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Research Article/ Araştırma Makalesi

Atient Complaints Towards the Field of Surgery in Türkiye: An Analysis of Comments on the Digital Platform

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Purpose: The purpose of the research is to examine patient complaints made on the "sikayetvar.com" website regarding the field of General Surgery in medicine in Türkiye

Method: In this retrospective study, complaints made to the "sikayetvar.com" website were examined using the content analysis method, one of the qualitative research methods. In the research, 359 posts on the internet about the General Surgery specialty in medicine in Türkiye, made on the "sikayetvar.com" website between January 1, 2023 and November 1, 2023, were examined. Complaints made; They are classified according to gender, whether the institution belongs to a public or private hospital, whether it is an inpatient, outpatient or emergency patient, type of surgical intervention, number of views of the complaint and the subject of the complaint.

Results: In the research, 335 (93.3%) of the complaints are related to interventions in the field of General Surgery. It was observed that 74 (20.6%) of the complaints were responded to. It was observed that the complaints from all outpatient clinic patients were significantly higher than the complaints from the service, patients who underwent surgical intervention, and patients who underwent endoscopy ($p<0.05$). Of the complaint categories, 214 (12.6%) were about lack of communication, 173 (10.2%) were about staff attitude, 159 (9.4%) were about lack of compassion, and 145 (8.5%) were about access and acceptance. It has been found to be related to vision.

Conclusion: Knowing the sources of patient dissatisfaction in general surgery department services may help to reduce the number of patient complaints and improve patient care. It is thought that these results may guide healthcare managers on effective complaint management and help to increase patient satisfaction.

Keywords: General surgery, Digital technology, Patient satisfaction

1.INTRODUCTION

The healthcare services market and its target audience differ greatly from other service sectors. Health care is considered a mandatory need and unless this service is met, the health of the individual deteriorates and may even result in loss of life. Health services, which are of vital importance, are included in professional services.[1] Developments in medical technologies that accompany the increase in healthcare institution alternatives along with competition, extended life spans, increased health literacy, improvement in living standards, policies affecting access to healthcare, changes in disease structures, rising education and awareness levels of healthcare consumers, increase in treatment methods, knowledge in the field of medicine. Many factors, such as developments in technology and technology, increase individuals' expectations of healthcare services.[2,3] Patients whose expectations are increasing and whose increasing expectations are not met are looking for alternative services and it is easy to access these alternatives. At this point, managers of healthcare institutions must define the needs and expectations of their patients in the best possible way and provide the necessary services in order not to lose them. Health institutions evaluate their service quality by revealing patient experiences and

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expectations. In this respect, identifying patient complaints and resolving them provides an advantage to the institution in two ways. The first of these is to determine what the patients' expectations are, and the second is to determine the areas that are going bad or need to be improved in the institution. Thus, it will contribute to improving the poor service provided and increasing the service quality.[3]

The internet, whose use is increasing day by day with the developments in technology, has become a part of daily life. While the world population reaches 8.1 billion in 2023, Türkiye's population has reached 85.59 million. While internet users worldwide have reached 5.16 billion (64.4%), this number has reached 71.38 million (83.4%) in Türkiye. Internet users in Türkiye spend an average of 7 hours and 24 minutes a day on the Internet from all devices. Users spend 4 hours and 26 minutes of this time connecting to the internet via their mobile phones. The primary reason why internet users use the internet in Türkiye to obtain information.[4,5] In health services, online internet use is increasing day by day.

Complaints are complex narratives that report perceived failures in health care delivery from the patient's perspective. According to Lovelock and Wright (2002), a complaint is a formal expression of dissatisfaction with the experience or any aspect of the service.[6] Complaint is the written or verbal expression of dissatisfaction resulting from non-fulfillment of needs, requests and expectations. Complaints may be related to mental, physical and emotional state.[7] Complaints are considered a valuable data source for many reasons. The concept that every complaint is a gift, which has become a popular adage of the 21st century, is very valuable for businesses as it provides valuable feedback regarding customer dissatisfaction. For healthcare institutions, complaints from patients and/or their relatives are not only an important indicator of problems in the healthcare system, but also a guide that helps solve the problems.[8]

Patient complaints in general surgery have been relatively understudied and, more importantly, continue to be an underutilized resource in addressing deficiencies in surgical clinics. Surgical departments around the world aspire to improve patient experiences and reduce complaints globally. However, there is limited published data on patient complaints in general surgery.[9] Internationally, patient complaint data, and hence patient satisfaction scores, are increasingly recognized as useful markers in evaluation. There is increasing awareness that clinically obtained data on surgical outcomes should be correlated with patients' perceptions and quality of care scores.[10] One of the most important points here is that general surgeons are the main target in such complaints. One of the most important reasons for this is that many of the treatments applied by surgeons often carry significant risks. Previous studies suggest that communication is one of the strongest influences on patient complaints and that good communication reduces complaints.[11] Additionally, studies have shown that 60–80% of surgeons identified as high-risk based on the number of complaints can achieve improvement with targeted interventions.[12]

The purpose of the research is to examine patient complaints made through the "sikayetvar.com" website regarding the specialty of General Surgery in medicine in Türkiye. The research also aims to identify common themes in patient complaints about the surgery department, better define the patient population making complaints, and systematically examine the reasons for complaints.

2. MATERIALS and METHODS

In the retrospectively designed research, complaints made to the *"sikayetvar.com"* website were examined using the content analysis method, which is one of the qualitative research methods. In the research, 359 of the 537 posts made on the internet about the medical expertise of general surgery in Türkiye between January 1, 2023 and November 1, 2023 on the *"sikayetvar.com"* site were included in the study and 1699 complaints of them were examined.

178 of these complaints were excluded from the study because they were related to the wrong department and the content of the complaint was unclear. This situation also shows the ignorance of the people complaining about the issue. A total of 359 complaints were examined between the dates specified in our research. Since consent is required from individuals over the age of 18 to register on the site, it is assumed that the complaints were made by individuals over the age of 18. Complaints made; They are classified according to gender, whether the institution is a public or private hospital, whether they are inpatients, outpatients or emergency patients, type of surgical interventions, whether only surgical intervention is performed, whether they are related to other departments, the number of views of the complaint and the subject of the complaint.

Three areas included in the coding taxonomy for patient complaints: "clinical" (complaints about the safety and quality of clinical care), "management" (complaints about the management of the healthcare institution) and "relations" (complaints about the healthcare personnel). The clinical domain is divided into "quality" and "safety" categories, the administrative domain is divided into "organizational issues" and "timing/access" categories, and the relations domain is divided into "communication", "humanity/caring" and "patient rights" categories.[7]

The study is limited to the complaints of 359 patients and their relatives made on the *"sikayetvar.com"* website in the field of general surgery, and it is assumed that the complaints are correct. The complaint was excluded from the study because it was not related to a interventions performed in the general surgery department and the content of the complaint was unclear.

2.1.Statistical Analysis

SPSS 24 statistical software package (Statistical Package for the Social Sciences – IBM®) was used to analyze the data collected in the study. Descriptive statistics regarding the distribution of responses to independent variables in the study are presented as numbers and percentages for categorical variables, and as mean, standard deviation and median for numerical variables. The compliance of continuous variables with the normal distribution assumption was evaluated with the Kolmogorov-Smirnow test. One Way Anova test was used for quantitative variables in pairwise and multiple comparisons. The frequency of complaints according to the type of general surgical interventions performed was compared using the chi-square test with Bonferroni correction. The results were evaluated as significant with a 95% confidence interval, $p<0.05$.

3.RESULTS

In this part of the research, 359 posts about the specialty of General Surgery in medicine in Türkiye made on the *"sikayetvar.com"* website between January 1, 2023 and November 1, 2023 were examined. The data obtained from Reader et al. It was analyzed by adopting a deductive approach using the text analysis method, one of the types of content analysis, in line with the patient complaint

taxonomy developed by.[7]

Of the individuals included in the study, 223 (62.1%) were women and 136 (37.9%) were men. While 219 (61.0%) of the hospitals complained about were public hospitals, 140 (39.0%) were private hospitals. While 61 (17.0%) of the patients who made complaints were inpatients, 267 (74.4%) were outpatients and 31 (8.6%) were emergency room patients (Figure 1). 255 (71.0%) of the complaints came from outpatient clinic patients, 37 (10.3%) from surgery, 8 (2.2%) from endoscopy and 59 (16.4%) from patients treated in the ward. 335 (93.3%) of the complaints were related to interventions performed only in general surgery. It was observed that 74 of the complaints (20.6%) received a response. Apart from general surgery services, the other complaints were 1 (0.3%) gynecology, 12 (3.3%) radiology, 1 (0.3%) anesthesia, 2 (0.6%) plastic complaints surgery, 2 (0.6%) were related to urology, 2 (0.6%) were related to cardiology and endocrine, 1 (0.3%) were related to neurology and 3 (0.8%) were related to orthopedics. The average number of views of the complaints was found to be 4949.99±5558.09 (Min-Max: 6-56116) (Table 1).

Figure 1.

Treatment places where complaints come from

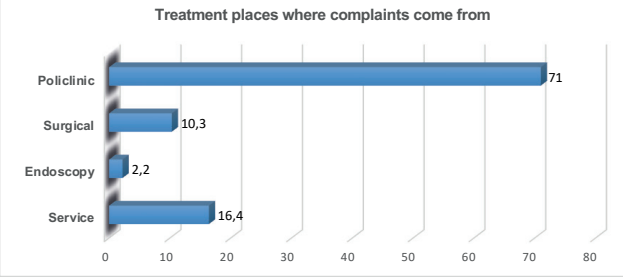


Table 2.

Demographic and clinical characteristics of the individuals in the study (n: 359)

Gender, n (%)	
Female	223 (62,1)
Male	136 (37,9)
Hospital Type, n (%)	
Public	219 (61,0)
Special	140 (39,0)
Patient's hospital status, n (%)	
Inpatient	61 (17,0)
Outpatient treatment	267 (74,4)
Emergency room	31 (8,6)
Places of treatment performed, n (%)	
Policlinic	255 (71,0)
Surgical	37 (10,3)
Endoscopy	8 (2,2)
Service	59 (16,5)
General Surgery Practices Only, n (%)	
Yes	335 (93,3)
No	24 (6,7)
Answer, n(%)	
Yes	74 (20,6)
No	285 (79,4)
Other Department Related (n:24), n (%)	
Gynecology	1 (0,3)
Radiology	12 (3,3)
Anesthesia	1 (0,3)
Plastic Surgery	2 (0,6)
Urology	2 (0,6)
Cardiology/Endocrine	2 (0,6)
Neurology	1 (0,3)
Orthopedics	3 (0,8)
Display, Mean ±Std	4949,99±5558,09 (Min-Max: 6-56116)
N:number, %: percent, Mean: Mean, Std: Standard Deviation	

It was observed that the complaints from all outpatient clinic patients were statistically significantly higher than the complaints from ward, surgery and endoscopy patients ($p < 0.05$) (Table 2).

Table 2.

Pairwise comparison of complaint frequency (per 100,000 interventions) between different radiological interventions

	Policlinic	Surgical	Endoscopy	Service
Policlinic		p=0,005[a]	p=0,001[a]	p=0,001[a]
Surgical			p=0,023[a]	p=0,258
Endoscopy				p=0,042[a]
Service				

[a] *Calculated with z test and post hoc Bonferroni correction for proportions*

In the research, 359 of the 537 posts made on the internet about the medical expertise of general surgery in Türkiye between January 1, 2023 and November 1, 2023 on the *"sikayetvar.com"* site were included in the study and 1699 complaints of them were examined.

It shows the distribution of complaints among different areas, categories and subcategories according to Reader et al.'s taxonomy of patient complaints. Of the total 1699 complaints, 225 (13.24%) were in the clinical field, 685 (40.32%) were in the management field, and 789 (46.44%) were in the communication field (Figure 2). 214 (12.6%) of the complaint categories were related to communication failure, 173 (10.2%) were related to staff attitude, 159 (9.4%) were compassion, 145 (8.5%) were access. and acceptance, 134 (7.9%) patient and staff dialogue, 125 (7.4%) bureaucracy, 102 (6%) service problems, 100 (5.9%) misinformation, 97 (5.7%) related to delays, 74 (4.4%) regarding recommendations, 54 (3.2%) regarding examinations, 47 (2.8%) regarding quality of care, 47 (2.8%) related to treatment, 46 (2.7%) finance and billing, 45 (2.7%) personnel and resources, 35 (2.1%) environmental, 32 (1.2%) errors in diagnosis, 29 (1.7%) safety events, 16 (0.9%) discharge, 7 (0.4%) patient journey, 6 (0%) 4) skills and behaviors, 5 (0.3%) for confidentiality, 3 (0.2%) for medication errors, 3 (0.2%) for consent, and 1 (0.06%) for abuse. It was observed that it was related to (Figure 3).

Figure 2.

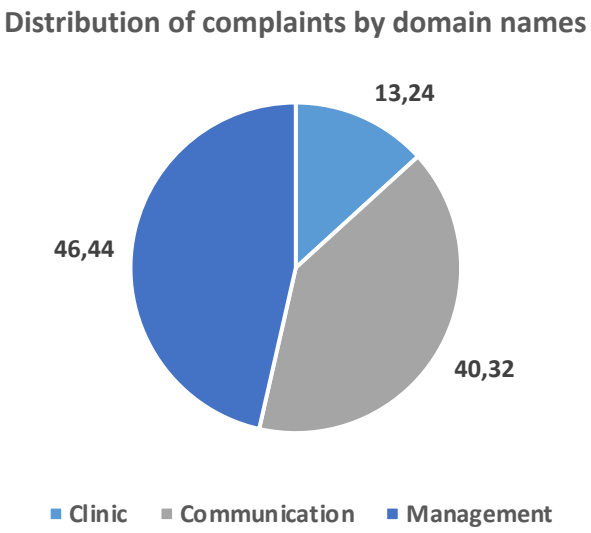
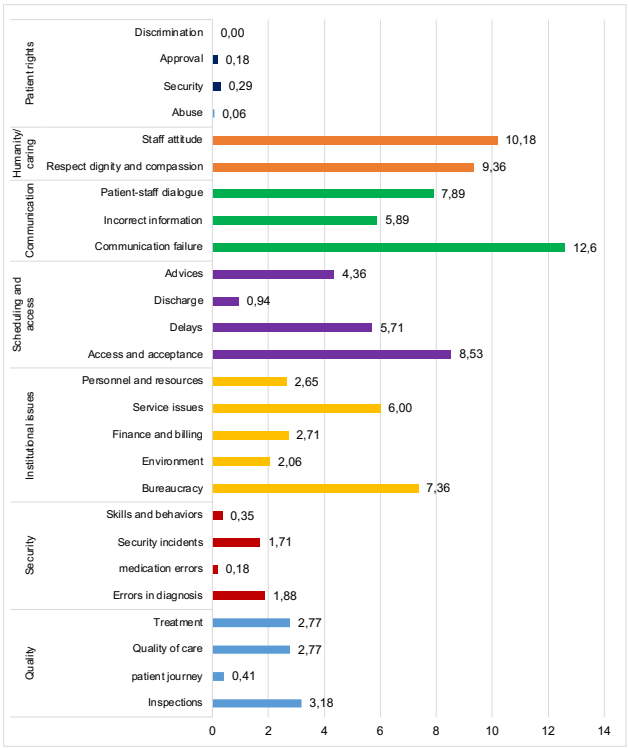


Figure 3.



4.DISCUSSION

In this research, the reasons for 359 complaints made by patients and their relatives to the "sikayetvar.com" website in the field of general surgery were examined, and the general profiles of the individuals who complained to the competent authorities about their dissatisfaction with the general surgery department were determined and the reasons for the complaints were systematically evaluated. There is no sufficient research in the literature on the frequency and reasons for complaints of patients and their relatives regarding the services of the general surgery department. Therefore, our research is an original study.

