Coronavirus Fear Scale X ± SD
Weekly working hours	P: 0.303	P: 0.644	P: 0.647	P: 0.014	P: 0.303	P: 0.166
Less than 40 hours	0.92±0.53	0.94±0.68	0.81±0.56	1.19±0.84	1.27±0.76	2.80±0.92
40–48 hour	0.64±0.53	0.86±0.62	0.66±0.60	0.60±0.49	0.91±0.58	2.21±0.82
More than 48 hours	0.80±0.92	1.01±0.94	0.77±0.81	0.78±0.73	0.92±0.56	2.08±1.07
Psychiatric diagnosis	P: 0.150	P: 0.069	P: 0.281	P: 0.011	P: 0.218	P: 0.619
Yes	0.84±0.49	1.18±0.50	0.81±0.50	1.14±0.64	1.19±0.70	2.34±0.90
No	0.66±0.59	0.86±0.67	0.67±0.63	0.62±0.53	0.91±0.58	2.21±0.86
With people over 65	P: 0.887	P: 0.926	P: 0.856	P: 0.654	P: 0.371	P: 0.010
Yes	0.66±0.58	0.89±0.67	0.64±0.60	0.70±0.57	1.02±0.61	2.76±0.80
No	0.67±0.59	0.88±0.67	0.68±0.62	0.64±0.55	0.91±0.59	2.15±0.85
Training status	P: 0.011	P: 0.004	P: 0.006	P: 0.022	P: 0.094	P: 0.026
Yes	0.61±0.55	0.79±0.59	0.59±0.53	0.60±0.54	0.88±0.56	2.29±0.87
No	0.96±0.68	1.28±0.82	1.08±0.84	0.86±0.58	1.13±0.67	1.88±0.77
Frequency of following news	P: 0.065	P: 0.001	P: 0.002	P: 0.741	P: 0.517	P: 0.001
Every day	0.62±0.51	0.74±0.53	0.52±0.48	0.65±0.54	0.88±0.54	2.47±0.80
Weekly	0.65±0.56	1.01±0.70	0.84±0.63	0.66±0.58	1.00±0.62	1.89±0.75
Rarely	0.71±0.67	0.87±0.77	0.72±0.73	0.56±0.51	0.89±0.66	1.92±0.87
Never	1.14±0.88	1.55±0.78	1.21±0.90	0.78±0.66	1.13±0.22	2.19±1.16
Needing help	P: 0.002	P: 0.000	P: 0.001	P: 0.020	P: 0.007	P: 0.002
Yes	0.79±0.60	1.08±0.66	0.84±0.66	0.74±0.57	1.03±0.59	2.42±083
No	0.54±0.55	0.66±0.60	0.50±0.52	0.55±0.51	0.81±0.57	2.00±0.85
Source of Help	P: 0.188	P: 0.000	P: 0.000	P: 0.180	P: 0.012	P: 0.146
– Family	0.70±0.45	0.85±0.52	0.69±0.57	0.66±0.30	0.90±0.46	2.46±0.85
– Friends	0.69±0.60	0.92±0.57	0.60±0.50	0.64±0.51	0.89±0.56	2.54±0.71
– Family and Friends	0.82±0.44	1.21±0.49	0.92±0.54	0.84±0.47	1.10±0.34	2.26±0.60
– Infection committee	0.41±0.52	0.53±0.50	0.36±0.55	0.74±1018	0.76±0.97	2.76±1.09
– Psychologist	1.08±0.58	1.58±0.87	1.17±0.96	1.30±0.61	1.95±0.50	2.71±0.89
– Needs help but cannot ask	0.93±0.74	1.40±0.81	1.20±0.81	0.78±0.73	1.17±0.63	2.11±1.04
– Not needed	0.57±0.57	0.68±0.60	0.53±0.54	0.56±0.52	0.82±0.59	2.06±0.87

n=149.

showed that the nurses who followed the news daily had a higher fear of coronavirus (X=2.47) than those who followed the news once a week (X=1.89).

A statistically significant difference was observed between whether the nurses needed personal or professional help during the COVID-19 pandemic and the subscales of anxiety (p=0.002), depression (p=0.000), negative self-perception (p=001), somatization (p=0.020), hostility (p=0.007), and fear of coronavirus (p=0.002), revealing that nurses' need for help was associated with anxiety, depression, negative self-perception, somatization, hostility, and fear of coronavirus. Among the nurses involved in the care of patients with COVID-19, the levels of anxiety (X=0.79), depression (X=1.08), negative self-perception (X=0.84), somatization (X=0.74), hostility (X=1.03), and fear of coronavirus (X=2.42) were found to be higher than nurses who did not need help.

Comparison of the correlation results of the Fear of Coronavirus (COVID-19) Scale with the subscales of the Brief Symptom Inventory revealed a statistically significant positive correlation between fear of coronavirus and anxiety subscale (r=0.188, p<0.05). On the other hand, no statistically significant positive correlation was found between the subscales of depression (r=0.092, p>0.05), somatization (r=0.153, p>0.05), negative self-perception (r=0.063, p>0.05), and hostility (r=0.087, p>0.05) in fear of coronavirus scale (Table 3).

Evaluation of the correlation results between the subscales of the Brief Symptom Inventory Scale revealed a statistically significant positive correlation between anxiety subscale and depression (r=0.816, p<0.05), somatization (r=0.718, p<0.05), negative self-perception (r=0.777, p<0.05), and hostility subscales (r=0.777, p<0.05). A statistically significant positive difference was found between the subscale of depression and somatization (r=0.683, p<0.05), negative self-perception (r=0.843, p<0.05), and hostility subscales (r=0.675, p<0.05). A statistically significant and positive correlation was found between the subscale of somatization and negative self-perception (r=0.571, p<0.05) and hostility subscales (r=0.641, p<0.05). A statistically significant positive correlation was found between the negative self-perception and hostility subscales (r=0.664, p<0.05) (Table 3).

Discussion

Healthcare workers are among the occupational groups with the highest risk during the COVID-19 pandemic which threatens everyone worldwide. While preventing the spread of infection and treating patients, it is also vital for healthcare professionals to protect their physical and psychological well-being[30].

Therefore, this study aimed to determine the effects of COVID-19 on the mental health of nurses caring for diagnosed or suspected cases of COVID-19. Thus, it aims to take precautions to protect nurses' mental

Table 3. *Results of correlation analysis between brief symptom inventory and fear of coronavirus (COVID-19) scores in nurses caring for COVID-19 patients*

		Covid score	Anxiety score	Depression score	Somatization score	Negative self score	Hostility score
Covid score	Pearson correlation	1	0.188*	0.092	0.153	0.063	0.087
	Sig. (2-tailed)	149	0.019	0.258	0.059	0.435	0.284
	n		149	149	149	149	149
Anxiety score	Pearson correlation		1	0.816**	0.718**	0.777**	0.710**
	Sig. (2-tailed)		149	0.000	0.000	0.000	0.000
	n			149	149	149	149
Depression score	Pearson correlation			1	0.683**	0.843**	0.675**
	Sig. (2-tailed)			149	0.000	0.000	0.000
	n				149	149	149
Somatization score	Pearson correlation				1	0.571**	0.641**
	Sig. (2-tailed)				149	0.000	0.000
	n					149	149
Negative self score	Pearson correlation					1	0.664**
	Sig. (2-tailed)					149	0.000
	n						149
Hostility score	Pearson correlation						1
	Sig. (2-tailed)						149
	n						

*: p<0.05
**:p<0.01
n=149.

health, apply necessary therapeutic strategies, and provide guidance for possible similar situations in the future.

A total of 149 nurses voluntarily participated in the study. Most participating nurses were women, more than half were in the 23–30 age group and single; most did not live with their families. In their study, Leodoro et al.[23] also found that 74.8% of the nurses were women and 66.8% were single. In the study of Sert et al.[31], 70.3% of the nurses were men, 64.5% were married, 59.4% had children, and 73.2% lived with their families. In the study of Karadem[32], 54.8% of the nurses were women, 60.7% were married, and 55.4% had children. Evaluation of these results demonstrates that most health workers consist of women, which is in parallel with the findings of our study. In the present study, most participants were single and did not have children, which is not in line with the findings of Sert et al.[31] and Karadem[32]. This difference may be because most participants were younger in our study.

In this study, which was conducted to assess the mental well-being of nurses caring for COVID-19 patients, a statistically significant difference was found between gender and fear of COVID-19, and the fear of coronavirus among female nurses was higher than among male nurses. The study of Karadem[32] determined a statistically significant difference between fear of COVID-19 and gender, reporting higher levels of fear of COVID-19 among women compared to men, which was consistent with the results of our study. The fact that women make up most of the nursing field and experience motherhood and maternal instincts may result in higher levels of fear of COVID-19 among female nurses.

In this study about marital status, the fear of Coronavirus was higher in married people. And there was a statistically significant difference between the number of children and their fear of COVID-19; the mean fear of COVID-19 score was higher among nurses with two or more children. In other words, the fear of coronavirus increased as the number of children increased in our study. However, the study of Karadem[32] reported no statistically significant difference between marital status and having a child and fear of COVID-19, which is not in compliance with the results of our study.

According to the study conducted by Karadem[32] on healthcare professionals, 452 participants reported not having a past psychiatric history, while 74 reported a past psychiatric history. Among those with a past psychiatric history, the mean scores of anxiety, depression, and fear of COVID-19 were higher. At the same time, a statistically significant difference was observed between anxiety, depression, and fear of COVID-19. Our study found that 94% of the participants did not have a past psychiatric history, while 6% had a previous psychiatric history. The results of our study revealed a statistically significant difference between prior psychiatric diagnosis and somatization, while there was no statistically significant difference between depression and fear of COVID-19. Although most of our study and Karadem's participants did not have a previously diagnosed psychiatric disorder, they exhibit differences based on depression and fear of COVID-19. In addition, the study conducted by Yas[30] on hospital workers reported that depression was statistically significantly higher in those with previously known psychiatric disorders. Thus, our study differs from the study conducted by Yas[30] based on a previous history of psychiatric diagnosis.

The study of Hacimusalar et al.[24] reported significantly higher rates of anxiety (92.2%) among those living together with high-risk individuals than those who do not (87.9%). The study conducted by Yas[30] reported that 45.1% of the participants lived together with individuals over 65 years of age or with high-risk diseases, while 52.8% of the participants with high levels of depression reported living together with individuals over 65 years of age or with high-risk diseases, with a statistically significant difference. On the other hand, 53.8% of the participants with high anxiety levels reported living together with individuals over 65 years of age or with a high-risk disease, with a statistically significant difference. In our study, 11.4% of the participants reported living with individuals over 65 years of age and 24.2% reported living with individuals with high-risk chronic diseases. In our study, no statistically significant difference was found between the depression and anxiety scores of the nurses living with individuals over 65 years of age. Again, in our study, no statistically significant difference was found between depression and anxiety in nurses living with individuals with high-risk chronic diseases. This may be because we had fewer participants with household members over 65 years of age or with high-risk chronic diseases. While the study of Karadem[32] reported no statistically significant difference between the levels of depression ($p=0.056$) and anxiety ($p=0.086$) among the participants with

household members over 65 years of age, the fear of COVID-19 (p=0.011) was statistically significant. Our study observed a statistically significant difference in the fear of COVID-19 scores of nurses with household members over 65 years of age. In our study, the scores of healthcare with household members over 65 years of age were not consistent with the study of Yas[30] and Hacimusalar et al.[24] while exhibiting consistency with the study of Karadem[32].

In our study, 81.9% of the nurses reported receiving training from the institution on protection against COVID-19, while 18.1% did not receive training. In our study, the anxiety, depression, negative self-perception, and somatization scores of the untrained nurses were higher than the trained ones. In contrast, the trained nurses had higher levels of fear of COVID-19. The study conducted by Karadem[32] showed that 53 participants reported having sufficient knowledge of COVID-19. At the same time, 474 stated that their knowledge was insufficient, in which a statistically significant difference was observed in the mean scores of anxiety (p=0.001), depression (p=0.002), and fear of COVID-19 (p=0.006) among the nurses who reported having sufficient knowledge and those who reported not having sufficient knowledge. Although training is thought to be a factor in alleviating psychological effects, our study and Karadem's[32] study similarly show that sometimes further knowledge of a subject may lead to negative psychological outcomes.

In the study of Karadem[32] on healthcare workers, 12 participants reported not following the news about the epidemic, while 515 did. However, there was no statistically significant difference between following the news about the pandemic and depression, anxiety and fear of COVID-19. In our study, 10 participants reported not following the news about the pandemic, while 139 reported following the news. In both studies, most participants followed the news about the pandemic. However, in our study, those who reported not following any news had higher depression and negative self-perception scores.

In contrast, those who reported following the news every day had higher fear of COVID-19 scores. In line with these results, high depression and negative self-perception scores among those who did not watch any news can be interpreted as these individuals trying to stay away from the facts by not watching the news in the sense of self-protection. In this regard, the study conducted by Karadem and ours differ from one another in terms of the psychological effects of this factor on the participants. Display of the increasing number of cases in the media, the uncertainty of how long the pandemic will last, the news about the death rates of frontline healthcare workers, and the attitudes of the general population towards healthcare workers may aggravate the fear of COVID-19 in nurses who follow the news every day[33]. The media's misrepresentation of the situation has caused the general population to easily marginalize healthcare workers returning from work, especially since they think that healthcare personnel are particularly susceptible to transmitting the virus on the way home[34]. As a result, some members of the society have stigmatized and excluded nurses, considering their potential to transmit the virus[35]. This has caused individuals to distance themselves from their colleagues and neighbors in their immediate surroundings[36]. Thus, the nurses feel lonely[35]. This situation can cause nurses to get depressed easily and create a negative self-image.

The study of Kackin et al.[35] determined that the nurses caring for COVID-19 patients in Türkiye were adversely affected by the pandemic both psychologically and socially, revealing that they needed psychosocial support and resource management although they used short-term coping strategies. They also faced stigmatizing attitudes and burnout and were at high risk for secondary traumas, as they witnessed illness and death. In our study, 52.3% of the participants needed personal and professional help during the pandemic. In our study, the nurses who reported needing help had significantly higher scores of anxiety, depression, negative self-perception, somatization, hostility, and fear of COVID-19 than those who did not need help. In the study of Karadem[32], a statistically significant difference between the scores of anxiety, depression, and fear of COVID-19 were of the nurses who did or did not need help. In the study of Yas[30], 17 (1.5%) participants received psychological support during the pandemic. Of the participants, 316 (28%) reported needing psychological help while 796 (70.5%) did not need help. 56.3% of those with depression reported needing help during the pandemic, which was statistically significant. 56% of those with anxiety reported needing psychological help during the pandemic, which was statistically significant. 57.6% of those with stress reported needing psychological help during the pandemic, which was statistically significant. Nurses who need personal and professional help are expected to experience more psychological problems, as shown by

the similar results in our study and those of Karadem[32] and Yas[30].

The results of our study are generally compatible with the literature and show that nurses are psychologically affected during the pandemic. Negative psychological outcomes among nurses may affect their personal lives and their role as caregivers, resulting in professional burnout shortly, which may further lead to resignation. The following recommendations should be taken into consideration to reduce the psychological effects and fear of COVID-19 in nurses;

- The psychological effects of the COVID-19 pandemic should be investigated in nurses working in other hospitals and clinics,
- A safe work environment should be provided by improving the working conditions of nurses,
- Regular training should be provided to nurses about COVID-19,
- Reliable sources and news programs that provide scientific data should be followed to access accurate information about COVID-19 in Türkiye and the World,
- Psychological counselling and support should be provided to nurses working in COVID-19 units, as the protection of the psychological well-being and mental health of nurses during the pandemic bears importance for the functioning of healthcare services. The hospital management and health managers should handle this issue carefully, and the necessary psychological support should be provided free of charge to minimize the possible negative effects. It is recommended to assign Clinical Ladder Program (CLP) nurses to these clinics and provide supervision in line with the needs of nurses who need support.

Statement of Ethics

Ethical approval was obtained from T. C. Ege University Medical Research Ethics Committee (TAEK) (number E-99166796-050.06.04-43828) and the Ministry of Health.

Conflict of Interest Statement

All the authors declare no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of the Effectiveness of Intercostal Nerve Block for Pain Management in Patients with Traumatic Rib Fractures

Travmatik Kosta Fraktürlerinde Interkostal Sinir Blokajının Ağrı Yönetimi Üzerindeki Etkisinin Araştırılması

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ABSTRACT

Aim: *Pain palliation is the most critical content of the treatment in traumatic rib fractures. The study aimed was to investigate the effect of including intercostal nerve block in the treatment of rib fractures on pain control.*

Material and Method: *Patients treated for traumatic rib fractures in the thoracic surgery clinic of our center between February 2022 and June 2022 were evaluated retrospectively. The characteristics of the patients, their visual analogue scale scores, analgesic medication needs, and hospital stay were recorded. The data of the patients who underwent intercostal nerve blockade and those who were treated with standard analgesic medications were compared.*

Results: *A total of 49 patients were included in the study. A total of 18 (36.7%) patients underwent daily intercostal nerve block. Standard pain treatment was applied to 31 (63.3%) patients. In the group of patients who underwent intercostal nerve blockade, the mean pain score on the third day and the mean need for non-steroidal anti-inflammatory medication were significantly lower.*

Conclusion: *In our study, the adding an intercostal nerve block to the treatment of rib fractures provided better pain control and reduced the need for analgesic medication.*

Key words: *chest trauma; intercostal nerve block; rib fractures*

ÖZET

Amaç: *Travmatik kosta fraktürü bulunan hastalarda ağrı palyasyonu tedavinin en önemli parçasını oluşturur. Bu çalışmada interkostal sinir blokajının kot fraktürlü hastalarda ağrı yönetimi üzerine etkisinin araştırılması amaçlanmıştır.*

Materyal ve Metot: *Şubat 2022 ile Haziran 2022 tarihleri arasında travmatik kot fraktürü tanısı ile takip edilmiş olan hastalar retrospektif olarak incelendi. Hastaların karakteristik özellikleri, vizüel analog skala skorları, analjezik medikasyon ihtiyaç durumları ve hastane yatış süreleri kaydedildi. İnterkostal sinir blokajı uygulanan ve uygulanmayan hastaların verileri karşılaştırıldı.*

Bulgular: *Çalışmaya toplamda 49 hasta dâhil edildi. 18 (%36,7) hastaya anajezik tedavinin bir parçası olarak interkostal sinir blokajı, 31(%63,3) hastaya ise standart ağrı tedavisi uygulanmıştı. İnterkostal sinir blokajı uygulanan grupta 3. Günde ölçülen ortalama vizüel analog skala skoru ve ortalama non-steroid antienflamatuvar ilaç doz ihtiyacı istatistiksel anlamlı olarak daha düşük bulundu.*

Sonuç: *Çalışmamız travmatik kot fraktürü bulunan hastaların yönetiminde tedaviye interkostal sinir blokajının eklenmesinin daha az analjezik medikasyon ile daha iyi ağrı kontrolü sağladığını göstermiştir.*

Anahtar kelimeler: *göğüs travması; interkostal sinir blokajı; kot fraktürü*

Introduction

Rib fractures are seen in approximately 10% of all traumas, and approximately 30% of severe chest traumas[1,2]. The location, number, and form of rib fractures are related to the severity and mechanism of trauma. The clinical spectrum can range from localized pain to the dramatic picture accompanied by severe hemopneumothorax and flail chest. Pain management is one of the most important components of treatment in patients with rib fractures[3]. Analgesic step therapy (analgesic ladder) recommended by the World Health Organization (WHO) is frequently used in pain palliation, and it can be combined with analgesic procedures including intercostal nerve block (INB), serratus ± pectoralis plane nerve block, and epidural anesthesia[4–6].

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This study aimed to evaluate the efficiency of intercostal nerve blockade on pain palliation in patients with rib fractures accompanying isolated chest traumas.

Material and Method

This study was approved by the Institutional Ethics Committee. Patients who were treated for isolated thoracic trauma in the thoracic surgery clinic of our center between February 2022 and June 2022 were evaluated retrospectively. Patients with at least 1 rib fracture detected radiologically were included in the study. Patients who underwent emergency or elective surgical intervention, had flail chest, underwent tube thoracostomy due to pleural complications, and were intubated due to respiratory failure were excluded from the study.

The WHO analgesic ladder strategy as a standard pain assessment (SPA) was used for the pain palliation of the patients. Additionally, INB was performed on the patients who accepted it. Intercostal nerve block was applied posteriorly, approximately 6 cm lateral to the midline, by injecting 2–3 cc of 0.25% cc bupivacaine at each level, covering the two upper and two lower sides of the affected ribs. This procedure was repeated daily. The patients were divided into two groups according to the application of INB. Pain follow-up of the patients was performed with a visual analogue scale (VAS) (0=No pain, 10=Worst pain). Characteristics of the patients, VAS scores, the administered non-steroidal anti-inflammatory drug (NSAID) doses, opioid drug needs, and hospitalization times were recorded from patient files and the hospital information system. The obtained data were compared between the two groups (INB vs SPA-only).

Statistical Analyses

Statistical analyses were performed via Statistical Package for Social Sciences (SPSS) program version 25.0 (SPSS Inc., Chicago, IL, USA). Normality of distribution was tested with the Shapiro-Wilk test for all numerical variables. Chi-squared or Fischer's exact tests were used to compare frequencies. Continuous variables are expressed as mean value ± standard deviation (SD) and discrete variables are expressed as numbers and percentages. The student's t-test was performed to analyze the differences between group means. Statistical significance was set at P-value <0.05 (All P values presented were 2-sided).

Results

A total of 49 patients were included in the study. The mean age was found to be 57.5±11.2. Four of the patients were female and 45 were male. The characteristics of the patients are summarized in Table 1.

A total of 18 (36.7%) patients underwent daily INB. Standard pain treatment was applied to 31 (63.3%) patients.

The number of median rib fractures was 3 (range, 1–7). The mean length of hospital stay was 4.7±1.7 days. Twenty-one (42.9%) patients needed opioid medication at least once. Tramadol hydrochloride 50 mg/ml (iv) was preferred as an opioid medication and was re-administered as needed.

The mean VAS score of the patients at the time of admission was 6.7±1.1, 3.9±1.0 on the first day, and 2.7±0.7 on the third day.

Table 1. *Patient characteristics*

Characteristic	INB (n=18)	SPA-only (n=31)	P-value
Age (mean ± SD)	58.8±10.7	56.7±11.6	0.54
Sex (male), n (%)	18 (100)	27 (87.1)	0.28
Comorbidities, n (%)			0.62
None	8 (44.4)	18 (58.1)	
HT	2 (6.5)	2 (11.1)	
DM	7 (38.9)	8 (25.8)	
COPD	1 (5.6)	1 (3.2)	
CAD	0 (0)	2 (6.5)	
Current smoker (yes), n (%)	15 (83.3)	19 (61.3)	0.20
Rib fracture (mean ± SD)	2.9±1.4	3.4±1.8	0.41
Pulmonary contusion (yes), n (%)	5 (27.8)	10 (32.3)	1.0
Pneumothorax (yes), n (%)	1 (5.6)	5 (16.1)	0.39
Hemothorax (yes), n (%)	2 (11.1)	7 (22.6)	0.45

CAD: Coronary artery diseases, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HT: Hypertension, INB: Intercostal nerve block, SD: Standard deviation, SPA: Standard pain assessment.

Table 2. *Outcomes associated with pain management*

Variables	INB (n=18)	SPA-only (n=31)	P-value
NSAID medication* need-Day 1, (mean ± SD)	2.1±0.8	3.3±0.9	<0.001
NSAID medication* need-Day 2, (mean ± SD)	1.8±0.7	3.0±0.8	<0.001
NSAID medication* need-Day 3, (mean ± SD)	1.7±0.8	2.9±0.8	<0.001
Opioid analgesic need (yes), n (%)	5 (27.8)	16 (51.6)	0.14
VAS-0 (mean ± SD)	6.9±0.9	6.7±1.1	0.44
VAS-1 (mean ± SD)	4.0±1.2	3.8±0.9	0.61
VAS-3 (mean ± SD)	2.4±0.6	2.9±0.7	0.019
Hospital stays (mean ± SD)	4.6±1.2	4.8±1.9	0.58

* Number of oral administration or injection.
INB: Intercostal nerve block, NSAID: Non-steroidal anti-inflammatory drug, SD: Standard deviation, SPA: Standard pain assessment, VAS: Visual analogue scale.

The comparison of VAS score, NSAID and opioid medication needs, and hospitalization days according to INB and SPA-only groups is summarized in Table 2. The mean number of NSAID doses needed on the first, second, and third days in the INB group was found to be significantly lower (Table 2). Although the rate of opioid use was higher and mean hospital stays were longer in the SPA group, this difference was not statistically significant (p=0.14; 0.58).

The mean VAS score measured on the 3rd day (VAS-3) was found to be statistically significantly lower in the INB group (2.4±0.6 vs 2.9±0.7, p=0.019).

No complication related to INB was observed in any of the patients.

Discussion

In this study, it was observed that INB provided better pain control than standard analgesic medications in traumatic rib fractures. Although INB has been emphasized as a fast and easy-to-apply and successful method in pain control in the literature, the number of comparative studies is few[6–8]. In the study of Yetim et al.[8], patients who followed up for rib fractures were examined in two groups according to the application of INB, and the amount of tramadol used in the group that was administered intercostal nerve block was found to be significantly lower. In a similar study, Hwang et al.[6] demonstrated rapid regression in pain scores after INB in patients with rib fractures compared to the control group. While we found a significant difference in the VAS scores measured only on the 3rd day in our study, the NSAID medication requirement on the first, second, and third days was significantly lower in the INB group.

Sheets et al.[9] compared the data of 116 patients (58 vs 58) who underwent epidural anesthesia and INB with liposomal bupivacaine for the management of rib fractures and found less intubation rate, shorter intensive care unit, and hospital stay in the group that underwent INB (p=0.015, 0.007, 0.020).

Although there are theoretical risks such as pneumothorax, intercostal artery-vein injury, intraneuronal-intrathecal injection, and skin-subcutaneous infection, the complication rates of intercostal nerve block are very low[10]. No complications related to INB were observed in our study.

There are also studies suggesting a continuous block system with the help of a special catheter as an alternative to repetitive injections[7–11]. Uhlich et al.[11], in their study of 933 patients with multiple rib fractures, showed that mortality and morbidity rates were significantly lower in the group in which continuous intercostal nerve block was added to the standard treatment.

Our study has some limitations. First, this is a retrospective study and there is a possibility of bias due to the nature of the study design. Secondly, due to the small number of patients, we were not able to homogenize the parameters, and this may have affected the results of the study.

Conclusion

Our study observed that INB provided better pain control and reduced the need for additional analgesic medication. Since it can be applied quickly and easily, it can be preferred for pain palliation in rib fractures.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Medical Education During the COVID-19 Pandemic: Habits, Computer Skills, Internet Use Disorder, and Success

COVID-19 Pandemisi Sırasında Tıp Eğitimi: Alışkanlıklar, Bilgisayar Becerileri, İnternet Bağımlılığı ve Başarı

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ABSTRACT

Aim: *COVID-19 pandemic had a significant impact on the way medical education is delivered. In most countries education was provided remotely. In this study, we aimed to study whether social and online habits, computer readiness, online communication skills, and Internet Use Disorder (IUD) were significant characteristics affecting the preferences of medical students for online or traditional classroom teaching in histology and embryology.*

Material and Method: *In 2019-2020, the fall semester for Turkish universities was face-to-face. Due to the COVID-19 pandemic, the spring semester of that academic year was online. We asked 1,144 public and private university students in Istanbul about demographic characteristics and their preferences in learning and general living, using two subscales of the Online Learning Readiness Scale (OLRS) and the Young Internet Addiction Scale. We compared online and face-to-face success levels using quiz results.*

Results: *Students generally preferred traditional lectures. However, those with higher OLRS scores preferred online lectures and learning materials and were more adapted to online living. Internet use disorder did not correlate with online lecture preferences. The results from private and public universities were not considerably different. The success levels after online lectures were better than after face-to-face lectures, which suggests that the preferences and satisfaction of students are different from their learning achievement.*

Conclusion: *Preferences of students should be the priority in planning medical education. They want online lectures available as complementary to face-to-face lectures. Therefore, instructors should improve their online communication and teaching skills to enhance students' online lecture satisfaction. The IUD does not possess a risk in this condition. Contrarily, regularly planned complementary online courses will enhance students online learning habits, online readiness and achievement and enables a more effective continuation of education in cases of natural disasters and pandemics.*

Key words: *distance education; histology; internet addiction disorder; online education*

ÖZET

Amaç: *COVID-19 pandemisinin tıp eğitimi üzerinde önemli bir etkisi oldu. Çoğu ülkede eğitim uzaktan yapıldı. Bu çalışmada, tıp öğrencilerinin sosyal ve çevrimiçi alışkanlıklarının, bilgisayar okur yazarlıklarının, çevrimiçi iletişim becerilerinin ve İnternet Kullanım Bozukluğunun histoloji ve embriyolojideki çevrimiçi veya geleneksel sınıf öğretimi tercihlerini etkileyen önemli özellikler olup olmadıklarını araştırmayı amaçladık.*

Materyal ve Metot: *2019-2020'de Türkiye'de üniversiteler için güz dönemi yüz yüze idi. Aynı akademik yılın bahar dönemi COVID-19 salgını nedeniyle çevrimiçi yapıldı. İstanbul'daki 1144 devlet ve özel üniversite öğrencisine, demografik özelliklerini, öğrenme ve genel yaşamdaki tercihlerini, Çevrimiçi Öğrenmeye Hazırlık Ölçeği'nin (OLRS) iki alt ölçeğinin yanı sıra Genç İnternet Bağımlılığı Ölçeği'ni kullanarak sorduk. Sınav sonuçlarını kullanarak çevrimiçi ve yüz yüze başarı düzeylerini karşılaştırdık.*

Bulgular: *Öğrenciler genellikle geleneksel dersleri tercih ettiler. Ancak, OLRS puanları daha yüksek olanlar çevrimiçi dersleri ve öğrenme materyallerini tercih ettiler ve çevrimiçi yaşama daha fazla adapteydiler. İnternet Kullanım Bozukluğu ile çevrimiçi ders tercihi arasında korelasyon yoktu. Özel ve devlet üniversitelerinden elde edilen sonuçlar ise önemli ölçüde farklı değildi. Çevrimiçi derslerden sonraki başarı seviyeleri, yüz yüze derslere göre daha iyiydi; bu da öğrencilerin tercihlerinin ve memnuniyetinin öğrenme başarılarından farklı olduğunu gösterdi.*

Sonuç: *Tıp eğitiminin planlanmasında öğrencilerin tercihleri ön planda tutulmalıdır. Öğrenciler, çevrimiçi dersleri yüz yüze derslerin tamamlayıcısı olarak istemektedirler. Bu nedenle eğitmenler, öğrencilerin çevrimiçi ders memnuniyetini artırmak için çevrimiçi iletişim ve öğretim becerilerini geliştirmelidirler. Bu durumda, internet kullanım bozukluğu bir risk oluşturmamaktadır. Aksine düzenli planlanan tamamlayıcı çevrimiçi dersler öğrencilerin çevrimiçi öğrenme alışkanlıklarını, çevrimiçi okuryazarlıklarını ve başarılarını artıracak ve eğitimin doğal afet ve pandemi durumlarında daha etkin devamını sağlayacaktır.*

Anahtar kelimeler: *uzaktan eğitim; histoloji; internet bağımlılığı; çevrimici eğitim*

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Introduction

Technology in education progressed rapidly in the last century[1]. Different nations led radical reforms by adapting information and communication technologies to their educational systems[2]. Those educational strategies were determined after considering student attitudes to technology and their computer skills amongst other specifications such as satisfaction[3].

Histology is the microscopic study of tissues and cells and is considered as microscopical anatomy. Embryology is the study of embryo and concerned with the formation and development of that. Both require theoretical knowledge and three-dimensional imagination, and they are compulsory courses in medical education. Therefore, histology and embryology lectures include practical sessions with microscopic specimen observation and drawing by students[4]. Theory sessions are supported with additional learning materials, such as microscopy images, videos and plastic models. On the other hand, virtual microscopy is becoming popular for histology and especially for pathology, but it has not replaced traditional microscopes in medical education worldwide[5–7].

The histology and embryology lectures are mainly face-to-face in medical education. However, medical education has been offered online in many countries during the COVID-19 pandemic[8]. Instructors and students had to switch to online courses in histology and embryology. Detailed evaluation of these experiences is likely to assist in optimizing online education. Therefore, it is essential to define practical online education-related factors and student preferences.

The medium of online education is the Internet, which is becoming a part of daily life for millions, simplifying processes from education to finance[9]. Despite its advantages, its psychological impacts may include depression, lowered mood, and behavioral addiction[10]. Internet Use Disorder (IUD) is described in the third section of the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, as an online gaming disorder (American Psychiatric Association 2013), and the International Classification of Diseases, 11th revision, includes the code "Gaming Disorder, predominantly online; 6C51," but debate continues about the existence of IUD[11–13]. Therefore, IUD is usually used not as a diagnosis but a tendency toward a high Young Internet Addiction Scale (YIAS) score[14]. The digital literacy is a need for academic purposes, but the effect of digital literacy on IUD is an ongoing debate[15,16].

In Türkiye, internet use is becoming widespread, especially among young people, and Internet related disorders are increasing[17]. Therefore, we investigated the prevalence of IUD and how it affects medical course preferences.

According to published research, levels of satisfaction with online education are affected by socio-demographics, instructor-student interaction, Internet self-efficacy, and other variables[18,19]. Our study aimed to investigate student habits, computer and Internet self-efficacy, online communication self-efficacy, and the effects of IUD on online course preferences, while comparing a public medical school with a private medical school. We examined these factors for theoretical and laboratory courses in histology and embryology with the hope that our findings may provide insight to adapt technologies for future medical education.

Methods

The study was conducted at the medical schools of two universities in the same Turkish province: Istanbul University (IU) and Istanbul Aydin University (IAU). A total of 1,144 volunteer undergraduate university students, who had histology and embryology courses in their first or second years, participated in the study. In the IAU group, 131 students were studying dentistry but taking medical school histology and embryology classes with the same curriculum and education staff. Students gave their informed consent to participate. The online survey was completed in a single attempt, through Microsoft Forms. The study was approved by the Clinical Research and the Social Research Committees of Istanbul University (08.06.2020-Number: 91654).

Questionnaires

The survey consisted of four parts: demographic characteristics, questions for evaluating different methods used in histology and embryology education, the computer and Internet self-efficacy subscale and online communication self-efficacy subscale of the Online Learning Readiness Scale (OLRS), and the Young Internet Addiction Scale (YIAS).

Sociodemographics

Sociodemographic characteristics included were gender (male or female), age, economic status, owning a personal computer, having a consistent Internet connection, accommodation during education, having a private study area during the pandemic, and having a private study area before the pandemic.

General Habits

Questions about regular life habits were concerned with online options, including "Have you ever had an online course before?", "Which way do you do your general shopping (online shopping or conventional shopping from store)?", "Which of the following would you choose when you want to learn a new skill (online course or traditional schooling/private course)?", and "What is your preferred way of socializing (digital platforms such as social media or face-to-face communication)?"

Online Learning Readiness Scale

The OLRS is a self-reported questionnaire consisting of 18 items. It includes five subscales: a) self-directed learning, b) motivation for learning, c) computer and Internet self-efficacy, d) learner control, and e) online communication self-efficacy[20]. This study used the validated Turkish version of the computer and Internet self-efficacy subscale and online communication self-efficacy subscale of the OLRS[21]. The Cronbach's alpha value of this version is 0.95.

Histology and Embryology Education

Students took theoretical and practical sessions of histology and embryology in the fall semester 2019 and spring semester 2020. Traditional classroom sessions were held in the fall semester and online sessions in the spring semester. This was similar at both universities because of the COVID-19 pandemic (Table 1).

The medical curricula were similar in line with the government's educational standards. Traditional theoretical sessions were face-to-face in a lecture hall or classroom. Traditional practical sessions were face-to-face in the basic sciences laboratory of the Histology and Embryology Department, where each student could study slides through their microscope. The slides were fixed cytological smears or 4-μm tissue sections, stained with various dyes such as hematoxylin and eosin for general nucleus cytoplasm differentiation, Masson's trichrome stain for connective tissue, silver stains for nervous tissue, or other special stains such as Diff-Quik or Papanicolaou for sperm. The same slides were used for traditional and online lectures. Online theory sessions used Adobe Connect software for distance learning adapted for medical education. The lecturer and their presentation could be seen and heard at the same time, with pointing on the presentation or whiteboard drawing, and screen share options. Their presentations included atlas drawings, slide images and videos, which they prepared with a microscope before the lecture. They gave online lectures with these materials and interactively discussed slides with students. Both online theory and practical sessions had a live chatbox and microphone option for each student to provide an interactive lecturer-student dialog. The computer programs and histology and embryology teaching methods of both universities were the same.

Table 1

Semester – Fall 2019	Semester – Spring 2020
Before lockdown	During Lockdown
Traditional face-to- face education for theoretical and practical lectures	Online theoretical and practical lectures, available also offline for rewatching

Because of the complex theoretical and visual content of histology and embryology, we developed questions about these different course methods to compare the perceptions and choices of students about lectures. Furthermore, we added a question for the after-pandemic courses: "Do you want to be able to watch face-to-face classes online as a part of formal education?"

Young Internet Addiction Scale

The YIAS consists of eight items, and respondents who answered "yes" to at least five were classified as an Internet-dependent[14]. The Turkish version, with a Cronbach's alpha value of 0.716, was used for this study[17].

Quiz

The IU students took an online quiz of 10 questions about what they learned in the online practical sessions in 2020. These results were compared with the previous year's traditional laboratory quiz results on the same histology and embryology topics.

Statistical analysis

Statistical Package for Social Sciences (SPSS) program version 22 software was used for all statistical analyses. Group differences involving demographic variables were computed by using chi-square and independent t-tests. The comparison of OLRS scores between the IUD group and the control group was assessed using the independent t-test. Binary logistic regression analysis was used to evaluate the relation of online learning readiness to demographic characteristics, regular life habits concerning online options, and histology and embryology education preferences. Statistical significance was defined as P <0.05. The normality of distribution of the data was evaluated by the skewness and kurtosis values.

