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New Method To Prevent Contamination In Minimal Invasive Surgery: Usage Of Endoprotector

Minimal İnvaziv Cerrahide Kontaminasyonu Önlemek İçin Yeni Yöntem: Endoprotektör Kullanımı

Betül Güzelyüz[1], Server Sezgin Uludağ[2], Engin Hatipoğlu[2], Egemen Özdemir[2], Sefa Ergün[2], Kemal Selçuk Şengün[3]

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ABSTRACT

Objective: To reveal the use of a material called endoprotector designed to prevent contamination in minimally invasive abdominopelvic surgery.

Methods: Endoprotector is formed by giving a circular shape to the transparent polyurethane material and passing around it in the form of a pürse-string with a surgical suture. This material, which is used in minimally invasive surgeries by inserting it into the abdomen through a trocar hole and laying it on the floor of the operating area, has been in the patent process.

Results: It is characteristic that it is a new product, called endoprotector, and the use of a laparoscopic protective drape is a new technique. At the end of the procedure, the extension of the suture shrinks by pulling from the trocar, and the formed pouch is taken out of the abdomen together with the trocar. Difficulty in removing the trocar from within is the only known shortcoming of the technique.

Conclusion: Endoprotector is designed to prevent contamination in minimally invasive surgery. It reduces peritonitis and intra-abdominal infections, the need for irrigation, and the use of drains, thus shortening postoperative ileus and hospital stay; and predicted to reduce outcomes such as tumor implantation.

Keywords: Minimally invasive surgery, intra-abdominal contamination, endoprotector

ÖZ

Amaç: Minimal invaziv abdominopelvik cerrahilerde kontaminasyonu önlemek için tasarlanmış endoprotector adlı gerecin kullanımını ortaya koymak.

Yöntemler: Endoprotektör şeffaf poliüretan malzemeye dairesel bir şekil verilerek etrafından cerrahi dikişle kese ağzı şeklinde geçilmesiyle oluşturulur. Minimal invaziv ameliyatlarda trokar deliğinden karın içine sokularak ameliyat bölgesinin zeminine serilen bu gereç, ulusal patent sürecindedir.

Bulgular: Endoprotector adı verilen başlı başına yeni bir ürün olması ve laparoskopik koruyucu örtü kullanımının yeni bir teknik olması karakteristiktir. İşlem sonunda süturun uzantısı trokardan çekilerek hazne haline gelen gereç, batın dışına alınır.

Sonuç: Endoprotector minimal invaziv cerrahilerde kontaminasyonu önlemek için tasarlanmıştır. Peritonit ve intra-abdominal enfeksiyonları, irigasyon ihtiyacını ve dren kullanımını azaltıp, böylece postoperatif ileusu ve hastanede kalış süresini kısaltması; ve tümör implantasyonu gibi sonuçları azaltacağı tahmin edilmektedir.

Anahtar Sözcükler: Minimal invaziv cerrahi, intra-abdominal, kontaminasyon, endoprotektör

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INTRODUCTION

Contamination of materials such as intestinal contents and bile into the abdomen causes peritoneal irritation and other infectious complications; minor or major contamination may occur during surgery, sometimes unintentionally as iatrogenic, and sometimes mandatory as required by the method applied. This contamination was controlled by irrigation and aspiration of the abdomen with physiological saline and placement of a drain in the operating area. When there is a possibility of contamination of luminal contents, such as during segmental intestinal resection in invasive abdominal surgeries, it is attempted to prevent contamination of surrounding tissues by covering the procedure area with sterile compresses before the procedure (1,2,3). In minimally invasive surgeries, for the contamination with intestinal contents occurring during the period between segmental bowel resection and performing intra-abdominal anastomosis, as well as in cases with a high probability of perforation, such as acute cholecystitis, and intra-abdominal transmission, such as appendiceal and ovarian tumors with mucinous component; today, there is no known application other than irrigation with physiological saline and placing a drain after the procedure; there is no barrier application to take precautions before contamination occurs. To not contaminate the incision line used during removal of the piece from the abdomen only after the resection is performed, specimen bags called endobags and wound protective rings called alexis are tools known to be used (4,5,6). In addition to the fact that these and similar materials do not have the features of preventing contamination into the abdomen; in minimally invasive surgeries, it is not easy to find foreign bodies such as dispersed stones, lost needles, etc. under minimally invasive conditions, and it is turned into an open area in order to provide adequate exploration; it is known that irrigation with physiological saline, wound protection rings, and specimen bags are useless in these cases, and even if these procedures and tools are tried, the time wasted can compete with the benefit (7). In invasive abdominopelvic surgeries, similar to the application of laying protective barrier covers such as sterile compresses on the area before procedures that will cause contamination such as bowel resections, during minimally invasive surgeries, before resection or before intervening in tissues-organs with a high perforation possibility, to prevent intraabdominal contamination or to prevent contamination such as needles, in surgical procedures where small sized foreign bodies are expected to be needed intensively; before starting the process, a protective barrier cover mechanism is designed around the process area that can be laid on the ground. The aim of this study was to present an invention called endoprotector, which is predicted to provide many benefits, such as minimizing infectious complications, such as postoperative peritonitis, intra-abdominal infection, and abscesses, and reducing the need for drain placement.

MATERIALS AND METHODS

The endoprotector, which is designed for use in minimally invasive surgeries, consists of a transparent polyurethane surface and a surrounding suture. The camera is used by placing the trocar and camera in the abdomen and after exploration, inserting it into the abdomen through the trocar hole and laying it on the appropriate surface. This material, which aims to prevent contamination in cases where there is a possibility of contamination such as the emergence of luminal contents during surgery, to safely remove foreign objects such as needles from the abdomen in cases where they are used, and to prevent these foreign objects from falling on a safe floor in case of possible loss, preventing both contamination, waste of time, and unnecessary laparotomy; it is used in cases where measures are required to be taken at the discretion of the surgeon. After the surgical procedure is completed, the suture material surrounding the drape is withdrawn by means of its extension outside the abdomen, and the transparent polyurethane dressing, which is widely laid, is brought to the shape of a pouch by shrinking, and the trocar is removed from the abdomen from the trocar site without any intra-abdominal contamination. At the design stage, this material has production features similar to those of tools produced from polyurethane material known as organ removal bags and wound retractors or wound protective rings, which enable the removal of resection specimens in laparoscopic surgeries on the market. Therefore, endoprotector, which can be easily produced professionally by all kinds of laparoscopic surgical equipment manufacturing institutions and organizations that produce using polyurethane; it can also be prepared in existing facilities. When it is produced in operating room conditions, the floor of the material can be prepared by cutting the camera sheath, which is a transparent structure and indispensable for every laparoscopy, in suitable sizes and giving it a circular shape. To complete the mechanism, the surgical suture material is passed around the prepared circular structure with suturing all around the pürse-string. After this procedure, which is performed under sterile conditions at the beginning of the operation, the appropriate folding process is performed and it is folded so that it can be easily inserted into the abdomen through the trocar hole and kept ready for use until the surgeon wants to use it (Figure 1). To ensure its original

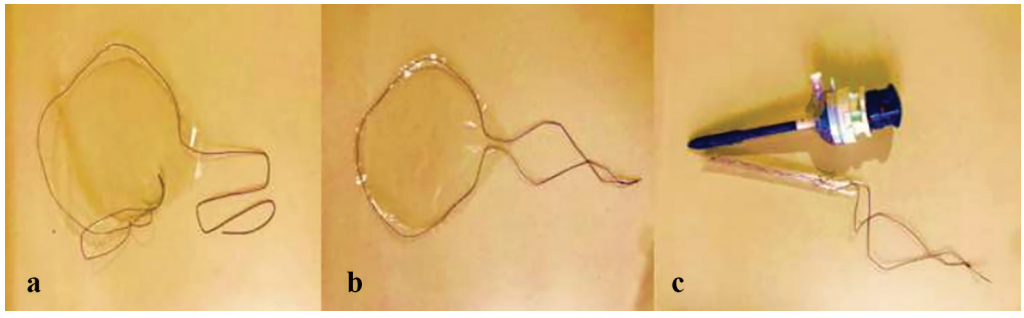

Figure 1. Preparation of Endoprotector (a,b). Transparent polyurethane circular structure and circumferential passage with suture material (c). After sthe suturing process, the appropriate folding process is performed, and the appearance is made ready for use by being folded in such a way that it can be easily inserted into the abdomen through the trocar hole.

production and safe reproduction, Endoprotector, which is in the national patent process with the application number 2021/015846, upon the application made by us to the Turkish Patent and Trademark Office on 1.10.2021, has proven to be safe in minimally invasive surgeries until its legal production. It is prepared in operating room conditions using available facilities, such as camera sheaths and surgical suture materials. Ethics committee approval was obtained for the use of the tool IUC-Clinical Research Ethics Committee, (approval number: E-83045809-604.01.01-340386, date: 01.03.2022). Surgery is performed after informed consent of each patient.

RESULTS

The invention is a protective cover that can be laid on the floor before the procedure in minimally invasive surgeries, and its main feature is that it is a new product on its own called an endoprotector. The circularly structured transparent polyurethane dressing can be formed into a pouch by shrinking using the suture surrounding this structure. In order to do this, first, in minimally invasive surgeries, after trocar entry, pneumoperitoneum creation, and surgical exploration, the area where the procedure will be performed and the risk of the surgery in terms of contamination are determined. Then, in cases where precautions should be taken before contamination occurs, the Endoprotector is rolled up in the form of a roll and left to the abdomen through the trocar hole, but taking care that the entire suture does not go into the abdomen, its extension is ensured to remain outside the trocar. The nylon floor, which is folded in the form of a roll, is placed on the floor of the area to be treated by being straightened using laparoscopic hand tools after the patient is positioned appropriately on the operating table. Protective cover that works in case of contamination during the procedure or when resection is performed without major contamination; at the end of the procedure, the extension of the suture outside the trocar is pulled, and it is contracted into a pouch shape. The contaminating material is pooled in this pouch. When the resection material is left on the floor after resection, conditions such as tumoral implantation and cellular transplantation will be prevented in the future. However, this material may not always fit in the pouch of the Endoprotector due to its dimensions. In this situation, it may be necessary to use other organ removal bags in the market to remove the resection material from the abdomen. When the procedure is completed, the material, which takes the shape of a pouch by shrinking through the suture, is removed from the abdomen by pulling it together with the trocar from the trocar entrance hole. Although no complications have been encountered in clinical trials in cases in which this material is used, it does not pose a known risk. In addition to its main objectives, such as preventing contamination and planting, it is expected to shorten the operation time and reduce the need for abdominal irrigation and drain use. However, for the purposes of preventing tumoral implantation and reducing infectious complications, this approach is not expected to provide significant additional benefits to patients with already known conditions, such as malignant ascites, diffuse intraabdominal abscess, and peritonitis. When considered in the direction of purpose-result, the main patient group for which this material will be used should be the patients who do not have these conditions.

DISCUSSION

Although postoperative infectious complications, such as surgical site infections, intraabdominal abscess development, wound dehiscence, and catheter-related complications, are less common than invasive surgeries, they continue to be a serious cause of morbidity in minimally invasive surgeries; peritoneal irritation, paralytic ileus, biliary peritonitis, anaphylaxis, and tumoral implantation may result in secondary manifestations (8). Although the use of perioperative abdominal compresses and lavage applications are known to prevent contamination in invasive surgeries; it is seen that some tools, such as wound protection rings and organ removal bags, used in minimally invasive surgeries do not provide a fully countermeasure mechanism (9,10). It is expected that the use of a material that will perform the same function as compresses laid on the floor in invasive surgeries will reduce contamination and complications, but it is hoped that this material will not cause harm. For this purpose, the endoprotector is designed to be produced from a transparent material in a size that does not hinder the manipulation of the surgeon and does not obscure the field of view. With the use of endoprotectors, it is expected that the use of intra-abdominal irrigation and drains will also decrease, along with a decrease in contamination. It is predicted that this will reduce postoperative prolonged ileus and other problems, such as drain-related infectious complications, prolonged hospitalization, and the need for antibiotic treatment (11,12). When resection is performed, the floor covering is expected to prevent contamination and cellular implantation; however, this material may not always fit in the pouch of the endoprotector due to its dimensions. In this situation, it may be necessary to use other organ removal bags on the market or other methods applied for this purpose in order to take the resection material from the abdomen (7,13,14). This is a prescribed situation, and the main use of the material is to prevent contamination; organ removal is only possible with small-sized resection materials, which is considered as one of the later features of the material that provides ease of use in selected cases.

CONCLUSION

The material, which aims to prevent the spread of the contamination material to the abdomen, is brought into the shape of a pouch by shrinking using a suture at the end of the process to achieve this. This structure is taken out of the abdomen by pulling together with the trocar from the trocar entrance hole. The only known shortcoming of this technique is the difficulty of removing the material from the trocar without contamination when it is in a shrunken structure. However, this situation is already known to exist in organ removal bags on the market, and no complications have been reported in the literature. However, this situation is expected to be overcome when professional production is achieved.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for the use of the tool IUC-Clinical Research Ethics Committee, (approval number: E-83045809-604.01.01-340386, date: 01.03.2022).

Informed Consent: Surgery is performed after informed consent of each patient.

Footnotes

Authorship Contributions

Concept: B.G., Design: B.G., Material: B.G., E.Ö., Data Collection or Processing: E.H., K.S.Ş., Analysis or Interpretation: Literature Search: S.E., Writing: B.G., S.S.U., Critical Review: B.G., S.S.U.

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Comparison of Computerized Tomography (CT) Scan, Clinical and Para-clinical Findings in Hospitalized Vaccinated and Unvaccinated COVID-19 Patients: A Pilot Study from Babol County

Hastanede Yatan Aşılanmış ve Aşılanmamış COVID-19 Hastalarında Bilgisayarlı Tomografi (BT) Taraması, Klinik ve Para-klinik Bulguların Karşılaştırılması: Babol İlçesinden Bir Pilot Çalışma

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ABSTRACT

Objective: Vaccination plays a crucial role in preventing severe lung disease and reducing hospitalization rates among patients with coronavirus disease-2019 (COVID-19). In this study, researchers compared lung computed tomography (CT) scans of vaccinated and unvaccinated individuals with COVID-19, along with clinical and para-clinical findings.

Methods: This study was conducted at Ayatollah Rouhani Hospital in Babol, Iran, between July and November 2021. The researchers selected 106 confirmed COVID-19 patients and divided them into two groups: 53 fully vaccinated individuals who received the Sinopharm vaccine and 53 unvaccinated individuals. Demographics, laboratory, and imaging data were collected.

Results: The mean age of hospitalized patients with COVID-19 was 59.8±16.1 years. The most common CT finding in both groups was bilateral ground glass opacities, observed in 95 patients (89.6%). Significant associations were found between the vaccinated and unvaccinated groups regarding hospital stay duration, oxygen saturation, intensive care unit admission, lactate dehydrogenase levels, and erythrocyte sedimentation rate index.

ÖZ

Amaç: Aşılama, koronavirüs hastalığı-2019 (COVID-19) olanlarda ciddi akciğer hastalıklarını önlemede ve hastaneye yatış oranlarını azaltmada önemli bir rol oynar. Bu çalışmada, araştırmacılar COVID-19'lu aşılanmış ve aşılanmamış bireylerin akciğer bilgisayarlı tomografi (BT) taramalarını klinik ve para-klinik bulgularla karşılaştırmıştır.

Yöntemler: Bu çalışma, Temmuz ve Kasım 2021 arasında İran'ın Babol kentindeki Ayatollah Rouhani Hastanesi'nde yürütülmüştür. Araştırmacılar, 106 doğrulanmış COVID-19 hastasını seçerek iki gruba ayırmıştır: Sinopharm aşısı olan 53 tam aşılanmış birey ve 53 aşılanmamış birey. Demografik, laboratuvar ve görüntüleme verileri toplanmıştır.

Bulgular: COVID-19 nedeniyle hastaneye yatırılan hastaların ortalama yaşı 59,8±16,1 olarak bulunmuştur. Her iki gruptaki en yaygın BT bulgusu, 95 hastada (%89,6) gözlenen bilateral buzlu cam opasiteleri olmuştur. Aşılanmış ve aşılanmamış gruplar arasında hastanede kalış süresi, oksijen satürasyonu, yoğun bakım ünitesine yatış, laktat dehidrogenaz seviyeleri ve eritrosit sedimantasyon hızı indeksi açısından anlamlı ilişkiler bulunmuştur.

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ABSTRACT

Conclusion: This study revealed no difference in the pattern of pulmonary involvement between vaccinated and unvaccinated individuals with COVID-19, except for the peribronchovascular pattern, which was more commonly observed in unvaccinated patients. Other common patterns of pulmonary involvement were also more prevalent among unvaccinated individuals. These findings emphasize the effectiveness of COVID-19 vaccination, as the vaccinated group had a lower rate of pulmonary involvement. This highlights the need for widespread vaccination to effectively combat COVID-19.

Keywords: COVID 19, vaccines, X-ray computed tomography

ÖZ

Sonuç: Bu çalışma, aşılanmış ve aşılanmamış COVID-19'lu bireyler arasında akciğer tutulumu örüntüsünde, aşılanmamış hastalarda daha sık görülen peribronkovasküler örüntü dışında hiçbir fark olmadığını ortaya koymuştur. Ayrıca, diğer yaygın akciğer tutulumu örüntülerinin de aşılanmamış bireyler arasında daha yaygın olduğu gözlenmiştir. Bu bulgular, aşılanmış grupta akciğer tutulumu oranının daha düşük olması nedeniyle COVID-19 aşılamasının etkinliğini vurgulamaktadır. Bu, COVID-19 ile etkili bir şekilde mücadele etmek için yaygın aşılamanın gerekliliğini ortaya koymaktadır.

Anahtar Sözcükler: COVID-19, aşılar, X-ray bilgisayarlı tomografi

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was officially declared a pandemic by the World Health Organization on March 11, 2020 (1). SARS-CoV-2 has the potential to spread rapidly among humans, currently (December 2024) infecting more than 776 million people worldwide and killing more than 7 million people (2). The virus is spread through respiratory droplets released when an infected person coughs, sneezes, breathes, or speaks. These droplets can be inhaled or land in the mouth, nose, or eyes of someone nearby. In some situations, SARS-CoV2 can be spread when a person is exposed to droplets or aerosols that stay in the air for minutes or hours as airborne transmission. Signs and symptoms may include fever, cough, fatigue, and early symptoms of loss of taste or smell. Other symptoms may comprise shortness of breath or difficulty breathing, muscle pain, sore throat, headache, chest pain, and diarrhea (3). Significant vaccination of at-risk groups and the general population is the most effective public health strategy for mitigating the COVID-19 pandemic (4). Although vaccines do not eliminate reinfection or infection, they certainly reduce the severity of symptoms and the likelihood of infection and improve patient survival(5). Sinopharm vaccine (BBIBP-CorV) is an inactivated vaccine produced in China that demonstrates 79.34% efficacy, which was available at the time of this study in Iran (6). At present (December 2024), according to information from the World Health Organization (WHO), the total number of SARS-CoV2 infections is more than 7.627.863, with 146,837 fatal cases in Iran. Moreover, more than 155 million doses of vaccine have been injected so far (December 2024), and the distribution of the vaccine in the study area is similar to that in other parts of Iran. Chest X-ray (CXR) is not a sensitive tool for detecting lung abnormalities at the onset of the disease. Computed tomography (CT) is considered the most effective method for detecting lung abnormalities, especially in the early stages of the disease, and it has a sensitivity of 97% for diagnosing COVID-19 (7). On high-resolution computed tomography (HRCT), ground-glass opacities (GGO) refer to the area of increased lung opacity in which the underlying bronchovascular markings are not obscured. GGO is the most common manifestation of pneumonia caused by COVID-19. The bilateral lower lobes are most commonly affected, and multilobar subpleural ground-glass opacities are observed in most cases (8). Lung parenchymal involvement is more common in nonvaccinated than in vaccinated patients. The vaccine also reduces the severity of the disease, as well as its symptoms (9). Several studies also found that there was a statistically significant correlation between vaccination status and lung lesions based on chest HRCT. As a result, the presence of vaccination reduces the severity of the CT severity score and improves the outcome in terms of survival of the patients (5). Other studies in India have indicated significantly lower CT severity scores in fully or partially vaccinated patients compared with nonvaccinated patients. Complete vaccination is critical for preventing severe lung disease (10). This study aimed to compare lung CT scans of vaccinated and unvaccinated individuals with COVID-19, along with clinical and para-clinical findings.

MATERIALS AND METHODS

This study was carried out at the Ayatollah Rouhani Hospital, Babol, Northern Iran, from August to December 2021 (five months). This retrospective cross-sectional study included 106 patients vaccinated with 2 doses of Sinopharm vaccine and nonvaccinated patients with reverse transcription-polymerase chain reaction (RT-PCR)-positive COVID-19, irrespective of age and sex. Patients were 53 in each group. All vaccinated patients received 2 doses of the Sinopharm vaccine. Our Sampling technique was purposive.

1) Inclusion criteria

• All hospitalized patients with positive RT-PCR results for SARS-CoV-2/Suspected for COVID-19 during the specified period

2) Exclusion criteria

• Patients who died or were discharged within the first 24 hours of hospitalization

• Pregnant patients

• Patients younger than 20 years

• Vaccinated patients who received only one vaccine dose or those who received the last vaccine dose within less than 2 weeks of admission

• Patients who have had symptoms for more than a week

This study was approved by the local ethics committee (approval number: IR.MUBABOL.HRI.REC.1400.235, date: 07.03.2022) at the Babol University of Medical Sciences, Babol, Iran, and written informed consent was collected from each patient. The data-capturing master sheet was maintained throughout the study. At enrollment of patients, demographic and baseline characteristics were recorded. CT findings were evaluated. Patient information was obtained using an information sheet that included laboratory data and radiological findings.

All scans were performed using 16 slices of SIMENS (Germany) CT scanner.

Scan Parameters**:**

1- Slice Thickness: 3.00 mm

2- Rotation Time: 0.6s

3- Scan time: 6.93 s

4- Pitch: 1.5

5- mAS: 35

6- Kvp: 110

Images were interpreted independently by two certified radiologists, blinded to the patient's names and clinical or other laboratory findings, and the abnormalities that were considered significant for the disease were recorded by them.

Statistical Analysis

Statistical analysis were performed using SPSS version 23.0 (SPSS Inc., USA). A descriptive analysis was performed on all data. The mean values were calculated for continuous variables. Quantitative observations are indicated by frequencies. A *p* value<0.05 was considered statistically significant. The intent and purpose of the study, as well as its procedures, risks, and benefits, were explained in an easy-to-understand local language, followed by oral and written consent from the Patients. All information and records are guaranteed to be treated confidentially.

RESULTS

A total of 106 RT-PCR-positive COVID-19 patients participated in our study at Ayatollah Rouhani Hospital, Babol, Northern Iran, from August to December 2021 (five months). Of these, 53 (50%) patients were vaccinated and 53 (50%) were unvaccinated. The mean age of the participants was 59.8±16.1 (age range of 21-94 years). The mean age of the vaccinated and unvaccinated participants was 59.2±14.6 (age range of 34-88 years) and in the unvaccinated group was 60.4±17.6, 6 (age range of 21-94 years). In this study, 65 (61.3%) patients were male and 41 (38.7%) were female. Regarding comorbidities, a history of smoking, hypertension, diabetes mellitus, chronic kidney disease, and obesity was not statistically significant (p>0.05). GGO were a predominant CT scan finding in our patients and were found in 95 (89.6%) of them. 52 (54.7%) were unvaccinated and 43 (45.3%) were vaccinated (p=0.004). Interlobular septal thickening was seen in 74 (69.8%) of the patients in whom 43 (58.1%) were unvaccinated and 31 (41.9%) were vaccinated (p=0.011). The next finding was rounded morphology found in 66 (62.3%) patients which were 30 (45.5%) unvaccinated and 36 (54.5%) vaccinated patients (p=0.229). Consolidation, Air bronchogram, Enlarged subsegmental vessels, Crazy paving, Linear opacities, Reverse halo sign, Pleural effusion, and Tree-in-bud were other CT scan findings that are shown in Table 1. The predominant distribution of lung parenchyma was Bilateral involvement. It was detected in 95 (89.6%) patients that 43 (45.3%) patients were vaccinated and 52 (54.7%) patients were unvaccinated (p=0.004). 90 (%84.9) patients had more than two lobes affected that 50 (55.6%) patients were unvaccinated and 40 (44.4%) patients were vaccinated (p=0.007). Peripheral involvement was the next finding that has been found in 88 (83%) patients that 49 (55.7%) patients were unvaccinated and 39 (44.3%) patients were vaccinated (p=0.010). Posterior, lower lung, peri-bronchovascular, and central were other distributions found in the CT scan that are also shown in Table 1. The mean time of hospitalization was 8 days, and vaccinated patients stayed for fewer days than unvaccinated patients (p=0.020). Also O_2 saturation percentage was higher in vaccinated patients at admission (p=0.001). Comparison of the cycle threshold value (Ct value) from the RT-PCR test, number of intensive care unit (ICU) admissions, and number of deaths during the time of hospitalization between the vaccinated and unvaccinated groups are shown in Table 2. Table 2 also shows some laboratory data of patients, including white blood cell (WBC) count, polymorphonuclear neutrophil percentage, lymphocytes percentage, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). LDH and CRP showed a statistically significant difference in vaccinated patients. Blood O_2 saturation percentage status in vaccinated and unvaccinated patients was divided into three groups: mild (O_2>94%), moderate (90%<O_2<94%), and severe (O_2<90%). Figure 1 shows that as the O_2 saturation percentage progresses, the number of vaccinated patients increases.

DISCUSSION

Due to the critical role of vaccination in COVID-19 prevention, the current cross-sectional study compared lung involvement between vaccinated and unvaccinated patients by performing HRCT. In the present study, GGO was our patients' predominant CT finding. It was found in 95 (89.6%) of them with a significant relationship between GGOs and being vaccinated or not, which was observed less in vaccinated patients compared with unvaccinated patients. In addition, consolidation was observed in 53 (50%) participants, with a significant relationship between consolidation and being vaccinated or not, which was also found less in vaccinated people compared with unvaccinated cases. In a similar study by Verma et al (11) GGOs and consolidation were significantly less in the group receiving the vaccine compared with the unvaccinated patients were significantly less. Interlobular septal thickening, air bronchogram, and linear opacities are also our other findings that respectively seen % in 69.8, 44.3%, and 35.8% of patients that were observed significantly more in unvaccinated patients than vaccinated ones, respectively, similar to the study of Hughes et al. (12), Zhu et al. (13), and Liu et al. (14), which showed the efficacy of vaccines against the severity of this disease.

In another part of the comparison of CT scan findings in this study, the distribution of lung involvement was investigated, and the predominant distribution of lung parenchymal involvement was bilateral involvement. It was observed in 95 (89.6%) patients, which was lower in vaccinated patients than in unvaccinated patients. Other distributions of lung involvement included more than two lobes affected (84.9%), peripheral (83%), posterior (52.8%), and lower lung (35.8%). These involvements were observed less frequently in vaccinated patients compared with unvaccinated patients (15), suggesting that vaccination is possibly an effective approach to prevent the occurrence and severity of this disease. The only distribution that showed a higher incidence among vaccinated patients was peri-bronchovascular involvement (35.8%), which requires further investigation to be clarified. According to the current study, the average length of hospital stay for vaccinated patients

Table 1. Computed tomography chest findings of patients with COVID-19 infection in correlation to vaccination status

Findings	Total (n=106) median ± sig.	Unvaccinated median ± sig.	Vaccinated median ± sig.	p
Ground glass opacities	95 (89.6%)	52 (54.7%)	43 (45.3%)	0.004
Interlobular septal thickening	74 (69.8%)	43 (58.1%)	31 (41.9%)	0.011
Rounded morphology	66 (62.3%)	36 (54.5%)	30 (45.5%)	0.229
Consolidation	53 (50%)	34 (64.2%)	19 (35.8%)	0.004
Air bronchogram	47 (44.3%)	31 (66%)	16 (34%)	0.003
Enlarged subsegmental vessels	12 (11.3%)	10 (83.3%)	2 (16.7%)	0.014
Tree-in-bud	1 (0.94%)	0 (%0)	1 (100%)	0.315
Pleural effusion	3 (2.8%)	2 (66.6%)	1 (33.3%)	0.558
Linear opacities	38 (35.8%)	25 (65.8%)	13 (34.2%)	0.015
Crazy paving	52 (49.1%)	25 (48.1%)	27 (51.9%)	0.698
Reverse halo sign	9 (8.5%)	7 (77.8)	2 (22.2%)	0.081
Bilateral	95 (89.6%)	52 (54.7%)	43 (45.3%)	0.004
More than 2 lobes affected	90 (84.9%)	50 (55.6%)	40 (44.4%)	0.007
Peripheral	88 (83%)	49 (55.7%)	39 (44.3%)	0.010
Posterior	56 (52.8%)	34 (60.7%)	22 (39.3%)	0.020
Lower lung	38 (35.8%)	29 (76.3%)	9 (23.7%)	0.001
Peri-broncho vascular	38 (35.8%)	12 (31.6%)	26 (68.4%)	0.005
Central	4 (3.8%)	1 (25%)	3 (75%)	0.308

was 6.9 days compared with 8.3 days for unvaccinated patients. The Ct values measured by real-time RT-PCR were 25 for vaccinated and 26.9 for unvaccinated patients. These data are also similar to those of Verma et al study that demonstrated the mean Ct value in vaccinated patients was less than that in unvaccinated patients (11). The percentage of O_2 saturation for vaccinated patients was 93.8% but it was 90.7% for unvaccinated patients. Seo et al (16) also found that unvaccinated patients significantly needed more complementary oxygen therapy, which is similar to the data of the current study and indicates the advantage of vaccination in reducing the severity of disease. Sikora et al. (17) showed that vaccination reduces the number of ICU admissions which is also similar to the current study in which a total of 14 (13.2%) patients were admitted to ICU whom 9 of them were unvaccinated and 5 were vaccinated. Although it was not significant, it indicates the efficacy of vaccination in reducing the excessive hospital load. Regarding the laboratory data, similar to the Rzymski et al. (18) study, this study showed no significant difference between the WBC count in vaccinated and unvaccinated patients. LDH levels were significantly higher in unvaccinated patients, similar to the study of d'Arminio Monforte et al. (19) which showed that LDH level changes were higher in unvaccinated patients. CRP levels also increased in unvaccinated patients, although it was not statistically significant, but similar to the study of Wang Y et al. (20) CRP levels were higher in unvaccinated patients. These data show that LDH and CRP levels can anticipate the severity of disease in patients (21). Lastly, unvaccinated patients had significantly higher ESR levels than vaccinated patients. Samrah et al. (22) also came to this conclusion and stated that high ESR was

Table 2. Parameters of patients with COVID-19 infection correlated with vaccination status

Parameters	Total Median ± sig.	Vaccinated Median ± sig.	Unvaccinated Median ± sig.	p
Hospital stays (day)	8±5.5	6.9±3.1	8.3±2.8	0.020
O_2 Saturation (%)	92.3±4.9	93.8±3.6	90.7±5.5	0.001
Cycle threshold value	26±4.2	25±4	26.9±4.2	0.023
ICU admission (number)	14	5	9	0.251
Deaths (number)	7	1	6	0.051
WBC	7647±4722	7236±4640	7662±4722	0.521
PMN (%)	75±14.3	73.9±16.7	76.1±11.7	0.757
LYM (%)	21.1±10.8	21.2±11.3	21±10.5	0.897
LDH	696.7±244.5	631±219.6	762±252.7	0.014
ESR	39.7±22.6	34.9±21.2	44.5±23.1	0.032
CRP	83 ± 67.1	76.5 ± 66.7	89.6 ± 66.7	0.436

WBC: White blood cells, PMN: Polymorphonuclear neutrophil, LYM: Lymphocytes percentage, LDH: Lactate dehydrogenase, ESR: Erythrocyte sedimentation rate, CRP: C-reaktif protein, Sig.:

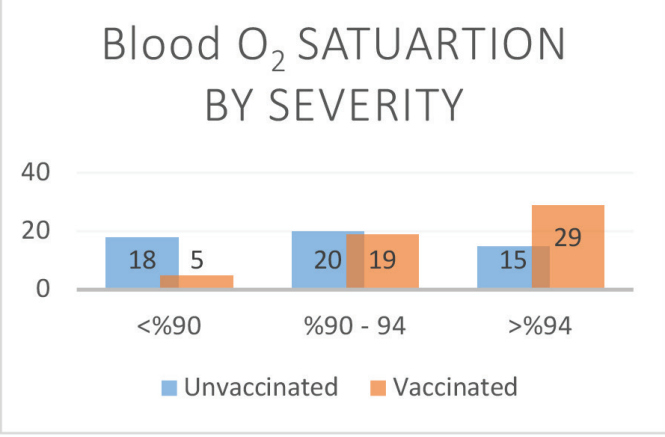

Figure 1. Distribution of O_2 saturation (%) according to severity

found to be a predictor of abnormal chest radiographs; therefore, this marker is expected to increase in patients with severe disease. One of the limitations of this study was that there was only one type of vaccine access, and vaccinated patients received only two doses, both of which can affect all the results. Therefore, other studies needed to be done in this field to compare all the existing vaccines and compare different doses.

CONCLUSION

Based on the results of this study, there was no difference between the pattern of lung involvement in the COVID-19 vaccinated and unvaccinated patients, but the pattern and severity of lung involvement in the vaccinated patients were lower than those in the unvaccinated patients. Additionally, there was a strong correlation between vaccination status and length of hospitalization, oxygen saturation, and the levels of the laboratory markers LDH and ESR levels. Those who had received vaccination had lower levels of LDH and ESR. Additionally, those who were fully vaccinated spent less time in the hospital, and vaccination reduces the number of ICU admissions and deaths; therefore, it can decrease the excess load of patients. These results indicate the effectiveness and necessity of COVID-19 vaccination.

Ethics

Ethics Committee Approval: This study was approved by the local ethics committee (approval number: IR.MUBABOL.HRI.REC.1400.235, date: 07.03.2022) at the Babol University of Medical Sciences, Babol, Iran.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.A., Concept: M.B., Design: M.B., Supervision: F.S., Resources: M.B., Material: M.B., F.S., Data Collection or Processing: H.A., G.H., Analysis or Interpretation: M.T., Literature Search: M.Baz., Writing: H.A., Critical Review: F.S.

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A Retrospective Aspect at the Evaluations of a University Clinical Research Ethics Committee: The Unseen Reasons Behind the Disapproved Studies

Bir Üniversite Klinik Araştırma Etik Kurulunun Değerlendirmelerine Retrospektif Bakış: Onaylanmayan Çalışmaların Arkasındaki Görünmeyen Nedenler

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ABSTRACT

Objective: The process of conducting medical research on human subjects is secured by a number of regulations from its planning phase through its publication as an original article. Ethics Committees (ECs) play an important role in the follow-up and evaluation of the study. In this study, we present an evaluation of the experiences of the "Clinical Research Ethics Committee" of a university.

Methods: The characteristics of EC applications, reasons for rejection (technical, scientific, ethical), and files that did not reapply to the committee after the revision request were analyzed.

Results: One thousand and fifty-seven (73.96%) of the 1429 files were accepted with minor corrections at the first examination and 15 files were rejected (1.04%). Of the applications, 357 (24.98%) were returned to the EC agenda with major correction requests. Scientific reasons were reported in 19 (90.5%) of the rejected files, ethical reasons were reported in 12 (57%) and technical reasons were reported in 8 (38.1). The rejection rate increased to 8.24% when the same files were reevaluated and did not reapply to the EC after the revision request (6.8%).

Conclusion: ECs seek revisions for a significant portion of submissions and offer researchers scientific and ethical advice. The majority of the applications were approved by this consultation. In our study, most of the files that did not receive approval from the EC were actually those that did not return after the revision request. The difficulties associated with the legislation appear to be an important reason for researchers to withdraw their application files.

Keywords: Ethics Committee, attitude, research, legislation

ÖZ

Amaç: Gönüllü insanlar üzerinde klinik araştırma yürütme süreci, planlama aşamasından makale olarak yayınlanmasına kadar bir dizi düzenlemeyle güvence altına alınmıştır. Etik Kurullar (EK), çalışmanın takibinde ve değerlendirilmesinde önemli bir rol oynar. Bu çalışmada, bir üniversitenin "Klinik Araştırmalar Etik Kurulu"nun deneyimlerinin bir değerlendirmesini sunuyoruz.

Yöntemler: EK başvurularının özellikleri, ret nedenleri (teknik, bilimsel, etik) ve revizyon talebinden sonra komiteye yeniden başvurmayan dosyalar analiz edildi.

Bulgular: Bin dört yüz yirmi dokuz dosyanın 1057'si (%73,96) ilk incelemede küçük düzeltmelerle kabul edildi; 15 dosya ise reddedildi (%1,04). Başvuruların 357'si (%24,98) büyük düzeltme talepleriyle EK gündemine tekrar alındı. Reddedilen dosyaların 19'unda (%90,5) bilimsel nedenler, 12'sinde (%57) etik nedenler ve 8'inde (%38,1) teknik nedenler mevcuttu. Düzeltme talebi ile gönderilen dosyaların %6,8'inde araştırıcılardan EK'a dönüş olmadı. EK tarafından tekrar değerlendirilen dosyalarda ret oranı %8,24 olarak bulundu.

Sonuç: EK başvuruların önemli bir kısmı için düzeltme/değişiklik talep etmekte ve araştırmacılara bilimsel ve etik önerilerde bulunmaktadır. Başvuruların çoğu bu öneriler doğrultusunda onaylanmıştır. Çalışmamızda EK'dan onay alamayan dosyaların çoğu aslında değişiklik/düzeltme talebinden sonra geri dönmeyenlerdi. Mevzuatla ilişkili zorluklar araştırmacıların başvuru dosyalarını geri çekmelerinin önemli bir nedeni gibi görünüyor.

Anahtar Sözcükler: Etik Komite, klinik araştırma, mevzuat

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INTRODUCTION

The processes from the planning of medical research for human benefit to its publication in a scientific journal are secured by a number of regulations (1,2). Ethics Committee play an important role in the follow-up of this process and evaluate the research both scientifically and ethically (3). The job descriptions and structure of ethical committees were defined in detail because of national and international regulations/declarations (3,4). In our national legislation in Türkiye, "Clinical Research Ethics Committee (EC)" should have the qualifications to evaluate the scientific, medical, and ethical aspects of the proposed research. It is also stated that the EC should take decisions independently and should be approved by the ministry of health (MOH), Turkish Medicines and Medical Devices Agency (TITCK) of the MOH to start their duties (3,5). In addition, due to the legislation in our country, there are different research ECs (such as social sciences research ECs) that are established by each research institution to evaluate research outside the legal framework (not under the supervision of the MOH).

All ECs are required to protect the rights, safety, and well-being of volunteers by guaranteeing that research is conducted to high ethical and scientific standards (6). In addition, it fulfills its responsibility to science by supporting research for the benefit of society. Although it is not directly included in the legislation, in fact, ECs protect investigators from possible risks. Each EC can take three types of decisions after evaluation: (1) acceptance, (2) a reasoned refusal, or (3) a decision to re-evaluate after amendment/correction. A scientific or ethical problem to be identified by the EC may cause possible harm to the researcher beyond harm to the volunteer or society. Perhaps it could put the investigator in a difficult position due to the law. Therefore, clearly stating the correction/amendment requests or rejection reasons contained in the reports of the ECs will also provide a guide for the solutions to possible problems.

When the literature is evaluated, the ethical and scientific reasons underlying the revision request and rejection decisions of the ECs have been revealed by many studies, including the rejection rate percentage (7). However, another important point is that the investigators withdrew the application files after the initial evaluation by the EC. Looking at the examples given from the literature, although the percentages of rejection and/or reasons for rejection of the ECs can be viewed, it is observed that the application was withdrawn by the researcher following the evaluation and reporting of the EC at a serious rate; the real cause of this withdrawal is not known. In this five-year period study, we want to evaluate not only the decisions of a university "Clinical Research Ethics Committee" but also the decisions of withdrawn or did not return to the EC following the first application and the first reporting of research files. The unique value of this article is that it sheds light on the reasons why researchers cannot fulfill the requests of the EC beyond the apparent reasons for refusal.

MATERIALS AND METHODS

The application files submitted to the Gazi University Faculty of Medicine Clinical Research EC between January 1, 2014, and December 31, 2018, were evaluated retrospectively. This research was approved by Gazi University Clinical Research Ethics Committee (approval number: 491, date: 07.08.2020). The research data were obtained from the information in the digital database and meeting notes. Research applications were evaluated in the following aspects: total number of applications, faculties of applicants, characteristics of the research, EC decisions (approved, rejected and requests for changes / corrections), reasons for refusal, number of applications withdrawn after the EC assessment, characteristics of the withdrawn applications, and decision-making time.

The reasons for rejection by the EC were evaluated in 3 groups. The main criteria under these three headings are summarized in Table 1. According to the criteria presented in Table 1, the reasons for refusal were categorized as scientific, ethical, and technical reasons and converted into numerical data.

Statistical Analysis

Descriptive statistics were used to evaluate the data obtained by transferring the data to the SPSS database. Number (n) and percentage (%) values were used for variables determined by number.

RESULTS

A total of 1429 applications were submitted during the 5-year period. Of these, 1221 were single-center research, while 208 applications were conducted in multi-centers. Of these, 1383 were national and 46 were international. When the research was evaluated due to their places of application, 1035 of them were from the Faculty of Medicine, 237 of them were from the faculty

Table 1. The reasons for rejection taken into account in research applications

Reasons for refusal		
Scientific reasons	**Ethical reasons**	**Technical reasons**
(1) The design and methods of the study are not sufficient or valid and reliable in order to achieve the objectives and hypothesis of the research. (2) Insufficient scientific and evidence-based justification for the purpose of the study, which is not supported by resources. (3) Lack of an expert/competent researcher on the subject	(1) Insufficient application of the principle of respect for the person/autonomy (Autonomy) (2) Insufficient application of the principle of respect for society (3) Insufficient application of the principle of justice (4) Failure of adequately applying the principle of not to give harm (5) The expectation of the utility principle is not sufficient	(1) Missing/incorrect forms (2) Incorrect application form (3) Missing permission letters

of health sciences, 58 of them were from the Faculty of Dentistry, and the remaining 99 were from other faculties (Figure 1). When the applications were evaluated in terms of research types, 1323 (92.58%) non-interventional clinical trials, 55 clinical drug phase trials, 15 non-drug clinical trials, 9 medical device studies, and 27 observational drug studies (Figure 2). When the research applications were evaluated in terms of EC decisions, it was seen that 1057 (73.96%) of the 1429 files were accepted with minor corrections at the first examination (Figure 3). We also report minor corrections. Before the next meeting's agenda, the EC approved the conduct of checks. Almost all of the files in which minor correction requests were made, correction/amendment requests were made on informed consent. Fifteen files were rejected in the first evaluation (1.04%). Of the applications, 357 (24.98%) were returned to the EC agenda with major correction requests (Figure 3). After the major correction request, 6 more files were rejected, and the number of rejected files increased to 21 (Figure 4). In 97 of the 357 applications sent back to the researcher with a major correction request (6.78%), the researcher did not make a correction and reapplied it to the EC, which defined the files as inconclusive. When 21 rejection files were evaluated together with these 97 applications, it was observed that 8.24% of the applications did not receive approval from the EC within the 5-year evaluation period. When these 97 files were examined in detail, it was seen that the basic correction request was incorrect in 48% of them. These files also required approval from the Ministry of Health of the Republic of Turkey after approval from the corporate EC. Other applications that did not reapply to the EC after correction were noted for methodological errors, problems in insuring volunteers, and budget problems. Of the 21 rejected applications, three were Phase 3 trials, 11 were non-interventional, and 7 are herbal product or food supplement research (Figure 5). Scientific reasons were reported in 19 (90.5%) of the rejected files, ethical reasons were reported in 12 (57%) and technical reasons were reported in 8 (38.1) of the rejected files (Figure 6). More than one reason for refusal was also recorded in the same file. The average decision-making time of the EC was 23.6 and 5.2 days; in the case of files with a request for correction, this period was 52.1 and 4.3 days.

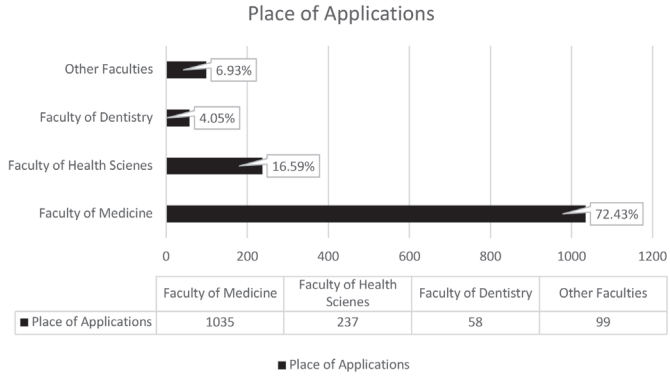

Figure 1. Distribution of the researches according to the places of application

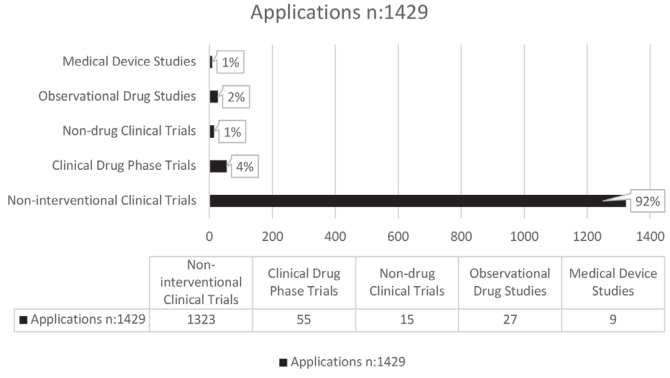

Figure 2. Distribution of total applications according to application types

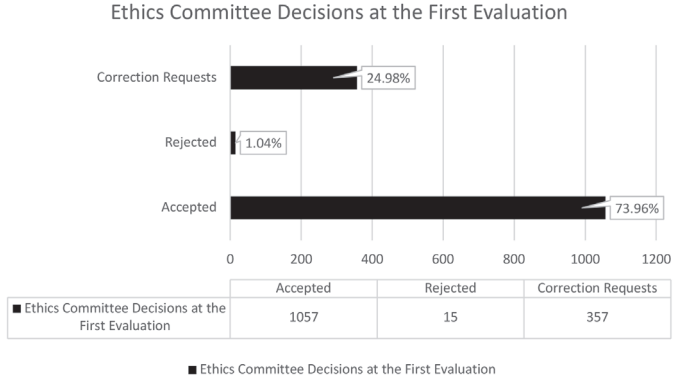

Figure 3. Decisions of the Ethics Committee as a result of the initial evaluation of a total of 1429 applications

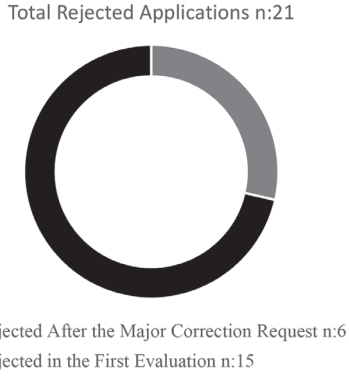

Figure 4. Distribution of the total 21 rejected applications according to the rejection time

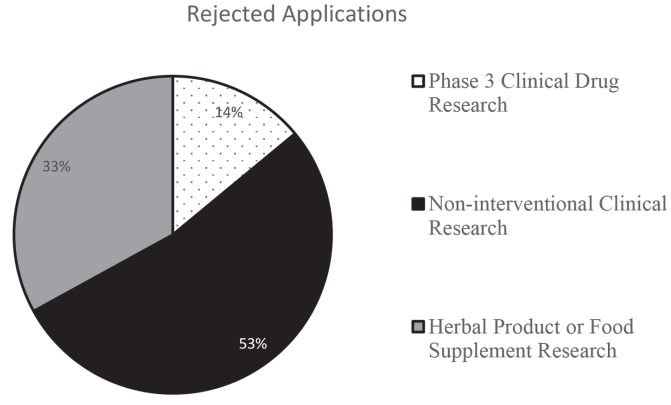

Figure 5. Types of rejected research

Figure 6. Percentage distribution of reasons for rejection in a total of 21 applications rejected by the Ethics Committee

DISCUSSION

In this study, in which the 5-year experience of the EC of a large university located in the capital of **Tü**rkiye was evaluated, the majority of applications (74%) were accepted at the first examination with minor corrections, and about a quarter requested major corrections.

When we have reviewed the literature, the evaluation of EC verdicts for 12 years in a study has shown 8% unconditional approval, 72% approved with minor revisions or conditions, and 20% major revision requested. It has been reported that no application was rejected in this study (8). In another study in which the decisions of the clinical research EC were evaluated, 1256 projects were reviewed. 68% of the projects were approved at the first meeting, and the decision-making period was days. It was stated that 97.5% of the applications were approved at the end of the process (9). In our research, 91.7% of all applications were accepted after revision. In another study by Bueno et al. (9), the reasons for revisions were inadequate use of language on the informed consent form (%32.2), the absence of enough information about the protocol on the informed consent form (%25.8), and related methodological and statistical issues of the protocol doubts (%77.1) have been reported. The results of this study are similar to our research. In our research, the reasons for rejection were largely scientific reasons, and in particular, insufficient and untrustable study design and methods to achieve the goals and hypotheses of the research. Bueno et al. (9) reported the lack of documentation and inaccuracy as a priority among other reasons for returning projects. They have also emphasized the need for explanations or consent for the participation of external organizations (incomplete signing of signatures), the non-compliance of the research team, and the lack of information about financial support in the research (9). Similarly, in our research, it was found that 48% of the files did not reapply due to revision request after the first application has been made with (incorrect) application forms that are not in accordance with the legislation. In addition, in our research, the most common problems observed under the heading of technical reasons for rejection are incomplete/erroneous forms, incorrect application forms, and missing permission letters from the necessary institutions, which includes 38.1% of all reasons for rejection. A survey conducted with multiple IRBs revealed that among the reasons for rejected studies and requesting revisions, problems with informed consent were identified. This was followed by the poor design of the studies, the fact that there were risks that could not be accepted by the subjects, and ethical or legal reasons (10). In another study, it was found that the researchers have received the most criticism regarding the preparation of the study methodology. Regarding the criticism of the method, it was reported that the inadequacy of statistical analyses and sampling errors were the most common. Similar to other studies, the leading correction requests have included reasons such as bias in consent, lack of mention of benefits, and lack of informing volunteers about the practices (11). In our research, almost all of the files that were decided both accepted with minor corrections and requested major revisions, there was a request for changes or corrections in the informed voluntary consent form. There were no rejected files owing to the informed voluntary consent form. Issues such as deficiencies/errors in the informed voluntary consent form, insufficient explanation of the expected benefit/harm from the research, and non-observance of the principle of justice were within the scope of ethical issues. In our research, ethical reasons account for 57% of the reasons for rejection, and these problems are encountered in one out of every two files. In our study, the rejection rate was found to be quite low, such as 1.5%. In 9 out of every 10 rejected files, the reason for rejection was scientific reasons. The rejection rate increased to 8.24% when evaluated together with the files that did not reapply to the EC after the revision request (6.8%). As a result, it was observed that around 8% of the files could not complete the EC process. When the literature was reviewed, there were also some studies in which the rejection rate found as 8% (5,6,9). In a study, according to the data of the EC of a university medical center, it was seen that 90.3% of applications were accepted and 9.7% were rejected. In this study, it was stated that a large proportion of the rejections were independent of the EC evaluation process, and only 1.2% of the protocols were unsuccessful after the review. The most common reasons were unacceptable risks and inadequate methodology (12). In our study, most of the files that did not receive approval from the EC were actually those that did not return after the revision request. The EC consists of files that have not completed the evaluation process. When these files are examined, it is seen that 48% of them are studies that require a second approval from the central authority (Ministry of Health) after receiving approval from the EC. If it is to be evaluated specifically in our country, interventional research (drug research, medical device research or various interventional procedures, non-drug clinical studies) must also receive approval from the central authority (Ministry of Health, TITCK) after approval by the EC. In this type of research, which requires the approval of the central authority, there are different and detailed application forms, annexes of the application and a number of procedures (13). The fact that the researchers found all these processes very long and tiring and that some conditions seemed impossible to fulfill may be a reason why they did not reapply to the EC. According to the results of our research, among the revision requests in these files, the obligation to ensure volunteers and budget problems drew attention. The existence of compelling conditions may have also caused the EC review process to be interrupted. In our research, the majority of applications are noninterventional. This result also seems to reflect the difficulties associated with the

approval process for interventional research. On the other hand, it was seen that a significant part of the files rejected in our study were herbal product or food supplement research. In the legislation of our country, these studies require approval from the central authority after approval of the EC and are subject to drug-like review processes. There are detailed and compelling requirements for national and international legislation in drug research and other interventional research. It can be considered that researchers have difficulty fulfilling these requirements. Clinicians conducting research should be aware of the rules and regulations affecting human research (14). ECs should also guide clinical researchers to conduct high-quality studies with human participants.

In a study, it was stated that the consistency of the decisions of institutional ECs should be measured (15). Accordingly, it is important to undertake quality assessment and continuous improvement in decision-making. At this point, ECs should also evaluate their own decisions. In particular, rejection decisions must be in a way that does not cause suspicion. In our study, it was seen that rejection decisions were expressed with very clear and obvious reasons, and national and international legislation was cited for the justification of the decision. On the other hand, when there are changes in the structure of the boards, it is important that all board members are informed about the decision-making processes due to our national legislation. In addition, every board member should take the course of good clinical practice, including national/international regulations about clinical research. Our clinical research regulations and guidelines are regularly updated by the Ministry of Health.

Study Limitations

The main limitation of this research is the retrospective evaluation. Evaluation was performed on the limited available data. The evaluation could be performed over a longer period. Our starting point was in 2014. We took this point as the application of the new regulations which were revised at 2013 in our country. Therefore, a 5-year period was taken for the evaluation. Another point, we were particularly challenged regarding the status of the files sent to the upper approval authority. We have defined these as inconclusive files. As a result, we believe that we have received an answer to our research question.

CONCLUSION

As can be seen in both our research and other examples, ECs provide scientific and ethical advice to researchers with revision requests in a large part of the applications. With the help of this consultation, most applications were approved. The difficulties associated with the legislation appear to be an important reason for researchers to withdraw their application files. However, informing all researchers about national and international legislation will both save researchers time and reduce the burden of ECs.

Ethics

Ethics Committee Approval: This research was approved by Gazi University Clinical Research Ethics Committee (approval number: 491, date: 07.08.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: C.U., A.K.C., Design: C.U., A.K.C., Supervision: C.U., A.K.C., Resources: A.K.C., U.A., Material: C.U., Data Collection or Processing: A.K.C., U.A., Analysis or Interpretation: A.K.C., Literature Search: A.K.C., U.A., Writing: C.U., A.K.C., U.A., Critical Review: C.U., A.K.C., U.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Acute Bronchiolitis To Pediatric Inpatient Clinic In Patients Under 2 Years Old, Installed with Diagnosis Investigation of the Relationship of Bronchiolitis and Asthma

Pediatri Servislerine Akut Bronşiolit Tanısıyla Yatırılan 2 Yaşından Küçük Hastalarda Bronşiolit ve Astım İlişkisinin Araştırılması

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ABSTRACT

Objective: Previously considered a uniform disease, bronchiolitis has been revealed through research as heterogeneous, displaying varied phenotypes and clinical-histopathological differences among patients. Our study aimed to explore distinctions among children hospitalized with acute, severe bronchiolitis and identify potential asthma risk factors.

Methods: Between January 2017 and November 2022, we examined hospitalized children under 2 years with moderate to severe acute bronchiolitis. Disease severity was assessed using the bronchiolitis severity score developed by the Turkish Thoracic Society. The asthma risk was evaluated using the modified Asthma Predictive Index (mAPI) designed for predicting future asthma in bronchiolitis cases.

Results: A total of 156 patients were studied, with 41% having previous bronchiolitis hospitalizations (multiple hospitalization group) and 59% having first-time hospitalizations (first hospitalization group). Middle rales, wheezing, and tachypnea were more frequent in the multiple hospitalization group, with a 1-unit increase in respiratory rate, increasing readmission risk by 1.048 times. Assessing patients by "API", 64.1% were "API" (+) and 35.9% were "API" (-). Among "API"

ÖZ

Amaç: Bronşiolit klinik olarak tek hastalık olarak görülmüşsede, yapılan çalışmalar gerek viral etken özellikleri gerek hastalar arasında klinik ve histopatolojik farklılıklar bulunduğunu ve değişik fenotipleri olan, heterojen hastalık olduğunu göstermektedir. Amacımız; akut bronşiolit sebebiyle hastaneye yatırılan çocuklarda, hastalar arasındaki farkları araştırmak ve astım risk faktörlerini belirlemeye çalışmaktır.

Yöntemler: Hastanemiz pediatri servislerine Ocak 2017-Kasım 2022 tarihlerinde, 2 yaşından küçük, orta-ağır şiddette akut bronşiolitle yatırılan 156 hasta alınmıştır. Hastaların atak şiddetleri, Türk Toraks Derneği tarafından oluşturulan bronşiolit şiddet skoruna göre belirlenmiştir. Hastalarımızda bronşiolitlerde olası astımı öngörebilmek için kullanılan "modified Asthma Predictive Index" (mAPI) skoruna göre astım riski değerlendirilmiştir.

Bulgular: Yüz ellli altı hasta değerlendirilmiştir. Akut bronşiolitle daha önceden hastane yatışı öykülerine, ve mAPI özelliklerine göre değerlendirilmiştir. Hastalarımızın %41'i bronşiolit nedeniyle önceden hastaneye yatırılmış olup (çoklu yatış grubu) %59'u ilk kez yatırılmıştır (ilk yatış grubu). Orta ral, hışıltı ve takipne çoklu yatış grubunda daha fazla olup, aradaki fark istatistiksel olarak anlamlıdır. Hastalarımız,

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(+) patients, 69% were male, compared to 48.3% among "API" (-) patients-a significant difference. Wheezing occurred in 48% of "API" (+) patients and 30.3% of "API" (-) patients - also significant.