The results of this study are consistent with published studies from a demographic perspective; Female patients, outpatients and outpatients are the most common complaints.[13] When literature similar to our research is examined; McSweeney et.all. (2021) in their study, in which they retrospectively evaluated the complaint data of 219 patients in a single regional general surgery department in Australia, observed that the most complaint applications were made by women, with 64% (n: 139).[14] In their study where Alosaimi et al. (2018) evaluated 672 complaints in Saudi Arabia, they reported that the most complaint applications were made by women.[15] Unlike the results of our research, Hoşgör and Cengiz (2020) found in their study that the individuals who complained most about health services were high school graduates, in the age group of 41 and over, and male patients.[16] Although women in Türkiye experience more health problems, it is observed that those who apply to the patient rights unit are mostly men, due to the presence of a patriarchal structure in the traditional Turkish family structure and the status of being the head of the house that the society attributes to men.[17]

In our research, it was assumed that the complaints were made by individuals over the age of 18, as confirmation of being over 18 years of age was required to register on the *"sikayetvar.com"* website. Hoşgör and Cengiz (2020) reported in their research that the age group that filed the most complaints was 41 and over.[17] According to Önal and Civaner (2015), it was interpreted that individuals' awareness of defending their rights increases with advancing age.[18] In addition, the fact that elderly patients feel less fear of not being able to receive service due to their complaints about public health institutions can be seen as a reason for this situation.

As a result of our research, 255 (71.0%) of the complaints came from outpatient clinic patients, 37 (10.3%) were from surgery, 8 (2.2%) were from endoscopy and 59 (16.4%) were from patients receiving treatment in the service. It was observed that the complaints from all outpatient clinic patients were significantly higher than the complaints from ward, surgery and endoscopy patients ($p < 0.05$). Considering the medical units where complaints are made in the literature, in the study of Uludağ (2011): outpatient clinic, emergency, clinic, laboratory, imaging services, operating room, intensive care.[19] In Gürlek et al.'s (2011) study, clinic, outpatient clinic, laboratory, imaging services and emergency service;[20] In Zengin et al.'s (2013) study; outpatient clinic, laboratory, imaging, clinic and emergency department;[21] In the study of Bostan (2017), it was seen that there were outpatient clinics, emergency services, clinics, laboratories, intensive care units and operating rooms.[22] Unlike other studies on the subject in the literature, in this study, the first five medical units outside the field of general surgery where the most problems are experienced and therefore complained about are; 1 (0.3%) gynecology, 12 (3.3%) radiology, 1 (0.3%) anesthesia, 2 (0.6%)

plastic surgery, 2 (It was concluded that 0.6%) were related to urology, 2 (0.6%) were related to cardiology and endocrine departments, 1 (0.3%) were related to neurology and 3 (0.8%) were related to orthopedics departments. With a general evaluation, it can be stated that the medical units subject to complaints vary according to the databases where complaints are collected, time intervals, total number of complaints evaluated, types of hospitals complained about (public, private, university) and research structure/plan. Especially in the complaints obtained from "sikayetvar.com" e-complaint portal, as in this work plan, patients/patient relatives who make complaints do not always provide information about which medical units they receive service from and therefore what the medical branches or specialties are that are the subject of the complaint, but directly report the complaints to the patient. They can write about the topics they are interested in.

In the research, 359 of the 537 posts made on the internet about the medical expertise of general surgery in Türkiye on the *"sikayetvar.com"* site were included in the study and 1699 complaints of them were examined. In our research, nearly half of the 1699 complaints that constituted the most complaint reason, 789 (46.44%) were related to "Communication", followed by 685 (40.32%) problems related to "Management", and the main theme of the complaint was at least It was concluded that 225 of them (13.24%) were of "Clinical" origin. In this context, Karaağaç et al. (2018) analysed 493 complaints about 26 private hospitals operating in Ankara on "sikayetvar.com" portal on 26 private hospitals operating in Ankara by Karaağaç et al. (2018) [Management (35%) >Clinical (33.3%) >Relationships (31.6%)]2 and the findings of the systematic study conducted by Reader et al. (2014) to develop the related taxonomy [Management (35.1%) >Clinical (33.7%) >Relationships (29.1%)] were found to contrast with the findings of this study.[7] In another study by Chaulk et al. (2019) where 87 patient complaints were examined using the same taxonomy, the main themes of the most important complaints were; It has been reported that Clinical, Relationships and Management.[23] It is possible to interpret these results obtained in terms of the main theme as private healthcare business managers should focus more on problems and complaints, especially those arising from "Management".

In our research, following the complaints related to the main theme, the categories determined to cause the most complaints by patients and their relatives are as follows; 214 (12.6%) were related to communication failure, 173 (10.2%) were related to staff attitude, 159 (9.4%) were compassion, 145 (8.5%) were access and acceptance, 134 (7.9%) patient and staff dialogue, 125 (7.4%) bureaucracy, 102 (6%) service problems, 100 (5.9%) incorrect information, 97' 5(5.7%) about delays, 74 (4.4%) about recommendations, 54 (3.2%) about examinations, 47 (2.8%) about quality of care, 47 (2%) 8) treatment related, 46 (2.7%) finance and billing, 45 (2.7%) personnel and resources, 35 (2.1%) environmental, 32 (1.2%) diagnostic errors. It has been revealed that there are errors in diagnosis. In the international literature, service delivery;[24,25] the physical environment/environment where service delivery takes place; service access and patient admission interventions;[26] It is known that complaints have been reported regarding delay/timing problems due to long waiting times,[27], violation of patient/relative privacy,[28] and problems of respect-dignity and being cared for.[25]

In our research, 335 (93.3%) of the complaints were only related to the interventions performed in general surgery, and it was observed that only

74 (20.6%) of the complaining patients and their relatives received a response to their complaints. In parallel with the findings of this study, in the studies conducted by Moghadam et al. (2010) in Iran and Taylor et al. (2002) in Australia, complaints were resolved with explanation and/or thanks in a large proportion (>90% and >73%, respectively). In other words, it has been reported that complaints result in the satisfaction of healthcare users.[29] In addition, the fact that relevant studies do not include information on the average time it takes for complaints to be resolved makes it impossible to make more accurate comments.

In our research, 219 (61.0%) of the hospitals complained about were public hospitals, while 140 (39.0%) were private hospitals. Hoşgör and Cengiz (2020) reported in their study that the types of hospitals to which the most complaints were made were public (42.1%), university (26.2%) and private (10.5%) hospitals, respectively.[16] This situation can be interpreted as the fact that public and university hospitals in Türkiye now prioritize providing patient/patient-relative-oriented services, just like private healthcare enterprises, care about the opinions and suggestions expectations of healthcare service recipients, and wish to be preferred by them again.

Surgeons face challenges in communication and care in all aspects of surgical care. In the outpatient setting, time pressure, inadequate staffing, and patient education are clear hazards to patient communication. It is well known that effective healthcare encourages apologies or empathy with the patient and clear explanation of events that have occurred. In fact, patients who complain almost always expect an apology, an explanation of what happened, or a factual response to be included. Only a small proportion of patients who file a complaint are interested in financial compensation.[30]

This research had some limitations. The research is limited to the complaints of 359 patients and their relatives made to the *sikayetvar.com* website regarding the field of general surgery between January 1, 2023 and November 1, 2023, and it is assumed that the complaints are correct. The fact that a specific complaint taxonomy is not used in most of the research makes it difficult to reach a complete unity of definition regarding the reasons for complaints, and this may lead to subjectivity when classifying the reasons for complaints. The complaint was excluded from the study because it was not related to a intervention performed in the general surgery department and the content of the complaint was unclear.

5.CONCLUSION

This research was carried out by examining the complaints regarding the online general surgery section offered in Türkiye on *"sikayetvar.com".* It is thought that the results obtained in the study can guide healthcare business managers in effective complaint management and help improve patient satisfaction. Knowing the sources of patient dissatisfaction with the services provided in general surgery departments can help reduce the number of patient complaints and improve patient care. We think that more personalized contacts between general surgeons and patients and their relatives may reduce the frequency of complaints. Additionally, complaints regarding health services associated with general surgery departments in different countries can be compared. The fact that a specific complaint taxonomy is not used in most of the studies makes it difficult to reach a complete unity of definition regarding the reasons for complaints, and this may lead to subjectivity when classifying the reasons for complaints. It may be suggested that subsequent studies be conducted

with larger sample sizes and in a regional comparative manner, and from this, a national complaint taxonomy can be developed and introduced into the literature.

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Conflict of Interest:

There is no conflict of interest between the authors.

Idea and design in our research:

Idea and design in our research: AŞ, Supervision; MY, Collection and Processing of Data; MY, Analysis and Interpretation of Data; AE, Writing of the Manuscript; All authors agreed to be responsible for the accuracy and completeness of the study.

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Research Article/ Araştırma Makalesi

Predictive Factors for Severe and Critical Coronavirus Disease-19 in Young Adults

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Purpose: Advanced age is associated with a poor prognosis in Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The present study investigated the predictive factors for disease severity in young adults.

Method: Our study is a descriptive cross-sectional study. A total of 399 patients with SARS-CoV-2 aged under 60 who had been hospitalized at our hospital were retrospectively evaluated. Patients were stratified into mild, moderate, severe, and critical groups according to their respiratory rate, SpO2, and PaO2/FiO2 levels. The relationship between the signs and symptoms on hospital admission and the disease severity was evaluated.

Results: The patients were classified as mild (n:112), moderate (n:192), severe and critical (n:95) according to disease severity. The mean age was 44. 43 of 399 patients were followed in the intensive care unit, and 17 patients died. According to the binary logistic regression analysis, advanced age, hypertension, dyspnea on admission, elevated CRP, decreased lymphocyte and eosinophil count, multiple bilateral ground glass appearances, and consolidation independently predicted the severity of the disease.

Conclusion: The signs and symptoms should be evaluated in detail also in young patients with SARS-CoV-2. If risk factors are detected, they should be monitored more closely to predict a poor prognosis..

Keywords: SARS-CoV-2, Young adult, Prognostic factors

1.INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), which has rapidly spread from Wuhan, China, to the whole world in 2019, has led to the SARS-CoV-2 pandemic.[1] Approximately 2.978.935 individuals have lost their lives due to SARS-CoV-2 until today.[2] Although the SARS-CoV-2-related mortality rate is lower than that determined in previous SARS-CoV (13%) and MERS-CoV (35%)-related cases of pneumonia, SARS-CoV-2 is more contagious.[3] SARS-CoV-2 was found to be more severe and fatal in the elderly with underlying comorbid conditions, although SARS-CoV-2 -related mortality is relatively lower in the general population.[4] On the other hand, a severe disease course has been frequently reported also in healthy young adults.[5] The present study aimed to investigate the predictors of severe disease in young adults under the age of 60 infected with SARS-CoV-2.

2. MATERIALS and METHODS

2.1.Patient Collection Data

Our study is a descriptive cross-sectional study. Sakarya University Training and Research Hospital is the medical center where SARS-CoV-2 patients have been followed since the emergence of the pandemic in the city of Sakarya, which has a population of over 1 million. The University Hospital has a bed capacity of approximately 750 patients. Our study is a single-center retrospective study. The predictive factors for disease severity were evaluated in 399 SARS-CoV-2 infected patients under the age of 60 years. Patients aged

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between 18 and 60 years who had been followed up at Sakarya University Training and Research Hospital between 11 March and 30 July 2020 with proven SARS-CoV-2 infection through real-time protein chain reaction (RT-PCR) test were included in the study. The first case was enrolled to the study at 15 March. The baseline demographic, laboratory, and clinical characteristics were obtained from hospital database system. The hematological and biochemical test results on admission and the consequences of computed tomography (CT) of the thorax were evaluated.

The study was performed in accordance with the ethical considerations of the Helsinki Declarations. The Ethics Committee of Sakarya University School of Medicine approved this study. (Approval number is: 71522473/050.01.04/530)

2.2. Definitions

The diagnosis of SARS-CoV-2 was made based on the current guideline of the World Health Organization (WHO).[6] The patients were allocated to three groups according to the disease severity: mild, moderate, severe, or critical.[7] Disease severity was comprehensively assessed by systemic symptoms (e.g., fever, pulmonary manifestations), physical examinations of lungs, and radiological imaging.The mild disease was described as; mild symptoms and no radiological evidence of pneumonia on thorax CT. The moderate disease was characterized as fever, mild respiratory signs or symptoms, and radiological evidence of pneumonia on CT. Severe disease was defined as severe dyspnea, respiratory rate ≥30/minute, finger oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and lung infiltrates >50% of the lung field within 24–48 h. Patients with respiratory failure who required ICU monitoring and treatment, septic shock, or multiple organ failure were defined as 'critically ill'.

2.3. Statistical Analysis

The compliance of numerical variables obtained from patient groups to normal distribution was examined by visual and analytical methods, and non-normally distributed parameters were defined by specifying the median and interquartile distribution and categorical variables by specifying percentage and number. Mann-Whitney U test was used for continuous variables that were not distributed normally, and the Kruskal Wallis test was used when there were more than two variables. Post hoc analyzes were performed in the analyzes comparing more than two groups.

Ordinal logistic regression was performed to predict the severity of the disease in three patient groups. For good fit in regression analysis, the nagelkerke value has been studied. A test of parallel lines was conducted.

The situations where the P value is less than 0.05 will be evaluated as statistically significant results. SPSS 20.0 program was used while evaluating the study data.

3. RESULTS

3.1. Clinical Characteristics

A total of 399 patients (190 females) were included in the study. The mean age of the patients was 44. The patients were allocated to three groups according to the disease severity: mild, moderate, severe, and critical. Of the 399 patients, 112 (28%) had mild, 192 (49%) had moderate, and 95 (23%) had severe and critical illness. The disease severity increased with age ($p<0.001$). Table 1 shows the clinical characteristics and comorbidities at the time of admission. Severe disease was more common among males. Cough, fatigue, and fever were the most common symptoms on admission. Dyspnea was more common in the severe illness group compared to the mild and moderate groups

(p<0.005). At least one comorbidity was detected in 98 patients. The frequency of hypertension and diabetes increased with the disease severity (p<0.005).

3.2. Laboratory Data

The laboratory parameters have been presented in Table 2.

Alanine aminotransferase (ALT), aspartate transaminase (AST), lactate dehydrogenase (LDH), creatine phosphokinase, C -reactive protein (CRP), serum ferritin, plasma random glucose, and the D-dimer levels at the time of admission were higher in patients with severe illness compared to those in the mild and the moderate illness groups (p<0.001). The monocyte, lymphocyte, and eosin-

Table 1.