Results

Demographics

Of 1,144 participants, 70 returned missing or incomplete data. The final online survey questionnaire results comprised 1,074 medical students (541 male, 50.4%; 533 female, 49.6%) from public (838, 78%) and private (236, 22%) medical schools. Of the respondents, 179 (16.7%) reported that they had taken an online course before. This was higher in private university students than public university students (36% vs 11.2%, χ^2=81.54, P <0.001). A statistically significantly different number of students between the private and public university groups preferred online education for overall university education (Table 2). Preference for overall online university education was significantly different; of the public university group, 42.2% reported that they preferred online courses, compared to 20.8% in the private university group (χ^2=39.23, P <0.001) (Table 2).

Of the total sample, 465 students (43.3%) reported social media as their principal reason for Internet use, while 183 (17%), 339 (31.6%), and 87 (8.1%) students primarily used it for education and research, visual content and gaming, respectively. The differences between the public and private university groups were not statistically significant.

Most students (879, 81.8%) reported the city center as their regular place of accommodation before university, while 38 (3.5%) and 157 (14.6%) came from rural areas and suburbs, respectively.

Table 2. *Public and private university participants' socio-demographic data, OLRS scores, histology and embryology education preferences, and regular life habits concerning online and face-to-face options.*

	Total (1074)
Economicaly independence	880 (82.3%)
Having a private place to study	820 (76.4%)
Having a personal computer	926 (86.2%)
Having a constant internet connection	884 (82.3%)
Online course experience in the past	179 (16.7%)
Blended course preference after pandemic	862 (80.3%)
Higher Young Internet Addiction Score	379 (35.3%)
Online learning readiness score (OLRS)	
Computer/internet self-efficacy	10.8±2.8
Online communication self-efficacy	10.5±2.6
Histology and embryology online theory education	
Asking questions	277 (41.6%)
Learning better	244 (30.1%)
Prefer	257 (27.8%)
Histology and embryology online practical education	
Asking questions	123 (13%)
Learning better	96 (9%)
Prefer	103 (10.2%)
Online shopping preference	385 (35.8%)
Online course preference for learning a new skill	278 (25.9%)
Preferences for online histology materials	280 (26.1%)
Distance problem between campus and accommodation	335 (31.2%)

Education Preferences of Students At Private and Public Universities

Table 2 compares self reported histology and embryology theoretical and practical education preferences of the students. Among all students, 41.6% asked questions with more confidence, and 30.1% learned better in online theory education. These numbers were higher for the public university than the private university (46.2% vs 26.9%, χ^2=18.7, P <0.001; 32.2% and 23.2%, χ^2=5.6, P=0.017). Public university students were more likely to prefer online theoretical education (30.3% vs 19.3%, χ^2=9.5, P=0.02).

Practical education preferences for histology and embryology differed significantly between the public and private university groups. Online, classroom, and laboratory practical sessions were preferred by 10.4%, 3.4%, and 86.2% of public university students, respectively, compared to 9.8%, 16.8%, and 73.4% of private university students (χ^2=51.7, P <0.001).

Relationship Between Education Preferences, Life Habits, and Demographics

Gender, having a personal computer, having past experience of an online course, IUD, purpose of Internet

Table 3. *Histology and embryology education preference differences by socio-demographic data and regular life habits concerning online options.*

	Online (257/27.8%)	Traditional (667/72.2%)
Economically independent *	222 (86.4%)	533 (80.3%)
Having a private place to study **	212 (82.5%)	490 (73.5%)
Having a constant internet connection ***	231 (89.9%)	526 (78.9%)
Prefer online courses ***	190 (73.9%)	144 (21.6%)
Higher Young Internet Addiction Score	98 (38.4%)	228 (34.8%)
Internet shopping preference **	107 (41.6%)	217 (32.5%)
Online course preference for learning a new skill ***	99 (38.5%)	131 (19.6%)
Digital platform preference for socializing ***	65 (25.3%)	79 (11.8%)
Online learning material preference for histology and embryology **	79 (30.7%)	150 (22.5%)
Have distance problem between school and home **	101 (39.3%)	188 (28.2%)

Chi-square test * p<0.05; ** p<0.01; *** p<0.001

Table 4. *Online learning readiness level by demographic characteristics, histology and embryology education preferences, and regular life habits concerning online options.*

	Computer/internet self-efficacy scores (mean)	Online communication self-efficacy scores (mean)
Prefer online courses (yes/no)	11.4±2.7/10.4±2.7***	10.9±2.6/10.3±2.6***
Young Internet Addiction Score (high/low)	10.7±2.9/10.8±2.7	10.3±2.6/10.7±2.6*
Histology and embryology theory education		
Asking questions		
online lessons/class lessons	11.3±2.6/10.2±2.9***	11±2.5/10.3±2.8***
Learning better		
online lessons/class lessons	11.1±2.9/10.4±2.8***	10.7±2.5/10.2±2.7*
Prefer		
online lessons/class lessons	11.4±2.8/10.5±2.7***	10.9±2.7/10.4±2.6*
Histology and embryology practical education		
Asking questions		
online lessons/class lessons/lab lessons	11.2±3/9.7±2.9/10.8±2.7***	11.5±2.6/10±2.6/10.3±2.6***
Learning better		
online lessons/class lessons/lab lessons	11.6±3/9.2±2.9/10.7±2.7***	11.2±2.5/9.3±3/10.5±2.6***
Prefer		
online lessons/class lessons/lab lessons	11.6±3/9.4±2.7/10.9±2.7***	11.4±2.5/9.8±2.5/10.4±2.6***
Preference for histology learning materials		
online/printed	11±2.6/10.4±2.9***	10.7±2.5/10.3±2.7**
Shopping preferences (online/traditional store)	11±2.8/10.6±2.7**	10.8±2.7/10.3±2.6*
Preference for learning a new skill		
online courses/traditional courses	11.3±3/10.6±2.7***	11.1±2.7/10.3±2.6***
Preferences for socializing		
Digital platforms /face-to-face communication	11.1±2.6/10.7±2.8	10.7±2.7/10.5±2.6
Economically (independence /dependence)	11±2.6/9.4±2.9***	10.6±2.6/10.03±2.9**
Having a computer (yes/no)	11.0±2.7/9.4±2.8***	10.5±2.4/9.9±2.7**
Constant internet connection (yes/no)	11.1±2.6/9.2±3.0***	10.7±2.5/9.6±2.8***

Independent t-test * p<0.05; ** p<0.01; *** p<0.001

use, and accommodation did not differ between students who preferred online or face-to-face lectures. However, economic independence, having a private place to study, having a constant Internet connection, online course preference, digital or face-to-face communication for socializing, digital or hardcopy preference for studying histology and embryology, and distance between campus and accommodation differed between these two groups (Table 3).

Relationship Between Education Preferences and Online Learning Readiness

The mean scores for the computer and Internet self-efficacy and online communication self-efficacy OLRS subscales were significantly higher in students who asked questions with more confidence and learned better during online histology and embryology education. Students who were more likely to prefer online theory

Table 5. *Binary logistic regression analyses of online learning readiness for histology and embryology education preferences, comparing online education and traditional education choices.*

Category	Beta	SE	OR	p-value
Computer/internet self-efficacy	0.08	0.03	0.92	p=0.007
Online communication self efficacy	0.03	0.03	0.97	p=0.29

SE: standard error; OR: odds ratio; adjusting for the covariate variables: university (public/private), regular life habits concerning online options, and constant internet connection.

education showed higher mean scores for each OLRS category (Table 4).

Table 5 shows the results of the logistic regression model used to compare online learning readiness levels and histology and embryology education preferences. University (public or private), regular life habits concerning online options, and having a constant Internet connection were analyzed in the model. Higher computer and Internet self-efficacy scores significantly predicted histology and embryology education preferences, whereas online communication self-efficacy scores were not a significant predictor for education preferences.

IUD Prevalence in Medical Students

Of the total sample, 35.3% of students were assessed as Internet-dependent according to the YIAS. Internet use disorder was significantly more prevalent in the public university group compared with the private university group (37.5% vs 30.1%, χ^2=4.4, P=0.036; Table 2). No significant differences between genders were found in the IUD group compared to the control group. No significant differences existed in choice of education method among the IUD group and control group. As shown in Table 4, the mean online communication self-efficacy score was significantly higher in the control group compared to the IUD group.

Quiz Results

The practice quiz was taken by 888 students in 2020 and 824 students in 2019. The success level of students in the online quiz was higher than the face-to-face quiz (88.06% vs 83.46%, P <0.001).

Discussion

In this study, we aimed to evaluate a variety of factors that may affect medical students' histology and embryology learning preferences.

The IU students described themselves as more economically independent, and they were more likely to have a private study space and a constant Internet connection than the IAU students (Table 2). This may be due to the large number of international students and students with full scholarships at IAU. The percentage of students with previous online course experience was higher at IAU. The preference for online learning for new skills was also higher at this private school. This suggests that previous exposure to online courses influences preferences for educational set-up. It is likely that developing online learning habits takes time and longer exposure may change preferences further. The online histology and embryology courses were the first online lecture experience for some students. In our study, the participants experienced traditional and online classes in the same academic year, potentially facilitating them to make a direct comparison.

In addition to cost and time efficiency, online courses have several other benefits, such as availability of offline documents and easy program management and monitoring. Moreover, students reportedly find blended courses more satisfactory than wholly online or classroom lectures[22]. A higher percentage of our students preferred regular classroom sessions over online classes, but most wanted blended courses after the pandemic (Table 2).

Many students had personal computers or tablets, and the rest used university library computers or shared the family computer (Table 2). Some students with limited resources tended to choose a smartphone over a personal computer. The evolved technology of smartphones enables most activities necessary for studying. Therefore, online courses or learning materials should not just be planned for personal computers but also be available through mobiles for the future. All of the online theory courses in this study were available through smartphones. However, the larger screens of computers provide a better opportunity for learning the basic or specialized tissue structures of histology and embryology accompanied by the instructions from the education staff. Students are more engaged and motivated when they interact with the instructor[19,23].

Medical students should adapt to technologies such as digital imaging and virtual microscopy since the United

States Food and Drug Administration has approved virtual microscope images to be used for diagnostic purposes[24]. This improvement will be applied even in other fields of medicine[25]. Therefore, medical students should have basic computer skills and be digital literate to enhance their vocational performance[26,27]. Each day, higher levels of technological skills are required. Without the necessary skills, students may develop a false perception of difficulty in learning higher computational skills, requiring much more effort from instructors[28].

We used two subscales of the OLRS to test readiness for online learning. Economic factors such as independence and indirectly related parameters such as having a personal computer and constant Internet connection correlated with computer and Internet self-efficacy scores and online communication self-efficacy scores. Computer and Internet self-efficacy and online communication self-efficacy are necessary for better online learning performance and can change students' perception of online or traditional lessons. The students with higher scores generally preferred online courses to learn new skills. Medical students with higher computer and online communication self-efficacy scores preferred online lessons for histology and embryology theoretical and practical sessions. They asked their questions online with more confidence, and they learned online better. We assume the low computer and Internet readiness of the general population of students made them choose campus sessions over online sessions. The full daily program of online medical lessons and uncertainty of the future because of COVID-19 could have influenced their apprehension. The online courses were not optional, they were obligatory in spring 2020 because of the lock-down and governmental politics in COVID-19 pandemics.

The IAU students reported campus longing more often because of missing the social activities of the private university in their lives. The preference for practical sessions in the classroom –a virtual session without microscopes– was higher at IAU than IU. The smaller number of students in each class at IAU is a probable explanation for this. Another possibility is that the curfew, and pandemic-related distress and worry could have meant that students equated everything about campus with life before COVID-19. Anxiety and anhedonia increased during COVID-19[27].

Similar characteristics were possible for educators. Their new work became conducting full-time e-teaching, converting theoretical lessons and designing practical learning material online, and finding solutions for ongoing projects or pandemic-related pauses of projects. E-teaching became necessary for the instructors as an educational and practical technique and informatics skill. However, this revolution required more comprehensive changes, developments and time in normal conditions[28]. Online lectures were implemented worldwide as quick solutions in spring 2020. Further improvements of technology will probably be incorporated in the future based on student feedback, which can be more easily collected with online education[22]. Effectively collected feedback reported that a slight reduction in teaching hours had little impact on medical student learning outcomes and satisfaction[29].

We assumed that regular habits could have an impact on the perception of histology and embryology learning online or face-to-face. The students who preferred online education were more likely to choose digital platforms for socializing instead of face-to-face communication. They also indicated choosing online instead of traditional courses to learn new skills. Students who choose to do their shopping online were more likely to prefer online histology and embryology education (Table 3).

Considering adaptation to online life, the reading habits for some have changed from hardcopy to online with time[30]. The behaviors, principles, and choices of people born after 1994, known as Generation Z, differ from those of older generations and tend to be more online[31]. Young people use the Internet for emailing, information searching, social networking and news reading at least once a day[32].

Histology and embryology educational preferences were not associated with gender. Gender did not affect computer and Internet self-efficacy scores or online communication self-efficacy scores, either. However, economic independence, having a computer and constant Internet connection, online course experience in the past, and preference for online courses in the future did vary by gender.

Students with better Internet skills asked questions with more confidence, learned better in online theory and practical sessions, and preferred these sessions and online histology learning materials. Online skills were concordant with online course preference when learning new skills. The digital literacy is important for academic competence. Some studies suggested that higher digital literacy could be linked to increase in IUD amongst adolescents and did not affect the educational

performance[33,34]. The difference could be because of the selected age group and the context of education of the subjects in this study. Another study reported that IUD is an increasing danger for medical students and the lower YIAS scores were associated with higher information literacy[35].

Internet addiction scale scores represent a possible negative for these students. Computer and Internet self-efficacy scores were not associated with IUD. However, the students with lower online communication self-efficacy scores had higher YIAS scores. We suggest that self-perception of low online communication skills may be due to social insecurity, shyness or low self-esteem, which can be considered factors for IUD[36,37]. A psychometric self report instrument was used in this study because of a lack of an standardized test for IUD. Therefore, the cut off scores gave only a hint towards the IUD tendency.

The students had better quiz scores after online courses than after traditional courses in our study. This result matches with recent studies[38]. However, some past studies have found that online learning outcomes did not differ from traditional education outcomes[39,40]. The reasons for this change are the evolution of software, increased experience of instructors and faster Internet. Student satisfaction is profoundly affected by their interaction with the instructor[41]. If the online learning environment enables functional communication, many students ask questions or discuss online more easily[42]. The most critical factor is the perceived technical, peer and instructional support[43].

The success levels after the online histology and embryology courses were better than after the traditional courses. Nevertheless, students overall preferred face-to-face courses over online courses. However, students with higher online readiness scores preferred online courses. The inevitable truth is that the computer and online skills of the next generation will increase. On the other hand, we found that computer and Internet readiness did not correlate with IUD. Literature supports that students want digital histology learning materials as complementary to laboratory lectures with microscopes[44]. The students in our study were willing to continue with traditional courses, but they also wanted access to these lectures online or offline. Therefore, we should adapt histology and embryology courses online together with face-to-face lectures according to students' requests and the increasing computer use of young people.

Conclusion

In this study, we showed first time in the literature that IUD is not associated with online course preferences, and it is not a danger for young people with high computer/internet readiness and high online communication skills. Behavioral patterns, such as internet habits, yield students learning material preferences, therefore they are useful for planning a complete online or an online assisted medical education. The instructors should improve themselves for better online teaching and communicating skills to ameliorate all students' online lecture perception, because the success levels of medical students are higher after online lectures. On the other hand, the technical support by the university as large screens for each student and satisfactory interactive online lectures in the program should be planned. This improvement and repetitive online sessions would enhance students' online lecture satisfaction, online learning habit, and achievement.

Histology and embryology have highly visual content and are basic scientific fields. This study was designed in this context. Further detailed studies should be planned and conducted for other preclinical and clinical areas of medical education according to the requirements of each specific discipline.

List of Abbrevations

Internet Use Disorder: IUD

Young Internet Addiction Scale: YIAS

Online Learning Readiness Scale: OLRS

Istanbul University: IU

Istanbul Aydin University: IAU

Conflict of Interest

The authors declare that they have no known competing financial interests that have effect the research in this paper.

Ethical Approval

The study was approved by the clinical research committee and the social research committee of IU.

Informed Consent

Students gave their informed consent to participate. All methods were performed in accordance with the relevant guidelines and regulations.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

A Retrospective Analysis of Renal Transplantation Patients: A Single Center Experience

Renal Transplantasyon Hastalarının Retrospektif Analizi: Tek Merkez Deneyimi

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ABSTRACT

Aim: *In this study, we aimed to present demographic characteristics of the patients having undergone renal transplantation in our hospital between February 2017 and September 2020, to convey the experience of cadaver and living donor renal transplantation in our center, and to reveal the causes of allograft dysfunction in late posttransplant follow-ups.*

Material and Method: *The study included 25 patients having undergone renal transplantation in our hospital and were followed up in the nephrology clinic between February 2017 and September 2020. Then, we retrospectively analyzed their demographic characteristics, clinical and laboratory findings, transplantation types, kidney donor characteristics, renal failure etiologies, pre-transplant dialysis modalities, post-transplant complications, rejection attacks, graft loss, and causes of mortalities.*

Results: *The mean follow-up period of 25 renal transplant patients (17 males and 8 females with a mean age of 46.96±2.67 years) was 26.28±2.76 months. While living transplantation was performed in 16 patients, the others received cadaveric renal transplants. Five patients underwent pre-emptive renal transplantation, and three were recruited for transplant for the second time. The underlying cause of chronic kidney disease was unknown in 24% of the patients (first), while vesicoureteral reflux (VUR) and diabetes were the primary causes of the disease in 16% (second). The most prevalent cause of temporary or permanent impairment in allograft functions was urinary tract infection with 42.8%. It was more common in female patients (25%) and patients with a diagnosis of VUR (20%).*

Conclusion: *Overall, our findings documented that urinary system infections are common following renal transplantation, which brings adverse effects on allograft functions. VUR-led renal failure and female gender are among the factors that facilitate urinary system infection.*

Key words: *renal transplantation; kidney function tests; urinary tract infection*

ÖZET

Amaç: *Çalışmamızda, Şubat 2017 – Eylül 2020 tarihleri arasında hastanemizde böbrek transplantasyonu yapılan hastaların demografik analizinin sunulması, merkezimizin kadavra ve canlı vericili renal transplantasyon deneyiminin aktarılması, posttransplant geç dönem takiplerindeki allograft fonsiyon bozukluğu nedenlerinin ortaya konulması amaçlanmaktadır.*

Materyal ve Metot: *Çalışmaya Şubat 2017 – Eylül 2020 tarihleri arasında hastanemizde böbrek nakli yapılan ve nefroloji kliniğinde izlenen 25 hasta dâhil edildi. Bu hastaların demografik özellikleri, klinik ve laboratuvar bulguları, nakil tipleri, böbrek verici özellikleri, böbrek yetmezliği etiyolojileri, nakil öncesi diyaliz modaliteleri, nakil sonrası gelişen komplikasyonları, rejeksiyon atakları, graft kaybı ve ölüm nedenleri geriye dönük olarak incelendi.*

Bulgular: *Çalışmaya dâhil edilen 25 böbrek nakli hastasının (17 erkek, sekiz kadın, yaş ortalaması 46,96±2,67 yıl) ortalama izlem süresi 26,28±2,76 aydı. Hastaların 16'sına canlı, dokuzuna ise kadavradan böbrek nakli yapıldı. Beş hastaya pre-emptif renal transplantasyon, üç hastaya ise ikinci kez böbrek nakli yapıldı. Hastaların %24'ünde kronik böbrek hastalığı nedeni belli değildi (birinci sırada). Vezikoüreteral reflü (VUR) ve diyabet %16 sıklıktaydı (ikinci sırada). Allograft fonksiyonlarında geçici veya kalıcı bozuklukların en sık nedeni ise %42,8 ile üriner sistem enfeksiyonuydu. Üriner enfeksiyon kadın hastalarda (%25) ve VUR tanılı hastalarda (%20) daha sıktı.*

Sonuç: *Genel olarak, bulgularımız, üriner sistem enfeksiyonlarının, allogreft fonksiyonları üzerinde olumsuz etkilere neden olan renal transplantasyonu takiben yaygın olduğunu belgelemiştir. Vezikoüreteral reflü kaynaklı böbrek yetmezliği ve kadın cinsiyet üriner sistem enfeksiyonunu kolaylaştıran faktörler arasındadır.*

Anahtar kelimeler: *böbrek nakli; böbrek fonksiyon testleri; idrar yolu enfeksiyonu*

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Introduction

End-stage renal disease (ESRD) refers to a stage where the glomerular filtration rate falls below 15 ml/min/1.73 m^2 and renal replacement therapy (RRT) is needed[1]. The ideal option for RRT is considered renal transplantation[2].

Renal transplantation has become a popular RRT option among patients and physicians, particularly with the recent improvements in immunosuppressive therapy. Although dialysis treatments may replace 10–15% of kidney functions, kidney functions can be improved almost entirely with renal transplantation. Besides, the contribution of renal transplantation to national economies is undeniable, though. Whereas 3500 renal transplant operations are performed per year in our country, 85% of these operations are carried out from living kidneys and 15% from cadaveric kidneys[3].

In this study, we aimed to present the demographic characteristics of all ESRD patients having undergone renal transplantation in our hospital between February 2017 (the date of our first renal transplantation) and September 2020 (the date when our transplant operations were suspended due to the SARS-Cov2 pandemic), to convey our experience in living and cadaveric renal transplants, to reveal and discuss allograft dysfunction in late post-transplant follow-ups in light of the relevant findings in the literature.

Material and Method

Patients

Although 152 patients were followed up in our renal transplant clinic, only adult patients were included in our study, and those undergoing an operation outside our hospital were excluded from the study. Therefore, we retrospectively analyzed 25 patients having undergone renal transplantation between February 2017 and September 2020.

Data Collection

We retrospectively extracted the findings (demographic data (age, gender, nationality, donor type), ESRD etiologies, pre-transplant dialysis types, post-transplant complications, rejection attacks, graft loss, and causes of mortality) from patient files. We then transferred all parameters to a database for further analysis. Considering the retrospective design of the study, we could not obtain informed consent from the patients. The Clinical Research Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital granted ethical approval to our study (103/07 dated 01.25.2021). All procedures were carried out in accordance with ethical rules and the principles of the Declaration of Helsinki.

Patients' Pre- and Post-transplant Follow-ups

While living and cadaveric donor transplant recipients received induction therapy with monoclonal (basiliximab) or polyclonal (anti-thymocyte globulin-ATG) antibodies and pulse steroids according to their sensitization. Triple immunosuppressive therapy consisting of tacrolimus/cyclosporine, mycophenolate mofetil/mycophenolate sodium, and steroids was preferred in the maintenance therapy. For prophylaxis of infection, all patients were given trimethoprim/sulfamethoxazole for six months, valganciclovir for three months, and nystatin for one month. Post-transplant follow-ups of the patients were performed once a week in the first month, once every two weeks in the second and third months, once every three weeks until the sixth month, once a month from the sixth month to one year, and between three and six months after one year.

Defining Post-transplant Complications

Allograft dysfunction was defined as an increase in serum creatinine levels of at least 25% compared to baseline values. Urine amount <100 cc/day was accepted as anuria. Moreover, urinary system infection was defined as an infection of the urinary epithelium as well as lower (cystitis) and upper urinary tract infection (pyelonephritis). A dialysis need in the first week following transplantation was evaluated as delayed graft function. Finally, findings consistent with drug toxicity in kidney biopsies performed after impaired graft functions were accepted as calcineurin inhibitor toxicity.

Statistical Analysis

The normality assumption was checked using the Kolmogorov Smirnov test. We presented continuous variables with normal distribution as M ± SD, while categorical variables were shown as percentages and numbers. We performed statistical analyses using the Statistical Package for Social Sciences (SPSS) program version 25.0 (SPSS Inc., Chicago, IL).

Results

Of the 25 patients included in the study, 8 were females and 17 were males with a mean age of 46.96±2.67 years. Considering the operations by years, 11 transplants (44%) were performed in 2017, 4 (16%) in 2018, 5 (20%) in 2019, and 5 (20%) in 2020 (Fig. 1). Twenty of the patients were Turkish, and 5 were foreign nationals.

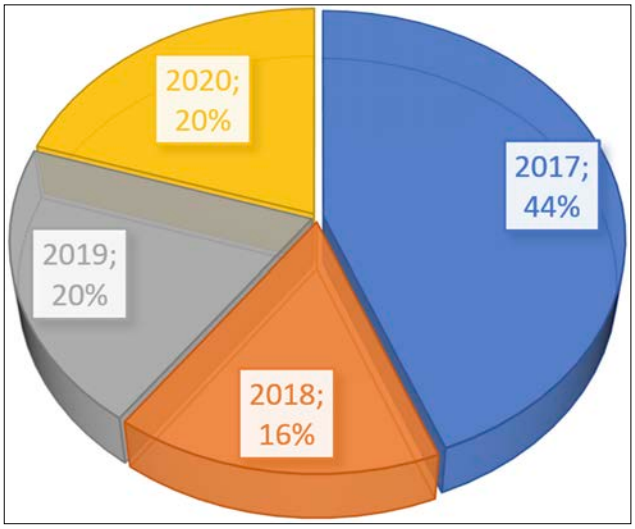

Figure 1. *Distribution of kidney transplantation by year.*

Table 2. *Causes of allograft dysfunction in the post transplant follow-up*

Etiology	Total	Living	Cadaveric
Urinary System Infection	3	2	1
Acute + Chronic Allograft Nephropathy	1	1	-
Calcineurin Inhibitor Toxicity	1	1	-
Renal Cortical Infarction	1	1	-
Acute Tubular Necrosis	1	-	1

Table 1. *Etiologies of renal failure of patients*

	n (%)
Unknown origin	6 (% 24)
Diabetes mellitus	4 (% 16)
Vesicoureteral Reflux (VUR)	4 (% 16)
Chronic Glomerulonephritis	2 (% 8)
Polycystic Kidney Disease	2 (% 8)
Amyloidosis	2 (% 8)
Arterial Hypertension	2 (% 8)
Postrenal events (Ureteropelvic Stenosis, Nephrolithiasis)	2 (% 8)
Pyelonephritis	1 (%4)

Besides, while living transplantation was performed in 16 patients, the others received cadaveric renal transplants (Fig. 2). When it comes to ESRD etiologies, renal failure of unknown cause ranked the first (Table 1).

The number of patients undergoing pre-transplant and peritoneal hemodialysis was 16 and 4, respectively. Five patients underwent pre-emptive renal transplantation, and three were recruited for transplant for the second time (Fig. 3). Besides, twelve donors were males, and 13 were females with a mean age of 46.08±2.74 years. Three of the donor kidneys were right-sided, and 22 were left-sided.

We investigated the causes of allograft dysfunction in the post-transplant follow-ups (Table 2). Laboratory data of patients with allograft dysfunction in post-transplant follow-up are presented (Table 3). Allograft biopsy was performed in 2 patients due to unexplained renal dysfunction and two patients due to anuria. We detected acute tubular necrosis in 1 patient, calcineurin inhibitor toxicity in 1 patient, acute pyelonephritis in 1 patient, and chronic renal cortical infarction in 1 patient. The most prevalent cause of allograft dysfunction was found to be urinary tract infection. Of these patients, 2 were females, and 1 was a male who had a diagnosis of vesicoureteral reflux (VUR) and used a clean intermittent catheter (CIC). Cytomegalovirus and BK virus infections were not detected in the patients during the post-transplant follow-ups. Moreover, new-onset diabetes

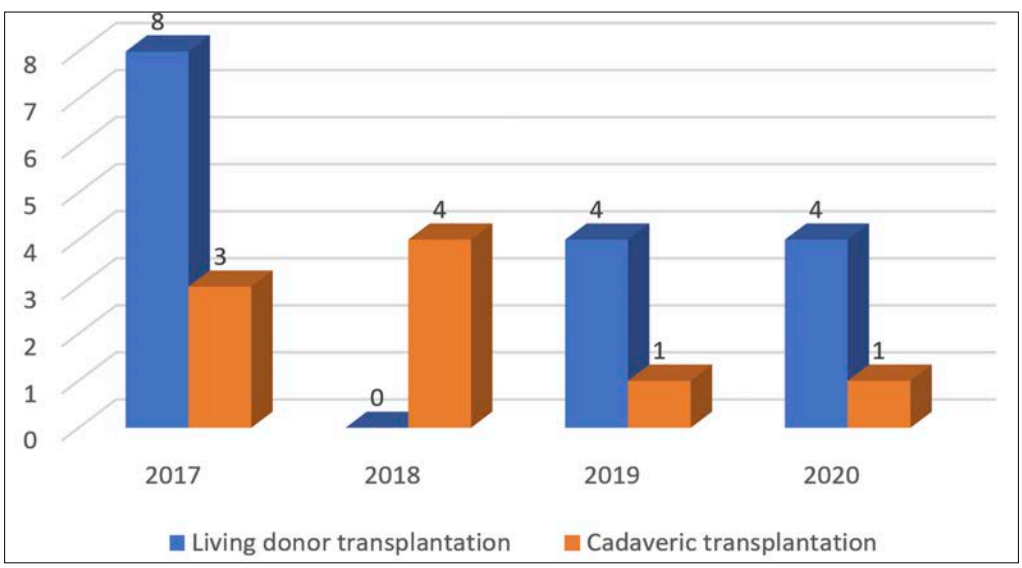

Figure 2. *Living donor and cadaveric kidney transplantations by year.*

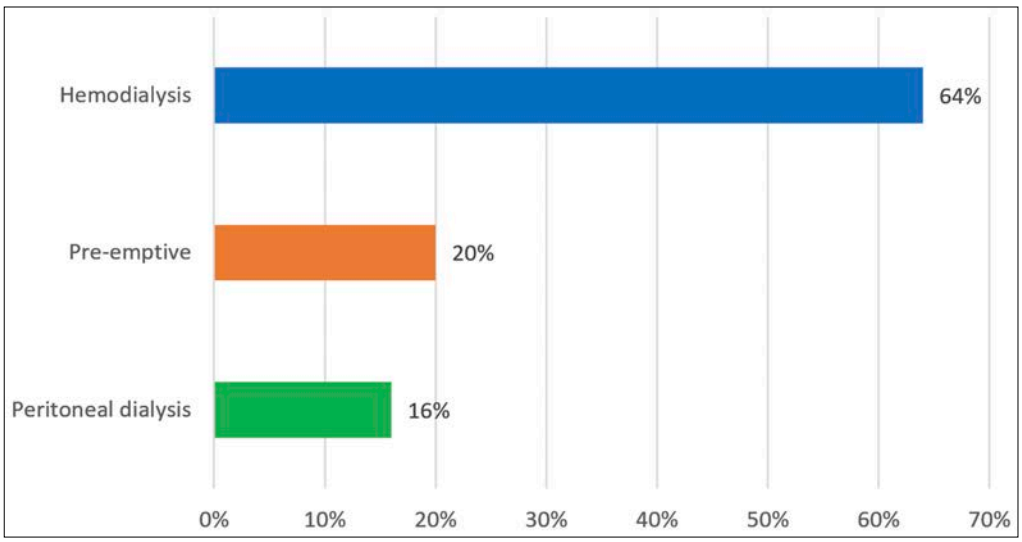

Figure 3. *Pre-transplantation distribution of patients by their RRT modalities.*

Table 3. *Biochemical parameters of allograft dysfunction in the post transplant follow-up*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Etiology	urinary tract infection	urinary tract infection	urinary tract infection	Calcineurin Inhibitor toxicity	Renal cortical infarction	Acute Tubular Necrosis	Acute, chronic allograft nephropathy
Ure (mg/dl)	65	52	68	58	66	45	85
Cre (mg/dl)	1.5	1.42	1.6	1.9	2	1.62	2.2
Na (mmol/L)	134	137	143	138	139	141	135
K (mmol/L)	4.7	5.1	4	5.3	4.4	4.9	5.1
Ca (mg/dl)	8.6	9	8.3	8.8	8.1	8.4	8.1
P (mg/dl)	5.2	4.8	4.5	4.9	5.3	5	5.4
PTH (pg/ml)	96	115	190	185	267	204	308
wbc(10^3/μL)	14.5	13.3	15.6	8.7	9.2	10.2	10.1
Hgb (g/dl)	12.2	11.9	11.5	11	10.5	10.8	10.1
Plt (10^3/μL)	115	170	145	168	175	163	179
Ph	7.36	7.32	7.4	7.38	7.28	7.33	7.27
HCO_3 (mEq/L)	22	21.1	25	24.3	19.2	20.2	18.3

after transplantation (NODAT) was not observed among the patients. Graft loss occurred in 4 patients; while two losses were from living kidneys, two were from cadaveric kidneys. Unfortunately, three patients died due to non-nephrological causes (infective endocarditis, acute coronary syndrome, and SARS-CoV-2).

Discussion

The first successful renal transplant was carried out in the world in 1954[4] and our country in 1975 by Haberal et al[5]. Recent years have witnessed increased numbers of kidney transplant operations and transplant patients in our country. According to the data from the Turkish Society of Nephrology, a total of 2499 renal transplants were performed in 2020[6].

The very first renal transplant operation was performed in our hospital in 2017, and a total of 25 transplants were performed until the SARS-CoV2 outbreak. Of our patients, 16 (65.21%) received transplants from living donors, and 9 (34.79%) received cadaveric transplants. Considering the patients undergoing renal transplantation in our country in 2020, 90.04% were transplanted from living donors, and 9.96% were the recipients of cadaveric transplants[6]. According to the 2019 Registry Report of the Turkish Society of Nephrology, the rate of renal transplantation from a cadaver was 20.61%[7]. The low rate of cadaveric renal transplants in 2020 may be attributed to the decrease in cadaveric donations due to the pandemic.

Although renal transplant patients often show a varied age distribution, it was previously reported that

the best transplant results are achieved among patients aged 10–50 years[8]. In our study, the mean age of transplant recipients was 46.96±2.67 years. It is well known that donor age also matters in graft survival[9,10]. We found that the donors were relatively young with a mean age of 46.08±2.74 years. Interestingly, in a study involving 284 renal transplant recipients, allograft harvesting from elderly (≥65 years) and even very elderly (≥75 years) donors provided superior patient survival compared to dialysis modalities[11]. Thus, considering the superiority of renal transplantation over dialysis modalities, clinicians are better not to hesitate to obtain allografts from elderly or very elderly donors.

According to the 2020 Report of the National Nephrology, Dialysis and Transplantation Registration System, in the etiologies of ESRD of patients undergoing renal transplantation, the first three ranks were occupied by unknown causes (20.06%), glomerulonephritis (19.20%), and diabetes mellitus (18.91%)[6]. In our study, the order in the etiologies of ESRD was unknown causes with 24% and diabetes mellitus and VUR with 16%. Compared to the general population, the VUR rate was found to be higher in our hospital.

In the same report, pre-transplant dialysis modalities of the patients were grouped as pre-emptive transplantation with 53.62%, hemodialysis with 34.65%, transplantation with 8.16%, and peritoneal dialysis with 3.56%[6]. In our study, it is noteworthy that our pre-emptive transplantation rate was low compared to the average in Türkiye, which may be attributed to the failure of our chronic kidney patients in their follow-ups in the outpatient clinic.

In the follow-ups of the patients, allograft dysfunction was most frequently due to urinary tract infection. In the literature, the most common infection in the post-transplant period is shown to be urinary system infection, which may be confronted frequently as in our study[12], and advanced age, female gender, VUR, azathioprine use, and cadaver-derived donors may predispose to this condition[13]. Two of our patients with urinary infections were women, and one was diagnosed with VUR.

During the follow-ups, three patients (12%) were mortal; two (8%) died from infection, while one (4%) died from cardiovascular causes. Immunosuppressive therapy in renal transplant patients predisposes them to infections[14]. Our findings revealed that the infection was the most common cause of post-transplant mortality among the patients.

Conclusion

In our study, we evaluated the demographic characteristics and late-stage allograft dysfunction of the patients having undergone cadaveric and living donor renal transplantation in our organ transplant center between 2017 and 2020. Overall, we determined that allograft dysfunction was primarily associated with urinary tract infection, which may be predisposed by primary renal failure and female gender. Yet, the insufficient number of patients in our study urges the need for more comprehensive research on the subject.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Effect of Glomerular Filtration Rate and Troponin on the Prognosis of Patients with COVID-19

COVID-19 Hastalarında Glomerüler Filtrasyon Hızı ve Troponinin Prognoza Etkisi

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ABSTRACT

Aim: *During the pandemic, clinicians have generally focused on treating respiratory tract infections. It determined that all organs are affected over time, especially the heart and kidneys, and the clinic deteriorates rapidly. We aimed to determine whether serial glomerular filtration rate and troponin tests would predict prognosis in patients with COVID-19.*

Material and Method: *One hundred seven patients diagnosed with COVID-19 were included in this study. We evaluated in-hospital mortality based on the presence and absence of troponin elevation and renal dysfunction at patients' first and last examinations. We also investigated the correlation of both troponin elevation and renal dysfunction with age, pneumonia severity, and each other.*

Results: *Most surviving patients were female, and the average age was younger than the other group. The most common comorbidity was hypertension. It was observed that the patients with a high last glomerular filtration rate, low last troponin test, and low pneumonia severity survived. The most important factors affecting the prognosis were the severity of pneumonia and the last glomerular filtration rate.*

Conclusion: *Based on the conclusion from this study, the prognosis of patients with rapidly worsening cardiac and renal function can deteriorate. Those tests require close monitoring.*

Key words: *COVID-19; glomerular filtration rate; troponin; pneumonia severity; prognosis*

ÖZET

Amaç: *Pandemi sürecinde klinisyenler genel olarak solunum yolu enfeksiyonlarının tedavisine odaklanmışlardır. Başta kalp ve böbrekler olmak üzere tüm organların zamanla etkilendiği ve kliniğin hızla bozulduğu belirlendi. Glomerüler filtrasyon hızı ve troponin testlerinin takibinin, COVID-19 hastalarında prognozu tahmin edip edemeyeceğini belirlemeyi amaçladık.*

Materyal ve Metot: *Bu çalışmaya COVID-19 tanısı alan 107 hasta dâhil edildi. Hastane içi mortaliteyi, hastaların ilk ve son muayenelerinde troponin yüksekliği ve böbrek fonksiyon bozukluğu olup olmamasına göre değerlendirdik. Ayrıca hem troponin yüksekliği hem de böbrek fonksiyon bozukluğunun yaş, pnömoni şiddeti ve birbiriyle ilişkisini araştırdık.*

Bulgular: *Hayatta kalan hastaların çoğu kadındı ve yaş ortalaması diğer gruptan daha gençti. En sık eşlik eden hastalık hipertansiyondu. Son glomerüler filtrasyon hızı yüksek, son troponin testi düşük ve pnömoni şiddeti düşük olan hastaların hayatta kaldığı görüldü. Prognozu etkileyen en önemli faktörler pnömoninin şiddeti ve son glomerüler filtrasyon hızıydı.*

Sonuç: *Bu çalışmadan elde edilen sonuca göre, kalp ve böbrek fonksiyonları hızla kötüleşen hastaların prognozu kötüleşebilir. Bu testler yakın takip gerektirir.*

Anahtar kelimeler: *COVID-19; glomerüler filtrasyon hızı; troponin; pnömoni şiddeti; prognoz*

Introduction

Since the COVID-19 (Coronavirus Disease) pandemic, caused by SARS-CoV-2 (Severe Acute Respiratory Syndrome-Coronavirus 2), affected the whole world since 2019, it has been thought to cause more respiratory tract infections. It has been determined that over time, trauma develops mainly in the veins, and therefore all organs may be affected. The primary reason for this is hypoxia. The damage is exacerbated by cellular lesions and cytokine storms, which develop after hypercoagulation[1]. In COVID-19 disease, the most feared ischemic findings. The organs most affected by this condition are the heart and kidneys. In the dysfunction of these organs, the risk of developing multiorgan failure increases, and the prognosis worsens rapidly[2,3].