Conclusion: The majority of bronchiolitis cases were linked to asthma, with a significant 48.7% having a family history. This major risk factor implies a prevalent asthma phenotype. Moreover, 41% of patients with repeated hospitalizations and 64.1% API (+) reinforce this view. In summary, an early identification of patients at risk of asthma is crucial for tailoring appropriate treatment and safeguarding lung function.

Keywords: Astma, bronchiolitis, phenotyphe, child, viruses, wheezing

"API"e göre değerlendirildiğinde; hastaların %64,1'inin "API" (+), %35,9'unun "API" (-)'tir. "API" (+) hastaların %69'u erkek, "API" (-) hastaların %48,3'ü erkek olup aradaki fark istatistiksel olarak anlamlıdır. "API" (+) hastaların %48'inde hışıltı, "API" (-) hastaların %30,3'ünde hışıltı duyulmuş, aradaki fark istatistiksel olarak anlamlıdır.

Sonuç: Çalışmamızda bronşiolit geçirenlerde birçoğunun astımla ilişkili olduğunu düşündüren bulgular görülmüştür. Ailede astım öyküsünün %48,7 olup bu durum astım yönünden bilinen en büyük risk faktörüdür. Bu sebeple hastalarımızın birçoğunun astım fenotipinde olduğunu düşünmekteyiz. Ayrıca %41 çoklu yatış öyküsü, %64,1 API (+) olması bu görüşümüzü desteklemektedir. Astım yönünden riskli hastaların erken dönemde belirlenmesi, doğru tedavinin ayarlanması ve hastanın akciğer fonksiyonlarının korunması önemlidir.

Anahtar Sözcükler: Astım, bronşiolit, fenotip, çocuk, hırıltı

INTRODUCTION

Bronchiolitis is an acute obstructive infection characterized by bronchospasm, necrosis of epithelial cells, increased mucus production, submucosal edema, and inflammation in the small airways (bronchioles) caused by viruses (1,2). This terminology is used for children under the age of 2 in the United States and our country, whereas in Europe, Canada, and Australia, it is applied to children under the age of 1 (2-4). The bronchioles form a large area of 140 m² throughout the lungs. Their total volume is 4.500 mL (5). Bronchioles, which create such a large volume and area, have two significant differences from other airways: first, their lumen diameters are very narrow, ranging from 0.5 to 1 mm. Second, cartilage, which provides the tone of the airways and is abundantly present in medium- and large-sized bronchi, is absent in bronchioles. This absence makes them prone to collapse during illness (5,6). Although all respiratory viruses can cause acute bronchiolitis, severe cases are often associated with respiratory syncytial virus (RSV) and rhinovirus (RV) (7). Throughout the world, all infants encounter respiratory viruses soon after birth. This case usually presents as a simple upper respiratory tract infection (URI). However, in 20-50% of cases, instead of URI, lower URI or bronchiolitis is diagnosed (1,2,4). The most important symptoms include cough, mucus (wheezing), shortness of breath, and wheezing respiration (wheezing). Decreased feeding and restlessness may accompany. Nasal flaring and retraction due to the use of accessory respiratory muscles may be observed. Expiration may be prolonged. On auscultation of the lungs, the rales, medium rales, and wheezing can be heard, depending on the severity of the obstruction (1,4,8).

Approximately 3.2-7.8% of bronchiolitis cases are severe and require hospitalization for treatment (4). In 16-60% of patients hospitalized with an acute bronchiolitis diagnosis, it is observed that bronchiolitis attacks recur after recovery, and many of these patients are later diagnosed with asthma (1,9). It has even been reported that long initial attacks can be classified as bronchiolitis (10). Although bronchiolitis has long been seen clinically as a single disease, it is now understood that not every patient with bronchiolitis has the same characteristics (11,12). Recent studies have increasingly revealed both clinical and histopathological differences among patients (13,14). This evidence indicates that bronchiolitis is a heterogeneous disease with various phenotypes. Identifying the phenotypes associated with asthma is crucial for ensuring appropriate treatment and preventing future impairment of respiratory function and development of chronic persistent asthma (12).

The aim of our study was to investigate differences among children hospitalized for the treatment of acute severe bronchiolitis to identify risk factors for asthma.

MATERIALS AND METHODS

Case Selection and Study Design

Our study included patients aged below 2 years who were hospitalized for acute bronchiolitis between January 2017 and November 2022 at Gazi University Medical Faculty Hospital's Pediatrics department. All hospitalizations were reviewed, and a total of 156 cases. Patients were initially assessed using emergency department records, while subsequent evaluations relied on file records during admission to pediatric and infection services.Initial attack severity was determined using the Turkish Thoracic Society's bronchiolitis severity score (8). Patients with moderate to severe attacks were included and categorized as mild, moderate, or severe. Starting from 2020, all hospitalized patients underwent a COVID-19 polymerase chain reaction test; those who were negative were placed in the wards. The study excluded outpatients with treated bronchiolitis and children with non-bronchiolitis chronic or systemic illnesses.

Work Plan

For each patient, a "case report form" was created, documenting disease history from parents, personal and family history, initial emergency department examination, and laboratory results. Upon admission, patient SpO_2 was measured using a Covidien Nellcor pulse oximetry device. Prior to any treatment, complete blood counts were conducted on peripheral venous blood samples at our hospital's hematology laboratory. For patients investigated for causative agents, PCR analysis of nasopharyngeal samples (Fast Tract Respiratory Pathogens 21; Siemens Healthcare GmbH, Germany) detected causative agents. The test covered RSV A/B, Rhinoviruses, Influenza A/B Viruses, H1N1, Parainfluenza (PIV 1, PIV 2, PIV 3, PIV 4), Coronaviruses (NL63-229E-OC43-HKU1), Metapneumoviruses A/B, Bocaviruses, Adenoviruses, and Parechoviruses. A multiplex real-time PCR panel simultaneously detected Enteroviruses, Mycoplasma pneumoniae, *Bordetella Pertussis*, and Legionella Pneumonia.

All patients underwent assessment using the "modified Asthma Predictive Index" (mAPI) score based on recorded data (15). The asthma risk score (Table 1) gages asthma risk in under-three-year-olds with recurrent bronchiolitis. A major criterion and two minor ones indicate high future asthma risk (15). All 156 patients were categorized as "API" positive or negative, facilitating comparison. However, blood-specific IgE and skin prick tests for aeroallergen sensitization were not performed during hospitalization. Thus, the first two parameters were used as the major criteria for our patients.

Ethics Committee Approval

Our study was approved by the Gazi University Faculty of Medicine Local Ethics Committee (approval number: 805, date: 14.12.2020).

Statistical Analysis

Data analysis employed the "SPSS for Windows 11.5" software. The parameters were categorized as categorical or numerical variables. The frequency distribution (count, percentage) and descriptive statistics (mean, standard deviation) were applied. Pearson's chi-square test, Fisher's chi-square test, continuity correction chi-square test, Student's t-test, and Mann-Whitney U test were used. Significance was determined at $p<0.05$, considering Type 1 error levels below 5% as statistically significant.

RESULTS

Patient Characteristics

Table 2 Assesses the traits of patients aged below 2 years admitted to the Gazi University Faculty of Medicine Hospital's Pediatrics departments from January 2017 to November 2022.

Previous Hospitalization Status of Patients With Bronchiolitis (Number of Hospitalization Groups)

Patients were categorized by prior acute bronchiolitis hospitalization history. Among the 156 patients, 64 (41%) had prior hospitalizations (multiple hospitalization group), while 92 (59%) had first-time acute bronchiolitis admissions (first hospitalization group). When the two groups were compared in terms of age and gender, no statistically significant difference was found (p=0.25 and p=0.25, respectively) (Table 3).

Evaluation of Hospitalization Number Groups Based on Respiratory System Examinations At Admission

Patients in both the multiple and initial hospitalization groups underwent respiratory examination. Patients in the multiple hospitalization group exhibited higher rates of moderate rales and wheezing compared with those in the initial hospitalization group, with a significant difference (p=0.04, p=0.037, respectively), as indicated in Table 4. Increased respiratory rate (tachypnea) was also found in more patients in the multiple hospitalization group, and there was a statistically significant difference between the groups (p=0.008) (Table 4). Upon analyzing patients in the multiple hospitalization group based on physical examination, a rise of one unit in the respiratory rate amplified readmission risk by 1.048 times. Alternatively, tachypnea heightened readmission likelihood by a factor of one [p=0.004, OR: 1.048, CI: 95% (1.015-1.081)], detailed in Table 5.

Bronchiolitis Agents in Our Patients (PCR Results)

Respiratory tract PCR was performed in 92 (58.9%) of the 156 patients included in this study. The viral agent results are presented in Table 6. In a total of 48 (71.6%) of 67 patients hospitalized with a diagnosis of acute bronchiolitis and PCR positivity, RSV or RV was found to be the causative agent. These 48 patients were defined as "RSV+RV group". Another 19 (28.4%) patients with bronchiolitis associated with other viral agents were defined as "other agents group". No causative agent was detected in 25 (27.2%) of 92 patients in whom PCR was performed. These patients were defined as "PCR (-) group". When the RSV+RV Group was compared with the "other factors group", no statistically significant difference was found in age and gender (p=0.32, p=0.58, respectively). No statistically significant age or gender differences existed between the PCR (+) and PCR (-) groups (p=0.26, p=0.60, respectively). Upon assessing hospitalization duration, no statistically significant distinctions emerged among the groups (p=0.55, p=0.40, respectively), as shown in Table 7.

Table 1. Modified "asthma predictive index" (15)

Major criteria	Minor criteria
1. Doctor-diagnosed asthma in the mother or father	1. Accompanied by food allergy
2. Doctor-diagnosed atopic dermatitis	2. Wheezing outside the URTI
3. At least 1 aeroallergen sensitivity	3. Eosinophilia in peripheral blood (≥4%)

URTI: Upper respiratory tract infection.

Table 2. Patient characteristics (n=156)

Age, month (± SD)	11.8 (±7.06)
Gender, n (%)	
Female	59 (37.8)
Male	97 (62.2)
Number of hospitalizations with a previous diagnosis of bronchiolitis, n (%)	
First hospitalization	64 (41)
Multiple hospitalizations	92 (59)
Duration of hospitalization	
Mean days (± SD)	4.7 (±3.1)
Median, day (range)	4 (1-17)
Mode of delivery, n (%)	
Cesarean section	89 (57.1)
Vaginal	67 (42.9)
Premature birth	36 (23)
Low birth weight (< 2500 g)	3 (1.9)
Mechanical ventilation during the neonatal period	17 (10.8)
Premature	14 (8.9)
Term	3 (2.4)
Atopic Dermatitis, n (%)	34 (22.4)
Asthma in the family, n (%)	76 (48.7)

SD: Standard deviation

Evaluation of Bronchiolitis Agents According To Physical Examination Findings

The physical examination findings of 67 patients hospitalized with acute bronchiolitis and PCR (+) and 25 patients with PCR (-) were assessed. In the PCR (+) group, no statistically significant variation was noted in physical examination findings between patients with RSV+RV-related bronchiolitis and those linked to other viral agents (p=0.81, p=1.00, p=0.96, p=0.74, p=0.54, p=0.43, respectively).

Table 3. Characteristics of patients with previous hospitalization for bronchiolitis

	Multiple hospitalization (n=64)	First hospitalization (n=92)	p
Age			p=0.25*
Mean, months (± SD)	12.6 (±7.1)	11.4 (±7.1)	
Median, month (range)	11.5 (1-24)	10 (1-24)	
Gender, n (%)			p=0.25**
Female	21 (32.8)	39 (42.3)	
Male	43 (67.2)	53 (57.7)	

*Mann-Whitney U test, **Student t-test, SD: Standard deviation

Table 4. Respiratory system examinations at first admission according to hospitalization groups

	Multiple hospitalization (n=64)	First hospitalization (n=92)	p
Rhonchus, n (%)			p=0.52*
Yes	61 (95.3)	84 (91.3)	
No	3 (4.7)	8 (8.7)	
Medium rale, n (%)			p=0.04**
Yes	36 (56.2)	37 (40.2)	
No	28 (43.8)	55 (59.3)	
Wheezing, n (%)			p=0.037**
Yes	33 (50.8)	32 (34.7)	
No	31 (34.1)	60 (5.9%)	
Breath retraction, n (%)			p=0.33***
Yes	53 (82.8)	69 (75)	
No	11 (48.5)	23 (25)	
Respiratory rate			p=0.008****
Mean, min. (± SD)	58.5 (±10.8)	53.4 (±12.4)	
Median, min. (range)	60 (34-84)	55 (30-90)	
SpO_2 (%)			p=0.45****
Mean, min. (± SD)	92.4 (±4.2)	92.1 (±3.9)	
Median, min. (range)	93 (84-100)	93 (82-100)	

*Fisher's exact chi-square test, **Pearson's chi-square test, ***Yates's correction chi-square, ****Independent group t-test, min.: Minimum, SD: Standard deviation

There was no statistically significant difference between the PCR (-) group and the PCR (+) group in terms of physical evaluation (p=0.66, p=0.43, p=1.00, p=1.00, p=1.00, p=0.15, p=0.76) (Table 8)

Evaluation of The Patients Regarding The "Asthma Predictive Index" Status

All 156 patients hospitalized with a diagnosis of acute bronchiolitis were evaluated according to the "API" criteria described in detail in Table 2 in the materials and methods section.

Of the 156 patients included in our study, 100 (64.1%) were "API" positive, and 56 (35.9%) were "API" negative. When the groups were compared, there was no significant difference between them in terms of age (p=0.28), but there was a significant difference in terms of gender, with more male patients in the "API" positive group (p=0.017) (Table 9).

Respiratory Examination Findings of The "API" Groups At The Initial Presentation

When comparing "API" positive and "API" negative patients' physical evaluations, wheezing was significantly more prevalent in the "API" positive group (p=0.048) as indicated in Table 8. Similarly, comparing "API" positive and "API" negative patients based on physical evaluations, tachypnea was notably higher in the "API" negative group, with a significant difference (p=0.014), as detailed in Table 10.

Agents Detected By PCR Test In "API" Groups

The agents of bronchiolitis detected by PCR in our patients were analyzed in detail according to their API status. When the patients in whom PCR-detected bronchiolitis agents were compared based

Table 5. Association between hospitalization group and risk factors

Risk factor	OR	95% CI	p
Respiratory rate (min.)	1.048	1.015-1.081	0.004
Wheezing	1.71	0.85-3.47	0.13
Medium ral	1.85	0.92-3.69	0.81
Food allergy	2.63	0.83-8.34	0.10

OR: Odds ratio, CI: Confidence interval, min.: Minimum

Table 6. Results of 92 patients who underwent PCR test

Positive PCR , n (%)	67 (72.8)
RSV (single agent)	27 (40.3)
Rhinoviruses	21 (31.3)
Rhinovirus (single agent)	15 (71.4)
Rhinovirus + Parainfluenza virus	3 (14.2)
Rhinovirus + Adenovirus	2 (9.5)
Rhinovirus + Metapnomovirus	1 (4.7)
Adenoviruses	2 (2.9)
Bocaviruses (single agent)	6 (9)
Bocavirus + Adenovirus	1 (16.6)
Influenza viruses A/B	10 (15)
Mycoplasma	1 (1.5)
Negative PCR	25 (27.2)

PCR: Polymerase chain reaction, RSV: Respiratory syncytial virus

on their "API" status, no statistically significant difference was found between them (p=0.53) (Table 11).

DISCUSSION

In this study, 156 patients admitted to the pediatric health and disease departments of our hospital with a diagnosis of moderate to severe acute bronchiolitis were analyzed. The aim of this study was to determine common features among these patients as well as clinical differences, specifically to identify those with asthma-like phenotypes. It is known that asthma often begins with recurrent bronchiolitis in childhood (10,16). A family history of asthma is the most well-established risk factor (15-17). In our patients, the rate of family history of asthma was as high as 48.7%. No biomarker predicts which young children with recurrent bronchiolitis will develop asthma (17). To identify such children in advance, indices that include certain risk factors are used. One commonly used index is the modified "API" (15). According to the modified "API", the probability of developing asthma after the age of 3 years in patients with API positivity is 90% (15). In our study, the prevalence of modified "API" positivity criteria was as high as 64%. The high rates of recurrent attacks and "API" positivity suggest that there is a significant number of children with asthma phenotypes in our study group. Our analysis revealed that 62.2% of patients were male. Mansbach et al. (18) reported that 59%

Table 7. Evaluation based on the causative agents of bronchiolitis

	PCR (+) (n=67)			PCR (-) (n=25)	
	RSV + RV (n=48)	Other factors (n=19)	p		p***
Age					
Mean, months (± SD)	12.3 (±7.4)	14.5 (±7.7)	p=0.32**	11 (±6.5)	p=0.26*
Median, month (range)	10.5 (1-24)	17 (1-24)		9 (1-24)	
Gender, n (%)					
Female	23 (47.9)	7 (36.8)	p=0.58*	9 (36)	p=0.60**
Male	25 (52.1)	12 (63.2)		16 (64)	
Duration of hospitalization				4.7 (±3)	
Mean, days (± SD)	5.5 (±3.4)	5.5 (±4.3)	p=0.55**	5 (1-10)	p=0.40*
Median, day (range)	5 (1-15)	4 (1-17)			

*Mann-Whitney U test, **Yates's correction chi-square, ***Evaluation of PCR (-) group and PCR (+) group, PCR: Polymerase chain reaction, RSV: Respiratory syncytial virus, RV: Rhinovirus, SD: Standard deviation.

Table 8. Evaluation of respiratory system findings based on bronchiolitis agents

	PCR (+) (n=67)			PCR (-) (n=25)	
	RSV + RV (n=48)	Other factors (n=19)	p		p****
Rale, n (%)					
Yes	22 (45.8)	10 (52.6)	p=0.81*	10 (23.8)	p=0.66*
No	26 (54.2)	9 (47.4)		15 (76.2)	
Rhonchus, n (%)					
Yes	42 (87.5)	17 (89.5)	p=1.00**	24 (96)	p=0.43**
No	6 (12.5)	2 (10.5)		1 (4)	
Wheezing, n (%)					
Yes	18 (37.5)	10 (52.6)	p=0.96*	10 (23.8)	p=1.00*
No	30 (62.5)	9 (47.4)		15 (76.2)	
Breath retraction, n (%)					
Yes	38 (79.2)	16 (84.2)	p=0.74**	21 (84)	p=1.00**
No	10 (21.8)	3 (15.8)		4 (16)	
Respiratory rate					
Mean, min. (± SD)	54.7 (±12.5)	55.9 (±13.3)	p=0.54***	60.5 (±12.5)	p=0.15***
Median, min. (range)	57 (30-80)	58 (30-72)		60 (40-90)	
SpO_2					p=0.76***
Mean, % (± SD)	92.4 (±3.8)	93.1 (±4.5)	p=0.43***	93 (±4)	
Median, % (range)	92 (82-98)	95 (82-100)		94 (84-100)	

*Yates's correction chi-square, **Fisher's exact chi-square test, ***Mann-Whitney U test, ****Evaluation of PCR (-) group and PCR (+) groups, min.: Minimum, PCR: Polymerase chain reaction, RSV: Respiratory syncytial virus, RV: Rhinovirus, SD: Standard deviation.

of patients under the age of 2 with acute bronchiolitis were male. It is believed that bronchiolitis is more common in boys because of the narrower bronchial diameters, higher airway resistance, and slower airflow rates in men (2,4). In our study, 89 out of 156 patients (57.1%) were born by cesarean section. The high rate of cesarean births was consistent with the findings of Douglas et al. (19) reported that the

Table 9. Evaluation of patients according to the "API"

	API (+) n=100	API (-) n=56	p
Age			
Mean, months (± SD)	12.1 (±7.1)	11.5 (±7.1)	
Median, month (range)	11 (1-24)	10.5 (1-24)	p=0.28**
Gender, n (%)			
Female	31 (31)	29 (51.7)	p=0.017*
Male	69 (69)	27 (48.3)	

*Mann-Whitney U test, **Yates's correction chi-square, API: Asthma predictive index, SD: Standard deviation.

Table 10. Physical examination findings of "API" groups at admission

	API (+) n=100	API (-) n=56	p
Rhonchus, n (%)			
Yes	93 (93)	52 (92.8)	p=1.00*
No	7 (7)	4 (57.2)	
Rale, n (%)			
Yes	49 (49)	24 (42.8)	p=0.46**
No	51 (51)	32 (57.2)	
Wheezing, n (%)			
Yes	48 (48)	17 (30.3%)	p=0.048***
No	52 (52)	39 (69.7%)	
Breath retraction, n (%)			
Yes	78 (78)	44 (78.5)	p=1.00***
No	22 (22)	12 (21.5)	
Respiratory rate (min.)			
Mean, min. (± SD)	53.8 (±12.2)	58.8 (±11.1)	p=0.014****
Median, min. (range)	56 (30-84)	60 (35-90)	
SpO_2			
Mean, (± SD) %	92,6 (±4.1)	92.9 (±3.8)	p=0.67****
Median, (range) %	93 (82-100)	94 (85-99)	

*Fisher's exact chi-square test, **Pearson's chi-square test, ***Yates's correction chi-square, ****Mann-Whitney U test, API: Asthma predictive index, SD: Standard deviation.

Table 11. Bronchiolitis agents detected by PCR test in "API" groups

	API (+) n=41	API (-) n=26	p
RSV+RV (n, %)	31 (75.6)	17 (65.4)	p=0.53*
Other factors (n, %)	10 (24.4)	9 (34.6)	

*Yates's correction chi-square, PCR: Polymerase chain reaction, API: Asthma predictive index, SD: Standard deviation.

incidence of bronchiolitis was 15-37% higher in patients who had a cesarean delivery than in those born vaginally. Contact with the mother's vaginal flora in vaginally born infants leads to more diverse and healthy microbiota colonization in both the gastrointestinal and respiratory tracts (20). This treatment may also protect against bronchiolitis. A study conducted by Alan et al. (21) in our country, evaluating 20,183 newborns, reported a higher incidence of RSV-associated bronchiolitis in premature or low birth weight newborns. In our study, we had 3 low birth weight patients, and a sample size comparable to that of normal birth weight infants could not be established. The survival rates of premature infants have significantly increased in recent years, and the associated conditions have become better understood. Lung development begins before birth and continues until the age of 2 years, indicating that premature infants are born with less developed lungs and are at higher risk of severe RSV infections during the first year (21,22). Additionally, the frequent occurrence of bronchopulmonary dysplasia in premature infants increases the risk of severe bronchiolitis (23). Mechanical ventilation during the neonatal period can lead to lung cell damage, inflammation, surfactant dysfunction, and persistent lung damage (23). In our study, 23% of patients had a history of premature birth, and 10.8% had a history of mechanical ventilation during the neonatal period. This may represent an additional risk factor for the development of moderate to severe bronchiolitis.

It is known that children with atopic dermatitis and food allergies during infancy have an increased risk of developing asthma (15). Although all our patients were a selected group with severe bronchiolitis, the rates of atopic dermatitis and food allergies were lower than expected (22.4% and 9.6%, respectively). These conditions may be missed if they are clinically mild or enter remission significantly during the first year (1,2,21,24). Because our study included patients aged up to 2 years and assessed retrospective records, the observed rates for these risk factors may be lower than expected. Among the 156 patients in our study, 64 (41%) were previously hospitalized for acute bronchiolitis and were classified as having multiple hospitalizations. The relationship between recurrent bronchiolitis and asthma development becomes causal, especially in severe cases. A cohort study involving 38 centers across Europe, Africa, and the Americas tracked 343 children with bronchiolitis and reported that the severity of previous bronchiolitis was the most important risk factor for future asthma development ($p<0.05$, OR: 1.21, CI% 95) (25). Epidemiological studies have reported that 16-60% of severe bronchiolitis requiring hospitalization experience recurrent attacks (1,9). As all patients with bronchiolitis in our study were in infancy, this period corresponds to the time when lung and immune system maturation is at its fastest (26,27). In cases of severe and recurrent attacks, inflammation, airway epithelial damage, and necrosis can also occur, leading to barrier loss and airway fibrosis. The emergence of chronic structural changes is important as it lays the groundwork for persistent asthma (13). In this relationship, genetic predisposition, prenatal risk factors, and environmental factors also play a role as epigenetic factors (4,17). Given these findings and the fact that 64 patients with recurrent attacks had a history of severe attacks, we considered these patients to have asthma phenotypes. A comparison of respiratory system examination findings recorded at the time of initial presentation, significant differences were observed. The frequency

of respiratory rate, wheezing, and rales was higher in the multiple hospitalization group than in the first hospitalization group, and the differences were statistically significant (p=0.008, p=0.037, p=0.04, respectively). These significant differences suggest that patients in the multiple hospitalization group experienced more severe bronchiolitis than those in the first episode. Wheezing, even during the initial attack, provides prognostic and phenotypic clues. Arroyo et al. (28) conducted a clinical study with 50 children under 2 years old hospitalized for acute viral bronchiolitis confirmed by PCR and found that the wheezing group had higher levels of asthma-specific Th2 cytokines (IL-13, IL-4) in nasal secretions. They also showed that children with wheezing during an attack had more frequent hospital admissions for asthma later. These authors highlighted that different phenotypes exist among patients with severe bronchiolitis, and those with wheezing during the attack might have asthma. In our study, wheezing was more frequently observed in the recurrent bronchiolitis group, which was associated with a higher number of children with asthma phenotypes. When these three examination findings with statistical significance were evaluated with linear regression analysis, only the respiratory rate was significantly more important in our patients with recurrent bronchiolitis, with each unit increase in the respiratory rate increasing the hospitalization rate by 1.07 times. This indicates that the respiratory rate is an important predictor of hospitalization. In fact, respiratory rate is also considered a major risk factor for mortality in pediatric intensive care units, as indicated by the "PRISM" score (29). The etiology of bronchiolitis was investigated using PCR in 92 patients (58.9%). Among the 67 patients who tested positive by PCR, 71.6% had RSV or RV as the pathogen of bronchiolitis, or both. RSV or RV are commonly found in severe bronchiolitis cases (7). Many epidemiological studies have investigated the relationship between bronchiolitis pathogens and later asthma development. Sigurs et al. (30) conducted a long-term follow-up study and reported that infants with RSV bronchiolitis before the age of 1 had a 7.2-fold higher risk of asthma at age 18, and RSV bronchiolitis in infancy was a stronger risk factor than a family history of asthma. In a study including 349 children under 2 years with acute bronchiolitis, those with RV bronchiolitis were reported to use more prophylactic asthma medications than those with other pathogens, with this difference being statistically significant (31). Overall, most controlled, long-term cohort studies have shown that RSV is a more frequent bronchiolitis pathogen in younger infants, while RV is more common in older children, and both are closely related to asthma phenotypes (12). Considering all other data, the high rates of RSV and RV in our patients may indicate a higher risk of asthma among the children in our study group. Additionally, among the 100 patients with positive "API" considered to be at high risk for asthma, RSV or RV was isolated in 75.6% of the PCR results. Routine PCR testing is not recommended for acute bronchiolitis (4). In our study, nearly half of the patients (41%) did not undergo PCR testing. If pathogen investigations had been conducted in these patients, we might have found statistically significant differences based on "API" characteristics and previous bronchiolitis attacks. Among the 67 patients for whom we could identify the bronchiolitis pathogen using PCR, no significant differences in respiratory system examination findings were found between different pathogens. Guilbert et al. (32) conducted a long-term follow-up study in a birth cohort with asthma risk factors and found that children with RV bronchiolitis had significantly impaired respiratory function compared with those with other viral pathogens (p<0.001 for FEV1; p<0.001 for FEF25-75), and this was related to future asthma development. They did not find any relationship with RSV or other pathogens. Since there was no difference between pathogen groups in our study and it was not a long-term follow-up study, we cannot comment on this matter. Comparison of respiratory system physical examination findings at initial presentation with "API" evaluations revealed no statistically significant difference in some aspects. However, the higher number of crackles, medium rales, and rhonchi in the "API" positive group caught our attention. Wheezing was more frequently reported in the "API" positive group, and the difference was statistically significant. It is known that wheezing may not always be present in every bronchiolitis attack, even if severe (4,8). However, epidemiological studies have shown that wheezing attacks are more closely associated with future asthma development (9,13,14). In our study, although there was no statistically significant difference between the "API" positive and negative groups, the presence of more patients with previous bronchiolitis and more frequent PCR positivity for RSV and RV in the "API" positive group suggests that wheezing in this group may indicate an asthma phenotype. Currently, bronchiolitis is recognized as not a single disease but one that varies in clinical severity and prognosis depending on the viral pathogen, along with the patient's respiratory function, immune response, and genetic characteristics. Acute bronchiolitis may recur frequently in some patients, and these patients are often diagnosed with asthma later in life. Therefore, more extensive long-term studies involving larger patient populations are needed to identify high-risk patients early and adjust treatment accordingly.

Study Limitation

We can consider the limited number of cases a constraint in our study. Moreover, the inability to conduct respiratory viral PCR tests for each patient can also be regarded as a limitation.

Ethics

Ethics Committee Approval: Our study was approved by the Gazi University Faculty of Medicine Local Ethics Committee (approval number: 805, date: 14.12.2020).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.K., İ.T., Design: S.K., İ.T., Supervision: T.B.D., M.P., A.T., H.T., N.M.K., A.T.A., H.T., Resources: S.K., İ.T., Material: T.B.D., M.P., A.T., H.T., N.M.K., A.T.A., H.T., Data Collection or Processing: S.K., İ.T., T.B.D., M.P., A.T., H.T., N.M.K., A.T.A., H.T., Analysis or Interpretation: S.K., İ.T., Literature Search: S.K., İ.T., T.B.D., M.P., A.T., H.T., N.M.K., A.T.A., H.T., Writing: S.K., İ.T., T.B.D., M.P., A.T., H.T., N.M.K., A.T.A., H.T., Critical Review: İ.T.

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Beauty Beyond the Golden Ratio: A Study of Perception Regarding Facial Proportions and Symmetry in the Turkish Population

Altın Oranın Ötesinde Çekicilik: Yüzü Kapsayan Oranlar ve Yüz Asimetrisi Üzerine Çalışma

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ABSTRACT

Objective: The authors examined the effect of previously described facial proportions and facial asymmetry on the perception of beauty and attractiveness. The optimal values of four different facial ratios and the optimal degree of asymmetry were examined.

Methods: In this study, 10 faces were adjusted to reference values and -5%, -2.5%, +2.5%, and +5% deformations were created. Participants were asked to select via online survey the most and least attractive face between 5 photographs of the same person with different facial ratio values. Finally, split-face imaging was used to generate right and left-symmetrical images. These images along with the original images were questioned to determine the most and least attractive.

Results: The most attractive face was closer to the reference ratio, whereas the least attractive face was most distant from the reference. Both left and right symmetrical faces were considered less attractive than natural asymmetrical faces.

Conclusion: Standardized "golden" ratios are effective reference points for the perception of facial attractiveness although deviation from these proportions does not always imply that a face will not be perceived as attractive, as some degree of asymmetry also contributes to facial attractiveness and beauty.

Keywords: Esthetics, face, ratios, facial asymmetry, cosmetic surgery, plastic surgery

ÖZ

Amaç: Yazarlar, daha önce tanımlanan yüz oranlarının ve yüz asimetrisinin güzellik ve çekicilik algısı üzerindeki etkisini incelemektedir. Dört farklı yüz oranının optimal değerleri ve yüzün optimal asimetri derecesi araştırılmaktadır.

Yöntemler: Bu çalışmada 10 yüz referans değerlerine ayarlandı ve -%2,5, -%5, +%2,5 ve +%5 deformasyonlar oluşturuldu. Katılımcılardan, çevrimiçi anket yoluyla aynı kişinin farklı yüz oranı değerlerine sahip 5 fotoğrafı arasından en çekici ve en az çekici yüzü seçmeleri istendi. Son olarak, sağ ve sol simetrik görüntüler oluşturmak için bölünmüş yüz görüntüleme kullanıldı. Bu görseller orijinal görsellerle birlikte katılımcılara en çekici ve en az çekici olanı belirlemek için soruldu.

Bulgular: En çekici yüz referans oranına daha yakındır, en az çekici yüz ise referanstan en uzaktır. Hem sol hem de sağ simetrik yüzlerin, doğal asimetrik yüzlerden daha az çekici olduğu tespit edildi.

Sonuç: Standartlaştırılmış "altın" oranlar, yüz çekiciliğinin algılanması için etkili referans noktalarıdır, ancak bu oranlardan sapma her zaman bir yüzün çekici olarak algılanmayacağı anlamına gelmez, çünkü bir dereceye kadar asimetri de yüzün çekiciliğine ve güzelliğine katkıda bulunur.

Anahtar Sözcükler: Estetik, yüz, oranlar, yüz asimetrisi, estetik cerrahi, plastik cerrahi

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INTRODUCTION

It is accepted that facial proportions with ideal values contributes to facial attractiveness (1-5). The "ideal" values for facial proportions are remarkable when assessing the face during perioperative processes, as well as for patients' personal satisfaction when looking in the mirror (6). Therefore, defining optimal facial proportions is of significant importance.

The golden ratio is found everywhere in nature, such as in flower petals, the milky way, and the human face (7). Similarly, there are various other reference ratios in the face, which do not strictly conform to the standard golden ratio value yet are still acknowledged as such (8). Various studies also show that faces lacking the golden ratio can still be perceived as attractive (9). In addition, studies comparing individual faces with their artificially created symmetric versions have shown that our eyes have a unique ability to detect the "natural" (8,10). One probable reason for this may be the contribution of natural and unique facial asymmetry on people's perception of facial beauty. In this study, we investigated the effect of facial asymmetry on the perception of facial attractiveness while studying the potential threshold of asymmetry and facial proportions that can be considered the foundation of facial beauty.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of Koç University (approval number: 086.IRB3.047, date: 2021). Informed written consent was obtained from each participant prior to the study. As asymmetry was a key factor to consider in the study methodology, ratios in which facial asymmetry was expected to be prominent were selected. The chosen ratios covered the vertical and horizontal aspects of the span of the whole face as well as important structures such as the lips, chin, cheek, nose, eyes, and temples. The reference values of the four proportions were based on previously conducted comprehensive facial ratio studies (Figure 1) (2,3,8). An online survey was created using Qualtrics (Qualtrics XM, USA). The 53-question survey consisted of questions regarding proportions, symmetry, and personal demographic information, such as age and gender. The survey link was sent to Koç University medical students and faculty via scholar email groups and online chat platforms and was also shared with lay people via social media.

Five healthy female and five healthy male adults from the Turkish population without significant facial marks or deformities were selected to create a ratio database for analysis. First, each volunteer was scanned with a computerized facial visual scanner (VECTRA XT, Canfield Scientific, USA) for standardized imaging. The faces were then adjusted according to the reference values for each ratio, and then deformed images with +2.5%, +5%, -2.5% and -5% percentile changes were created. A total of 60 images (six images per participant) were generated consisting of one original image, one with respect to reference values of ratios, and four with +2.5%, +5%, -2.5% and -5% percentile changes (Figure 2). The original face was placed in order with the other images according to the value of the examined proportions. Participants were asked to choose the most and the least attractive images.

For the second part of the study, left and right mirror images were created using the same software. Participants were asked to compare the original image with modified left and right symmetric images for each face and provide their ranking on attractiveness (Figure 3).

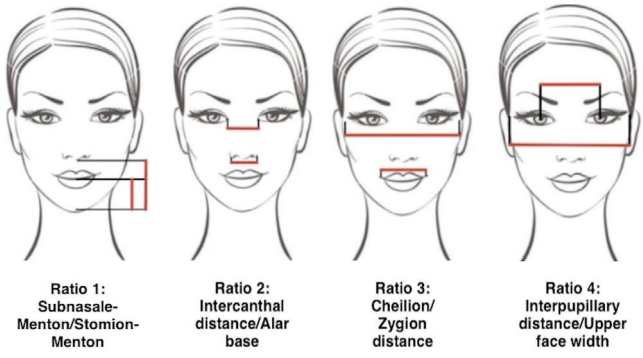

Figure 1. Facial proportions used in the study

Statistical Analysis

The software SPSS 21.0 (IBM, USA) was used, and the confidence interval was set to 95%. For total and gender-related analyses, frequencies and percentage distributions of the most attractive and least attractive choices were inquired. Correlations between the most and least attractive faces according to participant age and gender were calculated using the chi-squared test. Statistical significance was considered for p values less than 0.05.

RESULTS

A total of 72 participants completed the survey (48 female, 24 male). The mean age of the participants was 30.29 years (18-65 years). In the first part of the survey, participants selected the most attractive face among the six variations for ten different faces, individually adjusted for the four ratios (Chart 1). Overall, a moderately shorter chin (+2.5%) was chosen as most attractive for the proportion of chin height, while the majority chose the tallest chin (-5%) as least attractive. Although relatively close between ratios, the relatively narrow nose image (+2.5%) was the most attractive ratio for nose width, while the widest nose (-5%) was the least attractive. The moderately narrow lip (-2.5%) was attributed to the most attractive lip width; and the widest one (+5%) as the least. Regarding the temporal width, majority of participants selected the original face as the most attractive face, while the largest temporal width (-5%) was selected as the least attractive (Figure 4). When the gender of the images was considered, no significant difference was found for chin and lip size. For alar base width, the most attractive choices were the narrowest nose (+5%) for females and both the original nose size and the moderately large nose size (20.8% each) for males. Conversely, the least attractive alar base width for both genders was the widest. For temporal width, the most attractive choice was the reference image for females and the original image for males, while the least attractive were the face with the largest temporal width for females and the face with the narrowest temporal width for males. In the second part of the study, questions comparing the original image versus left and right symmetric mirror images revealed an overall distribution of 36.1% in favor of the original image, 40.1% for the right, and 23.8% for the left symmetric image. However, only 12.9% chose the original image, while 60% chose the left symmetric image, and 27.1% chose the right symmetric image as the least attractive

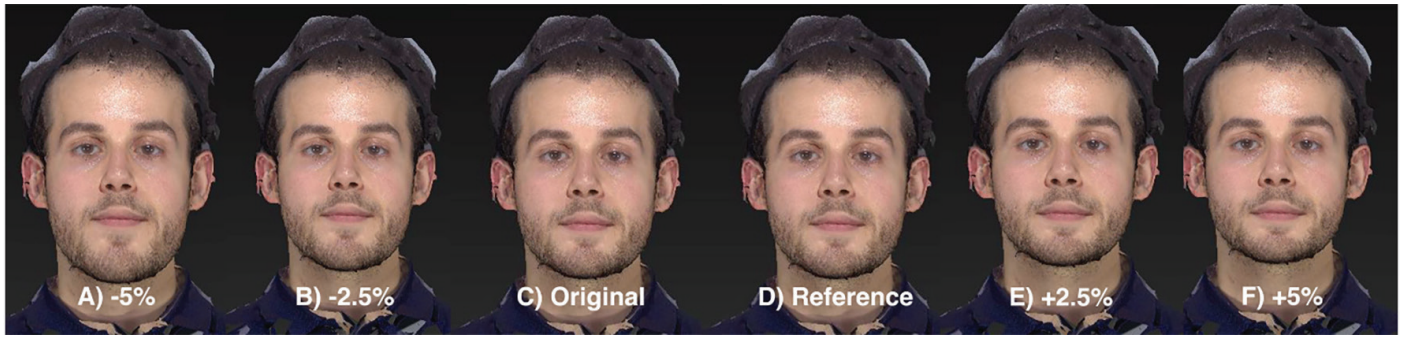

Figure 2. Example questionnaire strip with changes in chin height

Figure 3. Example questionnaire strip with original (A), left (B), and right (C) symmetric images

(Figure 5). Furthermore, a formula for an "asymmetry score" was generated for each of the 10 original faces to assess the level of asymmetry in each one. The formula was adapted from Tamir et al. (9) c-value formula. There were two asymmetry scores for each face: one for the right symmetrical face and one for the left symmetrical face. To calculate the asymmetry score of the right half, the difference between the values of a proportion of the original face and the right symmetrical face was divided by the ratio of the original face. The same calculation was applied to determine the asymmetry score of the left half. As a result, each original face had two asymmetry scores, indicating the amount of variation from the original face. The correlation between selections and their asymmetry scores was examined, and a relationship was identified. With asymmetry scores below 0.7, the results showed that there was a significant tendency to like the original image the most, and the closest mirror image was the second. However, with asymmetry scores greater than 0.7, participants didn't gravitate toward these images. These findings suggest that minimal asymmetry contributes to beauty.

DISCUSSION

There are a variety of beauty standards for each culture and nationality. Results of this study show that the beauty standards of the Turkish population are in correlation with the generally accepted terms of beauty in terms of the studied ratios. Considering chin height, participants chose an "average" size, which is consistent with other studies in the literature (3,9). However, younger participants had a wider distribution of choices for the size of an ideal chin size, whereas older people had a narrower distribution. Therefore, age is an important factor in the perception of beauty. In addition, it is known that some facial structures get smaller with aging, such

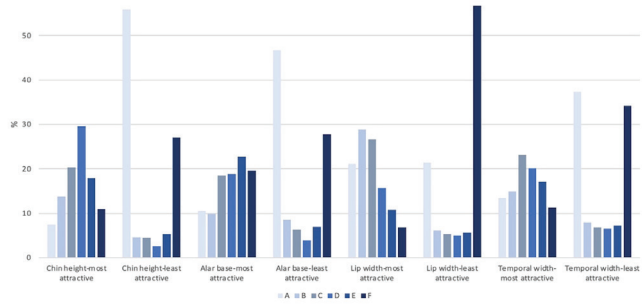

Figure 4. Results for facial ratios (%)

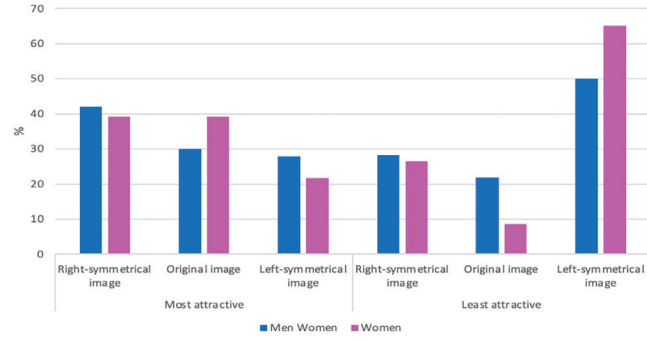

Figure 5. Results for the symmetrical derivations of the face (%)

as the temporalis muscle, maxillary bony prominences, become smaller with aging. Hence why dermal fillers in these anatomical regions serve as the foundation for reconstituting volume loss. When comparing preferences regarding alar base size, the survey participants preferred a wider alar base for men and a narrower one for women. This difference seems to be reasonable because we have the knowledge that wider and more prominent structures on the facial midline contribute to a more "masculine" image, while thinner and smaller facial attributes contribute more to a "feminine" appearance (11). This trend is reflected in the increasing popularity of rhinoplasty procedures with many women undergoing surgery to reduce their nose size. The least attractive face regarding the temporal width was selected as the face with the narrowest bitemporal distance. As confirmed through the results of the study, sunken and narrow temples can contribute to an older and less attractive look. Hence the reason that treating the temple region with dermal fillers is a sought-after procedure for facial rejuvenation.

Regarding the results of the asymmetry study, the original face was least likely to be chosen as the least attractive option. Our results were consistent with the literature, which stated that some degree of asymmetry contributes to facial attractiveness and our perception of beauty (8,9). In this study, we aimed to further analyze the impact of asymmetry on beauty by investigating the perception of attractiveness through facial ratios in combination with asymmetry. Through this, we were able to determine the optimal range of asymmetry that can contribute to attractiveness, which is the main contribution of our study to the existing literature. A number of studies have investigated the effects of gold ratios on the perception of beauty. However, these studies did not consider the influence of asymmetry. When examining the horizontal distances and ratios of the face, the effect of asymmetry should be considered. One side of the face may contribute more, while the other side contributes less, and this difference may be what creates a unique sense of beauty. As the main contribution of the existing literature, our study investigated this topic in combination with facial ratios. Apart from analyzing the combined asymmetry results, a separate analysis for each face was also conducted. When participants chose the least attractive face, they never chose the original face as least attractive, except for two people's faces. Out of the ten faces, eight were found to be most attractive, so additional calculations were conducted for the two odd results for which one of them had values of the four proportions very close to the reference values. Thus, one of these odd results can be clearly explained by this fact, proving that both ratios and asymmetry contribute to attractiveness. In contrast, apart from conforming to the "golden ratio", a slight amount of asymmetry definitely contributes to attractiveness by providing a natural touch and making the faces of 8 billion uniquely different.

CONCLUSION

Countless studies have been conducted in the search to find a "geometrical formula of beauty". The gold standard has been the tool of choice in most of these studies. However, do all beautiful faces have perfect ratios? It is generally acknowledged that symmetry contributes to beauty, but this is not always the case when it comes to our perception of beauty. In addition, there are many contributors to beauty that we overlook, such as minor flaws, personal and cultural preferences, and national differences. Thus, regarding our study based on the Turkish population, the golden ratio contributes to facial attractiveness, but some amount of asymmetry is clearly a cofactor, as some faces lacking the golden ratio but with a certain degree of asymmetry can still be perceived as attractive. When planning any surgical beautification procedure, an approach that combines geometry and symmetry should lead to better results. Nevertheless, informing patients about the individuality that asymmetry provides to facial features and its contributory effect to beauty can be an important part of the consultation. In a society where beauty is defined through filters, a reminder that a certain degree of asymmetry and minor flaws can enhance beauty is refreshing.

Ethics

Ethics Committee Approval: The study protocol was approved by the Ethics Committee of Koç University (approval number: 086. IRB3.047, date: 2021)

Informed Consent: Informed written consent was obtained from each participant prior to the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.Ö., L.C.M., B.S.K., Concept: Ö.Ö., L.C.M., B.S.K., Design: Ö.Ö., L.C.M., B.S.K., Data Collection or Processing: Ö.Ö., L.C.M., B.S.K., Analysis or Interpretation: Ö.Ö., L.C.M., B.S.K., Literature Search: Ö.Ö., L.C.M., B.S.K., Writing: Ö.Ö., L.C.M., B.S.K.

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Identification And Classification of Tattoos In Autopsies; A Retrospective Study

Otopsilerde Karşılaşılan Dövmelerin Retrospektif Olarak Tanımlanması Ve Sınıflandırılması

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ABSTRACT

Objective: Figures created under the skin using Indian ink or carbon are called tattoos. Each figure has different meanings, such as freedom and sexuality. In forensic medicine, tattoos are used for human identification. Tattoos can help determine the origin of death by providing information about individuals' lifestyles. Our study aims to analyze the profile of tattoos, define and classify tattoos, and emphasize their importance in forensic medicine. Additionally, we aimed to reveal whether there was a difference between the origins of death in our cases.

Methods: Tattoos found in cases of natural death and suicide who underwent autopsy between 01/01/2020 and 31/07/2022 in Denizli, were evaluated retrospectively. Analysis was performed using the parameters of number, location, and type of tattoos. This study included 19 natural deaths and 35 suicides. There were 29 (82.9%) male, 6 (17.1%) females who committed suicide. In the natural deaths, there were 16 (84.2%) male, 3 (15.8%) were female. The mean age of suicide cases was 30.34±9.47, natural deaths was 43.84±10.7.

Results: We did not find a significant difference in the number, type, and location of tattoos between suicides and natural deaths. The mean number of tattoos was higher in suicides than in natural deaths, but there was no statistically significant difference in the total number of tattoos between the two groups (p=0.647). Suicides tended to have a higher mean number of shape/geometric/illustrative tattoos, and animal/creature tattoos, compared to natural deaths.

ÖZ

Amaç: Deri altına çini mürekkebi, karbon gibi boyalar kullanılarak oluşturulan şekillere "tatuaj/dövme" denir. Her şekil özgürlük, cinsellik gibi farklı anlamlar içerir. Adli tıpta dövmeler, kimliklendirme amacıyla kullanılır. Dövmeler, bireylerin özgeçmişi ile ilgili bilgiler sunarak ölüm orijininin belirlenmesine yardımcı olabilir. Çalışmamızın amacı; vücut dövmelerinin profilini analiz etmek, karşılaştığımız dövmeleri tanımlamak ve sınıflandırmak ve dövmelerin adli tıp açısından önemini vurgulamaktır. Ayrıca çalışmamızda, olgularımızın ölüm nedenleri arasında anlamlı bir fark olup olmadığını ortaya koymayı amaçladık.

Yöntemler: Denizli'de 01/01/2020-31/07/2022 tarihleri arasında medikolegal otopsi yapılan, orijini doğal ölüm ve intihar olan olgularda bulunan dövmeler retrospektif olarak değerlendirildi. Dövme sayısı, bulunduğu vücut bölgesi ve türü parametreleri esas alınarak analiz yapıldı. Çalışmaya, 19 doğal ölüm ve 35 intihar olgusu dahil edildi. İntihar olgularının 29 (%82.9)'u erkek ve 6 (%17.1)'sı kadın idi. Doğal ölüm olgularının ise, 16 (%84.2)'sı erkek ve 3 (%15.8)'ü kadın idi. İntihar olgularının yaş ortalaması 30.34±9.47 olup, doğal ölümlerin 43.84±10.7 idi.

Bulgular: İntihar ve doğal ölümler arasında dövme sayısı, türü ve yeri açısından anlamlı bir fark tespit edilmedi. Ortalama dövme sayısı, intiharlarda doğal ölümlere göre daha yüksekti, ancak iki grup arasında toplam dövme sayısı açısından istatistiksel olarak anlamlı bir fark yoktu (p=0.647). İntihar olguları, doğal ölümlere göre daha fazla sayıda şekil/geometrik/ilüstrasyon ve hayvan/yaratık dövmesine sahip olma eğilimindeydi.

This study was presented under the title "The Relationship Between Tattoos and Suicide" in the oral presentations category at the 3rd International 19th National Forensic Sciences Congress held on 03-06 November 2022. However, it has not been published in full text in the congress proceedings book or anywhere else.

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Conclusion: In our study, the tattoos were described in detail, analyzed according to the origin of death, and contributed to the literature on tattoo figures.

Keywords: Tattoos, autopsy, suicide, forensic medicine

Sonuç: Çalışmamızda dövmeler detaylı olarak tanımlandı. Ölüm orijinleri de dikkate alınarak analiz yapıldı ve elde edilen bilgilerle literatüre katkı sağlandı.

Anahtar Sözcükler: Tatuaj, dövme, otopsi, intihar, adli tıp

INTRODUCTION

Tattoos are created by injecting various dyes, such as Indian ink (1), indigo (1), or carbon (1), under the skin using various techniques. Tattoos are a multidisciplinary formation involving criminology, anthropology, and forensic sciences. With these figures, people wanted to show other people the group they belonged to, their religious beliefs, social status, profession, emotions, and thoughts (2). Tattoos express love, independence, challenge, and sexual preferences. Most young people acquire tattoos to seek identity, accept, and self-expression (2). Although the prevalence of tattoos was found to be 10-16% in adults in studies, it was understood that this rate increased to 25% in some age groups (3-6). Tattoos are associated with sailors, prisoners, and gang members, depending on their design, location, and number. The characteristics of the tattoo may provide clues specific to the deceased individual's past (3,4). It may also help determine the origin of death. For example, drug addicts may opt for tattoo motifs featuring marijuana leaves or a syringe (3). Some tattoo figures may depict people's political views or religious beliefs (4). Text tattoos include names and dates that are important to people (3). It has also been observed that tattoos are associated with psychopathologies such as depression, suicidal tendencies, and psychiatric disorders (5,7).

Determining the identities of people is necessary in forensic medicine (8). In autopsies, tattoos are included in external examination and can help identify unidentified bodies (8). Fingerprint or DNA analysis is the primary method for identifying unidentified bodies. Scars, nevi, and tattoos on people's bodies are secondary methods. Primary methods are expensive and can exceed the budget (9). However, tattoos are secondary identifiers that are useful for identifying disaster victims, especially in natural disasters where many bodies are found (9).

In forensic medicine, the origins of death are categorized as accidental, suicidal, homicidal, natural, and unknown (10). Many studies have been conducted on whether tattoos, which show meaningful signs of people's lives, manifest in different ways among the origins of death (11,12). In this study, we aimed to analyze the profile of tattoos, which is the reflection of symbolism on the human body, and to help forensic experts identify and classify these types of tattoos while practicing their profession. Additionally, we aimed to reveal whether there was a difference between the origins of death in our cases and to emphasize the importance of tattoos in forensic medicine.

MATERIALS and METHODS

In this study, tattoos were found in natural death and suicide cases over 15 years of age and those who underwent autopsy between 01/01/2020-31/07/2022 at Pamukkale University Faculty of Medicine, Department of Forensic Medicine, were retrospectively evaluated. The reason why suicide and natural deaths were chosen was to reveal whether there was a statistical significance between these two types of death origin in terms of the number, type, and location of tattoos. This study included 19 natural deaths and 35 suicide cases. The origin was determined from the crime scene investigation reports and witness statements in the forensic investigation file. There were 29 (82.9%) male and 6 (17.1%) female in the suicide cases. In the natural deaths, there were 16 (84.2%) male and 3 (15.8%) were female. The mean age of suicide cases was 30.34±9.47 years and natural deaths was 43.84±10.7 years. In this study, the tattoos were analyzed based on the number, type, text language, location parameters. The age, sex, and cause of death parameters were also considered. The number of tattoos was classified as 1, 2-3, 4-6, and 7 or more. The types of tattoos were categorized: shape/geometric/illustrative, lettering (text), initial letter, animal/creature, number, and portrait. The locations were classified as head/neck, chest, right upper extremity, left upper extremity, back, abdomen, right lower extremity, and left lower extremity. Before starting the study, permission was obtained from the Pamukkale University Non-Interventional Clinical Research Ethics Committee (approval number: 12, date: 16.08.2022). This study was conducted in line with the principles of the Declaration of Helsinki.

Statistical Analysis

All statistical analyses were performed using SPSS version 29. Descriptive statistics were presented as frequencies and percentages for categorical variables, mean, standard deviation, median, and interquartile range (IQR) for continuous variables. The normality of distribution of the variables was checked using the Kolmogorov-Smirnov test. The Chi-square test was used to compare categorical variables. Mann-Whitney U test and Kruskal-Wallis tests were used to compare continuous variables because the data did not fit the normal distribution. All comparisons were two-sided, and a p-value <0.05 was considered significant

RESULTS

In Pamukkale University Faculty of Medicine, Department of Forensic Medicine, 1199 autopsy were performed between 01/01/2020 and 31/07/2022. It was observed that 300 (25%) of these cases were natural deaths, 221 (18%) were suicides. Tattoos were found in 19(6%) cases of natural deaths and 35(16%) cases of suicide. In our study, there were 29 (82.9%) male and 6 (17.1%) female in the suicide cases. In the natural deaths, there were 16 (84.2%) male and 3(15.8%) female (p=0,899). When we compared the cases according to age, suicide cases had a significantly younger mean age (Mean±standard deviation (SD)=30.34±9.47 years) compared to natural deaths (Mean±SD=43.84±10.7 years) (p<0.001). Most suicide cases (n=27, 77.2%) were between 1939 years of age, whereas only 31.6% (n=6) of natural deaths occurred in this age group (Table 1). When we looked at the causes of death; natural deaths were due to cardiac diseases. As for suicides; there were 25 (71.4%) participants were

hanging, 7 (20%) had gunshot wounds, 1(2.9%) had drug intoxication, 1 (2.9%) had a stab wound, and 1 (2.9%) had jumped from a height. The mean tattoo number in females (Mean±SD=5.22±5.49) were higher than that in males (Mean±SD=3.36±4.19), but this difference was not statistically significant (p=0.180). The mean tattoo number in cases aged 19-29 (Mean±SD=6.13±7.18) were higher than that in the other age groups. However, it was also not statistically significant (p=0.172). Although the mean number of tattoos in suicides (Mean±SD=4.03±5.18) were higher than that in natural deaths (Mean±SD=3.00±2.49), there was no statistically significant difference in the total number of tattoos between the two groups (p=0.647). When we analyzed the number of tattoos according to subgroups; by sex, there was no statistically significant difference in the number of tattoos between males and females (p=0.059). There was no statistically significant difference in the number of tattoos among different age groups (p=0.463). 50% of people aged 30-39 (n=9) had one tattoo and 75% of people aged 50-59 (n=3) had one tattoo, while 20% of people aged 19-29(n=3) had seven or more tattoos and 50% of people aged 60 or more(n=1) had seven or more tattoos. Manner of death also did not exhibit a statistically significant difference in the number of tattoos (p=0.812). 11.4% of suicides (n=4) had seven or more tattoos and 25.7% of suicides(n=9) had 4-6 tattoos, compared to 15.8%(n=3) and 15.8%(n=3) of natural deaths, respectively (Table 2). The current study revealed that the most common type of tattoo among both suicide and natural death cases was shape/geometric/illustrative, with 68.9% (n=24) and 68.4% (n=13), respectively, followed by lettering 62.9% (n=22) and 52.6% (n=10) respectively. The least common type of tattoo among both suicide and natural death cases was number 5.7% (n=2) and 5.3% (n=1) respectively, followed by initial letter, with 11.4% (n=4) and 15.8% (n=3), respectively. The only type of tattoo that showed a noticeable difference between suicide and natural death cases was animal/creature, with 14.3% (n=5) and 31.6% (n=6) respectively, but this difference was not statistically significant (p=0.166). Our study showed that; the most common language among both lettering (text) and initial letter tattoos was Turkish, with 71.9% (n=23) and 71.4% (n=5) respectively. The distribution of initial letter and lettering(text) tattoos did not differ significantly between the specified languages (p=0.244, 1). The most common suicide location was the left upper extremity, with 77.1% (n=27), followed by the right upper extremity, with 51.4% (n=18). The least common locations of suicide were the abdomen and right and left lower extremities, with 2.9% (n=1) each. The most common location among natural death was the left upper extremity, with 68.4% (n=13), followed by the right upper extremity 68.4% (n=13). The least common locations of natural death were the head/neck and abdomen, with 0% (n=0) each. The only tattoo location that showed a noticeable difference between suicide and natural death was the head/neck, with 11.4% (n=4) and 0% (n=0) respectively, but this difference was not statistically significant (p=0.285). When we evaluated the relationship between the total number of tattoos and tattoo types in our study; cases with suicides and shape/geometric/illustrative tattoos had a significantly higher mean number of tattoos (Mean±SD=5.13±5.94) compared to those without such tattoos (p=0.007). Cases with suicides and animal/creature tattoos had a significantly higher mean number of tattoos (Mean±SD=8.40±9.91) compared with those without such tattoos (p=0.033). Cases who died by natural causes had significantly more lettering(text) tattoos (Mean±SD=4.30±2.75) than those who did not (p=0.015). Specifically, cases with suicides tended to have a higher mean number of shape/geometric/illustrative tattoos, and animal/creature tattoos, compared to those with natural deaths (Table 3). Cases with suicides had significantly more tattoos on their head/neck (Mean±SD=10.50±10.66), chest (Mean±SD=7.42±7.77), back (Mean±SD=6.20±4.14), and right upper extremity (Mean±SD=6.33±6.44) than cases with natural deaths (p=0.029, 0.023, 0.047, and <0.001 respectively). Natural deaths also had significantly more tattoos on their chests (Mean±SD=6.40±2.07) than suicides (p=0.002) (Table 4). The tattoos used in our cases are described in detail in Tables 5 and 6.