Clinical characteristics and comorbidities of SARS-COV-2 patients

Variables	All (n=399)	Disease Severity			p
		Mild (n=112)	Moderate (n=192)	Severe (n=95)	
Age (years)	44 (36-54)	37 (28-46)1)2)	44 (38-53)2)	52 (45-57)	<0.001
Sex					0.025
Male	209 (52.4)	57 (50.9)	91 (47.4)2)	61 (64.2)	
Female	190 (47.6	55 (49.1)	101 (52.6)	34 (35.8)	
Smoking	12 (3)	1 (0.9)	7 (3.6)	4 (4.2)	-
Symptoms					
Fever(>38 C)	166 (41.6)	39 (34.8)	82 (42.7)	45 (47.4)	0.172
Cough	262 (65.7)	68 (60.7)	134 (69.8)	60 (63.2)	0.231
Shortness of breath	120 (30.1)	18 (16.1)2)	46 (24) 2)	56 (58.9)	<0.001
Sputum production	9 (2.3)	-	2 (1)	7 (7.4)	-
Myalgia	158 (39.6)	38 (33.9)	85 (44.3)	35 (36.8)	0.169
Headache	56 (14)	14 (12.5)	31 (16.1)	11 (11.6)	0.496
Diarrhea	34 (8.5)	4 (3.6)	20 (10.4)	10 (10.5)	0.087
Loss of appetite	41 (10.3)	10 (8.9)	23 (12)	8 (8.4)	0.555
Loss of taste	47 (11.8)	12 (10.7)	27 (14.1)	8 (8.4)	0.347
Loss of smelling	51 (12.8)	13 (11.6)	28 (14.6)	10 (10.5)	0.568
Comorbidities					
At least one comorbidty	98 (24.6)	6 (5.4) 1)2)	40 (20.8) 2)	52 (54.7)	<0.001
Hypertension	54 (13.5)	4 (3.6)1)2)	26 (13.5) 2)	24 (25.3)	<0.001
Diabetes	48 (12)	3 (2.7)1)2)	23 (12) 2)	22 (23.2)	<0.001
Chronic kidney failure	11 (2.8)	1 (0.9)	3 (1.6)	7 (7.4)	-
Malignancy	10 (2.5)	-	1 (0.5)	9 (9.5)	-
Asthma	8 (2)	-	3 (1.6)	5 (5.3)	-
Coronary artery disease	9 (2.3)	1 (0.9)	4 (2.1)	4 (4.2)	-
COPD	8 (2)	1 (0.9)	1 (0.5)	6 (6.3)	-
Covid 19 patient in family	132 (33.1)	35 (31.3)	66 (34.4)	31 (32.6)	0.851

Note: Data are median (IQR) or n (%). P value denotes the comparison among mild, moderate and severe illness group. [1)] and [2)] signify $P < 0.05$ for post-hoc comparison.
[1)]Refers to comparison between the moderate group and the mild group.
[2)]Refers to comparison between the severe group and the moderate group or the mild group.
IQR, interquartile range; COPD, chronic obstructive pulmonary disease.

ophil counts were low in the severe illness group (p<0.005).

3.3. Radiological Data

Thorax computed tomography (CT) findings have been presented in Table 3.

Ground glass appearance was detected in 340 patients. Lung involvement was not seen in 59 patients (14.8%). The rate of multiple ground glass appearances and the presence of consolidation increased as the disease severity increased (p<0.001). The absence of ground glass appearance and focal involvement in a single lobe was more common in the mild and moderate illness group (p<0.001).

3.4. Predictive Factors

According to the binary logistic regression analysis, advanced age, hypertension, dyspnea on admission, elevated CRP, reduced lymphocyte and eosinophil count, multiple ground glass appearances, and consolidation independently predicted the disease severity (Table 4).

4. DISCUSSION

In our study, the rate of severe illness was 23%, similar to a previous study.[8] In that study, the presence of fever and anorexia on admission was shown to predict severe illness. In our study, severe illness was found to be 2,74-fold greater among symptoms on admission in patients with dyspnea. In a recent study, the development of dyspnea was found to be related to delayed admission to the hospital and delayed treatment.[5] This condition may be associated with a poor prognosis, although not evaluated in our study. This was suggested to be related to dyspnea being more common among patients who present to the hospital late. In a study supporting this, the time from onset to dyspnea was 5.0 days, 7.0 days to hospital admission, and 8.0 days to ARDS.8 Furthermore, dyspnea can predict a poor prognosis as it can be related to lung involvement.

In many studies, advanced age was reported to predict mortality independently in SARS-CoV-2 patients.[9] Although the patients included in our study were below 60 years of age; the disease severity was found to increase 1.05- fold with each year. The increase in the disease severity with growing age also in young patients was shown to be related to pathophysiological changes, such as changes to the immune cell repertoire, the epigenome, the NAD+ levels, inflammasome activity, biological clocks, and covalent modifications of human and viral proteins.[10] Decreased airway viral clearance and decreased protective barrier functions also lead to disease progression.[11]

In the logistic regression analysis, elevated CRP and lymphopenia predicted the disease severity in young patients. Similarly, lymphopenia was shown to be the strongest predictor of severe disease in healthy young individuals diagnosed with COVID-19.5 The primary pathophysiological mechanism of severe SARS-CoV-2 infection is cytokine storm-related tissue and organ damage. Many studies indicate that pro-inflammatory cytokine release induces lymphopenia in viral infections.[12] In addition, the release of inflammatory cytokines like IL-1, IFN-γ, and IL-6 leads to lymphopenia by inhibiting T cell proliferation.[13] CRP is an inflammatory marker that also increases in acute systemic inflammatory syndromes triggered by viral infections. Similar to our study, CRP elevation was shown to predict severe illness development in SARS-CoV-2 patients.[14] Elevated CRP resulting from SARS-CoV-2-related pro-inflammatory cytokine release and increased inflammatory response is suggested to be associated with a poor prognosis and death.[14,15]

Table 2.

Laboratory findings on admission of SARS-COV-2 patients

Variables	All (n=399)	Disease Severity			p
		Mild (n=112)	Moderate (n=192)	Severe (n=95)	
Laboratory findings [1)]					
ALT <50 (µ/l)	28 (19-40)	22(16-31) [1)2)]	28 (19-41)	32(25-51)	<0.001
AST <40 (µ/l)	28 (22-38.25)	24 (19-31)[1)2)]	28(23-36) [2)]	36(26-55)	<0.001
Total bilirubin (µmol/l)	0.5 (0.3-0.6)	0.45 (0.3-0.6) [2)]	0.5 (0.3-0.6)	0.5 (0.4-0.7)	0.056
Blood glucose(mmol/l)	106 (95-123)	98 (93-107) [1)2)]	108 (96-124) [2)]	117(104-144)	<0.001
CK(U/L)	88 (58-151)	82 (54-121) [2)]	87 (61-168)	104 (63-195)	0.046
LDH(U/L)	244 (197-319)	208(178-241) [1)2)]	247(202-305) [2)]	339(244-414)	<0.001
Na(mEq/L)	138 (135-140)	139(136-140) [2)]	138(136-140) [2)]	136(134-138)	<0.001
K(mEq/L)	4.1 (3.8-4.4)	4.1 (3.9-4.4)	4.1 (3.8-4.3)	4.1 (3.7-4.4)	0.474
C-reactive protein (mg/l)	13.4 (4-51)	5 (3-14.5) [1)2)]	12.5 (5-42) [2)]	62(19-119)	<0.001
D-Dimer(mg/dl)	301(167.7-564)	241(110-411) [1)2)]	301(185-538) [2)]	457(234-826)	<0.001
Ferritin(µ/l)	127 (44-328)	68 (20.2-153) [1)2)]	125 (47-290) [2)]	313 (105-871)	<0.001
INR	1.1 (1-1.16)	1.07 (1-1.1) [2)]	1.1 (1-1.1) [2)]	1.1 (1-1.2)	0.005
Lactat(mmol/L)	1.7 (1.3-2.2)	1.7 (1.3-2.1) [2)]	1.6 (1.12-2.1) [2)]	1.9(1.6-2.5)	0.001
White blood cell count (×109/l)	5.6 (4.5-7.2)	6.01 (4.83-7) [1)]	5.2(4.3-6.5) [2)]	6.1 (4.6-8)	0.001
Haemoglobin (g/l)	13.3 (12.2-14.3)	13.3(12.4-14.5)	13.3(12.3-14.4) [2)]	13(11.1-14.1)	0.029
Platelet count (×109/l)	192 (161-245)	208(166-253) [1)]	184(158-222)	189(153-302)	0.029
Neutrophil count (×109/l)	3.5(2.6-4.8)	3.55 (2.6-4.9) [2)]	3.2 (2.4-4.4) 2)	4.3(3-5.8)	<0.001
Lymphocyte count (×109/l)	1.4 (1.05-2)	1.84 (1.3-2.4) [1)2)]	1.5 (1.1-1.8) [2)]	1.1 (0.7-1.4)	<0.001
Eosionophil					
(×109/l)	0.01(0.002-0.05)	0.03 (0.003-0.1) [1)2)]	0.01 (0.001-0.04)	0.008 (0.003-0.02)	<0.001
Monosit(×109/l)	0.4 (0.3-0.5)	0.4 (0.3-0.6) [1)2)]	0.37 (0.3-0.5)	0.3 (0.2-0.5)	0.001
MPV(fl)	9 (8.2-9.8)	8.8 (8.2-9.88)	9.05(8-9.8)	8.9 (8.1-9.9)	0.678
PCT	0.1 (0.1-0.2)	0.17 (0.1-0.2) [1)2)]	0.1 (0.1-0.19)	0.1(0.1-0.2)	<0.001
RDW	15.3 (13.9-16.4)	15.3(15.7-16.4)	15.2(13.1-16)	15.4(14.3-16.4)	0.403
PDW	17.8 (16.8-18.9)	17.7(16.6-18.6) [2)]	17.7(16.6-18.7) [2)]	18.1(17.3-19.1)	0.014
Prognosis					
Recovery	382 (95.7)	112	192(99.5)	78 (82.1)	<0.001
Exitus	17 (4.3)	-	-	17 (17.9)	-
ICU hospitalization	43 (10.8)	-	2 (1)	41 (43.2)	<0.001

Note: Data are median (IQR) or n (%). P value denotes the comparison among mild, moderate and severe illness group. [1)] and [2)]Signify P < 0.05 for post-hoc comparison.
[1)] Refers to comparison between the moderate group and the mild group.
[2)] Refers to comparison between the severe group and the moderate group or the mild group.

ALT, alanine transaminase; AST, aspartate transaminase; CK, creatine kinase; LDH, Lactate dehydrogenase; Na, sodium; K, potassium; INR, international normalized ratio; MPV, mean platelet volüme; PCT, plateletcrit; RDW, Red Cell Distribution Width; PDW, platelet distribution width; ICU, intensive care unit; IQR, interquartile range.

Table 3.

Chest CT findings on admission of SARS-COV-2 patients

Variables	All (n=399)	Disease Severity			p
		Mild (n=112)	Moderate (n=192)	Severe (n=95)	
Chest CT findings					
Ground glass appearance	340 (85.2)	60 (53.6) 1)2)	188 (97.9)	92 (96.8)	<0.001
Single lobe focal ground glass	44 (11.0)	24 (21.4) 1)2)	12 (6.3)	8 (8.4)	<0.001
Multiple unilateral glass	13 (3.3)	5 (4.5)	7 (3.6)	1 (1.1)	-
Multiple bilateral glass	301 (75.4)	49 (43.8) 1)	167 (87.0)	85 (89.5)	<0.001
Consolidation	127 (31.8)	17 (15.2) 1)2)	58 (30.2) 2)	52 (54.7)	<0.001
Pleural effusion	9 (2.3)	2 (1.8)	1 (0.5)	6 (6.3)	-
Peripheral lung involvement	283 (70.9)	59 (52.7) 1)2)	155 (80.7)	69 (72.6)	<0.001

Note: Data are median (IQR) or n (%). P value denotes the comparison among mild, moderate and severe illness group. 1) and 2)Signify P < 0.05 for post-hoc comparison.
1) Refers to comparison between the moderate group and the mild group.
2)Refers to comparison between the severe group and the moderate group or the mild group.

Table 4.

Results of ordinal logistic regression model using three levels of severity as response

Variables	Estimate	Std. Error	Wald	OR	p	95% Confidence Interval	
						Lower Bound	Upper Bound
Age (years)	.049	.013	14.7	1.05	<0.001	1.024	1.076
C-reactive protein (mg/l)	.016	.003	23.072	1.016	0	1.009	1.022
INR	.451	.270	2.784	0.637	0.095	.375	1.082
Lactate	.178	.094	3.565	1.195	0.059	0.993	1.438
Lymphocyte count (× 10^9 per L)	-.366	.146	6.312	1.6	0.012	.521	0.923
Eosionophil count (× 10^9 per L)	-2.608	1.259	4.288	14	0.038	0.006	0.870
Haemoglobin (g/L)	-.117	.075	2.395	1.25	0.122	.768	1.032
White blood cell count (× 10^9 per L)	.004	.035	.016	1.004	0.9	.938	1.076
Female sex (vs male)	.109	.26	.176	1.115	0.675	0.67	1.858
Fever (temperature ≥38°C)	-.296	.238	1.547	1.4	0.214	.467	1.186
Ground-glass opacity	-3.184	.508	39.278	24.3	<0.001	0.015	0.112
Consolidation	-.851	.260	10.721	2.34	0.001	0.257	.711
Multiple bilateral pulmonary infiltration	-1.006	.310	10.518	3.3	0.001	0.199	.672
Hypertension	-,782	,346	5,100	2.18	0.024	0,232	,902
Diarhea	-,788	,409	3,705	2.5	0.054	0,204	1,015
Shortness of breath	-1,010	,269	14,043	2.74	<0.001	0,215	,618
Cough	,207	,252	,673	1,230	0.412	,750	2,016

OR, odds ratio.

Lung damage develops as a result of cytokine release from pneumocytes and cytokine storm as a result of binding of SARS-CoV-2 to ACE-2 receptors in alveolar epithelial cells.[16] Hence, the findings of CT of the thorax are crucial in diagnosing SARS-CoV-2 and predicting the disease severity. The Chinese Medical Association Radiology Branch divided CT findings into four categories, and bilateral patchy ground glass appearance was reported to be typical for early-stage lung involvement. The presence of consolidation due to the accumulation of exudate in the alveoli and the interstitial space is observed in stages two and three.[17] In our study, the disease severity was found to be 24,39-fold greater among patients with ground glass appearance and 2.34-fold greater among patients with consolidation.

Similarly, while consolidation was reported in patients with severe and advanced stage illness in a study, the mortality rate was said to be higher in patients with consolidation.[18,19] The presence of consolidation is suggested to be related to increased viral load and related necrotizing bronchitis and widespread alveolar damage.[20] The patients who had consolidation on hospital admission are thought to have presented late, so they should be monitored closely.

ACE-2 receptors on which SARS-CoV-2 binds are known to be also found in the cardiovascular system.[21] Many studies have been conducted investigating the influence of hypertension on SARS-CoV-2 due to the role of ACE-2 in the pathogenesis of hypertension.[22] Increased cytokine release and inflammatory changes found in the pathophysiology of hypertension may partially explain the poor prognosis in hypertensive patients with SARS-CoV-2.[23] Studies investigating the relationship between hypertension and SARS-CoV-2 prognosis have yielded different results. In a meta-analysis evaluating 30 studies, hypertension was associated with severe SARS-CoV-2 and increased mortality.[24] In a study including 44672 patients, hypertension was shown to be related to increased mortality, independent of age.[25] In another study analyzing more than 17 million patient records, hypertension was reported not to increase mortality significantly but lead to a mild risk increase. This increased risk was associated with hypertension being more common in advanced age.[26] In our study, the disease was found to be 2.18-fold more severe among hypertensive patients independent of age and other variables. In conclusion, the present study has revealed the predictive factors for severe SARS-CoV-2 development in patients under 60. It is recommended that patients who present to the hospital with these symptoms be monitored more closely.

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Conflict of Interest

The Authors declare that there is no conflict of interest

Author Contributions

A.V. planned the methodology, built the hypothesis of the article, and wrote the manuscript; H.D.O. and A.C.U. were responsible for data management and reporting collected data; G.G.B. provided access to crucial research components (personnel,

equipment, environment), and E.G and O.K. were responsible for the Ethical Approval process; E.K and A.O. were responsible for the statistical interpretation and conclusion of the results and reviewed the article scientifically, besides its spelling and grammar, before submission.