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Myocardial injury, manifested by elevations in cardiac troponin, is common in patients with COVID-19, and has also been suggested as a prognostic factor[4,5]. The pathogenesis of myocardial damage in COVID-19 has not been established. Still, it is likely multifactorial, including the patient (sex, age, race, and chronic diseases) and disease (SARS-CoV-2 infection induced cardiomyocyte injury and necrosis, inflammation, endothelial damage and hypoxia) specific factors[6]. Therefore, there are important knowledge gaps in understanding the epidemiology and clinical implications of myocardial injury, and markers of myocardial injury should be investigated in COVID-19 by independent prognostic comparative studies. The GFR (Glomerular filtration rate) is used as a measure of kidney function that worsens concomitantly with COVID-19 infection[7]. Some of the mechanisms of kidney injury have been described, including endothelial and tubular damage due to direct infection of SARS-CoV-2 in the kidneys, as well as secondary mechanisms (severe inflammation, hemodynamic factors, microvascular thrombosis, hypoxia) associated with the COVID-19[8]. Although low GFR levels have been described in patients with COVID-19, limited studies describe the relationship between GFR levels and mortality[9].

This study was conducted to predict prognosis in examinations taken at the time of admission and during the follow-up of the patients, with the GFR and cardiac markers.

Material and Method

Study Design

This study was designed to be a single center, retrospective, and observational cohort. Between March and December 2020, patients diagnosed with COVID-19 and receiving outpatient or inpatient treatment were tried to be examined. The data was obtained from the hospital archive, computer records and health system records of the patients. The local Ethics Committee (P202200021-03) has approved this study.

Patient Selection and Clinical Outcomes

This study randomly selected 107 patients over 18 years of age, who were diagnosed with COVID-19 (viral pneumonia detected by PCR [polymerase chain reaction] + or thorax tomography), and who applied to the Emergency Service during the pandemic period. The examinations of the patients at the first application, last if they received inpatient treatment, or tests on the last date of application to the COVID outpatient clinic if they were discharged were examined. Glomerular filtration rate (GFR) and troponin values and pneumonia severity were recorded in these tests. The pneumonia severity score was visually (semiquantitatively) evaluated in chest CT images of each patient. The pneumonia severity score was assessed by a simple CT scoring method described by Chen et al.[10]. The pneumonia severity score was categorized as follows: mild (peripheral and subpleural ground glass attenuation)=1 point, moderate (the high-density shadow of plaques involving multiple lung lobes (≥3), ground glass, cloud flocculent or paving stone like changes, at least two lung lobes show pulmonary consolidation, local pulmonary fibrosis, and air bronchograms sign)=2 points, and severe (diffuse consolidation [minimum of 80% of pulmonary or involving of 4 lobes] or cord like changes, and fibrosis)=3 points according to radiological results for each patient. Glomerular filtration rate value was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) estimating equations using the serum creatinine value[11]. Patients who received dialysis treatment and a diagnosis of myocardial infarction were excluded from this study. The effects of GFR, troponin, pneumonia severity at admission, and other diseases' presence on the prognosis were investigated.

Statistical Analysis

The data were analyzed using Statistical Package for Social Sciences (SPSS) program version 20.0 (SPSS Inc., Chicago, USA). Differences between demographic and laboratory data (GFR and troponin I) of the COVID-19 patients are analyzed using Student's T-test and Chi-square test. Pearson's correlation coefficient was used to analyze the relationship between clinical parameters. The point biserial correlation coefficient analyses the relationship between clinical parameters and mortality rate. A p value is less than 0.05 are considered statistically significant.

Results

Fifty-one patients included in the study were female (46.7%), and 56 were male (53.3%). The gender difference did not affect prognosis ($p>0.05$). The persons who died were older (mean age 71±10.36) (Table 1). All patients had signs of pneumonia of varying severity, and it was observed that they received

antiviral, symptomatic and anticoagulant treatment. Twenty-two patients (20.5%) died. Last GFR (L-GFR) (p=0.000007) and Pneumonia severity score (p=0.001) were the parameters with the greatest difference between the group of patients who died compared to subjects who survived. Interestingly, no statistically significant difference was observed between the mean values of the first GFR (F-GFR), first troponin (F-Troponin), and last troponin (L-Troponin) when patients who died were compared with subjects who survived (p>0.05) (Table 2). Some patients had more than one comorbidity, and the percentage of patients receiving hypertension treatment was high. Chronic obstructive pulmonary disease, diabetes mellitus, hypertension, chronic renal failure, and hyperlipidemia comorbidities did not affect mortality rates (p>0.05) (Table 3).

Table 1. *Demographic data of the COVID-19 patients*

Variables	Non-survivors Mean ± SD (n)	(%)	Survivors Mean ± SD (n)	(%)	P
Age (years)	71±10.36	20.5	63±11.79	**79.5**	**0.005**
Sex					
Female	8	7.5	43	**40.2**	0.234
Male	14	13.1	42	39.3	

SD: Standard deviation.

Table 2. *Comparison of patients' test results average*

	Non-survivors	Survivors	p
First GFR (mL/min/1.73 m²)	74.91±27.83	87.72±33.74	0.104
Last GFR (mL/min/1.73 m²)	58.05±48.03	100.98±35.13	**0.000007**
First Troponin I (pg/mL)	26.45±26.18	18.44±23.08	0.161
Last Troponin I (pg/ml)	69.59±112.13	32.31±125.40	0.207
Pneumonia severity score	2.59±0.67	1.98±0.76	**0.001**

GFR: Glomerular filtration rate.

Table 3. *Patients' comorbidities rate*

Comorbidities	Odds ratio (95% CI)	P
COPD	0.627 (0.072–5.497)	0.671
DM	1.636 (0.605–4.426)	0.329
HT	1.959 (0.698–0.500)	0.197
CRF	1.600 (0.289–8.859)	0.587
Hyperlipidemia	1.184 (0.296–4.730)	0.811

COPD: Chronic Obstructive Pulmonary Disease; DM: Diabetes Mellitus; HT: Hypertension; CRF: Chronic Renal Failure; CI: Confidence Interval.

According to statistical analyses in Table 4. There is a strong negative correlation between L-GFR and age (rp=-0.380**, p<0.0001). A strong positive correlation exists between F-Troponin and age (rp=0.394**, p<0.0001).

There is a strong negative correlation between F-GFR and F-Troponin (rp=-0.452**, p<0001), and there is a negative correlation between L-GFR and L-Troponin (rp=-0.251**, p=0.009).

A strong positive correlation exists between pneumonia severity and age (rp=0.323**, p=0.001). A strong negative correlation exists between F-GFR and pneumonia severity (rp=-0.302**, p=0.002). A strong positive correlation exists between F-Troponin and pneumonia (rp=0.253**, p=0.008).

A solid and positive significant relationship exists between age and prognosis (rp=0.271**, p=0.005). A strong negative correlation exists between L-GFR and prognosis (rp=-0.418**, p<0.0001). A strong positive correlation exists between pneumonia severity and prognosis (rp=0.321**, p=0.001). There is no significant relationship between F-GFR, F-Troponin, L-Troponin and prognosis (p>0.05).

Discussion

This study has been trying to determine whether deteriorated GFR and increased troponin values can determine the prognosis during COVID-19 infection.

Table 4. *Percentmap of data results*

	Age	F-GFR	L-GFR	F-Troponin	L-Troponin	Pneumonia	Prognosis
Age	100%	37%	38%	39%	31%	32%	27%
F-GFR	-0.365**	100%	67%	45%	15%	30%	16%
L-GFR	-0.380**	0.674**	100%	40%	25%	36%	42%
F-Troponin	0.394**	-0.452**	-0.397**	100%	67%	25%	14%
L-Troponin	0.307**	-0.146	-0.251**	0.674	100%	2%	12%
Pneumonia	0.323**	-0.302**	-0.360**	0.253**	0.016	100%	32%
Prognosis	0.271**	-0.158	-0.418**	0.137	0.123	0.321**	100%

F-GFR and F-Troponin: First value; L-GFR and L-Troponin: Last value.
Percent map representing the correlation between continuous features included in mortality risk prediction model for COVID-19 using Pearson's correlation and Point biserial coefficient. The percentage in the plot represents the correlation coefficients. The higher the rate stronger the monotonic relationship. The lower, the weaker the monotonic relationship. The rate represents the absolute value of the correlation coefficient. The numbers in the lower triangle represent the value of the correlation coefficient.

In this study, the mean age of the discharged patients was observed to be lower than the ex-patients, and the prognosis of the male population was poor. According to this result, it can be said that the young population survived the disease with fewer complications, and the female population was more successful in complying with the hygiene conditions and preventing infection[12]. Research has shown that as age increases, troponin increases and GFR decreases[13]. Therefore, the elderly population can be considered vulnerable to COVID-19 infection.

It has been determined that the SARS-CoV-2 virus enters the cell using ACE-2 (Angiotensin Converting Enzyme-2). Since this enzyme is found in the kidneys, heart, lungs, and intestines, these organs are exposed to toxic effects[14].

An acute or chronic condition in which the functions of two organs are impaired is known as cardiorenal syndrome[15]. As seen in many diseases, this is also the case with COVID-19 infection[16]. The most critical mechanism in acute renal injury is thrombus in COVID-19, which develops with hypoxia after endothelial damage, coagulation, and hormone mechanism disruption. After inflammation, the number of cells in the immune system increases, the release of cytokines and the trauma and formation of thrombus become more severe, and a vicious cycle develops. Furthermore, using antibiotics or anti-virals in treatment also negatively affects this process[17]. A significant problem may occur because of resistant bacteria from the antibiotics used[18]. In a post-mortem study, tubular damage has been demonstrated to develop post-COVID-19 infection[19]. Cardiac damage is thought to be caused by a similar mechanism. Cardiac markers increase with dysfunction that develops with increased adrenergic activity in respiratory problems, increased myocardium workload, vasculitis development, and direct toxic effect of the virus[20,21]. In other studies, the prognosis of patients with high troponin levels was poor[22,23]. Likewise, in this study, the prognosis was poor in the patient group with a decreased GFR, increased troponin, and the continuation of these conditions.

In a different research, pneumonia severity and the incidence of acute renal injury were directly proportional. Especially in patients who developed ARDS (Acute Respiratory Distress Syndrome) and received mechanical ventilator support, this situation was found to be more severe[24]. In this study, the severity of pneumonia was the most significant factor affecting the prognosis. This may have been caused by the ongoing hypoxia-induced coagulation cascade triggering the development of multiorgan dysfunction. The increase in GFR values in surviving patients and the decrease in troponin values support this theory. Therefore, adding an anticoagulant was a good choice in patients with increased troponin levels and decreased GFR. That group is a micro-macro thrombus that was considered[25]. The fact that some patients died despite administering anticoagulants shows that DIC (Disseminated Intravascular Coagulopathy) may have begun.

Organ dysfunction may occur during infection or treatment, but irreversible results are more common in viral infections. This situation includes other diseases, viral load, old age, the type of treatment applied, and the immune system response to them[26,27]. For COVID-19 infection, since the tendency of the virus to form vascular pathology is detected at a higher rate, multi-organ dysfunction is observed more quickly[28].

In this study, the rate of patients receiving hypertension treatment is higher than in the others. As a result, they may be considered the population most affected by COVID-19[29].

Limitations of the Study

This study determined that other diseases did not directly affect the prognosis. This result may have been due to the small study population, but it should be noted that multiple factors determine the prognosis during infection.

Conclusion

It seems that the SARS-CoV-2 virus is a pathogen that destroys the system. Therefore, the clinician should be alert to upper and lower respiratory tract infections and pathology that may develop in all organs. As a result, with COVID-19 disease, impaired renal and cardiac function can predict prognosis. Therefore, supportive treatment, timely consultation, and even classification will be beneficial.

Complying with the rules of protection from the virus and hygiene individually and participating in vaccination programs as a social responsibility should be considered. This vulnerable population with co-morbidities should also have easy and reliable access to health services[30].

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Vitamin D, Vitamin B12 and Ferritin Levels in Children Presenting with Malnutrition Complaints

Malnütrisyon Şikâyetiyle Başvuran Çocuklarda D Vitamini, Vitamin B12 ve Ferritin Düzeyleri

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ABSTRACT

Aim: *In this study, it is aimed to examine the levels of [25(OH)D], vitamin B12 and ferritin, which we think are associated with the disease, in children who apply with the complaint of protein and energy deficiency.*

Material and Method: *The [25(OH)D] level of 1377 people who applied to the hospital, the vitamin B12 level of 1366 people and the ferritin level of 1384 people who applied to the hospital were included in the study. Hospital references for children were used for vitamin D [25(OH)D], vitamin B12 and Ferritin levels.*

Results: *When [25(OH)D] levels were examined in the study; Approximately 27% of the children had vitamin D deficiency [25(OH)D] <20 ng/mL, 7.19% had excessive [25(OH)D] deficiency and 6.68% had a high level of vitamin D deficiency. When vitamin B12 levels were examined, Vitamin B12 levels were low in 5.2% of the children (B12<191 ng/L) and high in 14.35%. Considering the ferritin levels, ferritin levels were low in 49.35% of children (ferritin level <30 µg/L).*

Conclusion: *It was observed that B12, [25(OH)D] and ferritin levels of patients with PEM could vary according to geographical regions. For this reason, we think it is necessary to focus on the age range of 6–24 months, where the incidence of micronutrient deficiencies and infectious diseases is the highest.*

Key words: *PEM; child; vitamin D; vitamin B12; ferritin*

ÖZET

Amaç: *Bu çalışmada protein ve enerji yetersizliği şikâyetiyle başvuran çocuklarda hastalıkla ilişkili olduğunu düşündüğümüz [25(OH)D], vitamin B12 ve ferritin düzeylerinin incelemesi amaçlanmaktadır.*

Materyal ve Metot: *Hastaneye başvuran 1377 kişinin [25(OH)D] düzeyi, 1366 kişinin vitamin B12 düzeyi ve hastaneye başvuran 1384 kişinin ferritin düzeyi çalışmaya dâhil edildi. D vitamini [25(OH)D], vitamin B12 ve Ferritin düzeyleri için hastanenin çocuklar için belirlediği referanslar kullanıldı.*

Bulgular: *Çalışmada [25(OH)D] düzeyleri incelendiğinde; Çocukların yaklaşık %27'sinde D vitamini eksikliği [25(OH)D] <20 ng/mL, %7,19'unda aşırı [25(OH)D] eksikliği ve %6,68'inde yüksek düzeyde D vitamini eksikliği saptanmıştır. B12 vitamin düzeyleri incelendiğinde; B12 vitamini düzeyi çocukların %5,2'sinde düşük (B12<191 ng/L), %14,35'inde yüksekti. Ferritin seviyelerine bakıldığında; Çocukların %49,35'inde ferritin seviyeleri düşüktü (ferritin seviyesi <30 µg/L).*

Sonuç: *Protein ve enerji yetersizliği (PEM) hastalarının B12, [25(OH)D] ve ferritin düzeylerinin coğrafi bölgelere göre değişebildiği görüldü. Bu nedenle mikrobesin eksikliklerinin ve bulaşıcı hastalıkların görülme sıklığının en yüksek olduğu 6–24 ay yaş aralığına odaklanılması gerektiğini düşünüyoruz.*

Anahtar kelimeler: *PEM; çocuk; D vitamini; B12 vitamini; ferritin*

Introduction

It is defined as protein-energy malnutrition (PEM) in the clinical-pathological picture that occurs in case of insufficient intake of one or more nutrients in a way that disrupts the body balance[1]. Childhood malnutrition accounts for approximately half (45%) of all deaths among children under the five worldwide[2]. Growth in children; It is an increase in body volume and mass with an increase in cell number and size. On the other hand, the development expresses bodily maturation with the change of cell, tissue and structure content[3]. The malnutrition rate is still high in developing countries[4]. Malnutrition affects one in nine people worldwide, and this rate seems to increase even more in low-income countries, especially among children younger than five years old. Malnutrition in early childhood can have harmful neurodevelopmental effects, with significant

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increases in lifelong cognitive, neurological, and mental health problems, and its consequences may spread to future generations[5]. 25-Hydroxy Vitamin D [25(OH) D] is a steroid vitamin that dissolves in adipose tissue. The most important effects are to keep calcium (Ca) and phosphor (P) levels in the normal physiological range along with parathyroid hormone (PTH) and thus to provide optimum bone mineralization[6].[25(OH)D] deficiency in children is one of the main causes of rickets. Rickets; Insufficient intake of [25(OH)D] occurs due to malabsorption, insufficient exposure to sunlight, and increased need during rapid growth, and the most common type is [25(OH)D] and/or caused by calcium deficiency. nutritional rickets[7]. Vitamin B12 deficiency in childhood is a rare disease with nonspecific symptoms. It was stated that many cases were exclusively breastfed and were children of mothers with low cobalamin levels. The development of the patients is normal in the early period. It is reported that symptoms and signs such as megaloblastic anemia, loss of acquired motor abilities, and growth and development retardation can be seen around 3–8 months[8]. Ferritin protein is found in body cells and especially in cells known as hepatocytes which make up approximately 75% of the liver, bone marrow and immune system cells. Ferritin, which is responsible for storing iron taken through food and releasing when necessary, is also defined as the body's iron store[9]. This study examines the levels of [25(OH)D], vitamin B12, and ferritin, which we think are associated with the disease, in children presenting with protein and energy deficiency complaints.

Materials and Methods

It was approved by a state University Ethics Committee (decision no: 2022/108, date: 21.09.2022). In the study, the results of vitamin B12, [25(OH)D] and ferritin levels requested from patients who applied to Health Sciences University Diyarbakir Gazi Yaşargil Training and Research Hospital between July 2020 and June 2022 were retrospectively analyzed. The reference range used by the hospital for children was taken as an example to diagnose vitamin B12, ferritin and vitamin D [25(OH) D] levels and to determine their normal ranges. Based on the reference ranges of 191–663 ng/L for Vitamin B12 and 30–400 μg/L for ferritin levels, results were grouped as low, normal and high levels. In addition, determining the degree of [25(OH)D] level <10 ng/mL severe deficiency, 10–19 ng/mL mild deficiency, 20–50 ng/mL normal, 51–80 ng An increased risk of hypercalciuria/ mL was assessed as >80 ng/mL of toxicity. The patients' data were obtained from electronic health records in the hospital database. Therefore, an informed consent form was not obtained from the patients. B12 levels of 1366 people, [25(OH)D] of 1377 people and ferritin levels of 1384 people who applied to the hospital were included in the study. B12, [25(OH)D] and ferritin levels were determined according to the age and gender of the patients. Patient names were kept confidential in the data analysis, and ethical rules were followed. The ages of children under the age of five included in the study were evaluated by dividing them into three groups: 6–24 months, 25–48 months and 49–60 months[10–11]. Serum B12, [25(OH)D], and ferritin levels were analyzed using the electrochemiluminescence method with a roche cobas device and an immunoassay system.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 21.0 package program (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The conformity of the data to the normal distribution was examined with the Kolmogorov-Smirnov test. Nonparametric tests were applied because they did not fit the normal distribution. The Mann-Whitney U test was used to determine whether there was a significant difference between children's Vitamin B12, [25(OH)D] and ferritin levels according to gender. Kruskal-Wallis test was used to determine whether the difference between the mean ages was significant. Frequency distributions, numbers, percentages, median, minimum and maximum values were given in descriptive statistics. A value of $P < 0.05$ was considered significant.

Results

The age and gender status of malnourished patients admitted to the hospital were divided into groups, and descriptive statistics, frequency distributions, and median, minimum and maximum values were given in the tables. Vitamin B12 and ferritin levels and [25(OH) D] vitamin levels are grouped according to the reference ranges used by the hospital for children, and the frequency distributions of low, normal and high level results by age and gender are given in Table 1. When [25(OH)D] levels were examined in this study, approximately 27% of the children (n=1377) had vitamin D deficiency (25(OH)D <20 ng/mL), of which 7.19% had excessive [25(OH)D] deficiency, and 6.68% had high levels of toxic [25(OH)D]. When children with [25(OH)D]deficiency are examined by gender; It has

Table 1. *Distribution of [25(OH)D], Vitamin B12 and Ferritin levels of children with malnutrition by age and gender*

	Age						Gender					
	6–24 month		25–48 month		49–60 month		Female		Male		Total	
	n	(%)*	n	(%)*	n	(%)*	n	(%)*	n	(%)*	n	(%)
[25(OH)D]												
<10 ng/mL	67	4.86 10	28	2.04 5.47	4	0.29 2.05	50	3.63 6.6	49	3.56 7.92	99	7.19
10–19 ng/mL	130	9.44 19.40	106	7.71 20.70	34	2.46 17.44	135	9.80 17.81	135	9.80 21.81	270	19.61
20–50 ng/mL	329	23.89 49.10	278	20.19 54.30	119	8.64 61.02	404	29.34 53.30	322	23.38 52.02	726	52.72
51–80 ng/mL	101	7.34 15.08	65	4.75 12.69	24	1.74 12.31	111	8.06 14.64	79	5.74 12.76	190	13.80
>80 ng/mL	43	3.13 6.42	35	2.51 6.84	14	1.01 7.18	58	4.21 7.65	34	2.47 5.49	92	6.68
Total	670	48.66 100	512	37.2 100	195	14.14 100	758	55.05 100	619	44.95 100	1377	100
Vitamin B12												
<191ng/L	52	3.81 7.76	11	0.80 2.18	8	0.59 4.19	33	2.42 4.37	38	2.78 6.23	71	5.20
191–663 ng/L	515	37.7 76.87	414	30.31 81.98	170	12.44 89.01	601	44 79.50	498	36.45 81.64	1099	80.45
>663 ng/L	103	7.54 15.37	80	5.86 15.84	13	0.95 6.80	122	8.93 16.13	74	5.42 12.13	196	14.35
Total	670	49.04 100	505	36.97 100	191	13.98 100	756	55.35 100	610	44.65 100	1366	100
Ferritin												
<30 µg/L	345	24.93 51.11	244	17.63 47.56	94	6.79 47.96	324	23.41 52.01	359	25.94 47.17	683	49.35
30–400 µg/L	330	23.84 48.89	269	19.44 52.44	102	7.37 52.04	299	21.60 47.99	402	29.05 52.83	701	50.65
>400 µg/L	0	0	0	0	0	0	0		0		0	0
Total	675	48.77 100	513	37.07 100	196	14.16 100	623	45.01 100	761	54.99 100	1384	100

* Values in the first row represent the percentage in the total, the values in the second row indicate the percentage in the group.

been determined that the rate of low levels in boys is higher than that of girls, and when looked at the age groups, it is seen at the highest rate of approximately 14% in 6–24-month-old children. There is a decrease in vitamin D[25(OH)D] deficiency rates as age progresses. When vitamin B12 levels were examined, they were found to be low (B12<191 ng/L) in 5.2% of children (1366), and high in 14.35%. When children with vitamin B12 deficiency are examined by gender, it is seen that the rates of low levels in girls are lower than in boys. When analyzed according to age groups, it is seen that the lowest rate is 3.81% in children aged 6–24 months. When the ferritin levels were examined, they were found to be low (ferritin level <30 µg/L) in 49.35% of children (n=1384). When the ferritin level was evaluated according to age, it was found that the lowest rate of 24.93% was seen in children aged 6–24 months, and there was a decrease in ferritin deficiency rates as age progressed. When the ferritin level is examined by gender, it has been determined that it is relatively lower in boys than in girls (male: 47.17%; Female 52.01%). The demographic information of the patients and the median, minimum and maximum levels of B12, [25(OH)D] and ferritin are given in Table 2. When the children under the age of five included in the study were examined according to their gender; For B12, the number of females was 756, the number of men was 610, for [25(OH)D] the number of women was 758, the number of men was 619, for ferritin the number of women was 623. The number of men was 761; the median B12 level was 384.5 ng/L in men, 409.5 ng/L in women. [25(OH)D] level was 31 ng/mL in females and 29 ng/mL in men, and ferritin level was 29 µg/L in women and 31 µg/L in men. The difference between the medians of B12 level, [25(OH)D] level and ferritin levels by gender was found to be statistically significant (p<0.05) (Table 2).

Table 2. *Evaluation of malnutrition patients by gender*

	Female			Male			p-value
	(n)	Median	Min-Max	(n)	Median	Min-Max	
B12(ng/L)	756	409.5	54–1759	610	384.5	78–1394	0.03
[25(OH)D] (ng/mL)	758	31	4–190	619	29	4–154	0.01
Ferritin (µg/L)	623	29	2–154	761	31	2–190	0.01

Table 3. *Evaluation of malnutrition patients by age*

	6–24 ay			25–48			49–60			P
	n	Median	Min-Max	n	Median	Min-Max	n	Median	Min-Max	
B12(ng/L)	670	384	54–1759	505	414	109–1527	191	382	88–1145	0.01
[25(OH)D] (ng/mL)	670	29	4–190	512	30.5	4–179	195	31	6–154	0.15
Ferritin (µg/L)	675	29	2–190	513	30	2–179	196	30.5	3–154	0.13

B12, [25(OH)D], and ferritin levels according to the age of the patients are given in Table 3. For B12, the number of patients aged 6–24 months was 670 median of 384 ng/L; the number of patients 25–48 months was 505 median of 414 ng/L; and the number of 49–60 patients was 191 median of 382 ng/L. The difference between the age groups of B12 levels according to the age of the children was found to be statistically significant (P <0.05). When paired comparisons were made, p=0.015 between 49–60 and 25–48, and p=0.004 between 6–24 and 25–48 were found to be significant. For [25(OH) D] vitamin, the number of patients 6–24 months old was 670 median of 29 ng/mL, the number of patients 25–48 months was 512 median 30.5 ng/mL, the number of 49–60 patients was 195 median 31 ng/mL. The difference between age groups was not statistically significant (p>0.05). For ferritin, the number of patients aged 6–24 months was 675 median of 29 µg/L; the number of patients 25–48 months old was 513 median of 30 µg/L; and the number of 49–60 patients was 196 median of 30.5 µg/L. The difference between age groups was not statistically significant (p>0.05) (Table 3).

Discussion

Protein-energy malnutrition (PEM) is one of the most common health problems in developing countries and mostly affects children between six months and five years[12]. Protein-energy malnutrition is seen at a rate of 11% to 69.5% in children aged 0–6 years in Türkiye, depending on different regions and settlement characteristics, and emerges as an important health problem[13,14]. Malnutrition kills more than 5 million children each year. In developing countries, 1–5% of children under five die from severe malnutrition[15]. Protein-energy malnutrition is common in developing countries and poor areas of developed countries. In this case, the most affected age group is infants and children under five[16,17]. Adequate nutrition in children; It is possible by taking and using the calories, protein, vitamins, minerals and trace elements necessary for maintaining life and adequate growth[18–19]. In a study by Nahide et al. with 134 patients, it was stated that 30.6% of children had [25(OH)D] deficiency[20]. Similarly, in a study conducted in Pakistan, it was stated that [25(OH)D] deficiency in children was 33.6%[21]. A study conducted in sub-Saharan Africa between 2012 and 2014 stated that the prevalence of [25(OH)D] in children is 28%[22]. In this study, the rate of [25(OH)D] deficiency in children was 27%. This rate was slightly below the literature rates. In a study conducted by Anver J et al. (2020) on 60 children with malnutrition, they stated that 18.3% of the children had low levels of vitamin B12 and these low rates were higher in boys[23]. Ng'eno et al. examined the vitamin B12 levels of 2166 children in 2017; 30.2% of the children reported low (vitamin B12 level <150 ng/L) vitamin B12 levels, which were lower in younger children and relatively higher in females than men, and stated that it was low at high rates[24]. In a study by Karagül and Yiğit (2022), in which they examined the vitamin B12 levels of 1874 children, they reported that vitamin B12 deficiency in children was 6.29%[25]. A study by Çolak et al. (2019) on 7310 children found the rate of children with vitamin B12 deficiency to be 16.9%[26]. In this study, it was found that vitamin B12 levels were low in 5.2% of the children, the miscarriage rates were higher in men than in women, and low rates were also higher in younger age groups. Vitamin B12 deficiency rates in the literature vary from country to country and even from region to region. It can be said that this is due to the nutritional characteristics of the studied populations and the different cut-off points of vitamin B12 levels in the laboratory.

Vitamin B12 deficiency rates in our study are similar to some studies in the literature but differ from other studies. These differences are due to the high cut-off point (B12<191 ng/L). According to age groups, it is similar to the literature, vitamin B12 deficiency in childhood is a rare disease with nonspecific symptoms. It has been reported that many cases are exclusively breastfed and children of mothers with low cobalamin levels[8]. Studies have been published reporting that malnutrition in the population may differ between genders. In a study by Şensoy et al., women's malnutrition rate was higher than that of men[27]. In our study, men's malnutrition rate in was higher than women's. This may be due to the difference in the study's number of patients and population. In a study on micronutrient deficiency among children in China, it was reported that there was no significant difference in B12 between genders[28]. A study conducted in India between 6–59 months of age reported that B12 deficiency is more pronounced in children under 24 months[29]. In our study, B12 was found to be 384 ng/L in children aged 6–24 months, 414 ng/L in children aged 25–48 months, and 382 ng/L in children aged 49–60 months. We think this is because children aged 6–24 months do not get enough B12 in their breast milk. In the 25–48 month old, it is seen that the child gets enough B12 from the foods he eats. However, low B12 again draws attention at 49–60 months of age. This draws attention to the fact that the child is at the age of 4–6 to start nursery or kindergarten, and does not get enough nutrition in this period. [25(OH)D] Vitamin deficiency is common in children and is accepted as a major health problem worldwide[30]. Walli et al.'s study on [25(OH)D] reported that 56.7% of malnourished people were men[20]. In our study, the level of [25(OH)D] vitamin in females was higher than in men and a statistically significant difference was found according to gender. Walli et al.'s study on [25(OH)D] reported that malnourishment was seen in children under two[20]. When the [25(OH)D] vitamin levels are evaluated according to age groups in our study, it is seen that it is 29 ng/mL in 6–24 months old, 30.5 ng/mL in 25–48 month old, 31 ng/mL in 49–60 month old. In our study, it is noteworthy that there is an increase in [25(OH)D] vitamin levels depending on age. It can be said that this increase is due to the increase in the duration of contact with the sun due to age progression. Serum ferritin level plays an important role in the diagnosis of iron deficiency. However, acute and chronic infections and liver disorders affect ferritin levels in PEM patients and act as acute phase reactants[31]. Saka et al. reported that ferritin levels were higher in female[32]. In our study, ferritin levels were found to be significantly lower in women compared to men. The reason for this difference in our study; It may have been caused by the population included in the study and the effect of geographical conditions. Wang et al.'s study of children under the age of three reported that the prevalence of anemic was higher in children under the age of two[33]. In our study, when the ferritin level was evaluated according to age, it was found to be 29 μg/L at 6–24 month old, 30 μg/L at 25–48 month old, 30.5 μg/L at 49–60 month old. In our study, it is noteworthy that there was an increase in the ferritin levels of the patients depending on age. It can be said that this is because adequate amounts of iron are not transferred with breast milk until babies are 24 months old, and it increases with additional food supplements at later ages.

Limitations of the Study

The main limitation of our study is that it was retrospective and the height and weight of the patients were not on the system. However, different results could have been obtained had the prospective study method been used.

Conclusion

In conclusion, B12, [25(OH)D], and ferritin levels of patients with PEM may vary according to geographical regions depending on regional dietary habits. Complementary nutrition interventions often focus on the 6–24 month age range, where growth stagnation, micronutrient deficiencies and the highest incidence of infectious diseases in developing countries, also need to consider gender situations. Therefore, effective interventions in reducing malnutrition should be a high priority. While the entire 6–60 month range is important, various interventions should be targeted in the first two years.

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Conflict of Interest

The authors declare they do not have any conflict of interest.

Author (s) Contribution

VT planned, conducted research work, and drafted the manuscript. ET guided the research.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Effect of Vaccination on Biochemical and Inflammatory Markers in Hospitalized COVID-19 Patients

Hastanede Yatan COVID-19 Hastalarında Aşılamanın Biyokimyasal ve İnflamatuar Belirteçler Üzerine Etkisi

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ABSTRACT

Aim: *Coronavirus disease 2019 (COVID-19) vaccines have been proven beneficial in preventing hospitalization, serious illness, and death. However, whether immunization affects biochemical and inflammatory markers, prognostic factors in hospitalization remain unknown. The effects of vaccination status on blood biochemistry and inflammatory markers were investigated in our study of patients hospitalized with COVID-19.*

Material and Method: *A total of 107 patients comprising 67 unvaccinated and 40 vaccinated individuals who were hospitalized for COVID-19 from two different centers between November 1, 2021, and January 1, 2021, were included in our study. The patients' demographics, comorbidities, and biochemical and inflammatory markers were recorded during hospitalization.*

Results: *We identified 107 patients (62 men and 45 women; mean age, 63.7±14.8 years), with a mean age of 68.6±12.2 (37–89) and 60.7±15.5 (27–88) for the vaccinated and unvaccinated groups (p=0.005), respectively. Lymphocyte level in the 0–55 age group was 1.4±0.46×109/L in vaccinated patients and 0.96±0.5×109/L in unvaccinated patients. The difference was statistically significant (p=0.05). The lactate dehydrogenase (LDH) value was higher in the unvaccinated patients in all age groups (0–55 and over 55 years old) (p=0.04). Using logistic regression analysis, LDH was demonstrated to be a predictive factor for admission to the intensive care unit (ICU) in the 0–55 age range of unvaccinated patients. It was determined that the increase in LDH in all age groups elevates the ICU admission risk by 1.004 times.*

Conclusion: *Our study showed that COVID-19 vaccination is effective against lymphopenia induced by COVID-19 in people under 55 and LDH in people of all ages. The impact of vaccination status on LDH may be meaningful, considering that elevated LDH has been associated with a higher risk of ICU support, mortality, and complications.*

Key words: *COVID-19; COVID-19 vaccine; lactate dehydrogenase; lymphopenia*

ÖZET

Amaç: *Koronavirüs 2019 hastalığı (COVID-19) aşılarının hastaneye yatış, hastalık ağırlığı ve ölümleri önlemede yararlı olduğu kanıtlanmıştır. Ancak bağışıklanmanın hastaneye yatışta prognostik faktörler olan biyokimyasal ve enflamatuvar belirteçleri etkileyip etkilemediği bilinmemektedir. COVID-19 ile hastaneye yatırılan hastalarda aşılama durumunun kan biyokimyasal ve enflamatuvar belirteçler üzerindeki etkileri araştırılmıştır.*

Materyal ve Metot: *Çalışmamıza 1 Kasım 2021 – 1 Ocak 2021 tarihleri arasında iki farklı merkezden COVID-19 nedeniyle hastaneye yatırılan 67 aşısız, 40 aşılı olmak üzere toplam 107 hasta dâhil edildi. Hastaneye yatış sırasında hastaların demografik özellikleri, komorbiditeleri, biyokimyasal ve enflamatuvar belirteçleri kaydedildi.*

Bulgular: *Aşılı ve aşısız gruplar için yaş ortalaması sırasıyla 68,6±12,2 (37–89) ve 60,7±15,5 (27–88) olan 107 hasta (62 erkek ve 45 kadın; ortalama yaş, 63,7±14,8) değerlendirildi (p=0,005). Sıfır ila elli beş yaş grubunda lenfosit düzeyi aşılılarda 1,4±0,46×109/L, aşısızlarda 0,96±0,5×109/L idi. Fark istatistiksel olarak anlamlıydı (p=0,05). Tüm yaş gruplarında (0–55 ve 55 yaş üstü) aşılanmamış hastalarda laktat dehidrojenaz (LDH) değeri daha yüksek bulundu (p=0,04). Lojistik regresyon analizi kullanılarak, LDH'nin 0–55 yaş aralığında aşılanmamış hastalarda yoğun bakım ünitesine (YBÜ) yatış için öngörücü bir faktör olduğu gösterildi. Tüm yaş gruplarında LDH artışının yoğun bakıma yatış riskini 1,004 kat artırdığı belirlendi.*

Sonuç: *Çalışmamızda COVID-19 aşısının her yaştan insanda LDH'nin yanı sıra 55 yaş altı kişilerde COVID-19'un neden olduğu lenfopeniye karşı etkili olduğu izlenmiştir. Yüksek LDH düzeyinin daha fazla YBÜ desteği, mortalite ve komplikasyon riski ile ilişkili olduğu düşünüldüğünde, aşılama durumunun LDH üzerindeki etkisi önem teşkil edebilir.*

Anahtar kelimeler: *COVID-19; COVID-19 aşısı; laktat dehidrogenaz; lenfopeni*

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Introduction

The disease caused by a new coronavirus, which first appeared in Wuhan, China in late 2019 and subsequently spread to other countries, was named Coronavirus disease 2019 (COVID-19) in February 2020 and declared a pandemic in March by the World Health Organization (WHO). Pneumonia due to SARS-CoV-2 has caused significant morbidity and mortality worldwide, especially among those with comorbidities. As of April 2022, approximately 486 million individuals had been infected worldwide, with over 6 million deaths.