Table 1. Comparison of suicide and natural death cases by age

Age	Suicide	Natural Death
Mean±SD	30.34±9.47	43.84±10.7
p	<0.001	
Age groups	n (%)	n(%)
15-18 years	3 (8.6)	0 (0)
19-29 years	12 (34.3)	3 (15.8)
30-39 years	15 (42.9)	3 (15.8)
40-49 years	4 (11.4)	8 (42.1)
50-59 years	0 (0)	4 (21.1)
≥60 years	1 (2.9)	1 (5.3)
p value	<0.001	

*The Chi-square test was used for comparison by age groups. Mann-Whitney U test was used for comparison by age means,
SD: Standard deviation

Table 2. Distribution of tattoos by sex, age groups, manner of death

Characteristics	Number of tattoos			
	1 n (%)	2-3 n (%)	4-6 n (%)	≥7 n (%)
Sex				
Male	19 (42.2)	11 (24.4)	11 (24.4)	4 (8.9)
Female	1 (11.1)	4 (44.4)	1 (11.1)	3 (33.3)
p	0.059			
Age groups				
15-18 years	1 (33.3)	1 (33.3)	1 (33.3)	0 (0)
19-29 years	3 (20.0)	4 (26.7)	5 (33.3)	3 (20.0)
30-39 years	9 (50.0)	3 (16.7)	5 (27.8)	1 (5.6)
40-49 years	4 (33.3)	5 (41.7)	1 (8.3)	2 (16.7)
50-59 years	3 (75.0)	1 (25.0)	0 (0)	0 (0)
≥60 years	0 (0)	1 (50.0)	0 (0)	1 (50.0)
p	0.463			
Manner of death				
Suicide	12 (34.3)	10 (28.6)	9 (25.7)	4 (11.4)
Natural death	8 (42.1)	5 (26.3)	3 (15.8)	3 (15.8)
p	0.812			

*The Chi-square test was used

Table 3. Comparison of tattoo types

	Suicide deaths	Natural deaths	All deaths
Type of tattoo	**Total number of tattoo Mean±SD**	**Total number of tattoo Mean±SD**	**Total number of tattoo Mean±SD**
Shape/geometric/ illustrative			
Yes	5.13±5.94	3.38±2.53	4.51±5.04
No	1.64±1.02	2.17±2.40	1.82±1.59
p	0.007	0.170	0.003
Lettering (Text)			
Yes	4.19±6.02	4.30±2.75	4.72±5.18
No	2.54±2.98	1.56±1.01	2.14±2.39
p	0.068	0.015	0.003
Initial letter			
Yes	3.50±1.00	5.67±4.04	4.43±2.69
No	4.10±5.51	2.50±1.89	3.55±4.64
p	0.312	0.180	0.114
Animal/creature			
Yes	8.40±9.91	4.67±3.20	6.36±6.94
No	3.30±3.76	2.23±1.73	2.98±3.29
p	0.033	0.131	0.015
Number			
Yes	1.50±0.70	2.00	3.67±1.52
No	4.00±5.34	3.06±2.55	3.67±4.55
p	0.189	1	0.311
Portrait			
Yes	6.83±9.49	8.00	8.67±3.28
No	3.45±3.81	2.72±2.24	3.29±0.48
p	0.271	0.106	0.094

*Mann-Whitney U test was used,
SD: Standard deviation

Table 4. Comparison of total number of tattoos by location

	Suicide deaths	Natural deaths	All deaths
Location of tattoo	**Total number of tattoo Mean±SD**	**Total number of tattoo Mean±SD**	**Total number of tattoo Mean±SD**
Head/neck			
Yes	10.50±10.66	-	10.50±10.66
No	3.19±3.58	3.00±2.49	3.12±3.18
p	0.029	-	0.022
Chest			
Yes	7.42±7.77	6.40±2.07	7.12±6.54
No	2.26±1.35	1.79±1.12	2.08±1.27
p	0.023	0.002	<0.001
Back			
Yes	6.20±4.14	5.50±3.53	6.00±3.69
No	3.67±5.31	2.71±2.31	3.32±4.45
p	0.047	0.128	0.010
Abdomen			
Yes	9.00	-	9.00
No	3.88±5.19	3.00±2.49	3.57±4.40
p	0.155	-	0.120
Right upper extremity			
Yes	6.33±6.44	3.69±2.72	5.23±5.31
No	1.59±0.87	1.50±0.83	1.57±0.84
p	<0.001	0.075	<0.001
Left upper extremity			
Yes	4.44±5.66	3.69±2.72	4.20±4.87
No	2.63±2.92	1.50±0.83	2.14±2.28
p	0.164	0.075	0.023
Right lower extremity			
Yes	4.00	-	4.00
No	4.03±5.26	3.00±2.49	3.66±4.47
p	0.477	-	0.447
Left lower extremity			
Yes	12.00	4.00	8.00±5.65
No	3.79±5.07	2.94±2.55	3.50±4.35
p	0.127	0.392	0.089

*Mann-Whitney U test was used,
SD: Standard deviation

DISCUSSION

Our study is important in forensic medicine because it includes forensic autopsy cases. The study contributes to the literature on different tattoo figures for studies examining tattoo profiles in larger populations and in many cases. Additionally, the study revealed that there may be a relationship between tattoos and suicide, and the importance of tattoos in terms of forensic medicine was emphasized.

Sex

It was determined that there were more men than women in our study. However, no statistically significant difference was detected in the number of tattoos according to sex. In another study conducted in our country, it was observed that 92.1% of the tattooed cases were males (13).

Age

When the cases in our study were evaluated according to age groups; it was observed that in the natural death group, most cases were in the 40-49 age group, and in the suicide group, most cases were in the 30-39 age group. In similar studies; in the study of Kayser et al. (13) it was understood that 44% of the cases were in the 19-29 age group. It was observed that the mean number of tattoos was higher in this age group.

Body Locations of Tattoos

The preferred body location for tattooing may be related to the individual's personal, social, or professional situations. While some people prefer visible parts of their body, such as hands and arms,

Table 5. Tattoos of natural deaths

Case No	Age	Sex	Total number	Type	Locatıon	Some Details
1	54	M	1	Animal/creature	RUE	-Eagle
2	55	M	1	Shape/geometric/illustrative	RUE	-Salvador Dali's chart of melting clocks
3	42	M	4	Lettering (text)	RUE	-"İnsafsız"
				shape/geometric/illustrative animal/ creature	LUE	-Heart-sword
						-Snake wrapped around a sword
4	37	M	3	Lettering (text)	RUE	-"Börteçine"
				shape/geometric/illustrative	LUE	-3 crescents-stars
5	38	M	1	Lettering (text)	RUE	-"Tolgahan" ın an unıdentıfıed fıgure
				shape/geometric/illustrative		
6	42	M	2	Shape/geometric/illustrative	RUE	-Map like figure
7	48	M	1	Lettering (text)	LUE	-Meanıngless word (arabıc)
8	44	F	7	Lettering (text)	RUE	-Understandable words
					LUE	
					Chest	
9	67	M	8	Lettering (text) shape/geometric/ illustrative	RUE	-Birds-gun
					LUE	-"dilek"-"ermiş"
				portrait	Chest	- Woman portraıt
				ınitial letter	Back	
				animal/creature		
10	29	M	6	Lettering (text)	RUE	-"Annem"
				shape/geometric/illustrative animal/ creature	LUE	-Trıbal pattern
					Chest	- King's crown
						-Unıdentıfıed creature
11	29	F	2	Lettering (text)	RUE	-"Duduş"
					LUE	-"İbrahim"
12	37	M	1	Shape/geometric/illustrative	RUE	-Saılor anchor
13	45	M	1	Animal/creature	LUE	-Dragon
14	49	M	1	Initial letter	LUE	-"E"-"H"
15	41	M	8	Lettering (text)	RUE	-Flower
				shape/geometric/illustrative ınitial letter	LUE	-Crescent
				animal/creature	Chest	-Stars
						-Points
						-Heart
						-"Neşenur"
						-"İlle de sen"
						-"I"-"k"
						-wolf
						-Bird
16	52	F	2	Shape/geometric/illustrative number	LUE	-Unidentifıed figure
						-44
17	58	M	1	Shape/geometric/illustrative	LUE	-Star
						-Crescent

Table 5. Tattoos of natural deaths

Case No	Age	Sex	Total number	Type	Locatıon	Some Details
18	43	M	3	Lettering (text) shape/geometric/illustrative	Chest Back	-Sword -“Allah var gam yok melakem” -“Gallo”
19	23	M	4	Shape/geometric/illustrative	RUE LUE LLE	-Unıdentifıed figure

LLE: Left lower extremity, LUE: Left upper extremity, RLE: Right lower extremity, RUE: Right upper extremity

Table 6. Tattoos of suicides

Case No	Age	Sex	Total number	Type	Location	Some Details
1	37	M	1	Lettering(text)	RUE	-“Sensizim”
2	31	M	1	Portrait	RUE	-Woman with a gun
3	23	M	26	Shape/geometric/illustrative lettering(text) animal/ creature portrait	Head/Neck RUE LUE Chest	-Bird-rose -Gun-star -Rocket-bottle -Unidentified figures -“Taylor gang or die” -Man portrait
4	31	F	4	Shape/geometric/illustrative lettering(text) initial letter	RUE LUE Back RLE	-“Galiya” -Seaningless words -Unidentified figures - King’s crown
5	30	M	1	Shape/geometric/illustrative	LUE	-Puzzle
6	27	M	1	Lettering(text)	LUE	-“Canım annem”
7	21	M	1	Shape/geometric/illustrative	Chest	-Star
8	36	M	2	Shape/geometric/illustrative	LUE	-Heart-flower
9	42	M	1	Lettering(text)	Chest	-“Vera”
10	65	M	2	Shape/geometric/illustrative Initial letter	LUE	-Cyprus map -“Ktbk”
11	37	M	4	Lettering(text) animal/creature	RUE LUE Chest	-“Sevilay” -“Gülüşüm” - Wolf head - Runic 4 letters
12	26	F	2	Shape/geometric/illustrative Lettering(text)	Chest	-“Kağan” - King’s crown
13	27	M	1	Lettering(text)	LUE	-Meaningless word (chinese)
14	44	M	2	Shape/geometric/illustrative animal/creature	LUE Back	-Rose-dragon

Table 6. Continued

Case No	Age	Sex	Total number	Type	Location	Some Details
15	25	F	18	Shape/geometric/illustrative lettering(text)	RUE LUE Chest	-Rose-heart -Bird-star -King's crown -Infinity figure -"Annem"-"ela" -"Sedat"-"aras" -"Azra"
16	23	M	2	Lettering(text)	LUE	-"Mısram" -"Annem"
17	40	F	2	Lettering(text) portrait	RUE LUE	-Che portrait -"Sedefim"
18	17	M	6	Shape/geometric/illustrative lettering(text)	RUE LUE Chest	-Chamomile -King's crown -Cats -"Annem"-"bedel" -"Eftal"
19	42	M	2	Shape/geometric/illustrative	RUE LUE	-Chamomile -Unidentified figure
20	25	M	12	Shape/geometric/illustrative	RUE LUE Chest Back LLE	-Unidentified figure -Tribal pattern
21	33	M	1	Shape/geometric/illustrative	LUE	-Tribal pattern
22	25	M	5	Shape/geometric/illustrative lettering(text)	RUE LUE Chest	-Unidentified figure -Tribal pattern -"Vedat" -"Havva"-"mert"
23	32	M	4	Shape/geometric/illustrative lettering(text) initial letter portrait	RUE LUE	-Bjk flag -Atatürk portrait -"Gökhan" -Arabic letters -"La vittoria sara nostra"
24	36	M	1	Shape/geometric/illustrative	LUE	-Sword
25	17	F	1	Shape/geometric/illustrative	LUE	-Angel wings
26	19	M	5	Shape/geometric/illustrative lettering(text) animal/creature number portrait	RUE	-Smoking in the mouth -Devil-lips -Broken chain -"Yes"-"beast" -"Enjoy every day" -Woman portrait
27	17	M	3	Shape/geometric/illustrative lettering(text)	Head/Neck RUE LUE	-"Marley"-"tim" -Rose

Table 6. Continued

Case No	Age	Sex	Total number	Type	Location	Some Details
28	31	M	1	Lettering(text)	Chest	-“Alibuba”
29	33	M	1	Lettering(text)	LUE	-“Trust nobody”
30	22	M	4	Shape/geometric/illustrative initial letter number	Head/Neck Back LUE	-Kalashnikov -Lion king
31	30	F	9	Shape/geometric/illustrative lettering(text)	Head/Neck RUE Chest Back Abdomen	-Baby-crown -Infinity figure -Flower -“Sedat”
32	35	M	3	Lettering(text)	RUE LUE	-“Eylül” -“Ezgi” -“Gülçin”
33	23	M	3	Shape/geometric/illustrative portrait	LUE	-Scissors -Smiling face
34	30	M	5	Shape/geometric/illustrative lettering(text) animal/creature	RUE LUE	-“Sevcan”- “zalim” -star -wolf
35	30	M	4	Shape/geometric/illustrative lettering(text)	RUE LUE Chest	-“Gazi M. Kemal” -“Ömer-bahar” -“My life my rules”

LLE: Left lower extremity, LUE: Left upper extremity, RLE: Right lower extremity, RUE: Right upper extremity

others may choose invisible areas like genitals or breasts, to be more sexually attractive (14). It was observed that the most preferred location in our study was the left upper extremity. In a similar study, it was observed that 60.6% of the tattoos were on the arm, 12.7% on the hand, and 10.1% on the shoulder. In this regard, the suitability of the skin structure and esthetic factors could be important factors (13). It was understood that one patient in our study had a tattoo to hide the cesarean section scar in her abdomen (Figure 1).

Types of Tattoos and Tattoo Figures

Tattoos are a form of communication that people use to communicate or express themselves. Our study showed that the most common type of tattoo was shape, geometric, or illustration. In a similar study, lettering(text) was found to be the most common type of tattoo (13). It was understood that lettering (text) tattoos were the second most common. It is understood that not much work has been done on the language of textual tattoos. The most common language detected in our study was Turkish. We think that this may be because we studied a small but local population. A study found that white Hispanics preferred Spanish, whereas non-Hispanic whites preferred English (5). We believe that the tattoo language chosen by people is mainly related to the country and culture in which they live, although they may also prefer different languages due to cultural interaction and influence from the media.

Figure 1. A tattoo with flower and bird figures (at the tips of the arrows) in suicide case no. 31 was made to hide the cesarean section scar on the abdomen

A wide variety of figures were found in the shape, geometric, and illustration tattoos in our study. Additionally, it was seen that there were different figures in the animal-createature and portrait tattoos (Tables 5-6). While some people prefer more primitive figures and prison tattoos, others prefer figures from works of art with fine lines (15). As a matter of fact, in our study, "Salvador Dali’s melting clocks painting" was found in 1 case (Figure 2a). In the literature, we see that in some cases there are commemorative tattoos that remind family members (16); in some cases, political or racist tattoos

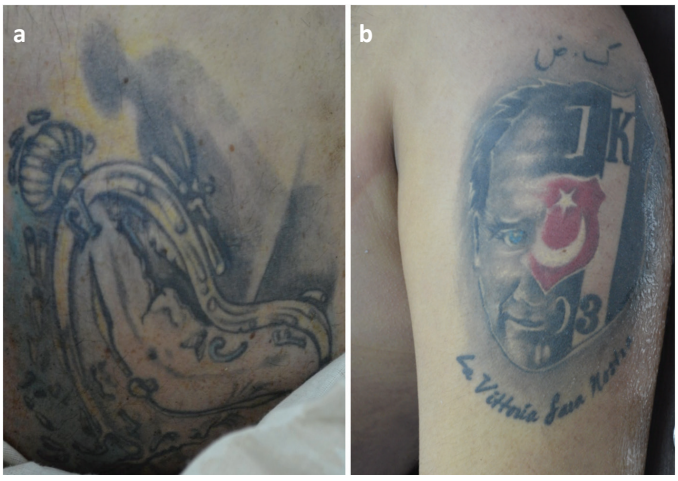

Figure 2. (a): A tattoo figure designed as "Salvador Dali's Melting Clocks Painting" in the lateral region of the proximal part of the right upper extremity in case no: 2 (at the tips of the arrows). (b): Tattoo figures designed as a portrait of "Atatürk" (at the tip of the left arrow) and the BJK flag (at the tip of the right arrow) in the lateral region of the proximal part of the left upper extremity in suicide case no: 23.

featuring Ned Kelly, swastikas, or power figures have been detected (17). In our study, there was a portrait of "Atatürk" in 1 case (Figure 2b), a portrait of "Che" in 1 case, crescent star figures in 1 case, and the names of family members in more than one case. It is clear from these examples that each individual has different emotional and thought motivations when seeking a tattoo.

The current study revealed that the mean number of tattoos was higher in suicide cases with tattoos of shape/geometric/illustrative or animal/creature. Similarly, the risk of suicide was found to be high in subjects with "Ned Kelly" tattoos (17). Our study showed that the mean number of tattoos was higher in suicide cases, but no statistically significant difference was detected between the two groups. In the literature, the shape and meaning of tattoos are believed to be more important than their number (18). When we analyzed all the results obtained from our study, we found that the number of tattoos was not associated with suicide risk. To reveal the relationship between tattoos and suicide risk, individuals' psychiatric disorders and sociodemographic characteristics should also be evaluated in addition to tattoo content (7). In the literature, a study contained data on the figures and meanings of tattoos (19). For example; images such as daggers and skulls: pride in the use of violence; ankle chains: imprisonment; flowers on the forearm: a criminal lifestyle is adopted; it carries meanings (19). Similar figures were also found in our study (Figures 3a,3b). For example, one of our patients had a tattoo containing a "chain" figure, and this patient preferred hanging with a chain as a suicide method (Figure 3c). The meaning behind tattoos can provide clues about a person's background and current life. Future studies could investigate the association between the population and specific tattoos using data obtained from a wide range of different populations subdivided according to their epidemiological characteristics. Likewise, by analyzing the meanings of tattoo figures according to people's behavioral characteristics, comprehensive data records can be created regarding the meaning of the figures. Elucidating the meanings of tattoo figures will also help approach cases in clinical

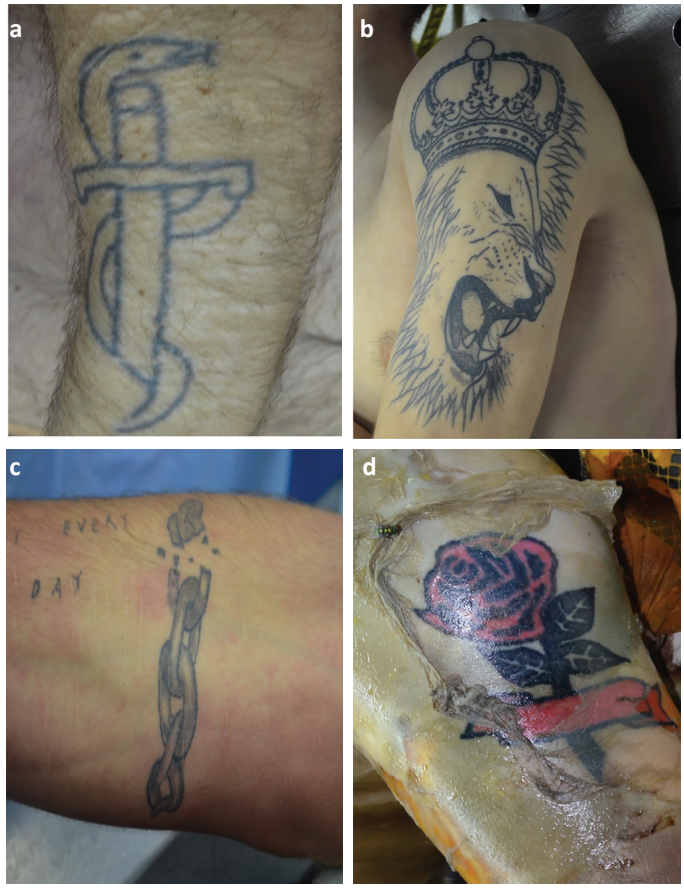

Figure 3. (a): A primitive tattoo with a snake (at the tip of the left arrow) wrapped around a sword (at the tip of the right arrow) in the lateral region of the right upper extremity in natural death case no: 3. (b): A tattoo with lion king in the lateral region of the left upper extremity in suicide case no. 30 (at the tip of the arrow). (c): A tattoo with broken chain in the antecubital region of the right upper extremity in suicide case no: 26 (at the tip of the arrow). (d): A tattoo with rose in the lateral region of the left upper extremity in suicide case no: 14. Despite skin slippage and discoloration rose tattoo is recognizable on a decomposed corpse (at the tip of the arrow)

forensic medicine. In forensic science, tattoos not only give clues about a person's life but also help identify unidentified corpses and contribute to the investigation. It can speed identification, especially during large mass disasters where many unidentified bodies are found (8,9). Because tattoo pigments spread into the deep layers of the dermal tissue, tattoos can be distinguished even in corpses where decomposition has begun or whose integrity has been compromised (3). In our study, the tattoo in a decayed patient was easily distinguished and contributed to identification (Figure 3d). Tattoos are skeletal identifiers, such as wormian bones, that are used to identify unidentified corpses (20). As the analysis of wormian bones contributes to the reconstruction of the biological profile (20), tattoos can also aid in reconstructing the biological profile of corpses, with the information obtained from more comprehensive studies that analyze the frequency of specific tattoo figures in a specific age, gender, or society. In addition, observing tattoo figures in individuals with specific psychopathological diagnoses may potentially aid in the early detection of some psychopathologies (5,7). Standardization of the definition and classification of tattoos

is necessary for objective research. For example; If a “rose” tattoo as a figure is reported as a “flower”, it will cause data confusion (21). In Brookes and Thompson’s study, tattoo motifs are categorized as human forms, animals, plants, flags, objects, symbols, abstractions, and other images in an ANSI/NIST ITL 1-2000 classification (22). In our study, tattoo types were categorized as shape/geometric/ illustrative, lettering(text), initial letter, animal/creature, number, and portrait. We hope that the detailed tattoo figures in our study will contribute to comprehensive studies to be carried out.

Study Limitations

The limitations of this study were that the data belonged to a single center, the total number of cases was low, and thus, the type of tattoos and figures did not show sufficient variety.

CONCLUSION

In conclusion, tattoos are important in forensic medicine. Tattoo figures that provide clues about people’s lives are not only a part of external examination but can also contribute to determining the origin of death. Our study included medicolegal autopsy cases. Unlike previous studies, the present study examined all tattoo figures on the body of the cases, and all figures were described and classified in detail. The study differs in that the relationship between tattoos and suicide was investigated. Our study contributes to the literature on different tattoo figures to examine tattoo profiles in larger populations. The study revealed that there may be a relationship between tattoos and suicide. More comprehensive studies on this subject are required.

Ethics

Ethics Committee Approval: It was obtained from the Pamukkale University Non-Interventional Clinical Research Ethics Committee (approval number: 12, date:16.08.2022). This study was conducted in line with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: H.K.A.Ö., K.A., Design: H.K.A.Ö, K.A., A.K.D., Supervision: K.A., A.K.D., Resources: K.A., Material: H.K.A.Ö, Data Collection or Processing: H.K.A.Ö, Analysis or Interpretation: H.K.A., K.A., A.K.D.,

Literature Search: H.K.A., K.A., A.K.D.,Writing: H.K.A., K.A.

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Impact of Pandemic Measures on Emergency Department Visits: A Comparative Analysis of Medico-Legal Cases Before and During COVID-19

Pandemi Kısıtlamalarının Acil Servis Başvurularına Etkisi: COVID-19 Dönemindeki Adli Olguların Öncesindeki Dönem ile Karşılaştırmalı Analizi

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ABSTRACT

Objective: Proper analysis of the pandemic is vital for correctly managing future crises, predicting the problems encountered, reducing their effects, and taking appropriate precautions. In this study, we aimed to compare cases of emergency department (ED) in a tertiary care adult ED during the pandemic and the pre-pandemic periods to evaluate the effect of lockdowns and similar restrictive measures.

Methods: "Pandemic period" was defined as the period between 11.03.2020 and 11.03.2021, and "pre-pandemic period" was defined as the period between the same dates in the previous year. Thousand cases (500 from each period) were selected by sampling method among 7137 medicolegal cases presented to the Adult ED in these two years. The total number of ED admissions and medico-legal cases' quality, frequency, and diversity were compared.

Results: Total admissions to the adult ED decreased by 42.8% during the pandemic period compared with the pre-pandemic period. Although medico-legal cases also decreased, their proportion in all admissions increased by more than 50%. Leaving the hospital voluntarily reduced significantly (p<0.001). There was a significant decrease in the daily average number of medico-legal cases during the full-day lockdowns of the pandemic compared with all other periods (p<0.001). Medico-legal cases decreased on weekends when the lockdown was imposed more frequently (p<0.046). In the pandemic, traffic accidents increased due to motorcycle accidents (p<0.010).

ÖZ

Amaç: Gelecekteki krizlerin doğru yönetimi, karşılaşılan sorunların öngörülmesi, etkilerinin azaltılması ve uygun önlemlerin alınabilmesi için pandemi döneminin doğru analiz edilmesi büyük önem taşmaktadır. Bu çalışmada, bir üçüncü basamak yetişkin acil servisine pandemi ve pandemi öncesi dönemlerde başvuran olguların karşılaştırılması amaçlanarak, sokağa çıkma yasakları ve benzeri kısıtlayıcı önlemlerin etkilerinin değerlendirilmesi hedeflenmiştir.

Yöntemler: "Pandemi dönemi" 11.03.2020 ile 11.03.2021 tarihleri arasındaki süre olarak tanımlanırken, "pandemi öncesi dönem" bir önceki yılın aynı tarih aralığını kapsamaktadır. Bu iki yıl içerisinde acil servise başvuran toplam 7137 adli olgu arasından örnekleme yöntemiyle seçilen 1000 (her dönemden 500) olgu incelenmiştir. Bu örneklem üzerinden, acil servise toplam başvuru sayıları ile adli olguların niteliği, sıklığı ve çeşitliliği karşılaştırılmıştır.

Bulgular: Pandemi döneminde yetişkin acil servise toplam başvurular pandemi öncesi döneme kıyasla %42,8 oranında azalmıştır. Adli olgular da azalmasına rağmen, toplam başvurular içindeki oranı %50'den fazla artış göstermiştir. Hastaneden kendi isteğiyle ayrılma oranı anlamlı şekilde azalmıştır (p<0,001). Pandemi sürecindeki tam gün sokağa çıkma yasakları sırasında günlük ortalama adli olgu sayısında, diğer tüm dönemlere kıyasla anlamlı bir düşüş saptanmıştır (p<0,001). Sokağa çıkma yasağının daha sık uygulandığı hafta sonlarında adli olgu sayısında azalma görülmüştür (p<0,046). Pandemi döneminde motosiklet kazalarına bağlı olarak trafik kazalarında artış gözlenmiştir (p<0,010).

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ABSTRACT

Conclusion: During the pandemic, the significant decrease in overall ED visits compared with the number of medico-legal cases and the decline in the behavior of leaving the hospital voluntarily can indicate the high number of unnecessary green zone admissions in ordinary times. The change in living and consumption habits caused by the pandemic may also have changed the frequency and epidemiological distribution of forensic cases, such as motorcycle accidents.

Keywords: COVID-19 pandemic, lockdown, medico-legal cases, emergency department

ÖZ

Sonuç: Pandemi döneminde adli olgu başvurularına kıyasla acil servise yapılan toplam başvuruların sayısındaki belirgin düşüş, ve hastaneden kendi isteğiyle ayrılma davranışındaki azalma, olağan zamanlarda gereksiz yeşil alan başvurularının yüksekliğine işaret ediyor olabilir. Pandeminin sebep olduğu yaşam ve tüketim alışkanlıklarındaki değişiklikler, motosiklet kazaları gibi adli olguların sıklığını ve epidemiyolojik dağılımını da değiştirmiş olabilir.

Anahtar Sözcükler: COVID-19 pandemisi, sokağa çıkma yasağı, adli olgular, acil servis

INTRODUCTION

A pandemic is the spread of a disease or infectious agent to a large area in various countries, continents, or the world, affecting a large part of society and causing an epidemic (1). Throughout history, humanity has been tested many times by infectious diseases, leading to pandemics. During pandemics such as cholera, plague, and Spanish flu, many deaths occur at a level that changes the structure and order of society (1-4).

Similar to previous outbreaks, humanity has faced a pandemic in recent history. Coronavirus disease 2019 (COVID-19) was declared a pandemic on March 11, 2020. In the following periods, to minimize social contact, various measures were taken, and lockdowns were implemented from time to time. Although a specific treatment has not yet been developed, the disease has started to lose its effect over time with the impact of the vaccines produced. Cases and deaths due to the disease have decreased worldwide (5-7). Finally, on May 5, 2023, the World Health Organization (WHO) announced that COVID-19 no longer constitutes a "global health emergency" (8).

In addition to disease, lockdowns and related restrictions profoundly influenced various aspects of human life. Consequently, there has been a notable shift in the volume of applications to the emergency department (ED), which serves as the first point of contact. The most obvious examples of this situation are the changes in parameters such as ED workload, access to healthcare services, frequency, and epidemiological distribution of medico-legal cases during the pandemic. It is expected that ED admissions will decrease with the effect of restrictions during the pandemic, which has been shown by many studies. For instance, Law et al. (9) reported that visits to EDs related to nonfatal injuries decreased by 25% during the pandemic. Although total ED admissions have reduced significantly, there are studies indicating that serious emergencies such as stroke and cardiac conditions have decreased very slightly, and even resuscitation and emergency triage rates have increased (10,11).

Even though the pandemic has ended, it is necessary to understand this period in all its aspects to evaluate the impact of these and similar crises on human health, healthcare services, and health systems to make predictions about the problems that will arise and to take measures against these problems.

Within this scope, in this study, we aimed to compare the cases presented to a tertiary care adult ED during the pandemic and the pre-pandemic periods to evaluate how lockdowns and similar restrictive measures affected the total number of ED admissions, the quality, frequency, and diversity of medico-legal cases, and to discuss the measures to be taken.

MATERIALS and METHODS

Population and Sample

In our study, the "pandemic period" was defined as the period between 11.03.2020 and 11.03.2021, and the "pre-pandemic period" was defined as the period between the same dates in the previous year. The sample of our study consisted of the total number of patients admitted to the adult ED of Gazi University Hospital during the two periods. This retrospective study included medico-legal cases aged over 18 years. In calculating the sample size using the Open Epi program, 7137 medicolegal cases admitted to the ED within the last 2 years were used as references for the study population. With an unknown frequency of 50% and a margin of error of 3%, the number of cases to be included in the study was calculated as 927 with a design effect of 1.0, and 1000 cases were included in the study with 8% missing data. Half of these 1000 cases were selected from the pandemic period, and the other half were selected from the pre-pandemic period. First, the patients in each period were given a sequence number from old to new according to their admission dates, and then 500 patients to be included in the sample were selected from these numbers by systematic sampling method.

Hospital information management system records were used to obtain information about medicolegal cases presented to the adult ED. The pandemic and pre-pandemic periods were compared in terms of admission day, gender, age, event exposed, estimated event manner*, work accident, home accident, domestic violence, and discharge status.

*In the legal system of Türkiye, the precise manner of forensic events is determined by prosecutors' offices or courts at the end of the process. Therefore, the manner of the incident, which was decided according to the information obtained from the medico-legal reports of the cases within the scope of the study, was named the "estimated event manner."

In addition, a comparison was made by dividing the pandemic period into subgroups to determine the effect of full-day or certain-hour lockdowns imposed during the pandemic on the number of medicolegal cases. The days when the lockdown lasted for 24 hours were classified as "full-day lockdown", when the lockdown was at certain hours of the day, were classified as "partial lockdown", and the remaining days were classified as "no-lockdown" days of the pandemic.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was obtained from the Ethics Commission of Gazi University (approval number: E-77082166-604.01.02-72964, date: 12.04.2021).

Statistical Analysis

Statistical Package for Social Sciences (SPSS 25.0) statistical software was used in the data analysis of the study, and values with p≤0.05 (two-way) were considered statistically significant. Continuous data were defined as mean, median, maximum-minimum, and categorical data with frequency and percentage values in the statistical analysis. The compatibility of variables in groups with normal distribution was evaluated with the “Shapiro-Wilks Test". In the data that were determined not to show normal distribution as a result of the evaluation, “Mann-Whitney U Test” was used for pairwise comparison, and “The Kruskal-Wallis Test” was used for the comparison of more than two groups. “The chi-square test” was used to compare categorical data.

RESULTS

In the pre-pandemic period, the total number of admissions to the ED was 72.726, and the number of medico-legal case admissions was 3811. Meanwhile, the total number of admissions was 41.596, and the number of medico-legal case admissions was 3326 during the pandemic period. During the pandemic, there was a 42.8% decrease in the number of total admissions and a 12.7% decrease in the number of medico-legal case admissions. The rate of medico-legal cases in total admissions was 5.24% (n=3.811) in the pre-pandemic period and 7.99% (n=3.326) in the pandemic period. The rate of medico-legal cases in total admissions increased significantly during the pandemic period (p=0.027).

Among the 500 medico-legal cases included in the study with the systematic sampling method from both periods, the number of women was 151 (30.2%) in the pre-pandemic period, while it was 124 (24.8%) in the pandemic period (p=0.056). The median age of medico-legal cases in the pre-pandemic period was 32 (18-88), whereas it was 33 (18-91) in the pandemic period (p=0.433).

In addition to the pandemic and pre-pandemic periods, pandemic subgroups were compared regarding the average daily number of medico-legal cases. The analysis revealed that the daily average number of medico-legal cases decreased significantly in the full-day lockdown subgroup compared with all other periods and subgroups (p<0.001) (Table 1). No significant differences were found in other comparisons between periods and subgroups.

Table 1. Comparison of the average daily number of medicolegal cases presented to the ED according to periods and subgroups

Periods	Average daily medicolegal case (n)	p*
Pre-pandemic period	10.5	0.725
Pandemic period	9.18	
Pre-pandemic period	10.5	**<0.001**
Full-day lockdown	6.42	
No-lockdown days of the pandemic	9.48	**<0.001**
Full-day lockdown	6.42	
Partial lockdown	9.48	**<0.001**
Full-day lockdown	6.42	

*p≤0.05,
ED: Emergency department

A comparison of the periods in terms of the forensic event type leading to ED visits revealed that the rate of ED visits due to traffic accidents was significantly higher during the pandemic period (p=0.015). In-group analysis showed that this difference was caused by motorcycle accidents, which occurred more frequently during the pandemic period (p=0.010). No significant difference was detected between the periods of in-vehicle and out-of-vehicle traffic accidents. In addition, cases of poisoning and injury by an object were found to be significantly higher in the pre-pandemic period. Although the number of animals in the sample was small, the number of animal attacks was significantly higher during the pandemic period. No significant differences were found between the periods in terms of other event types (Table 2).

No significant difference was found between the periods in terms of the estimated event manner (Table 3). Although there was a 3% decrease in occupational accidents during the pandemic period compared with the pre-pandemic period, no significant difference was found (Table 4). Although the number of home accidents and domestic violence cases in the sample was small, it was observed that home accidents decreased and domestic violence increased during the pandemic period; however, these changes were not significant. Medico-legal admissions to the ED decreased significantly on weekend days during the pandemic period (p=0.046). Moreover, the number of those who voluntarily left the hospital before the treatment process was completed also significantly reduced during the pandemic period (p<0.001) (Table 4).

Table 2. Distribution of forensic event types according to periods

Forensic event	Pre-pandemic period n (%)	Pandemic period n (%)	p*
Traffic accidents	117 (23.4)	151 (30.2)	**0.015**
Passenger	78 (15.6)	89 (17.8)	0.195
Pedestrian	22 (4.4)	22 (4.4)	0.353
Motorcyclist	16 (3.2)	40 (8)	**0.010**
Unknown	1 (0.2)	0 (0.0)	0.437
Falls	74 (14.8)	77 (15.4)	0.791
Blunt force	78 (15.6)	64 (12.8)	0.205
Intoxication	37 (7.4)	18 (3.6)	**0.008**
Sharp force	51 (10.2)	69 (13.8)	0.080
Firearm wounds	5 (1.0)	4 (0.8)	1.000
Burn injuries	6 (1.2)	3 (0.6)	0.506
Animal attacks	2 (0.4)	9 (1.8)	**0.034**
Injuries by a tool or machine**	124 (24.8)	98 (19.6)	**0.048**
Other***	6 (1.2)	7 (1.4)	0.780

*p≤0.05,
**Injuries by a tool or machine are used to describe injuries that occur mostly in occupational accidents and cannot be included in other classes, such as extremities caught in a tool or foreign body in the eye,
***Other: each group consists of injuries resulting from multiple causes, such as electrical injuries, explosive injuries, sexual assault, and hangings, or injuries resulting from multiple causes, with 2 or fewer cases in each group

Table 3. Distribution of estimated event manner according to period

Estimated event manner	Pre-pandemic period n (%)	Pandemic period n (%)	p*
-Accident	383 (76.6)	389 (77.8)	0.651
-Injury due to an attack	86 (17.2)	80 (16.0)	0.610
-Suicide attempt or self-harm	28 (5.6)	31 (6.2)	0.687
-Unknown	3 (0.6)	0 (0.0)	0.249

*p≤0.05

Table 4. Distribution of occupational accidents, domestic accidents, domestic violence, time of admission, and leaving the hospital voluntarily by periods

	Pre-pandemic period n (%)	Pandemic period n (%)	p*
Occupational accident	212 (42.4)	196 (39.2)	0,167
Domestic accident	10 (2.0)	3 (0.6)	0.052
Domestic violence**	7 (1.6)	12 (2.6)	0.356
Weekend admission	148 (29.6)	120 (24.0)	**0.046**
Leaving the hospital voluntarily	46 (9.2)	16 (3.2)	**0.000**

*p≤0.05,
**In 86 cases (53 cases in the pre-pandemic period and 33 cases in the pandemic period), information on domestic violence could not be reached

DISCUSSION

In our study, total admission to the adult ED decreased by 42.8% compared with the pre-pandemic period during the pandemic period. Although medico-legal cases also reduced (12.7%), since the decrease in total admissions was more pronounced, we found that the proportion of medico-legal cases in all ED admissions increased by more than 50% (pre-pandemic: 5.2%, pandemic: 8%). In addition, we observed that patients' behavior of "leaving the ED voluntarily" decreased significantly during the pandemic. We found that medical-legal case admissions decreased significantly, especially during the full-day lockdown. In relation to this, we observed that weekend applications were also reduced during the pandemic. Furthermore, contrary to expectations, we observed a significant increase in traffic accidents during the pandemic. This increase was mainly due to the rise in motorcycle accidents.

Numerous studies have shown that total ED admissions decreased during the pandemic. Moreover, in accordance with the results of our research, Isik et al. (12) determined that although the number of forensic cases decreased during the pandemic compared with the pre-pandemic period, the rate of forensic cases in all ED admissions increased during the pandemic. One reason for this may be that people want to protect their legal rights even if there is no health risk in forensic incidents or that they have to be taken away. In addition, another reason may be that unnecessary green zone admissions, which constitute a significant portion of ED admissions, decreased to a greater extent than forensic cases during the pandemic. In a systematic review in which 81 studies from 20 countries were analyzed, it was reported that the use of healthcare services decreased by 37% on average during the pandemic, similar to the result in our study, and the highest rates of decline were seen in the mildest diseases (13). Another situation that may be affected by changes in unnecessary green space applications is the behavior of "leaving the hospital voluntarily". We observed that the number of those who voluntarily left the hospital during the pandemic decreased significantly. In the pre-pandemic period, some of the unnecessary green zone admissions to the hospital may have shown a higher rate of leaving because they did not have a condition requiring urgent medical attention. In the pandemic period, on the contrary, due to the decrease in unnecessary green zone applications, EDs became less crowded, and access to healthcare services became more effortless, which may have led to a decline in patients' behavior of leaving the hospital.

Although the average daily number of forensic cases decreased partially during the pandemic in our study, no significant difference was observed between the two periods. However, when the subgroups of the pandemic period were analyzed to evaluate the specific effects of the lockdown, a significant decrease was observed in the full-day lockdown subgroup compared to both the pre-pandemic period and other subgroups of the pandemic (partial lockdown days and no-lockdown days of the pandemic). This decrease may be due to the fact that lockdowns lasted all day and sometimes even for days. People were always at home, and their social and business participation was significantly restricted. Thus, the number of outpatients and forensic incidents decreased. Another study finding supporting the decline in medico-legal cases on full-day lockdown days is the significant reduction of medico-legal case admissions on weekend days during the pandemic. Because in Türkiye, full-day lockdowns were generally applied on weekends. On partial lockdown days, people continued their social and business lives to some extent. This situation may have enabled the number of medico-legal case admissions during the partial lockdown periods to approach the pre-pandemic period and the no-lockdown periods of the pandemic.

In general, traffic accidents are expected to decrease due to restrictions during the pandemic. Similarly, in a study evaluating the global impact of the pandemic on traffic accidents, a significant decrease in traffic accident deaths was observed in 32 out of 36 countries in April 2020 compared with the same month of the previous year. The annual evaluation of the same study showed that in the pandemic year (2020), there was a decrease in deaths due to traffic accidents in 33 of 42 countries compared with the pre-pandemic year (2019) (14). Another meta-analysis, which included 13 studies from 11 countries, reported that traffic accidents decreased significantly during the pandemic (15). Contrary to expectations, no significant difference was found between the two periods in terms of in-vehicle and out-of-vehicle traffic accidents, and total traffic accident admissions and motorcycle accident admissions were found to be significantly higher during the pandemic than during the pre-pandemic period. Similarly, in a study by Demir et al. (16) examining occupational accidents during the pandemic, an increase in motorcycle courier accidents was found. We believe that this significant increase in motorcycle accidents and consequently in traffic accidents can be explained by the revival in the cargo and motor courier sectors as a result of the change in consumer

behavior due to the effect of lockdowns and stay-at-home policies implemented during the pandemic and the increase in internet shopping and home delivery requests.

In addition, in our study, it was observed that poisonings decreased significantly during the pandemic. When poisonings were analyzed on a case-by-case basis to determine the cause of the decrease, it is noteworthy that food poisonings were more common in the pre-pandemic period. As a result, the reduction in food poisoning during the pandemic may have resulted from people being more careful against infectious agents during this period and, therefore, being more attentive to personal hygiene and food cleanliness.

Although the number of cases in our sample was small, animal attacks increased during the pandemic. When animal attacks were analyzed on a case-by-case basis, we found that most attacks were carried out by dogs. Although some studies report that dog attacks decreased or did not change during the pandemic, many studies report an increase (17-21). According to these studies, the increase is due to increased interaction with house dogs due to lockdowns and stay-at-home policies, and children are the most frequently injured. In our research, we observed that working adults were primarily exposed to dog attacks during work. One of the reasons for this may be stray dogs. Moreover, no significant difference was found when the lockdown days were compared with the other days of the pandemic to evaluate whether the deserted streets due to the lockdown affected this increase.

Considering the literature in terms of other types of forensic events in Table 2 (fall, blunt force, sharp force, firearm, and burn injuries) during the pandemic, it is seen that the authors reached different results. Abhilash et al. (22) reported that the incidence of falls decreased during the pandemic, while Hazra et al. (23) reported that the incidence of falls from height decreased, but the incidence of falls from their level increased. Chiba et al. (24) found an increase in sharps and firearm injuries during the pandemic and a decrease in assault crimes in the study of Balmori de la Miyar et al. (25). Georgeades et al. (26) reported that pediatric burn cases increased during the pandemic, whereas Chawla and Papp (27) reported that the incidence of kitchen-related burns in adults did not change during the pandemic. In our study, no significant differences were found between the two periods for fall, blunt force, sharp force, firearm, and burn injuries.

In our study, although there was a slight decrease in occupational accidents during the pandemic compared with the pre-pandemic period, no significant difference was found between the periods. In the study by Nuñez et al. (28) a significant decrease in injuries due to occupational accidents was found in the initial period of the pandemic. A study by Demir et al. (16) observed that occupational accidents decreased in total during the pandemic but increased in some sectors, especially in the transport sector due to accidents involving motor couriers and in the health sector due to increased workload. In the literature on occupational accidents in general, a significant decrease was found in the pandemic compared with the pre-pandemic period, and it is thought that this situation is because only compulsory occupational groups work during lockdown periods, while other occupational groups primarily work from home. The reason for the lack of a significant decrease in occupational accidents during the pandemic in our study can be explained by the substantial increase in motorcycle accidents, which are primarily occupational accidents, as discussed above. On the other hand, the injuries that occur mainly in occupational accidents, such as extremities being stuck in a tool or foreign body penetration into the eye, which we define as “injury by an object” in the table of forensic event types, were significantly higher in the pre-pandemic period. This result may indicate that injuries in work branches other than motor vehicle use decreased during the pandemic.

Contrary to expectations, a decrease in home accidents was observed during the pandemic. This may be because our sample’s total number of home accidents was small and may not reflect an accurate picture. However, in the literature, an increase in home accidents was generally found during the pandemic, and it was thought that this was due to the increased risk of exposure to home accidents of people who spend more time at home (29).

With the pandemic measures, the number of people calling hotlines in Türkiye (country) increased by 55% in April 2020 and 78% in May 2020 compared with previous months. The most common reason for applications in April was sexual violence, while the most common reason for applications in May was psychological violence (30,31). In the European member states of the WHO, it has been reported that there is a 60% increase in the number of calls to emergency lines because of intimate partner violence (32). Again, in a systematic review and meta-analysis on domestic violence, it was stated that domestic violence increased during the pandemic (33). In general, an increase in cases of domestic violence has been found in the literature during the pandemic, and it has been suggested that spending more time together in a closed environment such as home may increase the risk of conflict between family members (34-37). In addition, the stress, economic, social, and psychological changes caused by the pandemic can also be considered to trigger domestic violence cases. Although there was an increase in cases of domestic violence in our study, no significant change was found between the two periods. This may be because the number of cases in our sample was small, and our study may not reflect the accurate picture, although there was a significant difference. Other reasons for not finding a significant difference, even if domestic violence is higher, may be the victim’s hesitation to report due to the obligation to be in the same house during the pandemic, fear of the attacker being aware of the report, or the attacker preventing the report.

Despite a minimal decrease in assault injuries during the pandemic, no significant difference was found between the periods in this study. In the study conducted by Isik et al. (12) no significant difference was observed between the pandemic and pre-pandemic periods regarding injuries due to assault. However, in the literature, it was reported that there was a general decrease in injuries due to attacks during the pandemic. For instance, according to a global study with data collected from 27 cities in 23 countries, pandemic-era restrictions led to a decrease in all types of crime (37%), with the most minor reduction in homicide (14%), while the overall average of assault crimes decreased by 35% (38).

Although there was a minimal increase in suicide attempts or self-harm behaviors during the pandemic, no significant difference was found in the study. Similarly, Pirkis et al. (39) reported that suicide rates in most countries remained unchanged. However, they observed an increase in suicide attempts in some countries in

their data from 33 countries (39). Conversely, there are also studies indicating that there is a significant increase in suicide attempts and self-harm behavior during the pandemic period (40,41). Although it cannot be generalized, this increase in suicide attempts or self-harm behavior may be due to situations such as fear of virus transmission, economic difficulties, social isolation, uncertainty, chronic anxiety, and stress caused by the pandemic, which may increase or exacerbate psychiatric disorders (24,40,42).

CONCLUSIONS

One of the remarkable results of our study is that it indirectly showed that EDs were occupied with unnecessary green zone admissions. The appropriate use of EDs will facilitate access to healthcare services for those with indications, reduce the intensity of EDs and burden on health workers, ensure more efficient healthcare services, and reduce costs. Another outcome of our study was that medico-legal cases decreased significantly only during full-day lockdowns rather than during the pandemic in general or partial lockdown periods. Furthermore, during the pandemic, the increase in motorcycle accidents detected indicates that changes in living and consumption habits caused by events that affect society as a whole, such as the pandemic, may also change the nature of forensic events. To minimize the effects of pandemics and similar disasters that are likely to occur in the future, it is vital to predict possible problems. Within this scope, we believe that our study will contribute to the literature by describing the effects of the changes caused by the pandemic on social life and the natural consequences of these changes on medico-legal cases.

Ethics

Ethics Committee Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was obtained from the Ethics Commission of Gazi University (approval number: E-77082166-604.01.02-72964, date: 12.04.2021).

Informed Consent: Retrospective study.

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Footnotes

Authorship Contributions

Concept: T.A., B.D., Design: A.Ö., Supervision: A.Ö., B.D., Resources: T.A., B.D., Material: M.B.C., Data Collection or Processing: M.B.C., A.Ö., T.A., Analysis or Interpretation: M.B.C., A.Ö., Literature Search: M.B.C., A.Ö., Writing: A.Ö., M.A.A., Critical Review: M.B.C., A.Ö., M.A.A.

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Effect of COVID-19 Pandemic on Emergency Service Suicide Applications in a Tertiary Psychiatric Clinic in Türkiye

Türkiye'de Üçüncü Basamak Bir Psikiyatri Kliniğinde COVID-19 Pandemisinin Acil Servis İntihar Başvurularına Etkisi

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ABSTRACT

Objective: During the COVID-19 pandemic, several studies have reported increased suicidality. The widespread negative impacts of the pandemic, such as the economic downturn, isolation, and quarantine, have contributed to the complex interaction of factors influencing suicidal behavior. This study aimed to compare the clinical characteristics of individuals with suicidal thoughts/attempts between the pandemic and the pre-pandemic period.

Methods: This descriptive study retrospectively evaluated the data of patients between 2018 and 2022. The period from March 2020 to March 2022 was defined as the "pandemic period", while the period from March 2018 to March 2020 was labeled as the "pre-pandemic period". While 185 patients applied to the emergency department due to suicidal thoughts/attempts in the pre-pandemic period, the number of cases consulted during the pandemic was 150.

Results: During the COVID-19 period, 21% of patients were evaluated due to suicidal thoughts/attempts. In the pre-pandemic period, this rate was approximately 20%. There was no statistical difference between the groups in terms of age, suicide method, or lifetime psychiatric diagnoses. The proportion of males who presented with suicidality during COVID-19 was significantly higher.

Conclusion: Pandemics can create social trauma and increase suicide rates. Gender roles, such as men being more inclined to conceal their complaints and feeling more economically responsible, may have increased the rates of suicidality during the pandemic. The mental, physical, and social impacts of the pandemic should be assessed in this context, and necessary precautions and interventions should be planned.

Keywords: COVID-19, depression, emergency service, pandemic, suicidal attempt, suicidal ideation

ÖZ

Amaç: COVID-19 salgını sırasında, çeşitli çalışmalar intihar eğiliminin arttığını bildirmiştir. Ekonomik gerileme, izolasyon ve karantina gibi salgının yaygın olumsuz etkileri, intihar davranışını etkileyen faktörlerin karmaşık etkileşimine katkıda bulunmuştur. Bu çalışma, pandemi dönemi ve pandemi öncesi dönem arasında intihar düşünceleri/girişimleri olan bireylerin klinik özelliklerini karşılaştırmayı amaçlamıştır.

Yöntemler: Bu tanımlayıcı çalışma, 2018 ile 2022 arasındaki hastaların verilerini retrospektif olarak değerlendirmiştir. Mart 2020 ile Mart 2022 arasındaki dönem "pandemi dönemi" olarak tanımlanırken, Mart 2018 ile Mart 2020 arasındaki dönem "pandemi öncesi dönem" olarak sınıflandırılmıştır. Pandemi öncesi dönemde intihar düşüncesi/girişimi nedeniyle acil servise başvuran hasta sayısı 185 iken, pandemi döneminde konsülte edilen olgu sayısı 150 dir.

Bulgular: COVID-19 döneminde hastaların %21'i intihar düşünceleri/girişimleri nedeniyle değerlendirilmiştir. Pandemi öncesi dönemde bu oran yaklaşık %20'dir. Gruplar arasında yaş, intihar yöntemi veya yaşam boyu psikiyatrik tanılar açısından istatistiksel bir fark saptanmamıştır. COVID-19 sırasında intihar eğilimi gösteren erkeklerin oranı anlamlı olarak daha yüksektir.

Sonuç: Pandemiler sosyal travma yaratabilir ve intihar oranlarını artırabilir. Erkeklerin şikayetlerini gizlemeye daha yatkın olması ve ekonomik olarak daha fazla sorumlu hissetmesi gibi cinsiyet rolleri, pandemi sırasında intihar oranlarını artırmış olabilir. Pandeminin ruhsal, fiziksel ve sosyal etkileri bu bağlamda değerlendirilmeli, gerekli önlemler ve müdahaleler planlanmalıdır.

Anahtar Sözcükler: COVID-19, depresyon, acil servis, pandemi, intihar girişimi, intihar düşüncesi

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INTRODUCTION

Suicide, defined as the act of intentionally causing self-harm that results in varying degrees of fatality, is a significant public health issue both in our country and worldwide (1). Approximately 800.000 individuals take their own lives due to suicide each year, with reported suicidal attempts being 30-40 times higher than this number (1). According to the Turkish Statistical Institute, suicide rates in Türkiye have increased by 89% over the past 20 years (2). The coronavirus disease-19 (COVID-19) pandemic, which started in December 2019 in China and spread worldwide, caused significant disruptions across various aspects of life, persisted for approximately two years. During the COVID-19 pandemic, the causes of suicide were extensively studied. Although some researchers did not find a significant difference in the number of completed suicides before and during the pandemic (3-5), other studies highlighted specific factors associated with an increase in suicidal tendencies (6-9). A study conducted in Türkiye in 2022 reported no increase in completed suicides during the pandemic period; however, hanging as a method of suicidal attempt was more common among individuals who were married, employed, and had mood disorders (3). Suicidal behaviors can arise from biological, psychological, environmental, and economic factors (10). A systematic review published in 2022 indicated some degree of heterogeneity in the factors influencing suicidal behaviors during the COVID-19 pandemic; economic downturn, psychiatric vulnerability, isolation and quarantine, health concerns, and relational difficulties were reported as the most prominent reasons for the development of suicidal behaviors (11). It is believed that during the early stages of the pandemic, social isolation, restricted access to healthcare services, and intra-family conflicts particularly contributed to an increase in suicide risk among vulnerable groups (12). Increases in unemployment, economic hardships, and elevated stress levels were associated with increased suicidal thoughts or attempts, especially during the pandemic's later stages (11). Considering both the early and later effects of the pandemic, the importance of resilience in relation to stress is evident. Apart from the exacerbation of existing mental disorders, the increase in rates of depression, anxiety disorders, eating disorders, and alcohol and substance use disorders in at-risk individuals can also lead to an increased risk of suicide (12). The widespread negative impacts of the pandemic have contributed to the complex interaction of factors influencing suicidal behavior. Continuing to monitor and address these factors is crucial for implementing effective prevention and intervention programs. There are only a few studies in our country that have evaluated the relationship between the pandemic and suicide (12-15). Gazi University Faculty of Medicine Hospital is one of the six centers in Ankara province that offer psychiatric inpatient services. Approximately 550-600 patients visit the emergency department annually due to psychiatric complaints and are evaluated from a psychiatric perspective. This study aimed to examine the clinical and sociodemographic characteristics of individuals presenting to the Gazi University Faculty of Medicine Hospital emergency department with suicidal thoughts or attempts during the pandemic and investigate whether there were differences compared with the pre-pandemic period, thus contributing to the literature.

MATERIALS AND METHODS

Study Design and Participants

This descriptive cohort study retrospectively evaluated the data of patients who presented to the emergency department of Gazi University Faculty of Medicine Hospital with suicidal thoughts or attempts and for whom psychiatric assessment was requested between March 2018 and March 2022. Patient data were categorized into groups based on the dates of admission, and the number and other characteristics of cases in the pre-pandemic and pandemic periods were statistically compared. The period from March 2020 to March 2022 was defined as the "pandemic period", while the period from March 2018 to March 2020 was labeled as the "pre-pandemic period". Through the hospital information management system, records of patients referred from the emergency department to the psychiatry department for reasons such as suicidal attempts, suicidal ideation, drug and other substance intoxication, and self-harming behaviors were examined. Patients deemed to have a history of suicidal thoughts or attempts based on the records were included in the study. Suicidal attempts were defined as behaviors in which a person intentionally engaged in actions endangering their life. It was determined that 188 out of 900 cases presented to the emergency department for psychiatric evaluation in the pre-pandemic period due to suicidal thoughts or attempts. During the pandemic period, 156 out of 691 patients who underwent consultation in the emergency department were evaluated for suicidal thoughts or attempts. Patients who did not await psychiatric evaluation and/or whose data could not be accessed for any reason, as well as those for whom evaluation results indicated no history of suicide, were not included in the study. Three patients in the pre-pandemic period and six patients in the pandemic period were excluded from the study because they left the hospital without completing medical procedures. In total, 335 patients constituted the study population. From the records of patients; sociodemographic information, past psychiatric history, and history of alcohol and substance abuse were obtained. Due to the significance of the relationship with suicide, the method of suicide and whether alcohol use was associated with suicidality at admission were investigated. Psychiatric diagnoses were determined according to the DSM-5 criteria using information from the records. In case of disagreement regarding diagnoses, a consensus was reached through a joint evaluation by all researchers. Patients were divided into two groups based on characteristics of suicidal behavior at admission. Patients were classified as planned suicide if they exhibited features such as having suicidal thoughts days before the suicide attempt, planning the time or method of suicide, or leaving a will or note to their relatives. On the other hand, patients who made a sudden decision to attempt suicide did not plan the act and did not have continuous, repetitive suicidal thoughts in the past few days were classified as impulsive suicide. Ethical approval for the study was obtained from the Gazi University Ethics Committee (approval number: 202-002, date: 21.12.2021). This study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the world medical association Declaration of Helsinki-Ethical Principles For Medical Research Involving Human Subjects revised in 2013.