Ethical Statement

The study was performed in accordance with the ethical considerations of the Helsinki Declarations. The Ethics Committee of Sakarya University School of Medicine approved this study. (Approval number is: 71522473/050.01.04/530)

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Research Article/ Araştırma Makalesi

Use of Residuals and Rank Product in Detection of Outlier in Survival Analysis with Crimean-Congo Hemorrhagic Fever Data

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Purpose: Survival analysis is a statistical method used in many fields, especially in the field of health. It involves modeling the relationship between the survival time of individuals after a treatment or procedure and the event called response. The presence of outliers in the data may cause biased parameter estimations of the established models. Also, this situation causes the proportional hazards assumption to be violated especially in Cox regression analysis. Outlier(s) are identified with the help of residuals, Bootstrap Hypothesis test and Rank product test.

Method: In R.4.0.3 software, outlier(s) are determined on a clinical dataset by the Schoenfeld residual, Martingale residual, Deviance residual method and Bootstrap Hypothesis test (BHT) based on Concordance index, and Rank product test.

Results: After the cox regression established by the backward stepwise and robust cox regression, it was observed that the established models did not fit. So, the outlier(s) determined by the methods mentioned.

Conclusion: It was decided that only one observation could be excluded from the study. As in the survival data, in many data types, outliers can be detected and further analyzes can be applied by using the methods mentioned.

Keywords: Outliers, Residuals, Concordance index, Rank product

1.INTRODUCTION

Survival analysis is a process that involves modeling relationships with time in the occurrence of the event. Clinically, it involves examining the relationships between an individual's survival time after a particular treatment or procedure and the event occurring in response. At the same time, the effect of independent variables on survival time can be modeled. The occurrence of the event usually occurs as death. If the event has not occurred, those individuals are included in the study as censored. Cox regression analysis is frequently used to examine the effect of independent variables on survival time.[1] For this analysis, which is a semi-parametric model, the variables in the model must satisfy the proportional hazards assumption. This assumption means that the hazard ratio is constant over time. The presence of outliers in the variables in the data indicates that the Cox regression coefficients deviate from the true value. Therefore, it causes wrong findings in parameter estimation.[2] There are studies in the literature on outlier detection in wide areas such as normal data, multivariate normal data, censored data, negative data, time series data, gene expression data.[3] As in these studies, the evaluation of the adequacy of the established models has an important place in the diagnostic procedures. A large part of this process includes the evaluation of residuals. There are many residual methods in the literature. In this study, Schoenfeld residual, Martingale residual, Deviation residual and Concordance index based Bootstrap Hypothesis methods are used.

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In the study, effective observations are obtained with the rank product test by using the results of the residuals and concordance c-index-based Bootsrap Hypothesis test in outlier detection. Outlier(s) are be identified with the help of residuals and Rank product test.

2.MATERIALS and METHODS

Study Selection: With the help of the data obtained by Aktaş et al.[4], who worked on 209 patients diagnosed with CCHF (Crimean-Congo Hemorrhagic Fever) between May 2010 and September 2015 in Tokat State Hospital. The study data was approved by the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee. The data set consists of clinical information on 48 covariates of 209 patients.[4] Analyses were performed using the packages "survival"[5], "coxrobust"[6], "BCSOD"[7], "qvalue"[8] in R 4.0.3[9] software.

2.1.Cox regression model

Cox regression model, which is a frequently used method in survival analysis, examines the relationship between survival time as the dependent variable and one or more independent variables on which the effect is investigate.[1,10]

$$h(t,X) = h_0(t)\exp(\beta' X), \qquad (1)$$

In the equation, $\beta=(\beta_1,\ldots,\beta_p)$ are the unknown regression coefficients, h_0 (t) is baseline hazard and $X=(X_1,\ldots,X_p)$ is the covariate vector.[11] Although Cox regression analysis is a frequently used model, the Cox robust regression model is recommended because the presence of outliers causes large changes in parameter estimations.

2.2.Cox robust regression model

This model is obtained by weighting the partial likelihood function in the Cox regression model.[12,13]

Let m(t,X) be a weight function, where m_ij=m(t_i,X_i) ve m_i=m_ii=m(t_i,X_i) are the weight 1≤i≤j≤n. Robust state of partial likelihood function for parameter estimation is

$$\sum_{i=1}^{n} m_i \delta_i \left[X_i - \frac{\sum_{j\geq i} m_{ij}\exp(X_j^T\beta)X_j}{\sum_{j\geq i} m_{ij}\exp(X_j^T\beta)} \right] = 0 \qquad (2)$$

This model reduces the contribution of outliers to the model in parameter estimation.[14]

2.3.Outlier detection methods in survival analysis

2.3.1.Residuals

In the detection of outliers that have a significant effect on parameter estimation, it is important to use residuals to reveal whether the established model meets the assumptions.

2.3.2.Schoenfeld

Schoenfeld residuals, also known as a,score residual, are used to test the proportional hazards assumption in the Cox regression model. This type of residual has a set of values for each independent variable in the model, rather than one value for each observation.[15] To test he assumption that Schoenfeld residuals do not depend on time, Schoenfeld stated that the ith residual can be plotted against t_i to test the assumption that the residuals are not time dependent. Schoenfeld residual is

$$\hat{r}_{(i)} = X_i - \frac{\sum_{j\in R_i} X_j e^{(\hat{\beta}^T X_j)}}{\sum_{j\in R_i} e^{(\hat{\beta}^T X_j)}} \qquad (3)$$

Where t_i is ith survival time and X_i is covariate vector and R_i is risk set.

Kumar and Klesjö found that the partial residuals

estimated against time should be randomly distributed around 0. Therefore these residuals are summed to zero.[16]

2.3.3.Martingale

Barlow and Prentice[17] proposed the type of residual named Martingale-based residual or Martingale residual. Martingale residual for ith individual is

$$\widehat{M}_i = \delta_i - \widehat{H}_0(t_i)\exp\left(\hat{\beta}^T X_i\right) \qquad (4)$$

Where δ_i is event. Martingale residuals take values between -∞ and 1. It shows an asymmetrical distribution. A value close to 1 indicates a shorter than expected survival time, a large negative value indicates a long survival time.[18,19]

2.3.4.Deviance

Deviance residuals proposed by Therneau, Grambch and Fleming[20] were converted from Martingale residuals. These residuals are given as

$$d_i = sign(\widehat{M}_i)\sqrt{2}\left[-\widehat{M}_i - \delta_i \log\left(\delta_i - \widehat{M}_i\right)\right]^{1/2} \qquad (5)$$

They are distributed symmetrically around zero.

2.3.5.The Concordance c-index

This method proposed by Harrell et al.[21] to demonstrate the performance of survival analyses. It measures the probability of a higher prediction in the individual in whom the event occurred for the first time. This statistics, which is sensitive to outliers, measures how well the predicted values fit with the rank-ordered response variables[14]. The error rate is calculated as 1-c and c represents the Harrell concordance index. Error rates range from 0 to 1, with a value of 0 indicating the best accuracy. There are 3 alternative methods for outlier detection in survival analysis using the c index: (1) One-Step Deletion, (2) Bootstrap Hypothesis test and (3) Dual Bootstrap Hypothesis test.

Bootstrap Hypothesis test which will be used in this study, tests concordance variation over bootstrap samples without ith individual.

Hypotheses for ith. observation are given as

$$H_0: \delta C_i \leq 0,\ H_1: \delta C_i > 0 \qquad (6)$$

Where ⟦δC⟧_i=C_(i-) -C_all, C_(i-) is the c-index of model establised without i. individual ve C_all is the c-index of model with all variables.

The smallness of the p values obtained from the hypotheses indicates the observation is outlying.

2.3.6.Rank Product Test

Rank product test is a method used to derive an overall conclusion from the findings obtained from the methods used to identify outliers. This method, which is a non-parametric statistical method, was first used in meta-analysis and microarray studies.[22,23] In this method, the aim is to provide a unified definition with the ranking obtained from the methods used.[24]

Let n, m be the number of individuals and the outlier detection method, respectively. Let *Pij*,

be the outlyingness of ith individual for jth method, with 1≤i≤n and 1≤j≤m.

The deviance rank is given as

$$R_{ij} = rank\left(P_{ij}\right), \quad 1 \leq R_{ij} \leq n. \qquad (7)$$

For each method, the lowest ranks obtained indicate more outliers than the others. After obtaining ranks for each method, the rank product is defined as

$$RP_i = \prod_{j=1}^{m} R_{ij}. \qquad (8)$$

To determine the statistical significance of ⟦RP⟧_i, the permutation approaach[23], logarithm approach[25], and exact probability[26] are used. The algorithm in this study produces accurate approximate p values based on the geometric mean of the upper and lower bounds, defined recursively. Since more than one test is performed here, the problem of increasing type I error in multiple tests is encountered. For this problem, false discovery rate (FDR), which is less conservative than the Bonferroni correction, is preferred.[27] The FDR, the expected rate of false positives among all significant tests, ranks the p-values in ascending order and divides them by percentiles. FDR is determined by the q-value.

3.RESULTS

It was aimed to create an application area in determining residual value with the help of the data obtained by Aktaş et al.[4], who worked on 209 patients diagnosed with CCHF (Crimean-Congo Hemorrhagic Fever) between May 2010 and September 2015 in Tokat State Hospital. The study data was approved by the Tokat Gaziosmanpaşa University Clinical Research Ethics Committee. The data set consists of clinical information on 48 covariates of 209 patients.[4]

Analyses were performed using the packages "survival", "coxrobust", "BCSOD", "qvalue" in R 4.0.39 software. The dimensionality reduction was performed on the data set using backward stepwise method in Cox regression analysis.

In the data set, the variables Gender, Treatment, Fibrinogen, Alp (Alkaline Phosphatase), D_bil (Direct bilirubin), Ldh (Lactate dehydrogenase), T_bil (Total bilirubin), Mono (Monocytes), Hgb (Hemoglobin), Inr (International normalized ratio), Aptt (Activated partial thromboplastin time), Ferritin obtained after backward stepwise method in Cox regression analysis were included in the model. In R 4.0.3, the package "survival" is used to obtain Cox regression model, Schoenfeld Residuals, Martingale residuals, deviance residuals. The package "coxrobust" is used to obtain Cox robust regression model. The package "BCSOD" is used to perform Bootstrap Hypothesis test based on Concordance c-index. Finally, the package "qvalue" is used to obtain q-values.

Descriptive statistics for the variables to be used in the model are given in Table 1.

Firstly, we modeled the Cox regression model using the function "coxph" in the library "survival". A robust method of Cox regression was used to show consistency with previous Cox regression analysis results. The library "coxrobust" package was used for robust cox regression model (Table 2).

From the result, the results are not consistent with the previous cox regression model. In Cox robust model, gender and treatment variables are statistically significant for a 5% level of significance (Table 2).

First, proportional hazards assumption, which is the Cox regression model assumption, needs to be tested. We tested proportional hazards assumption using the function "cox.zph" in library "survival".

Figure 1 show that the proportional hazards assumption of the established model is met. The p value for all variables is above 0.05. So, the proportional hazards hypothesis is not violated.

Table 1.

General distribution of variables in the model

Qualitative variables		n (%)	
Prognosis	Alive	181 (86.6)	
	Death	28 (13.4)	
Treatment	Support treat.	182 (87.1)	
	Support treat+Antiviral	27 (12.9)	
Gender	Female	82 (39.2)	
	Male	127 (60.8)	
Quantitative variables		Mean±SD	Median [Q1-Q3]
Fibrinogen		289.89±92.01	279[234-356]
Alp		131.88±103.31	95[66-158]
D_bil		0.61±1.44	0.2[0.13-0.39]
Ldh		976.31±1001.08	583[362-1201]
T_bil		0.95±1.47	0.49[0.32-0.82]
Mono		0.28±0.27	0.17[0.09-0.35]
Hgb		12.99±2.16	13.23[11.9-14.6]
Inr		1.25±0.45	1.14[0.98-1.37]
Aptt		50.79±23.82	42[35.2-60]
Ferritin		6790.29±12754.84	2000[646-4432]

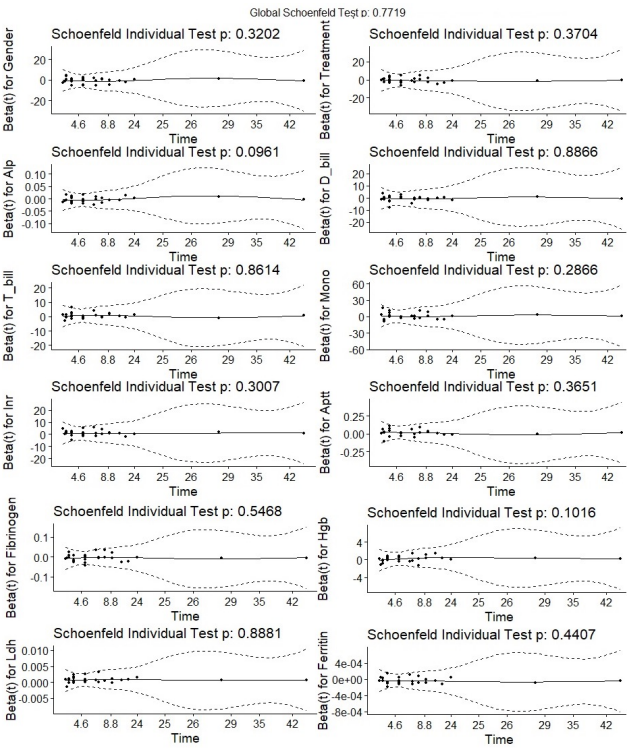
Table 2.

The results on the Cox Regression, Robust Cox Regression and Final Cox Regression

Variables	Cox Regression			Robust Cox Regression			Final Cox Regression		
	coef	HR	p	coef	HR	p	coef	HR	p
Gender	-0.746	0.525	0.156	-1.739	0.843	0.039	-1.198	0.567	0.035
Treatment	-0.650	0.615	0.291	-2.319	0.877	0.008	-1.748	0.752	0.020
Fibrinogen	-0.005	0.003	0.086	-0.006	0.005	0.223	-0.008	0.003	0.012
Alp	-0.003	0.002	0.146	-0.009	0.004	0.021	-0.006	0.003	0.023
D_bill	-0.592	0.456	0.194	-1.074	1.110	0.332	-0.859	0.499	0.085
Ldh	0.001	0.000	<0.001	0.001	0.001	0.020	0.001	0.000	<0.001
T_bill	0.642	0.383	0.094	1.056	1.040	0.311	0.878	0.430	0.041
Mono	0.992	1.011	0.327	1.889	1.950	0.333	2.027	1.069	0.058
Hgb	0.207	0.125	0.099	0.225	0.138	0.104	0.202	0.117	0.084
Inr	0.884	0.460	0.055	1.535	1.080	0.155	1.439	0.620	0.020
Aptt	0.018	0.008	0.017	0.050	0.014	<0.001	0.032	0.009	<0.001
Ferritin	0.000	0.000	0.009	0.000	0.000	0.046	0.000	0.000	<0.001

Figure 1.

Schoenfeld residual plot for independent variables



Martingale and deviance residuals were used for outlier detection. The function "resid" was used for martingale and deviance residuals. From martingale and deviance residuals, there are 6 common outliers. These outliers can also be see in the figure 2.

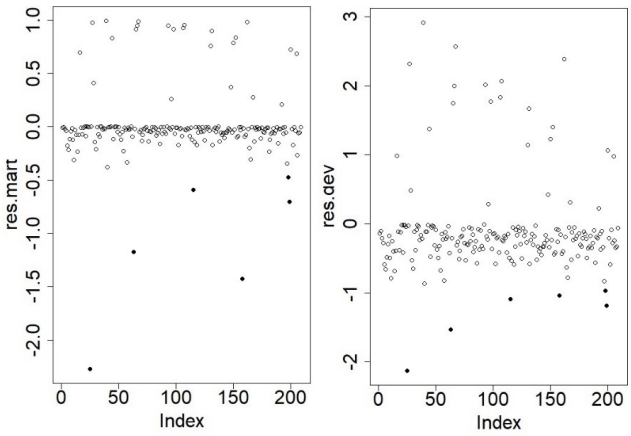


Figure 2.