Infection can arise in numerous tissues of the body due to the extensive tissue distribution of the viral receptor in COVID-19. The etiology of the disease is influenced by viral and immune system factors[1]. COVID-19 is a systemic infection with major implications on the hematological system and hemostasis. Lymphopenia, thrombocytopenia, lactate dehydrogenase (LDH), C-reactive protein (CRP), and increased biomarkers, including serum procalcitonin and ferritin, appear to be poor prognostic indicators. In addition, high D-dimer levels are associated with disease severity and coagulopathy consequences[2].

Although vaccination is the most effective approach to managing the pandemic, the vaccination rates in most nations remain below the goal level. Effective vaccination has been shown to be potent against hospitalization, severe illness, and death from COVID-19[3–5]. However, whether immunization affects biochemical and inflammatory markers, which are prognostic factors in hospitalization, remains unknown. In our study, the effects of the vaccination status of patients hospitalized for COVID-19 on blood biochemical, inflammatory parameters, and disease course were investigated.

Materials and Methods

Our study comprised 67 unvaccinated and 40 vaccinated patients more than 18 years of age with positive polymerase chain reaction (PCR) who were hospitalized for COVID-19 between November 2021 and January 2021 at two different centers. Individuals who had at least two doses of COVID-19 vaccine (inactivated/mRNA) were considered vaccinated cases. Individuals who have not been vaccinated against COVID-19 or those for whom more than six months between the date of COVID-19 disease and the last vaccine have lapsed were considered unvaccinated cases. The patients with previous COVID-19 disease within the last 6 months, hematologic malignancies, active inflammatory diseases, pregnancy, previous liver diseases (alanine aminotransferase (ALT) and aspartate aminotransferase (AST) above 3 times of upper normal limit or bilirubin above 2 mg/dl) and kidney diseases (serum creatinine level above 1.5 mg/dl) were excluded from the study. At the time of hospitalization, the patients' demographics and comorbidities like diabetes mellitus, systemic hypertension, coronary heart disease, chronic lung diseases, and cerebrovascular accidents were recorded. In addition, full blood count, CRP, procalcitonin, D-dimer, LDH, ferritin, and fibrinogen levels were recorded. Oxygen saturation, oxygen support therapy, length of stay, and intensive care requirements were evaluated. All patients were evaluated for the lung involvement of more than 50% during initial hospitalization by two chest disease specialists separately. The data were analyzed using the Statistical Package for Social Sciences (SPSS) program version 22 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used as the normal distribution test. Parametric tests were prioritized in the analysis of data that fit the normal distribution, while nonparametric tests were preferred in the analysis of data that did not fit the normal distribution. The Mann-Whitney U test and binary logistic regression were used in the analysis. $P<0.05$ was considered statistically significant. The study protocol was approved by the ethics committee.

Results

We enrolled 107 patients (62 men, 45 women; mean age 63.7±14.8 years) in this study. There are two types of vaccines available in Türkiye. Amongst the vaccinated patients, eight received two doses of BNT162b2 (BioNTech), six received two doses of Sinovac (whole-virion inactivated vaccine), 13 received three doses of Sinovac, 12 received two doses of Sinovac and one dose of BioNTech, and one received two doses of Sinovac and two doses of BioNTech. The mean age of the patients in the vaccinated and unvaccinated groups was 68.6±12.2 (37–89) and 60.7±15.5(27–88) ($p=0.005$), respectively. The vaccinated group was older than the unvaccinated group, but there was no statistical difference in terms of gender or comorbidity between the two groups (Table 1). At least one comorbidity was present in 67.5% of the vaccinated individuals and 68% of the unvaccinated patients, respectively. The most common comorbidity was hypertension (42.5%) in the vaccinated group and diabetes mellitus (25.4%) in

Table 1. *Distribution of vaccinated and unvaccinated patients based on demographic and radiological features, oxygen saturation, comorbidity, and mortality*

	Vaccinated (n: 40)(%)	Unvaccinated (n: 67)(%)	p
Gender			0.17
Male	26 (65%)	36 (46%.3)	
Female	14 (35%)	31(53%.7)	
Mean age (year)	68.6±12.2 (37–89)	60.7±15.5 (27–88)	0.005
Oxygen saturation (%)	90.4±6.4 (75–98)	89.4±6.6 (70–98)	0.5
Radiological involvement >50%	10 (25%)	24 (35%.8)	0.3
Length of hospitalization (day)	12.4±8.2	13.6±13	0.11
ICU requirement	10 (25%)	21 (31%.3)	0.31
Exitus	2 (5%)	6 (9%)	0.36
Comorbidity	27 (67%.5)	46 (68%.7)	0.53
HT	17 (42%.5)	16 (23%.9)	0.037
DM	12 (30%)	17 (25%.4)	0.38
CVD	9 (22%.5)	15 (22%.4)	0.58

ICU: intensive care unit; HT: hypertension; DM: diabetes mellitus; CVD: cardiovascular disease.

Table 2. *At the time of admission for hospitalization, 104 patients' mean (± SD) laboratory results.*

	Vaccinated (n=40)	Unvaccinated (n=67)	p
White blood cell ($\times10^9$/L)			
>55 year old	8.7 (±4.4)	9.3 (±5.9)	0.5
≤55 year old	8.8 (±1, 7)	6.84 (±3.4)	0.1
Neutrophil ($\times10^9$/L)			
>55 year old	7.01 (±3.1)	7.3 (±5.5)	0.4
≤55 year old	6.3 (±0.9)	5.4 (±3.3)	0.2
Lymphocyte ($\times10^9$/L)			
>55 year old	1.03 (±0.6)	1.25 (±1.5)	0.9
≤55 year old	1.4 (±0.5)	0.96 (±0.53)	0.05
Hemoglobin (g/dL)			
>55 year old	12 (±2.2)	12 (±2.2)	0.7
≤55 year old	12.5 (±1.2)	13.1 (±1.6)	0.5
Platelets ($\times10^9$/L)			
>55 year old	213 (±78)	229 (±139)	0.8
≤55 year old	208 (±46)	234 (±102)	0.7
LDH (U/L)			
>55 year old	375 (±255)	390 (±173)	0.05
≤55 year old	255 (±88)	455 (±238)	
Ferritin (ng/m)			
>55 year old	401 (±402)	554 (±1174)	0.6
≤55 year old	187 (±162)	495 (±811)	0.4
CRP (mg/L)			
>55 year old	120 (±94)	99 (±73)	0.4
≤55 year old	70 (±78)	63 (±47)	0.6

LDH: Lactate dehydrogenase; CRP: C reactive protein.

the unvaccinated group. There was no statistically significant difference in oxygen saturation levels between the vaccinated and unvaccinated groups (90.4±6.4 vs 89.4±6.6, p=0.5). Those with more than 50% radiological involvement in the vaccinated and non-vaccinated groups were determined to be 25% and 35.8% (p=0.3), respectively. There was no statistically significant difference between the non-vaccinated and vaccinated groups on the day of hospitalization (13.6±13 vs 12.4±8.2, p=0.11) and the requirement for intensive care (25% vs 31.3%, p=0.31). Table 1 shows the distribution of vaccination status based on demographic and radiological features, oxygen saturation during hospitalization, comorbidities, and death. Given that biochemical and inflammatory markers were evaluated between the two groups, the lymphocyte level in the 0–55 age group was 1.4±0.46 x 10^9/L in the vaccinated and 0.96±0.5x 10^9/L in the unvaccinated patients. The difference was statistically significant (p=0.05). The LDH value was higher in the unvaccinated patients in

all age groups (0–55 and over 55 years old) (p=0.04). Using logistic regression analysis, LDH was demonstrated to be a predictive factor for admission in the intensive care unit (ICU) in the 0–55 age range of unvaccinated patients. It was determined that the increase in LDH in all age groups raises the risk of admission to the ICU by 1.004 times. No significant differences in the serum levels of CRP, procalcitonin, D-dimer, ferritin, or fibrinogen levels were observed between the two groups (Table 2). Since fibrinogen and D-dimer could not be studied over a period of time in the hospital, these parameters were evaluated in only 66% and 65% of the patients, respectively.

Discussion

The results of our study showed that efficient COVID-19 vaccination is effective against lymphopenia induced by COVID-19 in people under the age of 55, as well as LDH in people of all ages. Lactate dehydrogenase was demonstrated to be a predictive factor for admission to the ICU in unvaccinated patients. It was determined that the increase in LDH in all age groups raises the risk of admission to the ICU by 1.004 times.

Despite new vaccines and diagnostic approaches, COVID-19 is still a global health issue. The immunological response to SARS-CoV2 infection remains complicated and poorly understood. Malik et al.[6] found in their systematic review and meta-analysis that specific biomarkers were associated with poor outcomes in hospitalized COVID-19 patients. These biomarkers included decreased lymphocyte count, decreased platelet count, and elevated CRP, creatine kinase, procalcitonin, D-dimer, LDH, AST, ALT, and creatinine. Other studies showed that lower lymphocyte count was a typical feature of SARS-CoV-2 infection and associated with increased mortality, ARDS, ICU care, and severe COVID-19[7,8]. In our study, lymphocyte counts were significantly higher in the vaccinated group under 55 years of age compared to the unvaccinated group. According to Huang et al.'s meta-analysis[8], the correlation between lymphopenia and severe COVID-19 was higher in younger patients. One potential hypothesis to explain such a result was that immune system aging may result in a relatively consistent decrease in lymphocyte count due to a relatively "nonreactive" immunological state. However, highly active lymphocyte kinetics may be affected by a wide range of insults and comorbidities in the younger population, resulting in a relatively higher mean difference. According to this hypothesis, the vaccine's enhanced effect on lymphocyte count in our patient population can be explained by the more active cell kinetics in the young population. Some factors have been suggested to explain lymphopenia in COVID-19. The first is that lymphocytes express ACE2, which is known as a SARS-CoV-2 receptor; thus, the virus attacks lymphocytes directly[9]. The second theory is that elevated proinflammatory cytokines in COVID-19 patients may result in lymphocyte apoptosis[10]. Another factor is concomitant lactic acid acidosis, which is common in cancer patients and may inhibit lymphocyte proliferation[2].

High LDH levels reflect cellular damage due to plasma membrane damage. Han et al.[11] found that the levels of LDH in the early stage of severe COVID-19 cases can be a good predictor of lung injury. Increased LDH has been associated with a higher risk of ARDS, ICU support, and death[2]. Das et al.[12] demonstrated that elevated peak LDH levels in MERS-CoV patients might suggest underlying lung tissue damage. High initial and peak LDH levels have also been found to be good independent predictors of poor clinical outcomes in SARS patients. Furthermore, high peak LDH levels were independent indicators of more severe lung injury in this study[13].

In recent investigations, non-survivors had higher LDH, procalcitonin, and serum ferritin levels than survivors[2]. Other laboratory values did not show a statistically significant difference between the vaccinated and unvaccinated groups in our study, which may be attributed to the limited number of patients. At the same time, the vaccinated group was composed of mostly elderly patients. The fact that the vaccinated and unvaccinated groups were different in age may have made us unable to clearly observe the response of the vaccine to inflammatory parameters. For the same reason, the more than 50% radiological involvement, hospitalization, and oxygen saturation level, which may reflect the impact of vaccination on the course of the disease, may be caused by the vaccine recipients' older age and the small number of patients in the trial. Future research should concentrate on changes in biomarker levels in a larger population. Probable discrepancies between the vaccinations administered may also become apparent.

This study has some limitations. For a certain period of time, fibrinogen and D-dimer could not be analyzed in our hospital. As a result, the number of samples tested for coagulopathy is less than the total number of

samples. Another limitation is that the vaccinated and unvaccinated groups were similar in terms of comorbidity and gender, but the vaccinated group was older. This could have an impact on the blood parameters measured in our research. Biochemical differences between the subgroups of vaccinated individuals could not be examined due to the low number of vaccinated patients.

Conclusions

The results of our study underscore that COVID-19 vaccination is effective against lymphopenia induced by COVID-19 in people under the age of 55, as well as LDH in people of all ages. Therefore, the impact of vaccination status on LDH may be important, considering that elevated LDH has been associated with a higher risk of ARDS, ICU support, mortality, and complications.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Is the Success and Safety of Retrograde Intrarenal Surgery Related to the Opacity Status of Kidney Stones? A Critical Evaluation

Retrograd İntrarenal Cerrahinin Başarısı ve Güvenliği Böbrek Taşlarının Opaklık Durumuyla İlişkili midir? Kritik Bir Değerlendirme

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ABSTRACT

Aim: *This present study aimed to investigate the possible effect of the opacity status of kidney stones on the success and complication rates observed during and after retrograde intrarenal surgery (RIRS).*

Material and Method: *This study analyzed the data of 642 kidney stone cases who underwent flexible ureteroscopy between February 2014 and April 2022. In all patients, non-contrast computed tomography and kidney-ureter-bladder (KUB) radiography were performed preoperatively to evaluate the anatomy of the collecting system and the structure of the kidney stone. The patients were divided into two groups as opaque and non-opaque according to the opacity evaluation based on the preoperative KUB image. While 359 patients had radiopaque stones, 283 patients had non-opaque stones. Both groups were compared in terms of certain preoperative data, postoperative outcomes, and complications.*

Results: *Cases with non-opaque stones were ahead of the other group in terms of the American Society of Anaesthesiologists (ASA) score, diagnosed diabetes mellitus, Charlson Comorbidity Index, and body mass index. In the third postoperative month, there was no statistically significant difference between the two groups in terms of stone-free status (72.1% vs 75.3%, p=0.212). Postoperative infective complications and hospital stays were comparable across the two groups, despite the non-opaque stone group being substantially older and farther along in terms of comorbidities.*

Conclusion: *This study's results showed that RIRS could be applied with successful outcomes regardless of the opacity status of renal stones.*

Key words: *opaque; non-opaque; RIRS; kidney stones*

ÖZET

Amaç: *Bu çalışmada, böbrek taşlarının opasite durumunun, retrograd intrarenal cerrahi (RIRS) sırasında ve sonrasında gözlenen başarı ve komplikasyon oranları konusundaki potansiyel etkisi araştırıldı.*

Materyal ve Metot: *Çalışmamızda Şubat 2014-Nisan 2022 tarihleri arasında böbrek taşı nedeniyle fleksibl üreteroskopi yapılan 642 hastanın verileri incelendi. Tüm hastalarda, preoperatif olarak toplayıcı sistemin anatomisini ve böbrek taşının yapısını değerlendirmek amaçlı kontrastsız bilgisayarlı tomografi ve böbrek-üreter-mesane grafisi uygulandı (KUB). Preoparatif dğerlendirmedeki KUB görüntüsü baz alınarak yapılan opasite değerlendirmesine göre hastalar opak ve non-opak olamak üzere iki gruba ayrıldı. Üç yüz elli dokuz hastada radyoopak taş bulunurken, 283 hastada non-opak taş saptandı. Her iki grup, belirli preoperatif veriler, postoperatif sonuçlar ve komplikasyonlar açısından karşılaştırıldı.*

Bulgular: *Non-opak taşlı olgular American Society of Anesthesiologists (ASA) skoru, Charlson Komorbidite İndeksi, diabetes mellitus tanısı ve vücut kitle endeksi açısından diğer grubun önündeydi. Ameliyat sonrası 3. ayda her iki grup taşsızlık açısından anlamlı bir fark göstermedi (%72,1'e karşı %75,3, p=0,212). Opak olmayan taş grubu ortalama yaş komorbiditeler açısından anlamlı olarak daha önde olmasına rağmen, postoperatif enfeksiyöz komplikasyonlar ve hastanede kalış süreleri her iki grupta da benzerdi.*

Sonuç: *Sonuçlarımız, böbrek taşlarının opasite durumuna bakılmaksızın RIRS'nin başarılı sonuçlarla uygulanabileceğini gösterdi.*

Anahtar kelimeler: *opak; non-opak; RIRS; böbrek taşları*

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Introduction

The interventional treatment of symptomatic urinary stones has changed tremendously in the last three decades due to advances in instrumentation and technology[1]. As a result of these advances, minimally invasive treatment alternatives such as extracorporeal shock wave lithotripsy (ESWL), retrograde intrarenal surgery (RIRS), and percutaneous lithotripsy (PCNL) have largely replaced open surgery with prominently safe and effective results[2]. Regarding the minimally invasive surgery of upper urinary system stones, PCNL is performed in a single session with significantly higher stone-free rates (SFR) for the treatment of large stones (>20 mm). On the other hand, ESWL and RIRS demonstrate comparable success rates to PCNL for moderate-sized (10–20 mm) stones and have a less invasive nature than PCNL[3]. The European Association of Urology (EAU) Urolithiasis Guidelines recognize ESWL and RIRS modalities as equally effective treatment modalities for kidney stones less than 20 mm in diameter; PCNL is still recommended as the first-line treatment for stones larger than 20 mm[4].

As mentioned above, as a result of the developments in flexible fiberoptic endoscopy systems and the use of the Holmium-YAG laser in stone disintegration, RIRS has significantly altered the endourological management of medium-sized kidney stones in the last two decades[5]. Urologists perform many procedures, including ureteroscopy, under fluoroscopic guidance[6]. Fluoroscopy helps the surgeon to evaluate the anatomy of the involved reno-ureteral unit, the position of the ureteric access sheath, the location of the guidewire, and lastly, give information about the presence of kidney stones and fragments in the collecting system during the procedure. While most calcium-containing stones can be easily seen on X-ray, struvite, apatite, and cystine stones are semi-opaque and are not very clearly identifiable on the kidney-ureter-bladder radiograph (KUB) examination. However, radiolucent stones such as uric acid, ammonium urate, and xanthine stones can not be observed in KUB unless they contain other components[7]. Visibility of the stone on preoperative radiological images is highly helpful in determining the stone (s), monitoring the course of the procedure in terms of the efficiency of disintegration, and evaluating the presence/size of the residual fragments after the procedure, particularly during endourological stone removal procedures. For this reason, it has been a matter of interest whether the visualization of the stone in fluoroscopy during the operation is a condition that affects the success of the operation. Since the primary goal of the research was to look at how the stone's detectability in fluoroscopy during RIRS influences the surgery, the opacity was categorized using preoperative KUB, which has a technical infrastructure comparable to fluoroscopy.

This present study aimed to investigate the possible effect of the opacity status of kidney stones on the success and complication rates observed during and after retrograde intrarenal surgery (RIRS).

Material and Method

Patients who attended our clinic and were treated for kidney stones with RIRS between February 2014 and April 2022 were evaluated retrospectively. All experiments were conducted in accordance with the Helsinki Declaration and were sanctioned by our institution's ethical committee (80576354–050–99/93). Patients who had ureteral stents placed prior to surgery, those with ureteral strictures, those with a single kidney or an ectopic kidney, and those who had a ureteral rupture or avulsion during surgery were not included in the study. All study requirements were met for 642 patients.

Kidney-ureter-bladder radiography and non-contrast computerized tomography (NCCT) were conducted on all patients to analyze details about the collecting system's anatomy and the characteristics of the stones. Whenever it was deemed required, further radiological assessment procedures and urinary ultrasonography (USG) were carried out. Non-opaque stones' sizes were calculated using the greatest diameter established in the NCCT, whereas opaque stones' sizes were estimated utilizing KUB.

Before the operation, it was required that the patients' urine cultures were negative. Data from NCCT, KUB, and USG were examined in accordance with the opacity features of the stones to ascertain whether or not the stones had been cleared 3 months after surgery. Stone particles less than 3 mm in size were regarded to have been successfully removed.

These operations were all performed while the patient was in the lithotomy position and under general anesthesia. With the aid of fluoroscopy, a ureteral access sheath (UAS) was inserted (9.5/11.5 Fr; Cook Medical; Bloomington, IN). A fiberoptic flexible ureteroscope of 7.5 Fr diameter was used to access the collecting system (Storz FLEX-X2). The stones were disintegrated using a holmium laser and a 273 fiber.

Fragments >3 mm were retrieved from patients with a nitinol basket (ZeroTipTM; Cook Urological Inc.). A few of the smaller pieces were permitted to pass through on their own. During the preoperative examination, the KUB images of the patients were categorized into two groups according to the status of opacity shown by the stones. Group O is for cases whose stones are opaque in the KUB, while Group NO is for those whose stones are translucent.

Statistical Analysis

Utilizing IBM Statistical Package for Social Sciences (SPSS) program version 22.0, statistical analyses were carried out (IBM Inc, Chicago, IL, USA). To determine whether or not the data were normally distributed, we utilized the Kolmogorov-Smirnov test. The means were compared using an independent sample t-test with normally distributed data. When comparing non-normally distributed samples, the Mann-Whitney U test was utilized. The Chi-square or Fisher's exact test was used to evaluate categorical data. We used a cutoff of p 0.05 to indicate statistical significance.

Results

The results showed no significant difference between the two groups regarding gender distribution. However, Group NO has a significantly higher mean age value when compared with the cases with opaque stones. (48.43±14.71 vs 52.86±14.85, p<0.001). In addition, patients in Group NO had higher mean ASA scores and a higher rate of diagnosed DM (9.7% vs 21.6%, p<0.001) than the other group. Likewise, patients in Group NO were found to have higher Charlson Comorbidity Index (1.32±1.51 vs 2.04±2.03, p<0.001) values and higher mean body mass index values (27.44±4.39 vs 28.96±4.89, p<0.001). The rate of multiple stones was significantly higher (51.3% vs 43.1%, p=0.024) in Group O. Also, the patients in Group NO were found to have higher usage of anticoagulants (10.6% vs 18.7%, p=0.002) and alpha-blockers (5.0% vs 8.8%, p=0.039). The clinical characteristics and laboratory results of patients are detailed in Table 1. Considering the laboratory findings, although the preoperative hemoglobin value was higher in Group NO (14.48±1.97 vs 14.16±1.96, p=0.046), no significant difference was found in postoperative values (14.43±1.86 vs 14.18±2.08, p=0.064). Evaluation of the hospitalization (2.56±2.54 vs

Table 1. *Clinical characterization and laboratory findings of patients*

		Group O (n=359)		Group N (n=283)		p
Gender	Male	235	65.5%	180	63.6%	0.342
	Female	124	34.5%	103	36.4%	
Age		48.43	±14.71	52.86	±14.85	<0.001
ASA	ASA 1	129	35.9%	62	21.9%	<0.001
	ASA 2	209	58.2%	187	66.1%	
	ASA 3	21	5.8%	34	12.0%	
Diabetes mellitus		35	9.7%	61	21.6%	<0.001
BMI (kg/m²)		27.44	±4.39	28.96	±4.89	<0.001
Charlson comorbidity index [Median (IQR)]		1	0–2	2	0–3	<0.001
Stone size (mm)		12.72	±5.26	12.22	±5.87	0.255
Lateralization	Right	161	44.8%	135	47.7%	0.261
	Left	198	55.2%	148	52.3%	
Localization	Other calyxes	226	63.0%	180	63.6%	0.465
	Lower calyx	133	37.0%	103	36.4%	
Parenchymal thickness (cm)		25.84	±7.83	26.64	±8.16	0.208
Number of Stones	Single	175	48.7%	161	56.9%	0.024
	Multiple	184	51.3%	122	43.1%	
Infundibulopelvic angle (º)		46.47	±16.70	46.75	±15.30	0.825
Alpha-blocker use		18	5.0%	25	8.8%	0.039
Anticoagulant use		38	10.6%	53	18.7%	0.002
Hydronephrosis		143	39.8%	128	45.2%	0.098
Preop Hg (g/dL)		14.48	±1.97	14.16	±1.96	0.046
Preop Cr (mg/dL)		0.97	±0.39	1.01	±0.41	0.193

ASA: American Society of Anesthesiologists; Hg: Hemoglobin; Cr: Creatinine; Postop: Postoperative; Preop: Preoperative.

Table 2. *Postoperative follow-up data*

	Group O (n=359)		Group N (n=283)		p
Postop Hg (g/dL)	14.43	±1.86	14.18	±2.08	0.064
Postop Cr (mg/dL)	0.94	±0.38	0.98	±0.40	0.252
Hospitalization (Day)	2.56	±2.54	2.50	±1.80	0.724
Postop fever	13	3.6%	9	3.2%	0.469
SFR (Postop 3rd month)	259	72.1%	213	75.3%	0.212

Hg: Hemoglobin; Cr: Creatinine; Postop: Postoperative; Preop: Preoperative; SFR: Stone-free rate

2.50±1.80, p=0.724) period and postoperative fever (3.6% vs 3.2%, p=0.469) rates again did not show any significant difference between the two groups. Last but not least, the SFR of both groups, evaluated at the postoperative 3rd month, was comparable (72.1% vs 75.3%, p=0.212) between the two groups of cases. Postoperative follow-up data were given in Table 2.

Discussion

With promising developments in endourology, kidney stone treatment with RIRS has become a game changer[8]. Plain X-ray was recommended to provide additional information in the presence of computed tomography rather than being a primary diagnosis tool in urolithiasis[9]. The issue which should not be ignored is that not all patients with urinary tract stones detected by CT can be seen in KUB. In a study performed, only 59 % of the ureteral stones detected on CT could be visualized in the KUB[10].

Gucuk et al., on the other hand, adopted a different strategy and sought to determine the effect of Hounsfield Units (HU) found in preoperative NCCT on the ultimate success of PCNL[11]. When the CT HU was above 1000, the SFRs were supposedly higher. Stones with HU 1000, which includes both opaque and lucent stones in KUB, had the lower SFR. According to a different study, 630 was the appropriate cut-off value for HU evaluated in NCCT to be perceived as opaque in KUB[12]. In a study looking at ureteral stones, this value was 800[13]. In other words, it is obvious that there is no predetermined threshold value for the HU value established in NCCT that causes stones to appear opaque in KUB. As a result, we select the KUB, which shares the same technological background as fluoroscopy, to classify the stones' opacity. We thought that KUB would provide us with more useful information regarding how well we could see the stone under fluoroscopy. Gucuk et al. classified stones exceeding 350 as opaque in contrast to us based on the HU value determined by the NCCT. The mean SFR was similarly lower with non-opaque stones, according to this study's findings[11].

One of the main findings in our study was that the patients in Group NO consisted of older cases associated with more comorbidities. Uric acid stones are the most prevalent kind of radiolucent stone[14]. Age, metabolic syndrome, and diseases such as diabetes mellitus increase the frequency of these stones[15]. This may be one of the reasons why Group NO was found to have a higher mean age value, ASA, Charlson Comorbidity Indices, presence of diabetes, and use of anticoagulants in our study. However, it would be speculative to claim this assumption since we do not have the stone analysis results of the patients. In another study focusing on this subject, patient groups with radiopaque and radiolucent stones showed a similar age distribution[16]. Similarly, in a study investigating the effect of stone opacity characteristics on percutaneous nephrolithotomy results, patients with opaque and non-opaque stones were found to have similar values in terms of age and body mass index (BMI)[17]. Contrary to the findings of this research, our Group NO patients had considerably higher mean BMI values. In addition, alpha-blocker use was greater in Group NO, according to our findings.

Previous research compared the efficacy and complications of RIRS[16], the difference between the two groups in terms of SFR and complications was insignificant. Still, in this investigation, researchers counted stones smaller than 4 mm as residual stones. Despite including stones under 3 mm in size as residual fragments in our analysis, we still did not find a discernible difference in SFR between the two groups. Fever is a predictor of postoperative infective complications, but we found no measurable difference in its occurrence across the groups. Although one group in our research did have a greater mean age value and related comorbidities, it is interesting to see that success rates and consequences are similar.

On the other hand, regarding the number of stones, the percentage of multiple stones was higher for Group O

in our study. Multiple stones have been proven to have a lower SFR after RIRS than single stones had in another research[18]. After a single treatment session, there was no significant difference between the groups in terms of SFR regardless of stone opacity, which was the primary outcome we were examining. It was not looked at whether or if varying quantities of stones affected SFR.

This present study suggested that fluoroscopy did not contribute positively to the success and safety rates of RIRS, where the results were found mostly to be related to surgical experience[19]. Although the primary goal of endoscopic stone surgery is to remove the stone load from the collecting system as much as possible in a single session, it is critical to reduce radiation exposure throughout the procedure[20]. We were inspired to look for strategies to limit the use of fluoroscopy during flexible ureteroscopic surgery because we had similar success treating stones that were not apparent on fluoroscopy. Given our data and previous literature in the field of radiation-free endoscopic stone treatment, it is highly likely that this will not be the wrong choice[21,22].

This research has certain limitations. The most important limitation is that our study has a retrospective design. In addition, our groups differ from each other in terms of some clinical data and demographic inputs. We did not have stone or metabolic analysis results that may explain this difference. The fact that the two groups showed different results in terms of demographic data can be seen as a limitation, but it is still significant that the complications were comparable between the groups. Despite all these limitations, this study will contribute to the literature as it reaches a sufficient number of patients and seeks ways to use fluoroscopy less during the operation.

Conclusion

Our results showed that RIRS could be applied with successful outcomes regardless of the opacity status of renal stones. Although patients with non-opaque stones appear to be older with higher comorbidities, both groups were found to have similar postoperative infectious complication rates. This study shows that the capacity to recognize kidney stones in intraoperative fluoroscopy does not improve the efficacy of RIRS for renal calculus, hence we think additional research needs to be done on RIRS without fluoroscopy. We think that further prospective cohort studies are required, ideally with a bigger sample size and a wider range of other variables, to shed light on this important topic.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Assessment of the Relationship Between Serum Albumin to Creatinine Ratio and Long-Term Mortality in Patients with ST-Segment Elevation Myocardial Infarction

ST-Segment Yükselmeli Miyokard İnfarktüslü Hastalarda Serum Albümin/Kreatinin Oranı ile Uzun Dönem Mortalite Arasındaki İlişkinin Değerlendirilmesi

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ABSTRACT

Aim: *In recent years, an increasing number of evidence suggests that the inflammation plays a significant role in the pathophysiology of ST-segment elevation myocardial infarction (STEMI). The association between inflammatory markers and renal functions in STEMI prognosis has been previously reported. No studies have investigated the ability of the serum albumin to creatinine ratio (sACR), defined as a prognostic score, to predict long term mortality in patients experiencing STEMI.*

Material and Method: *This retrospective study included 1133 patients experiencing STEMI. The study population was divided into two groups according to survival and analyzed whether the sACR was an independent predictor of long-term mortality.*

Results: *Out of 1133 patients, death was observed in 112 patients (9%) an average follow-up of 55 months. During the total follow-up period, patients were divided into two groups according to survival. Compared to the survival group, long-term mortality group was older, had a higher SYNTAX score and a lower sACR (p<0.05). Independent predictors of long-term mortality were found to be age, smoking, LVEF, and sACR (HR: 0.627 95% CI: 0.533–0.737; p<0.001). Receiver operating characteristic (ROC) curve comparisons for long-term mortality demonstrated that the sACR was a better predictor than both albumin and creatinine, separately.*

Conclusion: *The present study revealed that sACR is an independent predictor of long-term mortality in patients experiencing STEMI. As a marker which can be easily obtained and calculated, sACR can be an effective parameter used for prognosis estimation of STEMI.*

Key words: *serum albumin; creatinine; sACR; mortality; ST-segment elevation myocardial infarction*

ÖZET

Amaç: *Son yıllarda artan sayıda kanıtlara dayanarak enflamasyonun ST-segment yükselmeli miyokard enfarktüsünün (STEMI) patofizyolojisinde önemli bir rol oynadığını gözlenmiştir. ST-segment yükselmeli miyokard enfarktüsü prognozunda enflamatuvar belirteçler ile böbrek fonksiyonları arasındaki ilişki daha önce bildirilmiştir. Prognostik bir skor olarak tanımlanan serum albüminin kreatinin oranının (sACR) STEMI yaşayan hastalarda uzun vadeli mortaliteyi tahmin etme yeteneğini araştıran hiçbir çalışma yoktur. Bu çalışmada sACR, STEMI hastalarında prognostik önemi incelenmiştir.*

Materyal ve Metot: *Bu retrospektif tasarımlı çalışma, STEMI nedeniyle başvuran 1133 hastayı içermektedir. Çalışma popülasyonu, sağkalıma göre iki gruba ayrıldı ve sACR'nin uzun vadeli mortalitenin bağımsız bir göstergesi olup olmadığı analiz edildi.*

Bulgular: *Ortalama 55 aylık takipte, 1133 hastanın 112'sinde (%9) ölüm görüldü. Toplam takip süresi boyunca hastalar sağkalımlarına göre iki gruba ayrıldı. Sağkalım grubu ile karşılaştırıldığında, uzun dönem mortalite grubu daha yaşlıydı, SYNTAX skoru daha yüksek ve sACR daha düşüktü (p<0,05). Uzun vadeli mortalitenin bağımsız belirteçleri yaş, sigara, LVEF ve sACR olarak bulundu (HR: 0,627 %95 CI: 0,533–0,737; p<0,001). Uzun vadeli mortalite için ROC eğrisi karşılaştırmaları, sACR'nin hem albümin hem de kreatinin ayrı ayrı daha iyi bir belirleyici olduğunu gösterdi.*

Sonuç: *Bu çalışma, sACR'nin STEMI yaşayan hastalarda uzun vadeli mortalitenin bağımsız bir belirleyicisi olduğunu ortaya koydu. Kolaylıkla elde edilebilen ve hesaplanabilen bir belirteç olan sACR, STEMI'nin prognoz tahmininde kullanılan etkili bir parametre olabilir.*

Anahtar kelimeler: *serum albumin; kreatinin; sACR; mortalite; ST-segment yükselmeli miyokard enfarktüsü*

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Introduction

Ischemic heart disease is the most common cause of death worldwide and its incidence continues to increase[1]. Due to modern medical treatments and developments in reperfusion methods, in-hospital and long-term mortality rates have decreased[2,3]. Despite advances in potent medical drugs and percutaneous intervention techniques, ST-segment elevation acute myocardial infarction (STEMI) continues to be an important cause of death over the world[4].

In patients with STEMI, various biomarkers and biomarkers combinations have been investigated for the prediction of mortality. Serum albumin (SA) is a plasma protein and has an inverse association with inflammation and activation of the platelets. In addition, previous studies showed that plasma serum albumin level is a risk factor for the development of coronary artery disease[5–10]. Hypoalbuminemia, which defined as serum albumin level below 3.5 g/dl in plasma and associated with an enhanced risk of arterial and venous thrombosis, and cardiovascular and all-cause mortality in patients with acute coronary syndromes (ACS)[11–15].

There is a significant and inverse relationship between kidney functions and adverse cardiovascular events. In the literature, it has been shown that decreased renal functions is associated with increased mortality in patients with STEMI. High serum creatinine (sCr) concentration at admission is related with heightened risk of in-hospital and long-term mortality in patients with ACS. Besides, a rise in sCr levels in STEMI patients undergoing primary percutaneous coronary intervention (pPCI) during hospitalization is associated with poor myocardial blood flow and elevated risk of long-term mortality[16–19].

As a newly defined variable, serum albumin-creatinine ratio (sACR)[20] has been shown as a predictor of short-term mortality in ACS. However, the relationship between sACR and long-term mortality in patients with STEMI is unclear. We designed this study to investigate the importance of sACR in long-term mortality prediction in patients with STEMI.

Materials and Methods

Study Population

This was a retrospective study implemented between January 2015 and May 2017. A total of 1257 consecutive STEMI patients who had undergone primary percutaneous coronary intervention (pPCI) in Kafkas University Hospital were accepted to the study. Patients who were first diagnosed with STEMI and discharged healthy were included in the study population. Patients who were referred to elective or emergency coronary artery bypass graft surgery (CABG) or patients with history of CABG, chronic renal disease (hemodialysis dependent), malignancies, febrile conditions, autoimmune disorders, chronic hepatopathy or incomplete medical files or records were excluded from the study.

A total of 1133 patients met the inclusion criteria and were enrolled the study. The primary endpoint was all-cause mortality. In-hospital and post-discharge outcomes were collected from medical records, during hospital visits, or via telephone interviews.

The research protocols were as per the Declaration of Helsinki; the study was approved by the local ethical board.

Data Collection

Patients' data were obtained from hospital records and patient files. Patients' vital signs, treatment before admission, electrocardiographic and coronary angiographic features were collected at the time of admission. Information about laboratory tests and echocardiographic variables, in-hospital complications, and treatments received during hospital stay were collected before discharge from the electronic medical records at Kafkas University Hospital.

Laboratory and ECG Measurements

The STEMI diagnosis was made based on the current clinical guidelines[21]. Blood samples were collected from all patients during hospital admission and before discharge for the measurement of the values of albumin, creatinine and glucose along with other biochemical and hemogram parameters. sCr and SA levels were determined using an automatic biochemical analyzer (Roche Diagnostics Cobas 8000 c502, Indianapolis, USA). The sACR (g/mg) was calculated by dividing the serum albumin level by the creatinine level. The estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) formula. Acute kidney injury was defined as an increase of 25% or 0.5 mg/dL in creatinine level compared to that at baseline within 48 hours.