Statistical Analysis

IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. (IBM Corp, Armonk, NY) was used for statistical analysis. Descriptive statistics are presented as median, frequency distribution, and percentage. Because data related to age did not follow a normal distribution, median ages were used instead of mean ages. The normal distribution of variables was examined visually (using histograms and probability plots) and analytically (using the Kolmogorov-Smirnov/Shapiro-Wilk test). Nonparametric tests were employed to compare patient characteristics between the pre-pandemic and pandemic periods due to the lack of normal distribution. The chi-square test was used to compare categorical variables, and the Mann-Whitney U test was used to compare continuous variables. Differences with a two-tailed p-value 0.05 were considered statistically significant.

RESULTS

Sociodemographic and Clinical Variables

During the COVID-19 period, 21% of patients who applied to the emergency department of Gazi University Faculty of Medicine Hospital and requested psychiatric consultation were evaluated due to suicidal thoughts or attempts. In the pre-pandemic period, this rate was approximately 20%. Numerically, there was a decrease in emergency department visits for psychiatric complaints during COVID-19. However, when examined proportionally, the proportion of applications for suicidal thoughts or attempts did not change. In the first year following the start of the pandemic (early pandemic period), the most frequent applications due to suicide were in June (n=17) and then July (n=12). The monthly distribution of suicide applications during the late pre-pandemic and early pandemic periods is shown in Figure 1.

In both the pre-pandemic and pandemic periods, median ages for applications were calculated as 30 [min.-max. ages: (pre-pandemic versus pandemic) 18-79 vs 18-83]. There was no statistical difference between the groups in terms of median ages (p=0.873). When analyzed by age groups, it was observed that 31.9% of pre-pandemic applications were in the 18-24 ages, 38.9% in the 25-39 ages, 27.6% in the 40-64 ages, and 1.6% were 65 years and older. In the COVID-19 period, 30% of applications were in the 18-24 ages, 46% in the 25-39 ages, 20% in the 40-65 ages, and 4% were 65 years and older. Before the COVID-19 pandemic, 33.5% of patients presenting with suicidal thoughts or attempts were male, and 66.5% were female. During the pandemic period, 48% of cases were male, and 52% were female. The proportion of males presenting with suicidal thoughts or attempts during the COVID-19 period was significantly higher (x^2=7.243, p=0.007). No significant differences were found in other sociodemographic variables. The education level, marital status, and employment status of patients in the pre-pandemic and pandemic periods are presented in Table 1. No statistically significant differences were found between the groups in terms of emergency department application patterns, severity and type of suicide attempts, method used for suicide, and clinical variables related to psychiatric history. These results are summarized in Table 2. At the time of admission, 95 (51.4%) patients in the pre-pandemic group and 72 (48%) patients in the pandemic group did not use any psychotropic drugs. The most frequently used psychotropic drugs in both groups were antidepressants (pre-pandemic: 81.1% vs pandemic: 67.9%) and antipsychotics (pre-pandemic: 47.7% vs pandemic: 61.5%), respectively In the pre-pandemic group, 15 and 8 patients were taking mood stabilizers and 8 patients were taking benzodiazepines. In the pandemic group, 10 patients were using mood stabilizers, and 7 patients were using benzodiazepine. A total of 45.5% of patients in the pre-pandemic group and 46.1% in the pandemic group were receiving monotherapy.

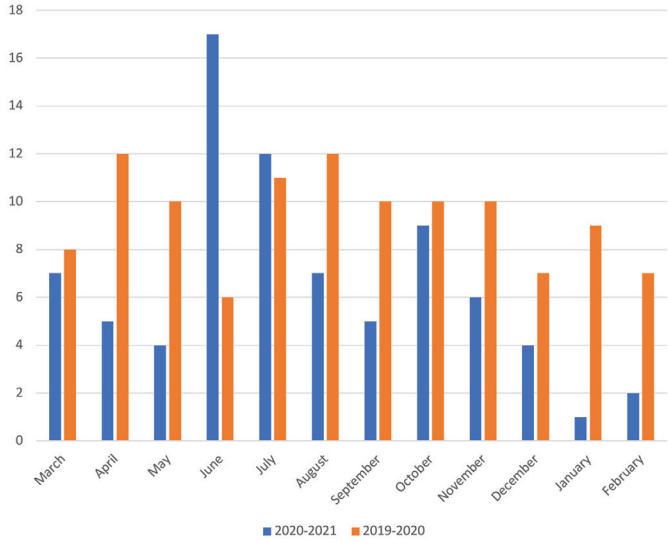

Figure 1. Monthly distribution of the late pre-pandemic period (2019-2020) and early pandemic period (2020-2021) in terms of suicide admissions

DISCUSSION

In this study comparing the clinical and sociodemographic data of patients who presented to the emergency department with suicidal thoughts or attempts during the pandemic and pre-pandemic periods, there was no increase in the rates of suicidal thoughts or attempts during the COVID-19 period. Those who attempted suicide did not differ in terms of the method, type, and severity of suicide, as well as previous psychiatric disorders. Intriguingly, the rate of men presenting with suicidal thoughts or attempts during the COVID-19 period was significantly higher than that during the pre-pandemic period. Studies conducted during the early stages of the COVID-19 pandemic indicated an increase in mental health disorders and, in line with this, an increase in suicidal thoughts or attempts due to factors like uncertainty about the disease, intense quarantine, and social isolation (16-18). However, conflicting results emerged from studies as the pandemic progressed. Some studies reported an increase in suicidal thoughts or attempts during the pandemic (19-22). Conversely, studies from different regions worldwide indicated either no increase or even a decrease in suicide-related deaths compared with pre-pandemic periods (3,6, 23-26). Variations in methodologies, study periods, and assessment methods across these studies contributed to the divergent findings. A meta-analysis published in 2023, including 45 studies, reported no increase in completed suicides during the pandemic, but an increase in suicidal thoughts or attempts (6). However, in our study,

Table 1. Sociodemographic characteristics of patients

	Pre-pandemic period (n=185)	Pandemic period (n=150)	X^2	p
Gender				
Male	62 (33.5%)	72 (48%)	7.243	**0.007***
Female	123 (66.5%)	78 (52%)		
Education level				
8<years	30 (22.9%)	24 (20.5%)	0.207	0.649
8≥ years	101 (77.1%)	93 (79.5%)		
Marital status				
Single	99 (53.5%)	80 (53.3%)	0.039	0.981
Married	59 (31.9%)	47 (31.3%)		
Divorced/widowed	27 (14.6%)	23 (15.3%)		
Employment				
Employed	83 (44.9%)	54 (36%)	3.2857	0.167
Unemployed/retired	67 (36.2%)	69 (46%)		
Student	35 (18.9%)	27 (18%)		
Living conditions				
Alone	32 (17.3%)	17 (11.3%)	2.359	0.125
With family/friends	153 (82.7%)	133 (88.7%)		

*p<0.05

Table 2. Clinical characteristics of patients

	Pre-pandemic period	Pandemic period	X^2	p
Admission type (n=185/150)				
Suicidal thoughts	37 (20%)	28 (18.7%)	0.094	0.759
Suicide attempt	148 (80%)	122 (81.3%)		
Suicide method (n=148/122)				
Lethal (hanging, jumping, gun-shot)	10 (6.8%)	8 (6.6%)	0.004	0.948
Nonlethal (intoxication, basic cutting)	138 (93.2%)	114 (93.4%)		
Type of suicide (n=148/122)				
Impulsive	125 (84.5%)	108 (88.5%)	0.9345	0.334
Planned	23 (15.5%)	14 (11.5%)		
Alcohol use during suicide attempt (n=146/117)	29 (19.9%)	25 (21.4%)	0.0901	0.764
Lifetime psychiatric diagnosis (n=185/150)	107 (57.8%)	94 (62.7%)	0.805	0.370
Type of psychiatric diagnoses (n=107/94)				
Mood disorders	72 (67.3%)	47 (50%)		
Psychotic disorders	14 (13.1%)	17 (18.1%)		
Alcohol and substance use disorders	5 (4.7%)	9 (9.6%)	7.5427	0.110
Anxiety disorders				
Others (personality disorders, dissociative disorders, etc)	11 (10.3%)	11 (11.7%)		
	5 (4.7%)	10 (10.6%)		

*p<0.05

we did not observe an increase in suicidal thoughts or attempts during the pandemic compared with the pre-pandemic period. Another study from our country showed no difference in emergency applications due to suicide attempts between the first six months after the pandemic and the same months of the previous year (27). In our country, factors such as shifted or remote work might have contributed to stress reduction. Moreover, quarantine measures, increased quality time among individuals living in the same household, and heightened communication and sharing might have acted as perceived social support, potentially mitigating the increase in suicidal thoughts or attempts. The relatively limited representation of individuals from a specific geographic region in our study and the small sample size may have influenced these outcomes. During the COVID-19 period, the rates of men seeking emergency care due to suicidal thoughts or attempts were statistically higher than those during the pre-pandemic period. In the literature, suicide attempts are reported to be more common in women, whereas completed suicides are more common in men (28). Some studies conducted during the pandemic have also reported a higher risk in men (29,30). Gender roles, such as men being more inclined to hide their complaints and seeking psychiatric help less frequently, may have combined with the traumatic impact of the pandemic to increase the rates of suicidal thoughts and attempts. The COVID-19 pandemic has caused unemployment, bankruptcies, and other economic difficulties around the world (31-33). In times of economic crisis, young married men face more difficulties than women because they take on the responsibility of providing income for their families (34). Sociologist Durkheim referred to these economic turmoil-triggered suicides as anomic suicides (35). Similarly, in our study, men's feeling of being financially responsible may have contributed to their higher suicide rates. From a sociodemographic perspective, most cases seeking help due to suicidal thoughts or attempts during both the pandemic and pre-pandemic periods were predominantly between the ages of 18-40, single, and most of them lived with their families or friends in our study. Generally, suicide attempts are reported to be more frequent among individuals aged 18-24, single, and living alone (28). During the pandemic, single individuals had a higher tendency tfor suicidal thoughts or attempts (36). Contrary to the literature, in our study, cases admitted with suicidal thoughts or attempts lived alone at a lower rate in both of the two periods. This situation could be attributed to the high prevalence of living with family despite being single in our country. Regarding employment status, although not statistically significant, a higher proportion of unemployed individuals was obtained among cases presenting with suicidal thoughts or attempts during the pandemic. The literature suggests that unemployment, financial difficulties, and economic uncertainty during the pandemic have increased the risk factors of suicide (37-39). Our study supports the notion that unemployment poses a higher risk of suicidal thoughts and attempts. When examining the clinical characteristics of the cases in both periods, impulsive suicide attempts were the most common, and less lethal methods were predominantly used. A study conducted in Spain reported that cases presenting with suicide attempts used more lethal methods and required more intensive care (40). In other studies evaluating suicide methods during the pandemic, drug overdose was reported to be the most frequently used method (12,39,41). Reduced access to other suicide methods due to restrictions and the majority of unplanned attempts may have led to the use of less lethal methods such as a suicide method. In our study, most patients presenting to the emergency department because of suicidal thoughts or attempts had a known mental disorder. This finding is consistent with studies reporting that completed and attempted suicides are more common among individuals with mental disorders (42,43). On the other hand, there was a higher rate of individuals without lifetime psychiatric disorders among those who presented during the COVID-19 period, but this result did not reach statistical significance, possibly due to the inadequacy of the sample size. Although not statistically significant, the increase in the proportion of patients without previously known mental disorders is noteworthy. Many studies have reported an increase in the frequency of mental disorders during the pandemic (44,45). Moreover, restricted access to healthcare, reluctance to seek hospital care due to quarantine measures, or fear of infection might have led to the inability of individuals to receive mental health assistance, contributing to an increase in suicidal thoughts and attempts. It is well known that depression is the most common mental disorder associated with suicide (46). In our study, depression was the most frequent mental disorder in both groups. Although not statistically significant, during the pandemic period, more cases were diagnosed with alcohol and substance use, psychosis, and other mental disorders. During the pandemic, restricted access to healthcare services, especially for patients with psychotic disorders, may have resulted in untreated conditions, disease relapse, and subsequent increases in suicidal thoughts and attempts. In a study comparing the six months since the beginning of the pandemic in Türkiye with the same months of the previous year, the most frequent psychiatric emergency applications were in June, July, and August 2020 (27). In our study, the most common emergency cases for suicidality occurred in June and then in July during a similar period. This result may have been influenced by the implementation of strict lockdown rules in our country in the first three months from the beginning of the pandemic and the fact that there was a common external threat for the entire society, such as the risk of contagion. Similarly, studies in different countries have shown a decrease in the suicide rate compared to previous years in the first three months when the lockdown policy was widespread (47-49). Moreover, previous studies have reported a decline followed by a delayed increase in suicide rates after national disasters, including Hurricane Katrina in 2005 or the September 11 terrorist attack in 2001. The initial drop is referred to as the pulling-together or honeymoon effect (50,51). The subsequent relaxation of lockdown rules and increased stress due to the ongoing risk of the pandemic and financial problems may have led to an increase in applications for suicidal thoughts or attempts. The literature suggests that unemployment, financial difficulties, and economic uncertainty during the pandemic have increased the risk factors of suicide (37-39). On the other hand, despite the partial reduction of lockdown rules, the continuation of stay-at-home and social isolation practices may have increased domestic violence, which may have led to an increase in the tendency to commit suicide. Various studies support this statement regarding the relationship between domestic violence and the pandemic (52-54).

Study Limitations

Our study has several limitations. The retrospective design and single-center nature of the study are the most significant limitations. Not assessing past suicidal thoughts or attempts and completed suicide rates in the study is another limitation. However, although this represents a small sample size, being the first study to compare suicidal thoughts or attempts before and during the pandemic period in our country adds value to the findings.

CONCLUSION

Suicide is a significant public health concern, both in our country and around the world. Situations like pandemics, wars, and natural disasters can create societal trauma, leading to an increase in mental disorders and associated suicide rates. The mental, physical, and social impacts of the pandemic should be assessed in this context, and necessary precautions and interventions should be planned. There is a need for more comprehensive studies in this field in Türkiye.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Gazi University Ethics Committee (approval number: 202-002, date: 21.12.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: B.K., Design: B.K., M.Ü., Supervision: S.C., Resources: B.K., Data Collection or Processing: H.G., B.Ü., H.C.S., Analysis or Interpretation: B.K., M.Ü., Literature Search: B.K., M.Ü., Writing: B.K., M.Ü., H.G., Critical Review: B.K., H.C.S., S.C.

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Decoding the Prognostic Significance of Lymphadenectomy Extent in Esophageal Cancer: A Navigational Study

Özofagus Kanserinde Lenfadenektomi Genişliğinin Prognostik Etkisinin Çözümlenmesi: Bir Yönlendirici Çalışma

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ABSTRACT

Objective: Esophageal cancer lacks a standard surgical approach, and opinions differ regarding the extent of lymphadenectomy. This study aimed to assess the correlation between the extent of lymphadenectomy, patient and tumor characteristics, and survival of esophageal cancer.

Methods: Data of 101 patients who underwent surgery for esophageal cancer between 1990 and 2022 were retrospectively analyzed. The mean survival and 1, 3, 5, and 10 year overall survival (OS) rates were examined. Overall survival rates for adenocarcinoma and squamous cell carcinoma were separately evaluated. The relationships among gender, age, tumor size, stage, total number of harvested lymph nodes, and survival were analyzed.

Results: Among 101 patients, 34 (33.7%) were female, and 67 (66.3%) were male, with a mean age of 61.01±12.01 years. Among the included patients, 82 (81.2%) had squamous cell carcinoma and 16 (15.8%) had adenocarcinoma. The mean follow-up was 61.2 months, and the OS averaged 61.01±12.01 months. Only the total harvested lymph node count had a statistically significant impact on survival (p=0.17).

Conclusion: There was a clear association between the total number of harvested lymph nodes and OS. In squamous cell cancers, the extent of lymph node dissection improves long-term survival. However, the routine use of extended lymphadenectomy for distal cancer remains a topic of debate.

Keywords: Esophageal cancer, lymphadenectomy, survival

ÖZ

Amaç: Özofagus kanserinde halen standart bir cerrahi yaklaşım mevcut olmayıp özellikle lenfadenektomi genişliği konusunda farklı görüşler mevcuttur. Bu çalışmada lefadenektomi genişliği ile hasta ve tümör karakteristikleri arasındaki ilişkinin ve sağkalıma etkisinin incelenmesi amaçlanmıştır.

Yöntemler: 1990 ile 2022 yılları arasında özofagus kanseri nedeni ile cerrahi uygulanan 101 hastanın verileri retrospektif olarak analiz edildi. Serideki ortalama sağkalım, 1, 3, 5, ve 10 yıllık genel sağkalım (GS) oranları incelendi. Ayrıca GS adenokarsinom ve skuamöz hücreli karsinom grupları için ayrı ayrı değerlendirildi. Cinsiyet, yaş, tümör boyutu, evre, toplam çıkarılan lenf nodu sayısı ile sağkalım arasındaki ilişki analiz edildi.

Bulgular: Yüz bir hastanın 34'ü (%33,7) kadın, 67'si (%66,3) erkekti. Ortalama yaş 61,01±12,01 idi. Hastalardan 82'si (%81,2) skuamöz hücreli karsinom, 16'sı (%15,8) adenokarsinom tanısına sahipti. Ortalama takip süresi 61,2 ay, GS ortalaması 59,2±42,12 aydı. Sadece toplam çıkarılan lenf nodu sayısının sağkalım üzerinde istatistiksel olarak anlamlı bir etki gösterdiği görüldü (p=0,17).

Sonuç: Toplam çıkarılan lenf nodu sayısı ile GS arasında net bir ilişki bulunmaktadır. Skuamöz hücreli kanserlerde, genişletilmiş lenfadenektomi uzun vadeli sağkalımı arttırır. Ancak, distal yerleşimli kanserlerde genişletilmiş lenfadenektominin rutin uygulanması halen tartışmalıdır.

Anahtar Sözcükler: Özofagus kanseri, lenfadenektomi, sağkalım

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INTRODUCTION

Esophageal cancer is characterized by its aggressive nature and high metastatic potential. Although the most prevalent histopathological type is squamous cell carcinoma, a remarkable increase in adenocarcinoma incidence, particularly in Western countries, has been observed over the past few decades (1-3). Despite surgery being the primary treatment, the overall 5-year survival rate varying between 15% and 25% has prompted a search for approaches to enhance treatment efficacy in esophageal cancer. However, there is still no standard algorithm for approaching esophageal cancer patients (4). Particularly, there are differences in opinion regarding surgical strategies and the extent of lymphadenectomy between Eastern and Western countries (5). Although neoadjuvant and/or adjuvant treatment regimens have been developed with the aim of improving prognosis, enhancing surgical procedures remains the ultimate goal. For patients with resectable non-metastatic cancer, radical en-bloc esophagectomy has been the standard treatment for many years (6). The combination of this approach with extended lymphadenectomy has generated conflicting views among Western and Eastern surgeons regarding its contribution to survival (3,5,7,8). Concerns regarding increased morbidity and mortality have led to a cautious approach toward the adoption of three-field lymphatic dissection in Western countries. However, Japanese researchers have reported significant survival advantages, and this strategy has been widely adopted as the standard for squamous cell carcinomas (9,10). According to the research conducted by Isono et al. (11) it was found that after radical en-bloc resection in thoracic esophageal cancers, the recurrence rate is significantly high in the upper mediastinal and cervical lymph nodes. The dissection of upper mediastinal, recurrent nerve, and neck lymph nodes reduces the recurrence rate and significantly increases survival (11). Kato et al. (12) reported that in transhiatal esophagectomy, metastatic lymph nodes can be left behind, leading to a recurrence rate of 50% in patients with pT1 cancer. These results have led to the adoption of radical esophagectomy, including three-field lymph node dissection, as the standard curative surgical approach for Japanese esophageal cancer treatment. Histopathology is a significant factor affecting survival in esophageal cancer. The extent of lymphadenectomy may vary according to the two common histopathological types (4). Lymph node status is a key determinant of survival. However, there are different opinions regarding the minimum number of lymph nodes that should be dissected for ideal treatment and staging (13). For node-negative squamous cell cancers, 5 year overall survival (OS) after surgery is reported to be 58%, whereas it decreases to 15.9% in cases with two or more lymph node metastases (14). The aim of this study was to evaluate the prognostic impact of lymphadenectomy extent in patients undergoing surgical treatment for esophageal cancer and to examine patient, tumor, and surgery-related factors influencing survival. The results are intended to provide guidance for determining the surgical approach and extent of lymphadenectomy in patients with resectable non-metastatic esophageal cancer.

MATERIALS AND METHODS

Between December 1990 and December 2022, data on patients who underwent surgery for esophageal cancer were retrospectively collected through the hospital information management system and patient files. The inclusion criteria for the study were as follows: (1) histopathological diagnosis of esophageal cancer preoperatively, (2) preoperative assessment confirming resectable and non-metastatic cancer, (3) surgeries performed by the same surgical team. The exclusion criteria were: (1) benign histopathology and (2) inability to access patient data. The study encompasses a prolonged timeframe during which all patients in the series underwent surgery performed by a senior surgeon who served as team leader throughout the entire period. Throughout this entire period, there has been no major change in the surgical technique of esophagectomy and lymphadenectomy; only technological advancements have been integrated into these procedures. The study cohort consists of a group of patients who underwent standard extended lymphadenectomy. All procedures in this study were carried out following the ethical standards of the institutional and/or national research committee, as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the local Gazi University Clinical Research Ethics Committee (approval number: 643, date: 31.07.2023). The demographic characteristics (age and gender), tumor localization (upper, middle, and lower), organ used for reconstruction, pyloric drainage status (piloroplasty, pyloromyotomy, or no drainage procedure), jejunostomy for nutrition, chemotherapy, and radiotherapy (neoadjuvant and/or adjuvant), early and late complications, mortality, histopathology results, differentiation, tumor diameter, total number of removed lymph nodes, number of metastatic lymph nodes, postoperative stage, and follow-up duration were recorded. The average survival (months) in the series and the 1, 3, 5, and 10 year OS rates were calculated. The OS rates of the adenocarcinoma and squamous cell carcinoma groups were evaluated separately. The relationship between gender, age, tumor diameter, stage, and total number of removed lymph nodes and survival was analyzed. All data were transferred to a computer environment, and SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Categorical measurements were presented as numbers and percentages, while continuous measurements were presented as mean, standard deviation, and range. The Kaplan-Meier estimator was used for survival analysis according to stage and histopathology type. Cox regression analysis was used to evaluate factors associated with OS. In all statistical analyses, $p<0.05$ value was set as statistically significant.

RESULTS

Among the 101 patients, 34 (33.7%) were female and 67 (66.3%) were male. The mean age of the patients was 61.01±12.01 years (range, 27-82). Tumors were localized in the upper esophagus in 6 patients (5.9%), middle esophagus in 57 patients (56.4%), and lower esophagus in 38 patients (37.6%). The histopathological results showed that 82 patients had squamous cell carcinoma (81.2%), 16 patients had adenocarcinoma (15.8%), 1 patient had both squamous cell carcinoma and leiomyosarcoma (1%), 1 patient had malignant melanoma (1%), and 1 patient had neuroendocrine tumor (1%). Upon examination of differentiation, 19 patients (19%) were poorly differentiated, 36 patients (36%) were moderately differentiated, 42 patients (42%) were well-differentiated, 2 patients (2%) were undifferentiated, and 1 patient (1%) was poorly differentiated. All adenocarcinomas were localized in the lower esophagus, as

expected. Among the squamous cell cancers, 5 (6.1%) were localized in the upper esophagus, 57 (69.5%) in the middle esophagus, and 20 (24.4%) in the lower esophagus. Regarding the organs used for reconstruction, 96 patients (95%) received a stomach, 3 patients (3%) received a jejunum, and 2 patients (2%) received the left colon. One patient (1%) underwent total gastrectomy. Pyloromyotomy and pyloroplasty were performed in 2 patients (2%), while pyloroplasty was performed in 96 patients (95%). Two patients (2%) did not undergo pyloric drainage. Jejunostomy for nutrition was performed in 71 patients (70.3%), but not in 30 patients (29.7%). Three patients (3%) received neoadjuvant chemotherapy, while 57 patients (56.4%) received adjuvant chemotherapy. Forty one patients (40.6%) did not receive any chemotherapy. Three patients (3%) received neoadjuvant radiotherapy, while 43 patients (42.6%) received adjuvant radiotherapy. Fifty five patients (54.5%) did not receive radiotherapy. Three patients who received neoadjuvant chemotherapy also received neoadjuvant radiotherapy. Consequently, the number of patients in the series who underwent neoadjuvant chemoradiation was limited to only 3 (3%). All of these patients have a diagnosis of squamous cell carcinoma, and the tumor was located in the upper esophagus.

Early postoperative complications were observed in 65 patients (64.4%), and late complications were observed in 14 patients (13.7%). The details of early and late complications are presented in Table 1. The perioperative mortality rate (within the first 30 days) was 2 patients (2%). One patient died on postoperative day 7 due to pneumonia and acute respiratory distress syndrome, while the other patient died on postoperative day 28 due to a cervical fistula and kidney failure. The mean tumor diameter was 4.62±1.57 cm (range, 0.6-9.5). The mean number of harvested lymph nodes was 62.2±27.81 (range, 9-138), and the mean number of metastatic lymph nodes was 2.14±6.25 (range, 0-58). For patients with adenocarcinoma, the mean number of harvested lymph nodes was 48.88±14.02 (range, 29-80), and the mean number of metastatic lymph nodes was 6.25±14.42 (range, 0-58). For patients with squamous cell carcinoma, the mean number of harvested lymph nodes was 65.41±29.33 (range, 9-138), and the mean number of metastatic lymph nodes was 1.22±1.78 (range, 0-7). The tumor characteristics of the two groups are presented in Table 2. Among patients with distal esophageal cancer who underwent three-field lymph node dissection, none had positive cervical lymph nodes. Staging was performed according to the current American Joint Committee on Cancer Staging System (8th edition staging esophagus and esophagogastric junction). According to postoperative staging, 21 patients (20.8%) were classified as stage 1, 36 patients (35.7%) as stage 2, 43 patients (42.6%) as stage 3, and 1 patient (1%) as stage 4. The distribution of patients according to disease stage is detailed in Table 3. The OS in the series was determined to be an mean of 59.2±42.12 months (range, 0-240). The median survival times for stages 1, 2, and 3 were 60, 60, and 59 months, respectively. The mean follow-up duration was 61.2 months (range, 0-244).

The 1, 3, 5, and 10 year OS rates in this series were 90.9%, 71.7%, 54.8%, and 16.7%, respectively. The 1, 3, and 5 year survival rates according to stages are presented in Table 4. The 1, 3, 5, and 10 year survival rates for the two main histopathological groups (adenocarcinoma and squamous cell carcinoma) are also presented in Table 4. The relationship between sex, age, tumor size, stage, total harvested lymph node count, and survival was examined, and only the total number of harvested lymph nodes showed a statistically significant effect on survival (p=0.17) [odds ratio=0.989, 95% confidence interval=0.980-0.998] (Table 5).

Table 1. Early and late complications after esophagectomy

Early complications	**Number (n)**	**Percentage (%)**
Pneumonia	34	52.3
Pneumonia + pneumothorax	1	1.5
Pneumonia + leakage	2	3.1
Pneumonia + fistula	3	4.7
Pneumonia + left vocal cord paralysis	4	6.2
Left vocal cord paralysis	1	1.5
Cervical leakage	2	3.1
Cervical bleeding	1	1.5
Trachea injury	2	3.1
Pneumothorax	1	1.5
Fistula	10	15.5
Wound infection	1	1.5
Lymphatic leak	1	1.5
Lymphatic leak + left vocal cord paralysis	1	1.5
Transient stenosis	1	1.5
Total	65	100
Late complications	**Number (n)**	**Percentage (%)**
Stenosis	10	71.4
Fistula	2	14.3
Pneumonia	2	14.3
Total	**14**	**100**

Table 2. Characteristics of patients with adenocarcinoma and squamous cell carcinoma

Characteristics	**Squamous cell carcinoma (n=82) (mean ± SD) (range)**	**Adenocarcinoma (n=16) (mean ± SD) (range)**
Age (year)	60.5±0.48 (27-81)	62.68±13.66 (38-82)
Tumor diameter (cm)	4.68±1.62 (0.6-9.5)	4.51±1.35 (2-7)
Total lymph nodes	65.41±29.33 (9-138)	48.88±14.02
Metastatic lymph node	1.22±1.78 (0-7)	6.25±14.42 (0-58)

SD: Standart deviation.

Table 3. Distribution of patients according to the stages

Stage	Number (n)	Percentage (%)
Stage IA	8	7.9
Stage IB	13	12.9
Stage IIA	5	5
Stage IIB	31	30.7
Stage IIIA	20	19.8
Stage IIIB	14	13.9
Stage IIIC	9	8.9
Stage IV	1	1.0
Total	**101**	**100**

Table 4. Overall survival by stages and histopathology

Stage	1 year survival (%)	3 year survival (%)	5 year survival (%)	Median survival (months)
Stage 1	86	81	17	60
Stage 2	86	76	13	60
Stage 3	82	63	12	59
Histopathology	**1 year survival (%)**	**3 year survival (%)**	**5 year survival (%)**	**10 year survival (%)**
Squamous cell carcinoma (n=82)	92.5	68	64.9	18.5
Adenocarcinoma (n=16)	83.3	49.2	0	0

Table 5. Regression analysis of factors affecting survival

Variable	p	OR (95% CI)
Gender	0.161	1.443 (0.864-2.411)
Age	0.165	1.014 (0.994-1.035)
Tumor diameter	0.251	0.909 (0.772-1.070)
Stage	0.095	1.145 (0.977-1.342)
Total lymph nodes	0.017	0.989 (0.980-0.998)

OR: Odds ratio, CI: Confidence intervale

DISCUSSSION

Esophageal cancer is globally known to be predominantly squamous cell carcinoma. However, in recent times, there has been a recent shift toward adenocarcinoma predominance in Northern and Western Europe, the United Kingdom, Australia, and the United States (1,3,15). In Western countries, the prevalence of distal esophageal adenocarcinoma, which is associated with gastroesophageal reflux disease and Barrett's esophagus (5). Nevertheless, globally, squamous cell carcinoma remains the dominant histopathological type in the distal esophagus. In our series, the incidence of adenocarcinoma was 15.8%, whereas squamous cell carcinoma accounted for 81.2% of cases, confirming that squamous cell carcinoma remains the dominant histopathological type in Eastern countries known as the "Asian Esophageal Cancer Belt". The sharp increase in the incidence of adenocarcinoma in Western countries has further highlighted the significance of esophageal cancer in terms of cancer-related mortality (3). The two histopathological types exhibit important differences in tumor behavior, disease-free survival, and OS. In our study, the 1, 3, and 5 year OS rates were found to be 90.9%, 71.7%, and 54.8%, respectively. Compared with the literature's reported overall 5 year survival rate of 15-25%, the rate of 54.8% can be interpreted as quite favorable (3,16). However, it is noteworthy that the OS rates differ when separately calculated for the two histopathologies. When the squamous cell carcinoma group is analyzed alone, the overall 5 year survival increases to 64.9%, whereas no patient in the adenocarcinoma group survives for 5 years. Therefore, we believe that the relative superiority of survival rates is significantly influenced by the number of squamous cell carcinoma cases in our study group (more than 5 times). OS in esophageal cancer ranges from 4% to 40%, depending on the stage (16). For early-stage squamous cell carcinomas, endoscopic treatment has been reported to achieve nearly 100% long-term survival rates (17). In our study, the 1 and 3 year OS rates were promising for different stages (1 year OS for stages 1, 2, and 3 were 86%, 86%, and 82%, respectively; 3 year OS for stages 1, 2, and 3 were 81%, 76%, and 63%, respectively). However, the 5 year survival rates were found to be low for all stages (5 year OS for stages 1, 2, and 3 were 17%, 13%, and 12%, respectively). The relatively low long-term survival rates, even in early-stage cases, are surprising. Although we could not fully demonstrate the negative impact of aggressive behavior and the tendency for lymphatic spread in adenocarcinomas, there are indications that suggest their significant contribution to these outcomes. When examining the characteristics of the adenocarcinoma and squamous cell carcinoma groups in our study, it is evident that they are quite similar in terms of age (62.68 versus 60.5 years) and mean tumor diameter (4.51 cm versus 4.68 cm). Despite the significant advantage in the mean total harvested lymph node count in the squamous cell carcinoma group (61.41 versus 48.88), the remarkably high mean number of metastatic lymph nodes in the adenocarcinoma group (6.25 versus 1.22) is striking. In esophageal cancer, achieving the optimal survival goal while balancing surgical burden and postoperative quality of life is challenging. Surgical approaches include open three-field dissection, radical esophagectomy, and minimally invasive esophagectomy (10,18,19). Despite technical advancements, high complication rates, especially anastomotic leakage, remain a significant concern (19). In Ivor Lewis esophagectomy, the incidence rate of anastomotic leakage in the mediastinum ranges from 7.71% to 15.2% (20,21). McKeown esophagectomy avoids the fatal effects of mediastinal leakage and provides advantages in terms of pulmonary infection, blood loss, resection segment length, and number of harvested lymph nodes, it has disadvantages in terms of cervical anastomotic leakage, stricture, operation time, and length of hospital stay (21).

In a study involving 17.395 patients, Connors et al. (22) reported overall morbidity and mortality rates of 50.7% and 8.8%, respectively, after esophagectomy. In our study, the early postoperative complication rate was 64.4%, and pulmonary complications were dominant. We believe that the high rate of pulmonary complications in our country may be related to the high rate of smoking and the fact that female patients remain obese despite weight loss due to cancer. In addition, the late complication rate was 13.7%, and the mortality rate was 2%. In the initial cases in our series, we did not use a feeding jejunostomy,

but the correlation between postoperative nutrition, recovery, and complication management led us to an increasing trend in using a feeding jejunostomy in later cases. The current literature supports the opening of a simultaneous feeding jejunostomy with major gastrointestinal surgeries like esophagectomy (23). In our study, the impact of gender, age, tumor size, stage, and the number of harvested lymph nodes on OS was investigated, and only the total number of harvested lymph nodes was found to be an independent factor. This result supports the notion that extended lymphadenectomy confers a survival advantage for esophageal cancer, which is particularly supported by studies originating from Asian countries. However, the lack of knowledge regarding the relationship between the extent of lymphadenectomy and morbidity does not justify the hypothesis of performing three-field dissection for every patient. Additionally, the absence of metastatic cervical lymph nodes in our series of patients with distal esophageal cancer who underwent three-field lymph node dissection raises the question of whether routine cervical lymph node dissection is necessary in these patients. A more reasonable approach would be to adopt a selective approach regarding the extent of lymphadenectomy.

Study Limitations

The most significant limitation of this study is its retrospective design. Due to the extensive time span covered by the study, the changes in the treatment strategies and their impact on the outcomes are significant. However, it should be noted that the entire series belongs to a senior surgeon in the position of team leader, and therefore, the surgical technique and dissection approach are standardized from this perspective. The positive or negative contributions of other treatments in combination with surgery are another subject of investigation. Indeed, neoadjuvant treatment may cause effects such as progression, loss of resectability, or morbidity and mortality secondary to adjuvant treatment. Some researchers have argued that the absence of involved lymph nodes after neoadjuvant chemoradiotherapy may be caused by the sterilizing effect of neoadjuvant treatment (5). Neoadjuvant chemoradiotherapy is widely recognized as a prognostic factor that influences both treatment response and survival. However, in our study, due to the limited number of patients receiving neoadjuvant chemoradiotherapy, specifically only 3 (3%), a robust statistical analysis concerning the impact of neoadjuvant treatment on survival was not feasible. Similarly, adjuvant therapies represent another perplexing limitation. The impact of adjuvant therapies on outcomes was not thoroughly examined in this study. Although these treatments have the potential to contribute positively to survival, they may also lead to treatment-related morbidity and mortality. Moreover, due to the broad time span of the study, inevitable changes in the indications and protocols for adjuvant chemotherapy are anticipated. These reasons have made it challenging to scrutinize the effects of adjuvant treatments in homogeneous subgroups.

CONCLUSION

There is a clear relationship between the total number of harvested lymph nodes and OS in esophageal cancer. In particular, three-field lymph node dissection and radical surgical approaches increase long-term survival in patients with squamous cell cancers. However, there is a debate regarding the routine use of extended lymphadenectomy in distal cancers. In esophageal cancer, which has unique anatomical, histopathological, and behavioral characteristics, the width of lymphadenectomy should be determined with a selective approach for each patient without deviating from the maximum survival target.

Ethics

Ethics Committee Approval: The study was approved by the local Gazi University Clinical Research Ethics Committee (approval number: 643, date: 31.07.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.Z.F., R.K., M.A., Design: S.Z.F., R.K., Supervision: S.Z.F., R.K., M.A., Data Collection or Processing: S.Z.F., R.K., Analysis or Interpretation: R.K., M.A., Literature Search: S.Z.F., R.K., M.A., Writing: S.Z.F., R.K., Critical Review: S.Z.F., R.K., M.A.

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The Importance of Detailed Audio-Vestibular Monitoring in Familial Non-Syndromic Hearing Losses: A Longitudinal Study

Genetik Non-sendromik İşitme Kayıplarında Kapsamlı İşitsel-Vestibüler Takibin Önemi: Boylamsal Bir Çalışma

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Objective: This study aimed to evaluate the audiological and vestibular findings of two family members with progressive sensorineural-type hearing loss at high frequencies according to age.

Methods: Pure tone audiometry, speech audiometry, and immittancemetry tests were performed for audiological evaluation of the two families participating in the study. A total of 11 volunteers were included: the mother, father, and three children from the first family; and the mother-father and four children from the second family. A videonystagmography was performed to rule out neurological diseases. A computerized dynamic posturography (CDP) was performed to evaluate postural control. Audiovestibular findings were recorded by year and analyzed using SPSS v.24. program.

Results: Sensorineural-type hearing loss, which was evident at high frequencies, was detected in all family members. A significant progressive deterioration was observed in the hearing thresholds of family members and in the CDP results over the years.

Conclusion: This study revealed that audiovestibular follow-up is essential for genetic hearing loss. The findings demonstrated the importance of follow-up and genetic counseling in terms of progressive hearing loss, even when newborns undergo hearing screening.

Keywords: Hearing loss, vestibular, genetic, gene mutation, early intervention, computerized dynamic posturography

Amaç: Bu çalışmada, yüksek frekanslarda progresif sensörinöral tip işitme kaybı olan iki aile bireylerinin yaşlara göre odyolojik ve vestibüler bulgularının değerlendirilmesi amaçlanmıştır.

Yöntemler: Çalışmaya katılan iki ailenin odyolojik değerlendirmesi için saf ses odyometrisi, konuşma odyometrisi ve immitansmetri testleri yapılmıştır. İlk aileden anne, baba ve üç çocuk; ikinci aileden anne-baba ve dört çocuk olmak üzere toplam 11 gönüllü çalışmaya dahil edilmiştir. Nörolojik hastalıkları ekarte etmek için videonistagmografi yapılmıştır. Postüral becerileri değerlendirmek için bilgisayarlı dinamik postürografi (CDP) yapılmıştır. Odyostestibüler bulgular yıllara göre kaydedilmiş ve SPSS v.24. programı kullanılarak analiz edilmiştir.

Bulgular: Tüm aile bireylerinde yüksek frekanslarda düşüş gösteren sensörinöral tip işitme kaybı tespit edilmiştir. Aile bireylerinin işitme eşiklerinde ve CDP sonuçlarında yıllar içinde belirgin progresif bir düşüş gözlenmiştir.

Sonuç: Bu çalışma, odyovestibüler takibin genetik işitme kaybı için önemli olduğunu ortaya koymuştur. Yenidoğan işitme taramasından geçilse bile progresif işitme kaybı açısından takibin ve genetik danışmanlığın önemi ortaya konmuştur.

Anahtar Sözcükler: İşitme kaybı, vestibüler, genetik, gen mutasyonu, erken müdahale, bilgisayarlı dinamik postürografi

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INTRODUCTION

Many studies on genetics and hearing have revealed that more than 95 genes are associated with non-syndromic hearing loss (1). Congenital hearing loss is a common problem affecting approximately 12 out of 1000 live births. Hereditary forms of hearing loss can be viewed as syndromic, with other additional concerns, or as non-syndromic forms (causing only hearing loss). Some epidemiological studies on this issue have indicated that approximately 50% of congenital hearing losses are genetic hearing losses (2,3). Approximately 20% of non-syndromic sensorineural hearing loss cases are autosomal dominant (DFN-A). This type of hearing loss usually has a delayed onset. Approximately 80% of non-syndromic sensorineural hearing loss cases are autosomal recessive (DFN-B), which is usually congenital, but some forms may occur later in life (4). Until now, a total of 125 deafness (DFN) mutations have been described in the literature, including 58 DFN-A loci and 63 DFN-B loci (4,5). Several genes play a role in many inner ear functions, such as hair cell movement, hair cell stimulation, intracellular transport, neurotransmitter release, and ionic homeostasis. The physiology and structure of the inner ear are more unique than those of other anatomical regions and are encoded by many genes. Some mutations in these related genes can result in sensorineural hearing loss (6-8). A number of studies have investigated the impact of genetic mutations on vestibular function (9-11). In individuals with *DFN* gene mutations, it has been reported that vestibular functions, as well as hearing performance, are adversely affected (9,10). In particular, in certain gene mutations, such as DFN-1, substantial loss of Scarpa ganglion cells can negatively affect the functions of vestibular cells (9). The close relationship between genetics and hearing loss has been a subject of interest for researchers for years. A review study showed that hearing loss affecting the inner ear is observed in people diagnosed with *DFN* gene mutations (2). A study on immigrants suggested that the Connexin protein, which is related to the *DFN* gene, causes congenital hearing loss (12). Genetic analysis of children with hearing loss born between certain years was performed, and hearing loss was observed in another study conducted in collaboration with the neonatal unit (13). A longitudinal analysis of hearing loss in a Dutch family revealed that mutations linked to the DFNA20/26 locus cause DFN-A sensorineural hearing loss (14). A longitudinal study of highly variable hearing loss due to POU4F3 (c.37del) across decades found early-onset and slowly worsening hearing loss (15). Many studies have been based on different loci regarding the characteristics and progression of *DFNA* genetically inherited sensorineural hearing loss (16,17). Some studies on audiological phenotype and progression have shown that *DFNA* gene mutations cause sensorineural and progressive hearing loss (18,19). Moreover, limited studies have been conducted on the vestibular skills of individuals with DFN-A inherited sensorineural hearing loss (10,20). The primary purpose of the current study was to present a longitudinal analysis of the audiological profile and vestibular skills of members of two families with *DFN* genetic hearing loss over the 5-year period. It is assumed that the current study will significantly contribute to the literature by evaluating vestibular performance along with the audiological phenotype and by following up the cases of two families for 5 years. To the authors' best knowledge, the current study may be helpful in counseling parents and their children regarding the prognosis of hearing loss, predicting recurrence in future children, and determining audiological intervention options.

MATERIALS AND METHODS

The Gazi University Rectorate Ethics Commission (approval number: 15, date: 05.09.2023). First, informed consent forms were obtained from the participants.

Participants

Two volunteer families with genetic hearing loss compatible with *DFN* gene transfer were included in the present study. A total of 11 volunteers were included: the mother, father, and three children from the first family; and the mother-father and four children from the second family. The audiological findings of the family members were followed at almost 1-year intervals for 4 years (three measurements). The vestibular results of the family members were also followed at nearly 1 year intervals for 5 years (four measurements). The socioeconomic and educational levels of families are moderate. The hearing aid use ranged from 2 to 3 years. In addition, all participants received limited benefit from hearing aids and did not use them regularly despite optimum fitting practices. The newborn hearing screening results of only two children and parents with hearing loss were unknown; the other children passed. The demographic characteristics of the volunteer family members are presented in Table 1.

Methods

The study design is longitudinal. The volunteer family members with genetic hearing loss were evaluated by air conduction and bone conduction hearing thresholds, speech recognition score, and uncomfortable sound separately for the right and left ears. The octave frequencies between 125 and 8000 Hz were examined using pure-tone audiometry. Pure tone hearing thresholds and speech audiometry were evaluated with supra-aural headphones, a B71 bone vibrator, and a GSI audiometer by a single researcher in a quiet-insulated cabin. The average pure-tone hearing thresholds (21) were taken as the mean air-conduction hearing thresholds at 500, 1000, 2000, and 4000 Hz (22). All volunteers were diagnosed with sensorineural hearing loss; no air-bone gap was detected in their hearing thresholds. In addition, a difference of at most 10 dB HL was observed between the right and left ears in terms of the average pure-tone hearing thresholds, and the volunteers' hearing losses were found to be symmetrical. Also, the MRI findings of all participants were reported as normal. The speech recognition test was performed using supra-aural headphones with a standard three-syllable word list (22). Although the volunteers did not complain of vertigo, they did complain of dizziness and imbalance. On the other hand, computerized dynamic posturography (CDP) and videonystagmography (VNG) tests were used to evaluate the vestibular skills of participants with hearing loss. The VNG ensures that clinicians can track and record eye movements in real-time. Eye movements were measured and analyzed using computer software and a video monitor. VNG refers to the center of the pupils, and the components of horizontal and vertical eye flicker were recorded in this study (23,24). VNG was used to rule out central vestibular pathologies. Since the VNG findings were not directly related to the study hypotheses, they were not analyzed in detail, and the

Table 1. Demographic information

CASES		Age	G	NHS	IHLC	MRI/CT (Cochlear/nerve anomalies)	HA	V/D
F-1	F1S1	13	F	P	Three years ago	N	One year	No
	F1S2	19	F	P	Five or six years ago	N	Two years	D
	F1S3	24	M	Unknown	Six or seven years ago	N	Two years	V/D
	F1F	59	M	Unknown	Since ten years old	N	Twenty years	V/D
	F1M	55	F	Unknown	No	Unknown	No	No
F-2	F2S1	12	M	P	Three years ago	N	Five years	No
	F2S2	13	F	P	Three or four years ago	N	Three years	No
	F2S3	17	F	P	Seven years ago	N	Three years	D
	F2S4	19	F	Unknown	Since eight years old	N	Three years	V/D
	F2M	44	F	Unknown	Since twelve or thirteen years old	N	No	V/D
	F2F	42	M	Unknown	No	Unknown	No	No

G: Gender, NHS: Newborn hearing screening, IHLC: Initial of hearing loss complaints, MRI: Magnetic resonance imaging, CT: Computer tomography, HA: Hearing aids, V: Vertigo, D: Dizziness, F-1: First family, F-2: Second family, S1: First sibling, S2: Second sibling, S3: Third sibling, S4: Fourth sibling, F1M: Mother in the first family, F2M: Mother in the second family, F1F: Father in the first family, F2F: Father in the second family, F: Female, M: Male, P: Pass, N: Normal

findings of all participants were obtained at normal reference values. The volunteers were invited to the clinic for their baseline vestibular assessment, where they underwent sensory organization testing (25) using the dynamic posturography system. The SOT test comprises six conditions, each performed in two replicates. These conditions are as follows: 1) eyes open, fixed visuality, and surface 2) eyes closed, fixed surface 3) eyes open, moving visual environment, and fixed surface 4) eyes open, fixed visual environment, and moving surface 5) eyes closed, moving surface 6) eyes open, moving visual environment, and moving surface. The CDP software calculates the scores for each condition and the composite score. During the posturography test, volunteers were supported with a seat belt as a precaution against falling (26,27). Accordingly, the VNG values of all the volunteers were normal with regard to the central vestibular system pathologies.

Statistical Analysis

The case data are presented as descriptive statistics. Descriptive statistics are presented as mean and direct numerical values. The averages of the siblings in each family were calculated to show the change in audiovestibular values over time. However, parental values with and without hearing loss were not included in the average and were presented separately in the graphs. While three measurements (1^{st}: First measurement, 2^{nd}: First-year measurement, 3^{rd}: Fourth year measurement) were used for pure tone audiometry thresholds, four measurements (1^{st}: First measurement, 2^{nd}: First-year measurement, 3^{rd}: third-year measurement, 4^{th}: fifth-year measurement) were used for vestibular evaluation.

RESULTS

The results of the study are presented according to progressive data and the results of each individual. Table 1 shows details about age, gender, newborn hearing screening, initial hearing loss, anomalies of the cochlear and/or acoustic nerve, duration of using hearing aids, and complaints related to vertigo and/or dizziness for a total of 11 individuals in both families. Most newborn hearing screenings were "pass" for hearing loss, and concerns about hearing loss in both families began in the post-lingual (>six age) period. Furthermore, no cochlear or nerve abnormalities were discovered based on the MRI and CT scan results.

Figure 1 shows an alteration in the individuals' pure-tone audiometry thresholds between 0.125 and 8 kHz for both families. The average of the mother's and father's hearing thresholds from the three measurements are shown separately in both graphs. The siblings' hearing thresholds at all frequencies were averaged and presented as three different measurements. As observed in both families, thresholds decreased at 1 kHz; however, this pattern was apparent in the second family. Observing the mother's threshold in the second family and the father's threshold in the first, it is found that while both thresholds of the mother and father were comparable to those of their siblings, the mother's threshold had more notable drops in the middle frequencies in the first family. Furthermore, Table 2 presents the average thresholds between 0.5-4 kHz and speech audiometry (speech recognition threshold, speech discrimination (SD), and loudness discomfort level) information about each member of the families. In relation to these findings, significant declines in SD scores were noted in conjunction with hearing progression in both families. The CDP results for general vestibular system functions are presented in Table 2. Figure 2 also shows the variation in the CDP SOT findings for the parents and siblings in both families according to the four measurements. Likewise, according to audiological data, the vestibular results differ by years and between family members. Proprioceptive and composite scores showed progression, particularly in vestibular scores, but somatosensory and visual scores showed no change. Figure 2 shows the average number of children, with the progression over time highlighted. However, the vestibular scores of each individual are presented in Table 2.

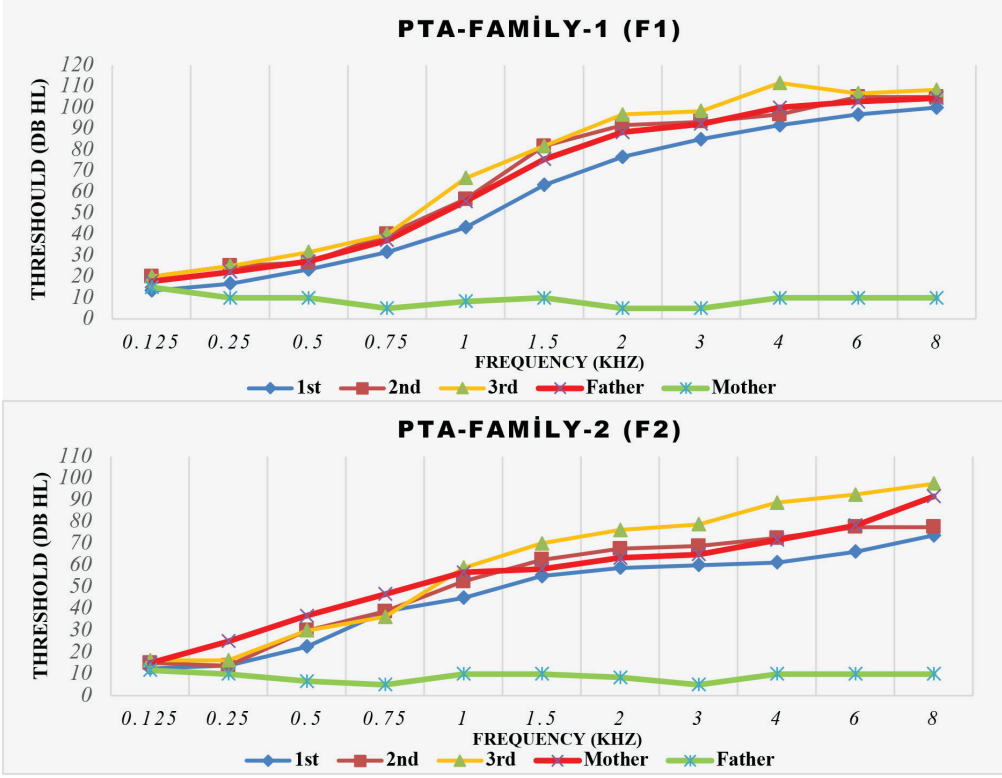

Figure 1. Pure tone audiometry hearing thresholds between 0.125-8 kHz of individuals in two families

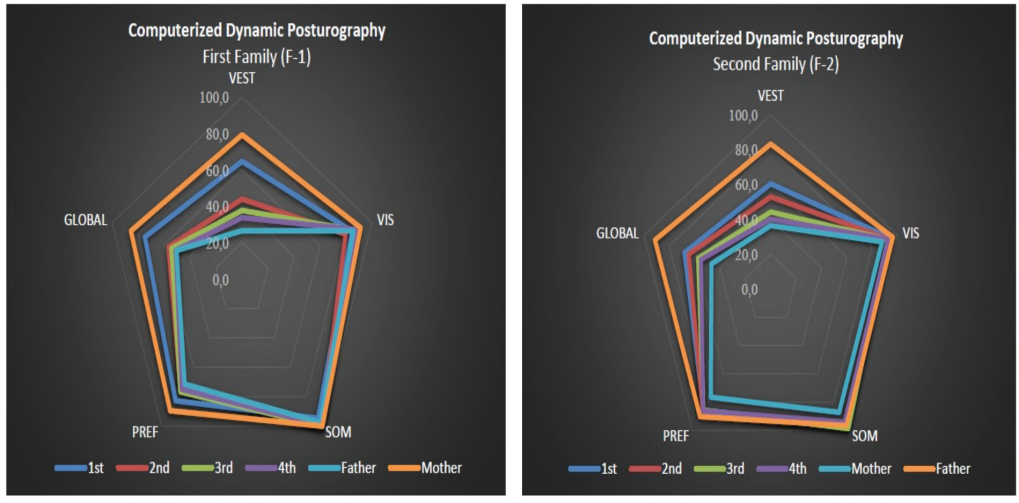

Figure 2. Computerized dynamic posturography sensory organization Test findings of families

DISCUSSION

This study examined post-lingual progressive sensorineural hearing loss with high-frequency slopeing longitudinally in two families with *DFN* gene mutations. In addition, follow-up data on the participants' vestibular performance were also presented. Although the genetic factors related to hearing are not fully understood, studies on this subject have been ongoing for 26 years. As in every disease group, a detailed evaluation of hearing is critical in the presence of genetic hearing loss. Although clinics have different practices in the assessment of genetic hearing loss, pure tone audiometry, tympanometry, otoacoustic emission, and auditory brainstem response are frequently used audiological evaluation tools in routine (28,29). The current study similarly evaluated participants longitudinally using pure tone audiometry, speech audiometry, immitanmetry, and vestibular tests. Accordingly, progressive and

Table 2. The average 0.5-4 kHz pure tone audiometry thresholds of individuals in both families, speech audiometry results, and sensory organization test results in computerized dynamic posturography

Cases		Audiometry				CDP				
		PTA dB	SRT dB	SD	LDL dB	SOM	PREF	VIS	VES	CS
F-1	S1	62.50	70	24	90	100	80	94	40	59
	S2	75	65	12	85	100	75	80	41	54
	S3	75	75	8	80	98	70	90	20	40
	F	75	95	0	80	90	64	85	20	41
	M	8.50	10	100	100	100	90	95	80	88
F-2	S1	67.50	50	70	100	97	85	88	35	52
	S2	56.25	35	52	90	100	82	96	51	57
	S3	67.75	45	50	90	90	88	96	25	49
	S4	60.75	45	60	85	90	90	90	50	62
	M	68.75	45	34	80	86	81	89	30	40
	F	8.75	10	100	100	92	91	94	90	94

CDP: Computerized dynamic posturography, PTA: Pure tone audiometry threshold (dB), SRT: Speech recognition threshold (dB), LDL: Loudness discomfort level (dB), SOM: Somatosensory score, VIS: Vısual score, HA: Hearing aids, V: Vertigo, D: Dizziness, F-1: First family, F-2: Second family, S1: First sibling, S2: Second sibling, S3: Third sibling, S4: Fourth sibling, M: Mother, F: Father, SD: Speech discrimination

low-frequency sensorineural-type hearing loss in the participants is similar to other genetically inherited non-syndromic hearing loss studies (30,31). It is known that genes related to hearing, such as *GJB2, GJB6, TECTA, POU3F4,* and *MYO7A*, play a role in many areas, such as forming the tectorial membrane in the inner ear, controlling neurotransmitter release, and coding transmembrane proteins, etc (30,32-36). Therefore, obtaining postlingual, progressive, sensorineural-type hearing loss, as in our current study, is compatible with this physiological function of the genes in the inner ear. Negative effects on the cochlea and related proteins lead to sensorineural-type hearing loss.