Martingale and deviance residuals

The other outlier detection method is the bootstrap hypothesis (BHT) based on the concordance c-index. The package "BCSOD" was used for BHT. Here the bootstrap number is 1000. The lowest p-values in table indicate outliers (Table 3).

Table 3.

Result of BHT on concordance c-index

id	exp infl	max	p-value
67	0.039	0.103	0.089
93	0.022	0.108	0.240
63	0.021	0.110	0.252
66	0.020	0.109	0.268
25	0.021	0.103	0.269

The top outliers are given in the table 3. Finally, to obtain an overall result, rank product test was used. In rank product test, we performed the algorithms p-values and q-values, respectively. p-values are obtained with the function "rankprodbounds". q-values are obtained with the package "qvalue". If we combine the results obtained, we obtain Table 4.

Table 4.

The results of the rank product test

id	rank_ martingale	rank_ deviance	rank_ bht	p values	q values
25	1	5	25	0.0002	0.0481
5	19	35	5	0.0097	0.4047
6	16	32	6	0.0089	0.4047
11	10	28	11	0.0090	0.4047
63	3	13	63	0.0071	0.4047
14	14	30	14	0.0169	0.5196
40	7	25	40	0.0199	0.5196
158	2	21	158	0.0189	0.5196
39	209	1	39	0.0229	0.5322
7	37	53	7	0.0367	0.5944
57	9	27	57	0.0370	0.5944
115	5	19	115	0.0299	0.5944
199	4	17	199	0.0362	0.5944
30	17	33	30	0.0438	0.6537
10	36	52	10	0.0479	0.6680
1	142	163	1	0.0572	0.7036

Since 25th observation has the smallest significant q-value, further analysis can be made by excluding this observation from the study. The Cox regression model after the 25th observation eliminated is given in Table 2. After eliminating an outlier, there is an increase in the number of significant variables in final cox regression model.

4.CONCLUSION

According to the results obtained from the clinical data set, the outliers detected according to martingale residual method, deviance residual method and BHT based on concordance c-index. As a general approach combining these methods, rank product test was used. In our clinical data set, there is one outlier. After eliminating the 25th observation, there was an increase in the number of significant variables in cox regression model. There are different residual methods in the literature to be used for the outlier detection.[14,19,28] In the rank product method, the aim is to provide a unified definition with the ranking obtained from the methods used. The rank product test can be applied by using these different methods. Presence of outlier causes the proportional hazards assumption to be violated especially in Cox regression analysis. In order to avoid this situation, it is recommended to use these methods for outlier detection. With this application, especially in survival data, it will find application in different disciplines.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

Author Contribution Statement

Concept/Design: OD. Analysis/Interpretation: OD, ÜE. Data Acquisition: OD, Writing: OD, ÜE. Revision and Correction: OD, ÜE. Final Approval: ÜE, OD.

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Research Article/ Araştırma Makalesi

Diagnostic Value of Serum Thiobarbituric Acid Reactive Substances Levels in Pediatric Acute Appendicitis

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Purpose: This study aims to show the diagnostic value of Serum Thiobarbituric Acid Reactive Substances in pediatric appendicitis.

Method: Eighty-five pediatric patients hospitalized in the pediatric surgery ward with acute appendicitis and a control group of 50 pediatric patients with unspecific abdominal pain were included in this prospective case-control study. Forty-five patients whose pathology specimens confirmed acute appendicitis made up the final appendicitis group.

Results: Patients with appendicitis had higher Serum Thiobarbituric Acid Reactive Substances ($p<0.001$) levels than the control group. In receiver operating characteristic analysis, areas under the curve were 0.654 for Serum Thiobarbituric Acid Reactive Substances.

Conclusion: Serum Thiobarbituric Acid Reactive Substances test of patients with appendicitis provides limited accuracy in the diagnosis of appendicitis.

Keywords: Appendicitis, Thiobarbituric Acid, TBARS, MDA, Oxidative stress, Pediatrics

1.INTRODUCTION

Acute appendicitis (AA) is an emergency surgical condition characterized by an inflammatory response. Diagnosis of AA remains a surgical challenge due to significant differences in clinical presentation. Misdiagnosis rates range from 5% to 30%, and a 5% to 15% misdiagnosis rate is considered acceptable to reduce the risk of perforation.[1–3]

The pathophysiology of AA is characterized by the luminal obstruction, which leads to increased permeability of the appendiceal mucosal barrier and triggers an inflammatory response.[4] Previous studies have explored various markers as diagnostic tools in acute inflammatory states.[5–7] There is substantial evidence indicating the involvement of reactive oxygen species (ROS), leading to oxidative stress, in the physiopathology of this inflammatory process. Evaluating oxidative stress in humans typically involves examining products caused by oxidative damage or identifying the antioxidant defense capacity of the body. However, there is a need for unanimity on the parameters to measure oxidative stress and antioxidant status in different pathologies.[8–10]

ROS are released from macrophages, neutrophils, and various tissue cells. Antioxidant enzymes (like superoxide dismutase and catalase) regulate ROS to maintain cellular oxidative balance by directly suppressing free radicals. Superoxide dismutase and catalase activities were previously investigated among patients with AA and healthy individuals.[11] Because ROS have extremely short half-lives, they are difficult to measure directly. Instead, has been investigated through the presence of lipid peroxidation products such as malondialdehyde (MDA) using the serum thiobarbituric acid reactive substances (TBARS) assay.

The diagnosis of AA is primarily based on the clin-

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ical history and physical examination, complemented by laboratory investigations such as white blood cell (WBC) count and differential blood count. For many years, these, along with C-reactive protein (CRP) levels, have been the main laboratory diagnostic methods for AA.[12] In addition, various techniques, including ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI), have been employed for early diagnosis.[13,14] However, given the controversy surrounding suspected cases of AA, more research is needed to reduce the rates of negative or unnecessary appendectomies and related complications. Despite advances in diagnostic and treatment technologies, AA remains a clinical challenge due to its high prevalence and varied clinical presentation. Moreover, the diagnostic value of extensively studied markers has yielded contradictory results. However, the routine use of excellent diagnostic methods such as ultrasound and CT is limited by their cost, ionizing radiation, and operator requirements, which restricts their availability in all healthcare institutions.

This study aims to contribute to the search for new markers that can provide additional information and improve the accuracy of AA diagnosis.

2. MATERIALS and METHODS

2.1.Patient Selection

The study was approved by the Clinical Researches Ethics Committee (2022/152). Eighty-five patients admitted to our hospital's Emergency Department (ED) with abdominal pain and were hospitalized in our pediatric surgery wards with the presumptive diagnosis of AA after anamnesis, physical examination, laboratory tests, and ultrasonography were included in the study. Fifteen patients were excluded from the study due to missing laboratory tests. Twelve patients were discharged with nonoperative management (NOM). A total of 58 patients underwent laparotomy with a diagnosis of AA during this study. Four cases that presented complicated acute appendicitis (AAWC) diagnoses during surgery were excluded. Based on the histopathological examination, 45 patients were included in acute appendicitis with no complications (AANC) subgroup. The histopathological examination results of nine patients were interpreted as normal appendectomy materials.

The control group consisted of 50 pediatric patients who applied to the ED with unspecific abdominal pain within the study period, for whom the diagnosis of acute appendicitis was excluded by anamnesis, physical examination, laboratory tests, and ultrasonography.

The informed consent form was taken from the individuals and their families in the study and control groups.

2.2.Collection and Storage of Blood Samples

Venous blood samples taken from the patients routinely during emergency service admissions were taken into anticoagulant-free biochemistry tubes under CLSI GP41-A6 guidelines. Blood samples for serum were centrifuged at 4000 rpm for 10 minutes after coagulation was completed. After the centrifuge, routine tests requested from the patients were studied immediately and the excess serum samples were kept at -80 ºC until the study day.

2.3.Biochemistry and Hemogram Measurement

Serum biochemistry parameters were studied in the Abbott Architect c16000 autoanalyzer, which makes spectrophotometric measurements by using commercial kits. Hemogram was studied from complete blood by using the flow cytometry method in the Sysmex XN-1000 autoanalyzer.

2.4.Serum TBARS Determination Study Protocol

100 µL of plasma was mixed with 500 µL of 10% TCA solution and vortexed. The mixture was incubated at 95°C for 10 minutes and then centrifuged at 4000 rpm for 10 minutes. 400 µL of the supernatant was taken and mixed with 200 µL of 0.67% TBA solution. The mixture was vortexed and incubated again at 95°C for 10 minutes. After incubation, it was centrifuged at 4000 rpm for 10 minutes. The resulting color was read at 532 nm and analyzed spectrophotometrically. The results were determined using a prepared 40-2.5 nmol/mL standard curve of 1.1.3.3-tetramethoxypropane and expressed in pmol/mL.

2.5.Statistical Analysis

The normal distribution of continuous data was tested with the Kolmogorov-Smirnov test, Histogram, and Q-Q plots. Parametric data were reported as mean and standard deviation (SD), nonparametric data were reported as median and IQR and categorical variables were reported as number and frequency (%).

Student t-test was used to analyze continuous variables, as in comparing TBARS levels between pathologically confirmed acute appendicitis and healthy control groups. Pearson's Chi-square test was used to compare categorical variables. Receiver operating characteristic (ROC) curve analysis was conducted for continuous variables and the areas under the curve (AUC) were calculated. Cut-off points were determined using the Youden index and diagnostic value criteria were calculated with 95% confidence intervals. Significance was accepted as $p < 0.05$ in statistical analysis. All analyses were made with R based Jamovi statistical program (version 1.1.5.0; https://jamovi.org) and Statistical Package for Social Sciences (SPSS version 26).

3.RESULTS

Eighty-five AA cases were analyzed from September 2022 to March 2023, younger than 18 years. The negative appendectomy (NA) rate was 15.5% (9 of 58). The AANC group comprised 31 male patients (68.9%) and 14 female (31.1%). The mean age of the AANC group was 11.4 (4.29) years, while the mean age of the control group was 10.9 (3.44) years. Age was not significantly different between the AANC and the control groups ($p=0.411$) (Table 1). WBC, ANC and TBARS levels were significantly higher in AANC patients versus healthy control subjects ($p<0.001$). The diagnostic values of statistically significant parameters were evaluated using ROC analysis. In the AANC group, AUC was above 0.900 for WBC and ANC, above 0.600 for while TBARS. ROC curves for laboratory data are given in Figure 1. TBARS cut-off value were calculated from the respective ROC curves. For TBARS, the cut-off value of >0.5 pmol/ml had a sensitivity of 64.4% and a specificity of 76% (AUC=0.654 ± 0.06; $p<0.001$). While a 70.4% (60.9-78.4) negative predictive value was found for TBARS, this rate was 94.2% (84.5-97.9) for WBC, and 92.5% (82.8-96.9) for ANC. Table 2 shows areas under the curve (AUC), cut-off values, sensitivities, specificities, positive predictive values (+PV), negative predictive values (-PV), positive likelihood ratio (+LR), negative likelihood ratio (-LR), and p values in the prediction of AA. Laboratory data of AANC, NA, NOM, AAWC, and Control groups are given in Figure 2.

Table 1.

Comparison of demographics and laboratory data between AANC and the control groups

Variables, Mean (SD)	AANC n=45	Control n=50	p value
Age	11.4 (4.29)	10.9 (3.44)	0.411
WBC (cells /mm3)	17530 (5360)	8156 (1541)	<0.001
ANC (cells /mm3)	13541 (5728)	4219 (1232)	<0.001
TBARS (pmol/ml)	0.591 (0.247)	0.459 (0.076)	<0.001
AANC: Acute Appendicitis with no Complications, WBC: White Blood Count, ANC: Absolute Neutrophil Count, TBARS: Thiobarbituric Acid Reactive Substances, SD: Standard Deviation			

Table 2.

Diagnostic accuracy metrics of WBC, ANC and TBARS in the diagnosis of acute appendicitis with no Complications

Metric	WBC	ANC	TBARS
AUC ± SE	0.986 ± 0.01	0.952 ± 0.02	0.654 ± 0.06
Cut off Value	10.750 cells/mm3	6.680 cells/ mm3	0.5 pmol/ ml
Sensitivity (95 % CI)	93.3 (81.7-98.6)	91.1 (78.8-97.5)	64.4 (48.8-78.1)
Specificity (95 % Cl)	98 (89.4-99.9)	98 (89.4-99.9)	76 (61.8-86.9)
+PV (95 % Cl)	97.6 (85.8-99.7)	97.6 (85.5-99.7)	70.7 (58.5-80.6)
-PV (95 % Cl)	94.2 (84.5-.97.9)	92.5 (82.8-96.9)	70.4 (60.9-78.4)
+LR (95 % Cl)	46.7 (6.7-325.4)	45.6 (6.5-317.8)	2.7 (1.6-4.6)
-LR (95 % Cl)	0.07 (0.0-0.2)	0.09 (0.0-0.2)	0.5 (0.3-0.7)
Accuracy (95 % Cl)	95.8 (89.6-98.8)	94.7 (88.1-97.3)	70.5 (60.3-79.4)
p-value a	0.001	0.001	0.003
WBC: White Blood Count, ANC: Absolute Neutrophil Count, TBARS: Thiobarbituric Acid Reactive Substances, AUC: Area Under the Curve, CI: Confidence Interval, LR: Likelihood Ratio, PV: Predictive Value, a: The value in groups were calculated by using ROC curve.			

Figure 1.

Receiver operating characteristic (ROC) curve analyses of important parameters for the diagnosis of appendicitis (WBC, ANC and TBARS)

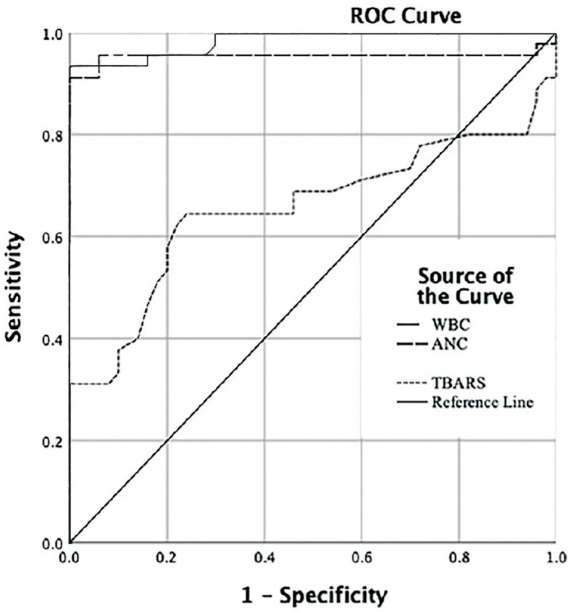
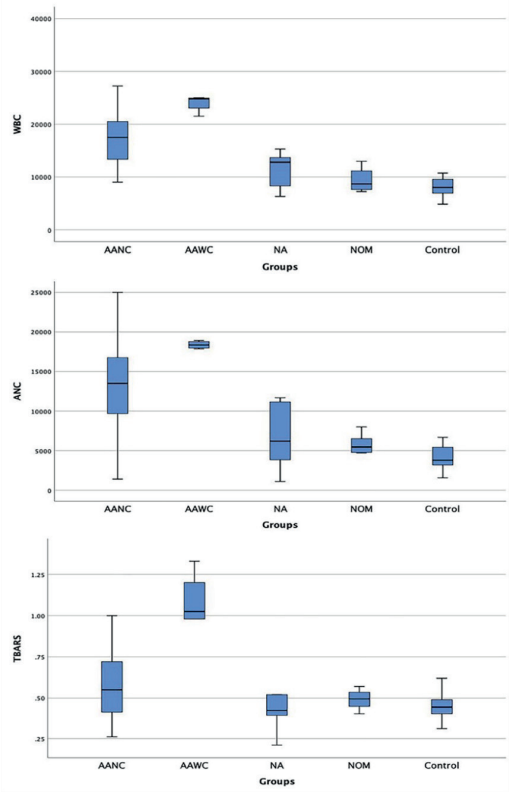


Figure 2.