Table 1. *Baseline clinical characteristics of sACR groups in STEMI patients*

	All-Cause of Mortality			
Variables	Long-term survivals, n: 1021	Long-term mortality, n: 112	Total patients, n: 1133	p value
Age	55±12	66±13	56±12	<0.004
Female gender, n (%)	177(17.3%)	26(23.2%)	203(17.9%)	0.124
Diabetes, n (%)	222(21.7%)	42(37.5%)	264(23.3%)	<0.004
Hipertansiyon, n (%)	397(38.8%)	64(57.1%)	461(40.7%)	0.002
Smoking, n (%)	445(43.6%)	59(52.7%)	504(44.5%)	0.066
Killip class >1, n (%)	134(13.1%)	47(42%)	181(16%)	<0.001
Systolic blood pressure, (mm/Hg)	132±29	125.6±46	132±31	<0.004
Heart rate, bpm	77±15	81±23	77±16	<0.004
Hemoglobin (g/dL)	13.7±1.7	12.9±2.2	13.8±1.8	<0.004
WBC Count (/1000)	12.1±3.5	13.9±5.5	12.8±3.8	<0.004
Glucose (mg/dL)	126(104–165)	148(116–233)	127(105–171)	<0.004
sACR	4.5±1.1	3.4±1.5	4.4±1.2	<0.001
Creatine (mg/dl)	0.88±0.21	1.19±0.49	0.91±0.27	<0.004
Serum albumin (g/dl)	3.77±0.47	3.41±0.52	3.75±0.48	<0.004
Peak Creatine Kinase MB (ng/mL)	170.5(100–298)	359(178–498)	180.5(103–321)	<0.004
Left Ventricular Ejection Fraction (%)	48±8	38±9	46±8	<0.001
Bazal syntax score	16.3±4.3	19.3±5.3	16.6±4.5	<0.001

sACR: serum albumin to creatinine ratio; WBC: white blood cell.

Statistical Analysis

The statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) program version 22.0 (SPSS Inc., Chicago, IL). Kolmogorov-Smirnov test was used for the normality of the data set. Continuous variables were expressed as mean ± standard deviation or median [interquartile range] (25th–75th percentiles) in terms of data distribution and normality. T-test or Mann-Whitney U test was performed to compare variables between two groups. Continuous variables were compared between the groups using analysis of variance and the Kruskal-Wallis H-test. Fisher's exact test or chi-square test was used for comparison of Categorical variables that were presented as numbers (percentage). Multivariate Cox regression analysis was performed to identify independent predictors of long-term death using variables that showed a statistically significant association with all-cause death in univariate analysis. Multicollinearity between the serum creatinine/albumin ratio and sCr and SA levels was assessed by eigenvalues and condition indices. Linearity was tested following the logarithmic transformation of each parameter. The receiver operating characteristic (ROC) curve was utilized to derive the best cut-off values of the sACR for predicting all-cause mortality. The method proposed by DeLong et al. was then used to compare the ROC curves of creatinine, albumin, and sACR to predict all-cause mortality. P<0.05 was considered statistically significant.

Results

A total of 1133 STEMI patients with an average age of 56.4±12.3 years were included the study and the median follow-up was 55 months. During the total follow-up period, 112 patients were died. According to survival, patients were divided into two groups. Compared to the survival group, long-term mortality group was older and had a higher prevalence of diabetes, hypertension, and smoking (p<0.04). Also, they had higher systolic blood pressure, heart rate, Killip class, white blood cell (WBC) count, level of hemoglobin and creatinine, and SYNTAX score. Additionally, patients with long-term mortality had lower albumin levels, left ventricular ejection fraction (LVEF) and a lower sACR (p<0.05). The baseline demographic, clinical, and laboratory parameters are shown in Table 1.

To identify independent predictors of all-cause mortality, we performed a multivariate Cox regression analysis with a stepwise retrospective model by using variables associated with cardiac mortality in univariate analyses. Multivariate analysis showed age, smoking, LVEF, and sACR (HR: 0.627 95% CI: 0.533–0.737; p<0.001) to be independent predictors of all-cause mortality (Table 2).

In ROC curve analyses, the area under the curve (AUC) of sACR was 0.756. The cut-off value for serum creatinine/albumin ratio that indicates long-term mortality was 3.51 with 58.9% sensitivity and

Table 2. *Univariate and multivariate analysis of all-cause long-term mortality*

Variable	Univariate analysis of long-term mortality			Multivariate analysis of long-term mortality		
	Hazard ratio	95% C. I.	P value	Hazard ratio	95% C. I.	P value
Age (years)	1.070	1.054–1.087	<0.001	1.047	1.028–1.065	<0.001
Smoking	1.678	1.468–1.983	0.04	1.514	1.002–2.287	P=0.049
sACR	0.395	0.334–0.467	<0.001	0.627	0.533–0.737	<0.001
LVEF	0.862	0.841–0.883	<0.001	0.891	0.863–0.921	<0.001

sACR: serum albumin to creatinine ratio; LVEF: left ventricular ejection fraction.

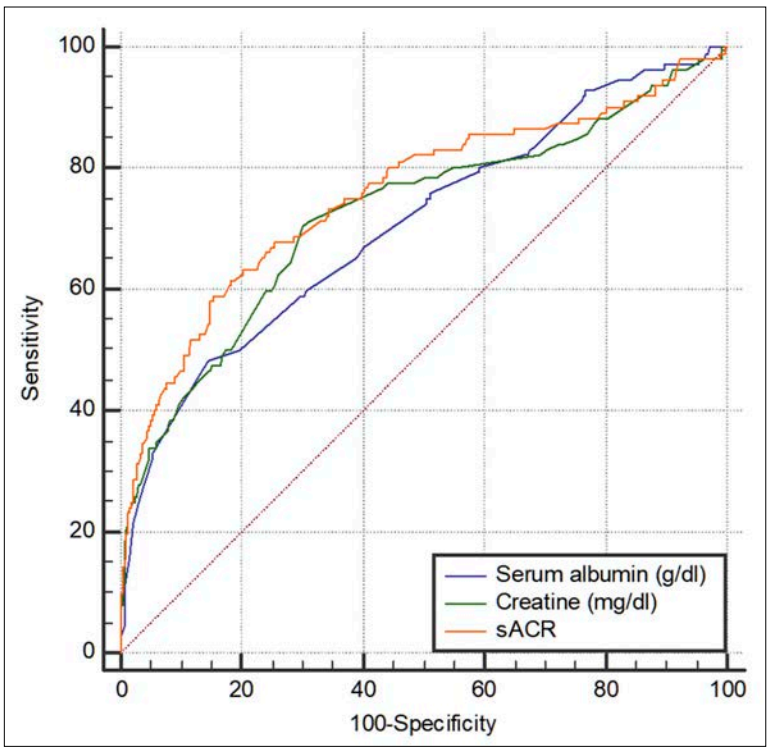

Figure 1. *Comparison of ROC curves between albumin, creatinine and sACR for predicting all-cause mortality.*

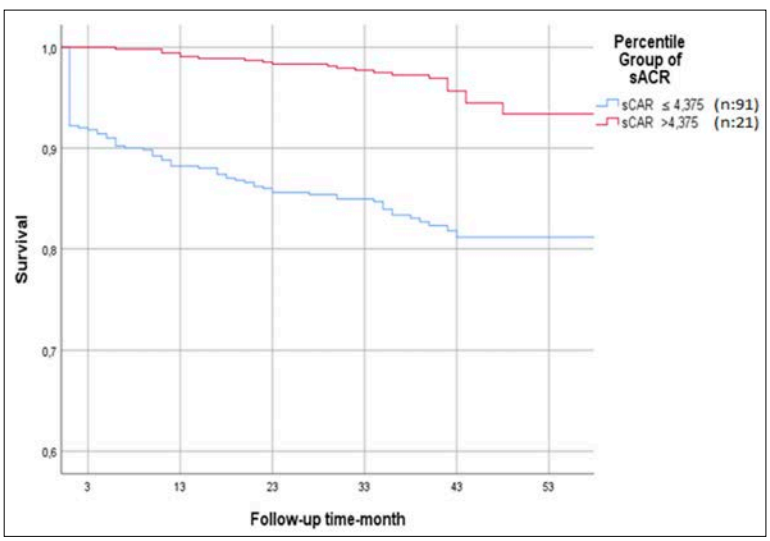

Figure 2. *Kaplan-Meier survival curves according to serum albumin to creatinine ratio (sACR).*

84.5% specificity. Receiver operating characteristic curve comparisons were performed to assess whether sACR had an additional prognostic value over creatinine and albumin levels. The AUC value of sACR was found to be significantly higher than creatinine (difference between areas: 0.03 95% CI: 0.006–0.06 p=0.01) and albumin level (difference between areas: 0.05 95% CI 0.005–0.09 p=0.02) in predicting long-term mortality (Fig. 1).

The study population were divided into two groups based on the median value (4.375) of the sACR; to assess the ability of mortality forecast: low sACR (≤4.375) and high sACR (>4.375) groups. The low sACR group was older and they had higher WBC counts and glucose levels. Moreover, the low sACR group had greater creatinine levels, peak CK-MB, and SYNTAX scores while demonstrating lower serum albumin levels and LVEF. The findings of the sACR groups are provided in Table 3. An analysis of the sACR groups demonstrated that low sACR patients (n=91) had greater all-cause mortality rather than high sACR (n=21) (P <0.001). Kaplan-Meier survival curves according to a cut-off value of sACR are shown in Fig. 2.

Discussion

In this study, we evaluated the prognostic value of sACR for predicting long-term all-cause mortality in patients with STEMI. A low sACR was associated with all-cause mortality and an independent predictor of mortality in patients with STEMI.

Table 3. *Demographic, clinical, and laboratory parameters of patients with low and high sACR*

Variables	sCAR ≤4.37 (n: 565)	sCAR >4.37 (n: 568)	P value
Age	59±12	54±12	<0.001
Female gender, n (%)	87(15.4%)	116(20.4%)	0.027
Diabetes, n (%)	139(24.6%)	125(22%)	0.302
Hypertension, n (%)	244(43.2%)	217(38.2%	0.080
Smoking, n (%)	300(53.1%)	329(57.9%)	0.102
Killip class >1 on admission (%)	117(20.7%)	64(11.3%)	<0.001
Systolic blood pressure, mm Hg	131±35	132±28	0.436
Heart rate, bpm	77±18	77±14	0.805
Hemoglobin (g/dL)	13.6±1.9	13.8±1.7	0.003
WBC Count (/1000)	12.5±4.1	12.1±3.4	0.022
Glucose (mg/dL)	130(105–178)	125(105–160	0.033
sACR	3.49±0.74	5.32±0.86	<0.001
Creatine (mg/dl)	1.07±0.29	0.75±0.11	<0.001
Serum albumin (g/dl)	3.56±0.44	3.94±0.45	<0.001
Peak Creatine Kinase MB (ng/mL)	191(113–338)	167(94–306	<0.001
Left Ventricular Ejection Fraction (%)	45±9	48±8	<0.001
Basal SYNTAX score	17.2±4.7	16.04±4.2	<0.001
Long-term Mortality, n	91	21	<0.001

sACR: serum albumin to creatinine ratio.

ST-segment elevation myocardial infarction (STEMI) is one of the primary causes of death in developed countries[21]. Recent studies have investigated and demonstrated the relation between clinical, laboratory, and hemodynamic parameters and survival in STEMI patients. In our study, 112 patients died during long-term follow-up. Consistent with the previous findings[22–24], patients with long-term mortality had higher heart rate, levels of glucose and creatinine, and SYNTAX scores and lower systolic blood pressure, levels of albumin, LVEF, and sACR ($p<0.004$) when compared to the survivors in our study.

ST-segment elevation myocardial infarction is an acute clinical condition accompanied by inflammation, platelet aggregation, and coagulation[25]. Serum albumin, which is a negative acute-phase reactant protein, has several functions such as antioxidant and anticoagulant activity, promotion of the formation of anti-inflammatory mediators, and the preservation of vascular integrity[26,27]. Previous studies states that low serum albumin levels in STEMI patients are related with poor survival and hypoalbuminemia has a prognostic value in patients with ACS. Hypoalbuminemia was also connected with multi-vessel coronary artery disease (high SYNTAX score) and no-reflow in patients with STEMI and was related to long-term all-cause cardiac mortality[28–30]. In our study we found low serum albumin levels in patients with long term mortality, similar to the literature. Serum albumin has well known anti-inflammatory, anticoagulant, and anti-platelet aggregation activity[27]. STEMI, as a clinical condition accompanied by inflammation causes a decrease in serum albumin levels. Due to low levels of albumin; increased oxidative stress, platelet activation and aggregation may lead the worsening of the clinical illness and results in elevated mortality. Similar to these findings, we observed in patients with poor long term survival has low serum albumin levels.

Impaired kidney functions were associated with an increased risk of cardiovascular disease and worse cardiovascular outcomes. Renal insufficiency was measured by corrected creatinine clearance or sCr level has already been investigated and found to be an independent predictor of mortality in patients with ACS[16–19]. Elevated sCr level has an association with coagulation, fibrinolysis, endothelial dysfunction, and anemia. Retrospective analyses demonstrated that impaired renal functions and elevated sCr concentration on admission increase the risk of death in patients with STEMI and are independent predictors of mortality[31,32]. In our study parallel with the recent findings, sCr levels were found higher in patients with long-term mortality.

sACR represents the ratio of serum albumin to creatinine level. Levels of serum albumin and creatinine were shown to be associated with poor cardiac endpoints[20]. Recent studies have shown that sACR was more significant in predicting prognosis compared to albumin or creatinine levels alone. We hypothesized that merging

these parameters may enable us to obtain a more sensitive and stable index of mortality in patients with STEMI. In line with our expectations, a low sACR was an independent predictor of poor surveillance. Also we found that sACR had a higher prognostic ability for predicting all-cause mortality compared to serum albumin (AUC: 0.706) or sCr (AUC: 0.723).

In the present study, a low sACR was associated with a high SYNTAX score, lower ejection fraction (EF) and high Killip class compared to high sACR. A low sACR related to a high SYNTAX score may reflect a high coronary atherosclerotic burden that is associated with adverse cardiac events and poor prognosis[33]. A low sACR was also associated with low EF and heart failure. The development of heart failure may be due to escalated myocardial damage and reduced myocardial reserve. The presence of heart failure with reduced LVEF is one of the most important predictors of long-term mortality in patients with STEMI[21]. Poor outcomes may have been seen in the low sACR group because of the relationship between low sACR and low LVEF.

In this study, our results demonstrate that sACR may have an additional prognostic value for the development of an individual-risk approach and surveillance of STEMI patients who underwent a pPCI. Patients with a reduced sACR may require more frequent follow-up and intense therapy. Moreover, as an easily accessible parameter, sACR is simply to calculate, and it can be standardized without additional cost, thus offering increased prognostication of these patients.

Statement of Ethics

Our institutional human research ethics committee approved this prospective study (Approval no: 80576354-050-99/85).

Conflict of Interest Statement

None to declare.

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The authors have no conflicts of interest to declare.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The White Blood Cell Count to Mean Platelet Volume Ratio (WMR) is Associated With Syntax Score in Patients With ST-Segment Elevation Myocardial Infarction

Beyaz Kan Hücresi Sayısı/Ortalama Trombosit Hacmi Oranın ST-Segmenti Yükselmeli Miyokard Enfarktüslü Hastalarda SYNTAX Skoru ile İlişkisi

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ABSTRACT

Background: *ST-segment elevation myocardial infarction (STEMI) is the most common reason for mortality worldwide. Scoring systems such as Syntax score plays a significant role in risk stratification in these patients. Besides, as a simple and easily applicable marker, white blood cell count to mean platelet volume ratio (WMR), which could play a vital role in identifying risky patients, has emerged as an indicator of inflammation in atherosclerotic disease. In the current study, we aimed to investigate the predictive role of WMR for Syntax score in patients with STEMI.*

Material and Method: *Demographics, comorbidities, and laboratory results on the admission of hospitalized 335 patients with STEMI were analyzed. The study population was divided into two groups according to the syntax score median of the study population (Syntax score median=19). Findings were compared between Syntax score <19 and Syntax score ≥19 groups.*

Results: *The Pearson correlation value between WMR and Syntax score was 0.415 (p<0.001). One hundred and sixty four patients were assigned to the Syntax score <19 group, 171 patients were designated as Syntax score ≥19 group. White blood cell count to mean platelet volume ratio was significantly higher in the Syntax score ≥19 group than the Syntax score <19 group [median (IQR), 1.56 (1.28–1.81) vs 1.32 (1.16–1.5), p<0.001]. White blood cell count to mean platelet volume ratio was an independent predictor according to multivariate analysis [Odds ratio (95% CI), 1.26 (1.08–1.47), p=0.002].*

Conclusion: *In patients with STEMI, WMR is significantly correlated with high syntax score. It could provide supportive data for early risk stratification and optimized approach. Consequently, therapeutic methods may be wellplanned to avoid a poor outcome in these patients.*

Key words: *ST-segment elevation miyocardial infarction; syntax score; white blood cell; mean platelet volume*

ÖZET

Amaç: *ST-segment yükselmeli miyokard enfarktüsü (STEMI) dünya çapında en yaygın ölüm nedenlerindendir. Syntax skoru gibi skorlama sistemleri, bu hastalarda risk sınıflandırmasında önemli bir rol oynar. Ayrıca, basit ve kolay uygulanabilir bir belirteç olarak, riskli hastaların belirlenmesinde hayati bir rol oynayabilecek beyaz kan hücresi sayısının ortalama trombosit hacmine oranı (WMR), aterosklerotik hastalıkta enflamasyonun bir göstergesi olarak ortaya çıkmıştır. Bu çalışmada, STEMI hastalarında WMR'nin Syntax skoru için prediktif rolünü araştırmayı amaçladık.*

Materyal ve Metot: *ST-segment yükselmeli miyokard enfarktüsü tanısı ile hastaneye yatırılan 335 hastanın demografik özellikleri, komorbiditeleri ve laboratuvar sonuçları incelendi. Çalışma popülasyonu, çalışma popülasyonunun syntax skor medyanına (Syntax skor medyan=19) göre iki gruba ayrıldı. Bulgular Syntax skoru <19 ve Syntax skoru ≥19 olan gruplar arasında karşılaştırıldı.*

Bulgular: *Beyaz kan hücresi sayısının ortalama trombosit hacmine oranı ile Syntax skoru arasındaki Pearson korelasyon değeri 0,415 (p<0,001) bulundu. Yüz altmış dört hasta Syntax skoru <19 grubuna, 171 hasta Syntax skoru ≥19 grubuna ayrıldı. Beyaz kan hücresi sayısının ortalama trombosit hacmine oranı, Syntax skoru ≥19 olan grupta Syntax skoru <19 olan gruptan anlamlı olarak daha yüksekti [ortanca (IQR), 1,56 (1,28–1,81) ve 1,32 (1,16–1,5), p<0,001]. Beyaz kan hücresi sayısının ortalama trombosit hacmine oranı, çok değişkenli analize göre bağımsız bir belirleyiciydi [Odds oranı (%95 GA), 1,26 (1,08–1,47), p=0,002].*

Sonuç: *ST-segment yükselmeli miyokard enfarktüsü hastalarında WMR, yüksek syntax skoru ile anlamlı şekilde ilişkilidir. Erken risk sınıflandırması ve optimize edilmiş yaklaşım için destekleyici veriler sağlayabilir. Sonuç olarak, bu hastalarda kötü bir sonlanımdan kaçınmak için terapötik yöntemler iyi planlanabilir.*

Anahtar kelimeler: *ST-segment elevasyonlu miyokard infarktüsü; syntax skoru; lökosit; ortalama trombosit hacmi*

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Introduction

Acute coronary syndrome (ACS) is a disease characterized by rupture of atherosclerotic plaque in most cases followed by complete or incomplete thrombosis of the coronary arteries[1]. Despite the ongoing amelioration in related mortality rates, ACS remains the most common cause of death worldwide[2]. In parallel, ST-segment elevation myocardial infarction (STEMI), a life-threatening complication of coronary artery disease (CAD), is among the leading causes of morbidity and mortality worldwide[3].

The SYNTAX [Synergy (SYNergy) between Taksus (TAXus) and percutaneous coronary intervention and cardiac surgery] scoring system is an anatomical scoring system that measures the complexity of a coronary lesion in addition toits features such as its morphology and location in the coronary vascular system[4]. It has been shown that the SYNTAX score can predict short- and long-term mortality in patients who were operated on due to CAD[4]. It has been reported that the severity of CAD, which is commonly graded based on SYNTAX scores calculated from coronary angiography, was closely correlated with poor prognosis in ACS[4].

To date, the relationship between the SYNTAX score and various hematological and biochemical parameters in ACS patients has been investigated in many studies[5–7]. White blood cells (WBCs) play a crucial role in the progression of atherosclerosis and in the destabilization and rupture of a plaque, leading to thrombotic events. Additionally, WBCs and platelets have potential roles in the pathogenesis of STEMI[1,8]. The mean platelet volume (MPV), which is a highly sensitive marker of platelet activity, can be used to correlate the pathophysiology of thrombosis and inflammatory diseases[9]. The platelet size, which is expressed as MPV, has also been shown to predict cardiac deaths or major adverse cardiac events (MACEs) following percutaneous coronary intervention (PCI)[10]. The WMR value, which is the ratio of WBC count to MPV, is used as an indicator of inflammation in patients with atherosclerotic disease[9,10]. In this context, the objective of this study is to investigate the relationship between WMR, clinical prognosis and SYNTAX score in patients with STEMI.

Methods

The study population consisted of patients hospitalized between 2016 and 2020 with the diagnosis of STEMI. Among the patients whose demographic characteristics, comorbidities, and laboratory results were reviewed retrospectively, 37 patients who did not give consent, who received steroid or non-steroidal anti-inflammatory therapy, and who had blood diseases that could affect blood parameters, including cytopenia, were excluded from the study. The remaining 335 patients were included in the study sample. The study protocol was approved by the local ethics committee (Ethics Committee of the Dean of the Faculty of Medicine of Kafkas University-80576354-050-99/197 numbered ethics committee approval). The study was conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients included in the study sample.

SYNTAX scores were calculated from the angiographic images of the patients. Blood parameters of all patients were evaluated. Biochemical and complete blood count (CBC) data were obtained from venous blood samples taken from patients at admission. Blood samples were collected in standard tubes containing EDTA (ethylenedinitrilotetraacetic acid). All samples were processed in the XE 5000 (Sysmex, Norderstedt, Germany) device for 60 minutes, and the relevant blood values were obtained. White blood cell count to mean platelet volume ratio was calculated using WBC and MPV values. The diagnosis of STEMI was made based on the criteria available in the most recent guidelines[11]. The study sample was divided into two groups of 171 patients with a SYNTAX score ≥19 and 164 patients with a SYNTAX score <19. The groups were analyzed comparatively on the basis of the variables examined within the scope of the study. Evaluation of cineangiographic imaging results was performed by two experienced cardiologists blinded to study data using the Axiom (Siemens Medical Solution, Erlangen, Germany) workstation. Each lesion with a diameter stenosis ≥50% in coronary vessels ≥1.5 mm in diameter was scored using the online SYNTAX score calculator. In cases where two cardiologists could not reach a consensus on the coronary lesions, the final score was determined by averaging the scores calculated by each cardiologist.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) program version 23.0 (Social Science Statistical Program for Windows Program, version 23.0, IBM Company, Armonk, NY, USA, 2015) software package. Descriptive statistics were expressed as mean ± standard deviation or median (0.25–0.75 percentiles) depending on whether the respective data were determined to conform to the normal distribution in the case of numerical variables and as number (n) and percentage (%) values in the case of categorical variables.

Normality assumptions in the case of numerical variables were analyzed with the Shapiro-Wilk test. Categorical data were analyzed with Pearson's chi-squared and Fisher's exact tests. The differences between the two groups were evaluated with the student's t-test in the case of data that were determined to conform to the normal distribution, and with the Mann-Whitney U test for data that did not conform to the normal distribution. Spearman's correlation coefficient was used to evaluate the relationships between continuous variables. Univariate and multivariate logistic regression analyses were used to identify independent risk factors associated with an in-hospital MACE.

The receiver operating characteristic curve (ROC) analysis was used to evaluate the predictive power of the SYNTAX scores and WMR values for MACEs and the area under the curve (AUC) within a 95% confidence interval (CI), and the sensitivity and specificity of these markers. Maximum Youden index values were determined as optimal cut-off points. Univariate and multivariate analyses of independent predictors of MACEs were performed using the Cox proportional hazards regression model. The variables significantly associated with MACEs in univariate analyses were further subjected to multivariate analysis. The corresponding 95% CI and odds ratio (OR) values were reported. Probability (p) values ≤0.05 were deemed to indicate statistical significance.

Results

A total of 335 STEMI patients with a mean age of 56.4±11 years were retrospectively included in the study sample. The patients' baseline demographic, clinical and laboratory data were analyzed and compared between groups. The results of the comparative analysis are given in Table 1. There was no significant difference between the patient group with a SYNTAX score <19 and the patient group with a SYNTAX

Table 1. *Demographic, clinical, and laboratory characteristics*

	Overall (n=335)	Syntax Score <19 (n=164)	Syntax Score ≥19 (n=171)	P-value
Male, n (%)	275 (82.1)	134 (48.7)	141 (51.3)	0.887
Age (years), mean ± SD	56.4±11	55.1±11	57.7±10	0.035
WMR	1.41 (1.20–1.64)	1.32 (1.16–1.5)	1.56 (1.28–1.81)	<0.001
Killip class 2–4, n (%)	64 (19.1)	15 (9.1)	49 (28.7)	<0.001
Ejection Fraction (%) median [IQR]	45 (40–50)	45 (41.5–52)	44 (35–50)	<0.001
Initial Vital Signs				
SBP (mmHg), median [IQR]	135 (120–147)	130 (119–140)	135 (121–161)	0.015
Heart Rate, median [IQR]	80 (70–88)	78 (70–85)	82 (71–92)	0.016
Laboratory findings at admission				
Hgb (g/dL), median [IQR]	13.9 (13–15.1)	13.8 (12.9–14.9)	14 (13.1–15.2)	0.223
WBC (× 10^3/μL), median [IQR]	12.8 (11.1–14.5)	11.9 (10.4–13.6)	13.8 (12.1–16.2)	<0.001
PLT (× 10^3/μL), median [IQR]	260 (222–298)	257 (216–290)	261 (225–301)	0.201
MPV	9 (8.2–9.8)	9 (8.2–10)	9 (8.2–9.8)	0.816
Neutrophil	10 (8–11.9)	8.87 (7.55–10.73)	11 (9.15–13.35)	<0.001
Lymphocyte	1.8 (1.28–2.5)	1.8 (1.29–2.41)	1.7 (1.26–2.5)	0.878
eGFR (mL/min), mean ± SD	85±23	89±23	81±23	0.002
Comorbidities				
Hypertension, n (%)	153 (45.7)	63 (38.4)	90 (52.6)	0.012
Diabetes, n (%)	78 (23.3)	30 (18.3)	48 (28.1)	0.039
Cigarette smoking, n (%)	190 (56.7)	94 (57.3)	96 (56.1)	0.912
COPD, n (%)	19 (5.7)	8 (4.9)	11 (6.4)	0.639
CKD (eGFR <60 mL/min/m^2), n (%)	34 (10.1)	12 (7.3)	22 (12.9)	0.105

WMR: white cell blood count to mean platelet volume; SBP: systolic blood pressure; Hgb: hemoglobin; WBC: white blood cell count; PLT: platelet; MPV: mean platelet volume; eGFR: estimated glomerular filtration rate; BNP: B type natriuretic peptide; CRP: C-reactive protein; CK: creatine kinase; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; SBP: systolic blood pressure; WBC: white blood cell count.

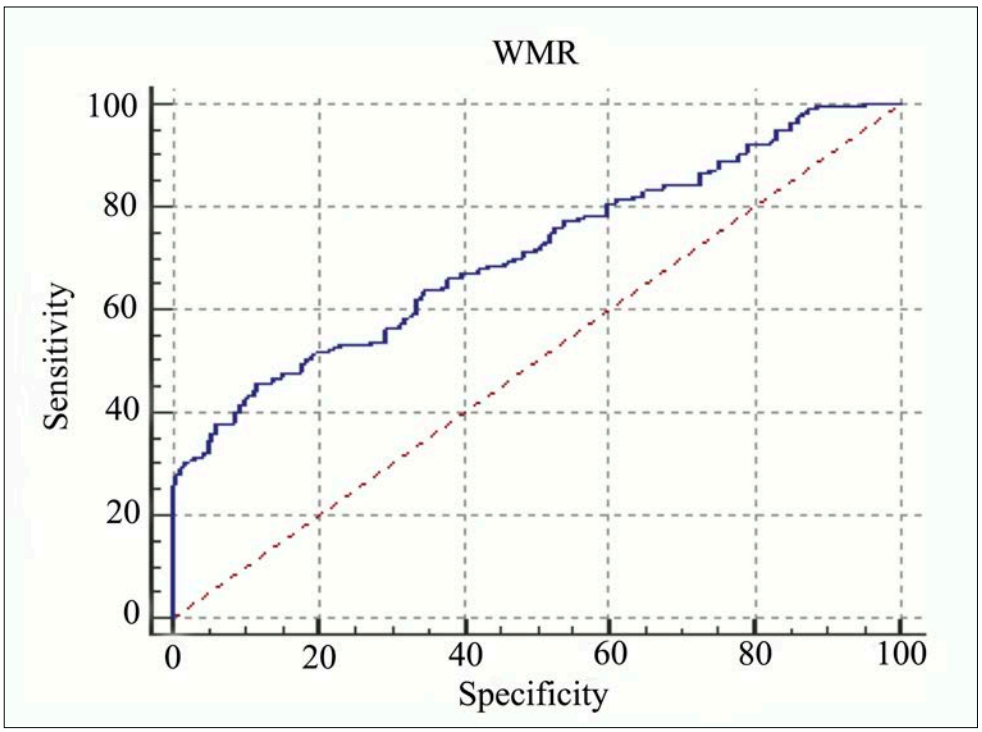

Figure 1. *Receiver operating characteristic (ROC) curve analysis of the WMR for Syntax Score ≥19.*

Table 2. *Univariable and multivariable predictors of syntax score*

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P value	OR (95% CI)	P-value
Age	1.02 (1.00–1.04)	0.034	1.03 (1.00–1.06)	0.031
WMR	20 (8.46–51.68)	<0.001	1.26 (1.08–1.47)	0.002

OD: odds ratio; WMR: white cell blood count to mean platelet volume; SBP: systolic blood pressure; WBC: white blood cell count; eGFR: estimated glomerular filtration rate; CK: creatine kinase.

score ≥19 in terms of gender, smoking status, presence of chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD), and hemoglobin (Hgb), platelet (Plt), MPV, and lymphocyte values. The number of patients with Hypertension (HT) and Diabetes Mellitus (DM) was significantly higher in the patient group with a SYNTAX score ≥19 than in the patient group with a SYNTAX score <19. In addition, the mean age of the patient group with a SYNTAX score ≥19 was also significantly higher than the patient group with a SYNTAX score <19 (55.1±11 years vs. 57.7±10 years, p=0.035). White blood cell count to mean platelet volume ratio value was statistically significantly higher in the patient group with SYNTAX score ≥19 (OR: 1.56; 95% CI: 1.28–1.81) compared to the patient group with SYNTAX score <19 (OR: 1.32; 95% CI: 1.16–1.5) (p<0.001). Additionally, according to the Killip classification, the number of patients with class 2–4 symptoms was higher in the patient group with a SYNTAX score ≥19 compared to the patient group with a SYNTAX score <19.

The ejection fraction (EF) was significantly higher in the patient group with a SYNTAX score <19 compared to the patient group with a SYNTAX score ≥19 [45% (min: 41.5, max: 52) vs 44% (min: 35, max: 50), p<0.001].

A comparison of patients' vital signs values at admission revealed that the number of patients with low systolic blood pressure (SBP) and high heart rate was significantly higher in the patient group with a SYNTAX score of ≥19 compared to the patient group with a SYNTAX score of <19.

Additionally, the mean glomerular filtration rate (GFR) of the patient group with a SYNTAX score <19 was significantly higher than the patient group with a SYNTAX score of ≥19 (89±23 vs. 81±23, p=0.002).

The Pearson correlation coefficient between the WMR value and SYNTAX score was calculated as 0.415 (p<0.001). White blood cell count to mean platelet volume ratio was significantly higher in the patient group with a SYNTAX score ≥19 than in the patient group with SYNTAX score <19[median WMR (interquartile range (IQR): 1.56 (min: 1.28, max: 1.81) vs. 1.32 (min: 1.16, max: 1.5), p<0.001]. The results of the multivariate analysis indicated that WMR was an independent predictor [OR: 1.26 (min: 1.08, max: 1.47) (95% CI), p=0.002] (Table 2).

The results of the ROC analysis of WMR in the patient group with a SYNTAX score ≥19 are shown in Fig. 1. The cut-off value was determined as 1.6044×10^3/μL, with a sensitivity of 45.61% and a specificity of 88.41%. The AUC was calculated as 0.708.

Discussion

The findings of the study revealed a significant correlation between WMR values and high SYNTAX scores in patients who underwent angiography for STEMI. In addition, WMR was found to be an independent predictor based on the results of the multivariate analysis. It has long been recognized that inflammation contributes in a complex way to the development, progression and destabilization of atherosclerotic plaques. Platelets, leukocytes, and vascular endothelial cells trigger atherosclerotic plaque rupture in ACS by interacting with each other through a series of inflammatory mediators or markers that act simultaneously[12].

The SYNTAX scoring system is one of the most useful tools that objectively measures the severity of CAD in daily clinical and interventional practices. As is known, the SYNTAX scoring system is an anatomical scoring system that can measure the morphology, location and type of the lesion in patients with CAD[4]. The relationship between high SYNTAX scores and poor cardiovascular outcomes has also been reported[4].

It has been previously reported that several hematological indicators such as WBC, RDW, and MPV/lymphocyte ratio have prognostic value in predicting the SYNTAX score in ACS patients[7,9,13,14]. The MPV value, which refers to the mean platelet volume, is one of the parameters related to platelet activation. It is known that larger platelets are more active and thrombogenic[15]. On the other hand, it has been reported in different studies that an increase in the WBC count strongly predicts morbidity and mortality in addition to the SYNTAX score in ACS patients[16]. There are studies in the literature examining the relationship of WMR with SYNTAX scores or CAD severity in ACS patients[7,9].

The number of patients with HT and DM was significantly higher in the patient group with a SYNTAX score ≥19 compared to the patient group with a SYNTAX score <19 (p=0.012 and p=0.039, respectively). It is known that diabetes, especially DM or type 2 diabetes, is a risk factor for CAD[17]. The PROCAM (Prospective Cardiovascular Munster) study, in which myocardial infarction patients were followed for 4 years, revealed a strong correlation between HT and CAD[18].

The mean age of the patient group with a SYNTAX score ≥19 was higher than the patient group with a SYNTAX score <19. Indeed, in another study, age was found to be an independent predictor of the SYNTAX score[19].

The comparison of the GFR values of the two groups indicated that the mean GFR of the patient group with a SYNTAX score <19 was significantly higher than the patient group with a SYNTAX score of ≥19. Similarly, it was reported in another study that GFR was a strong predictor of high SYNTAX scores[19].

Given that steroid group drugs can affect the WBC subgroups of the patients, patients using these drugs were excluded from the study. The increase in the WBC count due to glucocorticosteroids (GCS) is referred to as "glucocorticoid-induced leukocytosis". Contrary to the said increase in the WBC count mainly in neutrophilic cells, the number of other circulating cells, especially eosinophils, decreases[20].

White blood cell count to mean platelet volume ratio values cannot replace clinical assessment, coronary angiography, and markers of myocardial injury. However, the results of this study demonstrated that WMR values can be used in the initial clinical evaluation of patients with STEMI in an integrated manner with other assessment tools.

Conclusion

The findings of this study revealed a significant correlation between the WMR values and high SYNTAX scores in STEMI patients. In this context, WMR can provide supportive data in predicting the severity of CAD in STEMI patients, in the early risk stratification of STEMI patients, and in determining an optimized

therapeutic approach. This way, the necessary therapeutic methods can be better planned to avoid a possible poor outcome in STEMI patients. However, large-scale studies are needed on using WMR values in clinical practice.

Exclusion Criteria from the Study

Exclusion criteria from the study were lack of patient consent, use of steroid or non-steroidal anti-inflammatory drugs, and the presence of blood disorders that could affect blood parameters, including cytopenia.

Limitations of the Study

As seen in comparable studies, the study's retrospective, observational, nonrandomized, single-center design inherently included limitations and biases.

Conflict of interest disclosure

All authors have no conflict of interest.

Statement of Ethics

The local ethics committee approved the study protocol (Ethics Committee of Kafkas University Faculty of Medicine) (Approval No: 80576354-050-99/197).