Another study investigating hearing loss transmitted by *DFNA41* gene mutation longitudinally revealed progressive bilateral postlingual hearing loss, but reported gender differences, and the age at onset of hearing loss was between 25 and 35 years of age (37). The current study differs in that there were no significant gender differences in the audiovestibular findings and the age at onset of hearing loss. This may be due to the effects of different gene loci. In a study conducted on twins (38), it was emphasized that there was more interference in the high-frequency region, similar to the current findings. This may be because proteins located in the basal region of the cochlea are more susceptible to mutation. In addition, hearing deterioration, starting first in the high-frequency region (6 kHz, 8 kHz), can be a key indicator in the diagnosis of genetic hearing loss. These findings demonstrate the importance of monitoring high-frequency hearing thresholds in the general population (38,39). This approach may enable earlier recognition and rehabilitation of hearing loss. Similar to our current study, another study presented a profile of the genetic etiology of hearing loss in families with hearing loss. The five most common hearing loss genes are *SLC26A4, MYO7A, GJB2, CIB2,* and *HGF,* respectively (36,40). There should be more studies on genetic hearing loss, including the current study. Genetic screenings and counseling services are essential for the early diagnosis and treatment of hearing loss (29,41,42). Because genetic hearing loss is progressive, this study demonstrates the importance of monitoring patients for genetic hearing loss even if they pass the newborn hearing screening. On the other hand, to the best of the authors' knowledge, there are limited studies (43,44) investigating vestibular skills in people with genetic hearing loss. The possible reason for this may be that the mutation in the relevant gene also affects the vestibular pathways. Vestibular diseases may also occur due to genetic congenital hearing loss and inner ear anomalies (44). Due to the limited number of studies investigating vestibular progression in genetic hearing loss, there are limitations in interpreting the findings (45). On the other hand, assuming that hearing is one of the senses that provide postural control, hearing loss is an expected explanation for the current worse posturography results. Additionally, according to the authors, this study significantly contributes to the literature by revealing progressive vestibular deterioration. One of the strengths of the current study is that the hearing and vestibular skills of volunteer families were followed over the years without loss of data. The results of the present study will allow the development of more effective genetic diagnostic tools, assist in accurate genetic counseling, and guide experts. These findings are also valuable for interpreting the pathogenicity of variants potentially associated with hearing loss. On the other hand, more studies are needed to ensure the best treatment and follow-up of genetic hearing loss. In addition, it is essential to implement vestibular screening protocols in addition to hearing screening in newborns and to include genetic counseling and consultations in newborn screening protocols, even if the newborn has undergone hearing screening. In non-syndromic progressive hearing loss, it is crucial for audiologists and otolaryngologists to recommend genetic consultation for early diagnosis and treatment. Referring to family members for genetic testing provides valuable information about the inheritance pattern and risk factors of the disease. Audiological monitoring should include comprehensive assessments, such as high-frequency audiometry, vestibular evaluation, and auditory

perception assessment. Monitoring audiological and vestibular functions, genetic counseling, psychosocial support, and technological interventions are beneficial recommendations for improving patients' quality of life.

Study Limitations

The limitations of the study are that the patients could not receive complete genetic counseling, genetic screening, genetic counseling services are not widespread in our country, and auditory electrophysiological tests could not be included.

CONCLUSION

In non-syndromic progressive hearing loss, it is crucial for audiologists and otolaryngologists to recommend genetic consultation for early diagnosis and treatment. Referring to family members for genetic testing provides valuable information about the inheritance pattern and risk factors of the disease. Audiological monitoring should include comprehensive assessments, such as high-frequency audiometry, vestibular evaluation, and auditory perception assessment. Monitoring audiological and vestibular functions, genetic counseling, psychosocial support, and technological interventions are beneficial recommendations for improving patients' quality of life.

Ethics

Ethics Committee Approval: Gazi University Rectorate Ethics Commission approved this study (approval number: 15, date: 05.09.2023).

Informed Consent: Informed consent forms were obtained from the participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., N.Y.G., Concept: B.K., N.Y.G., Design: B.K., N.Y.G., Supervision: B.K., N.Y.G., Resources: B.K., N.Y.G.,

Material: B.K., N.Y.G., Data Collection or Processing: B.K., Analysis or Interpretation: B.K., N.Y.G., Literature Search: B.K., N.Y.G., Writing: B.K., N.Y.G., Critical Review: B.K., N.Y.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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Evaluation of Medical School Students in Terms of Attention Deficit Hyperactivity Disorder and Emotional Regulation Difficulties

Tıp Fakültesi Öğrencilerinin Dikkat Eksikliği Hiperaktivite Bozukluğu ve Duygu Düzenleme Güçlükleri Açısından Değerlendirilmesi

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ABSTRACT

Objective: The symptoms of attention deficit hyperactivity disorder (ADHD) affect individuals' education, quality of life, work, and social life. Studies have indicated that adults with ADHD often experience emotion dysregulation as much as they exhibit the core symptoms of the disorder, leading to significant problems in social life. This study aimed to evaluate ADHD symptoms and emotional regulation difficulties in medical students studying at a university hospital.

Methods: The research was conducted between 20.10.2021 and 20.11.2021 in the family medicine department of a university hospital. The sociodemographic data form, adult ADHD Self-Report Scale (ASRS), and difficulties in emotion regulation scale (DERS) were administered to the participants online via Google surveys. The study sample was grouped according to the total ASRS score of the participants.

Results: A total of 552 participants were included in the study. Participants were divided into 3 groups: high probable ADHD (HP-ADHD), probable ADHD (P-ADHD), and without ADHD (WO-ADHD) according to the ASRS cutoff score. The HP-ADHD group had higher DERS total score and all subscale scores than the WO-ADHD group ($p<0.001$ for all analyses). The ASRS total scores were positively correlated with the DERS total scores ($r=0.643$, $p<0.001$). In addition, suicide attempts, forensic event history, and class failure were

ÖZ

Amaç: Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) belirtileri bireylerin eğitim, yaşam kalitesi, iş ve sosyal yaşamlarını etkilemektedir. Araştırmalar, DEHB'li yetişkinlerin bozukluğun temel belirtilerini gösterdikleri kadar sıklıkla duygu düzenleme güçlüğü yaşadıklarını ve bunun da sosyal yaşamda önemli sorunlara yol açtığını göstermektedir. Bu çalışmada, bir üniversite hastanesinde öğrenim gören tıp öğrencilerinde DEHB belirtileri ve duygu düzenleme güçlüklerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Araştırma 20.10.2021-20.11.2021 tarihleri arasında üniversite hastanesinin aile hekimliği bölümünde yürütülmüştür. Katılımcılara sosyodemografik veri formu, Erişkin DEHB Öz Bildirim Ölçeği (ASRS) ve Duygu Düzenleme Güçlüğü Ölçeği (DDGÖ) Google anket sistemi üzerinden çevrimiçi olarak uygulanmıştır. Çalışma örneklemi katılımcıların toplam ASRS puanına göre gruplandırılmıştır.

Bulgular: Çalışmaya toplam 552 katılımcı dahil edilmiştir. Katılımcılar ASRS kesme puanına göre yüksek olasılıklı DEHB (AGYOD), olası DEHB (AGOD) ve DEHB olmayan (AGDO) şeklinde 3 gruba ayrılmıştır. AGYOD grubunun DDGÖ toplam puanı ve tüm alt ölçek puanları AGDO grubuna kıyasla daha yüksek bulunmuştur ($p<0.001$ tüm analizler için). ASRS toplam puanları ile DERS toplam puanları arasında pozitif korelasyon saptanmıştır ($r=0.643$, $p<0.001$). Ayrıca, intihar girişimi, adli

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ABSTRACT

significantly more frequent in the HP-ADHD group than in the WO-ADHD group (p<0.001, p=0.043, p=0.024 respectively).

Conclusion: There is a significant correlation between ADHD and emotional regulation difficulties, which may cause clinical diversity that may cause problems in different areas of life in adults.

Keywords: Adult ADHD, emotion regulation difficulties, medical student, family medicine, psychiatry

ÖZ

olay öyküsü ve sınıfta kalma; AGYOD grubunda AGDO grubuna kıyasla anlamlı derecede daha yüksek oranda bulunmuştur (p<0.001, p=0.043, p=0.024 sırasıyla).

Sonuç: DEHB ile duygu düzenleme güçlükleri arasında anlamlı bir ilişki vardır ve bu durum yetişkinlerde yaşamın farklı alanlarında güçlüklere neden olabilecek klinik çeşitliliğe sebep olabilir.

Anahtar Sözcükler: Erişkin DEHB, duygu düzenleme güçlükleri, tıp öğrencisi, aile hekimliği, psikiyatri

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterized by decreased sustained attention, increased impulsivity, or hyperactivity (1,2). Epidemiological studies have indicated that ADHD is present in approximately 5-10% of children and adolescents and approximately 4% of adults (3,4). Research suggests that all or a subset of the disorder's symptoms can persist into adulthood in about 50% of the cases. The symptoms of ADHD that begin in childhood and continue into adulthood adversely affect individuals' education, quality of life, work, and social life (3,5). The symptoms and problem areas observed in adults may differ from those in children. Attention deficits may manifest as easily diverted attention, difficulty in focusing, forgetfulness, careless errors, and difficulty in organizing. In contrast, hyperactivity may present as restlessness and difficulty in sitting still for extended periods. Impulsivity may be observed as impatience, hastiness, challenges in planning and execution, and problems in executive functions (3). Moreover, impulsive traits in adults with ADHD are known to increase the likelihood of substance abuse and risky behaviors, such as reckless driving (6). ADHD can coexist with numerous psychiatric disorders. It has been observed that 34% of adult women with ADHD and 50% of men with ADHD have at least one psychiatric disorder. Mood disorders, anxiety disorders, antisocial personality disorder, and substance use disorders are common comorbidities associated with ADHD (7). Studies have indicated that adults with ADHD often experience difficulties in emotion regulation as much as they exhibit the core symptoms of the disorder, leading to significant problems in social life (8). Emotion regulation refers to the external and internal processes utilized by an individual to monitor and modify their emotional responses to achieve their goals (9). In other words, emotion regulation can be defined as processes that influence which emotions one has, how one experiences them, and how they express them (10). Rapid and poorly controlled shifts in emotions, impatience, frequent and easy discomfort, and quick temper for minor reasons are examples of emotion regulation difficulties (8,11). Effective emotion regulation can reduce emotional responses to anxiety-provoking situations, whereas difficulties in this area can lead to the development of mood and anxiety disorders (12).

Although studies in the literature have evaluated university students with ADHD and various clinical characteristics, the studies conducted in this field are limited. This study aimed to evaluate ADHD symptoms and emotional regulation difficulties in students studying at the medical faculty of a university hospital. The study hypothesizes that students with a high probability of ADHD will have higher emotional regulation difficulties than those without. We believe that this research will shed light on future studies on ADHD and its clinical implications in adulthood and contribute to the literature.

MATERIALS AND METHODS

Sample of the Study

The research was conducted between 20.10.2021 and 20.11.2021 at a university hospital's department of family medicine and was conducted according to the Helsinki protocol. Necessary permissions for the research were obtained from the Health Sciences Non-Interventional Clinical Research Ethics Committee of İnönü University (approval number: 2021/2540, date: 19.10.2021). The inclusion criteria were students at the university's medical faculty and research volunteer. The exclusion criteria were not having the cognitive capacity to complete the scales used in the study and having a psychiatric disease that could affect emotional regulation (such as schizophrenia, schizoaffective disorder, bipolar disorder, etc.). A sociodemographic data form and scales necessary for the research were distributed online to medical faculty students via the Google survey system. The snowball sampling system included 552 participants in the study. The sociodemographic data form, adult ADHD Self-Report Scale (ASRS), and difficulties in emotion regulation scale (DERS) were applied to the participants. The study sample was grouped according to the total ASRS score of the participants. Those with a total ASRS score of 24 and above were named the high probable ADHD group (HP-ADHD), those between 17-23 were named the probable ADHD group (P-ADHD), and those 16 and below were named the without ADHD group (WO-ADHD). Online consent was obtained from all participants.

Applied Psychiatric Evaluation Scales

Adult Attention Deficit Hyperactivity Disorder Self-Report Scale Adult ADHD Self-Report Scale (ASRS): This scale was developed by the World Health Organization to screen for ADHD (13). Turkish validity and reliability studies on the scale were conducted by Dogan et al. (14). It comprises two subscales, each comprising nine attention deficit and hyperactivity/impulsivity items.

Difficulties in Emotional Regulation Scale (DERS): This scale was developed by Gratz and Roemer (15) to assess emotional regulation difficulties. The validity and reliability of the scale was examined by Ruganci and Gençöz (16). The ASRS assessing difficulties in emotion regulation consists of six subscales: lack of awareness of emotions (awareness), lack of understanding of emotions (clarity), lack of acceptance of emotions (non-acceptance), limited access to emotion regulation strategies perceived as effective (strategies), difficulties in impulse control when experiencing negative emotions (impulses),

and difficulties in goal-oriented behaviors when experiencing negative emotions (goals). The scale comprises 36 items and does not have a cut-off point. An increase in each subscale and the total score indicates an increase in difficulty experienced in regulating emotions.

Sociodemographic Data Form: Prepared based on information obtained from previous studies, this form collects participants' data on age, gender, history of psychiatric-physical diseases, failure in class, and substance experience.

Statistical Analysis

This study summarized quantitative (numeric) variables as median (min.-max.), while qualitative variables were presented as numbers and percentages. The Shapiro-Wilk test was used to assess the normal distribution of quantitative variables. The Kruskal-Wallis H-variance analysis was employed to determine if there was a significant difference in quantitative variables between groups. Post hoc multiple comparison tests after this analysis were conducted using the Conover test. The Pearson chi-squared test was used to investigate whether there was a significant difference between groups regarding qualitative variables. Post hoc multiple comparison tests after this analysis were conducted using the Bonferroni correction for significance between two proportions. Correlations between ASRS scores and DERS scores were investigated using Spearman's rank-order correlation. A p-value of ≤0.05 was set as the level of statistical significance. The analyses were conducted using the Kruskal-Wallis software developed by the department of biostatistics and medical informatics of the medical faculty (http://biostatapps.inonu.edu.tr/kruskalwallis/) and the IBM SPSS Statistics 26 package program.

RESULTS

Clinical and Sociodemographic Features of the Groups

A total of 552 participants were included in the study. The mean age of the participants was found to be 20.6±2. Of them, 335 (60.7%) were female and 217 (39.3%) were male. According to the ASRS cut-off scores, 76 participants were included in the HP-ADHD group, 239 in the P-ADHD group, and 237 in the WO-ADHD group. When the groups were evaluated in terms of psychiatric disease history, suicide attempt, forensic event history, and failure in class, there was a statistically significant difference between the groups ($p=0.028$, $p<0.001$, $p=0.042$, $p=0.023$). The HP-ADHD group had a higher proportion of psychiatric disease, suicide attempts, forensic events, and class failures than the WO-ADHD group. When groups were compared in terms of substance experiences, they were similar to each other. Contrary to expectations, the WO-ADHD group had a higher percentage (3.4%) of participants with substance experience. In terms of psychiatric disease history, the most common history in all three groups was anxiety disorder. The history of ADHD was 5.3% in the HP-ADHD group, 0.8% in the P-ADHD group, and 0.8% in the WO-ADHD group. When the groups were compared in terms of psychiatric disorders other than ADHD, psychiatric disorders were higher in the HP-ADHD group. However, this difference did not show statistical significance between the groups ($p=0.080$). The clinical and sociodemographic characteristics of the groups are presented in Tables 1 and 2.

Comparison of Groups by Scale Scores

When the groups were evaluated in terms of the ASRS total and subscale scores, a statistically significant difference was detected between them ($p<0.001$ for all analyses). The HP-ADHD group had higher ASRS total and subscale scores than the P-ADHD group, and the P-ADHD group had higher scores than the WO-ADHD group. When the groups were evaluated for DERS total and subscale scores, a statistically significant difference was detected between them ($p<0.001$ for all analyses). Excluding the awareness subscale, the HP-ADHD group had higher scores on all other subscales and the DERS total score than the WO-ADHD group, and the P-ADHD group had higher scores than the WO-ADHD group ($p<0.001$ for all analyses). A comparison of the scale scores between the groups is presented in Table 3.

Evaluation of Correlation Between ASRS and DERS Scores

The ASRS total scores were positively correlated with the DERS total scores ($r=0.643$, $p<0.001$). In addition, all subscale scores were positively correlated with themselves ($p<0.001$ for all analyses). The correlation between participants' ASRS scores and DERS scores is given in Table 4.

DISCUSSION

Emotional regulation difficulties in ADHD have become a focal point for researchers, and various studies conducted on the subject recently. Researchers have noted that emotional dysregulation in adult ADHD is as significant as core symptoms, and due to these difficulties, individuals with ADHD face challenges in social and academic domains (8). Furthermore, ADHD has been reported to increase the risk of other psychiatric disorders throughout life, as well as failures in educational and vocational areas, criminal incidents, accidents, social disabilities, and addiction (1,17). As indicated in the diagnostic criteria for adult ADHD, rather than being a mental disorder, it's proposed that patients may present to clinicians with different clinical characteristics that can impair functionality in various areas (8). In this study, we aimed to evaluate medical faculty students' perceptions of ADHD and emotional regulation difficulties.

Research has frequently indicated that psychiatric comorbidities accompany ADHD, emphasizing the significant role of emotional regulation skills development in co-diagnosis (12). The most common psychopathologies coexisting with ADHD are mood and anxiety disorders, substance use disorders, and personality disorders. These studies highlight the challenges in diagnosing ADHD in adults and underscore the fact that ADHD is often not adequately recognized and treated. Early identification and treatment of ADHD and its psychiatric comorbidities in adults can potentially alter the trajectory of psychiatric morbidity in later life (18). Faraone et al. (17) discussed the clinical heterogeneity of ADHD, stating that a small number of patients have no psychiatric comorbidities, but some present with complex issues such as communication disorders, intellectual disabilities, specific learning difficulties, sleep disorders, anxiety and mood disorders, autism spectrum disorders, tic disorders, disruptive behavior disorders, and substance use disorders. Our findings related to psychiatric comorbidity were consistent with the literature (17,18). In our study, a significantly higher rate of psychiatric illness history was found in the HP-ADHD

Table 1. Comparison of the groups in terms of clinical and sociodemographic features

			Groups			Total	Pearson chi-square		Pairwise comparisons	
			HP-ADHD[1]	P-ADHD[2]	WO-ADHD[3]		Test statistic	p		
Gender	Female	n	52	147	136	335	3.057	0.217	-	
		%	68.4%	61.5%	57.4%	60.7%				
	Male	n	24	92	101	217				
		%	31.6%	38.5%	42.6%	39.3%				
Psychiatric illness history	Yes	n	12	28	15	55	7.183	0.028	Yes	1;2 p=0.990
		%	15.8%	11.7%	6.3%	10.0%				1;3 **p=0.030**
										2;3 p=0.120
	No	n	64	211	222	497			No	1;2 p=0.990
		%	84.2%	88.3%	93.7%	90.0%				1;3 **p=0.030**
										2;3 p=0.120
Family history of psychiatric illness	Yes	n	19	37	26	82	9.086	0.011	Yes	1;2 p=0.176
		%	25.0%	15.5%	11.0%	14.9%				1;3 **p=0.007**
										2;3 p=0.439
	No	n	57	202	211	470			No	1;2 p=0.176
		%	75.0%	84.5%	89.0%	85.1%				1;3 **p=0.007**
										2;3 p=0.439
Physical illness	Yes	n	6	15	17	38	0.290	0.865	-	
		%	7.9%	6.3%	7.2%	6.9%				
	No	n	70	224	220	514				
		%	92.1%	93.7%	92.8%	93.1%				
Suicide Attempt	Yes	n	13	13	9	35	17.738	<0.001	Yes	1;2 **p=0.004**
		%	17.1%	5.4%	3.8%	6.3%				1;3 p**<0.001**
										2;3 p=0.990
	No	n	63	226	228	517			No	1;2 **p=0.004**
										1;3 p**<0.001**
		%	82.9%	94.6%	96.2%	93.7%				2;3 p=0.990
Forensic event history	Yes	n	4	4	2	10	6.363	0.042	Yes	1;2 p=0.250
		%	5.3%	1.7%	0.8	1.8%				1;3 **p=0.043**
										2;3 p=0.990
	No	n	72	235	235	542			No	1;2 p=0.250
		%	94.7%	98.3%	99.2%	98.2%				1;3 **p=0.043**
										2;3 p=0.990
Failure in class	Yes	n	21	50	34	105	7.581	0.023	Yes	1;2 p=0.668
		%	27.6%	20.9%	14.3%	19.0%				1;3 **p=0.024**
										2;3 p=0.180
	No	n	55	189	203	447			No	1;2 p=0.668
		%	72.4%	79.1%	85.7%	81.0%				1;3 **p=0.024**
										2;3 p=0.180

The Pearson chi-square test was utilized to investigate whether there was a significant difference between groups in terms of qualitative variables. Post-hoc multiple comparison tests after this analysis were conducted using the Bonferroni-corrected significance test. ADHD: Attention Deficit Hyperactivity Disorder, HP-ADHD: High Probable ADHD, P-ADHD: Probable ADHD, WO-ADHD: Without ADHD, p<0.050.

Table 2. Comparison of the groups in terms of smoking, alcohol and substance experience

			Groups			Total	Pearson chi-square	
			HP-ADHD	P-ADHD	WO-ADHD		Test statistic	p
Smoking	Yes	n	11	29	26	66	0.683	0.711
		%	14.5%	12.1%	11.0%	12.0%		
	No	n	65	210	211	486		
		%	85.5%	87.9%	89.0%	88.0%		
Alcohol	2-3 times/week	n	3	0	3	6	9.193	0.056
		%	3.9%	0.0%	1.3%	1.1%		
	Rare	n	15	42	38	95		
		%	19.7%	17.6%	16.0%	17.2%		
	None	n	58	197	196	451		
		%	76.3%	82.4%	82.7%	81.7%		
Substance experience	Yes	n	2	1	8	11	5.512	0.064
		%	2.6%	0.4%	3.4%	2.0%		
	No	n	74	238	229	541		
		%	97.4%	99.6%	96.6%	98.0%		

Pearson's chi-square test was utilized to investigate whether there was a significant difference between groups regarding qualitative variables. ADHD: Attention Deficit Hyperactivity Disorder, HP-ADHD: High pobable ADHD, P-ADHD: Probable ADHD, WO-ADHD: Without ADHD, $p<0.050$.

group than in the WO-ADHD group. The most frequently reported psychiatric illness in the HP-ADHD group was anxiety disorder (6.6%. The history of ADHD was higher in the HP-ADHD group than in the other groups, but was present in only 4 (5.3%) patients. This finding suggests, as also noted in the literature, that ADHD in adults may not be adequately diagnosed (18). The high rate of psychiatric illness in the HP-ADHD group might lead to diagnostic confusion. Substance misuse or addiction is approximately twice as prevalent in individuals with ADHD compared with the general population (18). The relationship between substance use disorders and ADHD is believed to stem from similar neurobiological mechanisms and factors, such as coexisting psychiatric disorders, impulsivity, novelty-seeking, and self-medication for ADHD symptoms (19). It has been noted that individuals with ADHD often resort to substance use for sleep disturbances or emotional regulation (18). ADHD in childhood and adolescence has been indicated as a strong predictor of tobacco, alcohol, and substance use in adulthood (20). Individuals with comorbidity of ADHD and substance use disorder have been shown to experience more significant problems in social and academic domains, along with decreased quality of life (21). In contrast to previous studies (18-20), no significant difference was found between the groups in terms of substance experience. Because substance use is illegal in our country, participants might not have answered this question objectively, which could have influenced our findings. Park et al. (22) indicated a strong relationship between adult ADHD symptoms and suicidal tendencies. Research focusing on increased suicide risk in ADHD has centred on typical comorbidities, specific personality traits, and cognitive impairments that may predispose individuals to suicidal behaviors. In their study, Park et al. (22) demonstrated a significant relationship between ADHD symptoms and nicotine addiction, alcohol misuse/addiction, mood disorders, bipolar disorder, major depressive disorder, anxiety disorders, obsessive-compulsive disorder, somatoform disorder, and post-traumatic stress disorder. Although many studies have reported that ADHD diagnosis is an independent risk factor for suicide, it is believed that coexisting comorbidities such as affective disorders, anxiety disorders, and substance use mediate this risk (23). Impulsivity, a core symptom of ADHD, plays a crucial role in impairing decision-making processes in patients (24). Impulsivity is a personality trait characterized by behaviors without consideration of consequences. Individuals with ADHD can be prone to making hasty and risky decisions when confronted with life's dilemmas and crises because of the disease's associated impairments in decision-making, inattentiveness, and impulsivity. Instead of securing long-term gains or devising successful strategies, these cognitive tendencies may drive individuals to prefer immediate escape from stressful events, which can include suicidal actions (25). Consistent with previous studies (25), our study found a significantly higher incidence of history of suicide attempt in the HP-ADHD group than in the other groups. However, we believe that other possible psychiatric comorbidities and clinical features may also play a role in reaching this outcome. Individuals with ADHD can face legal problems due to persistent symptoms of ADHD. Longitudinal studies have shown that untreated ADHD cases in adulthood demonstrate risk behaviors like alcohol and substance addiction, criminal tendencies, self-harm, and traffic accidents (26). Numerous studies in the literature have shown that individuals with ADHD are more frequently penalized in various settings (27). Consistent with previous studies, our study found a significantly higher incidence of forensic event history in the HP-ADHD group than in the WO-ADHD group. It has been shown that cognitive skills can be impaired due to ADHD's core symptoms, namely inattention, hyperactivity/impulsivity, or their combination. Numerous studies have shown that attention disorders at an early age are linked to future difficulties in reading, mathematics,

and overall school performance (28). It should be noted that individuals with ADHD are more likely to repeat grades and have a lower academic success level than the general population (29). Our findings related to academic performance were consistent with those of previous research. Our study found a significantly higher rate of failure in class in the HP-ADHD group than in the WO-ADHD group. ADHD is a psychiatric disorder with a high genetic predisposition. A study conducted in our country reported that 6.8% of the parents of children with ADHD met the diagnostic criteria for adult ADHD (30). It is important to note that the genetic transition risk in ADHD is higher in females, suggesting that environmental factors are more predominant in males. In contrast, genetic factors are more significant in females. It has been highlighted that there is a higher incidence of psychiatric illness in parents of children with ADHD compared with the control group (30). Consistent with previous studies, our study found a significantly higher incidence of psychiatric illness history in families in the HP-ADHD group than in the WO-ADHD group.

In adults with ADHD, researchers like Wender, Brown, Conner, and Barkley, who developed alternative models, have all emphasized the significance of emotional symptoms in ADHD (8). Retz et al. (8) indicated that the psychopathological presentation and functional

Table 3. Comparison of the groups regarding age and scale scores

	Group			p	Pairwise comparisons
	HP-ADHD[1]	P-ADHD[2]	WO-ADHD[3]		
Age	21 (18-27)	20 (17-26)	20 (17-28)	0.263	-
Attention deficit	25 (10-35)	18 (4-23)	12 (0-16)	<0.001	1;2 p<0.001
					1;3 p<0.001
					2;3 p<0.001
Hyperactivity impulsivity	21.5 (9-36)	17 (6-23)	11 (0-16)	<0.001	1;2 p<0.001
					1;3 p<0.001
					2;3 p<0.001
ASRS total	45 (34-67)	34 (23-44)	24 (0-32)	<0.001	1;2 p<0.001
					1;3 p<0.001
					2;3 p<0.001
Awareness	15 (6-25)	14 (5-25)	12 (5-21)	<0.001	1;2 p=0.160
					1;3 p<0.001
					2;3 p<0.001
Clarity	17 (5-25)	13 (5-25)	10 (5-23)	<0.001	1;2 p<0.001
					1;3 p<0.001
					2;3 p<0.001
Non-acceptance	17 (6-30)	13 (6-30)	10 (6-30)	<0.001	1;2 p=0.001
					1;3 p<0.001
					2;3 p<0.001
Impulse	19.5 (6-30)	15 (6-29)	11 (6-23)	<0.001	1;2 p<0.001
					1;3 p<0.001
					2;3 p<0.001
Goals	20 (8-25)	18 (6-25)	14 (5-24)	<0.001	1;2 p<0.001
					1;3 p<0.001
					2;3 p<0.001
Strategies	26.5 (11-40)	21 (8-39)	15 (8-33)	<0.001	1;2 p<0.001
					1;3 p<0.001
					2;3 p<0.001
DERS total	118 (53-169)	96 (48-152)	74 (40-130)	<0.001	1;2 p<0.001
					1;3 p<0.001
					2;3 p<0.001

Kruskal-Wallis H variance analysis was employed to determine if there was a significant difference between groups regarding quantitative variables. Post-hoc multiple comparison tests after this analysis were conducted using the Conover test. ADHD: Attention Deficit Hyperactivity Disorder, ASRS: Adult ADHD Self-Report Scale, DERS: Difficulties in emotion regulation scale, HP-ADHD: High probable ADHD, P-ADHD: Probable ADHD, WO-ADHD: Without ADHD, p<0.050

impairments in adult ADHD cannot be entirely accounted for by classic ADHD symptoms, such as inattention, hyperactivity, and impulsivity. They highlighted that individuals with ADHD have difficulty coping with stress because of mood variability, get angry frequently and quickly, and have high emotional reactivity. Moreover, these individuals often experience interpersonal relationship problems, and a significant portion of their reasons for medical consultations are related to these interpersonal issues (8). In a study conducted by Surman et al. (31) it was noted that ADHD individuals with intense emotion regulation difficulties, as compared to those without such intense difficulties, had a higher rate of functional impairment, divorce, risk of traffic accidents, and risk of arrest. In another study, emotional lability, comorbidity, and functional impairment in adults with ADHD were examined; a higher prevalence of emotional lability was reported in ADHD adults than in controls. It was observed that hyperactivity/impulsivity is a stronger predictor of emotional lability than subsyndromal symptoms, and emotional lability independently contributed to daily functional impairments. Attention was drawn to the fact that some scale scores assessing emotional lability (e.g., affective lability-anger subscale) were higher in ADHD individuals showing antisocial behavior than in those who did not. In conclusion, it was suggested that emotional lability in ADHD is related to the disorder itself rather than comorbid conditions and might elucidate some disturbances not explained by the disorder's classic symptoms. It has also been stated that routine screening for emotional lability, which can lead to long-term problems in adult

Table 4. Evaluating the correlation between participants' scale scores

		AD	H/I	ASRS	AWR	CLR	NAC	IMP	GOA	STR	DERS
AD	r	1	0.506	0.879	0.370	0.532	0.430	0.503	0.580	0.541	0.621
	p		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	552	552	552	552	552	552	552	552	552	552
H/I	r	0.506	1	0.856	0.205	0.407	0.352	0.519	0.364	0.436	0.490
	p	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	552	552	552	552	552	552	552	552	552	552
ASRS	r	0.879	0.856	1	0.335	0.544	0.453	0.589	0.549	0.565	0.643
	p	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	552	552	552	552	552	552	552	552	552	552
AWR	r	0.370	0.205	0.335	1	0.534	0.335	0.312	0.264	0.370	0.552
	p	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	552	552	552	552	552	552	552	552	552	552
CLR	r	0.532	0.407	0.544	0.534	1	0.537	0.587	0.520	0.639	0.790
	p	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001	<0.001
	n	552	552	552	552	552	552	552	552	552	552
NAC	r	0.430	0.352	0.453	0.335	0.537	1	0.639	0.501	0.726	0.817
	p	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	<0.001
	n	552	552	552	552	552	552	552	552	552	552
IMP	r	0.503	0.519	0.589	0.312	0.587	0.639	1	0.633	0.769	0.855
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001
	n	552	552	552	552	552	552	552	552	552	552
GOA	r	0.580	0.364	0.549	0.264	0.520	0.501	0.633	1	0.648	0.752
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001	<0.001
	n	552	552	552	552	552	552	552	552	552	552
STR	r	0.541	0.436	0.565	0.370	0.639	0.726	0.769	0.648	1	0.913
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001		<0.001
	n	552	552	552	552	552	552	552	552	552	552
DERS	r	0.621	0.490	0.643	0.552	0.790	0.817	0.855	0.752	0.913	1
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	
	n	552	552	552	552	552	552	552	552	552	552

Correlations between ASRS and DERS scores were investigated using Spearman's rank-order correlation. ADHD: Attention Deficit Hyperactivity Disorder, AD: Attention Deficit, H/I: Hyperactivity/impulsivity, ASRS: Adult ADHD Self-Report Scale, AWR: Awareness, CLR: Clarity, DERS: Difficulties in emotion regulation scale, GOA: Goals, IMP: Impulse, NAC: Non-acceptance, STR: Strategies, p<0.050

ADHD, is essential (32). Barkley and Murphy (33) in their research, proposed that dysfunctional emotion regulation in ADHD is associated with a lower level of psychosocial functionality, diminished parenting skills, vocational problems, risky driving behaviors, and criminal activities. Our findings on emotional regulation difficulties were consistent with those of previous studies. In the results of our study, except for the awareness subscale, all subscale scores and the DERS total score were significantly higher in the HP-ADHD group than in the P-ADHD group and in the P-ADHD group than in the WO-ADHD group. A significant positive correlation was found between the ASRS scores and the DERS total and subscale scores. The higher prevalence of emotion regulation difficulties in the HP-ADHD group might have contributed to the higher incidence of psychiatric illness history, suicide attempts, and forensic event history, as well as the higher frequency of failure in class, which could indicate psychosocial functionality. Given the high comorbidity rates in adult ADHD (7) and the belief that difficulties in emotion regulation play a key role in the development of many other mental disorders (12), addressing emotion regulation difficulties in adults with ADHD during treatment could make therapeutic interventions more effective. Numerous studies have reported the positive effects of cognitive behavioral therapy (CBT) on ADHD symptoms and comorbid psychiatric diseases. Research on the impact of various models, such as dialectical behavioral therapy and mindfulness meditation training, on ADHD treatment is ongoing (34). Therapeutic approaches that target and improve problematic stages of the emotion regulation process can contribute to symptom reduction. For instance, if an individual with ADHD has a deficit in the emotional awareness dimension, mindfulness meditation training may be beneficial in enhancing the individual's sensitivity. There is a need for further research that examines models other than CBT to evaluate the efficacy of psychotherapy in ADHD. Our study has some limitations. In previous studies in the literature, patients diagnosed with ADHD through clinical examination were included and evaluated. However, in our research, the subjects were not psychologically examined; scales were used for mental state assessment. Participants were assessed based on symptom levels determined by the scales and grouped as HP-ADHD, P-ADHD, and WO-ADHD. Therefore, it was not possible to discuss the diagnoses. This situation may have affected our results and limited our study. Because our research was cross-sectional, the results showed the current states of the participants, preventing further comments on the causality and longitudinal progression of the results. This is another limitation of our research. Another area for improvement was that participants may have provided objective answers to some questions, such as their history of forensic events or substance experiences. This may have affected our results. Since no detailed inquiry was made into the content of the forensic event during the study, further comments on whether these incidents constitute a crime could not be made. This is one of the limitations of our research. Our study had some strengths. We included the vast majority of medical faculty students in the study. This was one of the strengths of our research. It was important for the groups to be similar in terms of variables such as age, gender, and physical illness to minimize other factors that might affect the results, and this was a characteristic that strengthened our study. Although many studies have examined ADHD and various clinical features in university students, our study is one of the few studies evaluating ADHD and emotion regulation difficulties. This was another strength of our study. In conclusion, in our study, except for the awareness subscale, all other subscale scores and the DERS total score were significantly higher in the HP-ADHD group than in the P-ADHD group and in the P-ADHD group than in the WO-ADHD group. Moreover, compared with the WO-ADHD group, the HP-ADHD group had a significantly higher history of psychiatric illness, suicide attempts, forensic event history, failure in class, and family history of psychiatric illness. In adulthood, ADHD can present not only due to core symptoms and additional emotional regulation difficulties and academic, social, and other problems. Individuals with ADHD may face legal issues due to ongoing symptoms of ADHD. Follow-up studies have shown that untreated individuals with ADHD in adulthood display risk behaviors such as alcohol and substance addiction, criminal tendencies, self-harm, and traffic accidents. The family medicine system constitutes the basic tier of our country's health system. Although overlooked ADHD cases often present to family physicians with complaints of inattentiveness and difficulty concentrating (35), ADHD can manifest in various clinical forms in adulthood compared with childhood (36). Given the risks associated with ADHD in adulthood, family physicians must be aware of the clinical presentation of adult ADHD and to refer undiagnosed, overlooked cases that raise suspicion to a psychiatrist. This will be of great importance to both individual and public health. We believe that within the realm of preventive medicine, ADHD in childhood could be included in family medicine screening programs, and there is a need to develop primary health policies in this area. Our study will shed light on further research in this field and contribute to the literature. Additional studies examining ADHD and emotion regulation difficulties in adults with larger sample sizes are needed.

Ethics

Ethics Committee Approval: Necessary permissions for the research were obtained the Health Sciences Non-Interventional Clinical Research Ethics Committee of İnönü University (approval number: 2021/2540, date: 19.10.2021).

Informed Consent: Online consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: A.A., M.A., Design: A.A., M.A., E.B.S., Supervision: E.B.S.,

Data Collection or Processing: A.A., A.K.A., Analysis or Interpretation: A.A., A.K.A., Literature Search: A.A., M.A., E.B.S., B.K.T., Writing: A.A., Critical Review: E.B.S., B.K.T.

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Frequency of Chromosome Disorders In Patients with Sperm Number Anomaly

Sperm Sayısı Anomalisi Olan Hastalarda Kromozom Bozukluklarının Sıklığı

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ABSTRACT

Objective: Chromosome abnormalities play an important role in male infertility. The rate of chromosome disorders in infertile men is higher as 5.8% when compared to the normal population (0.5%).

Methods: This study aimed to determine the frequency of cytogenetic abnormalities in infertile men with abnormal sperm counts and to show that rare chromosomal rearrangements can be detected by karyotyping.

Results: In our clinical practice, we detected nearly all chromosome numerical and structural anomalies involved in infertility. It includes inversions, translocations, deletions, insertions, complex rearrangements, isochromosomes, Klinefelter syndrome, mosaicism, and 47, XYY.

Conclusion: Our results emphasize the importance of conventional cytogenetic analysis for infertile males. The detection of rare or known chromosome abnormalities will prevent unnecessary investigations and enable us the application of precision in medicine.

Keywords: Abnormal sperm counts, chromosome abnormalities, genetic counselling

ÖZ

Amaç: Kromozom anormallikleri erkek infertilitesinde önemli bir rol oynamaktadır. İnfertil erkeklerde kromozom bozuklukları oranı normal popülasyona (%0,5) göre %5,8 kadar yüksektir.

Yöntemler: Çalışmamızda sperm sayısı anormal olan infertil erkeklerde sitogenetik anormallik sıklığının belirlenmesi ve nadir görülen kromozomal yeniden düzenlemelerin karyotipleme ile tespit edilebileceğinin gösterilmesi amaçlanmıştır.

Bulgular: Klinik pratiğimizde infertiliteye yol açan kromozomların sayısal ve yapısal anomalilerinin neredeyse tüm spektrumunu tespit etmekteyiz. Bu, İnversiyonları, translokasyonları, delesyonları, insersiyonları, karmaşık yeniden düzenlemeleri, izokromozomları, Klinefelter sendromunu, mozaikliği ve 47, XYY'yi içermektedir.

Sonuç: Sonuçlarımız infertil erkeklerde geleneksel sitogenetik analizin önemini vurgulamaktadır. Nadir veya bilinen kromozom anormalliklerinin tespiti, gereksiz araştırmaları önleyecek ve kişiye özel tedavilerin uygulanmasına olanak sağlayacaktır.

Anahtar Sözcükler: Anormal sperm sayısı, kromozom anomalileri, genetik danışma

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INTRODUCTION

Infertility is increasing in various global communities and is defined as the inability to achieve pregnancy after continuous, unprotected sexual intercourse for at least a year or more. Around 15% of couples are affected by this condition. 40-50% due to male factors (1,2). Mechanical issues, unexplained cases, and identifiable genetic defects are the predominant factors contributing to male infertility. Genetic defects include four groups: (1) Y chromosome deletions, (2) single gene disorders, (3) multifactorial causes, and (4) structural and numerical chromosome abnormalities (3). Male infertility generally lies in abnormal semen analysis. Abnormal semen analysis does not always indicate infertility; it only lowers the probability of pregnancy. Patients with nonobstructive abnormal sperm counts have an increased risk of chromosomal abnormalities. Infertile men exhibit a higher chromosome anomaly rate (5.8%) in contrast to the lower rate observed in the general population (0.5%) (4). This means a fold increase. Chromosomal anomalies are documented at rates of 10.00-23.62% in cases of nonobstructive azoospermia and 1.10-13.33% in cases of severe oligozoospermia (5). Complex chromosomal rearrangements (CCR) refer to structural abnormalities that entail a minimum of three chromosomes, each with three or more breakpoints (6). CCRs are rare occurrences and can manifest as balanced, unbalanced, familial, or spontaneous occurrence. The majority of individuals carrying CCR are female, with a minority being male (7). The identification of most male carriers with CCRs has been through infertility assessment, whereas a minority has been identified through abnormalities in children or recurrent abortions (8,9,10). The risk of conceiving offspring with diverse anomalies and experiencing reproductive failure is heightened among CCR carriers because of segregation of the derivative chromosome or meiotic failure (11,12,13). Female CCR carriers are typically identified following the occurrence of babies with congenital abnormalities or experiencing recurrent abortions. Nevertheless, male CCR carriers do not always exhibit infertility or subfertility; in several cases, infertility issues arise as a result of hypospermatogenesis or spermatogenic failure. Several documented cases highlight the occurrence of CCRs in males diagnosed with oligozoospermia or azoospermia (14). In this study, we aimed to determine the types and frequency of chromosome abnormalities in patients with abnormal sperm counts.

MATERIALS AND METHODS

Karyotype results of patients with abnormal sperm counts who applied to the cytogenetic laboratory of Başkent University Genetic Diseases Diagnosis Center between January 2007 and December 2019 were retrospectively evaluated. Numerical and structural chromosomal anomaly distribution was determined according to sperm counts. 968 males were divided according to the sperm count of semen analysis into azoospermia (group 1), oligozoospermia (group 2), and oligoastenozoospermia (group 3). This study was approved by Başkent University Institutional Review Board (approval number: KA 24/108, date: 06.03.2024) and supported by Başkent University Research Fund.

Statistical Analysis

Standard cytogenetic investigations were conducted using established methods for phytohemagglutinin-stimulated cultures of peripheral blood lymphocytes. Chromosome spreads underwent processing for the analysis of GTG bands. Chromosomes were subjected to GTG banding following the standard karyotyping protocol, with an examination of 30 metaphases and interpretation carried out at resolution levels of 450 and 650 bands. Fluorescence in situ hybridization (FISH) was conducted on metaphases from transformed lymphoblast cell lines using human probes, following standard protocols and manufacturer's manuals (15).

RESULTS

All detected anomalies in our cases fall into the first group. The number of patients with sex chromosome abnormalities was higher than that of patients with autosomal chromosome anomalies (17.56 and 0.72 %, respectively (Table 1). Although the numerical anomaly rate was 15.9%, the structural anomaly rate was lower (2.37%) (Table 2). A total of 154 numerical anomalies were detected. Klinefelter syndrome (KS) was the most common finding 15.56% (151 patients), from which mosaic karyotypes were identified as 47, XXY/ 46, XY in 12 patients. There is also another mosaic patient with 47, XXY/ 48, XXXY karyotype. 47, XYY karyotype was detected in one patient. A total of 21 structural anomalies were detected. We had 9 patients with 46, XX karyotype in whom was detected translocation between chromosome X p arm with chromosome Y p arm. The SRY gene is shown on the derivative X-chromosome's p arm by FISH. In total, 16 reciprocal translocations were performed. Deletions were detected in 2 patients. The other structural abnormalities included one complex abnormality, one insertion, and one isochromosome.

Complex Chromosomal Rearrangement

The proband (Figure 1, III-4) is a 38-year-old man with primer infertility. He has been married for 2 years and has no consanguinity with his wife. They have not tried assisted reproductive treatment (ART). He had a normal phenotype and hormone profile, azoospermia, and no sperm in TESE. He has no Y-chromosome microdeletion. Karyotype analysis (Figure 2a) is 46,XY,t(2;12) (p24:q21), ins(4;2) (q21;p13p24) and the result is confirmed by metephase FISH (Figure 2b). Proband has 2 brothers and 1 sister, all of whom have normal offspring. A

Table 1. Identified chromosomal anomaly frequencies in study groups.

Patients	Sperm anomaly	Autosomal abnormality n (%)	Sex chromosome abnormality n (%)	Total n (%)
Group 1	Azoospermia (n=920)	7 (0.72)	170 (17.56)	177 (18.28)
Group 2	Oligozoospermia (n=1)	-	-	0 (0)
Group 3	Oligoasthenospermia (n=37)	-	-	0 (0)
Total	(n=968)	7 (0.72)	170 (17.56)	177 (18.28)

family study for segregation analysis was offered, but it could not be done because the couple did not accept.

DISCUSSION

We retrospectively evaluated the karyotype results of 968 patients with abnormal sperm counts and detected chromosomal disorders only in patients with azoospermia. In our cohort of patients with azoospermia, the rate of chromosomal abnormalities was 18.28 %, which was close to that reported by Pylyp et al. (1) in Ukrainian patients (17%), Kleiman et al. (12) in Israel (16.6 %), and higher than previously reported by Kumtepe et al. (16) in Türkiye (12 %), Wang et al. (17) in China (8.5 %), Lakshmi Rao et al. (18) in India (7.9 %), and Gekas et al. (19) in France (6.9 %) (1,12,16,17,18,19). Being the most prevalent X-chromosome abnormality, KS is the most prevalent X-chromosome abnormality and is the most frequent genetic factor contributing to male infertility. Individuals diagnosed with pure KS (47, XXY), mosaic, or variant KS often experience significant impairment in spermatogenesis, resulting in severe oligozoospermia or azoospermia. Among infertile men, the prevalence of KS is notably higher, escalating from approximately 3% in unselected cases to approximately 13% in patients diagnosed with azoospermia. Hence, KS is the most common genetic cause of azoospermia (20,21). Males with KS commonly display phenotypic traits associated with hypergonadotropic hypogonadism and testosterone deficiency, only a subset (approximately 25% to 40%) of cases receive an accurate diagnosis (22,23). Lakshmi Rao et al. (18) and Kleiman et al. (12) reported the rates of KS in their cohort as (4.41%) and (5.5%) respectively (12,17). We identified 139 (14.36 %) pure KSs and 12 (1.2 %) mosaic types. This was not close to the rate reported by Pylyp et al. (1) among Ukrainian patients (64%) and (18%) respectively. Although oligozoospermia and normozoospermia patients were evaluated in the study mentioned above, all of our patients had only azoospermia. This may explain why the detected patient rates were different from ours. In the majority of cases, men with the 47, XYY karyotype are fertile, but they are observed more frequently within infertile populations, accounting for nearly 0.1%. In our study, we have one 47, XYY infertile man, which means 0.1%. Rearrangements among acrocentric chromosomes, including chromosomes 13, 14, 15, 21, and 22, result in Robertsonian translocations. This results in the loss of genetic material, resulting in a chromosomal complement of 45 chromosomes. This condition is observed in approximately 0.9% of men diagnosed with severe male factor infertility (24). Although it affects sperm production, we did not detect this in our patient group. The reciprocal translocation mechanism involves the exchange of genetic material between two or more chromosomes.

Table 2. Chromosomal disorders detected in patients

Chromosomal anomalies	Anomaly type	Karyotype	n (%)	Total number of participants (%)
Structural chromosomal anomalies	Inversions	46,XY,inv(10) (p13q22)	1 (0.1)	2 (0.2)
		47,XXY,inv(12)(p11.1q13.2)	1 (0.1)	
	Deletions	46,X,del(Y)(q11)	2 (0.2)	2 (0.2)
	Translocations	46,XY,t(5;8)(q12;p12)	1 (0.1)	16 (1.65)
		46,XY,t(Y;12)(q11.2;p13)	1 (0.1)	
		46,X,t(X;Y)(p22;p11)	9 (0.9)	
		46,XY,t(1;21)(q11;p12)	1 (0.1)	
		46,Y,t(X;3)(q26;q23)	1 (0.1)	
		46,XY,t(5;8)(q13;p13)	1 (0.1)	
		46,Y,t(X;11)(p22.1;q13)	1 (0.1)	
		46,XY,t(2;11)(q13;p15)	1 (0.1)	
	Insertions	46,XY,ins(2;5)(q13;q13.1q32)	1 (0.1)	1 (0.1)
	Complex reerangement	46,XY,t(2;12)(q24;21),ins(4;2)(q21;p13p24)	1 (0.1)	1 (0.1)
	Isochromosome	46,X,i(Yp)	1 (0.1)	1 (0.1)
Numerical chromosomal anomalies	Klinefelter syndrome	47,XXY	139 (14.36)	139 (14.36)
	Mosaicism	47,XY,i(X)(q10)/47,XXY	2 (0.2)	14 (1.4)
		47,XXY/46,XY	8 (0.8)	
		47,XXY/48,XXXY	1 (0.1)	
		45,X/46,XY	2 (0.2)	
		47,XXY/46,XX/46,XY	1 (0.1)	
	47,XYY	47,XYY	1 (0.1)	1 (0.1)

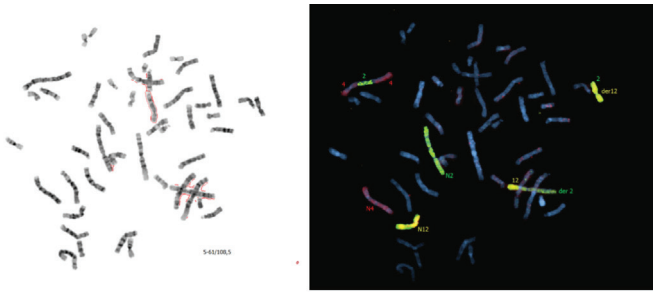

Figure 2. (a) Karyotype of the patient with complex chromosomal anomaly (left), partial karyotype of the chromosomes participating in the anomaly (right) (b), G-banded metaphase (left), and FISH imaging (right) on the metaphase by Whole chromosome probes for chromosome 2 (red), chromosome 4 (green), and chromosome 12 (yellow).

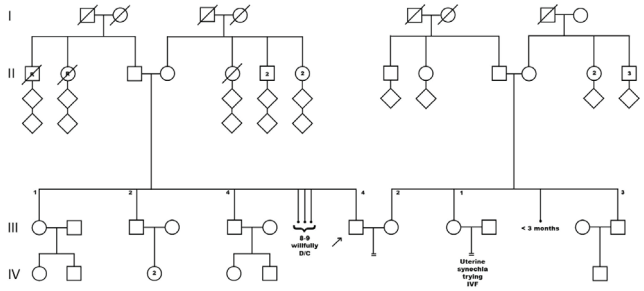

Figure 1. Pedigree of the CCR patient.

CCR: Complex chromosomal rearrangements

The prevalence of balanced chromosomal translocations is tenfold higher in infertile men, constituting a notable factor in male infertility (25). In this study, we have 16 reciprocal translocations in total. The most common (9 cases) was 46, X, t(X; Y), (p22;q11). 46 XX DSD (differences in sex development) were observed in phenotypically normal males. Various etiological theories have been proposed. SRY-positive individuals are expected to undergo crossover events between the pseudoautosomal regions of sex chromosomes during paternal meiosis (26). The existence of the SRY gene was demonstrated using FISH in all patients who were identified as XX males. Our findings support this theory. The isochromosome of Yp, i(Yp), is the least frequently observed structural rearrangement involving the Y chromosome (27). Individuals exhibiting delayed puberty, along with symptoms like gynecomastia, reduced growth rate, and infertility, and requiring testosterone treatment to induce the development of secondary sex characteristics may present with the potential effects associated with 45,X/46,X,i(Yp). We have one isochromosome 46,X,i(Yp) from 968 infertile males (0.1%). Complex chromosomal abnormalities (CCRs) are rare occurrences in the population, with approximately 255 documented cases to date (6). CCRs typically arise from either two concurrent classical translocations or jumping translocations, where a donor chromosomal segment is translocated to multiple recipient chromosome sites (28,29,30). In general, males with CCR exhibit issues related to infertility stemming from either hypospermatogenesis or spermatogenic failure (31). In this cohort, type 2 CCR was detected, and the rate of complex anomaly was 0.1%. In phenotypically normal individuals, a balanced CCR is typically observed. Such cases often have a familial component, which is primarily transmitted through female carriers. These cases are often referred for advanced maternal age, recurrent spontaneous abortion, or the birth of a malformed child (32-36). Transmission through males is a rare event (37, 38). A significant portion of CCR, approximately 70-75%, arises as de novo chromosomal rearrangements, predominantly of paternal origin (32). These are equally distributed among individuals with a normal phenotype (49%), and those displaying phenotypic abnormalities (51%). This distribution can be attributed to submicroscopic imbalances or other genetic defects (39-41). De novo balanced CCRs are often identified due to issues related to infertility, although a limited number of cases involving fertile carriers have also been documented (24,42-45). Using multicolor FISH technologies of sperm sorting studies, accurate procedures for on-site analysis of CCRs have been established to facilitate the offer of preimplantation genetic diagnosis (PGD) to couples easily. There are six cases of PGD in CCR carriers in whom spontaneous abortion did not occur (46,47). The detection of chromosomal disorders is important for predicting and preventing the risk of new pregnancies because they lead to unbalanced gametes. With karyotyping, in men with sperm number and structure anomalies, in addition to explaining the cause of their condition, future infertility treatment and options for having a healthy baby can also be determined. If any chromosomal abnormality is detected, PGD ought to be proposed to the patients as a solution to prevent such genotypic defects, which are the cause of different phenotypic abnormalities with undesired effects on health and the quality of life afterward in offspring (48). Pregnancy rates after transfer of an euploid/balanced embryo are 60%-70%, which is equivalent to the rate for euploid embryos in normal patients (49,50).

CONCLUSION

In conclusion, by chromosomal aberrations infertility in men can be caused (32). Each detected chromosomal disorder has its own hereditary and phenotypic risks. Therefore, determining the chromosomal aberration and explaining the risks specific to the detected condition to the family through genetic counseling are important for them to decide on pregnancy options and inform other family members at risk. For example, in patients with Yq del, the risk of transmission to male children and the resulting infertility should be explained. The family should decide on ART treatments after knowing these risks. Thus, the cause of men's infertility requires detailed comprehensive genetic counseling, especially to prevent recurrence in off spring. While PGD offers promise, it comes with challenges and ethical considerations. The accuracy of diagnosis, potential mosaicism, and the emotional impact on parents are critical aspects to navigate. Striking a balance between the benefits and ethical concerns is imperative to ensure the responsible and equitable application of PGD in the context of chromosomal rearrangements. Our results emphasize the importance of conventional cytogenetic analysis in infertile males. The detection of rare or known chromosome abnormalities will prevent unnecessary investigations and enable us the application of precision in medicine.

Ethics

Ethics Committee Approval: This study was approved by Başkent University Institutional Review Board (approval number: KA 24/108, date: 06.03.2024).

Informed Consent: Retrospective study

Footnotes

Authorship Contributions

Concept: M.N., E.A., Z.Y.Ç., Design: Z.Y.Ç., Supervision: Z.Y.Ç., Resources: M.N., E.A., Z.Y.Ç., Material: M.N., E.A., Data Collection or Processing: M.N., E.A., Z.Y.Ç., Analysis or Interpretation: M.N., E.A., Z.Y.Ç., Literature Search: M.N., E.A., Z.Y.Ç., Writing: M.N., E.A., Z.Y.Ç., Critical Review: M.N., E.A., Z.Y.Ç.

Conflict of Interest:

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Forensic Admissions of Geriatric Patients to the Emergency Department and Short-Term Mortality Rates

Geriatrik Hastaların Acil Servise Adli Başvuruları ve Kısa Dönem Mortalite Oranları

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ABSTRACT

Objective: The increasing number of geriatric admissions to emergency departments (EDs) necessitates a separate study of geriatric admissions for forensic reasons. This study investigated the reasons for geriatric forensic cases presented to the ED, the one-month mortality rates of these cases, and the factors affecting mortality.

Methods: This was a retrospective cohort study. All patients 65 years old and older who were reported as forensic cases and presented to the ED of a tertiary care hospital between June 2018 and April 2021 were included. Forensic diagnoses, type of injury, age, gender, Glasgow Coma Scale score, consultation details, outcomes, and 1-month mortality status were recorded.

Results: Among the 10.128 adult forensic presentations, 396 (3.9%) geriatric patient presentations were included in the study. The most common forensic diagnoses were motor vehicle accidents (24.2%) and pedestrian accidents (24.2%). Soft tissue injuries were the most common type of injury, followed by extremity fractures. Logistic regression analysis showed that age [odds ratio (OR): 1.095; 95% confidence interval (CI): 1.027-1.169], GCS (OR: 0.655; 95% CI: 0.560-0.765), number of consultations (OR: 1.840; 95% CI: 1.312-2.581), and pedestrian accidents (OR: 0.052; 95% CI: 0.006-0.460) were significantly associated with 1-month mortality.

Conclusion: Traffic accidents, including motor vehicle and pedestrian accidents, were the most common type of forensic cases in this group of patients. One-month mortality increased with age, number of consultations, low GCS, and absence of pedestrian accident.

Keywords: Geriatrics, forensic medicine, emergency medicine, mortality

ÖZ

Amaç: Acil servislere geriatrik başvuruların sayısının artması, adli nedenlerle geriatrik başvuruların ayrı bir şekilde incelenmesini gerektirmektedir. Bu çalışmada, acil servise başvuran geriatrik adli olguların nedenleri, bu olguların bir aylık mortalite oranları ve mortaliteyi etkileyen faktörler araştırıldı.

Yöntemler: Çalışma retrospektif bir kohort olarak planlandı. Haziran 2018 ile Nisan 2021 tarihleri arasında üçüncü basamak bir hastanenin acil servisine başvuran ve adli olgu olarak bildirilen 65 yaş ve üzeri tüm hastalar çalışmaya dahil edildi. Adli tanılar, yaralanma tipi, yaş, cinsiyet, Glasgow koma skalası skoru, konsültasyon detayları, sonuçlar ve 1 aylık mortalite durumu kaydedildi.