Box plots presenting the median of WBC, ANC and TBARS levels



4.DISCUSSION

Acute appendicitis is a condition characterized by inflammation of the appendix. This condition leads to tissue damage in the wall of the appendix.[14] Increased oxidative stress during the inflammatory process may contribute to cell damage and tissue degradation. Activation of inflammatory cells and release of cytokines can increase oxidative stress. In addition, due to tissue hypoxia caused by tissue damage, oxygen metabolism may be impaired, and oxidative stress may increase. Compared with the number of studies evaluating inflammatory markers in the diagnosis of acute appendicitis, only a limited number of studies have evaluated the diagnostic value of ischemic and oxidative stress-related markers. Some studies have shown increased oxidative stress markers in patients with acute appendicitis. Among these markers, parameters such as malondialdehyde (MDA), total oxidant capacity, nitric oxide (NO), and superoxide dismutase (SOD) be found. These findings suggest that oxidative stress may play a role in the pathophysiology of acute appendicitis.[8,15]

However, it has not been fully determined whether oxidative stress is the cause or consequence of acute appendicitis. Some research suggests that oxidative stress may contribute to the development of appendicitis, while others think that oxidative stress is a result of the tissue damage that occurs as a result of appendicitis.[8,11,15–17]

In this study, appendicitis patients were found to have higher TBARS levels compared to the control group. According to the ROC analysis results, AUC for TBARS was calculated as 0.654. This result suggests that the test provides limited accuracy for diagnosing appendicitis. The +PV (70.7%) and -PV (70.4%) are similar, indicating that the TBARS test provides limited value in diagnosing appendicitis. The +LR was 2.7 and the -LR was 0.5. These results show that the TBARS test alone is insufficient for diagnosing appendicitis and should be evaluated with other clinical and laboratory findings. A limited number of studies in the literature have investigated MDA levels in AA and have reported conflicting results. In the study of Machado et al., which compared AANC, AAWC, and Control groups, oxidative stress parameters exhibited different behaviors. The SOD, CAT, and TBARS levels did not show any significant difference among all assessed groups (SOD: p= 0.29, n= 41; CAT: p= 0.19, n= 40; and TBARS: p= 0.18, n= 63).11 In a study performed by Koltuksuz et al. involving pediatric patients with AA, MDA was found to be significantly elevated in cases of acute suppurative and acute perforated appendicitis when compared to cases of acute focal appendicitis and the control group.18 In the study of Hakkoymaz et al., no significant difference was found between MDA levels of AA patients and healthy controls (p= 0.107).[8]

5.CONCLUSION

The results show that TBARS levels can help diagnose appendicitis however provides limited accuracy. It is essential their usability in future research should be further examined.

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Research Article/ Araştırma Makalesi

The Effect of Ceftriaxone on Penicillin-Induced Epileptiform Activity in Rats: An Electrophysiological Study

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Purpose: Epilepsy is a set of chronic neurological disorders characterized by seizures associated with abnormal and uncontrolled neuronal activity of the brain. Glutamate is the main excitatory neurotransmitter in the central nervous system. Excitatory amino acid transporter-2 (EAAT2), one of the major glutamate transporters, is responsible for total glutamate intake. Ceftriaxone is a β-lactam antibiotic that increases EAAT-2 expression and functional activity. This study aims to investigate the effects of ceftriaxone on penicillin-induced epileptiform activity by using electrocorticography (ECoG) in anesthetized rats.

Method: In this study, 35 Wistar male rats were used. The rats were divided into five groups of 7. In group 1, 2.5 µL 500 IU of penicillin intracranially (i.c.) and 1 ml saline solution and intraperitoneally (i.p.) were given, respectively. In group 2, 200 mg/kg, i.p. of ceftriaxone was administered 30 minutes after penicillin. In group 3, 400 mg/kg of ceftriaxone was administered i.p. 30 minutes after penicillin. 500 mg/kg of sodium valproate was administered i.p. following 30 minutes of penicillin in group 4. In group 5, 400 mg/kg, i.p. of ceftriaxone and 500 mg/kg, i.p. of sodium valproate were administered 30 minutes after penicillin. After the surgical procedure the rats were placed in a stereotaxic device and electrocorticogram recordings were captured for 210 minutes.

Results: The acute treatment of ceftriaxone reduced spike-wave frequency and spike-wave amplitude of penicillin-induced epileptiform activity in the rats.

Conclusion: These findings suggest that acute ceftriaxone had an anticonvulsant effect on penicillin-induced focal onset epileptic activity. Ceftriaxone may have an anti-epileptogenic potential.

Keywords: Experimental epilepsy, Ceftriaxone, Electrocorticography

1.INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by seizures associated with abnormal and uncontrolled neuronal activity in the brain.[1] It affects about 1% of the world's population.[2] Although many antiepileptic drugs are used, they can't prevent seizures in 20-30% of patients.[3] Glutamate, the main excitatory neurotransmitter in the central nervous system (CNS), is the most abundant amino acid in the mammalian brain.[4] Glutamate is essential in many processes, such as learning, memory, cognition, and emotion.[5] Regulation of extracellular glutamate levels is necessary to maintain appropriate neuronal activity and function. In epilepsy, there is potential dysregulation of glutamatergic mechanisms and dysfunction of neuronal, glial, and/or neuronal-glial interactions. Glutamate is removed from the synaptic cleft by several high-affinity excitatory amino acid transporters (EAAT1-5). EAAT1 and EAAT2 are expressed in astrocytes and glial cell types.[6] It has been shown that mRNA and EAAT2 protein levels are decreased in the hippocampi of drug-resistant temporal lobe epilepsy patients with hippocampal sclerosis.[7] Homozygous EAAT2-deficient mice are characterized by increased extracellular glutamate concentration in the brain and show fatal spontaneous seizures.[8] Similar changes in EAAT2 expres-

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sion were seen in some different animal models of epilepsy.[9,10] Furthermore, it is noteworthy that ceftriaxone exerts an impact on EAAT2 expression. Ceftriaxone, a third-generation cephalosporin in the group of β-lactam antibiotics, is frequently used in skin and soft tissue infections, meningitis, pneumonia, and hospital-acquired infections.[11] It is of great interest as it modifies the course of various neurodegenerative diseases with multiple mechanisms. Ceftriaxone treatment has been shown to increase EAAT2 expression and cell viability and reduce glutamate-induced apoptotic cell death in primary rat cortical cell cultures.[12] It has been shown that ceftriaxone causes anticonvulsant effects by activating EAAT2, removing glutamate, and decreasing glutamate's concentration in the synaptic cleft.[13] EAAT2 is also known as glutamate transporter 1 (GLT-1). It is a protein that is a glutamate transporter in the CNS. GLT-1 is primarily expressed in astrocytes, which are non-neuronal cells in the brain. GLT-1 eliminates the neurotransmitter glutamate's potentially harmful effects by removing it from the synaptic cleft. The stimulation of GLT-1 expression by ceftriaxone is thought to rely on NF-kappa B (NF-κB, Nuclear Factor kappa B). When NF-kB is activated, it binds to the GLT-1 promoter region and increases transcription of this gene,[14] thereby reducing the concentration of glutamate in the synaptic cleft and decreasing the possible neurotoxic consequences of excessive glutamate.[15] Additionally, the ceftriaxone treatment has been shown in specific trials to reduce neuronal damage and enhance spatial memory and learning.[16] It has also established a beneficial effect in a model of pentylenetetrazole (PTZ)-induced convulsions.[17,18] There are also studies that cannot confirm the anticonvulsant effect of ceftriaxone.[19]

Animal models used in experimental studies of epilepsy shed light on its pathogenesis.[20] Experimental epilepsy induction is performed with penicillin applied topically or intracortically to the surface of the cortex. Penicillin induces acute focal epileptic activity similar to decreasing the activity of the γ-aminobutyric acid (GABA) inhibitory system in the brain and increasing glutamate, which has become the main excitatory neurotransmitter in the brain.[21] Penicillin diminishes the inhibitory effect of GABA, leading to overstimulation of nerve cells.[22] In this scenario, the impact of glutamate becomes more pronounced. Glutamate is the main excitatory neurotransmitter in the central nervous system and usually enhances nerve transmission. Due to the diminished inhibitory effect of GABA caused by penicillin, the effect of glutamate is amplified, paving the way for epileptic activity. Consequently, penicillin triggers epileptic activity by disrupting the balance of neurotransmitter levels in the brain.[23] This type of epileptiform activity model is frequently employed in laboratory studies to comprehend epilepsy mechanisms and investigate the effects of antiepileptic treatments.

The aim of this study is to investigate the effects of ceftriaxone on penicillin-induced epileptiform activity by using electrocorticography (ECoG) in rats.

2. MATERIALS and METHODS

2.1.Animals

In this study, 35 Wistar albino male rats weighing 200-250 g were used. Rats were housed in a 12-hour light-dark cycle (light between 07:00 and 19:00) and quiet rooms at 22-24°C ambient temperature. They were fed ad libitum with standard laboratory chow and tap water.

The animals were randomly divided into five groups (n=7) as follows.

(1) Penicillin (500 IU, 2.5 µl, intracranially (i.c.)),

saline solution 1 ml intraperitoneally (i.p.)

(2) Ceftriaxone (200 mg/kg, i.p.), penicillin (500 IU, 2.5 µl, i.c.)

(3) Ceftriaxone (400 mg/kg, i.p.), penicillin (500 IU, 2.5 µl, i.c.)

(4) Sodium valproate (500 mg/kg i.p.) plus penicillin (500 IU, 2.5 µl, i.c.)

(5) Ceftriaxone (400 mg/kg i.p.), sodium valproate (500 mg/kg i.p.), penicillin (500 IU, 2.5 µl, i.c.).

All experimental procedures were carried out based on the principles set in the European Union Directive (2010/63/EU). The experimental procedures of the study were approved by the Ethics Committee of the Tokat Gaziosmanpasa University, Tokat (2020-HADYEK-25).

2.2.Chemicals

1.25 mg/kg urethane (Sigma-Aldrich, USA) dissolved in distilled water 30 minutes before administering penicillin (25% solution) i.p. Penicillin G Potassium (Pen-G 1.000.000 IU vial, I.E., Ulagay, Turkey) is dissolved in distilled water to a concentration of 500 IU. to produce epileptiform activity. It will be in a volume of 2.5 µL administered i.c. 500 mg/kg sodium valproate (Depakin 400 mg/4 mL ampoule, Sanofi, France) and ceftriaxone 200 mg/kg and 400 mg/kg (Novosef, 1 g vial, Zentiva, Czechia) were dissolved with distilled water at the appropriate concentration and injected i.p.[24] Additionally, they were administered 30 minutes after the injection of penicillin.

2.3.Surgical Procedure

After anesthesia with urethane, the rats were placed in the stereotaxic device and fixed (Harvard Stereotaxic Instrument). Then an incision was made approximately 3 cm in the rostrocaudal plane. After the soft tissue over the left somatomotor cortex was removed, the skull bone was removed by thinning with a touring engine. For electrophysiological recordings, two Ag/AgCl ball electrodes were utilized, and one Ag/AgCl clamp electrode was used for grounding purposes. The positive electrode was placed 1 mm anterior to the bregma, 2 mm lateral to the sagittal suture, and the negative electrode was placed 5 mm posterior to the bregma and 2 mm lateral to the sagittal suture. A ground electrode was applied to the right ear. The rats' body temperature was kept at 37 °C throughout the experiment with a homeothermic blanket attached to a rectal probe (Harvard Instrument, USA). The preoperative and postoperative periods involved continuous monitoring of electrocorticographic (ECoG) activity, with the researcher actively observing and intervening to address any potential complications. Detailed observations were conducted by the researcher to identify possible complications during surgical procedures. In the event of any adverse effects attributed to the surgical intervention, immediate intervention by the researcher was implemented to ensure the improvement of records' quality and reliability after the surgical procedure.

The activity was recorded with electrodes placed on the MP 150-CE (Biopac Systems, USA) interface, upgraded to the MP 150 EEG-100C (Biopac Systems, USA), and transferred to the data recording system. The analog signals received from the cortex were converted into a digital value with the MP 150. Then it was transferred to the computer with the help of a USB cable. Brain activity viewed with AcqKnowledge 3.9.1 (Biopac Systems, USA) software. After the registration period ended, the frequency and amplitude of the epileptiform activity recordings were analyzed.

2.4.Induction of Epileptiform Activity

While the rats were in the stereotaxic unit, 2.5 µL of penicillin dissolved in distilled water was administered to the left somatomotor cortex, 3 mm lateral, 2 mm posterior, and 2 mm ventral from bregma[24] using a Hamilton microinjector (710 SNR, infusion rate 0.5 µL/min). The epileptiform activity caused by the internal administration of penicillin started to be recorded 1-2 minutes after the injection. First-group rats were given penicillin and saline solution. After 30 minutes of penicillin, the second and third groups were given 200 and 400 mg/kg of ceftriaxone, respectively, i.p. The fourth group was given sodium valproate after 30 minutes of penicillin. 30 minutes after penicillin administration, ceftriaxone 400 mg/kg, i.p. was given from the right, and sodium valproate 500 mg/kg, i.p. was given on the left to the 5th group.

2.5.Electrophysiological Processes

The experimental procedures were performed in the Gaziosmanpaşa University Faculty of Medicine Physiology Laboratory. Animals were brought to the laboratory one day before the experiment to facilitate their adaptation to the new environment and reduce stress. The recording of epileptiform activity induced by the administration of penicillin started after 2 minutes. ECoG activity was recorded for 210 min. Epileptiform activity stabilized after the 20th and 30th minutes of penicillin injection. The average spike and amplitude values between the 20th and 30th minutes of penicillin injection were accepted as the 1st-minute value. After 30 minutes, the averages of the spike frequency and amplitudes of the 1-minute slices were taken at 10-minute intervals. The 180-minute recording obtained 30 minutes after penicillin injection was divided into 10-minute periods. The number of spikes and the average number of spikes per minute were calculated by counting the peak-to-peak amplitudes.

2.6.Statistical Analysis

Statistical analysis was performed using 1-minute values taken at 10-minute intervals. These results were analyzed using the SPSS (Statistical Package for Social Sciences) 26.0 program for Windows. Since there were more than two independent groups, the Kruskall-Wallis test was used to compare continuous quantitative data between groups. Then the Man Whitney-U test was additionally performed to determine the differences. To identify the difference between repeated measurements within groups, the Wilcoxon test was applied. The obtained results were evaluated at a 95% confidence interval and a significance level of 5%. Data for all experimental groups used in the study were expressed as mean ± standard error of the mean (SEM). A p-value below 0.05 was considered significant.