Informed consent was obtained from all patients.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Ventricular Repolarization Markers and Fragmented QRS in Patients with Bipolar Disorder

Bipolar Bozukluk Tanılı Hastalarda Biyokimyasal Parametreler ile EKG'de Ventriküler Repolarizasyon Markırları ve Fragmente QRS

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ABSTRACT

Aim: *Bipolar disorder (BD) is one of the chronic psychiatric diseases. It has been reported that cardiovascular diseases are seen twice as often in patients with BD. Fragmented QRS (fQRS) has been found to be associated with myocardial scarring and is used as a marker of arrhythmia and mortality. Ventricular repolarization (VR) is often evaluated using QT interval and T wave measurement data. In our study, we aimed to evaluate fQRS, QTc interval, QT dispersion (QTd), Tp-e interval, Tp-e/QT ratio results and VR, together with blood biochemistry parameter results of cases with BD.*

Material and Method: *Our research was conducted with 51 people diagnosed with bipolar disorder and 52 healthy people as the control group. fQRS, QTc interval, QT dispersion (QTd), Tp-e interval, Tp-e/QT ratio were measured using 12-lead electrocardiography (ECG). The results of the data obtained from ECG and blood biochemistry parameter levels were used to compare the healthy and patient groups.*

Results: *Tp-e interval (p=0.018) and Tpe/QT ratio (p=0.036) were found to be statistically significantly higher and total cholesterol level (p=0.006) lower in patients with bipolar disorder compared to the control group.*

Conclusion: *An increased Tpe/QT ratio, along with a prolonged Tp-e interval, may be a useful marker of ventricular arrhythmia risk in individuals with fQRS BD.*

Key words: *bipolar disorder; ventricular repolarization; electrocardiography; fragmented QRS*

ÖZET

Amaç: *Bipolar bozukluk (BB) kronik psikiyatrik hastalıklardandır. Bipolar bozukluk tanılı hastalarda kardiyovasküler hastalıkların iki kat daha fazla görüldüğü bildirilmiştir. Fragmente QRS (fQRS) miyokardiyal skar ile ilişkili bulunmuş ayrıca aritmi ve mortalite belirteci olarak kullanılmaktadır. Ventriküler repolarizasyon (VR) sıklıkla QT aralığı ve T dalga ölçüm verileri kullanılarak değerlendirilir. Bipolar bozukluk tanısı olan olguların kan biyokimya parametre sonuçları ile birlikte fQRS, QTc aralığını, QT dispersiyonu (QTd), Tp-e aralığını, Tp-e/QT oranı sonuçları ile VR'u değerlendirmek çalışmamızda amaçlanmıştır.*

Materyal ve Metot: *Araştırmamız Bipolar bozukluk tanısı olan 51 kişi ve kontrol grubu olarak sağlıklı 52 kişi ile yapılmıştır. fQRS, QTc aralığı, QT dispersiyonu (QTd), Tp-e aralığı, Tp-e/QT oranı 12 derivasyonlu elektrokardiyografisi (EKG) kullanılarak ölçüldü. EKG'den elde edilen verilerin sonuçları ile kan biyokimya parametre düzeyleri sağlıklı ve hasta grubundaki olguları karşılaştırmak için kullanılmıştır.*

Bulgular: *Bipolar bozukluk tanısı olan olgularda Tp-e aralığı (p=0,018) ile Tpe/QT oranı (p=0,036) kontrol grubuna göre istatistiksel olarak anlamlı olarak daha yüksek, total kolesterol düzeyi (p=0,006) ise daha düşük bulunmuştur.*

Sonuç: *Artmış Tpe/QT oranı, uzamış Tp-e aralığı ile birlikte fQRS BB tanısı olan bireylerde ventriküler aritmi riskinin faydalı bir belirteci olabilir.*

Anahtar kelimeler: *bipolar bozukluk; ventriküler repolarizasyon; elektrokardiyografi; fragmente QRS*

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Introduction

The physical health of individuals with chronic psychiatric illness is worse than other people in the community[1]. It has been shown that the average life expectancy of these individuals compared to the general population is up to fifteen years shorter[2]. The main reason for this shortening in life expectancy is cardiovascular diseases. Adoption of a sedentary lifestyle, smoking, frequent consumption of alcohol, and caffeinated beverages, and consumption of high-calorie foods are among the reasons why heart diseases are more common in these individuals[3]. Furthermore, obesity, hypertension, diabetes, and hyperlipidemia are also important causes of cardiovascular mortality[4–6].

It has been reported that cardiovascular diseases comorbidly occur twice as frequently in individuals with bipolar disorder compared to the healthy control[7]. It has been shown that cardiovascular diseases are 3.9 times more common in men and 3.5 times more common in women in manic-depressive individuals compared to the general population[8]. Therefore, individuals with a diagnosis of bipolar disorder are at higher risk for cardiovascular diseases.

In individuals with bipolar disorder, deaths from causes related to cardiovascular diseases are 6.4 times higher in women and 3.8 times higher in men than in healthy individuals[8]. Cardiovascular diseases are the cause of 1/3 of disease-related deaths in these individuals. More than half of cardiovascular diseases are caused by ischemic heart disease. Hypertension, left ventricular hypertrophy, age, glucose intolerance, high serum cholesterol level, intraventricular conduction block, decreased pulmonary vital capacity and increased heart rate are risk factors for sudden cardiac death in these individuals[9].

Antipsychotic and mood stabilizer drugs are frequently used in the treatment of the bipolar disorder. These drugs increase the risk of cardiovascular disease. Lithium and valproic acid are the most commonly used mood stabilizers. Lithium can impair glucose metabolism as a result of causing weight gain[10.11]. Valproic acid, on the other hand, can cause serious metabolic side effects as a result of both weight gain and insulin resistance[12.13]. Today, second-generation antipsychotic agents are the most commonly used in the treatment and cause an increased risk of weight gain, insulin resistance, hyperlipidemia, and diabetes mellitus[14–16].

Electrocardiography is used frequently in cardiology. T wave evaluated on ECG may indicate ventricular repolarization. In the absence of structural heart disease, ventricular repolarization abnormalities may cause arrhythmias. As a result of the studies, it was determined that ventricular repolarization markers such as QT dispersion (QTd), Tp-e/QT ratio, QT and QTc interval, and Tp-e interval could predict life-threatening cardiac arrhythmias[17]. Another important parameter associated with ventricular repolarization is QT dispersion, which is equal to the difference between the maximum QT interval and the minimum QT interval in the standard 12-lead ECG. It is an indicator of the homogeneity of ventricular repolarization and thus of cardiac electrical stability. The greater the QT dispersion, the less homogeneous the ventricular repolarization, and thus the greater the cardiac electrical instability. It is known that increased dispersion of ventricular repolarization is also a serious risk for ventricular arrhythmias[18–20]. The Tp-e value, which is the T wave peak-to-end interval on the ECG, indicates ventricular repolarization. Moreover, the Tp-e/QTc ratio is a parameter used to evaluate ventricular arrhythmogenesis[21]. It has been reported that there is a relationship between the Tp-e interval and the increased Tp-e/QT ratio and the risk of ventricular arrhythmia[22–23]. fQRS has been associated with arrhythmia and mortality in coronary artery patients[24].

Fragmented QRS (fQRS) is an electrocardiography (ECG) finding that has been used frequently in recent years. It is defined as notching of the QRS complex in 2 consecutive leads in the absence of bundle branch block[25]. In a healthy heart, the electrical impulse takes place homogeneously in the myocardium. As a result of myocardial fibrosis, homogeneity in electrical conduction is impaired, and inhomogeneous conduction appears as fQRS on ECG. fQRS is seen in cases of structural myocardial damage[26.27]. fQRS detected in ECGs of people diagnosed with or suspected coronary artery disease is associated with myocardial scarring. . In addition, fQRS is more sensitive than Q wave in showing scar tissue[25]. It has also been suggested that fQRS may be a marker for mortality and arrhythmia in coronary artery disease[24].

Although many cardiac parameters have been examined in patients with bipolar disorder, there is no study examining fQRS and our study is the first of its kind. The aim of this study is to evaluate some blood parameters and ECG measurements in patients with bipolar disorder by comparing them with the control group.

Material and Methods

The research is of the case-control type. Before the cases were included in the study, the Ethics Committee of Kafkas University was consulted and approval was obtained in the session number 04 dated 26.02.2020. Our research was carried out at Kars State Hospital between 01/03/2020-01/06/2021.

The patient group with bipolar disorder who applied to the Kars State Hospital psychiatry outpatient clinic and the control group with healthy individuals with similar socio-demographic characteristics were formed. After the subjects were told what they should do in this study and our aim, their consent was obtained from those who agreed to participate in the study.

Inclusion criteria of the research: for the case group, being diagnosed with bipolar disorder, being between the ages of 18–65, agree to participate in research. For the control group, it was determined as being between the ages of 18–65 and agree to participate in research. Exclusion criteria of the stud: refuse to participate in research for both the case and control groups, dementia, mental retardation, heart valve disease, rhythm and conduction disorder, pericardial or myocardial disease, congenital heart disease, antiarrhythmic drug, known to affect QT interval or sympathetic nervous system activity identified as drug use.

Triglyceride, whole blood, fasting blood sugar, cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, high-sensitivity C-reactive protein (Hs-CRP) levels were measured in all subjects included in our study.

Electrocardiography of each case was taken. In these recordings, the filter was 100 Hz, the alternating current filter was 60 Hz, the paper flow rate was 25 mm/s, and the amplitude was 10 mm/mV. Tp-e/QT, QTc interval, Tp-e, and Tpe/QTc were calculated. QT and Tp-e duration measurements were made by the cardiologist using a magnifying glass. The ECGs were scanned into the Computer system and calculations were made. Two cardiologist performed separate, blinded measurements on a subset of ECGs. The heart rate at the time of recording was accepted as the resting heart rate. The interval from the beginning of the QRS complex to the end of the T wave was accepted as the QT duration. The longest QT duration measured from the 12 leads was defined as the maximum QT (QTmax) time, and the shortest QT duration was defined as the minimum QT (QTmin) time. QTd was calculated by subtracting the minimum QT duration from the maximum QT duration. Tp-e time was measured from lead V6. Measured values were corrected for heart rate using the Bazzett formula. Corrected QT time (cQT=QT/√(R–R interval) and corrected Tp-e time (cTp-e=Tp-e/√(R–R interval)) Tpe/QT ratio was calculated.

To calculate the dispersion values, the maximum and minimum values of each interval in the 12 leads were measured. The dispersion (d) values (QTd) of the relevant interval were calculated by subtracting the minimum value from the maximum value. According to the guidelines of the Society of Cardiology, we determined the cutoff value of 480 ms for Long QTC (LQTC) in our study[28].

Statistical Analysis

Statistical Analysis was performed in Statistical Package for Social Sciences (SPSS) program version 24.0 software (SPSS Inc., Chicago, IL). Kolmogorov-Smirnov test was used to evaluate the conformity of continuous variables to normal distribution. Normally distributed data were compared using the independent group t-test and non-normally distributed data using the Mann-Whitney U test. The Chi-square test was used to compare nominal variables. $P<0.05$ and $p<0.01$ values were considered statistically significant.

Results

Our research was conducted with 103 (54 men and 49 women) people. Fifty-one people (24 women and 27 men) were included in the patient group, and 52 people (25 women and 27 men) were included in the control group. Considering the mean age, it was 45.78±10.68 years in the patient group and 48.90±9.63 in the control group. There was no statistically significant difference between the two groups in terms of mean age and gender parameters (p=0.124 and p=0.918,

Table 1. *Comparison of the clinical and demographic data of the participants*

	Patient (n=51)	Control (n=52)	p
Age, Mean. ± Sd	45.78±10.68	48.90±9.63	0.124**
Male	27	27	0.918*
Female	24	25	
Smoker (%)	18 (35.3)	10 (19.2)	0.067*
Diagnosed with hypertension (%)	34(66.7)	35(67.3)	0.945*
Dignosed with diabetes (%)	4(8)	9(17.3)	0.159*
Diagnosed with hyperlipidemia (%)	17(34)	24(46.2)	0.211*
Family history of hypertension (%)	10(20)	11(21.2)	0.885*

Sd: Standart deviation; *: Chi-square test; **: Independent samples t test, Mann-Whitney U testi.

Table 2. *Comparison of the biochemical parameters of the participants*

	Patient (n=51) Mean ± Sd.	Control (n=52) Mean ± Sd.	p
Glucose	99.20±26.48	105.28±35.19	0.304***
LDL	100.87±35.86	114.42±36.75	0.066**
HDL	44.91±10.92	46.90±10.77	0.359**
Total Cholesterol	174.03±42.40	195.52±43.03	0.006***
Triglyceride	166.57±102.54	184.92±105.93	0.292***
Hs-CRP	5.98±13.62	2.91±1.88	0.989

LDL: low-density lipoprotein cholesterol; HDL: High-density lipoprotein cholesterol; Hs-CRP: High-sensitivity C-reactive protein; Sd: Standart deviation: *: Chi-square test; **: Independent samples t test; ***: Mann-Whitney U testi.

Table 3. *Comparison of the ECG findings of the participants*

	Patient (n=51) Mean ± Sd.	Control (n=52) Mean ± Sd.	P
Pulse	84.37±17.98	96.40±18.97	0.810***
Tpe	72.61±14.79	65.87±11.44	0.018***
Tpe/QT	0.19±0.36	0.17±0.34	0.036**
Tpe/QTc	0.17±0.03	0.17±0.12	0.06***
QTD	51.73±21.47	51.75±21.22	0.989*
	n (%)	n (%)	
fQRS	13(25.5)	6(11.5)	0.068*
Long QTC (>480 ms)	21(41)	24(46.2)	0.673*

Sd: Standart deviation; *: Chi-square test; **: Independent samples t test; ***: Mann-Whitney U testi.

respectively) (Table 1). In addition, no significant difference was found between the groups in terms of hypertension, hyperlipidemia and diabetes mellitus diagnoses (Table 1).

Except for 2 of the patients in the patient group, all of them were using 2nd generation antipsychotic drugs. Twenty-seven people were using sodium valproate, a mood stabilizer, and 18 people were using lithium. Six people were under treatment with only 2nd generation antipsychotic medication.

Considering the biochemistry parameters, no significant difference was found between the patient and control groups in terms of glucose, Hs-CRP, triglyceride, LDL, and HDL levels ($p>0.05$). A statistically significant difference was found between the groups in terms of total cholesterol values ($p<0.05$) (Table 2).

Considering the ECG parameters between the groups, there was no statistically significant difference between the two groups in terms of QTc interval ($p>0.05$), Tpe/QTc ($p>0.05$), QTd ($p>0.05$), fQRS ($p>0.05$), while Tp-Statistically significant difference was found between e/QT ($p<0.05$) and Tp-e ($p<0.05$) (Table 3).

Discussion

In this study, no statistically significant difference was found between the groups in terms of age and gender. There was no statistically significant difference between the groups in terms of medical conditions such as smoking, hypertension, hyperlipidemia, diabetes, family cardiac history. The fact that both groups have similar socio-demographic data is important in terms of giving accurate results in our study.

Hyperlipidemia is the primary risk factor for cardiovascular diseases. It is also known that hyperlipidemia is a risk factor for ischemic attack[29]. There is a relationship between total cholesterol level and deaths caused by coronary artery disease[30]. Total cholesterol level should be below 200 mg/dl, low molecular weight lipoprotein (LDL) cholesterol should be below 130 mg/dl, triglyceride value should be below 150 mg/dl, and HDL cholesterol should be 40–60 mg/dl[29]. Low HDL level is an important risk factor for cardiovascular diseases. It has been stated that a 1% decrease in HDL level increases the risk of heart disease by 2–3%. While low HDL levels are an important risk factor for CHD, high levels are considered a protective factor[29]. Considering the blood results, there was no statistically significant difference between glucose, LDL, triglyceride, and HDL levels between the two groups, but a significant difference was found between total cholesterol levels. Metabolic parameters, except for triglyceride values, were within normal limits in both groups.

Although the physiological role of Hs-CRP has not been fully demonstrated, it has been reported to be a marker of cardiovascular risk[30]. Abnormalities in Hs-CRP levels alone have been shown to be valuable in predicting mortality from myocardial infarction or heart disease, congestive heart failure, stroke, atrial fibrillation, peripheral vascular disease and sudden cardiac death. Hs-CRP value less than 1.0 mg/L is considered low risk[31]. Values between 1.0–3.0 mg/L are considered medium risk, and values higher than 3.0 mg/L are considered high risk[32]. According to the results of our study, there was no statistically significant difference between the patient and control groups in terms of Hs-CRP levels, while it was high risk in the patient group compared to the Hs-CRP value, but medium risk in the control group. In the light of the literature information we have given, it can be said that these people are at risk for cardiovascular diseases due to the high levels of triglycerides and Hs-CRP in the patients in the patient group.

When the ECG data were evaluated, there was a statistically significant difference between the two groups in terms of Tpe and Tpe/QT values, but no significant difference was found in terms of QTc, Tpe/QTc, QTd, or fQRS. Since there was a significant difference in Tpe and Tpe/QT between the two groups and the durations were longer in the patient group, we can say that people with a diagnosis of bipolar disorder are at higher risk in terms of cardiac arrhythmia.

In this study, LQTc was seen in 21 (41%) in the patient group and 24 (46.2%) individuals in the control group. But there was no statistically significant difference between the two groups. A systematic review found that antipsychotics (thioridazine, ziprasidone), second-generation antipsychotics (SGAs), (amisulpride and quetiapine) tri– and tetracyclic antidepressants, and some antidepressants (citalopram, fluoxetine, and paroxetine, venlafaxine) are associated with the highest risk for long QTc interval (LQTc)[33]. In our study, our patients were mostly using mood stabilizers and second generation antipsychotics. Medications are only one of several possible risk factors for QTc interval prolongation. There are also well-established non-drug risk factors based on the literature. Non-modifiable risk factors include female sex, advanced age, and metabolizer status[33]. In our study, there was no significant difference between the two groups, except for total cholesterol. Total cholesterol was significantly higher in the control group.

Our study has some limitations. Firstly, the sample group included individuals from only one center. Secondly, disease duration was not evaluated. Another limitation is the low number of cases in the case and control groups. However, this limitation may not be very significant because, in our a priori power analysis, it was sufficient to detect an effect of α=0.05, β=0.80, large (d=0.8), while it was sufficient for the case and control groups to consist of 26 individuals, whereas, in our study, 51 people are in the case group and 52 people are in the control group. It is thought that more precise data can be obtained by further studies with larger sample groups. The fact that structured psychiatric interviews were not conducted on the cases included in the study is another shortcoming of our study.

We analyzed the ECG results in order to determine the biochemical parameters that might be cardiac risk factors and cardiac pathologies in people who were under treatment for bipolar disorder. Considering the blood results, there was no statistically significant difference between glucose, LDL, triglyceride, and HDL levels between the two groups, but a significant difference was found between total cholesterol levels. When the ECG data were evaluated, there was a statistically significant difference between the two groups in terms of Tpe and Tpe/QT values, but no significant difference was found in terms of Qtc, Tpe/QTc, QTd, or fQRS. From the socio-demographic data, it was found that there was no significant difference between the two groups in terms of age and gender. We think that our study may be important because it is the first study to investigate fQRS in patients with bipolar disorder. Despite lack of statistical significance, number of fQRS seems greater in BD group which might propose an increased risk of ventricular arrhythmias if supposed by further larger-scale studies. Our study may guide multicenter studies with large participants to show that fQRS can be a biomarker that can be used to predict cardiac risk in patients with bipolar disorder.

Statement of Ethics

Our institutional human research ethics committee approved this prospective study (Approval no: 26.06.2020-06).

Conflict of Interest Statement

All the authors declare no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Methods of Coping With Psychological Pain and Stress in Antisocial Personality Disorder

Antisosyal Kişilik Bozukluğunda Psikolojik Acı ve Stresle Başa Çıkma Yöntemleri

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ABSTRACT

Aim: *Antisocial Personality Disorder (ASPD) is a personality disorder in which the person has difficulty controlling his behaviors and impulses, harming both himself and his environment. In our study, we aimed to examine the psychological pain experienced by people with ASPD and the methods of coping with the stress they use to combat it.*

Material and Method: *Forty patients and 40 healthy control groups were included in the study. Sociodemographic Data Form, Beck Depression Scale (BDI), Beck Suicide Scale (BSS), Psychache Scale (PS), and Styles of Coping with Stress (SCSS) were administered to the participants.*

Results: *The BDI (p=0.037), BSS (p=0.009), PS (p=0.008) and SCSS-helpless approach (p=0.01) scores of the patients in the patient group were significantly higher than the scores of the control group. On the other hand, the scores of SCSS-self-confident approach (p=0.001) and SCSS-searching for social support (p<0.001) were found to be significantly lower than the scores of the control group. In the patient group, there was a positive correlation between BDI and BSS, PS and SCSS-optimistic approach. On the other hand, there was a significant negative correlation between BDI and SCSS-self-confident approach and SCSS-seeking social support*

Conclusion: *In our study, depression, suicide, and psychological pain were found to be significantly higher in people with ASPD compared to the control group, and it was determined that they used ineffective coping strategies. We think that early interventions for the treatment of psychological pain, such as suicidal ideation, determination of depression, and providing support for using effective coping strategies, may be effective in preventing self-destructive behaviors or suicides in ASPD, and therefore may change the course of the disease.*

Key words: *antisocial personality disorder; psychache; depression; suicide; coping with stress*

ÖZET

Amaç: *Antisosyal Kişilik Bozukluğu (ASKB), kişinin davranış ve dürtülerini kontrol etmekte zorlandığı hem kendisine hem çevresine zarar verdiği bir kişilik bozukluğudur. Yaptığımız çalışmada ASKB tanılı kişilerde yaşadıkları psikolojik acıyı, bununla mücadele için kullandıkları stresle başa çıkabilme yöntemlerini incelemeyi amaçladık.*

Materyal ve Metot: *Çalışmaya 40 hasta ve 40 sağlıklı kontrol grubu dâhil edildi. Katılımcılara Sosyodemografik Veri Formu, Beck Depresyon Ölçeği (BDÖ), Beck İntihar Düşüncesi Ölçeği (BİDÖ), Psikolojik Acı Ölçeği (PAÖ), Stresle Başa Çıkma Tarzları ölçeği (SBÇTÖ) uygulandı.*

Bulgular: *Hasta grubunda bulunanların BDÖ (p=0,037), BİDÖ (p=0,009), PAÖ (p=0,008) ve SBÇTÖ-çaresiz yaklaşım (p=0,01) puanı kontrol grubunun puanından anlamlı şekilde yüksek; SBÇTÖ-kendine güvenli yaklaşım (p=0,001) ve SBÇTÖ-sosyal destek arama (p<0,001) puanı ise kontrol grubunun puanlarından anlamlı şekilde düşük bulunmuştur. Hasta grubunda bulunanlarda BDÖ ile BİDÖ, PAÖ ve SBÇTÖ-iyimser yaklaşım arasında pozitif yönde; BDÖ ile SBÇTÖ-kendine güvenli yaklaşım ve SBÇTÖ-sosyal destek arama arasında ise negatif yönde anlamlı bir korelasyon görülmüştür.*

Sonuç: *Yaptığımız çalışmada ASKB tanılı kişilerde depresyon, intihar ve psikolojik acının kontrol grubuna göre anlamlı olarak yüksek bulunmuş ve etkin olmayan başa çıkma stratejilerini kullandıkları tespit edilmiştir. Psikolojik acının, intihar düşüncesi, depresyonun belirlenmesi, etkin başa çıkma stratejilerini kullanmaları için destek verilmesi gibi tedavisine yönelik erken müdahalelerin, ASKB'de kendine ve çevreye zarar verici davranışlarının veya intiharların önlemesinde etkin olabileceği bu nedenle hastalığın gidişatını değiştirebileceğini düşünmekteyiz.*

Anahtar kelimeler: *antisosyal kişilik bozukluğu; psikolojik acı; depresyon; intihar; stresle başa çıkma*

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Introduction

Antisocial personality disorder (ASPD) is a personality trait that could be observed in childhood, characterized by difficulties in impulse control, leading to suicidal or harmful behavior[1]. Self-harm or self-mutilation is repetitive attempts that result in self-damage to the body[2]. Self-harm behavior sometimes could be prevented by simple interventions; however, it could lead to life-threatening injuries or death. Thus, the suicide rate, high in most personality disorders, is higher in ASPD[3]. A study reported that self-harm was higher especially in criminals with ASPDs, compared to non-criminal individuals[4]. Antisocial personality disorder was characterized by dangerous impulsive behavior and associated with premature death[5].

Statements such as 'I can' t bear the pain,' which are often observed in suicide notes, accurately describe psychological pain[6]. Psychological pain, which Bolger[7] described as the breakdown of the ego, entails negative emotions such as grief, sadness, shame, anger, loneliness, and despair[8]. Mental suffering could be so severe as to impair social, professional, and daily functions[9]. When it is intense and severe, suicide could be perceived as the only way to salvation[10]. Psychological pain has been accepted as the most significant predictor of suicide, resulting from the interaction between several factors[11]. Psychological pain could lead to physical pain due to the self-harm behavior, frequently observed in ASPD[12]. The patient often concentrates on the physical pain to alleviate and bear the severity of the pain[13]. In a study conducted with patients with a fatal physical disease and depressive disorder, most patients stated that psychological pain was more intolerable than physical pain[14].

Stress occurs when an individual cannot cope with an event or situation. The individual struggles to prevent psychological or physiological harm due to this disturbing emotion or to reduce its effects[15]. Cognitive and behavioral efforts to prevent the destructive effects of stress's and restore balance were called coping with stress[16]. While these efforts could sometimes reduce stress, they fail due to ineffective coping strategies[17]. It is known that coping with stress and coping strategies are associated with personality[18]. Based on personality traits or coping methods, similar events could lead to different consequences[19].

The present study investigates the correlation between psychological pain and coping strategies in antisocial personality disorder.

Materials and Methods

The Faculty of Medicine ethics committee approved the present study (no: 2021/12-16). This study was conducted in accordance with the Declaration of Helsinki (1983) standards. The study was conducted at Elazığ Fethi Sekin City Hospital Mental Health and Disorders Clinic between March and September 2022. The study was conducted with 40 antisocial personality disorder patients who presented to the Mental Health and Disorders outpatient clinic and were diagnosed based on DSM-5 criteria and met the study criteria, and 40 healthy controls without any mental disorder based on DSM-5. Structured interviews with the participants lasted about 30 minutes with the psychiatrist. The study data were collected with a sociodemographic data form, Beck Depression Inventory, Beck Scale for Suicidal Ideation, Psychache Scale, and Ways of Coping Scale and all participants signed a written consent form.

Antisocial personality disorder patients who were 18–65 years old, and without a known metabolic disease, physical pathology or any neurological disease were included in the study.

Data Collection Instruments

1. Sociodemographic Data Form: It was developed by the authors based on the aim of the study. The form aimed to collect demographic data such as age, marital status, education level, residency, employment, and economic status, and clinical evaluation data such as inpatient treatment anamnesis, smoking or alcohol use.

***2. Beck Depression Inventory (BDI)*:** The Turkish validity and reliability of the inventory was determined by Hisli[20] and the cut-off point of the scale was determined as 17.

***3. Beck Scale for Suicidal Ideation (BSSI)*:** It is a five-section scale developed to assess the severity of suicidal ideation[21]. The total score equals to the arithmetic sum of the subsection scores. The highest scale score is 38, and a high score indicates the severity of suicidal ideation. The Cronbach's alpha coefficient was determined as 0.84 in the Turkish language validity and reliability study[22].

***4. Psychache Scale (PS)*:** It is a 13-item self-report scale developed by Holden et al.[23] It was based on Shneidman's description of chronic, free-floating, non-situational, psychological pain observed due to the inability to fulfill vital psychological needs. The scale was applied to psychology students, and it was observed that it successfully separated those who had attempted suicide and those who had not. Psychache scale reveals the frequency of psychological pain rather than its severity. Turkish validity and reliability were established[24].

5. Styles of Coping with Stress (SCSS): It was developed by Folkman and Lazarus[25] in 1980 and adapted into the Turkish language by Şahin and Durak[26]. The scale includes 30 items and five sub-dimensions. The scale's reliability was determined as high (Cronbach Alpha coefficient=0.70).

Statistical Analysis

The study data were analyzed with Statistical Package for Social Sciences (SPSS) program version 22 software (SPSS Inc., Chicago, IL). Descriptive categorical data are presented in counts and percentages, and continuous data are presented in means and standard deviations. Chi-square analysis (Pearson chi-square) was conducted to compare the intra-group categorical data. Compliance of the continuous data to normal distribution was analyzed with the Shapiro-Wilk test.

Tablo 1. *Comparison of patient and control group demographics*

		Patient		Control		p*
		n	%	n	%	
Age, Mean ± SD		36.2±10.9		37.9±11.2		0.491**
Marital status	Unmarried	24	60.0	15	37.5	0.075
	Married	12	30.0	22	55.0	
	Divorced	4	10.0	3	7.5	
Education	Middle school or lower	23	57.5	15	37.5	0.073
	High school or higher	17	42.5	25	62.5	
Residence	Township	10	25.0	10	25.0	1.000
	Urban center	30	75.0	30	75.0	
Income	Low	30	75.0	8	20.0	<0.001
	Medium	8	20.0	29	72.5	
	High	2	5.0	3	7.5	
Employment	Yes	14	35.0	25	62.5	0.014
	No	26	65.0	15	37.5	
Smoking	Yes	23	57.5	15	37.5	0.073
	No	17	42.5	25	62.5	
Alcohol	Yes	16	40.0	3	7.5	0.001
	No	24	60.0	37	92.5	
Substance	Yes	19	47.5	1	2.5	<0.001
	No	21	52.5	39	97.5	
Mental disorder	Yes	27	67.5	4	10.0	<0.001
	No	13	32.5	36	90.0	
Mental disorder in the family	Yes	19	47.5	0	0	<0.001
	No	21	52.5	40	100.0	
Self-mutilation	Yes	29	72.5	2	5.0	<0.001
	No	11	27.5	38	95.0	
Suicide	Yes	18	45.0	2	5.0	<0.001
	No	22	55.0	38	95.0	
Medication	Yes	28	70.0	0	0	<0.001
	No	12	30.0	40	100.0	
Drug used	Mood stabilizer	4	14.3	-		-
	Antidepressant	3	10.7			
	Antipsychotic	1	3.6			
	Other	3	10.7			
	Multiple	17	60.7			

*Chi-square analysis; **Mann-Whitney U test; SD: Standard deviation.

Mann-Whitney U test was conducted to compare the paired group data. The Spearman correlation test was employed to investigate the correlations between continuous variables. The statistical significance level was accepted as $p<0.05$.

Results

The study was conducted with 80 participants (40 patients and 40 healthy controls). The mean age of the patients was 36.2±10.9, and it was 37.9±11 in the control group; there was no significant difference between the mean ages of the groups (p=0.491). The income level of the patient group was significantly lower when compared to that of the control group (p<0.001). The employment rate in the patient group (35%) was significantly lower when compared to the control group (62.5%) (p=0.014). Alcohol consumption (40%) was significantly higher rate in the patient group when compared to the control group (7.5%) (p=0.001). The substance abuse rate was significantly higher in the patient group (47.5%) when compared to the control group (2.5%) (p<0.001). The mental disorder rate was significantly higher in the patient group (67.5%) when compared to the control group (10%) (p<0.001). The prevalence of psychiatric disease in patient families (47.5%) was significantly higher when compared to the control group (0%) (p<0.001). The self-mutilation rate was significantly higher in the patient group (72.5%) when compared to the control group (5%) (p<0.001). The suicide rate was significantly higher in the patient group (45%) when compared to the control group (5%) (p<0.001). The drug use rate was significantly higher in the patient group (70%) when compared to the control group (0%) (p<0.001). Four (14.3%) out of 28 patients under medication used DDD, 3 (10.7%) used antidepressants, 1 (3.6%) used an antipsychotic, 3 (10.7%) used other medication, and 17 (60.7%) used multiple drugs (Table 1).

Tablo 2. *Comparison of the scale scores of the groups*

	Patient	Control	p*
	Mean ± SD	Mean ± SD	
BDI	10.9±6.5	7.9±6.4	0.037
BSSI	6.5±5.2	3.4±3.2	0.009
PS	24.3±10.3	18.7±7.6	0.008
SCSS-self-confidence approach	18.3±4.8	22.1±4.2	0.001
SCSS-optimism approach	11.0±3.4	11.9±1.9	0.149
SCSS-despair approach	15.2±3.8	12.8±4.8	0.01
SCSS-submissive approach	9.9±2.7	10.4±3.8	0.546
SCSS-social support	6.4±2.1	9.1±1.6	<0.001

* Mann-Whitney U test was applied; SD: Standard deviation; BDI: Beck Depression Scale; BSSI: Beck Scale for Suicidal Ideation; PS: Psychache Scale; SCSS: Styles of Coping with Stress.

The BDI (p=0.037), BSSI (p=0.009), PS (p=0.008), and SCSS-despair (p=0.01) scores of the patients were significantly higher when compared to the control group. However, SCSS-self-confidence (p=0.001) and SCSS-social support (p<0.001) scores were significantly lower in the patient group when compared to the control group (Table 2).

There were positive correlations between BDI and BSSI, PS and SCSS-optimism scores in the patient group. At the same time, there were significant negative correlations between BDI and SCSS-self-confidence and WCS-social support scores. There were positive correlations between BDI and PS and SCSS-despair, and a significant negative correlation between PS and SCSS-social support scores. There was a positive correlation between PS and SCSS-optimism, and significant negative correlations between PS and SCSS-self-confidence and SCSS-social support scores. There was a negative and significant correlation between the SCSS-self-confidence and SCSS-optimism subdimension scores (Table 3).

Discussion

Behavioral disorders and impulsivity in individuals with ASPD negatively affect their academic and professional achievements[27]. Similar to the findings reported in the literature, the present study demonstrated that the income levels and employment of the individuals with ASPD were lower when compared to healthy individuals.

It is known that substance abuse could lead to an antisocial lifestyle[28]. Furthermore, it was reported that aggressive behavior and impulse control disorder could lead to substance abuse[29]. Previous studies demonstrated that 80–85% of ASPD patients also meet the substance abuse disorder criteria[30,31]. In the present study, substance abuse disorder was identified in 47.5% of the ASPD patients, and a significant difference was determined when compared to the control group. Several traits associated with mood disorders such as emotional reactivity and impulsivity, are consistent with ASPD[30]. In a study investigating anxiety disorders in criminals with ASPD, it was reported that two-thirds of the participants exhibited anxiety symptoms at some point in their lives. Furthermore, it was observed that suicidal ideation and attempts were more common among

Tablo 3. *Correlation of scale scores in the patient group*

		BDI	1	2	3	4	5	6
BSSI (1)	r	0.714						
	p	0.000						
PS (2)	r	0.604	0.450					
	p	0.000	0.004					
SCSS-self-confidence approach (3)	r	-0.336	-0.120	-0.359				
	p	0.034	0.462	0.023				
SCSS-optimism approach (4)	r	0.354	0.307	0.548	-0.396			
	p	0.025	0.054	0.000	0.011			
SCSS-despair approach (5)	r	0.291	0.408	0.236	-0.021	0.104		
	p	0.068	0.009	0.143	0.898	0.524		
SCSS-submissive approach (6)	r	-0.063	0.083	-0.187	0.006	-0.230	0.129	
	p	0.700	0.612	0.247	0.970	0.154	0.426	
SCSS-social support (7)	r	-0.425	-0.394	-0.361	-0.141	0.097	-0.292	-0.008
	p	0.006	0.012	0.022	0.387	0.551	0.067	0.962

BDI: Beck Depression Scale; BSSI: Beck Scale for Suicidal Ideation; PS: Psychache Scale; SCSS: Styles of Coping with Stress.

criminals with anxiety disorders[31]. It was observed that self-mutilation attempts without suicidal ideation were more common in individuals with ASPD[32]. The present study determined that the patient group was diagnosed with more psychiatric diseases, exposed to pharmacotherapy compared to the control group. Thus, suicide and self-mutilation attempts were more frequent in this group. It could be suggested that the follow-up and treatment of psychiatric comorbidities in ASPD patients is important for patient functions.

The correlation between ASPD and depression could be due to environmental factors in a negative household. Antisocial personality disorder symptoms in adulthood are more likely in children with harsh, punitive parents or who experienced a traumatic childhood; not all individuals who were abused in childhood experience depressive symptoms in adulthood. In conclusion, genetic differences indeed play a key role[33]. In a study conducted with university students, it was reported that students with ASPD were more depressed[34]. Similarly, since the patient group experienced a significantly higher number of depressive symptoms when compared to the control group in our study, this finding was consistent with the literature.

Antisocial personality disorder leads to a higher number of suicidal attempts when compared to other personality disorders[35]. Negative emotions, low restraint, and impulsive and irresponsible behavior explain the correlation between ASPD and suicide[36]. In a study, the risk of suicide-induced mortality was almost three times higher for individuals with ASPD when compared to those without ASPD. Antisocial personality disorder patients are predominantly male, and ASPS is directly correlated with aggression, impulsivity, suicide risk level, and successful suicide[5]. A study conducted with prisoners reported that suicidal behavior was associated with impulsive and aggressive tendencies of highly antisocial individuals[37]. Similarly, the Beck suicidal ideation scale scores of individuals with ASPD were significantly higher when compared to the control group in the current study. Individuals with ASPD are often considered untreatable; however, early diagnosis and treatment could reduce behavioral problems and prevent suicide. We believe that public health interventions that address suicide risk should be developed for these individuals.

Psychological pain is the awareness of the impairment of an individual's ability to maintain personal integrity and social harmony. Most individuals experience psychological pain at some point in their lives. Psychological pain is frequently observed due to a terminal illness, grief, the end of a romantic relationship, traumatic childhood experiences, and significantly in personality disorders with impaired social conformity[38]. Psychological pain has been associated with a high prevalence of childhood abuse in women who suffer from borderline personality disorder[13]. A study comparing 50 female patients with borderline personality disorder and a healthy control group reported that the patient group experienced higher neutral and psychologically painful states compared to healthy controls[39]. This was associated with individuals with borderline personality disorder who experience difficulties in self-determination of emotional state, are biased in their perception of certain social stimuli, and are hypersensitive

to rejection[39,40]. Borderline individuals who are narcissistic might think that no one is interested in them and that everyone rejects them[41]. Similarly, individuals with ASPD feel lonely and depressed due to narcissistic tendencies[40]. In contrast, Caes et al.[42] reported that psychopathic traits reduce the ability to perceive the pain experienced by others, psychopathic individuals tolerate physical pain better, and most antisocial individuals self-mutilate to suppress psychological pain. The present study determined that individuals with ASPD experienced significantly higher psychological pain than the control group, and depression patients experienced more psychological pain when compared to non-depressed patients. It was determined that antisocial individuals with suicidal ideation experienced more psychological pain and were desperate. It was observed that antisocial individuals who felt psychological pain adopted a more optimistic approach and sought less social support. It could be suggested that depression symptoms could lead to psychological pain due to narcissistic disorder in ASPD patients, similar to those with borderline personality disorder.

Antisocial individuals are angry with themselves and others in stressful situations and generally avoid thinking about and experiencing them. Antisocial individuals are egocentric and react aggressively to any obstacle or disappointment. Avoiding the facts, they hide in fantasies, which sometimes take the form of pathological lies[43]. A previous study reported that coping does not play a significant role in distress experienced by prisoners with antisocial maladaptive personalities[44]. Another study found that these individuals were fearless and had social needs[45]. Evidence suggested that ASPD patients sought social support less[46]. Similarly, it was determined that individuals with ASPD sought less social support and adopted a less self-confident approach in our study. It should be noted that coping with maladaptive stress is a mediator between maladaptive personality and psychological distress, and interventions that encourage the adoption of more adaptive coping styles should be prioritized.

The present study has certain limitations. The present research was a cross-sectional study, limiting the conclusions on the causality between the variables. The data was only collected with self-report scales and the coping styles analysis could have been more objective if it had been based on third party observations and judgments. Although the number of participants provided an adequate sample size, studies that would be conducted with different traits and a larger sample size would contribute further to the literature.