Bulgular: Acil servise başvuran 10.128 yetişkin adli başvuru arasından 396 (%3,9) geriatrik hasta başvurusu çalışmaya dahil edildi. En yaygın adli tanılar motorlu araç kazaları (%24,2) ve yaya kazaları (%24,2) idi. Yumuşak doku yaralanmaları en sık görülen yaralanma türü olup, bunu ekstremite kırıkları takip etti. Lojistik regresyon analizi yaş (odds oranı (OR): 1.095; %95 güven aralığı (CI): 1.027-1.169), GKS (OR: 0.655; %95 CI: 0.560-0.765), konsültasyon sayısı (OR: 1.840; %95 CI: 1.312-2.581) ve yaya kazalarının (OR: 0.052; %95 CI: 0.006-0.460) 1 aylık mortalite ile anlamlı şekilde ilişkili olduğunu göstermiştir.

Sonuç: Motorlu taşıt ve yaya kazalarını içeren trafik kazaları, bu hasta grubunda en sık görülen adli olgu türüydü. Bir aylık mortalite yaş ve konsültasyon sayısının artışı ile, düşük GKS ve yaya kazası olmaması durumu ile artmıştır.

Anahtar Sözcükler: Geriatri, adli tıp, acil tıp, mortalite

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INTRODUCTION

Because of the worldwide increase in the geriatric population, geriatric patients account for an increasingly large percentage of emergency department (ED) visits (1). Members of this vulnerable patient population are more likely to be hospitalized, have more adverse outcomes, and require specialized healthcare (2-4). Atypical presentations, multiple comorbidities, and impaired cognitive function complicate the management of these patients (2). In addition, physiopathological changes leading to mental and physical deterioration with advanced age make geriatric patients more vulnerable to physical trauma and increase the adverse outcomes of trauma caused by themselves or by someone or something else (5). The geriatric patient population comprises approximately 7% of all forensic presentations in EDs (6). The mortality rates of these patients vary, and there is not enough data in the literature regarding the factors that contribute to mortality. On the other hand, longer life expectancy and the development of treatments for chronic diseases have enabled a growing number of older people to lead active lives. This longer life expectancy also increased the proportion of geriatric patients visiting the ED for forensic cases. It is important to analyze forensic cases in the geriatric population and investigate the mortality of these patients to draw attention to the cases and identify preventable causes. This study examined the causes of geriatric forensic cases presenting to the ED, the 1-month mortality of these cases, and the factors affecting mortality.

MATERIALS AND METHODS

This retrospective cohort study was designed. All patients aged 65 years who were reported as forensic cases and presented to the ED of a tertiary care hospital between June 2018 and April 2021 were included in the study. Ethical approval was obtained from the Gazi University Ethics Committee (approval number: E.88227, date: 21.05.2021). The patient data were evaluated using electronic medical records. Forensic diagnosis, type of injury, age, gender, Glasgow coma scale (GCS), consultation details, outcomes (whether hospitalization, discharge, or death), and 1-month mortality status were recorded. Forensic diagnoses included motor vehicle accidents, pedestrian accidents, falls, physical assaults, occupational accidents, abuse, stab-cut injuries, intoxication, suicides, and suspicious deaths. According to the law in Türkiye, all traffic accidents, occupational accidents, assaults, suicides, abuses, and intoxication should be forensically reported. In cases of falls, sharp injuries, and deaths, forensic reports should be prepared if a forensic incident is suspected. The types of injuries noted were soft tissue injury, fracture of extremity, cut, thorax injury, cranial pathology, vertebral fracture, maxillofacial fracture, pelvic fracture, abdominal pathology, cardiac arrest, drug intake, eye injury, chemical exposure, carbon monoxide poisoning, alcohol intake, and others.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 21 (IBM Corporation, Armonk, NY) and MedCalc® version 15.8 (MedCalc Software Ltd., Ostend, Belgium). Continuous variables are presented as median values and interquartile ranges (IQRs), whereas categorical variables are presented as frequencies and percentages. The normality of the continuous variables was evaluated using the Kolmogorov-Smirnov test. The differences between the continuous variables were determined using the Mann-Whitney U test. The categorical variables were compared using Pearson's $\chi 2$ test or Fisher's exact test. Odds ratios (ORs) are presented as 95% confidence intervals (CIs). A critical α value of 0.05 was considered statistically significant. A binary logistic regression model was constructed to identify factors predicting 1-month mortality. Each variable was tested in the univariate model, and comparisons with loose p-values of less than 0.1 were then tested in the multivariate model. Parameters containing fewer than 10 patients were not included in the analysis.

RESULTS

During the study period, 10.128 adult forensic patients visited the ED. Of all patients, 396 (3.9%) were geriatric presentations. The proportion of male participants was 56.8%, and the median age was 71 years (IQR 67-78). The most common forensic diagnoses were motor vehicle accidents (24.2%) and pedestrian accidents (24.2%). Seventy-one percent (71%) of patients were discharged from the ED. The number of patients who died within 1-month was 28 (7%). Of the patients diagnosed with abuse, 38.8% died within 1-month, accounting for 25% of the total 1-month mortality. Detailed patient characteristics, forensic diagnoses, and outcomes are summarized in Table 1. Soft tissue injuries (33.3%) were the most common type of injury, followed by extremity fractures (22.2%). Forty-nine patients (12%) had more than one diagnosis. The diagnosis data are presented in Table 2. The most frequently requested consultation was for orthopedics (25%). This was followed by neurosurgery, thoracic surgery, and plastic and reconstructive surgery at decreasing rates (13.1%, 10.3%, and 9.8%, respectively) (Figure 1). Multivariate logistic regression analysis (Hosmer-Lemeshow test, p=0.968) was performed to identify factors associated with 1-month mortality. Age (OR: 1.095; 95% CI: 1.027-1.169), GCS (OR: 0.655; 95% CI: 0.560-0.765), number of consultations (OR: 1.840; 95% CI: 1.312-2.581), and pedestrian accidents (OR: 0.052; 95% CI: 0.006-0.460) were predictors of mortality (Table 3).

DISCUSSION

In our study, most of the geriatric forensic cases that visited the ED were due to motor vehicle accidents and pedestrian accidents, accounting for half of all forensic cases. The most common types of injuries were soft tissue injuries and extremity fractures. The rate of 1-month mortality was 7%. Advanced age, lower GCS score at presentation, increased number of consultations, and absence of pedestrian accidents were associated with higher mortality rates. Many studies have found that traffic accidents are the most common forensic diagnosis in forensic cases involving EDs (7,8). With the increase in the elderly population, there has been an increase in the number of elderly people participating in traffic as drivers, passengers, and pedestrians (9). In this study, we classified traffic accidents as motor vehicle accidents and pedestrian accidents. The most common forensic diagnoses were motor vehicle accidents (24.2%) and pedestrian accidents (24.2%). In a study by Korkmaz et al. (10) 48.3% of the geriatric forensic cases involved traffic accidents, of which 6.3% involved pedestrian accidents. Dağar et al. (6) found that 53% of forensic cases involved motor vehicle collisions. According to a study by Lee et al. (9), the mortality rate of traffic

Table 1. Patient characteristics, forensic diagnoses, and outcomes and their association with one-month mortality

	Total n=396	One-month mortality Present n=28	One-month mortality Absent n=368	p
Age, median (IQR)	71 (67-78)	79.5 (75-90)	71 (67-76)	<0.001
Male gender, n (%)	225 (56.8)	18 (64.3)	207 (56.3)	0.408
GCS, median (min.-max.)	15 (3-15)	13.5 (3-14)	15 (15-15)	<0.001
Number of consultations, median (IQR)	1 (0-1)	2 (1-3)	1 (0-1)	<0.001
Forensic diagnoses, n (%)				
Motor vehicle accident	96 (24.2)	2 (7.1)	94 (25.5)	0.029
Pedestrian accident	96 (24.2)	3 (10.7)	93 (25.3)	0.083
Fall	53 (13.4)	5 (17.9)	48 (13)	0.562
Physical assault	44 (11.1)	0 (0)	44 (12)	0.058
Occupational accident	29 (7.3)	1 (3.6)	28 (7.6)	0.709
Abuse	18 (4.5)	7 (25)	11 (3)	<0.001
Stab-cut injuries	17 (4.3)	0 (0)	17 (4.6)	0.622
Intoxication	16 (4)	0 (0)	16 (4.3)	0.617
Suicide	13 (3.3)	2 (7.1)	11 (3)	0.232
Suspicious death	8 (2)	8 (28.6)	0 (0)	<0.001
Other	6 (1.5)	0 (0)	6 (1.6)	1.000
Outcome, n (%)				
Discharge from the ED	281 (71)	3 (10.7)	278 (75.5)	<0.001
Death in the ED	9 (2.3)	9 (32.1)	0 (0)	<0.001
Admitted to the ward	68 (17.2)	2 (7.1)	66 (17.9)	0.195
Admitted to the ICU	38 (9.6)	14 (50)	24 (6.5)	<0.001

GCS: Glasgow Coma Scale, IQR: Interquartile range, ED: Emergency department, ICU: Intensive care unit

Table 2. Injury types of forensic cases

Type of injury*	n (%)
Soft tissue injury	132 (33.3)
Fracture of the extremity	88 (22.2)
Cut	55 (13.8)
Thorax injury	51 (12.8)
Cranial pathology	29 (7.3)
Vertebral fracture	23 (5.8)
Maxillofacial fracture	17 (4.2)
Pelvic fracture	14 (3.5)
Abdominal pathology	10 (2.5)
Other	10 (2.5)
Cardiac arrest	9 (2.2)
Drug intake	9 (2.2)
Eye injury	7 (1.7)
Chemical exposure	6 (1.5)
Carbon monoxide poisoning	4 (1.0)
Alcohol intake	3 (0.7)

* One patient could have more than one diagnosis

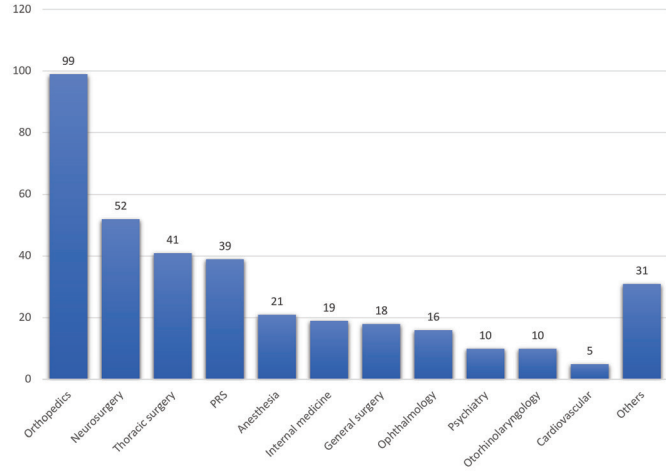

Figure 1. Number of consultations of forensic cases*

**One patient could have more than one consultation, PRS: Plastic and reconstructive surgery*

Table 3. Multivariate logistic analysis of factors associated with 1-month mortality

	OR	95% CI	p
Age	1.095	1.027-1.169	0.006
GCS	0.655	0.560-0.765	<0.001
Number of consultations (n=8)	1.840	1.312-2.581	<0.001
Pedestrian accident	0.052	0.006-0.460	0.008
Motor vehicle accident	0.452	0.084-2.444	0.356
Physical assault	0.000	0.000	-
Abuse	1.255	0.323-4.876	0.743

GCS: Glasgow Coma Scale, OR: Odds ratio, CI: Confidence interval

accidents was higher in elderly people than in those under 65 years of age. Since traffic accidents constitute almost half of all geriatric forensic cases, appropriate protective measures should be taken for this population. In the literature, falls constitute between 15% and 30% of geriatric cases presenting to the ED (2). Most geriatric patients presenting with trauma are fall cases (11,12). In our study, 13.4% of patients experienced falls. In a study on geriatric forensic cases, the rate of presentation of falls was 7% (6). Fall rates in geriatric forensic cases may not reflect all geriatric falls because not all falls are considered forensic cases. Previous studies have shown that abuse of elderly people has been detected at rates of up to 10% in high-income countries (13). Elderly abuse can occur in various forms, ranging from physical abuse to neglect (2). In our study, 4.5% of the forensic cases were cases of abuse, and 38.8% of the patients died within 1-month. Because diagnosis is not always easy, especially in cases of neglect, clinician suspicion is decisive. In the literature, it has also been noted that elder abuse is under-recognized by ED professionals (14). Various rates of abuse can arise from sociocultural differences, official practices, and different perspectives. In a study by Dağar et al. (6) an increase in in-hospital mortality was observed with increasing age in geriatric forensic cases, and falls from height were found to be associated with mortality. In the present study, advanced age was also associated with mortality. In addition, an increase in the number of consultations and a low GCS score were associated with mortality. These results are consistent with the patient's condition and disease severity, and it is important to draw the attention of clinicians to manage patients more carefully in the ED. In our study, orthopedics was the most consulted department (25%). Korkmaz et al. (10) reported the same results. In a study by Bağcı et al. (15) geriatric trauma patients were mostly hospitalized in the orthopedic clinic due to trauma presentations. In our study, 26.8% of the geriatric forensic cases were hospitalized in the ward or intensive care unit. In a study by Bağcı et al. (15) 30.1% of patients were hospitalized. Korkmaz et al. (10) reported that 35% of patients were hospitalized. The hospitalization rate was 14.7% in another study that analyzed all forensic cases (16). In a study by Çınar et al. (17) on forensic cases aged 18 years and younger, the hospitalization rate was 15%. These results show that geriatric forensic cases often require hospitalization. The single-center nature of the study is an important limitation. Therefore, the results of this study cannot be generalized to all patient groups. Since it is predicted that different forensic cases may be common in different regions, it is important to conduct multicenter studies to generalize the results. In addition, we only evaluated geriatric forensic cases and did not have data comparing them with young cases. Comparisons with all forensic cases may be necessary to obtain a better understanding of the specific conditions of geriatric cases. The study period overlaps the pandemic period. This was thought to have affected the number of patients, especially due to social restrictions.

CONCLUSION

By analyzing the presentations of this specific patient group, we found that traffic accidents, including motor vehicle and pedestrian accidents, are the most common types of geriatric forensic cases. In addition, the 1-month mortality rate of the patients increased with increasing age, a lower GCS score at presentation, an increased number of consultations, and an absence of pedestrian accident age. The growing eldery population and their increased involvement in active life are expected to increase the number of presentations of forensic incidents. Overall, the findings suggest that geriatric forensic cases are an important area of study and that efforts to prevent and treat these incidents will be increasingly important as the elderly population continues to grow.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Gazi University Ethics Committee (approval number: E.88227, date: 21.05.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: S.Y., M.A., F.B., Design: S.Y., M.A., Supervision: F.B., Resources: S.Y., M.A., Material: S.Y., Data Collection or Processing: S.Y., Analysis or Interpretation: M.A., Literature Search: S.Y., Writing: S.Y., Critical Review: M.A., F.F.

Conflict of Interest: No conflict of interest was declared by the authors.

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Assessment of the CALLY Index, a Novel Immunonutrivite Marker, in Perioperatively Treated Gastric Cancer Patients

Perioperatif Tedavi Görmüş Mide Kanseri Hastalarında Yeni Bir İmmünonutrisyonel Belirteç Olarak CALLY İndeksi Değerlendirilmesi

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ABSTRACT

Objective: This study aimed to investigate the prognostic significance of the C-reactive protein-albumin-lymphocyte (CALLY) index in patients with early-stage gastric cancer and compare it with other immune markers, such as systemic immune-inflammation index (SII), neutrophil lymphocyte ratio (NLR), and prognostic nutritional index (PNI).

Methods: We retrospectively analyzed patients with early-stage gastric cancer who received adjuvant or perioperative chemotherapy. Laboratory results were obtained from the preoperative period. The CALLY index was calculated as follows: serum albumin level (g/dL) x absolute lymphocyte counts (109/L) / CRP (mg/dL) x104.

Results: A total of 74 patients were included in the study. The median relapse-free survival (RFS) was 13.0 (95 %CI: 7.7-18.2) months in the low CALLY index group and 38.2 (95% CI:18.4-57.8) months in the high CALLY index group (p<0.001). The median overall survival (OS) was 25.0 (95% CI: 17.1-32.8) months in the low CALLY index group and 60.4 (95% CI:45.8-74.1) months in the high-CALLY-index group (p<0.001). In multivariate cox regression analyses, a low CALLY index was an independent risk factor for both relapse-free survival (RFS) and OS.

Conclusion: The CALLY index was a prognostic factor for both RFS and OS, with a higher prognostic value than other prognostic factors (NLR, PNI, SII).

Keywords: Gastric cancer, CALLY index, albumin, lymphocyte, CRP, prognostic

ÖZ

Amaç: Bu çalışma, erken evre mide kanserli hastalarda C-reaktif protein-albumin-lenfosit (CALLY) indeksinin prognostik önemini araştırmayı ve sistemik immün-inflamasyon indeksi (SII), nötrofil lenfosit oranı (NLR) ve prognostik nutrisyon indeksi (PNI) gibi diğer immün belirteçlerle karşılaştırmayı amaçladı.

Yöntemler: Adjuvan veya perioperatif kemoterapi alan erken evre mide kanserli hastalar retrospektif olarak analiz edildi. Laboratuvar sonuçları, ameliyat öncesi dönemden elde edildi. CALLY indeksi şu şekilde hesaplandı: serum albümin düzeyi (g/dL) x mutlak lenfosit sayısı (10^9/L) / C-reaktif protein (mg/dL) x 10^4.

Bulgular: Çalışmaya toplam 74 hasta dahil edildi. Düşük CALLY indeks grubunda medyan RFS 13,0 ay (95% CI: 7,7-18,2), yüksek CALLY indeks grubunda ise 38,2 ay (95% CI: 18,4-57,8) olarak bulundu (p<0,001). Medyan OS, düşük CALLY indeks grubunda 25,0 ay (95% CI: 17,1-32,8), yüksek CALLY indeks grubunda ise 60,4 ay (95% CI: 45,8-74,1) olarak tespit edildi (p<0,001). Çok değişkenli Cox regresyon analizlerinde, düşük CALLY indeksi hem nükssüz sağkalım (RFS) hem de genel sağkalım (OS) için bağımsız bir risk faktörüydü.

Sonuç: CALLY indeksi, hem RFS hem de OS açısından prognostik bir faktördü ve diğer prognostik faktörlere (NLR, PNI, SII) göre daha yüksek bir prognostik değere sahipti.

Anahtar Sözcükler: Mide kanseri, CALLY indeksi, albümin, lenfosit, CRP, prognostic

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INTRODUCTION

Adjuvant/perioperative chemotherapy is the standard treatment for early-stage/locally advanced gastric cancer after gastrectomy (1-3). Despite the use of adjuvant/perioperative chemotherapy, recurrence rates are substantial and vary according to the pathological tumor node metastasis (TNM) stage (4,5). It is critical to identify patients with a high relapse rate because this can affect follow-up and treatment strategies. Recently, researchers have explored biomarkers to predict the recurrence rate in addition to the pathological TNM stage in several solid tumors (6-9). Several markers have also been assessed in patients with early-stage/locally advanced gastric cancer (10-12). The neutrophil lymphocyte ratio (NLR) and systemic immune inflammation index (SII) are the most frequently investigated biomarkers (13,14). Recently, albumin and C-reactive protein (CRP) have started to be incorporated into these indicators because of their roles in cancer inflammation (15-17). The prognostic nutritional index (PNI), which was calculated using albumin and lymphocytes, was significant in gastric cancer because patients experienced weight loss and malnutrition after gastrectomy (18,19). The CRP albumin lymphocyte (CALLY) index is a recently validated biomarker for hepatocellular carcinoma (HCC) patients (20). The prognostic value of this treatment was assessed in the oral cavity, esophagus, non-small cell lung cancer, and colorectal cancer (21-24). However, the CALLY index has not yet been evaluated for early-stage gastric cancer. We aimed to assess the prognostic value of the CALLY index in patients with early-stage gastric cancer and compare it with conventional immune markers, such as the SII, NLR, and PNI.

MATERIALS AND METHODS

The study protocol was approved by the ethics committee of Gazi University Faculty of Medicine (approval number: 05, date: 12.03.2024). Patients did not provide written informed consent due to the retrospective study design. Every procedure was performed in accordance with the ethical guidelines and principles established by the Declaration of Helsinki.

Patients and Data Collection

We retrospectively included 74 patients diagnosed with an early-stage gastric cancer between May 2014 and August 2020. Medical records revealed clinical and pathological information including age, sex, preoperative CRP, albumin, and lymphocyte values, preoperative body weight, tumor invasion depth, lymph node metastasis, lymphovascular invasion (LVI), perineural invasion (PNI), differentiation type, and recurrence time. The American Joint Committee on cancer TNM staging system was used. Preoperative weight and height data of the patients were collected, and body mass index was calculated by dividing the weight (in kilograms) by the square of the height (in meters). CALLY index was calculated as follows: Serum albumin level (g/dL) x absolute lymphocyte counts (10^9/L)/CRP (mg/dL) x10^4. The SII was calculated using the following formula: [neutrophil (cellsx10^9/L) x platelet (cells x10^9/L)]/ lymphocyte (cells x10^9/L). PNI was formulated as: albumin (g/L) +5x L (109/L). NLR=N/L, SII=PxN/L (N: neutrophil, P: platelet, L: lymphocyte).

Statistical Analysis

Continuous variables are reported as means and standard deviations. Using Student's t-test, the means were compared. The Chi-square test or Fisher's exact test was used to compare groups whose categorical variables were calculated as numbers and percentages. Optimal cut-off values were determined using the receiver operating characteristic curve and were found to be 1.34 for the CALLY index. The optimal cutoff values were 2.4 for NLR, 48.5 for PNI, and 681x109/l for SII. Patients were divided into low and high according to cut-off values. Overall survival (OS) was defined as the interval between operation and death. The definition of recurrence-free survival (RFS) was the duration between gastric cancer surgery and recurrence. Using the Kaplan-Meier method was used to calculate survival curves. The log-rank test was used to determine the differences between the curves. Hazard ratios (HRs) were determined using Cox regression analyses. In the multivariate Cox regression analysis, all variables with a p value <0.05 in the univariate analysis were included. P value<0.05 was considered statistically significant, and a 95% confidence interval (CI) was determined. SPSS software (version 27.0; SPSS, Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Patient Characteristics

A total of 74 patients were included in the study. The median age was 60 (28-74) years. 28 (37.8%) patients were women. 18 (24.3%) had a signet ring cell component. Poor differentiation was observed in 11 (14.9%) of the samples. The baseline characteristics of the patients according to the CALLY index are demonstrated in Table 1. Her-2 and PD-L1 status was not known, since the study was retrospective and was not performed in the early stage due to the payment conditions of our country.

Recurrence-free Survival Analysis

At the end of the follow-up period, 35 (47.3%) patients had relapsed, and 18 (51.4%) of them were in the low CALLY index group. The median RFS was 13.0 (95% CI: 7.7-18.2) months in the low CALLY index group and 38.2 (95% CI:18.4-57.8) months in the high CALLY index group (p<0.001). According to univariate analyses, besides stage 2 disease, a high CALLY index (HR: 0.46; 95% CI: 0.29-0.73, p<0.001) and high PNI (HR: 0.55; 95CI: 0.35-0.86, p=0.01) was associated with a longer RFS. In the multivariate Cox regression analyses, only stage 3 disease (HR: 2.12; 95% CI: 1.26-3.55, p=0.004) and low CALLY index (HR: 2.16; 95% CI: 1.36-3.4, p<0.001) were independent risk factors for poor RFS. The Kaplan-Meier curve for RFS according to the CALLY index and Cox regression analyses is demonstrated in Figure 1 and Table 2.

Overall Survival Analysis

The median follow-up period was 33.5 months. The median OS was 25.0 (95% CI: 17.1-32.8) months in the low CALLY index group and 60.4 (95% CI: 45.8-74.1) months in the high CALLY index group (p<0.001). According to univariate analysis, other than stage 2 disease, a high CALLY index (HR: 0.45, 95% CI: 0.28-0.71, p<0.001) and a high PNI (HR: 0.53; 95% CI: 0.33-0.85, p=0.009) related to longer OS. In the multivariate Cox regression analyses, only stage 3 disease (HR: 2.49; 95% CI: 1.47-4.21, p<0.001) and low CALLY index (HR: 2.22; 95% CI: 1.39-3.54, p<0.001) were independent risk factors for poor OS. The Kaplan-Meier curve for OS according to the CALLY index and Cox-regression analyses is presented in Figure 2 and Table 3.

Table 1. Demographic and pathological features of patients according to the CALLY index

Features	Total (n=74)	CALLY index <1.34 (n=29)	CALLY index ≥1.34 (n=45)	p
Age (years)				
<65	49 (66.2%)	21 (28.4%)	28 (37.8%)	
≥65	25 (33.8%)	8 (10.8%)	17 (23.0%)	0.366
Gender				
Female	28 (37.8%)	13 (17.6%)	15 (20.3%)	
Male	46 (62.2%)	16 (21.6%)	30 (40.5%)	0.320
Perineural invasion				
Yes	43 (58.1%)	15 (20.3%)	28 (37.8%)	
No	31 (41.9%)	14 (18.9%)	17 (23.0%)	0.372
Lymphovasc. invasion				
Yes	47 (63.5%)	18 (24.3%)	29 (39.2%)	
No	27 (36.5%)	11 (14.9%)	16 (21.6%)	0.514
Differantiation				
Well	10 (13.5%)	2 (2.7%)	8 (10.8%)	
Moderate	34 (45.9%)	16 (21.6%)	18 (24.3%)	
Poor	11 (14.9%)	4 (5.4%)	7 (9.5%)	
Unknown	19 (25.7%)	7 (9.5%)	12 (16.2%)	
TNM stage				
Stage 2	28 (37.8%)	14 (18.9%)	14 (18.9%)	
Stage 3	46 (62.2%)	15 (20.3%)	31 (41.9%)	0.137
BMI				
<25	41 (55.4%)	15 (20.3%)	26 (35.1%)	
≥25	33 (44.6%)	14 (18.9%)	19 (25.7%)	0.609
NACT				
Yes	46 (62.2%)	15 (20.3%)	31 (41.9%)	
No	28 (37.8%)	14 (18.9%)	14 (18.9%)	0.137
Chemotherapy				
FOLFOX	28 (37.8%)	14 (18.9%)	14 (18.9%)	
FLOT	46 (62.2%)	15 (20.3%)	31 (41.9%)	0.137

BMI: Body mass index, FOLFOX: 5-fluourouracil, oxaliplatin, FLOT: 5-fluourouracil, oxaliplatin, docetaxel, TNM: Tumor node metastasis, NACT: Neoadjuvant chemotherapy

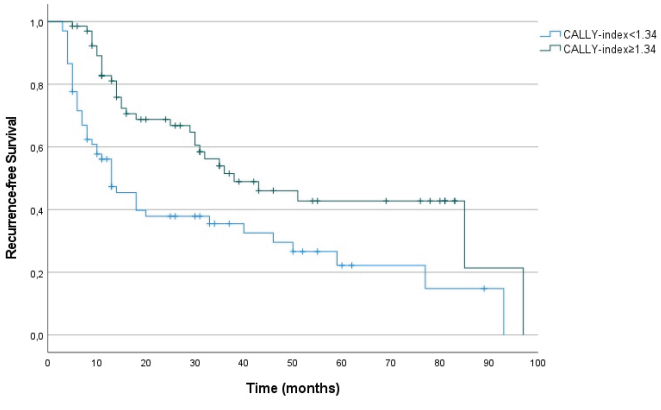

Figure 1. Kaplan-Meier curve for recurrence-free survival according to the CALLY Index

CALLY: C-reaktif protein-albumin-lenfosit

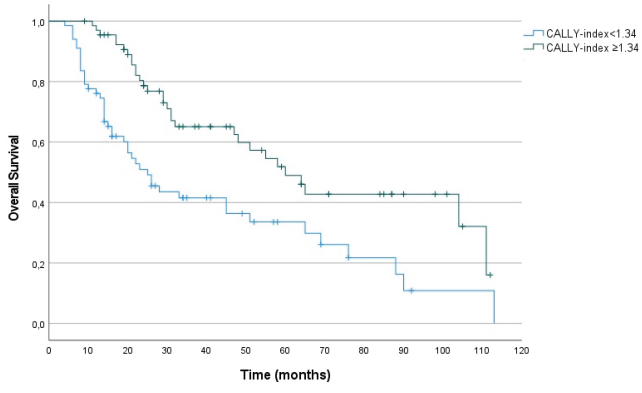

Figure 2. Kaplan-Meier curve for overall survival according to the CALLY index

CALLY: C-reaktif protein-albumin-lenfosit

Table 2. Univariate and multivariate analyses of recurrence-free survival

	Univariate analysis		Multivariate analysis	
Features	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age (years)				
<65				
≥65	1.07 (0.66-1.73)	0.78		
Gender				
Female				
Male	0.77 (0.48-1.23)	0.282		
TNM stage				
Stage 2				
Stage 3	1.99 (1.19-3.34)	**0.009**	2.12 (1.26-3.55)	**0.004**
Lymphovascular invasion				
Yes				
No	0.85 (0.54-1.34)	0.505		
Perineural invasion				
Yes				
No	0.97 (0.62-1.53)	0.908		
CALLY index				
Low				
High	0.46 (0.29-0.73)	**<0.001**	0.43 (0.27-0.69)	**<0.001**
PNI				
Low				
High	0.55 (0.35-0.86)	**0.01**	2.01 (0.56-7.23)	0.284
SII				
Low				
High	1.02 (0.65-1.60)	0.907		
NLR				
Low				
High	1.03 (0.66-1.61)	0.883		

CALLY: C-reactive protein-albumin-lymphocyte, SII: Systemic immun inflammation index, NLR: Neutrophil lymphocyte ratio, PNI: Prognostic nutritional index, TNM: Tumor, node, metastasis, HR: Hazard ratio, CI: Confidence interval

DISCUSSION

This study demonstrated that in patients with early-stage gastric cancer treated with adjuvant/perioperative chemotherapy, the CALLY index was a prognostic factor for both RFS and OS, with a higher prognostic value than other prognostic factors (NLR, PNI, SII). The CALLY index is calculated using serum albumin, lymphocyte, and CRP levels and serves as an index reflecting nutrition, immune status, and inflammatory response. Albumin, which is synthesized in the liver with a long half-life, often indicates nutritional status (25). Additionally, albumin can be used as an indicator of inflammatory response, with hypoalbuminemia having strong predictive value for poor prognosis in many cancers (26). Lymphocytes are essential cells in the host's cytotoxic immune response and have an important influence on the cell-mediated antitumor environment. Lymphopenia within the tumor suggests an insufficient host immune response against the tumor and an unfavorable prognosis (27). CRP, an acute-phase reactant protein regulated by interleukin 6, is a clinically recognized marker of inflammatory response (28). The CALLY index, which combines these three parameters, can serve as a comprehensive marker for cancer diagnosis. Furthermore, its calculation method is not complex and is easily accessible and inexpensive because it is based on laboratory parameters commonly used in practice. When the CALLY index was initially used in HCC, it was found to be much stronger than other indices and closely linked to cancer prognosis (20). Subsequently, the prognostic benefit of the CALLY index has been confirmed in several malignancies. A study involving 279 surgically treated patients with oral cavity cancer revealed that the preoperative CALLY index was a simple and inexpensive prognostic score (21). Another study involving 1260 patients with colorectal cancer reported that the CALLY index was independently associated with prognosis and had a higher clinical

Table 3. Univariate and multivariate analyses of overall survival

	Univariate analysis		Multivariate analysis	
Features	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p**
Age (years)				
<65				
≥65	1.31 (0.81-2.13)	0.259		
Gender				
Female				
Male	0.82 (0.51-1.32)	0.426		
TNM stage				
Stage 2				
Stage 3	2.21 (1.31-3.71)	0.003	2.49 (1.47-4.21)	**<0.001**
Lymphovascular invasion				
Yes				
No	0.95 (0.59-1.51)	0.834		
Perineural invasion				
Yes				
No	1.16 (0.73-1.85)	0.514		
CALLY index				
Low				
High	0.45 (0.28-0.71)	**<0.001**	0.40 (0.25-0.64)	**<0.001**
PNI				
Low				
High	0.53 (0.33-0.857)	**0.009**	1.58 (0.47-5.27)	0.456
SII				
Low				
High	1.10 (0.69-1.75)	0.668		
NLR				
Low				
High	1.13 (0.71-1.85)	0.602		

CALLY: C-reactive protein-albumin-lymphocyte, SII: Systemic immun inflammation index, NLR:neutrophil lymphocyte ratio, PNI:prognostic nutritional index, TNM:tumor,node,metastasis, HR: Hazard ratio, CI: Confidence interval

value (24). Moreover, a high CALLY-index with an optimal cutoff value of 3.0 was associated with better survival outcomes in patients with epithelial ovarian cancer patients (29). Although CALLY is significantly associated with prognosis in various cancers, the threshold value for CALLY varies. The best CALLY threshold in our study for non-linear relationships between CALLY and prognosis was calculated using the receiver operating characteristic curve. Consequently, CALLY was selected as the best potential indicator for the classification of nutrition and immune-inflammatory prognosis compared with other immune-inflammatory indices. Although previous studies have demonstrated the prognostic significance of the CALLY index in several cancers, no study has investigated its prognostic value of the CALLY index in early stage gastric cancer to date.

CONCLUSION

This study is the first to explore the prognostic value of the CALLY index in early-stage gastric cancer. The findings demonstrate that the CALLY index is a significant prognostic factor for both recurrence-free survival and overall survival. However, there are some limitations. First, this was a retrospective study and may have incurred selection bias. Second, the sample size was small, as patients with stage I disease and those treated with regimens other than FOLFOX and FLOT were excluded to create a more homogeneous group. Lastly, the optimal cutoff value for the CALLY index has not been uniformly reported across studies. Therefore, prospective studies with clearly defined cutoff values and larger cohorts are needed to validate its prognostic potential.

Ethics

Ethics Committee Approval: The study protocol was approved by the ethics committee of Gazi University Faculty of Medicine (approval number: 05, date: 12.03.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: O.A., N.Ö., Concept: K.B.Y., O.Y., Design: A.O., O.A., Supervision: A.O., Resources: N.Ö., Material: K.B.Y., O.Y., Data Collection or Processing: O.A., N.Ö., Analysis or Interpretation: O.Y., K.B.Y., Literature Search: K.B.Y., O.A., Writing: O.A., O.Y., Critical Review: A.O., N.O.

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Comparison of Laparoscopic Sleeve Gastrectomy and Intragastric Balloon Procedures

Laparoskopik Sleeve Gastrektomi ile İntragastrik Balon Uygulamasının Kıyaslanması

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ABSTRACT

Objective: We aimed to compare laparoscopic sleeve gastrectomy (LSG), which is proven to be effective for obesity, with intragastric balloon procedure (IGB), a minimally invasive technique.

Methods: The study included patients admitted to our surgical clinic between December 2018 and October 2021. During the study period, 106 patients with morbid obesity treated at our clinic were analyzed. The results of 65 patients who underwent LSG and 41 who underwent IGB were retrospectively evaluated. Demographic characteristics, body mass index, and comorbidities were recorded. Furthermore, the quality of life questionnaires that the participants completed before the treatment procedures and one year after the treatment were analyzed. p<0.05 value was considered statistically significant.

Results: The mean age of the patients was 42.97 years. The mean preoperative body weight and BMI value were 122.75±11.03 kg and 43.98±4.19 kg/m^2, respectively, for the LSG patients, while they were 122.75±11.03 kg and 43.98±4.19 kg/m^2, respectively, for the IGB patients. The mean length of hospital stay was 3.31±0.80 days in LSG and 1.12±0.40 days in IGB, and the mean operation time was 63.92±7.07 minutes in LSG and 21.66±4.39 minutes in IGB. Both results were statistically significant (p<0.05). There was no mortality, and one patient who underwent IGB experienced intolerance.

Conclusion: Both LSG and IGB procedures being performed today are effective methods for obesity treatment. However, LSG is more effective in improving obesity-related comorbidities and weight loss, whereas IGB is a safe method that is more easily applicable, reversible, and has lower complication rates.

Keywords: Laparoscopic sleeve gastrectomy, intragastric balloon, obesity

ÖZ

Amaç: Günümüzde obezite üzerine etkinliği ispatlanmış olan laparoskopik sleeve gastrektomi (LSG) operasyonu ile minimal invaziv bir teknik olan intragastrik balon (İGB) uygulamasını kıyaslamayı amaçladık.

Yöntemler: Çalışmamız Aralık 2018 ile Ekim 2021 tarihleri arasında cerrahi kliniğimize başvuran hastalar arasında gerçekleştirildi. Bu dönemde kliniğimizde morbid obezite nedeniyle tedavi görmüş olan 106 hasta incelendi. LSG yapılan 65 hasta ve İGB uygulanan 41 hastanın sonuçları retrospektif olarak değerlendirildi. Çalışmaya dahil edilen hastaların demografik özellikleri, vücut kitle indeksleri, komorbiditeleri kaydedildi. Ayrıca hastaların uygulanan tedavi prosedürleri öncesi ve tedaviden bir yıl sonra doldurmuş oldukları, yaşam kalitesini ölçen anketler analiz edildi. p<0,05 değeri istatistiksel olarak anlamlı kabul edildi.

Bulgular: Hastaların genel ortalama yaşı 42,97 idi. LSG cerrahisi uygulanan hastaların preoperatif vücut ağırlığı ve vücut kitle indeksi ortalamaları sırasıyla 122.75±11,03 kg ve 43,98±4,19 kg/m^2 idi. İGB uygulaması yapılan hastaların ise preoperatif vücut ağırlığı ve VKİ ortalamaları sırasıyla 122,75±11,03 kg ve 43,98±4,19 kg/m^2 idi. Ortalama hastanede kalış süresi LSG'de 3,31±0,80 gün, İGB'de 1,12±0,40 gün olarak; operasyon süresi LSG'de 63,92±7,07 dakika, İGB'de 21,66±4,39 dakika olarak bulunmuştur. Bulunan her iki sonuç istatistiksel olarak anlamlıdır (p<0.05). Çalışmaya katılan hastalarda mortalite kaydedilmedi. İGB yapılan bir hastada intolerans saptandı.

Sonuç: Günümüzde uygulanmakta olan LSG ve İGB prosedürlerinin her ikisi de obezitenin tedavisinde etkili yöntemlerdir. Bununla birlikte LSG, obeziteye bağlı komorbiditelerin iyileşmesinde ve kilo kaybında daha etkili iken; İGB, daha kolay uygulanabilir, reversibl ve daha düşük komplikasyon oranlarına sahip, güvenli bir yöntemdir.

Anahtar Sözcükler: Laparoskopik sleeve gastrektomi, intragastrik balon, obezite

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INTRODUCTION

Obesity is a health problem caused by an imbalance between energy intake and use of energy (1). In recent years, its prevalence has been increasing. It has been classified as a global epidemic by the World Health Organization (2). Although various definitions of obesity exist, body mass index (BMI) is currently used as a standardized measure to ensure consistency in practice (3). The value is calculated by dividing the weight in kilograms by the square of the height in meters.

It has been revealed that many diseases are associated with obesity from the past to the present. The primary diseases associated with obesity include type 2 diabetes mellitus (DM), dyslipidemia, hypertension, and obstructive sleep apnea syndrome (OSAS) (4-9). Alongside comorbidities, the financial burden of obesity and related health issues is increasing on healthcare systems (10,11). Numerous approaches have been developed to fight obesity in response to these challenges. Typically, these approaches are categorized into two main groups: Surgical and non-surgical methods. When healthy eating diets, physical activity, and behavioral therapies fail to produce desired outcomes, invasive and surgical methods with proven efficacy in weight loss are used (12). While laparoscopic sleeve gastrectomy (LSG) is the most common bariatric surgery carried out today, intragastric balloon procedure (IGB) is an increasingly popular method (13-15). IGB can be performed independently for weight loss, and there are instances where it is performed as a preparatory step preceding the intended bariatric procedure (16). The aim of this study was to investigate and compare the safety, efficacy, and impact on quality of life (QoL) between LSG and IGB, both of which are commonly used in bariatric surgery clinics.

MATERIALS AND METHODS

In this study, a total of 106 patients who underwent either LSG or IGB between December 2018 and October 2021 at our surgical clinic were retrospectively analyzed. While 65 of these patients underwent LSG, 41 underwent the IGB procedure. Participants were between 18-65 years of age. Furthermore, the study included patients with a BMI>40 kg/m^2 or those with a BMI>35 kg/m^2 accompanied with obesity-related comorbidities. Patient data were obtained from hospital archive files and the hospital's electronic operating system. Participants' demographic and clinical characteristics, such as type of procedure, age, gender, comorbidities, duration of the procedure, length of hospital stay, and complications, were examined and analyzed. In addition, body weight, BMI values, endoscopy forms recorded during the pre-procedure and 12-month post-procedure follow-up of the patients and our clinic's standardized questionnaires consisting of 40 questions assessing QoL were accessed and analyzed. In the questionnaire, the highest score was 100, with a higher score representing a higher QoL. Those with missing data were excluded from the study. Following the protocols of our bariatric surgery clinic, all patients were thoroughly briefed about the procedures and provided written informed consent before any intervention. All patients were evaluated by a multidisciplinary mechanism consisting of endocrinology, pulmonology, cardiology, psychiatry, and dietitian before the procedures were carried out by a surgical team experienced in bariatric surgery and endoscopy. The study was approved by the Selçuk University of Medical Sciences local ethics committee (approval number: 2024/171, date: 12.03.2024) and was conducted in accordance with the Declaration of Helsinki. LSG was performed under general anesthesia, and the IGB procedure was performed under sedation anesthesia. The IGB procedure was performed endoscopically while the patient was in the lateral decubitus position. The balloon was inflated in the stomach with 500 cc of saline solution and 50 cc of methylene blue, all within direct visualization through endoscopy, reaching a total volume of 550 cc. Six months after the procedure, endoscopy was performed to remove the balloon. The balloon was deflated entirely, and it was extracted using a specialized instrument during the endoscopic procedure. LSG was performed using a laparoscopic endostapler with standard vertical stomach transection. After both procedures, patients were admitted to the surgical department for treatment, follow-up, and observation. Follow-ups were organized at 2 weeks, 3-months, 6-months and 12-months after the procedures.

Statistical Analysis

The IBM SPSS version 20.0 software was used for the statistical analysis of the data. The Kolmogorov-Smirnov test was used to assess whether the variables had a normal distribution. To compare paired groups, the Student's t-test was used for normally distributed variables, and the Mann-Whitney U test was used for parameters without a normal distribution. Multivariate cross-tabulations were assessed using either the chi-square test or the Fisher Exact test. Pre- and postoperative recovery scores within the same group were analyzed using the Paired-Samples t-Test. Results were considered statistically significant when $p<0.05$.

RESULTS

The study included 106 patients. While 65 patients underwent LSG, 41 underwent the IGB procedure. Among them, 61 were female (57.5%), and 45 were male (42.5%). The mean age of patients who underwent LSG surgery was 42.17±7.70 years. The mean preoperative body weight and BMI of patients undergoing LSG surgery were 122.75±11.03 kg and 43.98±4.19 kg/m^2, respectively. The mean age of patients who underwent the IGB procedure was 44.24±9.40 years. The mean preoperative body weight and BMI of patients who underwent the IGB procedure were 122.75±11.03 kg and 43.98±4.19 kg/m^2, respectively. Patients undergoing LSG had preoperative comorbidities of hypertension (51/65, 78.5%), DM (33/65, 50.8%), dyslipidemia (43/65, 66.2%), and OSAS (13/65, 20%). Patients who underwent IGB had preprocedural comorbidities of hypertension (33/41, 80.5%), DM (20/41, 48.8%), dyslipidemia (27/41, 65.9%), and OSAS (9/41, 22%). The mean length of hospital stay was 3.31±0.80 (days) in the LSG group and 1.12±0.40 (days) in the IGB group. The mean operation time was recorded as 63.92±7.07 minutes in the LSG group and 21.66±4.39 minutes in the IGB group (Table 1). Short- and long-term complications of LSG and IGB were analyzed and documented during hospital stay and follow-up (Table 2). Conservative treatment was applied to 3 patients who experienced bleeding in the early postoperative period after LSG. No new surgical intervention was needed. Following the IGB procedure, one patient experienced intolerance to medical treatment, leading to premature removal of the gastric balloon before its scheduled duration. During the post-procedure follow-up, 10 patients (15.4%) in the LSG group

and 8 patients (19.5%) patients in the IGB group experienced gastroesophageal reflux (GER) symptoms. In the LSG group, 22 patients (33.8%) were diagnosed with esophagitis during the control endoscopy, whereas in the IGB group, only 2 patients (4.9%) patients were diagnosed with esophagitis. No mortality was noted among the participants. Improvements in the comorbidities of the patients at 12-month follow-up after the procedures are presented in Table 3. Statistically significant improvements in hypertension, DM, and dyslipidemia were observed after LSG compared with IGB ($p<0.05$). The comparison of patients' QoL scores between the LSG and IGB groups before and 12 months after the procedure, according to the results of the standardized QoL measurement questionnaire, is presented in Table 4. Despite a greater increase in QoL observed in the LSG group compared with the IGB group, there was no statistically significant difference between them ($p>0.05$). Moreover, the LSG and IGB groups were separately evaluated for their effects on QoL. The results demonstrated that both procedures led to improvements in QOL, as illustrated in Table 5.

Finally, the 12-month pre-procedure and post-procedure changes in body weight, BMI changes and weight loss rates of the participants were compared, as presented in Table 6.

DISCUSSION

Table 1. Demographic and clinical characteristics of the patients

	LSG, n=65 n (%)	IGB, n=41 n (%)	p
Age (Years)	42.17±7.70	44.24±9.40	0.360
Gender			
Female	38 (58.5)	23 (56.1)	0.810
Male	27 (41.5)	18 (43.9)	
Weight before the procedure (kg)	122.75±11.03	118.44±11.84	0.069
BMI before the procedure (kg/m^2)	43.98±4.19	43.32±3.69	0.078
Hypertension			
Yes	51 (78.5)	33 (80.5)	0.802
No	14 (21.5)	8 (19.5)	
Diabetes			
Yes	33 (50.8)	20 (48.8)	0.842
No	32 (49.2)	21 (51.2)	
Dyslipidemia			
Yes	43 (66.2)	27 (65.9)	0.975
No	22 (33.8)	14 (34.1)	
OSAS			
Yes	13 (20)	9 (22)	0.809
No	52 (80)	32 (78)	
Duration of hospital stay (days)	3.31±0.80	1.12±0.40	**<0.001**
Duration of procedure (minutes)	63.92±7.07	21.66±4.39	**<0.001**

LSG: Laparoscopic sleeve gastrectomy, IGB: Intragastric balloon, BMI: Body mass index, OSAS: Obstructive sleep apnea syndrome (Statistically significant p values are written in bold)

Table 2. Comparison of complications

	LSG n (%)	IGB n (%)	p
Pain			
Yes	15 (23.1)	5 (12.2)	0.207
No	50 (76.9)	36 (87.8)	
Bleeding			0.282
Yes	3 (4.6)	0 (0)	
No	62 (95.4)	41 (100)	
Esophagitis			
Yes	22 (33.8)	2 (4.9)	**<0.001**
No	43 (66.2)	39 (95.1)	
GER Symptoms			
Yes	10 (15.4)	8 (19.5)	0.581
No	55 (84.6)	33 (80.5)	
Intolerance			
Yes	0 (0)	1 (2.4)	0.387
No	65 (100)	40 (97.6)	

GER: Gastroesophageal reflux, LSG: Laparoscopic sleeve gastrectomy, IGB: Intragastric balloon

Table 3. Comorbidity assessment 12 months after LSG and IGB

	LSG n (%)	IGB n (%)	p
Hypertension			**0.001**
Improved	38 (74.5)	13 (39.4)	
Not improved	13 (25.5)	20 (60.6)	
Total	51 (100)	33 (100)	
Diabetes			**0.007**
Improved	24 (72.7)	7 (35)	
Not improved	9 (27.3)	13 (65)	
Total	33 (100)	20 (100)	
Dyslipidemia			**0.028**
Improved	29 (67.4)	11 (40.7)	
Not improved	14 (32.6)	16 (59.3)	
Total	43 (100)	27 (100)	
OSAS			0.609
Improved	11 (84.6)	6 (66.7)	
Not improved	2 (15.4)	3 (33.3)	
Total	13 (100)	9 (100)	

OSAS: Obstructive sleep apnea syndrome, LSG: Laparoscopic sleeve gastrectomy, IGB: Intragastric balloon

Obesity is a global public health problem with its increasing prevalence, affecting individuals of all ages (17,18). Numerous surgical and non-surgical interventions exist to address this condition, with new ones continually emerging alongside advancements in medical science (19-21). Bariatric surgery is the most effective treatment method for obesity (22). LSG is the most common bariatric procedure (23). However, surgical methods are invasive and generally lead to irreversible changes in body anatomy and physiology. Given this

awareness, IGB, despite being a relatively recent technique, has emerged as a noteworthy option for patients who prefer to avoid surgical interventions. In our study, in which we compared the LSG and IGB methods, the IGB application was attractive for patients given its shorter hospital stay and procedure duration. Furthermore, the fact that IGB does not require general anesthesia is another factor that simplifies the procedure. Complications that may occur following bariatric treatment procedures include pain, bleeding, GER symptoms, esophagitis, and intolerance. Control endoscopy should be particularly conducted in patients with symptoms of GER, such as chronic cough, epigastric pain, and regurgitation, to determine whether concurrent esophagitis exists. When evaluating the two procedures investigated in our study for complications, the esophagitis after LSG was significantly higher. According to the findings of a study published by Lim et al. (24) in 2020, some patients required revision surgery due to the occurrence of esophagitis that was resistant to medical treatment following LSG. Similarly, previous studies have indicated an increase in both the severity and prevalence of esophagitis following LSG (25). Although LSG tends to cause bleeding and pain to a greater extent than IGB, the observed differences were not statistically significant. However, a higher proportion of patients experienced GER symptoms with IGB than with LSG. Moreover, there is a risk of intolerance to IGB, which, if it occurs, may lead to incomplete treatment for the patient. Hypertension, DM, dyslipidemia, and obstructive sleep apnea syndrome are among the most prevalent obesity-related comorbidities. Upon analyzing the 12-month results of LSG and IGB, it became evident that LSG was notably better, particularly regarding improvements in comorbidities such as hypertension, DM, and dyslipidemia. Proportionally better outcomes were observed with LSG regarding improvement in OSAS. Nonetheless, as a minimally invasive method, IGB alone was also able to achieve significant reductions in comorbidities. One of the most comprehensive studies on this subject to date is a retrospective study conducted by Genco et al. (26) in Italy, which included 2515 patients. According to the study, the rate of improvement in comorbidities was 44.8% in patients who underwent IGB. Several studies have highlighted the beneficial effect of weight loss on comorbidities and associated mortality (27-32). In our study, both LSG and IGB were found to improve the QoL of the participants positively. Based on the patients' QoL scores before the procedure, the increase in LSG was higher than that of IGB at the 12-month follow-up, although not statistically significant. Pre-procedure QoL scores were higher in the IGB group. From this perspective, patients undergoing LSG initially have a lower QoL, and this factor should be considered when selecting the appropriate method for individual patients. Upon analysis of patients for weight loss and reduction in BMI, although both procedures proved to be viable options, our study revealed that LSG was more effective than IGB. Moreover, despite studies suggesting that IGB is suitable for patients with a BMI of 30-40 kg/m^2, the initial mean BMI for the IGB group in our study was above 40 kg/m^2, yet effective results were achieved (33).

Table 4. Comparison of the LSG and IGB groups in terms of quality of life

	LSG n=65	IGB n=41	p
Pre-procedure quality of life score	67.22±8.38	71.32±7.66	**0.021**
Quality of life score at 12-months post-procedure	84.12±5.31	85.51±5.10	0.340
Changes in quality of life scores	16.91±10.52	14.20±9.62	0.220

LSG: Laparoscopic sleeve gastrectomy, IGB: Intragastric balloon

Table 5. Evaluation of quality of life improvements within the groups

	Preprocedure quality of life score	Quality of life score at 12-months after the procedure	p
LSG	67.22±8.38	84.12±5.31	**<0.001**
IGB	71.32±7.66	85.51±5.10	**<0.001**

LSG: Laparoscopic sleeve gastrectomy, IGB: Intragastric balloon

Table 6. Comparison of the LSG and IGB methods in terms of their results

	LSG n=65	IGB n=41	p
BMI change (kg/m2)	11.12±5.02	8.12±5.41	**0.002**
Body weight change (kg)	37.11±12.89	27.51±13.87	**0.001**
Loss of excess weight (%)	59.86±6.36	45.27±6.02	**<0.001**

LSG: Laparoscopic sleeve gastrectomy, IGB: Intragastric balloon

Study Limitations

The retrospective nature, single-center design, and the absence of longer follow-up results were the limitations of this study.

CONCLUSION

Weight loss plays an important role in the successful management of obesity and its associated comorbidities. The method chosen to achieve weight loss should be both appropriate and effective while ensuring safety. LSG, which is a surgical intervention, is more effective in improving comorbidities and weight loss. On the other hand, IGB, which is a minimally invasive approach, is associated with fewer complications, shorter hospitalization and procedure durations, easier applicability, and reversibility.

Ethics

Ethics Committee Approval: The study was approved by the Selçuk University of Medical Sciences local ethics committee (approval number: 2024/171, date: 12.3.2024)

Informed Consent: Informed consent was optained.

Footnotes

Authorship Contributions

Concept: F.T., S.Y., Design: F.T., S.Y., Supervision: S.Y., Resources: F.T., S.Y., Material: F.T., S.Y., Data Collection or Processing: F.T., Analysis or Interpretation: F.T., S.Y., Literature Search: F.T., Writing: F.T., S.Y., Critical Review: S.Y.

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Effects of Resveratrol on the Kidney in Rats with Streptozotocin Induced Diabetic Nephropathy

Streptozotosin ile Diyabetik Nefropati Oluşturulan Sıçanlarda Resveratrolün Böbrek Üzerindeki Etkileri

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ABSTRACT

Objective: Diabetic nephropathy is one of the most significant causes of end-stage renal failure and is a common microvascular complication of diabetes (D). Resveratrol (RSV), a natural compound found in grape skins and red wine, has potent antioxidant properties. This study aimed to evaluate the effects of RSV in a streptozotocin (STZ)-induced diabetic rat model.

Methods: Animals were divided into four groups: control, RSV, D, and D + RSV. The diabetic group received a single intraperitoneal dose of STZ (65 mg/kg). After 2 weeks, rats with basal blood glucose levels >250 mg/dL were considered diabetic. RSV(10 mg/kg/day) was administered orally by gavage for 8 weeks. Metabolic analyses were conducted throughout the study. At the study's end, transmission electron microscopy and immunohistochemical analyses were performed. Additionally, the left kidney was isolated and suspended in an organ bath to study the functional changes without damaging the renal artery.

Results: In the study, increased transforming growth factor-beta, fibronectin and inducible nitric oxide synthase immunoreactivity, which are markers of D-induced renal degeneration, were partially

ÖZ

Amaç: Diyabetik nefropati, son dönem böbrek yetmezliğinin en önemli nedenlerinden biridir ve diyabetin (D) yaygın bir mikrovasküler komplikasyonudur. Üzüm kabuğu ve kırmızı şarapta bulunan doğal bir bileşik olan resveratrol (RSV), güçlü antioksidan özellikler gösterir. Bu çalışmada, streptozotosin ile oluşturulan D sıçan modelinde RSV'in diyabetik nefropati üzerindeki etkilerinin değerlendirilmesi amaçlanmıştır.

Yöntemler: Hayvanlar kontrol, RSV, D ve D + RSV olmak üzere dört gruba ayrıldı. D gruplara tek bir intraperitoneal doz streptozotosin (65 mg/kg) uygulandı. İki hafta sonra, bazal kan glukoz seviyeleri 250 mg/dL'nin üzerinde olan sıçanlar D olarak kabul edildi. RSV (10 mg/kg/gün) 8 hafta boyunca gavaj yoluyla oral olarak uygulandı. Çalışma boyunca metabolik analizler yapıldı. Çalışmanın sonunda, transmisyon elektron mikroskopisi ve immünohistokimyasal analizler yapıldı. Ek olarak, sol böbrek izole edildi ve renal artere zarar vermeden fonksiyonel değişiklikleri incelemek için bir organ banyosunda askıya alındı.

Bulgular: Çalışmada, D'nin neden olduğu böbrek dejenerasyonunun belirteçleri olan artmış transforme edici büyüme faktör-beta fibronektin ve indüklenebilir nitrik oksit sentaz immünoreaktivitesinin

This study was presented at the 42nd National Physiology Congress of the Turkish Society of Physiological Sciences (Düzce, 2016).

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reduced by RSV treatment. In group D, decreased endothelial nitric oxide synthase uptake (weak immune reactivity) was observed, whereas this uptake increased with RSV treatment (moderate immune reactivity). Furthermore, both angiotensin II and phenylephrine responses were reduced in group D treated with RSV. Vasodilator responses to acetylcholine were also reduced in this group.

Conclusion: RSV may protect against diabetic nephropathy by modulating key pathways involved in renal degeneration and vascular function and may have potential as a therapeutic agent for slowing disease progression.

Keywords: Resveratrol, diabetic nephropathy, proinflammatory cytokines, transmission electron microscope, renal vascular responses

RSV uygulaması ile kısmen azaldığı tespit edildi. D grupta endotelyal nitrik oksit sentaz tutulumunda azalma (zayıf immün reaktivite) gözlenirken, bu tutulum RSV tedavisi ile arttı (orta derecede immün reaktivite). Ayrıca, RSV ile tedavi edilen D grupta hem anjiyotensin II hem de fenilefrin yanıtları azaldı. Asetilkoline verilen vazodilatör yanıtlar da bu grupta azaldı.

Sonuç: RSV, böbrek dejenerasyonu ve vasküler fonksiyonda rol oynayan anahtar yolakları modüle ederek diyabetik nefropatiye karşı koruma sağlayabilir ve hastalığın ilerlemesini yavaşlatmada terapötik bir ajan potansiyeli olabileceği düşünülebilir.