3.RESULTS

3.1.Spike Frequency

In the acute penicillin epilepsy model, the mean spike frequency was 97.50 ± 1.78 spikes/min after penicillin microinjection. The mean spike frequency of the ceftriaxone (200 mg/kg and 400 mg/kg) and sodium valproate plus ceftriaxone 400 mg/kg groups after penicillin injection significantly reduced over 180 minutes (Table 1). The mean spike frequency of epileptiform activity in penicillin plus 200 and 400 mg/kg ceftriaxone groups were 65.21 ± 1.83 and 65.77 ± 2.23 spike/min, respectively. In addition, the mean spike frequency of the ceftriaxone (200 and 400 mg/kg) groups was statistically significantly lower than the group in which sodium valproate was administered after penicillin microinjection ($p<0.001$; 65.21 ± 1.83 spike/min vs. 93.71±2,18 spike/min and 65.77 ± 2.23 spike/min vs. 93.71±2,18 spike/min, respectively). The mean spike frequency of sodium valproate plus ceftriaxone 400 mg/kg group the following penicillin microinjection was significantly

decreased compared to the penicillin plus sodium valproate and penicillin group ($p<0.001$; 65.38 ± 2.52 spike/min vs. 93.71±2,18 spike/min and 65.38±2.52 spike/min vs. 97.50 ± 1.78 spike/min, respectively). The groups receiving ceftriaxone at doses of 200 mg/kg and 400 mg/kg exhibit a statistically significantly lower mean spike frequency compared to the group where sodium valproate is administered following penicillin microinjection. This suggests that ceftriaxone is more effective when compared to sodium valproate. The sodium valproate plus ceftriaxone (400 mg/kg) group demonstrates a statistically significantly lower mean spike frequency when compared to the group receiving sodium valproate after penicillin microinjection, as well as the group receiving only penicillin. This indicates that this combination is more effective than sodium valproate alone or penicillin alone.

The mean spike frequency values and the percentage change in spike frequency according to the groups for 180 minutes were presented in (Table 1, Figure 1) The first spike frequency value of the sodium valproate group after penicillin microinjection was higher than the first spike frequency value of the penicillin group. The 10th-minute spike frequency value of the penicillin-administered ceftriaxone 200 mg/kg group was lower than the 10th-minute spike value of the penicillin group. After the 10th minute, the spike frequency value of the penicillin-administered ceftriaxone 200 mg/kg group started to decrease significantly ($p<0.05$). The spike frequency value of sodium valproate plus ceftriaxone 400 mg/kg administered following the microinjection of penicillin decreased compared to the penicillin group ($p<0.05$). After penicillin microinjection, the 130th-minute spike frequency value of the penicillin plus sodium valproate plus ceftriaxone 400 mg/kg treatment group was lower than the same-minute value of the penicillin-applied sodium valproate group ($p<0.05$). At the same time, the spike frequency value of the penicillin plus sodium valproate plus ceftriaxone 400 mg/kg and alone penicillin plus ceftriaxone 400 mg/kg groups decreased the following 140th-minute compared to both the penicillin and sodium valproate groups following penicillin microinjection. The spike frequency value of the ceftriaxone 200 mg/kg group decreased significantly following 170th-minute after penicillin microinjection ($p<0.05$) (Figure 1). It has been observed that both ceftriaxone groups (200 mg/kg and 400 mg/kg) lead to a significant decrease in the mean spike frequency over 180 minutes compared to the groups treated with penicillin. Particularly, in the ceftriaxone 200 mg/kg group, a noticeable decline has been observed from the 10th minute onwards. The sodium valproate plus ceftriaxone 400 mg/kg group induces a significant reduction in the mean spike frequency over 180 minutes compared to the penicillin group. This combination has proven to be more effective than other treatment groups.

Figure 1.

*Graph of changes in spike Frequency over time in all groups. A statistically significant decrease was found in the ceftriaxone + sodium valproate group at 70 minutes and after (P = .043 < .05) (Multiple comparison tests were used. *P < .05, all groups were compared with the first-minute value).*

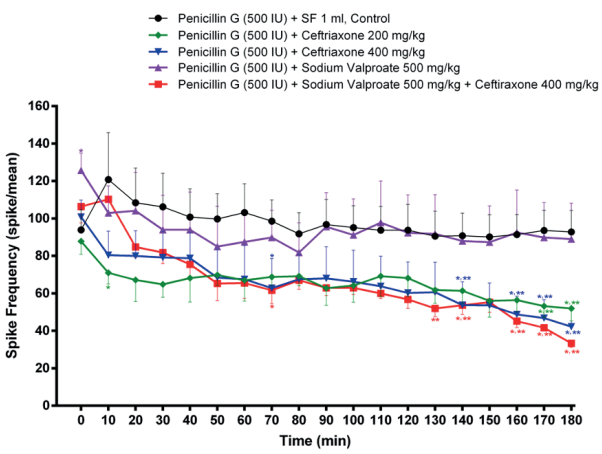


Table 1.
Percentage changes in spike frequency values according to the groups for 180 minutes (spike/min)

Groups	Penicillin	Ceftriaxone 200 mg	Ceftriaxone 400 mg	Sodium valproate 500 mg	Ceftriaxone + Sodium valproate
1st	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0
30st	110.78±8.26	73.80±5.37*	76.81±8.77*	72.94±10.3*	74.25±9.82*
60th	108.68±5.87	77.40±11.9*	64.53±13.2*	68.30±9.56*	55.74±9.67*
90th	102.62±5.04	72.04±8.94	66.21±12.9*	74.6±10.59	59.73±12.6*
120th	99.02±5.15	78.44±10.13	58.64±13.4*	71.58±11.70	55.68±12.9*
150th	96.35±5.56	66.62±11.67	55.69±11.3*	67.52±10.8*	49.12±10.5*
180th	99.05±4.39	60.80±8.25*	53.49±11.12*	68.86±10.35*	46.34±9.82*

The mean difference is significant at the 0.05 level.
Values expressed as mean±SD.
* $p<0.05$ different compared to penicillin group,
** $p<0.05$ different compared to penicillin plus sodium valproate group.

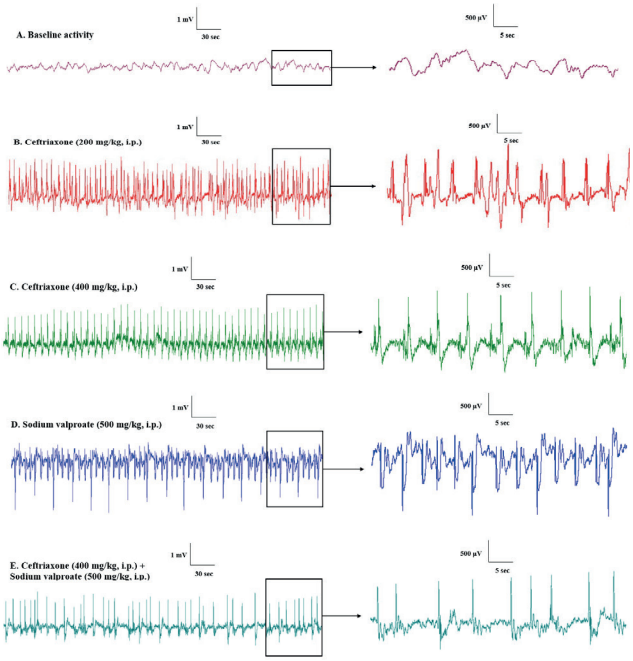
Although the spike frequency values of the penicillin group at all minutes were not significantly different from the first spike frequency value ($p>0.05$) in the penicillin plus ceftriaxone 200 mg/kg and ceftriaxone 400 mg/kg group, those significantly decreased compared to the first spike every 10 minutes for 180 minutes ($p<0.05$). In the sodium valproate applied group after penicillin microinjection, the frequencies of the all-minute spike decreased compared to the baseline, but the frequency of spikes significantly decreased after 60th minutes. Following the microinjection of penicillin, the spike frequency of the group that received ceftriaxone 400 mg/kg plus sodium valproate significantly decreased after 20th minutes compared to the baseline value.

Table 1 shows the comparison of the mean percentage spike change values of the groups. In the groups of sodium valproate, ceftriaxone (200 mg/kg and 400 mg/kg), and sodium valproate plus ceftriaxone 400 mg/kg administered following the microinjection of penicillin, the percentage change in all spikes during 180 minutes was significantly found to be lower than in the penicillin group ($p<0.05$). However, there was no significant percentage change in spike frequency during 180 minutes in the penicillin group (99.05±4.39 spike/min), the 200 and 400 mg/kg ceftriaxone groups after penicillin microinjection displayed a significant decrease in percentage spike frequency of approximately 40% and 47%, respectively in comparison with their baseline (60.80±8.25 spike/min, 53.49±11.12 spike/min, respectively). Furthermore, the percentage spike frequency change in the penicillin-applied sodium valproate groups group is almost 32% compared to baseline (68.86±10.35 spike/min). After penicillin microinjection, the percentage spike frequency of group sodium valproate plus ceftriaxone 400 mg/kg declined by about 54% in comparison with the baseline (46.34±9.82 spike/min). In conclusion, all treatment groups (sodium valproate, ceftriaxone 200 mg/kg, ceftriaxone 400 mg/kg, and sodium valproate plus ceftriaxone 400 mg/kg) exhibit a significant decrease in the rate of spike frequency compared to the penicillin group over the course of 180 minutes. The reduction in spike frequency is particularly pronounced in the ceftriaxone groups.

All group samples from the 60th and 70th minute of ECoG were obtained from epileptiform activity induced by penicillin as shown in Figure 2.

Figure 2.

A) Baseline activity, B) Ceftriaxone 200 mg, C) Ceftriaxone 400 mg, D) Sodium valproate, E) Ceftriaxone + sodium valproate samples from the 60th and 70th minute of ECoG obtained from epileptiform activity induced by penicillin.



3.2.Spike Amplitude

The mean levels of spike amplitude of groups are shown in Figure 3. The mean spike amplitude value of the penicillin group was significantly higher compared to the other groups ($p<0.001$; 0,111 ± 0,01 µV). Following penicillin microinjection, the mean spike amplitudes of ceftriaxone (200 mg/kg and 400 mg/kg), sodium valproate, and sodium valproate plus ceftriaxone 400 mg/kg groups were significantly decreased compared to the penicillin group ($p<0.001$; 0.063 ± 0.01 µV, 0.057 ± 0.01 µV, 0.060 ± 0.01 µV, 0.047± 0.01 µV, respectively). Moreover, the penicillin-applied sodium valproate plus 400 mg/kg ceftriaxone group mean spike amplitudes were lower than those of the penicillin plus ceftriaxone (200 mg/kg and 400 mg/kg) and sodium valproate groups ($p<0.05$; 0,047±0,01 µV). The mean spike amplitude values and spike amplitude percent change for each group throughout 180 minutes are displayed in Table 2, Figure 3. After penicillin microinjection, the mean amplitude values of the ceftriaxone (200 mg/kg and 400 mg/kg), sodium valproate, and sodium valproate plus ceftriaxone 400 mg/kg groups for 180 minutes for 10 minutes each were significantly lower than the mean amplitude values of the penicillin group ($p<0.05$). Furthermore, the spike amplitude mean of the penicillin plus sodium valproate plus 400 mg/kg ceftriaxone group was lower than the spike amplitudes of the penicillin-administered 200 mg/kg ceftriaxone and sodium valproate groups over 180 minutes ($p<0.05$). In summary, penicillin administration resulted in increased spike amplitude, and the subsequent administration of ceftriaxone, sodium valproate, and their combination led to significant decreases in spike amplitude compared to the penicillin group.

Figure 3.

*Graph of changes in spike amplitude frequency over time in all groups. A statistically significant decrease was found in the ceftriaxone + sodium valproate group at 10 minutes and after (P = .043 < .05) (Multiple comparison tests were used. *P < .05, all groups were compared with the first-minute value).*

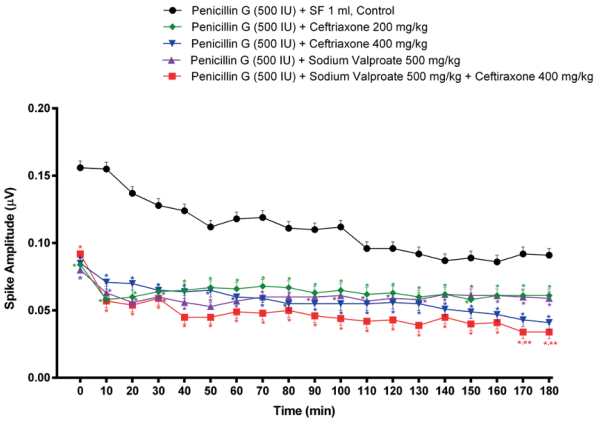


Table 2.
Percentage changes in amplitüde frequency values according to the groups for 180 minutes (spike/min)

Groups	Penicillin	Ceftriaxone 200 mg	Ceftriaxone 400 mg	Sodium valproate 500 mg	Ceftriaxone + Sodium valproate
1st	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0	100.0±0.0
30st	80,16±11,28	73,80±5,37	76,33±3,90	76,91±8,38	72,87±9,30
60th	74,08±13,53	77,40±11,92	66,95±7,41	81,48±13,33	68,24±11,86
90th	68,57±7,84	72,04±8,94	67,84±6,06	79,86±10,22	57,31±7,72
120th	61,54±7,47	78,44±10,13	67,01±9,21	79,56±11,77	54,16±10,91
150th	55,77±7,74	66,62±11,67	58,37±6,14	83,32±8,81*	53,98±9,95#
180th	57,66±9,05	60,80±8,25	52,92±10,13	79,39±10,20	44,62±9,37#

The mean difference is significant at the 0.05 level.
Values expressed as mean±SD.
* p<0.05 different compared to penicillin group,
** p<0.05 different compared to penicillin plus sodium valproate group.

Throughout the 180-minute duration, the spike amplitude values at the 80th minute in the penicillin group exhibited a significant decrease compared to its first spike amplitude values (p<0.05). In the penicillin plus 200 mg/kg ceftriaxone group, the 140th-minute amplitude value decreased significantly compared to the first amplitude value (p<0.05). The decrease in all spike amplitude values after the 10th minute was statistically significant compared to its spike initial amplitude value of the group penicillin administered 400 mg/kg of ceftriaxone (p<0.05). Significant decreases were observed in the penicillin plus sodium valproate group after the 20th minute compared to its initial spike amplitude value (p<0.05). The spike amplitude values of the group treated with penicillin plus sodium valproate plus 400 mg/kg ceftriaxone showed a significant decrease in all minute values during the 180 minutes compared to its initial spike amplitude value (p>0.05). These results indicate differences among treatment groups and highlight which combinations are more effective at specific time points.

The mean percent change in amplitude values of the groups over 180 minutes was evaluated based on time (Table 2). The penicillin group had a 43% change in mean amplitude value at the end of 180 minutes compared to its baseline value (57,66±9,05 μV). In addition, the 200 and 400 mg/kg ceftriaxone groups after penicillin microinjection displayed a decrease in percentage spike amplitude change of approximately 40% and 48%, respectively, in comparison with their baseline (60.70±7.25 μV, 52,92±10,13 μV, respectively). The percentage amplitude change in the penicillin-applied sodium valproate group is approximately 31% compared to its baseline value (79,39±10,20 μV). After penicillin microinjection, the percentage spike amplitude of group sodium valproate plus ceftriaxone 400 mg/kg declined by about 56% in comparison with the baseline (44,62±9,37 μV). These findings suggest that ceftriaxone diminishes the effects of penicillin. Additionally, the group treated with sodium valproate plus 400 mg/kg ceftriaxone appears to be more effective in reducing seizure activity.