In conclusion, the study findings demonstrated that although individuals with ASPD lack empathy and are irresponsible and reckless, these individuals (especially those with depression) could feel psychological pain and require social support. It could be suggested that early treatment of psychological pain, such as its identification, insight, and support for effective coping strategies, could prevent self-harm behavior or suicide in ASPD, changing the prognosis.

Statement of Ethics

The research was approved by Fırat University, Faculty of Medicine ethics committee (Approval no:2021/12-16).

Conflict of Interest Statement

All the authors declare no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Role of Parenchymal Thickness in Predicting the Amount of Bleeding During Percutaneous Nephrolithotomy

Parankim Kalınlığın Perkütan Nefrolitotomi Esnasındaki Kanama Miktarını Predikte Etmekteki Yeri

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ABSTRACT

Aim: *Percutaneous nephrolithotomy (PCNL) is the approved first-line treatment for complicated kidney stones larger than 2 cm. One of the most prevalent problems during PCNL is bleeding. The majority of bleeding is managed with conservative methods. This study aims to investigate the potential effect of parencyhmal thickness on the likelihood of bleeding during PCNL surgery.*

Material and Method: *The results of patients who underwent PCNL to treat kidney stones in our clinic between May 2016 and May 2022 were subjected to a retrospective data analysis. Demographic data of patients, characteristics of stones, operation time, access technique, pre-and postoperative hemogram values, transfusion, and renal parenchyma thickness were recorded.*

Results: *Of the 181 patients included in the study, 127 were male, 54 were female, and the mean age was 45.22 (±14). The mean Charlson Comorbidity Index of the patients was found to be 0.93 (0–5). Right PCNL was performed in 75 patients, and left PCNL in 106 patients. The mean stone size was 26.16 mm (±9.9), stone surface area was 343.14 mm² (±81 - 1507), and the stone density was 1115.52 HU (±390.52). 27.1% of the stones were non-opaque. The average parenchymal thickness was measured at 18.82 mm (±4.68). Patients who received blood transfusion were excluded from the study. While all bleedings were managed conservatively, embolization and nephrectomy were not required. The mean decrease in hemoglobin was 2.02 g/dl (0–4.4). Four patients exhibited a postoperative fever. When Spearman's correlation test was performed between the groups, a moderate correlation was observed between parenchymal thickness and hemoglobin decrease ($p<0.01$), and a weak correlation between stone surface area and hemoglobin decrease ($p<0.05$).*

Conclusion: *As a result, the parenchymal thickness can guide surgeons in estimating bleeding and planning blood requirements before surgery.*

Key words: *percutaneous nephrolithotomy; bleeding; parenchymal thickness*

ÖZET

Amaç: *İki santimetre ve üzerindeki ve kompleks böbrek taşlarının tedavisinde perkütan nefrolitotomi (PNL) ilk sırada önerilen tedavi seçeneğidir. Perkütan nefrolitotomi sırasında en sık karşılaşılan komplikasyonlardan biri de kanamadır. Kanamaların çoğu konservatif yaklaşımlarla kontrol altına alınmaktadır. Çalışmamızın amacı PNL ameliyatına bağlı kanama olasılığını tahmin etmek, parankim kalınlığının kanamaya olası etkisini saptamaktır.*

Materyal ve Metot: *Kliniğimizde Mayıs 2016 – Mayıs 2022 tarihleri arasında böbrek taşı tedavisi için PNL yapılan hastaların sonuçları retrospektif bir veri analizine tabi tutuldu. Hastaların demografik verileri, taşların özellikleri, ameliyat süresi, akses tekniği, preoperatif ve postoperatif hemogram değerleri, transfüzyon yapılıp yapılmadığı, böbrek parankim kalınlıkları kayıt altına alındı.*

Bulgular: *Çalışmaya dâhil edilen 181 hastanın 127'ü erkek, 54'i kadın ve yaş ortalaması 45,22 (±14) olarak tespit edildi. Hastaların Charlson Comorbidity Index ortalaması 0,93(±0–5) bulundu. Yetmiş beş hastaya sağ, 106 hastaya sol PNL ameliyatı yapıldı. Ortalama taş boyutu 26,16 mm (±9,9), taş yüzey alanı 343,14 mm² (±81–1507), taş dansitesi 1115,52 HU (±390,52) olarak ölçüldü. Taşların %27,1'si non-opaktı. Parankim kalınlıkları ortalaması 18,82 mm (±4,68) ölçüldü. Kan transfüzyonu yapılan hastalar çalışma dışında bırakıldı. Tüm kanamalar konservatif olarak kontrol altına alınırken, embolizasyon ve nefrektomiye gerek duyulmadı. Hemoglobin düşüşü ortalama 2,02 g/dl (0–4,4)'di. Dört hastada ise postoperatif ateş gözlendi. Gruplar arasında Spearman's korelasyon testi yapıldığında parankim kalınlığı ile hemoglobin düşüşü arasında orta düzeyde ($p<0,01$), taş yüzey alanıyla hemoglobin düşüşü arasında zayıf düzeyde ($p<0,05$) korelasyon gözlenmiştir.*

Sonuç: *Sonuç olarak parankim kalınlığı cerrahlara ameliyat öncesinde kanamayı tahmin etme ve kan gereksinimini planlamada rehberlik edebilir.*

Anahtar kelimeler: *perkütan nefrolitotomi; kanama; parankim kalınlığı*

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Introduction

The percutaneous nephrolithotomy (PCNL) method is accepted as the first choice in the surgical treatment of kidney stones larger than 2 cm according to stone guidelines[1]. Although advances in laser technology and flexible ureteroscopes continue rapidly, PCNL remains the gold standard in treating large stones. As an invasive method, bleeding is a frequent complication during PCNL surgery[2]. In PCNL, the caliceal papilla is desired for successful access and the infundibulum of the calyceal system is avoided to minimize bleeding. However percutaneous access is a controlled grade 4 trauma for the kidney and management of the bleeding is essential for PCNL[3]. Although a conservative approach is sufficient in most of the bleeding after PCNL, some patients (0.5–2.4%) may have severe bleeding requiring surgical intervention[4,5]. Our study aims to predict the probability of bleeding during and after PCNL surgery, determine risk factors, and reveal the relationship between parenchymal thickness and bleeding.

Materials and Methods

The whole methodology of the study complies with the Declaration of Helsinki. Our study was approved by the ethics committee of our institute (Ethics committee decision number: 80576354-050-99/166). Patients who underwent PCNL to treat kidney stones in our clinic between May 2016 and May 2022 were included in our study. Surgical procedures were performed by endourologists who are experienced in PCNL.

The study did not include patients with multiple calyx access, receiving blood transfusions, using anticoagulants or antiaggregants, and patients with anatomical variations such as horseshoe kidney, ptotic kidney, or malrotated kidney.

Non-contrast computed tomography and plain radiography were used for preoperative radiological evaluation in all patients. Renal parenchyma thickness measurements were taken from the thickest point of the axial section. The use of general anesthesia was standard practice in all procedures. All patients were positioned prone after placing the ureteral catheter on the side of the stone in the lithotomy position. The anatomy of the calyceal system was seen by introducing a contrast agent into the renal collecting system via the ureteral catheter. Then, access was obtained from the posterior calyx using an 18-gauge needle under C-arm fluoroscopy. Amplatz dilators up to 30 Fr were used to dilate the tract. After placing the Amplatz sheath, a 26 Fr nephroscope was inserted into the collecting system (Storz Medical AG, Kreuzlingen, Switzerland). Renal stones were disintegrated using pneumatics (Vibrolith®, ELMED). The stone fragments were extracted using forceps. In all patients, a 16 Fr nephrostomy was inserted in the renal pelvis after the procedure. When there were no complications, the nephrostomy was taken out on the third day. Plain radiographs of the kidney, ureter, and bladder were taken on the first postoperative day. The nephrostomy tube was clamped on the 3rd postoperative day. Nephrostomy catheters were removed in patients without pain. Antegrade nephroureterography was performed in patients with pain, and the nephrostomy catheter was removed after the insertion of a double-J catheter in patients with ureteral obstruction. Patients were checked out with non-contrast computed tomography in the third month after surgery. Remaining fragments ≤4 mm in diameter that did not cause occlusion, pain, or infection were considered clinically insignificant. Preoperative hemograms were obtained from the patients, and hemogram follow-up was performed during and after the operation. The difference between preoperative and postoperative (1st and 24th hour) hemograms was calculated and compared with parenchymal thickness, stone surface area, operation time, and residual stone size. The preoperative Charlson Comorbidity Index score of the patients was calculated.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) program version 22.0 was used for the statistical analysis (SPSS Inc., Chicago, IL, USA). Factors affecting the decrease in hemogram were investigated using Spearman/Pearson correlation. In addition, mean and frequency information of other information was obtained.

Results

When our results were evaluated, the following data were reached:

The study comprised 181 patients, 127 of whom were male and 54 of whom were female, with a mean age of 45.22 (14) years. The mean Charlson Comorbidity Index of the patients was found to be 0.93(0–5). In 75 patients, right PCNL was performed, and in 106 patients, left PCNL was conducted. The mean stone size

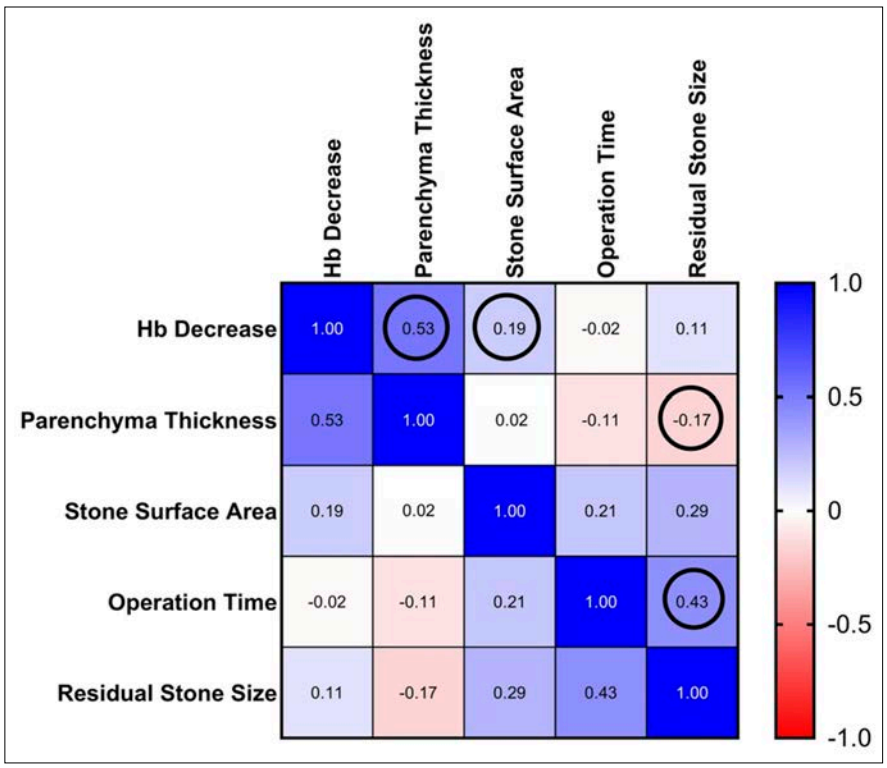

Figure 1. *Comparison of parenchyma thickness with hemoglobin decrease, stone surface area, operation time and residual stone size.*

was 26.16 mm (±9.9), the stone surface area was 343.14 mm^2 (±81–1507), and the stone density was 1115.52 HU (±390.52). 27.1% of the stones were non-opaque. Access was made using the bull's eye method in 53% and the triangulation method in 47%. The average operative time was 173.71 min (±46.2) was detected. In their 3-month CT follow-up, 48.6% of the patients had a residual greater than 4 mm. The average parenchymal thickness was measured as 18.82 mm (±4.68). While all bleedings were managed conservatively, embolization and nephrectomy were not required. Hemoglobin decreased by an average of 2.02 g/dl (0–4,4). Post-op fever was observed in 4 patients (Table 1).

When Spearman's correlation test was performed between the groups, a moderate correlation was observed between parenchymal thickness and hemoglobin decrease ($p<0.01$), and a weak correlation between stone surface area and hemoglobin decrease ($p<0.05$). In addition, a weak inverse association between parenchymal thickness and residual size was detected ($p<0.05$). As the operation time increased, the residual stone size increased significantly ($p<0.01$). Also, a moderate positive correlation was observed between the stone surface area and the residual stone size ($p<0.01$). No correlation was found between the duration of the operation and the decrease in hemoglobin (Fig. 1).

Table 1. *Patient demographics and pre- and post-operative parameters*

		Count	% or ± SD
Gender	Male	127	70.2%
	Female	54	29.8%
Age		45.22	±14
Charlson comorbidity index (min-max)		0.93	0–5
Lateralization	Right	75	41.4%
	Left	106	58.6%
Size (mm)		26.16	9.9
Hydronephrosis		143	79%
Access technique	Bull's eye	96	53%
	Triangulation	85	47%
Stone surface area (mm^2) (min-max)		343.14	81–1507
Localization	Single calyx or pelvis	143	79%
	Multicalyxel	38	21%
Hounsfield unit		1115.52	±390.52
Parenchyma thickness (mm)		18.82	±4.68
Opacity	Opaque	132	72.9%
	Non-opaque	49	27.1%
Operation time (min)		173.71	±46.20
Hb decrease (g/dL)(min-max)		2.02	(0–4.4)
Length of stay in hospital (day)		4.34	(2–28)
Postoperative fever		4	2.2%
Residual stone		88	48.6 %

Discussion

Until 30 years ago, open surgery was the standard treatment for urinary tract stones. Advances in ESWL, ureterorenoscopy and PCNL have enabled these methods to replace open surgery to treat stones. In treating large, multiple, and staghorn kidney stones, PCNL is recommended as the first choice instead of open surgery. Percutaneous nephrolithotomy is a safe and reliable method for treating kidney stones[1,6–10].

However, according to the results of different studies, a wide range of complication rates have been reported between 20.5% and 83%[2,6,11,12]. This shows that although PCNL is an endourological procedure, it is an invasive method with high complication rates. One of the most severe complications is bleeding. As long as bleeding can be controlled in PNL stages (renal puncture, tract dilatation, use of rigid nephroscopy, stone fragmentation), bleeding is a natural consequence According to studies, blood transfusion rates range from 1% to 34%.[4,6,13–15]. Fortunately, bleeding is controlled chiefly with conservative methods in most cases. Renal embolization and nephrectomy rates are as low as 0.5–2.4%[4,5]. In our study, no patient underwent nephrectomy or embolization due to bleeding.

In the literature, many factors that cause bleeding in PNL surgery have been investigated. These are stone size, type, stone surface area, hydronephrosis degree, number and technique of access, operation time, presence of diabetes mellitus in the patient, and BMI[14,16–21].

One of the criteria whose relationship with bleeding has been investigated is the parenchymal thickness[14,16,17]. Congenital and subsequent causes influence the parenchyma thickness of the kidney. The most common cause affecting renal parenchyma thickness is urinary tract obstruction. Urinary tract stones are the most typical cause of urinary tract obstruction. In wholly or partially obstructed systems, the thickness of the parenchyma becomes thinner. Concurrent infection of the blocked system causes a decrease in kidney functions and renal parenchyma thickness[22,23].

Rifaioglu et al. found that parenchyma thickness did not affect bleeding[18]. However, there was a positive correlation between parenchymal thickness and bleeding during PCNL in other studies[14,16,17]. In our study, in parallel with other studies, a moderate positive correlation was observed between parenchymal thickness and decrease in hemoglobin ($p<0.01$). Another factor affecting the decrease in hemoglobin in our study was the stone surface area. A weak correlation was observed between the stone surface area and the decrease in hemoglobin ($p<0.05$). This is because as the stone surface area increases, the bleeding may have increased due to repetitive manipulations for stone removal. In addition, our study determined that the duration of the operation and the presence of residual stones did not affect the amount of bleeding.

Limitations

One limitation of this study was that it was a retrospective single-institution study.

The findings may also have been influenced by the fact that many surgeons with varying degrees of experience performed the surgeries.

Despite all these negativities, it will contribute to the literature predicting intraoperative and postoperative bleeding before surgery.

Conclusion

As a result of our study, it was seen that the thickness of the parenchyma affects the bleeding. Parenchymal thickness can guide surgeons in estimating bleeding and planning blood requirements before surgery.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Multicenter Research of the Molecular Epidemiology of Carbapenem-Resistant *Acinetobacter baumannii* Infections

Karbapenem Dirençli Acinetobacter baumannii Enfeksiyonlarının Moleküler Epidemiyolojisinin Çok Merkezli Araştırması

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ABSTRACT

Aim: *Acinetobacter baumannii is an important pathogen causing concern worldwide with increasing antibiotic resistance. We aimed to provide epidemiological data and molecular differences between multidrug resistant A.baumannii isolates obtained from 7 different centers in Türkiye.*

Material and Method: *One hundred sixty-six multidrug-resistant A.baumannii strains were included in the study. All the isolates were tested for antibiotic susceptibility according to EUCAST criteria. To molecularly confirm the carbapenem-resistant A.baumannii isolates, the specific blaOXA-51-like gene region was detected by polymerase chain reaction (PCR) method. A possible phylogenetic relationship between multi-drug resistant isolates was investigated using Pulsed-field Gel Electrophoresis method.*

Results: *One hundred sixty-six carbapenem-resistant A.baumannii strains were evaluated by the ApaI-PFGE (Pulsed-field gel electrophoresis –PFGE) method using the CHEF-DRII electrophoresis system. A total of 51 clusters were grouped into 142 pulsotypes. Twenty clusters had single members. Thirty-one clusters had multiple members and were identified with the capital letters of the alphabet such as A, B, …, and Z26. It was observed that 40 PFGE profiles showed 100% related.*

Conclusion: *More intense contamination is in question in the provinces with many patients. In four of the seven different centers, more innocent results were obtained in terms of the number of samples, antibiotic resistance and clonal relationship when compared to the other three centers. However, this may be caused by the low population zone and inadequate health services. Regional or multicenter studies are minimal. Thus, further studies involving more centers and larger populations are needed. Consequently, the present study will shed light on future studies and create thriving literature on border regions.*

Key words: *A.baumannii; $_{blaOXA-51-like}$ gene; carbapenem-resistant; pulsed-field gel electrophoresis; PCR*

ÖZET

Amaç: *Acinetobacter baumannii, antibiyotik direnci giderek artan ve tüm dünyada endişe yaratan önemli bir patojendir. Türkiye'nin yedi farklı merkezinden temin edilen çoklu ilaca dirençli A.baumannii izolatları arasındaki epidemiyolojik verileri ve moleküler farklılıkları sağlamayı amaçladık.*

Materyal ve Metot: *Yüz altmış altı çoklu ilaca dirençli A.baumannii suşu çalışmaya dâhil edildi. Tüm izolatlar EUCAST kriterlerine göre antibiyotik duyarlılığı açısından test edildi. Karbapenem dirençli A.baumannii izolatlarının moleküler olarak doğrulanması amacıyla polimeraz zincir reaksiyonu (PCR) yöntemi ile spesifik blaOXA-51 benzeri gen bölgesi saptanmıştır. Çoklu ilaca dirençli izolatlar arasındaki olası filogenetik ilişki, Pulsed-field jel elektroforez (PFGE) yöntemi kullanılarak araştırıldı.*

Bulgular: *166 karbapenem dirençli A.baumannii suşu, CHEF-DRII elektroforez sistemi kullanılarak ApaI-PFGE yöntemi ile değerlendirildi. Toplam 51 küme 142 pulsotipte gruplandı. Yirmi kümenin tek üyeleri vardı. Otuz bir küme birden fazla üyeye sahipti ve A, B, … ve Z26 gibi alfabenin büyük harfleriyle tanımlanıyordu. Kırk PFGE profilinin %100 ilişkili olduğu görüldü.*

Tartışma: *Hasta sayısı fazla olan illerde daha yoğun bulaşma söz konusudur. Yedi farklı merkezden dördünde örnek sayısı, antibiyotik direnci ve klonal ilişki açısından diğer üç merkeze göre daha masum sonuçlar elde edildi. Ancak bunun nedeni nüfusun az olması ve sağlık hizmetlerinin yetersiz olması olabilir. Bölgesel ya da çok merkezli çalışmalar oldukça sınırlıdır. Bu nedenle daha fazla merkezi ve daha geniş popülasyonları içeren çalışmalara ihtiyaç vardır. Sonuç olarak bu çalışmanın sınır bölge olarak ileride yapılacak çalışmalara ışık tutacağı ve iyi bir literatür oluşturacağı kanaatindeyiz.*

Anahtar kelimeler: *A.baumannii, blaOXA-51 benzeri gen, karbapenem dirençli, Pulsed-field jel elektroforez, PCR*

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Introduction

Acinetobacter baumannii is an important pathogen causing concern around the world with an increasing antibiotic resistance. It is one of the leading healthcare-associated infection (HAI) agents, especially in intensive care units. It is most frequently encountered with nosocomial infections that can cause epidemics[1]. As *A.baumannii* has all antimicrobial resistance mechanisms, treatment with multi-drug resistance is also a major clinical difficulty in recent years[2]. Especially, the resistance of carbapenem reaches up to 90% throughout the world[3]. Thus, carbapenem-resistant *A.baumannii* (CRAB) is associated with a high mortality rate in healthcare institutions[4]. In addition, it is one of the critical priority pathogens in the list of World Health Organization (WHO). Today, cholistin is preferred in the treatment of high CRAB infection[2]. This is an extremely important public health problem due to increased incidence of HAIs, prolonged hospitalization, increased mortality rate, impaired quality of life, and economic losses[5]. Hospital-acquired infections are defined as one of the most serious patient safety problems in healthcare services around the world[6]. In recent years, surveillance and control programs are developed to prevent the increasing incidence of HAI and multiple antibiotic resistance. Each country and even each region has started to develop its own surveillance systems. In virtue of these strategies, significant reductions have been reported in the incidence of HAI[7]. Epidemiologic studies conducted on the clinical and molecular features of CDAB may aid infection control strategies. Pulsed-field gel electrophoresis (PFGE) technique is accepted as the golden standard for the genotyping of *A.baumannii*[8].

The primary aim of the current study is to determine the clonal relationships between *A.baumannii* strains, isolated from 7 centers (Adana, Ağrı, Ardahan, Iğdır, Kars, Mersin, and Van) in Türkiye, via PFGE method and to contribute to the surveillance system. There is no literature and surveillance data on this subject including the centers of study. Thus, the present study will be an important data source for the literature. Also, demographic characteristics between two regions will be compared.

Materials and Methods

Sample Collection

In the study, 166 multidrug-resistant (MDR) *Acinetobacter baumannii* strains from 7 centers (Adana, Ağrı, Ardahan, Iğdır, Kars, Mersin, and Van) in 2 regions (Çukurova and Eastern Anatolia) of Türkiye between 2019 and 2020 were included in the study. Of the total 166 strains belonging to different patients, 84 were isolated from the Eastern Anatolia region and 82 from the Çukurova region.

The clinical materials from which *A.baumannii* strains were obtained consisted of 32 (19.2%) blood samples, 42 (25.3%) sputum samples, 46 (27.7%) tracheal aspirate samples, 22 (13.2%) urine samples, 19 (11.4%) wound samples, and 5 (3%) pleural fluid samples. Among total samples, the most frequent isolation was obtained from tracheal aspirate samples with 46 (27.7%) strains and the lowest isolation was obtained from pleural fluid with 5 (3%) strains (Table 1).

Table 1. *Distribution of clinical materials according to the centers*

Centers	Sputum (n=42) (%)	Tracheal aspirate (n=46) (%)	Blood (n=32) (%)	Urine (n=22) (%)	Lesion (n=19) (%)	Pleural fluid (n=5) (%)	Total (n=166) (%)
Adana City Hospital	5 (11.9%)	14 (30.4%)	7 (21.8%)	4 (18.1%)	7 (36.8%)	2 (40%)	39
Mersin University Hospital	9 (21.4%)	13 (28.2%)	7 (21.8%)	7 (21.8%)	7 (21.8%)	0 -	43
Van State Hospital	11 (26.1%)	13 (28.2%)	9 (28.1%)	5 (22.7%)	1 (5.2%)	3 (60%)	42
Kars State Hospital	13 (30.9%)	0 -	5 (15.6%)	3 (13.6%)	0 -	0 -	21
Iğdır State Hospital	2 (4.7%)	4 (8.6%)	2 (6.2%)	3 (13.6%)	3 (15.7%)	0 -	14
Agri State Hospital	0 -	2 (4.3%)	2 (6.2%)	0 -	1 (5.2%)	0 -	5
Ardahan State Hospital	2 (4.7%)	0 -	0 -	0 -	0 -	0 -	2

Culture and Identification

The isolates were inoculated on 5% sheep blood agar and MacConkey agar media and incubated overnight at 37˚C for 18–24 hours. Phenotypic identification at species level was confirmed by colony morphology, microscope image, catalase, oxidase test, and biochemical tests[9]. The isolates were stored in blood glycerol broth at -20°C.

Antibiotic Susceptibility Tests

All the isolates were tested for antibiotic susceptibility against Amikacin, Ciprofloxacin, Gentamicin, Imipenem, Levofloxacin, Meropenem, Trimethoprim/Sulfomethoxazole, Ceftazidime, Piperacillin/Tazobactam (Sigma-Aldrich, USA) via liquid microdilution method according to EUCAST criteria. Kirby Bauer Disk Diffusion (KBDD) test was performed for carbapenem resistance[10,11].

Molecular Examinations

In order to molecularly confirm the CRAB isolates, the specific bla$_{OXA\text{-}51\text{-}like}$ gene region was detected by PCR method[12]. Possible phylogenetic relationship between multi-drug resistant isolates was investigated by using PFGE method.

Polymerase Chain Reaction (PCR)

Carbapenem resistance of *A.baumannii* strains was verified by identifying specific bla$_{OXA\text{-}51\text{-}like}$ gene region (Thermo Scientific™). O51-GD2M-F (5'–GACCGAGTATGTACCTG CTTCGACC-3') and O51-GD2M-R (5'–GAGGCTGAACAACCCATCCAGTTAACC-3') (497 bp) primary sequences were used.

DNA extraction

Pure bacterial colonies were incubated in 1 ml Luria Broth (10 g peptone, 5 g yeast extract, 5 g NaCl, 1000 ml distilled water) that was shared in eppendorfs, for 18 hours at 37°C. After incubation, eppendorfs were centrifuged at 13000 rpm for 5 min. Supernatant was discarded and 300 µl sterile water was added to the pellet at the bottom and pipetted. It was boiled at 100°C for 10 minutes, and then, centrifuged at 13000 rpm for 10 minutes. Of the supernatant, 200–250 µl was stored at -20°C in order to be used as template DNA.

Amplification

To the total reaction mixture prepared for amplification, 12.5µl Master Mix (Thermo Scientific™), 3µl template DNA, and 0.5µl of each primer (100 pmol/µl of stock solution) and sterile distilled water were added to reach a total reaction volume of 25µl. Thermal cycling (APPLIED BIOSYSTEMS 2720 Termal Cycler) parameters were applied as follows: initial denaturation at 94°C for 4 min; denaturation at 30 cycles of 94°C for 30 s; primer binding at 55°C for 30 s; chain elongation at 72°C for 1 min; and final elongation at 72°C for 7 min. The bands obtained as a result of the PCR products run on a 2% agarose gel in an electrophoresis tank were evaluated in a gel imaging device.

Pulsed-Field Gel Electrophoresis (PFGE) method

A.baumannii, identified by PCR at species level was cultured as a single colony on blood agar medium. After incubation at 37°C for one night, the purity of the culture was checked. The single colony forming in the medium was passed back to blood agar broth medium and left to incubate at 37°C for one night. The clonal relationship between the colonies in the pure culture obtained was investigated by PFGE method using ApaI restriction enzyme according to Pulsenet KEPA protocol[13]. Electrophoresis was performed on a CHEFF-DR II device (Bio-Rad Laboratories, Nazareth, Belgium) with an initial pulse time of 5 sec, end pulse time of 30 sec, current of 6V, and temperature of 14°C for 20 hours and DNA patterns were evaluated via the GelCompar II software. Dendogram of PFGE profiles was created by using UPGMA and clustering analysis was performed. According to the "Dice" similarity coefficient depending on bands, the relationship between strains with 80% or more similarity was determined. Clustering analyses were shown by capital letters (A, B, C, ...)[14].

Results

In the study, 166 CDAB strains were included between 2019 and 2020. Of the isolates, 84 belonged to Eastern Anatolia region and 82 to Çukurova Region. All of 166 *A.baumannii* strains isolated from 7 hospitals had specific *bla*$_{OXA\text{-}51\text{-}like}$ gene regions. In the distribution of clinical material of CDAB strains according to provinces, tracheal aspirate took place at the top at 4 centers. Among the total samples, the clinical material containing maximum *A.baumannii* was tracheal aspirate (27.7%) and pleural fluid (3%) contained minimum *A.baumannii* (Table 1).

Table 2. *Antibiotic resistance rates*

Antibiotics	Adana City Hosp. (n=39) (%)	Mersin Univ. Hosp. (n=43) (%)	Van State Hosp. (n=40) (%)	Kars State Hosp. (n=24) (%)	Iğdır State Hosp. (n=13) (%)	Ağrı State Hosp. (n=5) (%)	Ardahan State Hosp. (n=2) (%)	Total (n=166) (%)
Amikacin	35 94.5%	39 90.6%	30 75%	15 %62.5	5 38.4%	2 40%	2 100%	128 78%
Ciprofloxacin	39 100%	39 90.6%	39 97.5%	20 83.3%	10 76.9%	5 100%	2 100%	152 92.6%
Gentamicin	32 86.4%	39 90.6%	7 17.5%	18 75%	11 84.6%	5 100%	2 100%	114 69.5%
İmipenem	39 100%	43 100%	40 100%	24 100%	13 100%	5 100%	2 100%	166 100%
Levofoxacin	39 100%	39 90.6%	38 95%	19 79.1%	10 76.9%	1 20%	2 100%	146 89%
Meropenem	39 100%	43 100%	40 100%	24 100%	13 100%	5 100%	2 100%	166 100%
Trimethoprim/ Sülfometoksazol	34 91.8%	38 88.3%	30 75%	11 45.8%	5 38.4%	2 40%	1 50%	121 73.7%
Ceftazidime	39 100%	39 90.6%	38 95%	19 79.1%	6 46.1%	5 100%	2 100%	146 89%
Piperacillin/ tazobactam	39 100%	39 90.6%	38 95%	19 79.1%	6 46.1%	5 100%	1 50%	145 88.4%

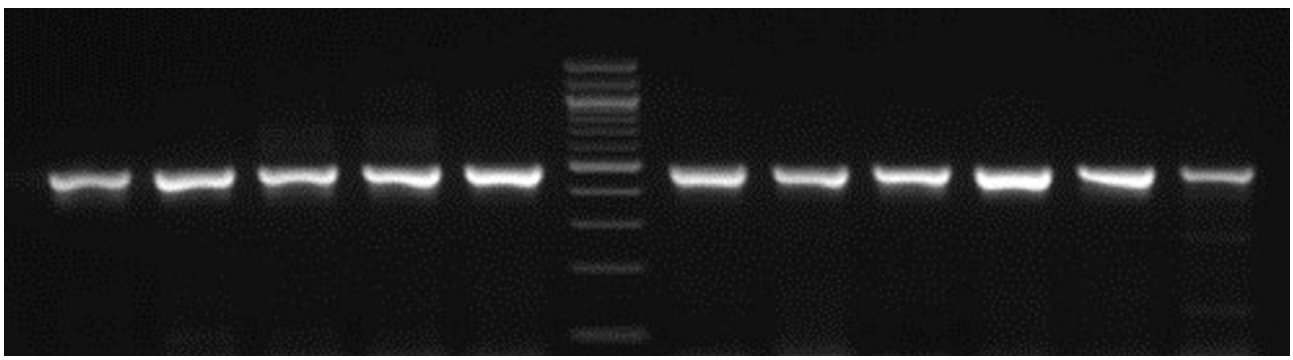

Figure 1. *PCR image of blaOXA-51-like gene regions in CRAB isolates.*

A.baumannii isolates, which were identified to species level from hospitals and whose antibiotic susceptibilities were determined, were verified by phenotypic and molecular tests again. Kirby Bauer Disk Diffusion test was performed to verify the resistance of carbapenem[10,11]. Carbapenem resistance was detected in all *A.baumannii* strains. As a result of the liquid microdilution method, Amikacin (78%), Ciprofloxacin (92.6%), Gentamicin (69.5%), Imipenem (100%), Levofloxacin (89%), Meropenem (100%), Trimethoprim/ Sulfamethoxazole (73.7%), Ceftazidime (89%), and Piperacillin/Tazobactam (88.4%) were found to be resistant with the rates given in parentheses. Except for carbapenem, the highest resistance was found in ciprofloxacin with the rate of 92.6%. The lowest resistance was found in gentamicin with a rate of 69.5% (Table 2). When the number of samples collected between the centers was compared, it was found that resistance rates were much higher in the provinces with high populations such as Adana, Mersin, and Van.

The presence of a specific $bla_{OXA\text{-}51\text{-}like}$ gene region was demonstrated by PCR for both carbapenem resistance and species identification in *A.baumannii* isolates. One hundred sixty-six isolates containing carbapenemase gene, i. e., specific $bla_{OXA\text{-}51\text{-}like}$ gene were included in the study (Fig. 1).

One hundred sixty-six CRABs were evaluated by ApaI-PFGE method using CHEF-DR II electrophoresis system. Clustering rate was calculated as 46.5%. Using the Gel COMPARE-II software system, a total of 51 clusters were grouped into 142 pulsotypes based on 80% or more similarity. Twenty clusters had single members. Thirty-one clusters had multiple members and identified with the capital letters of the alphabet such as A, B, ..., and Z26. Thirty-one clusters were distributed into pulsotypes identified as A1, A2, A3, ...Z26z1 (Fig. 2) in themselves.

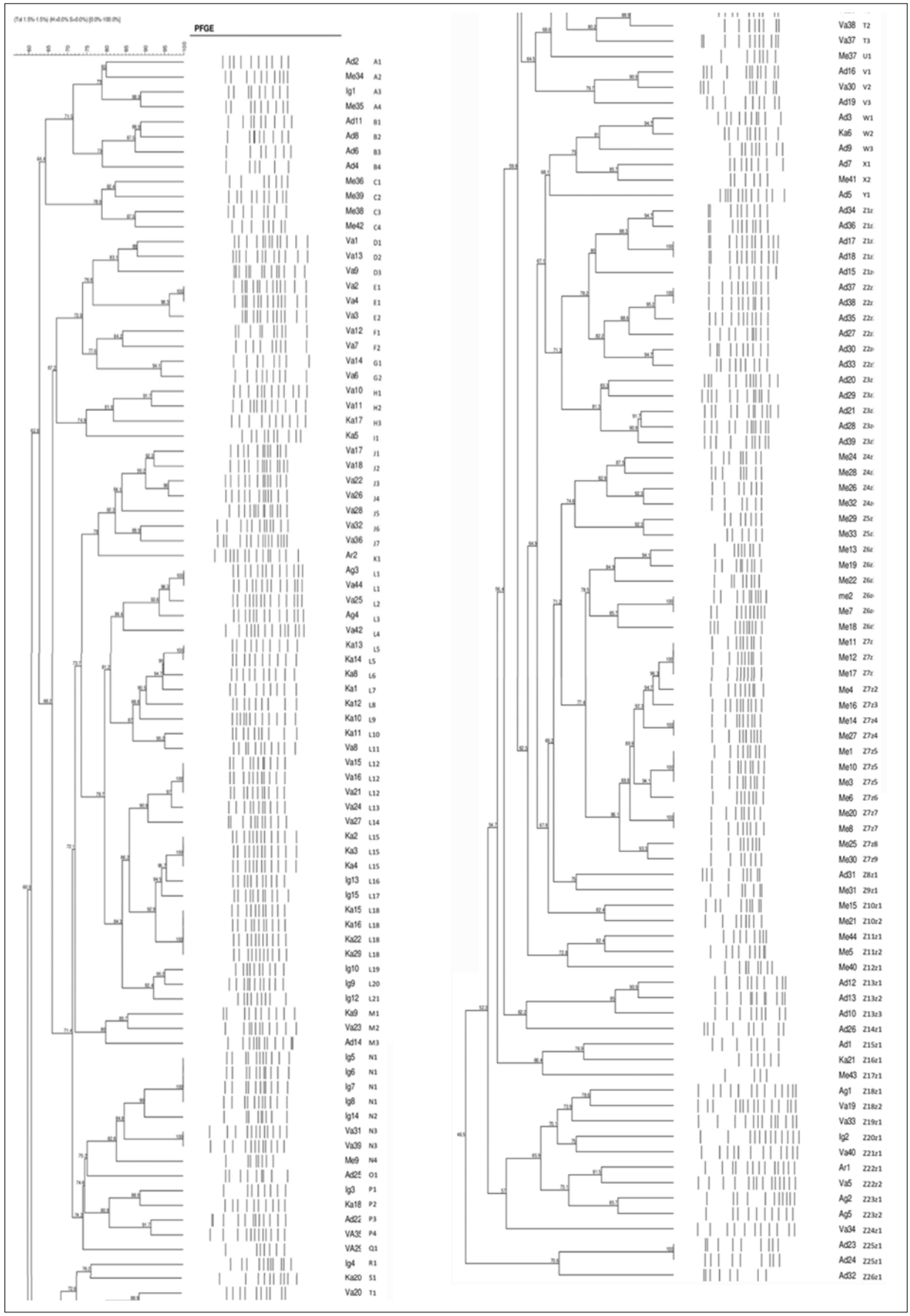

Figure 2. *Pulsed-field gel electrophoresis dendrogram image.*

Table 3. *100% related isolates by PFGE profiles*

Küme	Pulsotip	İzolat numarası
E	E1	Va2, Va4
L	L1	Ag3, Va44
	L5	Ka13, Ka14
	L12	Va15, Va16, Va21
	L15	Ka2, Ka3, Ka4
	L18	Ka15, Ka16, Ka22, Ka29
N	N1	Ig5, Ig6, Ig7, Ig8
	N3	Va31, Va39
Z1	Z1z3	Ad17, Ad18
Z2	Z2z1	Ad37, Ad38
Z6	Z6z4	Me2, Me7
Z7	Z7z1	Me11, Me12, Me17
	Z7z4	Me14, Me27
	Z7z5	Me1, Me3, Me10
	Z7z7	Me20, Me8
Z25	Z25z1	Ad23, Ad24

Va: Van; Ag: Ağrı; Ka: Kars; Ig: Iğdır; Ad: Adana; Me: Mersin.