Anahtar Sözcükler: Resveratrol, diyabetik nefropati, proinflamatuar sitokinler, transmisyon elektron mikroskobu, renal vasküler yanıtlar

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease with a high prevalence worldwide. It is characterized by hyperglycemia and is associated with a number of critical clinical complications, including nephropathy, retinopathy, neuropathy, and cardiomyopathy (1,2). Diabetic nephropathy (DN) is a microvascular complication that causes end-stage renal failure, impairs patients' quality of life, and ultimately leads to death. DN is observed in 30-40% of patients with type 1 and 2 DM (3,4). DN is characterized by the following pathological features: Glomerulosclerosis, excessive extracellular matrix deposition, glomerular hypertrophy, and basement membrane thickening (5). Hemodynamic changes are important in the pathogenesis of DN. Chronic hyperglycemia induces metabolic changes and dysfunction in endothelial-vascular smooth muscle cells, which in turn causes vascular dysfunction and hemodynamic changes in the kidneys (6). A growing body of evidence indicates that elevated blood glucose levels in DN are the result of a complex interplay between multiple factors, including advanced glycation end products and metabolic and hemodynamic processes, such as the renin-angiotensin system (7). The regulation of dietary habits using a diet based on fruits and vegetables can delay or prevent the progression of DM. Consequently, there has been a surge in interest in foods rich in polyphenols (8). Resveratrol (RSV) (3,4,5-trihydroxy stilbene, respiratuar sinsitiyal virus) is a natural phytoalexin that has been extensively studied in recent years. It is a polyphenolic compound that is primarily found in grains, fruits, vegetables, legumes, and plant-derived beverages, including tea, coffee, and wine (1,9). RSV exhibits a wide range of biological and pharmacological properties, including anti-diabetic, anti-carcinogenic, anti-inflammatory, anti-oxidative, and cardiovascular protective effects (1). The primary objective of DM treatment is to reduce blood glucose levels, enhance insulin sensitivity, and safeguard pancreatic cells (2,10). RSV has been demonstrated to possess anti-diabetic effects, exerting anti-hyperglycemic activity through the stimulation of intracellular glucose transport, a process that occurs independently of insulin (11). Additionally, it has been observed to reduce insulin secretion in the pancreatic cells of isolated rats and to protect pancreatic β cells in diabetic animals (12). Furthermore, it has been demonstrated that RSV can prevent DM-induced kidney damage and mesangial cell proliferation, as well as improve glomerular hypertrophy and mesangial cell glucolipotoxicity. This exerts a beneficial effect on renal function during DM (13). In light of the data presented in the literature, the aim of this study was to investigate the effects of RSV, an important antioxidant, on DN, one of the late-stage complications of diabetes (D), in rats that were made diabetic using streptozotocin (STZ).

MATERIALS AND METHODS

Study Design and Animals

Thirty adult male Wistar albino rats, whose weights varied between 250 and 300 g obtained from Gazi University Laboratory Animal Raising and Experimental Research Center and used in this study. The rats were fed freely in separate cages under a 12-hour dark cycle at temperatures above 24±2 °C with standard rat food and tap water. The relative humidity of the environment was maintained between 30% and 45%. The rats were housed in polycarbonate cages with sawdust underneath. The *in vivo* experiments of the study were carried out in the Gazi University Laboratory Animal Raising and Experimental Research Center and Gazi University Faculty of Medicine Physiology Department laboratory with the permission of the Gazi University Animal Experiments Local Ethics Committee (approval number: G.Ü.ET-11.086, date: 26.09.2011)

Experimental Design

The rats were divided into 4 groups.

1. Control group (C, n=6),
2. RSV group (RSV, n=8),
3. Diabetes group (D, n=8),
4. Diabetes + resveratrol group (D + RSV, n=8).

D was made intraperitoneally (i.p.) using a single dose of 0.1 M (pH:4.5) STZ (65 mg/kg) dissolved in cold citrate buffer (14). Seventy-two hours after STZ administration, rats with a fasting blood glucose >250 mg/dL were considered diabetic. For two weeks following the development of D, the blood glucose of the subjects was measured at specific intervals. During this period, approximately the stabilization of D was ensured. The control groups (C and RSV groups) were administered an injection of i.p. 1 mL of STZ solvent citrate tampon. Following a 2-week adaptation period, for a period of 8 weeks, the RSV groups (R and D + RSV) were administered RSV dissolved in 0,1 M ethanol of 96% at a dose of 10 mg/kg, and the Control and D groups were administered 0.1 M ethanol via oral gavage (15). The body weights, fasting blood glucose values, liquid intake, and urinary discharge of all subjects were noted at the beginning of the study (1st measurement) 2 weeks after the administration of STZ or citrate

tampon (2nd measurement), during the administration of RSV or ethanol, (3rd and 4th measurements), and prior to being sacrificed (5th measurement) by being placed in a metabolic cage mechanism. Glucose, blood urea nitrogen (BUN), calcium, creatinine, potassium, and sodium were examined in blood samples taken from the caudal vein of the rats at the beginning of the study; 2 weeks after the administration of STZ or citrate tampon, and before sacrifice. At the beginning and end of the experiments, glucose, ketone, nitrite/nitrate, leucocyte, bilirubin, albumin, and creatinine levels were analyzed in urine using Siemens Multistix 10 SG urine analysis test strips. 24 hours after the final gavage administration, the rats were sacrificed under intramuscular Rompun + Ketamin (50+60-100 mg/kg) anesthesia by drawing blood from the heart. After the completion of euthanasia, the left kidney was isolated without destroying the renal artery. The right kidney tissue was removed and placed in formalin for histopathological analysis.

Observation of Renal Vascular Responses

Following the development of nephropathy in the isolated perfused rat kidney, the left kidney was isolated without destroying the renal artery to study the functional changes. The solution was perfused using Krebs Hanseleit solution, hung in an isolated organ bath gassed with a mixture of 95% O2 and 5% CO2 and stabilized for approximately 40 min.

The contraction responses were then examined following the administration of bolus manner phenylephrine (Phe) at doses of 10-8, 10-7, 10-6, and 10-5 M, respectively, waiting for approximately 15 min for stabilization between each dose. After that, following the 20-minute stabilization period, Angiotensin II (Ang II) was administered at doses of 10-9, 10-8, 10-7 M respectively, waiting for approximately 15 minutes for stabilization between each dose. Finally, 20 µl 10-2 M Phe was added to 200 cc Krebs Hanseleit solution because the final concentration would be 10-6 M and perfusion pressure was expected to rise. While the increase continued gradually, as soon as the plateau phase was observed, acetylcholine (ACh) was administered at doses of 10-6, 10-5, 10-4 M, waiting for approximately 15 min for stabilization between each dose, and the contraction and relaxation responses were examined. Drug doses were determined following a comprehensive review of numerous studies in the literature pertaining to vascular responses. Dose ranges that were hypothesized to be suitable for our hypothesis were selected based on this evaluation (16-19).

Histological and Immunohistochemical Analyses

Transmission Electron Microscope (TEM) Study

Tissue samples were dissected into pieces of 1mm^3 were fixed in 2.5% 0.1 M phosphate buffered glutaraldehyde (pH 7.4) for 2-h. At the end of the fixation period, the tissues were washed with buffer three times and post-fixated for 1-h with 1% osmium tetraoxide. At the end of this period, tissues were dehydrated using a graded alcohol series. Finally, the tissues treated with propylene oxide were embedded in the embedding material prepared using the Araldite CY212 kit. The blocks were polymerized for 48-h in an incubator at 56 °C. The half-thin sections were stained with toluidine blue and examined under a light microscope. The thin sections obtained from the marked regions were stained with uranyl-acetate-lead-citrate and evaluated using a Zeiss EVO 010 transmission attachment scanning electron microscope (20).

Immunohistochemical Method

The tissue samples were fixed in 10% neutral formalin, and paraffin blocks were prepared after a routine light microscope study. For the sections placed on polylysine glass, the avidin-biotin peroxidase immune staining technique, one of the indirect immune-histochemical techniques, was used. Anti-transforming growth factor-beta (TGF-β), anti-inducible nitric oxide synthase (iNOS), anti-endothelial nitric oxide synthase (eNOS), and anti-fibronectin were used as primary antibodies. AEC and DAB were used as chromogens, and hematoxylin was preferred as the background stain. The prepared materials were studied using a Leica DM4000 computer-equipped photo-light microscope. For each antibody, score tables for all groups were prepared with respect to the cortex and medulla in the renal sections. 5 areas were chosen randomly on each glass with a magnification rate of x400 and the density of retention was scored semi quantitatively as follows: 0 (-, no retention), 1 (+, weak immunoreactivity), 2 (++, moderate immunoreactivity), 3 (+++, strong immunoreactivity) (21).

Statistical Analysis

The data were compared with Kruskal-Wallis and Mann-Whitney U nonparametric tests using the SPSS 20.0 statistical program. $P<0.01$ values were considered significant.

RESULTS

Fasting Blood Glucose, Body Weight, Liquid Intake and Amounts of Urinary Discharge

There were no changes in fasting blood glucose levels between the control and RSV groups for 8 weeks. In the diabetic groups (D, D + RSV), after STZ administration, symptoms of hyperglycemia, fasting blood glucose, increased fluid intake and urine output, and decreased body weight were detected.

Blood Biochemistry Findings

In the blood biochemistry analysis, a statistically significant increase in alkaline phosphatase (ALP) and alanine aminotransferase (ALT) levels due to chronic D and in BUN and creatinine levels due to deterioration in renal function were observed in the subjects. There was a decrease in the sodium, potassium, calcium levels. Improvements in these deteriorated parameters were not achieved with RSV treatment.

Immunohistochemical findings of eNOS retention

eNOS retention was found at the cortex and medula levels in the control group. In the glomeruli, retention varying from moderate to strong was observed in the proximal and distal tubules (Figure 1A). The retention in the medullar collecting ducts was cytoplasmic (Figure 1B). In the RSV group, the density of retention in some glomeruli and medullar collecting ducts was relatively decreased compared with the control group (Figures 1C, 1D). In the D group, degenerated tubules were observed in the cortex. Although eNOS immunoreactivity was found to have decreased significantly compared with the previously mentioned groups, moderate retention was observed in some

podocytes (Figure 1E). The retention in the medullar collection ducts decreased significantly compared with the two groups (Figure 1F). In the D + RSV group, eNOS retention in the Bowman capsule, especially at the glomerular level, increased compared with the D group. eNOS immunoreactivity detected in some veins of this group also caught our attention (Figure 1G). Retention in the medulla also increased compared with the D group, and the strong eNOS immunoreactivity in some regions attracted attention (Figure 1H).

Immunohistochemical Findings iNOS Retention

In the Control group, iNOS immune retention varied from weak to moderate in the medulla in some collecting ducts (Figure 2B). In the RSV group, expression was observed to have increased in the proximal and some distal tubules compared with that in the control group (Figure 2C). The retention rate in the medullary region was similar to that of the Control group (Figure 2D). In the D group, glomeruli shrank due to sclerotic changes in the cortex, and degenerated distal tubules drew attention. It was observed that iNOS immunoreactivity increased in the proximal tubules and was weak in the degenerated distal tubules and renal glomeruli (Figure 2E). The retention of duct iNOS in the medula increased dramatically (Figure 2F). In the D + RSV group, iNOS retention in the cortex was the same as that of the D group (Figure 2G), and it was observed to have decreased in the collecting ducts in the medulla (Figure 2H).

Immunohistochemical Findings-TGF-β Retention

In the cortex regions of the control and RSV groups, the retention was observed to be the same and very weak especially in glomeruli (Figure 3A, Figure 3C). While the retention in the medullary regions of the two groups was similar, the presence of strong coloration in some places in the RSV group attracted attention compared with the control group (Figure 3B, Figure 3D). In the D group, TGF-β retention was increased in both the cortex and medulla compared with the aforementioned groups (Figure 3E, Figure 3F). In the D + RSV group, similar to the previously mentioned group, distinct TGF-β expression was detected in degenerated tubules (Figure 3G, Figure 3F).

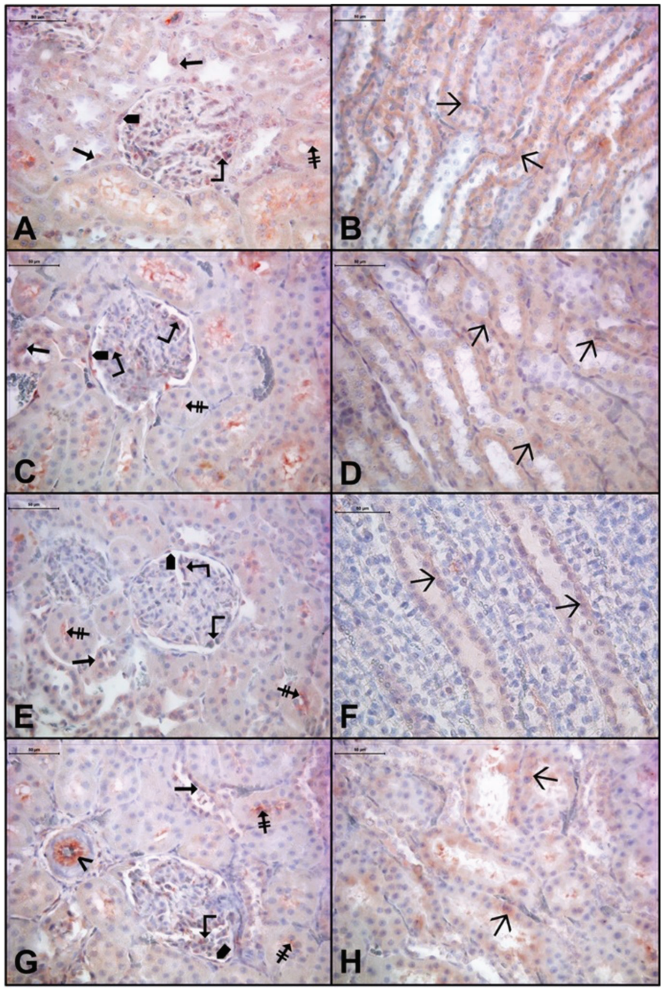

Figure 1. eNOS immunoreactivity; Control Group cortex (A), medulla (B), RSV Group cortex (C), medulla (D), Diabetes Group cortex (E), medulla (F), diabetes + resveratrol group cortex (G), medulla (H) areas.

↳ : Glomerul, ➡: Parietal lobe of Bowman capsule ‡: Proximal tubule, ➡: Distal tubule, ➔: Collector ducts, >: Blood vessel (Immunperoxidase-hematoxylinX400).

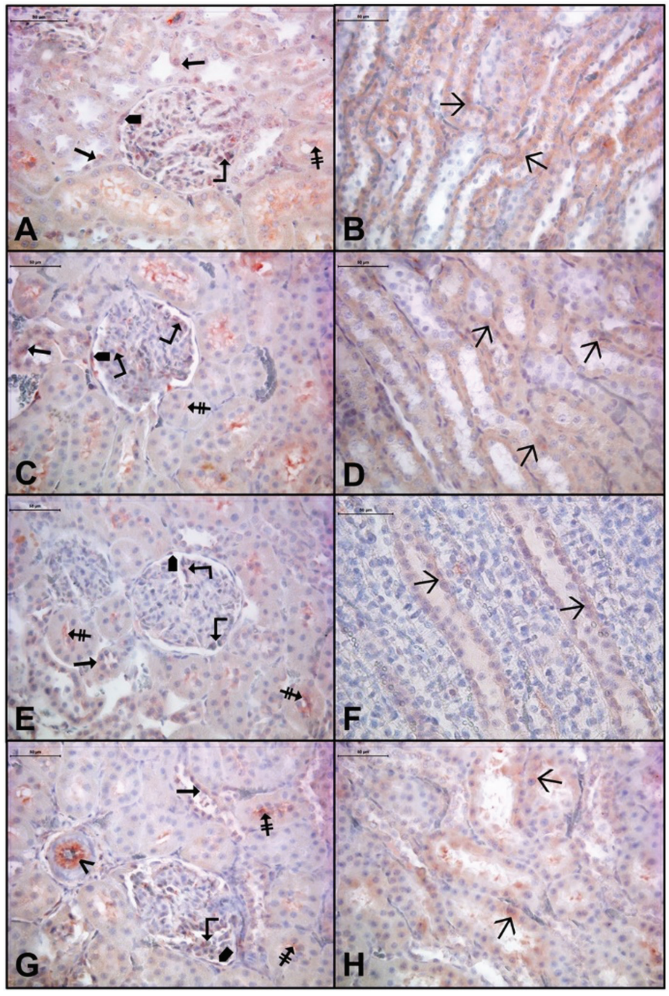

Figure 2. iNOS immunoreactivity; Control Group cortex (A), medulla (B); RSV Group cortex (C), medulla (D); Diabetes Group cortex (E), medulla (F); Diabetes+Resveratrol Group cortex (G), medulla (H) areas. ↳ : Glomerul, ‡: Proximal tubule, ➡: Distal tubule, ➔: Collector ducts, >: Degenerate tubules (Immunperoxidase-hematoxylinX400).

RSV: Respiratuar sinsitiyal virus

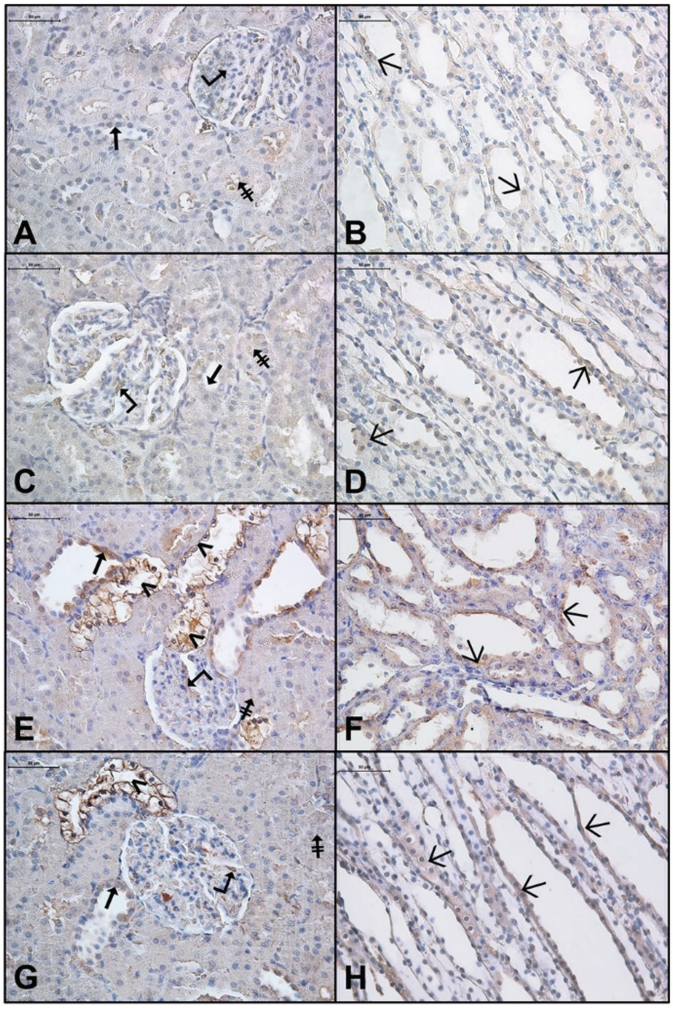

Figure 3. TGF-α immunoreactivity; Control Group cortex (A), medulla (B); RSV Group cortex (C), medulla (D); Diabetes Group cortex (E), medulla (F); Diabetes+Resveratrol Group cortex (G), medulla (H) areas. ↳: Glomerul, ‡: Proximal tubule, ➡: Distal tubule, ➔: Medullar zone, >: Degenerate tubules (Immunperoxidase-hematoxylinX400).

RSV: Respiratuar sinsitiyal virus

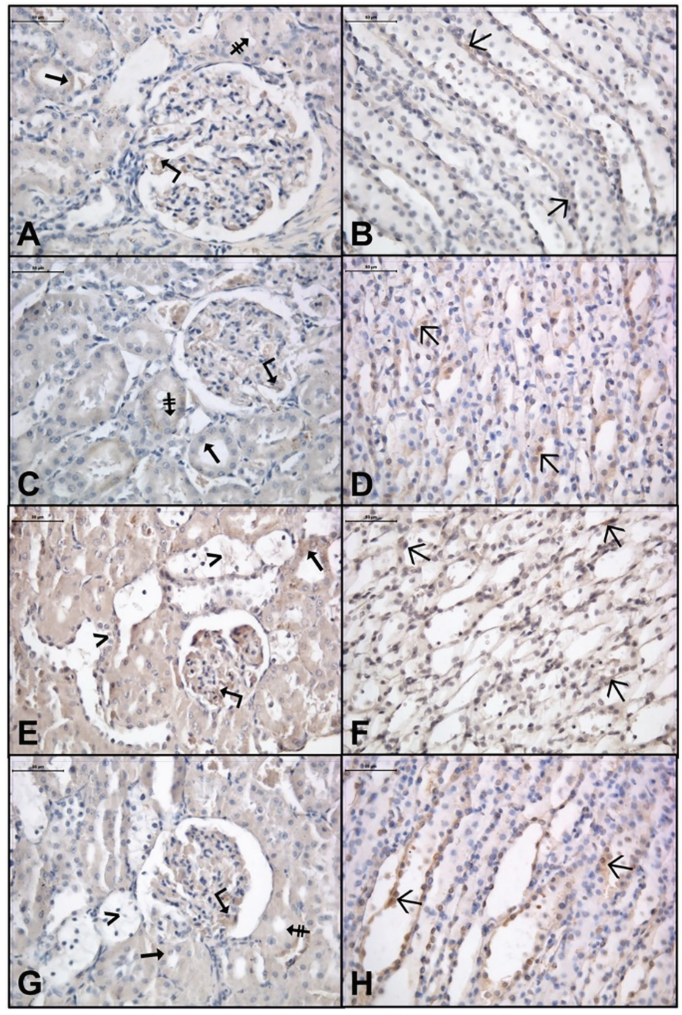

Figure 4. Fibronectin immunoreactivity; Control Group cortex (A), medulla (B), RSV Group cortex (C), medulla (D), Diabetes Group cortex (E), medulla (F); Diabetes + Resveratrol Group cortex (G), medulla (H) areas.

↳: Glomerul, ➡: Parietal lobe of Bowman capsule ‡: Proximal tubule, ➡: Distal tubule, ➔: Medullar zone, >: Degenerate tubules (Immunperoxidase-hematoxylinX400).

RSV: Respiratuar sinsitiyal virus

Immunohistochemical Findings-Fibronectin Retention

Weak TGF-β expression in the glomeruli was detected in both the control and RSV groups (Figure 4A, Figure 4C). In the RSV group, cells that exhibited strong immune positivity in certain areas compared with the control group attracted attention (Figure 4B, Figure 4D). In the D group, fibronectin retention was increased in the cortex and medulla compared with the other groups. The degenerated tubules observed in this group did not exhibit distinct immunoreactivity (Figure 4E, Figure 4F). In the D + RSV group, fibronectin retention in the cortex region decreased significantly compared with the D group. Moderate fibronectin retention was detected in the glomeruli (Figure 4G). In the medulla, cells that exhibited strong cytoplasmic retention were identified (Figure 4F).

Transmission Electron Microscopy (TEM) Findings

TEM studies performed, glomerular basal membrane (GBM), mesangium, capillary endothelial cells, and podocyte pedicles were examined. All structures in the Control and RSV-treated groups were normal. However, in the D group, wrinkling of the GBM and irregular thickness were observed. An electron-dense deposit was detected in the mesangial matrix. The loss of podocyte pedicels was observed in many areas. It was also found that capillary endothelial cells had undergone hyperplasia and had a hyperthropic appearance. Large vacuoles were detected in some endothelial cells (Figure 5I). In all sites examined in the D + RSV group, the above-mentioned structures were observed to be preserved. The endothelial cells had normal structures, and few cells had vacuoles. Loss of podocyte

pedicels was not observed. However, wrinkling was still present in some areas. The mesangium had a normal structure, and electron-dense deposits were not observed (Figure 5II).

Renal Vascular Responses

Phe Responses

Although there were no significant differences between the control group and RSV group, there was a significant increase in the D group in the Phe 10-6 and 10-5 doses when compared with the Control group ($p<0.01$). A significant decrease in all Phe doses in the D + RSV group was observed compared with the control group in terms of contraction responses ($p<0.01$) (Figure 6).

Angiotensin II Response

Although there were no significant differences among the Control, D, and RSV groups in the Ang II 10-9 and 10-8 doses, there was a significant increase in the contraction response of the RSV group in the Ang II 10-7 dose ($p<0.01$). A significant decrease was observed in the D+RSV group for all doses of Ang II in terms of contraction responses compared with the control group ($p<0.01$) (Figure 6).

Acetylcholine Responses

When the ACh relaxation responses were studied, a significant decrease in all doses of ACh was observed in the D + RSV group compared with the control group ($p<0.01$). There were no significant differences among the other groups at any dose (Figure 6).

DISCUSSION

DN significantly impairs patients' quality of life by inducing various abnormal physiological and structural changes that lead to renal function deterioration (22). The primary goal of DN treatment is to manage complications and slow the progression of kidney damage. It has been reported that improving abnormal physiological conditions caused by D, such as reducing proteinuria and controlling high blood pressure levels, can slow down the progression of DN (23). In recent years, extensive research has focused on the anti-diabetic and antioxidant properties of RSV in various animal models. Studies have shown that RSV can exert beneficial effects in animals with D, thereby improving the incidence of D. For instance, in similar studies examining STZ-induced D, RSV administration was reported to attenuate weight loss, lower serum glucose, insulin, triglyceride, and free fatty acid levels, and alleviate symptoms such as polyphagia and polydipsia (24,25). Contrary to many findings in the literature, our study did not observe a significant improvement in the characteristic symptoms of hyperglycemia, such as body weight loss, increased fluid intake, and urinary output, with RSV treatment. Blood biochemistry analyses revealed an increase in ALB, ALP, ALT, BUN, and creatinine levels, along with a decrease in sodium levels, in patients with D. These findings supported the deterioration in renal function due to D in our approximately 10-week old diabetic animals, and thus the DN we aimed to make. Furthermore, our study did not detect any significant improvement in the deteriorated

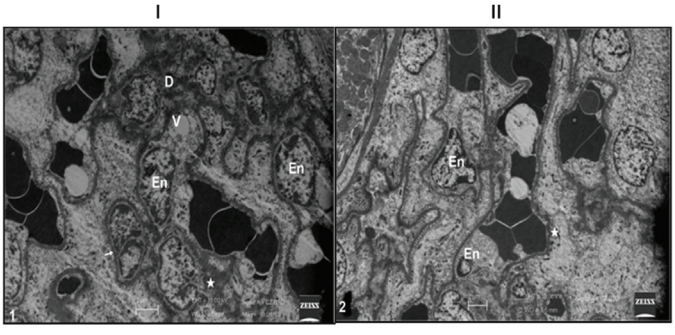

Figure 5. Electron microscobe findings on diabetes group (1) and diabetes + resveratrol group (2) En: capillaries endothelial cells with normal structures observed throughout the tissue, *: consulted GBM, ↑: Podocyte pedicelles (Uranil-acetate-Lead citrate x10000)

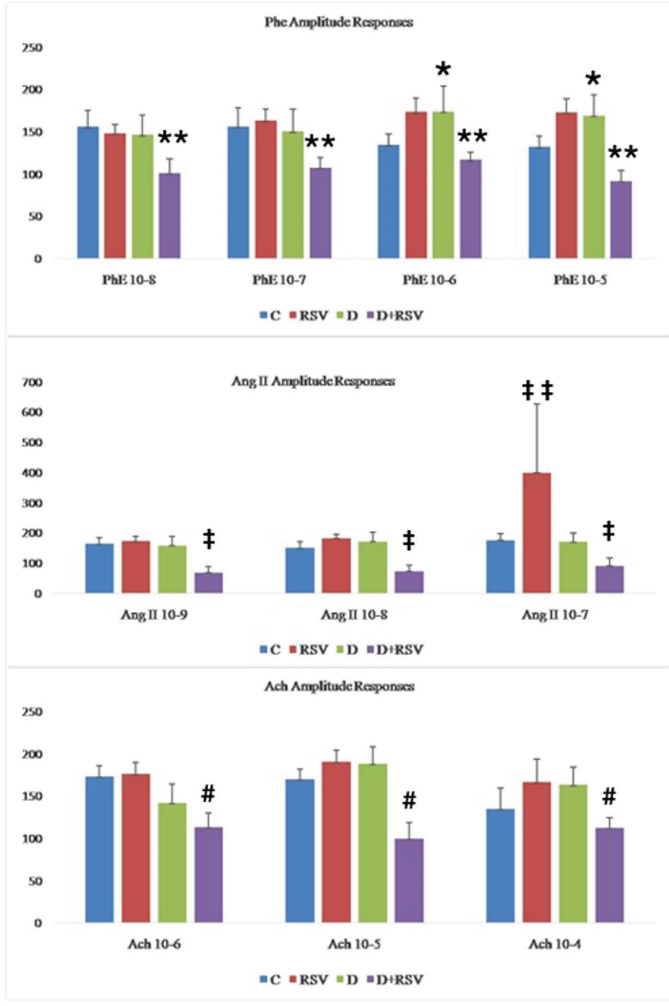

Figure 6. Phenilephrine, Angiotensin II, and Acetlycholine Amplitude Responses in Renal Artery

Phenilephrine;

* $p<0.01$compared with control group (for 10-6,10-5 doses)

** $p<0.01$ compared with the control and diabetes groups (for all doses)

Angiotensin II;

‡ $p<0.01$ compared with the control and diabetes groups (for all doses)

‡‡ $p<0.01$ compared with all groups (for 10-7dose)

Acetlycholine;

# $p<0.01$ compared with the control and diabetes groups (for all doses)

parameters with RSV administration, consistent with several studies in the literature. For instance, a study (26) reported no improvement in elevated aspartate transaminase (AST) and ALT levels in diabetic rats treated with RSV, whereas another study (27) observed no improvement in AST and ALT levels in pigs with metabolic syndrome following RSV treatment. DN is a pathological condition characterized by glomerular hypertrophy, GBM thickening, and an increase in extracellular matrix increase, and results in tubulointerstitial and glomerular fibrosis and sclerosis (28). Podocytes, which surround the capillaries in the Bowman glomeruli, play a crucial role in forming the filtration barrier together with renal endothelial cells (3). Thickening of GBM (29), the decrease in the number of podocytes associated with proteinuria, and loss of podocyte pedicels (30) are among recognized microscopic changes of DN. Our study results regarding the presence of proteinuria in urine and electron microscopy (EM) findings supported DN progression in individuals with D. EM studies revealed locally wrinkled and irregularly thickened GBM and electron-dense deposits in the mesangial matrix of diabetic animals. Contrary to the literature findings, our study did not observe complete recovery although locally wrinkled GBM persisted in the RSV-treated group. However, electron-dense deposits in the mesangial matrix and loss of podocyte pedicels were not observed in the RSV-treated group. Similar studies have reported improvements in GBM thickness, glomerular fibronectin, collagen IV, and TGF-β expression following RSV treatment in animals with D (15,31). In our study, we observed that although the wrinkling appearance in the GBM persisted locally in the RSV-administered diabetic group compared with the diabetic control group, no complete recovery was observed, as reported in the literature. However, RSV administration prevented electron-dense deposits in the mesangial matrix and loss of podocyte pedicels, in contrast to diabetic animals without RSV treatment. This finding is consistent with previous findings in which RSV reduced GBM thickness, mesangial cell numbers, and podocyte loss in diabetic rats. Additionally, diabetic kidneys typically exhibit various morphological anomalies, including tubular cell swelling, endothelial cell vacuolization, and glomerular hypertrophy (32). In our study, RSV-administered diabetic rats showed normal capillary endothelial cells and fewer vacuoles compared with untreated diabetic rats, consistent with studies demonstrating RSV's protective effects against renal hypertrophy (33,34). TGF-β is a multifunctional cytokine implicated in various cellular activities (35) and is one of the main effectors of structural changes in DN (28). TGF-β is known to induce renal hypertrophy, and RSV has been shown to inhibit TGF-β production and decreases collagen levels (36). Immunohistochemical analyses in our study revealed increased TGF-β expression in both the cortex and medullary regions of diabetic kidneys, supporting DN development. Conversely, RSV administration reduced TGF-β expression, consistent with the literature. Furthermore, we observed decreased eNOS and increased iNOS levels in the diabetic group. However, RSV administration increased eNOS levels, consistent with previous studies indicating the potential of RSV to enhance eNOS expression and nitric oxide (NO) production (37,38). In addition to evaluating biochemical and histological parameters, we assessed vascular responses in diabetic rat kidneys. Chronic hyperglycemia induces metabolic changes and dysfunction in endothelial and vascular smooth muscle cells, leading to vascular dysfunction and hemodynamic changes in the kidneys and other organs (6). The endothelium is vital for a variety of physiological functions in the vessel wall, including the regulation of vascular tone. The endothelial vasodilator NO produces various vasoactive mediators that act on vascular smooth muscle cells, such as vasoconstrictor endothelin (39). NO is produced by a mechanism stimulated by hormones such as ACh, bradykinin, and insulin and catalyzed by the nitric oxide synthase (NOS) enzyme. Increasing eNOS activation and expression, one of the NOS isoforms, causes glomerular and functional hemodynamic changes in the diabetic kidney (40). RSV has been reported to protect against ischemia-reperfusion injury in the kidney, heart, and brain (39,41). Our study revealed that RSV administration increased iNOS and eNOS expression in the cortex and medulla of the kidney, suggesting potential vasodilatory effects. These findings are consistent with studies showing RSV-induced renal vasodilation via endothelial-dependent NO production (42,43). In both studies, NOS inhibition or deendothelization partially reversed the vascular relaxation caused by RSV.

The contraction responses formed by both Phe and Ang II depend on the release of Ca^{+2} from the sarcoplasmic reticulum over isotol trisphosphate (IP3) and diacylglycerol within the cell following the stimulation of α1 receptors by Phe and the stimulation of angiotensin receptor 1 receptors by Ang II. In a study examining the cardiovascular effects of RSV, rats were fed corn syrup, which contains high fructose. It was observed that in the thoracic aortic rings of rats, despite the contraction response to Phe and relaxation response to ACh, RSV had a protective effect on the endothelium (44). Our results showed that both the Ang II and Phe responses were significantly reduced in rat kidneys isolated from diabetic rats treated with RSV. It is known that in hyperglycemia, KATP channels are closed. It has been shown that Ca+2 increase in cells is associated with the activation of K+ channels, KATP channel blockers inhibit Ca+2 increase (45), and RSV decreases the sensitivity of smooth muscles to Ca+2 and causes an increase in systolic Ca+2 in the endothelium (46). In our study, the significant improvement in the increased contraction responses mediated by increased Phe and ACh levels in the D group with RSV application also supports the findings in the literature. A study was reported in diabetic rats and showed that noradrenaline and ATP-mediated contraction responses significantly increased in vas deferens tissue, and RSV administration corrected this increase (47). In another study, the effect of RSV on Ca+2 levels in the heart valve endothelium was investigated. It has been stated that the endothelium - dependent relaxant effect of RSV is associated with an increase in Ca+2 levels in endothelial cells, but the inhibitory effect of vascular smooth muscle contraction may occur due to the decrease in Ca+2 levels (46). In our study, decreased vasoconstrictor responses were observed in the D group treated with RSV; inhibition of Ca+2 increase in D suggested that RSV might be due to the reduction of Ca+2 sensitivity of smooth muscles. It is thought that a significant decrease in the vasodilator responses of ACh in kidneys isolated from patients with D treated with RSV may also be through the same mechanism. By preventing an increase in intracellular Ca+2 in hyperglycemia, decreasing the sensitivity of RSV to Ca+2 may cause a decrease in response.

Study Limitations

In this study, we examined the protective effects of resveratrol against DN in an STZ-induced diabetic rat model. However, these findings

are limited to humans. We used a fixed dose of resveratrol (10 mg/kg/day); varying doses and treatment durations might yield more comprehensive results. The exact molecular mechanisms underlying the protective effects of resveratrol have not been fully elucidated. Although we conducted histopathological and functional analyses, advanced imaging and molecular techniques could provide deeper insights. Furthermore, resveratrol's effects were not compared with those of other treatments for DN, which limits our understanding of its relative efficacy.

CONCLUSION

RSV, which we administered to diabetic rats at a dose of 10 mg/kg/day for 8 weeks, did not generally cause a significant improvement in the biochemical findings of D. However, TGF-β, fibronectin, and iNOS immunoreactivity, which increased in line with the kidney degeneration caused by D decreased partially; It was observed that the level of eNOS, which decreased with D, increased. In the diabetic group treated with RSV, both the Ang II and Phe responses and the vasodilator ACh responses decreased in the same group. Based on the findings of our study, we can conclude that RSV does not have a very positive effect on the symptoms of D, as frequently stated in the literature. However, the results of our study are important in terms of demonstrating that RSV may have some protective effects against the negative effects of DN and shedding light on this issue. Since prevention or reduction of disease complications is important both for the patient and in terms of reducing health-related costs, the positive results of RSV on late-stage kidney damage of D in our study suggest that it may be a new treatment option for patients in the coming days, along with other literature information.

Ethics

Ethics Committee Approval: The study was approved by the Gazi University Animal Experiments Local Ethics Committee (approval number: G.Ü.ET-11.086, date: 26.09.2011).

Informed Consent: This study is not applicable because it involves animal subjects.

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Footnotes

Authorship Contributions

Concept: D.T., Ç.Ö., A.B., E.D., Design: D.T., Ç.Ö., S.E., E.D., G.T.K., G.G., Supervision: D.T., Ç.Ö., A.B., S.E., Resources: D.T., Ç.Ö., E.D., G.T.K., G.G., Material: D.T., Ç.Ö., E.D., G.T.K., G.G., Data Collection or Processing: D.T., Ç.Ö., Analysis or Interpretation: D.T., Ç.Ö., A.B., S.E., E.D., G.T.K., G.G., Literature Search: D.T., Ç.Ö., Writing: D.T., Ç.Ö., Critical Review: D.T., Ç.Ö., A.B., S.E., E.D., G.T.K., G.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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Coexistence of Ankylosing Spondylitis, Metabolic Syndrome and Gout Disease

Ankilozan Spondilit, Metabolik Sendrom ve Gut Hastalığı Birlikteliği

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ABSTRACT

Ankylosing spondylitis (AS) and gout are inflammatory diseases causing arthritis. Metabolic syndrome (MetS) is characterized by insulin resistance accompanied by systemic disorders, such as abdominal obesity, glucose intolerance or diabetes mellitus, dyslipidemia, hypertension, and coronary artery disease. Although a few studies have reported the co-existence of AS and gout as well as AS and MetS, there is no case report in the literature regarding the co-existence of AS, acute gout arthritis, and MetS. Here, we present a case who had all these disorders in together. In conclusion, this report aimed to call attention of involved physicians' about metabolic abnormalities, including gout and MetS, which might be accompany to AS. It would be useful for the prevention and treatment of such potential deleterious conditions in the clinical course or management of AS.

Keywords: Ankylosing spondylitis, metabolic syndrome, gout, arthritis, obesity

ÖZ

Ankilozan spondilit (AS) ve gut, artrite sebep olan inflamatuvar hastalıklardır. Metabolik sendrom (MetS), abdominal obezite, glukoz intoleransı veya diabetes mellitus, dislipidemi, hipertansiyon ve koroner arter hastalığı gibi sistemik rahatsızlıklar eşliğinde, insülin direnci ile karakterize bir sendromdur. AS ve gut birlikteliği gibi AS ve MetS birlikteliğine yönelik birkaç çalışma yayınlanmasına rağmen, literatürde AS, akut gut artriti ve MetS'un birarada olduğu bir olgu raporu bulunmamaktadır. Burada her üç bozukluğun birarada bulunduğu bir olgu sunulmaktadır. Sonuç olarak bu sunumda, AS'ye eşlik edebilen gut ve MetS gibi metabolik anormalliklerin varlığına yönelik olarak hekimlerin dikkatinin çekilmesi amaçlanmıştır. Bu durum, AS yönetimi sırasında bu gibi potansiyel zararlı durumların önlenmesinde ve tedavisinde yararlı olacaktır.

Anahtar Sözcükler: Ankilozan spondilit, metabolik sendrom, gut, artrit, obezite

INTRODUCTION

Ankylosing spondylitis (AS) and gout are two diseases that can cause inflammatory arthropathy. Although the association has been reported rarely, a recent case-control study reported that gout was more common in patients with AS than in the control group (1.94%, 0.56, odds ratio (OR): 3.53, respectively) (1). AS and gout have some common features, such as; being more common in males, genetic predisposition, joint and enthesis involvement, and good response to non-steroidal anti-inflammatory drugs (NSAIDs) (2,3). Metabolic syndrome (MetS) is an endocrinopathy that starts with insulin resistance and is accompanied by systemic disorders, such as abdominal obesity, glucose intolerance or diabetes mellitus, dyslipidemia, hypertension, and coronary artery disease (4). Studies have reported the prevalence of MetS in patients with AS to be 45.8 % and the prevalence of MetS in gout to be between 5% and 37% (5,6). There is no case report in the literature reporting the co-existence of AS, gout, and MetS in together. Here, we present a case of AS who developed MetS and gout arthritis during the disease course.

CASE REPORT

A 37-year-old male patient who had been followed up with the diagnosis of AS for about 17 years, applied to our clinic with complaints of pain, swelling, temperature increase, and redness in

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the right ankle and big toe that had started a few days earlier. The patient had no previous history of peripheral joint involvement or trauma. He had a history of methotrexate use for 2 years, infliximab for 2 years, adalimumab for 1.5 years, golimumab for 9 months, and secukinumab for 27 months previously given in different centers for the medical treatment of AS. Lastly, due to inadequate response to other medications, he was prescribed etanercept 50 mg/week. On the physical examination; patient was mobilized independently and unaided with antalgic gait on the right lower extremity. There was no neurological deficit. The right ankle and 1st metatarsophalangeal (MTP) joints were tender and swollen upon palpation. Joint range of motion was limited in the lumbar and cervical regions. Fabere-Fadir tests were positive bilaterally. Other findings were; fingertip-to-floor distance: 22 cm, chest expansion: 3 cm, Schober's test: 13 cm, waist circumference measurement: 103 cm (Figure 1), body mass index: 31.3, and arterial blood pressure: 140/95 mm/Hg. In the laboratory analysis consisting of the complete blood count and erythrocyte sedimentation rate were normal. In addition, other laboratory test results were; fasting blood glucose: 163 mg/dL (74-106 mg/dL), HbA1c: 6.0, uric acid: 11.9 mg/dL (4.8-8.7 mg/dL), alanine aminotransferase: 76 U/L (10-40 U/L), triglyceride: 321 mg/dL(<150 mg/dL), high-density lipoprotein (HDL) cholesterol: 32 mg/dL (<40 mg/dL), and C-reactive protein: 8.90 mg/L (0-7 mg/L) were measured, and HLA-B27 was positive. Conventional X-rays of the feet demonstrated non-specific findings for gout arthritis, including the secondary degenerative joint changes of 1st MTP joint (Figure 2).

The patient fulfilled harmonized MetS criteria described by Alberti et al. (7) with the current clinical and laboratory findings. It was accepted as gouty arthritis because of arthritis in the right ankle and 1st MTP joints (Figure 3) with high serum urate levels. An intramuscular single-dose corticosteroid injection (1 mL betamethasone dipropionate and betamethasone sodium phosphate) followed by oral indomethacin 100 mg/d for three days were given to the patient for acute gouty arthritis attack. After the attack subsided, he was treated with etanercept, allopurinol, and atorvastatin, besides dietary recommendations were advised and the patient was followed. No new gout attack was observed during follow-up visits. Informed consent was obtained from the patient.

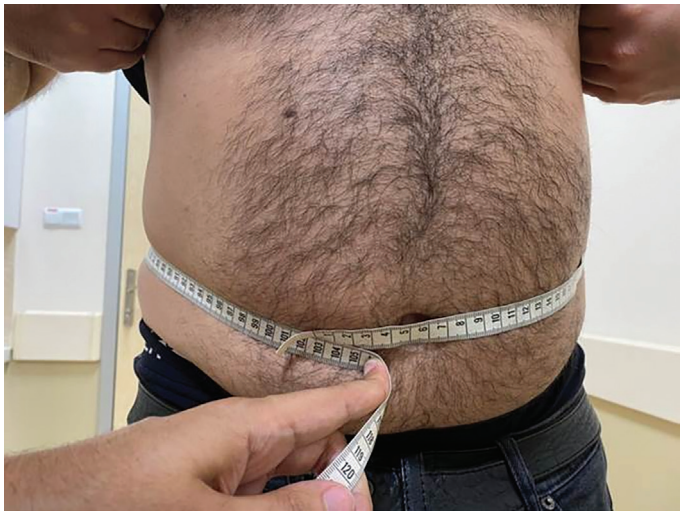

Figure 1. Waist circumference measurement of the patient

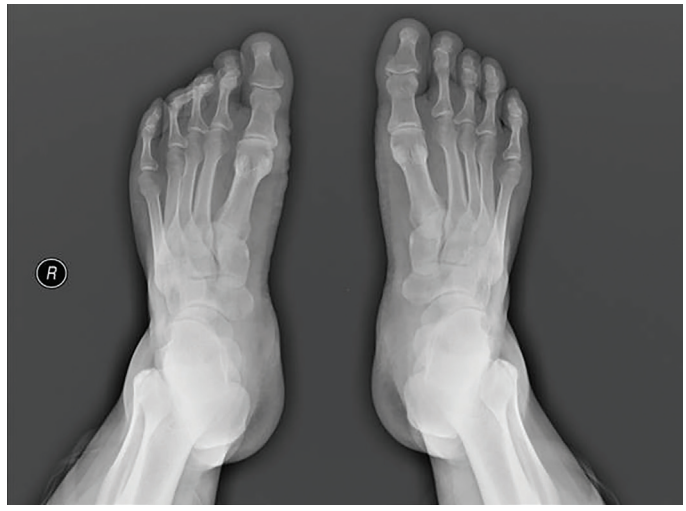

Figure 2. Degenerative changes in both 1st metatarsophalangeal joints and soft tissue swelling of the right ankle

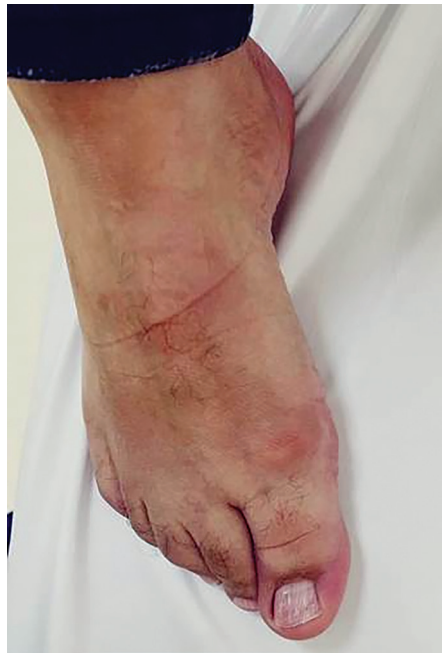

Figure 3. Acute arthritis of the right ankle and 1st metatarsophalangeal joints

DISCUSSION

AS is a chronic inflammatory rheumatic disease that mainly affects the axial skeleton, including the spine and sacroiliac joints, as well as the enthesis sites and peripheral joints (2). Gout is an autoinflammatory disease caused by the deposition of monosodium urate crystals in synovial joints. Gout has traditionally been associated with other comorbidities such as obesity, arterial hypertension, and abnormal lipid and glucose balance which are the components of MetS (8). Only a few previous studies rhave been found in the literature reporting the co-existence of gout and AS, and most of them reported an uncommon association. Recently, Ho et al. (9) analyzed 65 patients coexisting AS and gout and reported that

lower extremity joint involvement increased in patients with AS and gout, and that 61.5% of the subjects had first MTP joint involvement. Authors concluded that gouty arthritis should be kept in mind in the differential diagnosis of acute peripheral arthritis in patients with AS. In another study, it was reported that patients with AS had more gout than the control group (1.94%, 0.56, OR: 3.53, respectively). It is suggested that the use of NSAIDs in these patients might mask gout symptoms, which may be underestimation of the true prevalence of the coexistence of AS and gout (1). MetS is an endocrinopathy that starts with insulin resistance and is accompanied by systemic disorders, such as abdominal obesity, glucose intolerance or diabetes mellitus, dyslipidemia, hypertension, and coronary artery disease (4). Several diagnostic criteria for MetS have been described in the literature. Our patient met harmonized MetS criteria which consisted of increased waist circumference (≥80 cm in women, ≥94 cm in men), increased triglyceride level (≥150 mg/dL), low HDL level (<50 mg/dL in women, <40mg/dL in men), high blood pressure (SBP≥130 mmHg, DBP≥85 mmHg), and increased fasting blood glucose (≥100 mg/dL) (7). One potential mechanism underlying the association between AS and gout is MetS, which includes metabolic and cardiovascular risk factors such as obesity, visceral adiposity, hypertension, dyslipidemia, and insulin resistance. It is known that MetS is more common in patients with AS than in controls (5). MetS is also reported as common entity in hyperuricaemic and gouty patients (10). Nevertheless, gout might be overlooked or misdiagnosed in clinical practice as peripheral arthritic involvement might be associated with AS.

CONCLUSION

In conclusion, physicians should be aware of the development of metabolic diseases such as MetS and gout, which may cause increased cardiovascular risk and mortality in the management of patients with AS. Prophylactic and therapeutic options should be taken into consideration which will contribute to patients' quality of life.

Ethics

Informed Consent: It was obtained.

Footnotes

Authorship Contributions

Concept: E.K., Design: E.K., M.A., Data Collection or Processing: E.K., M.A., Analysis or Interpretation: E.K., M.A., Literature Search: M.A., Writing: E.K., M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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Carcinoma In Disguise-Atypical Presentation of Squamous Cell Carcinoma

Kılık Değiştirmiş Karsinom-Skuamöz Hücreli Karsinomun Atipik Sunumu

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ABSTRACT

Squamous cell carcinoma (SCC) of the nail unit is a rare malignant subungual tumor. There is often a delay in diagnosis and treatment as it can be often misdiagnosed as chronic paronychia, onychomycosis, pyogenic granuloma, subungual wart, or glomus tumor.

Here, we present a case of an elderly man who was brought to the out-patient department with a deformed appearance of the right fourth finger of his hand after 1 year. With a preceding history of trauma and two sessions of excision of the finger nail showing onychomycosis, the patient was admitted for further evaluation. Imaging in form of X-ray of the hand and Magnetic resonance imaging of the finger showed bony destruction of middle and distal phalanges, thereby favoring fungal osteomyelitis. However, incisional biopsy from the nail unit revealed suspicious of SCC. A multimodal approach to the tumor is required; however, surgical excision is the definitive treatment.

Keywords: Squamous cell carcinoma, nail bed, onychomycosis

ÖZ

Tırnak ünitesinin skuamöz hücreli karsinomu (SCC) nadir görülen malign bir subungual tümördür. Çoğunlukla kronik paronişi, onikomikoz, piyojenik granülom, subungual siğil veya glomus tümörü olarak yanlış tanı konulabildiğinden tanı ve tedavide sıklıkla gecikme olur.

Burada 1 yıl sonra sağ el dördüncü parmağında şekil bozukluğu şikayetiyle polikliniğe getirilen yaşlı erkek olguyu sunuyoruz. Daha önce travma öyküsü olması ve onikomikozu gösteren iki seans tırnak eksizyonu yapılması nedeniyle hasta ileri değerlendirme için yatırıldı. Elin röntgeni ve parmağın Manyetik rezonans görüntülemesi şeklindeki görüntüleme, orta ve distal falanjların kemik tahribatını gösterdi, bu da mantar osteomiyelitini destekledi. Ancak tırnak ünitesinden alınan insizyonel biyopside SCC şüphesi ortaya çıktı. Tümöre multimodal bir yaklaşım gereklidir; ancak cerrahi eksizyon kesin tedavidir.

Anahtar Sözcükler: Skuamöz hücreli karsinom, tırnak yatağı, onikomikoz

INTRODUCTION

Malignant tumors of the hand are rare, and squamous cell carcinoma (SCC) is the most common malignancy involving the nail unit (1,2). It can have various clinical presentations from nodules, papules, to ulcerated lesions, unusual presentations like warty growth, of this tumor have been reported. SCC typically has an indolent course and presents with mild symptoms. Most common site within the nail unit where it arises, most commonly from the subungual region (nail bed) (57.4%), rarely from the proximal or lateral nail folds (31.5%), and exceptionally from the hyponychium (finger pulp skin) (3). Compare to SCC onychomycosis of the hand represents about 30% of mycotic cutaneous infections with dermatophytes being the most common causative agent. However, bony involvement as fungal osteomyelitis is a rare condition with few reports involving the digits (4). In this case report, we outline a previous report of candidial onychomycosis in which the patient was suspected to have recurrence of the infection. SCC is known to have atypical presentations, and one must always suspect this tumor, especially in chronic cases.

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CASE REPORT

An 80-year-old man presented with complaints of an elongated right fourth finger of his hand since 1 year. A history of trauma to the finger by the rachis of coconut tree leaf 5 years back, following which he underwent excision of the nail. He underwent excision of the same deformed elongated nail again 1 year back, which on histopathology showed a cutaneous horn of the nail bed with candida infection. When he returned after the second recurrence, he experienced no fever or discharge from the nail. There was no history of skin malignancy. Examination revealed deformed right fourth finger with firm 3x3 cm irregular shaped swelling at the base of the nail and an elongated, pigmented nail with a hypertrophied nail bed and loss of flexion at distal interphalangeal joint (Figure 1). No local rise in temperature, tenderness, or axillary lymphadenopathy was noted. X-ray of the right hand was performed, which showed destruction of the distal phalanx terminal aspect of fourth finger (Figure 2,3) This was followed by MRI of the right fourth finger, which showed a deformed fourth digit with an ill-defined irregular heterogeneous altered signal intensity lesion (T1 hypointense T2 iso to hypointense heterogeneous STIR hyperintense signal with patchy areas of diffusion restriction) measuring 1.8x2.5x3.3 cm causing bony destruction and acro osteolysis of middle and distal phalanges and the intervening distal interphalangeal joint. The lesion was infiltrating the tendons of the flexor digitorum profundo's, flexor digitorum superficialis, and extensor digitorum and into the skin, subcutaneous tissue in the palmar and extensor aspects, and nail bed. Features favored fungal osteomyelitis/actinomycosis. (Figure 4). Incisional biopsy suggested suspicious of SCC. Ultrasound of right axilla showed no lymphadenopathy. Chest X-ray was not suggestive of pleural effusion or mass lesions. The full blood count was within normal limits. Amputation of the digit at the level of the proximal interphalangeal joint under brachial block (Figure 5). Gross swelling of size 3x2x1.5 cm was present near the proximal resected margin, with keratinous growth of size 6x2.5x1 cm at the distal end. Histopathology revealed

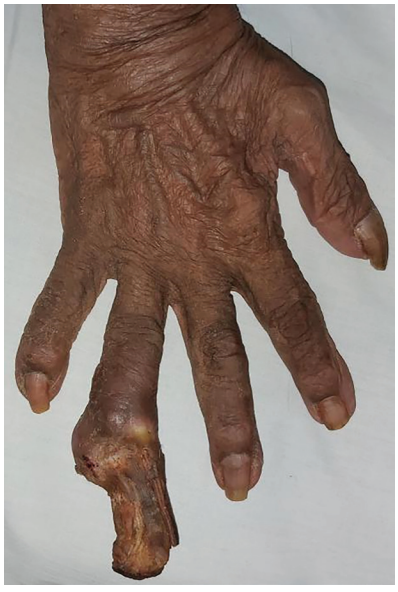

Figure 1. Clinical image

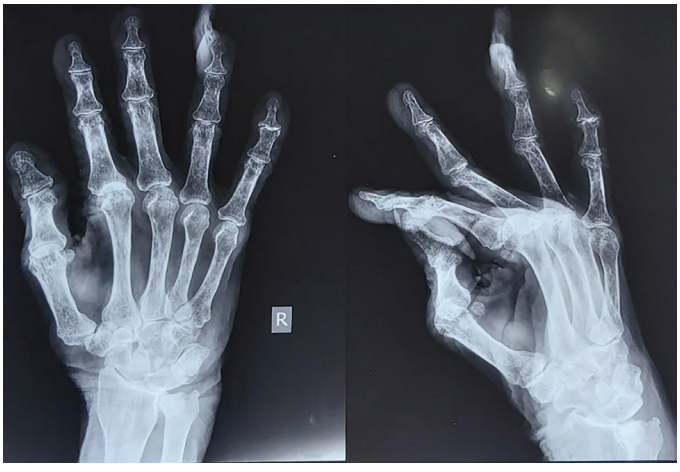

Figure 2. X-ray of right hand at initial presentation one year back

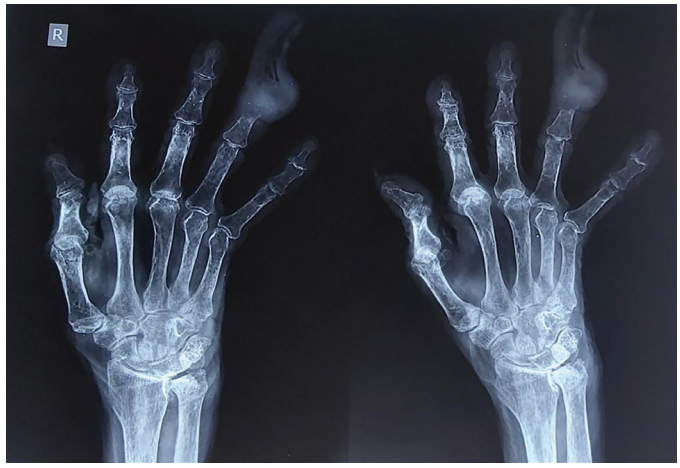

Figure 3. X-ray of right hand after recurrence

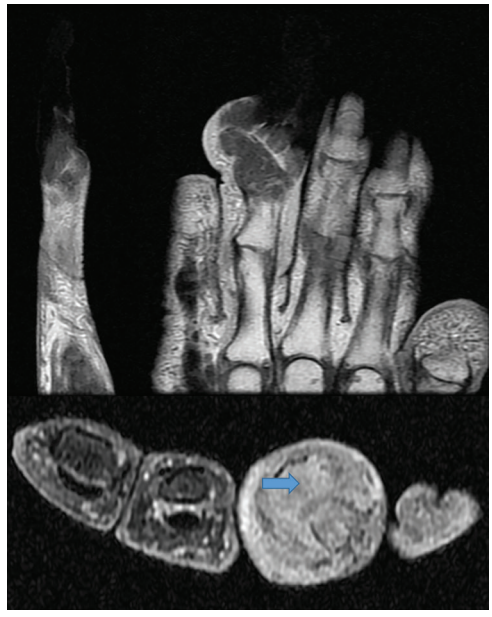

Figure 4. MRI images showing the lesion with bony destruction

MRI: Magnetic resonance imaging

well-differentiated SCC involving the dermis, subcutaneous tissue extending to the distal and middle phalanges (Figures 6-9). Resected margins, including the deep margin, were free from the tumor at distances of 1.5 cm from the skin, 1 cm from the soft tissue, and 1.5 cm from the proximal bone. The patient recovered well after surgery and was discharged. The patient was followed up after 2 weeks for suture removal. The stump was healthy (Figure 10) and the patient had no new complaints. He was called back after 1 month, and ultrasound imaging of the ipsilateral axilla revealed no lymph nodes. He is currently on follow-up for regular ultrasound of the axilla and clinical evaluation of stump for recurrence. Patient informed consent was taken about the disease and surgery, also explained about the complications and prognosis of disease. Informed consent was taken for the research publications.

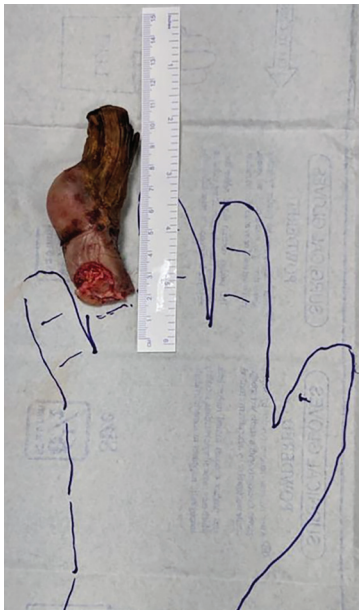

Figure 5. The intraoperative specimen

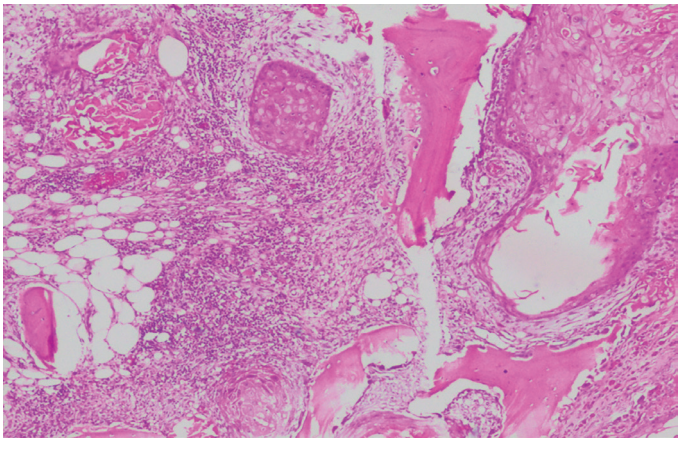

Figure 6. Section showing invasion of marrow space with extracellular keratin deposition

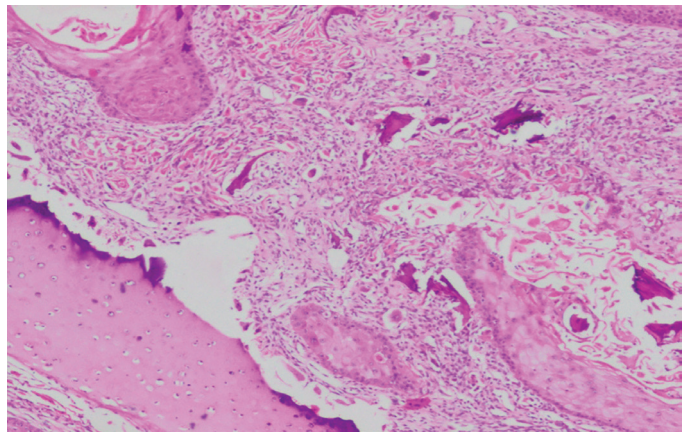

Figure 7. Section showing invasion of marrow space with extracellular keratin deposition

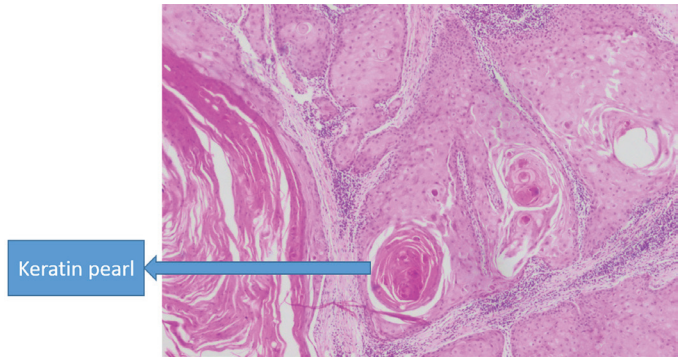

Figure 8. Well differentiated SCC with keratin pearl formation

SCC: Squamous cell carcinoma

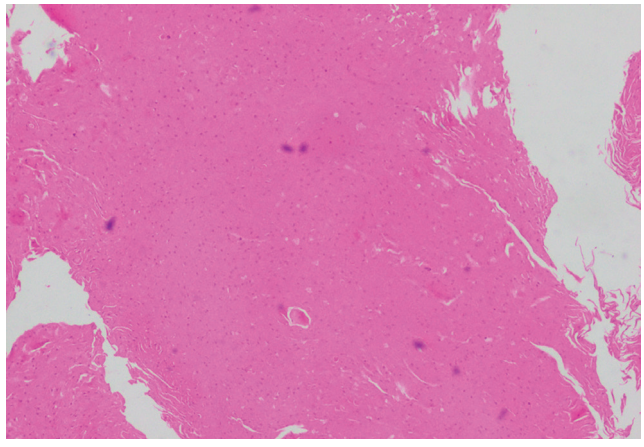

Figure 9. Keratinous horn

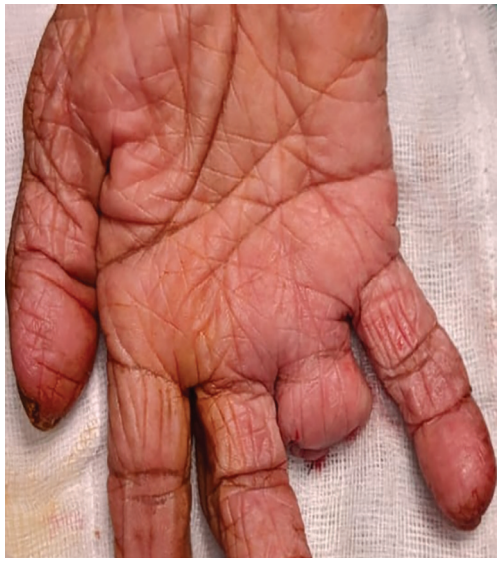

Figure 10. Amputated stump on follow-up

DISCUSSION

SCC occurs most commonly in men aged between 50 and 70 years and affects fingers more commonly than toes (5). Several causative agents predispose to subungual SCC, which includes human papilloma virus, chronic trauma, chronic inflammation, chronic infection, ionizing radiation, solar radiation, tar, arsenic, or other mineral exposure and immunosuppression (6,7). Bone involvement is seen in >20% of patients, whereas nodal involvement is seen in only 2% of patients (8). Radiological imaging is important in diagnosis and to rule out bony involvement. X-ray and computed tomography are useful in SCC-which appears as a crescent-shaped soft tissue mass with osteolytic defect of the associated phalanx, without periosteal reaction. A heterogeneous hypoechoic mass with irregular contours and posterior acoustic enhancement is the characteristic of SCC. Magnetic resonance imaging is superior to other radiologic imaging methods for soft tissue masses, as it has the capability of identifying the exact location and extension and helps in local staging for SCC (9).

Nail biopsy plays an important role in recurrent and persistent lesions for early detection of SCC and helps in prompt management. SCC has a multidisciplinary approach of management which includes Mohs micrographic surgery, amputation of the distal phalanx, electrosurgery, liquid nitrogen, photodynamic therapy, radiation therapy, intra-arterial infusion with chemotherapy, imiquimod, 5-fluorouracil, and lymph node dissection in case of metastasis which has to be ruled out by performing ultrasound of axilla or sentinel node biopsy. However, amputation of the digit has the highest cure rate and is indicated in case of long-standing carcinoma or bony involvement (10).

CONCLUSION

Nail unit SCC is a rare presentation and can have similar clinical picture as onychomycosis leading to delayed treatment. Hence, we would like to highlight the importance of performing a biopsy and prompt imaging on a long-standing recurrent nail unit lesion to achieve early diagnosis and appropriate surgical intervention.

Informed Consent: Informed consent was taken for the research publications.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.S.R., Concept: A.A., Design: A.G., Supervision: M.V.P., Resources: A.A., Material: A.G., Data Collection or Processing: K.S.R., Analysis or Interpretation: K.S.R., Literature Search: A.G., Writing: K.S.R., Critical Review: M.V.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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A Case of Tumid Lupus Erythematosus Successfully Treated with Topical Tacrolimus and Hydrocortisone 17-Butyrate

Topikal Takrolimus ve Hidrokortizon 17-Butirat ile Başarıyla Tedavi Edilen Bir Tumid Lupus Eritematozus Olgusu

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ABSTRACT

Tumid lupus erythematosus is an uncommon subtype of chronic cutaneous lupus erythematosus. Hereby, we report a 36-year-old male patient with tumid lupus erythematosus who presented with erythematous papules and plaques on the face and neck who showed significant improvement after treatment with topical tacrolimus and topical hydrocortisone 17-butyrate.

Keywords: Cutaneous lupus erythematosus, treatment, tumid lupus erythematosus

ÖZ

Tumid lupus eritematozus, kronik kutanöz lupus eritematozusun nadir görülen bir alt tipidir. Burada, yüz ve boyunda eritemli papül ve plaklarla başvuran ve topikal takrolimus ve topikal hidrokortizon 17-butirat tedavisi sonrasında belirgin iyileşme gösteren, tumid lupus eritematozuslu 36 yaşında bir erkek hastayı sunduk.

Anahtar Sözcükler: Kutanöz lupus eritematozus, tedavi, tumid lupus eritematozus

INTRODUCTION

Tumid lupus erythematosus is an uncommon subtype of chronic cutaneous lupus erythematosus. However, it has been suggested that tumid lupus erythematosus might be considered as a distinct entity since the relationship between the disease and systemic lupus erythematosus and serological abnormalities were scarce (1,2). Tumid lupus erythematosus affects females and males equally. The disease usually occurs in individuals aged 30-40 years. Nevertheless, the incidence and prevalence of this disease among different races and ethnicities remain unknown (2). Tumid lupus erythematosus is characterized by erythematous or violaceous annular plaques with edema in sun-exposed areas (2,3). The face, neck, chest, and back are the most commonly affected body areas. Various skin diseases, such as polymorphic light eruption, pseudolymphoma of the skin, and reticular erythematous mucinosis, should be included in the differential diagnosis of tumid lupus erythematosus. Topical and intralesional steroids, calcineurin inhibitors, antimalarial drugs, methotrexate, and mycophenolate mofetil are the treatment options (2). Patients with tumid lupus erythematosus should also be recommended to apply sunscreen regularly.

CASE REPORT

A 36-year-old male patient was admitted with a 6-year history of asymptomatic, erythematous plaques on the face. The lesions appeared on the cheek and gradually distributed to the face and neck. In addition, the patient stated that the lesions were exacerbated by ultraviolet radiation and heat exposure. Nevertheless, the patient reported no daily use of sunscreen. The patient was admitted to

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a dermatology clinic for skin lesion treatment a year ago. He was recommended to use 1% pimecrolimus cream and 0.05% clobetasol 17-propionate ointment twice daily for three months. However, the patient stated that he did not apply adequate treatment, and no clinical response was achieved. The past medical history was remarkable for hypertension and liver enzyme elevation associated with alcohol intake. However, regular use of any medication was denied. The family history was unremarkable. Dermatological examination revealed erythematous, squamous papules, and plaques on the face and neck (Figure 1a-c).

A skin biopsy was performed from an erythematous plaque on the patient's face to reach a definitive diagnosis. Histopathological examination revealed a normal epidermis, perivascular mononuclear inflammation involving plasma cells and lymphocytes, and mucin deposition in areas containing perivascular inflammation (Figure 2). Thus, the diagnosis of tumid lupus erythematosus was made based on clinical and histopathological findings. Among the laboratory tests, the biochemistry panel revealed increased levels of alanine aminotransferase (90 U/L, normal limit: <49 U/L), aspartate aminotransferase (60 U/L, normal limit: <34 U/L), triglyceride (210 mg/dL, range: 0-150 mg/dL) and decreased level of high-density lipoprotein cholesterol (27.1 mg/dL, normal limit: >49 mg/dL). Complete blood count revealed increased white blood cell count (12.2 $x10^3$/µL, range: 3.91-10.9 $x10^3$/µL) and absolute neutrophil count (8.2 $x10^3$/µL, range: 1.8-6.98 $x10^3$/µL). Complement C3 and C4 levels were within normal limits. The serum antinuclear antibody was negative, whereas the anti-SSA (anti-Ro) antibodies were positive. Anti-double-stranded (ds) DNA, anti-Smith (Sm), anti-SSB (anti-La), antineutrophil cytoplasmic antibodies, anticardiolipin IgM, and anticardiolipin IgG were also negative. The patient received 0.1% tacrolimus ointment and 0.1% hydrocortisone 17-butyrate cream twice daily. Moreover, the patient was recommended to regularly use a sunscreen with a sun protection factor of 50. A good clinical response was achieved four weeks after treatment; however, the lesions left hypopigmentation (Figure 1d-f). The patient gave written informed consent to publish the case details. The patient gave written informed consent to publish the case details.

DISCUSSION

Tumid lupus erythematosus is a rare type of chronic cutaneous lupus erythematosus that was first described in 1909. The diagnosis of tumid lupus erythematosus is not always easy to make since the disease is rare and shows different clinical and histopathological features compared with other chronic cutaneous lupus erythematosus lesions (1). Moreover, the association between tumid lupus erythematosus and systemic lupus erythematosus is uncommon. The disease presents with erythematous, indurated, annular papules, and plaques on the face and trunk exacerbated by sun exposure (2). Scleredema-like presentation and unilateral blaschkolinear distribution have also been reported in patients with tumid lupus erythematosus (3,4). The lesions heal without leaving scars or pigmentary changes (5,6). Antinuclear antibodies or anti-

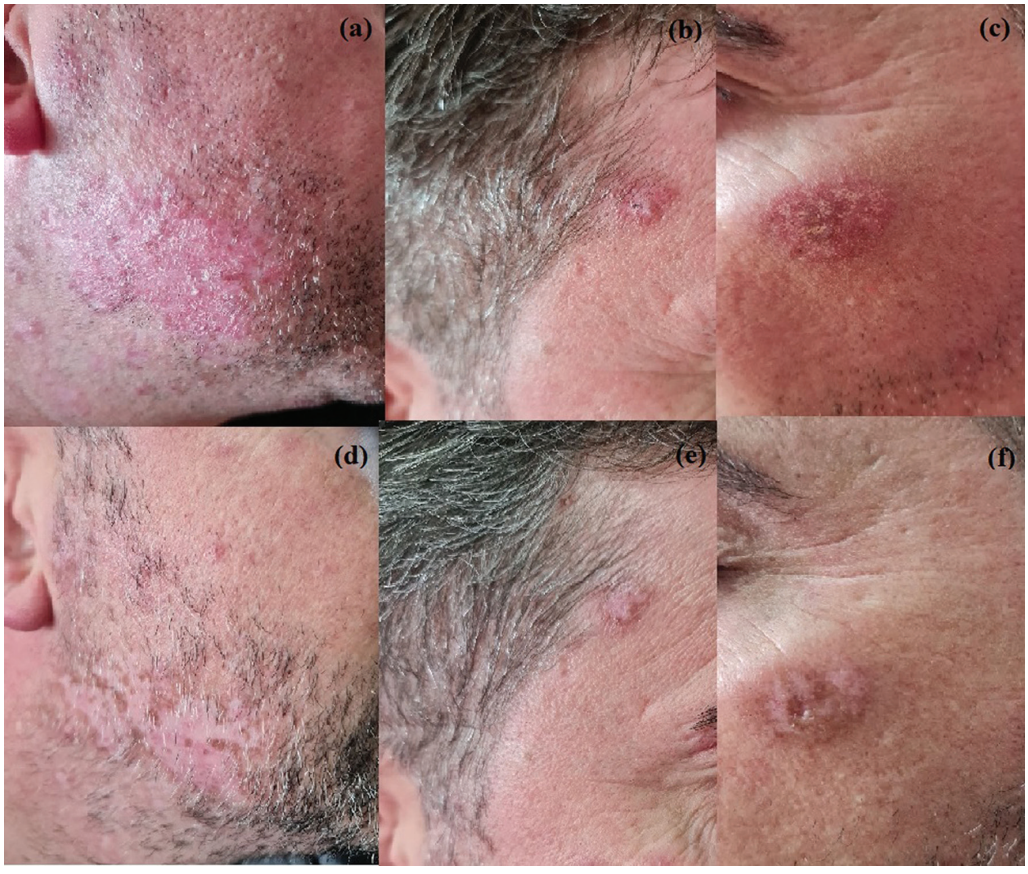

Figure 1. (a-c) Erythematous squamous papules, and plaques on the face and neck before treatment. (d-f) The lesions left hypopigmentation four weeks after treatment

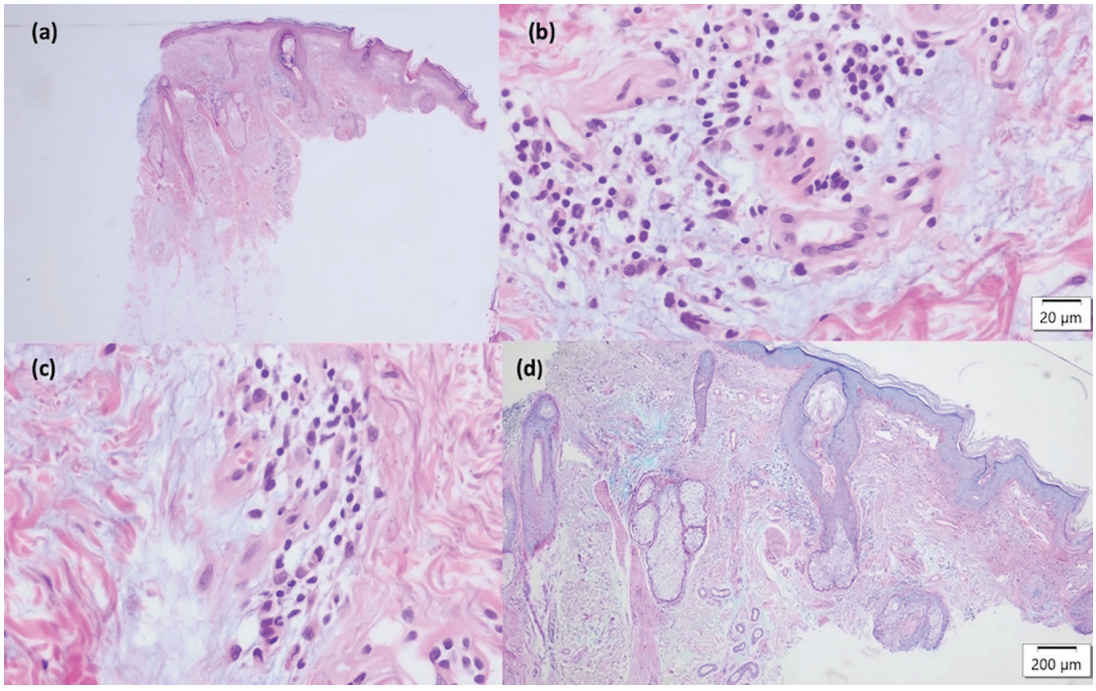

Figure 2. Histopathological examination revealed (a) Normal epidermis and skin appendages (Hematoxylin and eosin, x12.5). (b,c) Perivascular mononuclear inflammation involved plasma cells and lymphocytes (Hematoxylin and eosin, x400). (d) Mucin deposition in areas contained perivascular inflammation (Alcian blue, x200)

Ro/SSA, anti-La/SSB, anti-Sm, and anti-dsDNA antibodies are not detected in most patients. It has been suggested that sun protection and the use of topical corticosteroids and systemic antimalarial drugs might be effective for the treatment of tumid lupus erythematosus (6).

CONCLUSION

Herein, we present a rare case of tumid lupus erythematosus with erythematous, squamous papules, and plaques on the face and neck that rapidly responded to topical steroid and tacrolimus treatment. The presence of anti-Ro antibodies and lesions healed by leaving hypopigmentation, which were detected in our patient, were also uncommon findings in tumid lupus erythematosus. Our case will hopefully contribute to the literature by identifying the clinical features of the disease, improving diagnostic rates, and establishing the most appropriate treatment options.

Ethics

Informed Consent: The patient gave written informed consent to publish the case details.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.T., Concept: F.T., Design: F.T., Supervision: F.T., Ö.E., Resources: F.T., Material: F.T., B.Ö., Ö.E., Data Collection or Processing: F.T., İ.Ö., B.Ö., Ö.E., Analysis or Interpretation: F.T., B.Ö., Ö.E., Literature Search: F.T., Writing: F.T., İ.Ö., B.Ö., Ö.E., Critical Review: F.T., İ.Ö., B.Ö., Ö.E.

Conflict of Interest: No conflict of interest was declared by the authors.

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Examining the Effects of Tramadol, on the WADA Prohibited List, on Sports Performance

WADA Yasaklılar Listesine Giren Tramadolün Spor Performansı Üzerine Etkilerinin İncelenmesi

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ABSTRACT

Tramadol, an opioid analgesic, was added to the World Anti-Doping Agency (WADA) Prohibited List in 2024. Tramadol has been widely used by athletes to manage sports-related pain. Its intensive use, particularly in certain sports, has raised suspicions that it is being used as a doping agent. The potential to impair sports performance, cognitive side effects, and abuse have been investigated in several studies. This study reviewed the literature on tramadol and its effects on sports performance and explained the WADA process. In reviewing the literature, although studies have shown that tramadol does not affect performance, the World Health Organization has banned its use in competition in light of studies showing its effect on performance.

Keywords: Doping, sports pharmacy, opioid analgesic, WADA monitoring program, pain, performance enhancer

ÖZ

2024 yılı itibariyle opioid bir analjezik olan tramadol, Dünya Dopingle Mücadele Ajansı (WADA) Yasaklılar Listesine girmiştir. Tramadol, spora bağlı ağrıyı tolere etmek için sporcular tarafından son yıllarda sıklıkla kullanılmaktadır. Özellikle belirli branşlardaki yoğun kullanımı doping olarak kullanıldığı şüphelerini doğurmuştur. Spor performansını etkileme potansiyeli, bilişsel düzeydeki yan etki profili ve kötüye kullanım ihtimali çeşitli çalışmalarla araştırılmıştır. Çalışmamızda; tramadol ve tramadolün spor performansı üzerine etkileri ile ilgili literatür incelenmiş ve WADA tarafından yasaklanma süreci açıklanmıştır. Literatür değerlendirildiğinde, tramadolün performansı etkilemediğine dair çalışmalar bulunmasına rağmen, WADA tarafından performans üzerine olan etkilerini içeren çalışmalar göz önünde bulundurularak müsabaka içi kullanımı yasaklanmıştır.

Anahtar Sözcükler: Doping, spor eczacılığı, opioid analjezik, WADA izleme programı, ağrı, performans artırıcı

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INTRODUCTION

Tramadol, which has been in the WADA Monitoring Program for 12 years, has entered the WADA Prohibited List as of 2024, and its in-competition use by athletes is prohibited. Tramadol, included under the heading "Narcotics" on the 2024 WADA Prohibited List, is a weak opioid agonist and has an analgesic effect. It is used clinically to treat moderate to severe pain. It is preferred by athletes to relieve pain caused by the effort required by exercise or pain resulting from sports injuries (1). However, tramadol may provide an advantage in training and competitions because it can allow the athlete to tolerate pain by preventing or delaying the occurrence of pain. Therefore, it can be described as a performance-enhancing substance (2). Although it appears to have an indirect effect on performance compared with other banned substances (e.g., anabolic steroids), it has the potential to affect competition results for competitions won by minimal margins. In addition, it may impair cognitive performance with side effects, such as dizziness, drowsiness, and fatigue, and there is a possibility of causing accidents during competitions and harming athletes. Additionally, it has the potential for abuse, which is believed to affect sporting spirit (3). This study aimed to examine tramadol in detail, on the WADA Prohibited List as of 2024, and the reasons why it is preferred in sports, its effects on sports performance, and the banning process through WADA reports and literature data available in different databases (PubMed, Scopus, ScienceDirect and Web of Science). We believe that the current study may contribute to a better understanding of the current tramadol ban practice and increase the knowledge level of athletes and health personnel.

Doping

WADA: Prohibited List and Monitoring Program

The World Anti-Doping Agency (WADA) is an independent international organization established to combat doping in sports and to protect athletes and the spirit of sports internationally. For this purpose, WADA publishes the World Anti-Doping Code, the primary document that harmonizes the anti-doping policies, rules, and regulations of public authorities worldwide for sports organizations and monitors compliance with the World Anti-Doping Code (4). The World Anti-Doping Code, published on January 1, 2021 and still in force, prohibits "the presence of a prohibited substance or its metabolites or markers in an athlete's sample" and "the use or attempted use, possession, trafficking or attempted trafficking by athletes of a prohibited substance or prohibited method, or the administration or attempted administration of such substance or method to any athlete in competition" (4,5). Substances mentioned in anti-doping rule violations and prohibited for use by athletes are listed on the WADA Prohibited List. The Prohibited List identifies prohibited substances and methods with potential to enhance or mask performance. A substance or method is included in the Prohibited List if it meets any of the following three criteria.

1-Medical or other scientific evidence, pharmacological effects, or experience that the substance or method, alone or in combination with other substances or methods, has the potential to enhance or improve sports performance;

2-Medical or other scientific evidence, pharmacological effect or experience that the use of the substance or method represents an actual or potential health risk to the athlete;

3-WADA's determination that the use of the substance or method violates the spirit of sport. The Prohibited List, reviewed and updated annually by the WADA in consultation with experts, is published three months before it comes into force each year and enters into force on January 1. However, in exceptional cases, a substance or method may be added to the Prohibited List at any time of the year. Athletes and other persons are responsible for knowing the substances and methods included in the Prohibited List and what constitutes an anti-doping rule violation (4). WADA designed the WADA Monitoring Program to monitor and identify patterns of abuse of substances that are not on the Prohibited List but are potentially harmful in sports and to decide whether to include them on the Prohibited List (3,4). Within this program, WADA publishes the substances and methods to be monitored annually in the WADA Monitoring Program each year. Laboratories accredited or approved by the WADA will notify the WADA if the use of these substances is reported or their presence is detected. WADA annually provides sport-specific information on monitored substances to the International Federations and National Anti-Doping Organizations. The reported use or detection of a monitored substance is not considered an anti-doping rule violation (4). When the 2024 WADA Prohibited List and Monitoring Program was examined, tramadol was found to have left the WADA Monitoring Program, moved to the WADA Prohibited List, and was under the category of narcotics. Narcotics were recognized as doping substances and were included as "Narcotics and Analgesics" in the first prohibited products list published by the International Olympic Committee in 1968. It was included on the WADA Prohibited List as "Narcotics", first published in 2004. Substances in this category include potent analgesics that belong to the opioid class. These compounds substantially affect pain treatment and are prohibited for in-competition use.

Pain in Sports and Analgesic Use

Pain is an inevitable part of athletes' lives (6). This is because exercise causes pain and discomfort when performed at a certain intensity or for a long time (2). Peripheral muscle fatigue develops to a unique threshold for each individual, and when it reaches this critical threshold, exercise is either stopped voluntarily or the intensity of the exercise is significantly reduced (7). The feeling of pain caused by exercise has a negative impact on training and performance (2). Pain in athletes may be caused by exercise-related muscle pain or due to an injury. Injuries and associated pain can affect an athlete's occupational health and well-being. For example, injuries can lead to a painful rehabilitation process, may affect the results of the competition and the ranking, may lead to early or unwanted termination of a sporting career, may cause permanent disability, and can damage mental health throughout a sporting career. Since the sporting career depends on the functionality of the body, frequent or serious injuries pose a threat to athletes' careers (6). However, the view that "no pain, no gain" prevails in various sports branches (2). The effort required to achieve success in sports, the pain of competition, and health risks have been accepted by athletes, coaches, and sports medicine specialists. For this reason, athletes who are away from training and competition due to injury or disability may be under pressure to return to sports immediately. Similarly, medical staff may be subject to pressure and may be forced to negotiate between the recovery of athletes and the decision to return to competition quickly. This situation may sometimes result in

failure to pay attention to the health of the injured athlete, failure to return to sports activities too early, and use of analgesics to achieve this (6). The limited time allocated for the athlete's recovery causes a more frequent use of analgesic drugs and increases the risk of potential abuse and associated harm (1).

Analgesics and Sports Performance

Analgesics are commonly used by athletes. It has been established that athletes use analgesics four times more frequently than the general population of the same age (2). Athletes can use analgesics to relieve fatigue, inflammation, and pain caused by injuries or overtraining (3,8). In addition to their normal therapeutic uses, they can be used to accelerate recovery after exercise, increase performance or prevent performance decline due to pain or minor injuries, cope with stressors caused by injuries, or act as prophylactics (6). In a study conducted with Danish elite athletes (69.5%) and national team athletes (30.5%), almost all athletes (93%) used painkillers due to sports-related pain. In the study, athletes who had experience with pain relievers (93%, n=631) were asked about their reasons for using these products in sports. Although it was determined that the most common causes were to relieve headaches (82%) and to compete in a significant competition despite an injury or disability (64%), it was also found that the use to increase the level of performance in the competition/match (22%) was at a considerable rate (6).

The desire to achieve enhanced performance may lead athletes to use illegal substances. For example, in a study on drug use and doping knowledge in Italian male elite cyclists under 23 years of age (n=40), 75.0% (n=30) of the athletes used at least one drug in the last three months and a total of 84 drugs were used, including tramadol (3.3%). As a result of the study, it was determined that in addition to excessive use of prescription drugs, athletes have limited knowledge about doping (9). The tendency to use analgesics more frequently in and outside of competition than in the general population, to take more than one drug simultaneously, and to administer these drugs at higher therapeutic doses suggests that athletes use these analgesics to increase performance (2).

Analgesic Drugs

Analgesic drugs prevent or reduce pain perception through their effects on the central nervous system. Analgesics are an essential part of pain management in sports, and they are administered by athletes or healthcare professionals. The effects of analgesics depend on the type, dosage, and type of drug (6). Analgesics include non-opioid, adjuvant, and opioid analgesics (10).

Non-opioid Analgesics

Non-steroidal anti-inflammatory drugs (NSAIDs) paracetamol, and metamizole are non-opioid analgesics. NSAIDs, which comprise the majority of this class, have antipyretic, anti-inflammatory, and analgesic effects. Paracetamol and metamizole are antipyretic and analgesic drugs, but they do not have anti-inflammatory effects. The anti-inflammatory effects of drugs in this group are weaker than those of steroidal glucocorticoids. The analgesic effects of opioid analgesics are generally weaker than those of opioid analgesics, which have potent analgesic effects but do not have anti-inflammatory effects (10).

Adjuvant Analgesics

Adjuvant analgesics are a broad group of drugs that belong to different classes. Although these drugs are typically administered for indications other than pain management, they are used to treat a variety of painful conditions. This group includes tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, topical anesthetics, corticosteroids, bisphosphonates, and cannabinoids (11).

Opioid Analgesics

Opioid analgesics are alkaloid compounds obtained from Papaver somniferum L, and they relieve pain by acting on the central nervous system (12). Opioids are the most potent drugs used to treat severe pain, and they have been used for thousands of years.

Opioid analgesics exert their effects by imitating peptide hormones known as endogenous opioid peptides or endorphins. Endogenous opioid peptides are natural opioid receptor ligands (13). Opioid analgesics, like endogenous opioid peptides, exert their effects by binding to opioid receptors to reduce pain sensation (12). Opioid receptors include four classes: mu (μ/MOR), kappa (κ/KOR), delta (δ/DOR) opioid receptors, and nociceptin opioid peptide (NOP) receptors. All opioid receptors are broadly distributed in the central and peripheral nervous systems (13). μ-opioid receptors are responsible for analgesia, respiratory depression, euphoria, constipation, addiction, respiratory depression, nausea, and vomiting; κ-opioid receptors are responsible for analgesia, diuresis, sedation, and dysphoria; δ-opioid receptors are responsible for analgesia, convulsions, and anxiolysis (13,14). Although opioid drugs, also called narcotics, differ chemically, they exert their effects through μ-opioid receptors, which are their primary targets and to which they bind with high affinity (12). Opioid drugs consist of natural alkaloids such as morphine and codeine, as well as synthetic derivatives such as heroin, fentanyl, hydromorphone, methadone, buprenorphine, meperidine, oxycodone, and tramadol.

Tramadol

Discovery and Chemical Structures

Tramadol, an atypical opioid with strong analgesic activity, was first synthesized in Germany by Grünenthal GmbH in 1962 (12). Tramadol was approved in Germany in 1977 and was approved by the Food and Drug Administration (FDA) in 1995 (15,16).

The chemical formula of tramadol is 2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol (Figure 1). Tramadol, which can be obtained via chemical synthesis, is a mixture of both dextro (+) and levo (-) enantiomers (16).

Physiological and Clinical Effects

Since its discovery in 1962, *in vitro* and *in vivo* studies have demonstrated the potent analgesic activity of tramadol. Extensive clinical trials have demonstrated the efficacy and safety of tramadol for the treatment of moderate to severe pain, including inflammatory, postoperative, and cancer-related pain. Moreover, tramadol has been shown to be efficacious in relieving neuropathic pain, a type of pain for which the use of conventional opioids is constrained by the side effects associated with long-term treatment (15).

Tramadol has a moderate affinity for μ-opioid receptors (Ki=2.1 μM) and a weak affinity for δ- and κ-opioid receptors (Ki=57.6 μM and 42.7 μM, respectively). Its affinity for the μ-opioid receptor is approximately 6000 times less than that of morphine, 100 times less than that of dextropropoxyphene, 10 times less than that of codeine, and is equivalent to that of dextromethorphan (15,17,18). Tramadol differs from typical opioid drugs in that it modulates the reuptake of noradrenaline (NA) and serotonin (5-HT) monoamines in presynaptic terminals and is described as an atypical opioid (16,19). In addition to its effect on μ-opioid receptors, it blocks monoamine reuptake, leading to increased NA and 5-HT levels in central synapses. The mechanism of action of tramadol against pain is shown in Figure 2. Tramadol is a racemic mixture of dextro (+) and levo (-) enantiomers, and both enantiomers contribute to its analgesic effect through different mechanisms. The (+) enantiomer of tramadol has a stronger affinity for the μ-opioid receptor than the (-) enantiomer and inhibits serotonin reuptake by approximately four times more potently than the (-) enantiomer. The (-) enantiomer inhibits noradrenaline reuptake more potently (12,15,18,20). O-desmethyltramadol, the first hepatic metabolite of tramadol described in the literature, has a 200-fold greater affinity for μ-opioid receptors than the dextro form of tramadol and is responsible for the majority of opioid-induced analgesic effects associated with tramadol use (12,15,21,22).

Pharmacokinetic Properties

Tramadol is frequently prescribed today due to its effectiveness in treating moderate to severe pain. Tramadol is available in several pharmaceutical formulations, including capsules, tablets, syrup, cream, ointment, gel, and parenteral. After oral administration, tramadol is rapidly absorbed, reaching a peak serum concentration within 2 hours for capsules and 5 hours for sustained-release tablets. Oral bioavailability after a single dose was 70% due to hepatic first-pass metabolism. Tramadol is rapidly distributed in the body, with approximately 20% bound to plasma proteins. After a single oral dose of 100 mg, the half-life of tramadol is 5.1 hours, whereas that of the O-desmethyltramadol metabolite is 9 hours. The excretion of tramadol occurs almost exclusively (90%) via the kidney. Additionally, approximately 10-30% of tramadol is excreted as an unmetabolized drug, and 60% is excreted as metabolites (12,15,18). It has been reported that the most appropriate dose for moderate to severe acute pain is 3 mg/kg intravenously, and this dose application causes minimal respiratory depression (18). Clinically, tramadol is administered as 50-100 mg orally or parenterally every 6 hours in the treatment of pain. The analgesic effect of tramadol is about one-tenth that of morphine when administered parenterally and about one-third that of morphine when administered orally (23). The maximum tramadol dose is 400 mg/day (12).

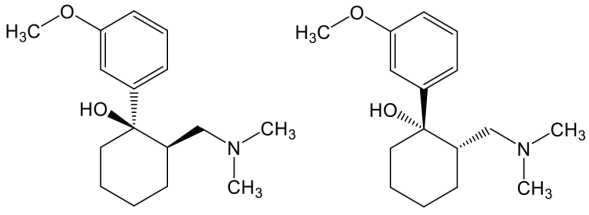

Figure 1. Tramadol [(1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol]

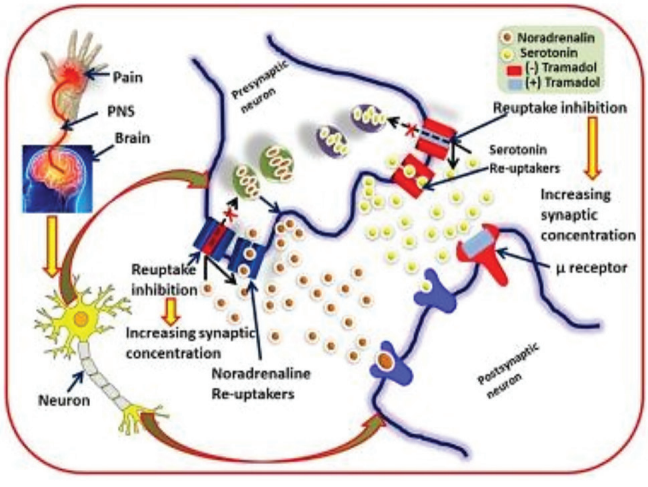

Figure 2. Mechanism of action of tramadol on pain

Side Effect Profile

The complementary and synergistic mode of action of the two enantiomers of tramadol, both opioid and monoaminergic, resulted in a significant reduction in the typical side effect profile of opioids. The safety profile and increased tolerability are other factors associated with racemic mixture preference. The order of side effects is (-) enantiomer > (+) enantiomer > racemate (18). In all areas of administration, the side effect profile of tramadol is dose-dependent, a mixture of opioid (indigestion, nausea, vomiting, fatigue, and drowsiness) and monoaminergic (headache, dizziness, dry mouth, and sweating) effects (18). The most common side effects are nausea, vomiting, dizziness, fatigue, drowsiness, sweating, and dry mouth. Less common side effects include diarrhea and cardiovascular complications (tachycardia and postural hypotension), whereas rare side effects include respiratory depression, seizure, tremor, bradycardia, anxiety, and psychosis. Coadministration of tramadol with other drugs or alcohol causes tramadol intoxication. In particular, symptoms of tramadol intoxication begin at doses above 500 mg and after 4 hours of administration. Tramadol overdose is associated with insomnia, drowsiness, nausea, irritability, hypertension, increased heart rate, seizures, coma, and serotonin syndrome (16). The side effects of tramadol in the treatment of acute and chronic pain are less frequent and intense than those of other opioids. Tramadol causes much less constipation, urinary retention, sedation, and respiratory depression than equivalent analgesic doses of other weak opioids. This increases its preference for long-term use (15,18,24).

Abuse and Addiction Profile

The pharmacodynamic and pharmacokinetic properties of tramadol are unlikely to cause addiction. Slight potential for abuse may arise because of its relatively low affinity for μ-opioid receptors and its effect on serotonin and noradrenaline, neurotransmitters that play critical roles in mood. Epidemiological data, controlled clinical trials, and post-marketing surveillance studies have shown that the development of tolerance and addiction is quite low, especially when compared to morphine. In addition, fewer withdrawal symptoms

were observed with tramadol use than with equivalent doses of other opioids (15,16,18).

Epstein et al. (23) compared the results of intravenous placebo, morphine (10 and 20 mg; iv), or tramadol (100 and 200 mg; iv) administration for 5 minutes to 10 experienced opioid addicts. No tramadol dose showed morphine-like effects, and there was little evidence of physical dependence. When the use of parenterally administered tramadol was evaluated, the abuse potential of tramadol was reported to be low. However, a different pattern of action was observed when tramadol was administered orally. In this study, placebo, oxycodone (20 and 40 mg; po), or tramadol (175, 350, and 700 mg; po) were administered orally to 12 experienced opioid addicts. Tramadol and oxycodone have been reported to decrease pupil diameter, increase ratings on the 'feel drug' and 'liking' scales, and be available for abuse. However, maximal responses to tramadol occurred much later than maximal responses to oxycodone (23). This delay, in effect, is thought to be related to the conversion of tramadol to the opioid agonist O-desmethyltramadol. Furthermore, since the formation of O-desmethyltramadol is mainly dependent on hepatic metabolism, the opioid agonist effect observed with oral administration cannot be observed with parenteral administration because O-desmethyltramadol concentrations are much higher after oral administration than after parenteral administration (25). Abuse reports obtained through a post-marketing surveillance program indicate that the abuse rate of tramadol is low, and the majority (97%) of abuse cases occur in individuals with a history of substance abuse (26,27). Tramadol abuse was investigated by Skipper et al. (28) among physicians who were concerned about substance abuse, and different results than expected were found. It was reported in the study that a total of 872 narcotic agents were mentioned by physicians and that opioids ranked second after alcohol in terms of abuse. Tramadol was the third most commonly reported substance among opioids, constituting 10% of all opioids mentioned in terms of abuse, leaving behind fentanyl, codeine, propoxyphene, oxycodone, morphine, and butorphanol (28). Addiction and abuse are not limited to patients with a previous history of opioid addiction, as shown in several cases in previous studies (29). For example, in a study conducted to investigate the drug addiction and abuse potential of tramadol in individuals without a history of substance abuse, it was observed that individuals without a history of substance abuse could become addicted to tramadol. In the study, high doses (750 mg-2000 mg) of tramadol were used, and it is stated that high doses abused for a long time probably increased the addictive potential of tramadol (30). Additionally, tramadol addiction may vary between individuals. CYP2D6 is a member of the cytochrome P450 (CYP450) enzyme family and is the main enzyme responsible for the formation of O-desmethyltramadol, the active metabolite of tramadol. The CYP2D6 gene is highly polymorphic and has genetic variants that can lead to poor, normal, or accelerated (ultra-rapid) tramadol metabolism. Therefore, patients who over-metabolize drugs with the CYP2D6 gene are at higher risk of tramadol opioid addiction. For this reason, it would be more accurate to evaluate addiction individually (13,31).

Tramadol Use in Sports

The analgesic approach pharmacologically constitutes the cornerstone of pain management in acute traumatic musculoskeletal injuries (32). Tramadol is a potent analgesic that can be used for pain management in severe sports-related injuries. In addition, it can be used by athletes because of its ergogenic effect, which can provide faster recovery between training sessions and reduce pain perception during training (3). Tramadol may enable athletes to perform beyond standard pain thresholds through analgesia resulting from its μ-opioid receptor agonist effect (2). In addition, although several studies (15,18) have shown that tramadol is unlikely to cause euphoria, its use by athletes may be linked to its mood-enhancing effects via its impact on serotonin and norepinephrine. Suppression of pain sensation, increased pain tolerance, and improved mood may encourage an athlete to push harder, leading to small performance gains (2,8). Tramadol is used by athletes to a considerable extent. In the study conducted by Baltazar-Martins et al. (3), the analysis of 9851 urine samples collected during competitions at national and international events was evaluated to assess the detection of tramadol levels at the Madrid Doping Control Laboratory between 2013 and 2017. The 135 urine samples analyzed were identified as "tramadol findings" because they contained urine tramadol concentrations above the WADA recommended limit of detection (LOD) (>50 ng/mL). Urinary tramadol concentrations ranged from 53.5 to 45 311 ng/mL, and the concentration of 113 samples (83.7% of the tramadol findings) was >1000 ng/mL. Although it is difficult to determine the dose of tramadol from tramadol concentrations in urine, it is known that ingestion of 100 mg of tramadol results in peak urine concentrations of ~100-150 ng/mL approximately 10-12 hours after ingestion. Accordingly, most of the tramadol findings in the present study corresponded to the use of tramadol doses above the therapeutic dose or the intake of tramadol over several consecutive days. It was also found that tramadol findings differed between sports branches in the study; 65.2% of tramadol samples were obtained from cycling athletes, 8.1% from triathlon, and 5.9% from rowing athletes. Tramadol was detected in 9.7% of the urine samples analyzed during cycling. In sports such as athletics, basketball, football, and aquatics, the prevalence of samples containing tramadol was <1% although some samples had urinary tramadol concentrations above 10.000 ng/mL. This may be a sign of tramadol abuse by some athletes involved in these sports. The urinary tramadol concentration found in some analyzed samples indicates that tramadol was taken at doses high enough to endanger athletes, especially in cycling races where the risk of accidents is frequent (3). According to the WADA 2017 Monitoring Program Figures Report, 122.706 urine samples were analyzed in WADA-approved laboratories, and 900 samples were determined to contain a concentration of tramadol above the LOD (>50 ng/mL). The overall prevalence of tramadol symptoms across all sports was 0.7%. Although the number of sports in which tramadol findings were detected was quite high, 60.9% of all tramadol findings were obtained in cycling, 9.8% in football, and 4.4% in athletics. Considering the number of samples analyzed on a branch basis, it is seen that the sports branches with the highest tramadol findings are cycling, rugby, and rowing (33).

According to the WADA 2018 Monitoring Program Figures Report, 130.701 urine samples were analyzed in WADA-approved laboratories, and 1160 samples were determined to contain a concentration of tramadol above the LOD (>50 ng/mL). The overall prevalence of tramadol symptoms across all sports was

0.9%. Although the number of sports in which tramadol findings were detected was still quite high, 49.5% of all tramadol findings were obtained in cycling, 14.1% in football, and 5.1% in athletics. Considering the number of samples analyzed on a branch basis, it is seen that the sports branches with the highest tramadol findings are cycling, rugby, and archery (34). As can be seen in the findings of the WADA Monitoring Program (33,34), tramadol has been frequently used by athletes in various sports, especially cycling. Sometimes, athletes may use tramadol to mask the pain caused by the injury and quickly return to sports activities before fully recovering. This situation has the risk of making the injury worse prolonging healing time, or causing permanent damage. Tramadol is a strong painkiller; if the athlete needs tramadol to relieve pain after an injury, the athlete's decision on whether or not to participate in the competition may need to be re-evaluated. Although tramadol can provide analgesic and ergogenic gains in sports, it can also cause conditions that may affect the safety of athletes during performance, such as dizziness, loss of alertness, drowsiness, and difficulty in concentrating (3,8). Decreases in cognitive function and lack of attention during some sports, such as cycling, can result in serious injuries (2). Chronic use of tramadol to manage exercise-induced pain may also result in addiction (3). Considering that athletes who use tramadol to increase performance use high doses, the risk of developing an addiction to the drug increases in such athletes. In addition, the type of tramadol used, age, gender, body weight, genetic polymorphisms, and mental disorders can significantly affect the rate of drug abuse (13,31). The International Cycling Union has stated that the commonly reported adverse side effects of tramadol, such as dizziness, drowsiness, and loss of attention, in addition to the risk of addiction, are incompatible with cycling races and endanger other competitors. Accordingly, to protect the health of each rider and ensure the safety of the competitions, the use of tramadol has been banned as of March 1, 2019 (35). When the literature is reviewed, it is seen that there are clinical trials (36-39) investigating the effects of tramadol on exercise performance; these trials are shown in Table 1. In one of these trials, Holgado et al. (36) tested the potential ergogenic effect of tramadol during cycling and whether it reduces the ability to focus on a specific task. The study was designed to be randomized, double-blind, placebo-controlled. The 19 men and 9 women, were given 100 mg tramadol or placebo orally. The study examined whether

Table 1. Clinical trials investigating tramadol and its effects on sports performance

Study	Study design	Participants	Dose	Results
Holgado et al. (36) 2018 first experiment	Randomized, double-blind, crossover-design, placebo-controlled	19 men, 9 healthy women volunteers	100 mg of tramadol or placebo	The average power output was higher with tramadol than with placebo (tramadol: 220 W and placebo: 209 W)
Holgado et al. (36) 2018 second experiment (36)	Randomized, double-blind, crossover-design, placebo-controlled	28 healthy volunteers	100 mg of tramadol or placebo	No significant difference was observed between tramadol and placebo regarding average power output (tramadol: 234 W and placebo: 230 W). No behavioral differences were found between the attention task conditions
Bejder et al. (37) (2020)	Randomized, double-blind, crossover-design, placebo-controlled	16 healthy male volunteers	100 mg of tramadol or placebo	No significant difference was observed between tramadol and placebo regarding average power output (tramadol: 298 W and placebo: 294 W) and performance time (tramadol: 1474 s and placebo: 1483 s). Tramadol did not impair the ability to complete a certain cognitive and fine motor task performance during submaximal exercise
Zandonai et al. (38) (2021)	Randomized, double-blind, crossover-design, placebo-controlled	29 healthy volunteers	100 mg tramadol/day 1.5 g of paracetamol or placebo	No significant difference was found between tramadol (227 W) and placebo (221 W) [only a significant difference was found between tramadol and paracetamol (213 W), but no difference was found between paracetamol and placebo]. It did not cognitively impair the ability to focus during high-intensity effort
Mauger et al. (39) (2023)	Randomized, double-blind, crossover design, placebo-controlled	27 healthy volunteers	100 mg of tramadol or placebo	Higher average power output (tramadol: 270 W and placebo: 261 W) and shorter performance time (tramadol: 3758 s and placebo: 3808 s) were found with tramadol compared with placebo

acute oral administration of tramadol improves performance by reducing perceived exertion and fatigue during a cycling time trial (first experiment). In another experimental design, in addition to the first experimental procedure, participants performed a visual task during the time trial to investigate whether information processing and behavioral responses in a sustained attention task would be affected by tramadol (second experiment). In the first experiment, the average power output with tramadol intake during the cycling time trial was found to be higher than that with placebo and was observed to improve trial performance by ~5%. It has been observed that the average heart rate obtained with tramadol intake is higher than that with placebo. However, in the second experiment, no difference in average power output was found between tramadol and placebo. Time-frequency analysis of electroencephalography data showed that tramadol has effects on brain functions related to stimulus processing. On the other hand, tramadol was found to have no effect on behavioral performance in the sustained attention task and did not impair cognitive performance in the ability to maintain attention during exercise. It has been stated that the reason for these different results between the first and second experiments is unclear (36). In another study, Bejder et al. (37) investigated the potential for a therapeutic dose of tramadol to affect average power output and motor-cognitive task performance during a cycling time trial. For this purpose, a randomized, double-blind, placebo-controlled trial was conducted with 16 highly trained cyclists. Participants were given 100 mg of tramadol or placebo, and the experiment consisted of an hour of submaximal effort followed by 15 km of cycling. It has been stated that taking 100 mg of tramadol did not increase the average power of highly trained cyclists. Additionally, 100 mg of tramadol did not impair cognitive and fine motor performance during submaximal exercise. However, during the study, three subjects taking tramadol reported nausea and vomiting upon completion of the experiment. The analysis after excluding these subjects showed that tramadol intake resulted in a higher mean power than placebo. This suggests that highly trained cyclists taking 100 mg of tramadol can improve their time trial performance without the occurrence of side effects. Additionally, the urinary detectability of 100 mg of tramadol ingestion in highly trained men was investigated, and it was found to be detectable for 24 hours. The analgesic effect of tramadol is expected to be negligible 24 h after ingestion; therefore, the detection window is sufficient for doping detection.

Zandonai et al. (38) aimed to test tramadol's potential ergogenic and cognitive effects of tramadol with those of placebo and paracetamol in a randomized, double-blind, and placebo-controlled study. Participants were orally administered 100 mg of tramadol, 1.5 g of paracetamol, or placebo and completed the cycling time trial. This study showed that 100 mg of tramadol did not cause changes in physical performance during a cycling time trial that included an attention task. It has been reported that tramadol provides a higher average power output than paracetamol, but there is no significant difference between tramadol and placebo (or paracetamol and placebo). Additionally, the results showed that tramadol increased behavioral and neural efficiency at rest but did not cognitively impair the ability to focus during high-intensity effort. Another finding was that although tramadol did not affect physical performance, it did affect the physiological responses recorded during exercise. Similar to the study by Bejder et al. (37) and the first experiment by Holgado et al. (36), tramadol caused a higher heart rate than placebo and paracetamol (38). The result obtained in the study by Zandonai et al. (38) that tramadol did not cause changes in physical performance is consistent with the results obtained from the second experiment by Holgado et al. (36) and the results obtained by Bejder et al. (37). However, this contradicts the findings of the first experiment of Holgado et al. (36). It is stated that this difference in results may be due to the error in the first experiment of Holgado et al. (36) or the inclusion of a cognitive task that would reduce the effect of tramadol in both the second experiment of Holgado et al. (36) and the study by Zandonai et al. (38). However, Bejder et al. (37) found that tramadol had no effect on physical and cognitive performance, although the study design did not include cognitive tasks. Regarding the different results obtained in the studies, it has been stated that tramadol may affect performance, but because this effect is relatively small, the trials conducted on this subject to date may have been insufficient to detect this effect (38). Mauger et al. (39) investigated the ergogenic effect of acute intake of tramadol on cycling performance, pain perception, and effort during constant-intensity cycling in a placebo-controlled study of highly trained cyclists. This study found that highly trained cyclists maintained a significantly higher power output and completed a competitive time trial significantly faster after the acute ingestion of 100 mg of tramadol. Tramadol reduced the perception of effort for a given power output but had no noticeable effect on pain intensity during cycling. When the previous studies in the literature are examined, in the first experiment by Holgado et al. (36), an average power output of 11 W (5%) higher with tramadol use was observed, while an average power output of 7 W was observed for participants who were not affected by the side effects of tramadol by Bejder et al. (37). Consistent with previous studies, Mauger et al. (39) found that participants taking tramadol achieved an average power increase of 9 W and an average improvement in the time to complete a cycling time trial of 1.3%. This difference would have a significant ergogenic effect on a group of highly trained cyclists and could change their ranking at the end of the competition (39).

Process of Entry of Tramadol Into the Prohibited List

Tramadol entered the WADA Monitoring Program for the first time in 2012 under the title of narcotics and was included in the Monitoring Program every year between 2012 and 2023 (40). In 2024, tramadol was removed from the WADA Monitoring Program and placed on the WADA Prohibited List (41).

In September 2022, with the recommendation of the Expert Advisory Group, an in-competition ban on tramadol was approved, and it was decided that this ban would be valid as of January 1, 2024. The purpose of the delay in implementation was stated to be to provide an additional year for communication and training of athletes, their communities, and medical staff to better understand the implementation of the tramadol ban in competitions. In addition, time has been given to the scientific community to determine the details of the relevant procedures, laboratories to update their procedures, sports authorities to develop educational tools for athletes and medical and support staff to consider the safe use of tramadol for clinical purposes in the anti-doping context (42,43). Monitoring data from the WADA Monitoring Program have shown the significant use of tramadol in sports such as cycling, rugby, and

football. WADA-funded research studies by Holgado et al. (36) and Mauger et al. (39) have been reported to confirm the potential of tramadol to improve physical performance in sports. Accordingly, the washout period for tramadol, i.e., the time between the last therapeutically administered dose of tramadol and the start of the in-competition period, was determined as 24 hours. Furthermore, as stated under the title of narcotics in the Prohibited List, all optical isomers of narcotics are prohibited; accordingly, both isomers of tramadol (dextro/levo) are prohibited for in-competition use (44,45).

DISCUSSION

It is believed that tramadol can improve exercise performance through its effects on effort, pain perception, and mood. Accordingly, clinical trials (36-39) investigating whether or not tramadol is doping have been conducted with a dose of 100 mg. However, evidence has shown that athletes who used tramadol in competitions took much higher doses (3). Doses above the therapeutic dose may have a more significant effect on performance improvement. Additionally, studies have addressed the acute use of tramadol; its effects with long-term effects have not been tested. Performance improvement may be beneficial for long periods of intense physical workloads. Furthermore, most studies have been conducted on male subjects. For this reason, there is a need for further studies examining the effects of tramadol at different doses and long-term use in sports, with the participation of more female participants. In addition, highly trained athletes may have higher pain tolerance due to regular training. Therefore, it is possible to obtain different results in highly trained athletes than in the general population. While examining the effects of tramadol on sports performance, studies on highly trained athletes are needed to provide more accurate results.

CONCLUSION

Athletes tend to treat exercise-induced pain and sports-related injuries with the use of analgesic drugs during training and competition. One of the preferred analgesics is tramadol, a weak opioid agonist used to treat moderate to severe pain. The efficacy of tramadol in a wide range of acute and chronic pain conditions, the availability of various formulations, and its low side effects compared with other opioids make tramadol a preferable option for athletes. Although tramadol is used to treat pain, it is believed that tramadol may improve sports performance through its effects on pain perception or mood. In this regard, various studies have investigated the effects of tramadol on performance, which has been included in the WADA Monitoring Program for 12 years. Some studies have shown that it affects performance, can be abused by athletes, and has the potential for cognitive effects. As a result, tramadol has been banned for in-competition use by WADA as of 2024 due to its effects on performance and potential for side effects. The use of doping by athletes to increase performance and achieve success in competitions can result in penalties, bans, and health damage. Athletes should be aware of the health effects of tramadol when used individually. Both athletes and their medical support staff should be aware of the tramadol prohibition. To avoid doping sanctions, athletes competing in competitions must stop using tramadol before the competition.

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Authorship Contributions

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