According to the results of the analysis, it was observed that 40 PFGE profiles showed 100% related profiles in different clusters. The clusters were formed of a total of 16 pulsotypes as 10 clusters with 2 members, 4 clusters with 3 members, and 2 clusters with 4 members (Fig. 3).

It was observed that E1, L1, L5, N3, Z1z3, Z2z1, Z6z4, Z7z4, Z7z7 and Z25z1 pulsotypes were gathered as 2-member; L12, L15, Z7z1, Z7z5 pulsotypes as 3-member, and L18 and N1 pulsotypes as 4-member (Table 3).

The largest cluster was found to be the 30-member cluster L, which was aggregated in 21 pulsotypes identified as L1, L2, L3, ...L21. Only isolates from the Eastern Anatolia region were found in cluster L. This was followed by the 15-member cluster Z7, which was grouped in 9 pulsotypes (Z7z1-Z7z9). The second largest cluster, cluster Z7, belonged to Mersin isolates only. Subsequent 8-member cluster N consisted of 4 pulsotypes grouped in N1-N4. Cluster J had 7 members and 7 pulsotypes, with each member having a different pulsotype. Clusters Z2 and Z6 consisted of 6 members grouped in 5 pulsotypes. Cluster Z3 was grouped in 5 pulsotypes, Z3z1-Z3z5 with 5 members. The smallest clusters were 2-membered F, G, X, Z5, Z10, Z11, Z18, Z22, Z23 and Z25 clusters. D, E, H, M, T, V, W and Z13 clusters were gathered in 3 pulsotypes which were 3-membered (Table 4).

Discussion

Acinetobacter baumannii has become one of the most serious threats especially in intensive care units where antibiotic treatment does not respond. In addition, they are also encountered as HAIs causing the most frequent reason of morbidity and mortality in the world. Multidrug-resistant *A.baumannii,* threatening community health, is between 3% and 17% among HAIs around the world. In Türkiye, this rate varies between 5% and 20%[15,16]. With surveillance studies, it is thought to be able to prevent both pandemic and infection by 70% all over the world. The studies based on

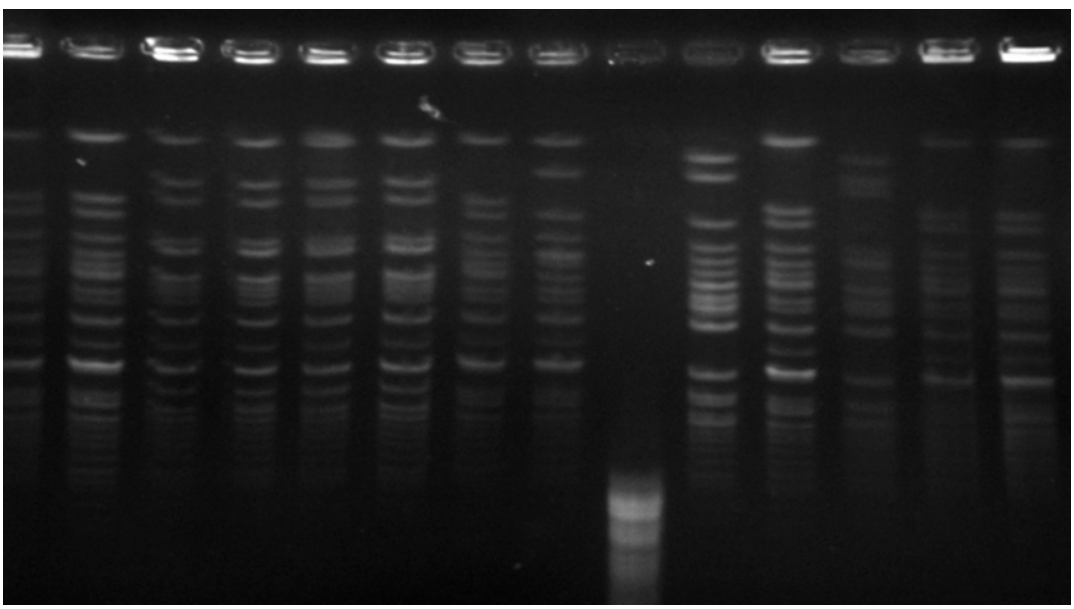

Figure 3. *Pulsed-field gel electrophoresis results image of 100% clonal related CRAB strains.*

Table 4. *Relationship status of PFGE pulsotypes*

Cluster	Pulsotype	Related pulsotypes			
		≥95	≥90	≥85	≥80
A	A1-A4		A3/A4		A1/A2/(A3-A4)
B	B1-B4		B1/B2	(B1-B2)/B3	(B1-B3)/B4
C	C1-C4			C3/C4	C1/C2/(C3-C4)
D	D1-D3			D1/D2	D3/(D1-D2)
E	E1-E2	E1/E2			
F	F1-F2				F1/F2
G	G1-G2	G1/G2			
H	H1-H3		H1/H2		(H1-H2)/H3
J	J1-J7	J3/J4	J1/J2/(J3-J4) J6/J7	(J1-J4)/J5	(J1-J5)/(J6-J7)
L	L1-L21	L1/L2/L3 L5/L6/L7 L10/L11 L12/L13 L15/L16/L17 L19/L20	 (L5-L7)/L8/L9 (L12-L13)/L14 (L15-L17)/L18 (L19-L20)/L21	(L1-L3)/L4 (L5-L9)/(L10,L11) (L12-L14)/(15-L18)/(L19-L21)	(L1-L4)/(L5-L11)/(L12-L21)
M	M1-M3			M1/M2	(M1-M2)/M3
N	N1-N4		N1/N2	(N1-N2)/N3	(N1-N3)/N4
P	P1-P4		P1/P2 P3/P4		(P1-P2)/(P3-P4)
T	T1-T3		T1/T2		(T1-T2)/T3
V	V1-V3		V1/V2		(V1-V2)/V3
W	W1-W3	W1/W2			(W1-W2)/W3
X	X1-X2			X1/X2	
Z1	Z1z1-Z1z4	Z1z1/Z1z2	(Z1z1-Z1z2)/Z1z3		(Z1z1-Z1z3)/Z1z4
Z2	Z2z1-Z2z5	Z2z1/Z2z2 Z2z4/Z2z5	(Z2z1-Z2z2)/Z2z3		(Z2z1-Z2z3)/(Z2z4-Z2z5)
Z3	Z3z1-Z3z5		Z3z3/Z2z4/Z3z5		Z3z1/Z3z2/(Z3z3-Z3z5)
Z4	Z4z1-Z4z4		Z4z3/Z4z4	Z4z1/Z4z2	(Z4z1-Z4z2)/(Z4z3-Z4z4)
Z5	Z5z1-Z5z2		Z5z1/Z5z2		
Z6	Z6z1-Z6z5	Z6z1/Z6z2		(Z6z1-Z6z2)/Z6z3 Z6z4/Z6z5	(Z6z1-Z6z3)/(Z6z4-Z6z5)
Z7	Z7z1-Z7z9	Z7z1/Z7z2/ /Z7z3 Z7z5/ Z7z6	(Z7z1-Z7z3)/Z7z4/ /(Z7z5- Z7z6)/Z7z7 Z7z8/Z7z9	(Z7z1-Z7z7)/(Z7z8-Z7z9)	
Z10	Z10z1-Z10z2				Z10z1/Z10z2
Z11	Z11z1-Z11z2				Z11z1/Z11z2
Z13	Z13z1-Z13z3		Z13z1/Z13z2	(Z13z1,Z13z2)/Z13z3	
Z18	Z18z1-Z18z2				Z18z1/Z18z2
Z22	Z22z1-Z22z2				Z22z1/Z22z2
Z23	Z23z1-Z23z2			Z23z1/Z23z2	

infection control and surveillance programs reported that HAI decreased by 32% in 5 years, and infection increased by 18% in the hospitals without surveillance programs[17,18]. According to surveillance studies covering Türkiye, Romania, Greece, Italy, Spain, Spain, and United Kingdom, carbapenem resistance is an important problem encountered in the treatment *of A.baumannii*[8,19].

Carbapenem-resistant *A.baumannii* is an important problem in the fight against infection in healthcare facilities. The World Health Organization reported in the Central Asian and Eastern European Surveillance of Antimicrobial Resistance Annual Report 2020 (CAESAR) that the rate of CRAB was less than 1% in Belgium, Denmark, Finland, Malta, the Netherlands, and Norway; whereas, in retrospective studies conducted in Southern and Eastern Europe, the rate of CAESAR was reported to be more than 50% in 290 countries.

Data of the study conducted for the Latin American surveillance study showed that the highest imipenem resistance was detected in Argentina (20%), Colombia

(14%), and Brazil (8.5%). Although it was reported that carbapenem resistance decreased periodically, it was reported that the rate of resistance increased up to 80% between 2008 and 2010[20]. In USA, 48% carbapenem resistance was reported[21]. In a recent study, it is worrying that the prevalence of carbapenem-resistant Acinetobacter was found as 50%, 85%, and 62–100% in Singapore, India and Pakistan, respectively[22]. Although the study groups and dates are different, increasing carbapenem resistance cannot be neglected. Carbapenem resistance was reported to be 71–72% between 2007 and 2011 at our country border (Van), which is adjacent to Iran and located in the eastern Anatolia of Türkiye[23]. Also in 2014, it was reported that the rate of carbapenem resistance in MDR *A.baumannii* was 98% upon the detection of the $bla_{OXA\text{-}51\text{-}like}$ gene region at the same center[24]. Over years, the increase in carbapenem resistance reaching 100%, was also supported by the current study. The rate of MDR *A.baumannii* isolated from another center in the same region (Kars) was reported as 39%[25]. In a study conducted in Iran at our border, *A.baumannii* was reported as 61.97% and carbapenem resistance as 38.03% in HAI[26]. Cholistin resistance is also reported in the resistance profiles of 50 CRAB strains collected from training hospitals in Iran[27]. Again, in an analysis performed on karst, it was reported that MDR *A.baumannii* isolates were among the gram (-) isolates most frequently isolated in the intensive care unit[28]. When 7 centers were examined in terms of antibiotic resistance in the present study, it was observed that the highest resistance belonged to Adana, Mersin, and Van centers. Resistance was found to be lower in rural areas with low population density. It is promising that no cholistin resistance was observed in any center. Such multi-center studies are needed regarding the epidemiology of antibiotic resistance, which is spreading rapidly today.

Pulsed-field gel electrophoresis is a standard method for the typing of the isolated MDR *A.baumannii* strains as a source of HAI. It is quite important to determine the clonal relationship, especially in multi-center studies. There are only three centers where PFGE typing is conducted among seven centers included in the study. Previously, no data were found at Ağrı, Ardahan, Kars, and Iğdır centers. Apart from these, in a study conducted with 69 CRAB isolates from Van province, it was reported that 62 (89.9%) of these strains were present in clusters and these strains were included in 16 clusters[29]. It is also reported that 9 out of 10 Acinetobacter strains were clonally related. In the present study, it was observed that 8 of 42 isolates that belonged to the same region had the same clone within 4 clusters and 28 of them were 80% related strains. In time, the increasing isolation of MDR *A.baumannii* and the high number of strains with similar genomes has become an endemic infection in the region. It also supports cross-contamination between the patients.

It was determined that 40 of 166 CRAB strains had the same genotype in 16 pulsotypes. Isolates of each center were similar among themselves. Eight isolates from Van province took place in 4 different pulsotypes, 9 isolates from Kars province in 3 pulsotypes, and 4 isolates from Iğdir province in a single cluster.

Among the strains isolated from Ağrı and Ardahan, 2 isolates in 1 cluster, 6 isolates in 3 different clusters from Adana, and 12 isolates in 5 pulsotypes from Mersin were 100% clonally related. Analysis data regarding the eastern Anatolia border regions of Türkiye are limited. When compared with the accessible epidemiological data, more intense contamination is in question in the provinces with a high number of patients. When compared with the studies conducted in different regions of Türkiye, it was found that both isolated *A.baumannii* strains and antibiotic resistance were at a lower incidence than other regions.

In 4 of the 7 different centers (Ağri, Ardahan, Iğdır, and Kars), more innocent results were obtained in terms of the number of samples, antibiotic resistance and clonal relationship when compared to other 3 centers (Adana, Mersin, Van). However, this may be caused by the low population zone and inadequate health services. Thus, further studies involving more centers and larger populations are needed. Consequently, we conclude that the present study will shed light on future studies, contribute to the surveillance system and create a well literature as a border region.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

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OLGU SUNUMU / *CASE REPORT*

Clinical Case Hidden in Young Patient is Ischemic Stroke

Genç Hastada Gizlenen Klinik Vaka İskemik İnme

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ABSTRACT

Stroke is a disease that can lead to severe sequelae and be fatal if not diagnosed early. While it is mainly seen in the older age group, it is rarely seen in the younger age group. A 23-year-old male patient presented to the emergency department with sudden onset of neurological symptoms. The fact that the patient was young and had promising clinical findings did not suggest the possibility of ischemic stroke in the first place. However, MRI imaging of the patient detected ischemic infarct areas in the brain. Various procedures were performed to investigate the etiological cause in the patient, but no pathological results were found. It was directed to the upper center for a more detailed examination. Early diagnosis of patients is crucial. An ischemic stroke should be considered in all patients with particular neurological symptoms, regardless of age.

Key words: *ischemic stroke; young stroke; emergency medicine*

ÖZET

İnme, erken teşhis konulamadığı durumda ciddi sekel bırakabilen ve ölümcül olabilen bir hastalıktır. En çok ileri yaşlarda görülürken nadir de olsa genç yaş grubunda da görülmektedir. Yirmi üç yaşında erkek hasta ani gelişen nörolojik semptomlarla acil servise başvurmuştur. Hastanın genç olması ve klinik bulgularının iyi olması iskemik inme olma ihtimalini düşündürmemiştir. Ancak hastanın ikinci başvurusu sonrasında detaylı inceleme yapıldığında beyin MR görüntülemesi yapılmış ve beyinde iskemik enfarkt alanları tespit edilmiştir. Hastada etiyolojik değerlendirme amacıyla detaylı olarak yapılan incelemelerde herhangi bir patolojik sonuç ortaya çıkmamıştır. Hasta daha detaylı inceleme amacıyla üst merkeze yönlendirilmiştir.

Nörolojik semptomu olan tüm hastalarda yaş farkı gözetmeksizin iskemik inme olabileceği mutlaka düşünülmelidir.

Anahtar kelimeler: *iskemik inme; genç inme; acil servis*

Introduction

Stroke is the second most common cause among diseases that cause sequelae and can be fatal worldwide[1]. Although it is a known fact that ischemic stroke is more common with increasing age, it is seen at a high rate of 10–20% in the 18–50 age group. The primary disease can cause the longest sequelae throughout human life[2]. With the increase in risk factors, ischemic infarction cases are now seen in the younger age group[3]. If the patient is 45 and under, it is considered a young stroke. The stroke frequency in this age group is around 2.5–40/100,000. When strokes are classified according to age group, 4%-10 of cases are encountered in young people[4].

Case Report

A 23-year-old male patient was applied to the emergency department with a sudden onset of lightning like headache, blurred vision, and occasional dizziness. The patient's vital signs were stable and his blood pressure was 127/84 mm/Hg, heart rate was 86/min, oxygen saturation was 98%, and fever was 36.3°C. On physical examination, GCS was 15, cerebellar tests were normal, pupils were isochoric and eye movements were regular. He used to smoke less than one pack a day, and he had no known additional disease. Since there was no deficit in the neurological examination, it was thought that he might have a migraine with aura, and computerized tomography of the brain was taken to

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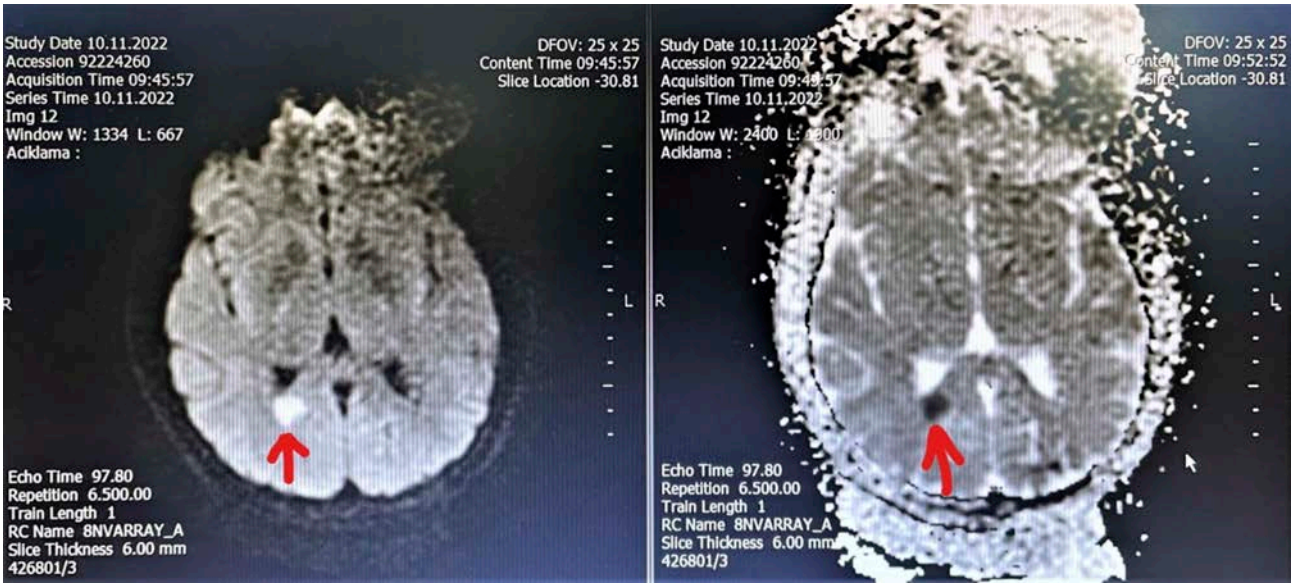

Figure 1. *Acute diffusion restriction in magnetic resonance imaging-1.*

Figure 2. *Acute diffusion restriction in magnetic resonance imaging-2.*

rule out. Since no pathology was detected in the imaging, he was observed for symptomatic treatment.

When the patient's clinical findings did not improve, brain diffusion MR imaging was performed. An acute infarct area with diffusion restriction was detected in the right medial occipitotemporal gyrus area and right posterior periventricular white matter on MR images (Fig. 1 and Fig. 2). The patient was admitted to the neurology service. Routine laboratory tests and lipid profile, ECG, contrast-enhanced brain MRI and MR angiography imaging, bilateral carotid color Doppler ultrasound, echocardiography, 24-hour Holter follow-up were performed in our patient in the studies performed in the neurology service, and no pathology was found. The infarct formed in the temporal region was ruled out regarding viral encephalitis. During the clinical follow-up, no fever was observed and the patient's symptoms decreased. During the service follow-up, low molecular weight heparin was administered subcutaneously at a dose of 0.4 mg 1*1. The patient was discharged with full recovery, but was referred to a tertiary healthcare institution for further investigation of developing ischemic stroke.

Discussion and Conclusion

Although there are many variable patient group applications in emergency services today, the number of admissions with neurological symptoms is substantial. The possibility of ischemic stroke is ignored, especially in the young age group, and there is a tendency towards symptomatic treatments. The younger age group is perplexed by the diagnosis of conversion. In the case of conversion, symptoms such as vision loss, double vision, headache, impaired consciousness, dizziness, movements resembling epileptic seizures, and motor and sensory loss such as paraesthesia may be observed[5]. Gilik et al. In the case they encountered in Ankara City Hospital, a 30 year old female patient was diagnosed with ischemic stroke[6]. Another confusing case may be migraine with aura. In addition to visual and sensory symptoms, severe recurrent headaches can be seen in migraine with aura[7].

In this case, the findings were initially evaluated toward of migraine with aura. Studies have shown that ischemic stroke is more common in women under 30[4]. However, in this case, a 23 year old male patient was diagnosed with ischemic stroke. Similarly, Bahadırlı et al. detected an ischemic stroke in a 15-year-old male patient[1]. In patients diagnosed with ischemic stroke at a young age, subsequent etiological investigations are significant. While atherosclerosis in large vessels and embolisms of cardiac origin are the most common, strokes of undetermined etiology are also considerably higher[4,8]. The most common cause of stroke in young patients is a stroke of unknown etiology[4,7–9]. In a study on the epidemiology and etiology of ischemic strokes in the young age group, smoking was found to be a risk factor with the highest rate[10]. In another study, smoking, hypertension, and dyslipidemia were the three most essential causes in young stroke patients[11]. In this case, smoking may have been an essential reason for the patient's ischemic stroke.

In patients presenting to the emergency department, especially with neurological symptoms, organic causes should be ruled out first, and then psychiatric reasons should be addressed. Although it was thought it might be a migraine with aura, it was misleading. Regardless of age, it should always be considered that patients may have an ischemic stroke, and the diagnosis and treatment process should be planned accordingly. Considering most studies, smoking is seen as a significant risk factor. Therefore, the patient should be questioned in the anamnesis.

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DERLEME / *REVIEW*

Regional Anesthesia in Ophthalmic Surgery

Göz Cerrahisinde Rejyonal Anestezi

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ABSTRACT

There are many anesthesia techniques for use in ophthalmic surgery. In selecting the technique to be applied, individual characteristics and anesthetic and surgical targets should all be considered for each patient. Regional techniques are preferred over general anesthesia due to their low complication rate and advantages. However, although it is relatively rare, regional techniques can also have life-threatening complications. Ophthalmologists and anesthesiologists should be prepared to handle the rare yet severe complications that the orbital regional anesthesia technique may cause. This study aims to uncover the regional anesthesia techniques used in ophthalmic surgeries and the complications that may arise.

Key words:ophthalmic *anesthesia; regional anesthesia; local anesthesia; ophthalmic surgery*

ÖZET

Oftalmik cerrahide kullanılan birçok anestezi tekniği vardır. Uygulanacak tekniğin seçiminde her hasta için bireysel özellikler, anestezik ve cerrahi hedefler göz önünde bulundurulmalıdır. Rejyonal teknikler komplikasyon oranlarının düşük olması ve avantajları nedeniyle genel anesteziye tercih edilmektedir. Bununla birlikte, nispeten nadir olmakla birlikte, rejyonal tekniklerin de hayatı tehdit eden komplikasyonları olabilir. Göz doktorları ve anestezistler, orbital rejyonal anestezi tekniğinin neden olabileceği nadir ancak ciddi komplikasyonlarla başa çıkmak için hazırlıklı olmalıdır. Bu çalışmanın amacı göz ameliyatlarında kullanılan rejyonel anestezi teknikleri ve oluşabilecek komplikasyonları ortaya çıkarmaktır.

Anahtar kelimeler: oftalmik anestezi; rejyonel anestezi; lokal anestezi; oftalmik cerrahi

Introduction

In ophthalmic surgeries, anesthesia targets and individual patient characteristics are prioritized in the choice of anesthesia technique. Cataract surgery is the most common ophthalmic surgery, and it is widely used in the elderly population with comorbidities. Because of its advantages and low complication rate, regional anesthesia is usually favored[1]. The surgeon's and patient's preferences, the patient's age, anatomical considerations, and comorbidities should all be considered when choosing regional anesthesia[2]. For a long time, eye blocks were restricted to retrobulbar (intraconal) anesthesia administered by surgeons. However, alternative regional methods have started to be used because of changes in surgical techniques and attempts to enhance patient safety[3]. The selected block method should provide adequate analgesia, akinesia, and eyeball hypotony[4].

The patient should be monitored, prepared by supplying an intravenous route, and sedation should be administered if needed[3,5]. There is no difference between the monitoring requirements for ophthalmic anesthesia in the awake patient and those required for procedures performed under general anesthesia[2].

The aim of this review is to provide information on regional anesthesia methods in ophthalmic surgery, including method selection, contraindications, and complications.

Retrobulbar (Intraconal) Anesthesia

Local anesthetic is applied to the space behind the eye. The optic nerve, the nerves that control the eye muscles

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Table 1. *Retrobulbar anesthesia complications*

Retrobulbar hemorrhage	Globe perforation
Retinal artery occlusion	Hypotony
Decrease in visual acuity	Optic nerve contusion
Amaurosis in the other eye	Optic atrophy
Muscle complications (ptosis, entropion, diplopia)	Brainstem anesthesia (as a result of subarachnoid or intradural injection)
Meningeal irritation	Central nervous system depression
Grand Mal seizure	Oculocardiac reflex stimulation (with globe compression)
Vasovagal bradycardia	Respiratory depression and arrest

and provide the sensation of the globe and surrounding structures are all contained in this space, which is surrounded by the muscles that move the eye[6].

The long sensory root of the ciliary ganglion is blocked in the retrobulbar method, resulting in anesthesia in all trigeminal branches[7]. Therefore, it is the quickest (less than 5 minutes) and most comfortable surgical technique[8,9]. However, it has a high complication rate (Table 1) and a greater loss of visual acuity than the peribulbar block[10].

Local anesthetic allergy, orbital infection, or inflammation are absolute contraindications to retrobulbar anesthesia. Increased globe axial length, bleeding diathesis, thyroid-associated orbitopathy, orbital space-occupying lesion, and previous scleral buckling surgery, on the other hand, are relatively contraindicated disorders[1].

Peribulbar (Extraconal) Anesthesia

By applying local anesthetic outside the muscle subject, anesthesia and akinesia are formed. The optic nerve is preserved, but additional anesthetics and multiple injections may be needed[11]. Anesthesia takes longer to begin, and periorbital ecchymosis is more likely[12].

The complications are the same as those associated with the retrobulbar block[10]. Peribulbar anesthesia has been recommended as a substitute because it has comparable effectiveness to retrobulbar injection, is simple, and has a lower rate of complications. However, also for peribulbar block, globe perforation, Brown's syndrome, strabismus, contralateral amaurosis, partial oculomotor nerve palsy, and respiratory arrest have all been recorded as complications[13].

After retrobulbar block, there have been cases of life-threatening brainstem anesthesia reported[11,14]. The local anesthetic agent directly enters the subarachnoid space and spreads to the central nervous system in brainstem anesthesia, which is the most serious of all complications. The cerebral duramater forms a sheath-like path for the spread of local anesthetic through the optic foramen in this potentially lethal case. The onset of symptoms following the block will range from 2 to 40 minutes. Even if the complication is unusual, it should not be overlooked, the patient should be closely monitored, and the necessary equipment should be on hand in the operating room in case of an emergency[11]. While the retrobulbar technique is most often associated with brainstem anesthesia, it can occur with any regional anesthesia technique[7,15]. Patients should be closely monitored during the procedure, and this should be done by someone who is not a member of the surgical team, using a monitor. This is because the full length of the surgical procedure takes almost 2–40 minutes.

Carneiro et al. compared peribulbar and retrobulbar block in patients with phacoemulsification. They reported that needle placement affects the distribution of anesthetic in the orbit and the quality of anesthesia, and that anesthesia is satisfactory if the needle placement is intraconal or contra-fixed. The retrobulbar block technique was found to be more effective[16]. The effect of retrobulbar block starts faster than peribulbar block and is associated with less chemosis[17]. Sirisha et al. concluded that preoperative preparation, appropriate drug, needle size and block type selection are essential for safe cataract surgery, and that almost ideal anesthesia is provided in cataract surgery with the double quadrant peribulbar anesthesia technique[18].

Table 2 lists the complications, symptoms, and treatments associated with regional techniques.

Sub-Tenon's (Parabulbar/Episcleral/Pinpoint) Anesthesia

It is the transconjunctival injection of an anesthetic agent into the sub-Tenon's space. This technique is at least as effective as the peribulbar method. It is suitable for use in cataracts, retinal photocoagulation, trabeculectomy, strabismus, and vitreoretinal surgery[10]. It is a

Table 2. *Regional anesthesia complications, symptoms and treatments2,7*

Common complications	Symptom	Treatment
Chemosis	Swollen conjunctiva	Not needed, light finger pressure
Subconjunctival hemorrhage	Bleeding	Not needed, light finger pressure
Pain	Unrest	Not needed
Rare complications		
Ecchymosis	Sudden periorbital bruising	Not needed
Retrobulbar hemorrhage	Arterial: sudden onset proptosis, increased intraocular pressure, decreased acuity Venous: slower onset, less pressure effect	Conservative: tamponade with external finger pressure, acetazolamide, mannitol Surgical: emergency lateral canthotomy, cantholysis, or orbital decompression
Globe injury	Sudden pain, change in visual acuity (May threaten vision)	Emergency ophthalmologic examination
Optic nerve damage	Altered acuity (May threaten vision)	Optic nerve sheath surgical decompression, Limited
Muscular paralysis	Diplopia, ptosis, gaze deviation/limitation	Causal treatment, Limited
Brainstem anesthesia	Neurological and cardiorespiratory changes (Life-threatening)	Supportive treatment

simple, safe, and effective method administered with a blunt needle[19]. It may be preferred particularly for patients with high myopia, scleral explants, and anticoagulants, as sharp needle blocks may increase their risk of complications. It is not, however, appropriate for surgery that requires intact conjunctiva, as is the case for most glaucoma procedures[20].

When compared to infiltration anesthesia, the major advantages of this technique are reduced patient anxiety besides globe and optic disc injuries, quick visual recovery, and avoidance of postoperative diplopia. Complications such as subconjunctival hemorrhage and chemosis, on the other hand, may arise. Nevertheless, it does not lead to complications such as acute ischemic optic neuropathy, extraocular muscle paralysis, increased intraocular pressure, globe perforation, periocular and retrobulbar bleeding[1].

Regional anesthesia techniques have a low rate of serious complications (0%, 07). When compared to the sub-Tenon's technique, sharp needle techniques were found to have a 2.5-fold increase in risk[7]. Table 3 compares the techniques of retrobulbar, peribulbar, and sub-Tenon's.

Subconjunctival Anesthesia

Subconjunctival anesthesia, an alternative to retrobulbar and peribulbar block, offers anterior segment anesthesia. It is used in pterygium excision, conjunctival biopsy and tumor excision, cataract, and glaucoma surgeries[5,10]. Its use with other types of block and intravenous sedation has been found to be safe and effective in evisceration surgery with transscleral implants[21]. Additional topical anesthesia may be needed. The surgeon can face challenges due to eye movements and inadequate iris anesthesia[10].

Topical Anesthesia

While needle blocks are preferred instead of general anesthesia for short surgical procedures (15–20 minutes), there has been a transition to topical anesthesia due to the potential harms of blunt needle insertion around the eyes[22]. Topical anesthesia refers to local anesthesia applied to the cornea and conjunctiva as drops or gels[23]. It has some disadvantages, including the lack of akinesia, low patient comfort, and anxiety. Patients should be carefully chosen for suitable procedures[12,23].

Topical anesthesia has recently gained popularity in cataract surgery. Phacoemulsification can be conducted under topical anesthesia[1]. In modern phacoemulsification cataract surgery, many surgeons use intracameral infiltration (irrigation fluids containing local anesthetics) besides topical anesthesia, which has decreased the need for the invasive block[20]. However, since extracapsular cataract surgery and small incision cataract surgeries without phacoemulsification require transscleral incisions, which are commonly used in developing countries, this procedure alone does not provide adequate anesthesia[20].

Drops such as 0.5% bupivacaine, 0.4% benoxinate, 4% lidocaine, and 0.5% proparacaine are preferred for topical anesthesia. However, it has been reported that frequent use of these drops in the preoperative period may cause corneal clouding. For this reason, the deep topical fornix nerve block (DTFNB) method was tried. In this method, small sponges with anesthetic solution are placed deep into the conjunctival fornix. Its advantage has been that it combines the safety, ease

Table 3. *Comparison of retrobulbar, peribulbar, and sub-Tenon's anesthesia10,18*

	Retrobulbar Anesthesia	Peribulbar Anesthesia	Sub-Tenon's Anesthesia
Advantages	Adequate akinesia and anesthesia Low volume Quick effect Low pressure in the orbit (but intraocular pressure may increase) Minimal anterior hemorrhage	Adequate akinesia and anesthesia Complications less than the retrobulbar technique Injection away from important structures of the apex No globe rotation Minimal anterior hemorrhage	Simple Adequate anesthesia Partial movement in the eyeball (at surgeon's request) Low volume Quick effect Relatively safe Low vision and life-threatening complications Less increase in intraocular pressure Effective time up to 60 minutes Less patient anxiety
Disadvantages	Requires experience Injection close to the important structures of the apex High complication rate Retrobulbar hemorrhage Loss of visual acuity Pain	Requires experience Even if the needle is tangent to the globe, important structures may be damaged. More volume Multiple injections Late-onset (up to 30 minutes) Periorbital ecchymosis and chemosis Intraocular pressure increase	Chemosis Conjunctival bleeding Risk of infection Difficult to apply in those with a background of previous or repeated eye operations

of administration and rapid onset of topical anesthesia with the wide anatomical distribution of retrobulbar anesthesia. In this method, 0.2% topical ropivacaine has become preferred over topical bupivacaine in cataract surgery due to its vasoconstrictive and long duration of action[22]. Wang et al. applied intracameral lidocaine in addition to topical anesthesia in small-incision cataract surgeries and showed that patients described less pain, were more comfortable, and collaborated better with the surgeon when compared to the group in which only topical anesthesia was applied[24].

This technique produces minimal pain with no intra- or postoperative complications including ptosis, globe perforation, or optic nerve lesions, and speeds up postoperative recovery. Pain from topical anesthesia, on the other hand, may lead to complications. Toxic effects on the corneal epithelium can occur when more than one topical anesthetic eye drop (3–5 times) is applied for analgesia. Additionally, topical anesthesia can reduce the surgeon's field of vision to the point that surgery becomes difficult. It may lead to pain, reduced lacrimation, and in extreme cases, severe keratopathy in the postoperative phase[1].

Intracameral Anesthesia

Iris and ciliary body anesthesia may not be adequately provided by topical anesthesia alone. In phacoemulsification surgery, using intracameral 0.5% lidocaine in addition to topical anesthesia improves cataract management[2]. Intracameral lidocaine improves analgesia, has a quick effect, and is a simple and safe tool for increasing patient cooperation during manipulation phases[7,25].

Limbal Anesthesia

It is a surface anesthesia technique that is used to prevent the potentially toxic effects of topical anesthesia on the cornea. It is the application of a cellulose ophthalmic sponge moistened with lidocaine hydrochloride without a preservative to the limbal region 45 seconds prior to the start of the surgery. It has the advantage of not including the epithelial involvement, allowing for a quicker visual recovery[1].

Use of Ultrasound in Ophthalmic Anesthesia

Visualization of needle placement helps to apply faster, safer and more successful eye blocks. Ultrasound is also useful for detecting needle or cannula-related problems. The use of color doppler allows to see fluctuations in ocular blood flow and to evaluate patients with compromised circulation[22]. Pre-block ultrasound evaluation may prevent the risk of perforation, especially in myopic patients due to the increased ocular dimensions[26]. In severe myopia, the risk of globe perforation increases up to 30 times[27]. Ultrasound is also useful to see the spread of local anesthetic. Luyet et al. showed that intraconal extension was correlated with the success of the block in their study in which they applied peribulbar block for posterior segment surgery[26]. Ultrasound-guided blocks may take longer, but this time will decrease as you get used to the technique over time[27].

Regional Anesthesia Contraindications

Patient unwillingness, local anesthetic allergy, and localized infection at the injection site are all absolute contraindications for regional anesthesia in ophthalmic surgeries. Anticoagulation, coagulation dysfunction for another cause, perforated globe, severe trauma, and cognitive impairment are, whereas, relative contraindications[23].

Anticoagulant treatment reduction or cessation prior to significant ophthalmic surgeries (e.g. orbital surgery) might be sufficient, but its suggestibility in cataract surgery is debatable. The risk of cost/benefit should be considered, as discontinuation of the anticoagulant may lead to thrombotic complications[2]. If the International Normalized Ratio (INR) is within the target value range, anticoagulant treatment is not a contraindication of sub-Tenon's anesthesia. When the INR value of a patient taking warfarin is less than 3.7, the risk of major hemorrhagic complications is relatively lower[23].

Because of the length, thickness, and application inadequacies of the needles used in regional techniques, a local anesthetic can spread centrally if the optic nerve sheath is perforated[28]. In other words, the properties of the needles used in the development of complications that can occur in invasive procedures are critical[28]. With the widespread use of ultrasonography instruments in recent years, safer blocks have been developed by examining anatomical patterns, needle advancement, and drug diffusion[27].

Conclusion

Since regional anesthesia procedures and local anesthetics have a lower complication rate than general anesthesia, they are commonly used in ophthalmic surgery. However, although the patient is conscious and defensive reflexes are protected in these methods, central nervous system involvement and respiratory depression may grow as a result of simultaneous sedation, leading to life-threatening complications. Preoperative evaluation of the patients is important. Patients who will not be given anesthesia should also be thoroughly checked for complications that might arise as a result of the local anesthetic effect, their age, co-morbid conditions, and drug use history. During the preoperative phase, patients should be fully informed of the surgical process and any potential complications, and their consent should be obtained. Just the anesthetized eye is visible during ophthalmic procedures as the patient's eye region is covered after it is prepared sterile. The patient's face is entirely covered so that no breathing motions or sounds can be observed. Cooperation with the elderly patient is also difficult. Therefore, it is critical to monitor these patients in order to identify potential complications, intervene early, and begin treatment. For this reason, the patient should be monitored with electrocardiogram (ECG), non-invasive blood pressure, and pulse oximetry in regional techniques, such as in general anesthesia, and an intravenous path should be available, as well as basic resuscitation devices in the operating room. As a result, the intraoperative and postoperative complications should be considered by the ophthalmologists and anesthesiologists, and they should be prepared for these complications.

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