4.DISCUSSION

In this study, the impact of ceftriaxone on spike frequency and amplitude alterations in the pathogenesis of epilepsy was examined utilizing the

penicillin-induced epilepsy model. While several studies in the literature have assessed the anticonvulsant effects of ceftriaxone[17,18,25], this research employs a distinct epilepsy model and methodology to comprehensively evaluate its anticonvulsant properties. The investigation demonstrated the anticonvulsant effect of 200 mg/kg and 400 mg/kg ceftriaxone on seizures induced by penicillin in rats. Rats pre-administered ceftriaxone exhibited a dose-dependent reduction in spike frequency and amplitude in electrocorticogram (EcoG) recordings. This positive effect became more pronounced when higher doses (400 mg/kg) of ceftriaxone were administered to the rats.

Epilepsy is a common chronic neurological disease in which motor coordination, sensory perception, and cognitive functions are altered due to the stimulation of neurons.[1] Although the physiopathological basis of epilepsy is not fully understood, it is thought that increased glutamate activity and decreased γ-aminobutyric acid (GABA) inhibitory activity (an imbalance between excitation and inhibition) may be associated with seizures and epileptogenesis.[26] Sodium valproate is an anticonvulsant medication used to treat various types of epileptic seizures, including generalized seizures, absence seizures, and focal seizures. It is thought to potentiate GABA activity by inhibiting the enzymes that catabolize GABA or by blocking the reuptake of GABA into glia and nerve endings. GABA is responsible for reducing the excitability of neurons and preventing excessive neuronal firing, which can lead to seizures.[28] It also modulates voltage-gated sodium channels, which are involved in the generation and spread of electrical impulses in neurons. Blocking these channels can help regulate the abnormal electrical activity that occurs during seizures.[29] In our study, in accordance with the literature, the administration of sodium valproate has been observed to exhibit a reducing effect on penicillin-mediated seizure activity.

Experimental epilepsy models are used to elucidate the pathogenesis of epileptic seizures and to develop new antiepileptic drugs. A simple and quick way to induce epileptic activity is the administration of chemical convulsants such as penicillin.[30] The penicillin model is preferred as an experimental epilepsy model to understand the pathogenesis of epileptic seizures and to develop new antiepileptic drugs. This is useful in triggering and observing epileptic seizures quickly in a laboratory setting. Application of penicillin to the cortex of experimental animals has resulted in recorded ECoG activity resembling acute focal epileptic seizures. These waves resemble interictal spikes observed in humans and this activity persists for approximately 2-4 hours.[31,32] Therefore, it is anticipated that the ECoG activity recorded over 210 minutes in the acut penicillin experimental studies provides ample time for spike analysis. In the penicillin focal epilepsy model, the impacts of different anticonvulsants like barbiturates, diphenylhydantoin, phenobarbital and diazepam, benzodiazepines, levetiracetam, carbamazepine, and ion channel blockers were investigated.[33] Penicillin increases glutamate release by inhibiting the GABAA receptor, resulting in rhythmic epileptiform discharge.[34] This mechanism results in rhythmic epileptiform discharge. The model can be utilized to understand the effects of drugs targeting GABA receptors and to develop drugs that modulate these receptors. In conclusion, the penicillin model is frequently chosen in epilepsy research due to its ability to rapidly induce epileptic seizures in laboratory conditions and to evaluate the effects of various antiepileptic drugs. Penicillins and cephalosporins' ability to induce convulsions has been linked to their blockage of GABA receptors. Among the cephalosporins, ceftriaxone

has demonstrated some antiepileptic indications of epileptogenic activity.[35]

Ceftriaxone, one of the most effective beta-lactam antibiotics, has been studied in vitro models of ischemia and motor neuron degeneration. Beta-lactam antibiotics have been reported to have neuroprotective properties.[36] Ceftriaxone improves neurogenesis and enhances motor function in rats.[37,38] It was shown that ceftriaxone is neuroprotective in several neurological diseases such as Parkinson's disease, Huntington's disease, ALS,[39] and accelerated aging.[40] Rothstein et al. reported that more than five days of ceftriaxone treatment was sufficient to increase EAAT2 (GLT-1; slc1a2) expression.[41] Ceftriaxone also activates the transcription factor nuclear factor-κB (NF-κB). NF-κB then binds to the glutamate transporter-1 (GLT-1) promoter, enhancing the transcription of the GLT-1 gene.[42] The GLT-1 downregulation and glutamate accumulation in the brain has been associated with many neurological diseases, including amyotrophic lateral sclerosis,[43] Alzheimer's disease,[44] several forms of epilepsy,[8] and ischemia/stroke and traumatic brain injury.[45] GLT-1 removes more than 95% of synaptic glutamate in the forebrain of animals.[46] The ceftriaxone treatment after traumatic brain injury has been shown to restore the expression of GLT-1 and reduce post-traumatic seizures in rats.[47] On the other hand, it enhanced GLT-1 expression and its biochemical and functional activity in the brains of rats and mice both in vitro and in vivo.[41]

The results indicate that ceftriaxone antibiotics are neuroprotective and antioxidant, possibly via upregulating GLT-1, which reduces glutamate chemical transmitter and Ca^{+2} overload, the primary processes causing increased reactive oxygen species (ROS) formation in the hippocampus during epileptic seizures.[48] Altas et al. showed that its treatment caused a considerable increase in glutathione peroxidase and superoxide dismutase (SOD) activity while decreasing malondialdehyde (MDA) in ischemia-exposed rat brains.[49] Furthermore, the concentration-dependent increase in ex vivo production of the neuroprotective protein GLT-1 by ceftriaxone indicates its potential to reduce glutamate excitotoxicity by activating metabotropic glutamate receptor (mGluR) receptors.[50-53] The antioxidant properties of ceftriaxone and its ability to reduce glutamate toxicity may unveil its antiepileptic characteristics. This indicates the anticonvulsive efficacy of ceftriaxone in reducing glutamate excitotoxicity during the acute period.

In a limited number of studies, ceftriaxone's antiepileptic activity was documented. Recent research suggests that ceftriaxone may have an anti-epileptic impact because it increases glutamate reuptake by GLT-1.[54] Different effects of it are shown on neurotransmitters involved in epileptogenesis. The primary outcome is a suppression of the GABA signaling pathway, suppressing postsynaptic GABA ion channels and thus reducing GABA-mediated inhibitory transmission. The convulsant effects of beta-lactam antibiotics such as ceftriaxone are shown to be caused by this.[55] In one study, 100 or 200 mg/kg, ceftriaxone treatment for 27 days reduced burning scores, restored motor and cognitive functions, and increased antioxidative activities in a PTZ-induced rat epilepsy model.[13] Uyanikgil et al. demonstrated that ceftriaxone has protective effects on PTZ-induced convulsions.[18] This impact can be explained through improved GLT1 expression and activation.[17,41] Additionally, Hussein et al. reported that ceftriaxone had an antiepileptic effect in the PTZ rat model by increasing oxidative stress markers such as SOD and MDA.[56] Similarly, our study revealed antiepileptic effects associated with both low and high doses of

ceftriaxone.

This study demostrated that ceftriaxone decreased the spike-wave number and spike amplitude in the experimental model of epilepsy induced by penicillin. The effects of ceftriaxone administered acutely at different doses (200 mg/kg and 400 mg/kg) in the penicillin model of epilepsy were investigated. The alone and combined administration of ceftriaxone and sodium valproate significantly affected penicillin-induced seizures. A combination of high-dose ceftriaxone and sodium valproate significantly attenuated spike frequency and amplitude latency in seizures. The effects of ceftriaxone on the experimental model of epilepsy induced by penicillin have not been demonstrated in previous studies, and this study has the potential to provide an original contribution in this context. These findings indicate that ceftriaxone may have potential antiepileptic efficacy, representing a preliminary study in this regard.

5.CONCLUSION

Epilepsy stands out as one of the most prevalent and significant neurological disorders worldwide. The goal of antiepileptic drug therapy is to achieve a seizure-free state with minimal side effects. Our study has demonstrated a protective effect of ceftriaxone on penicillin-induced seizures. This study is the first to investigate the effect of ceftriaxone on penicillin-induced epileptic seizures. However, we believe that more precise and valuable results will be obtained through molecular analyses of the anticonvulsant effects of ceftriaxone. Further research is needed to explore the impact of GLT-1 levels, oxidative stress markers, and other measurement indicators on seizures. The lack of investigation into the potential side effects of ceftriaxone in the study constitutes a limitation of this research. In clinical trials, the safety, efficacy, and potential side effects of ceftriaxone in epilepsy patients should be assessed. Further elucidation of possible adverse effects and their consequences can be provided through more comprehensive biochemical, cellular, and histopathological investigations. Possible questions related to the use of ceftriaxone may include dosage, treatment duration, side effects, and interactions with other antiepileptic drugs. Therefore, further research is necessary to validate these findings for clinical application and establish specific treatment protocols.

Conflicts of Interest

The authors declare there is no conflict of interest.

Acknowledgments

We appreciate the cooperation of all the experimenters who participated in this research.

Authors' Contributions

ZA: Conceptualization, Project administration, Resources, Software, Visualization, Data curation, Formal Analysis, Resources, Writing.

SO: Conceptualization, Formal Analysis, Data curation, Resources, Software, Validation, Writing – original draft.

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Research Article/ Araştırma Makalesi

Evaluation of the Frequency of Non-Motor Symptoms in Idiopathic Parkinson's Disease by Gender and Disease Stage

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Purpose: Idiopathic Parkinson's Disease (PD) is a chronic, progressive, neurodegenerative disease affecting basal ganglia, especially the substantia nigra pars compacta, and dopaminergic neurons in the brain stem. Although PD is defined as a movement disorder with motor symptoms, it also affects many systems such as limbic, autonomic, gastrointestinal, and genitourinary systems. The aim of our study is to evaluate the frequency of NMS in PD, which is often overlooked in clinical practice and has serious effects on patients' quality of life

Method: A total of 97 patients were included in the study, 31 of whom were in the mild stage, 30 in the moderate stage, and 36 in the severe stage. REM sleep behavior disorder (RBD), constipation, presence of hyposmia-anosmia, history of appendectomy and excessive daytime sleepiness, depression, orthostatic hypotension, apathy, forgetfulness, hallucinations, sleep problem, pain, fatigue, dizziness, and frequent urination findings have been noted from patients files.

Results: There was no significant difference ($p > 0,05$) between the rates of appendectomy, prodromal stage symptoms, and NMS between genders (Table 2). Only forgetfulness, dreaming and fatigue were found to be statistically significantly ($p<0,05$) lower in mild-stage PD patients than in the moderate and severe stages.

Conclusion: In conclusion, NMS consists of many neuropsychiatric, autonomic, and sensory symptoms that can be seen in every stage of PD from the prodromal stage to the severe stage, and they increase the disability caused by the motor findings of PD and decrease the quality of life.

Keywords: Parkinson's disease, Non-motor symptoms, Disease stage, Gender

1.INTRODUCTION

Idiopathic Parkinson's Disease (PD) is a chronic, progressive, neurodegenerative disease affecting basal ganglia, especially the substantia nigra pars compacta, and dopaminergic neurons in the brain stem in the central nervous system.[1,2] Among neurodegenerative diseases, it is the second most common disease following Alzheimer's disease.[3] The cardinal motor signs of PD are resting tremor, rigidity, and bradykinesia, while autonomic signs, and cognitive, behavioral, and psychiatric symptoms called non-motor symptoms (NMS) are often accompanied.[4] Although PD is defined as a movement disorder with motor symptoms, it also affects many systems such as limbic, autonomic, gastrointestinal, and genitourinary systems. Accordingly, NMS such as anxiety, apathy, depression, sleep disorders, cognitive disorders, constipation, and frequent urination may accompany the manifestation of PD. Although NMS is seen from the early stage of the disease, they become more prominent in the severe stage, become more disabling than motor symptoms, and are often overlooked in clinical practice.[5] The fact that NMS can be seen before motor symptoms appear also suggests that they may be important markers in the early diagnosis of PD. However, the fact that dopamine replacement therapies used in the treatment of PD target

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motor symptoms put NMS into the background.[6] The aim of our study is to evaluate the frequency of NMS in PD, which is often overlooked in clinical practice and has serious effects on patients' quality of life.

2.MATERIALS and METHODS

Patients who were admitted to Sakarya University Training and Research Hospital Movement Disorders Outpatient Clinic between March 2022 and March 2023 and who were diagnosed with PD according to MDS Clinical Diagnostic Criteria for Parkinson's Disease, Postuma et al. 2015, were included in the study.[7] Patients who followed up with the diagnosis of secondary parkinsonism, vascular parkinsonism, and Parkinson's plus syndrome were not included in the study. The files of all patients were checked retrospectively, and the patient's age, gender, educational status, age of disease onset, disease duration, disease type (1-Tremor dominant type, 2-Akinetic rigid type, 3-Mixed type), and the drugs they used were noted from the patients' files. In classification according to disease type, Stebbins et al., (2013), Movement Disorders, article was taken as the source and patients were classified as tremor dominant, akinetic rigid and mixed type according to the ratio of MDS-UPDRS scores.[8] MDS-UPDRS Part III Motor Examination and H&Y scales were documented from patients' files. Afterward, the patients were divided into 3 groups as mild stage, moderate stage, and severe stage. We combined literature and examination findings in staging. We especially used the article that "Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale" in Parkinsonism and Related Disorders journal published by Martínez-Martín et al. in 2015.[9] Those with a UPDRS score below 20 and H&Y stage 1 were considered mild stage, those with a UPDRS score between 20 and 30, and H&Y stage 1 and 2 were considered moderate stage, and those with the UPDRS score 30 and higher, and H&Y stage 3 and higher were considered severe stage. At the same time, those without limitations in their daily life activities and not needing levodopa were classified as mild stage, those needing levodopa and with initial daytime motor fluctuations were staged as moderate and finally, those with important dyskinesias and motor fluctuations as well as non-motor symptoms, qualified as severe stage. A total of 97 patients were included in the study, 31 of whom were in the mild stage, 30 in the moderate stage, and 36 in the severe stage. REM sleep behavior disorder (RBD), constipation, presence of hyposmia-anosmia, history of appendectomy and excessive daytime sleepiness, depression, orthostatic hypotension, apathy, forgetfulness, hallucinations, sleep problem, pain, fatigue, dizziness, and frequent urination findings have been noted from patients' files. For the diagnosis of RBD, an RBD screening questionnaire was applied to the patients during their outpatient visits, and those who scored 7 and above were accepted as RBD (+). Before starting the study, approval was obtained from the ethics committee of our university.

In the descriptive statistics of the data, mean, standard deviation, median, min, max, frequency, and ratio values were used. The distribution of the variables was measured by the Kolmogorov-Smirnov test. T-test, Kruskal-Wallis, or MannWhitney U tests were used for the analysis of quantitative independent data depending on the data distribution. In the analysis of qualitative independent data, the chi-square and Fischer's exact test were used as appropriate. The Spearman test was used for correlation analyses. SPSS 28.0 program was used in the analyses.

3.RESULTS

The ages of the cases ranged from 38 to 89, with a mean age of 64,00±10,30, and 51,80% (50) of

them were male and 48,20% (47) were female. Considering the age of onset of the disease, it was seen that 23,60% (22) of those with the disease started under the age of 50, 62,30% (61) who started the disease between the ages of 50-70, and 14,20% (14) who started the disease at the age of 70 and over. The disease duration was the shortest 1 year and the longest 26 years. The UPDRS values of the patients ranged from 5-76, and the mean UPDRS score was 26,41±16,01. H&Y values ranged from 1 to 5, with a mean H&Y of 2,01±0,99. 32,10% (31) of the patients were mild stage, 31,10% (30) moderate stage, and 36,80% (36) severe stage. 50,90% (49) of the patients were akinetic rigid type, 39,60% (38) tremor dominant type, and 9,40% (10) mixed type. The daily total Levodopa doses of the patients ranged from 138 mg/day to 1600 mg/day, and the mean daily total Levodopa dose was 705,40±376,60.

13,20% (12) of the patients had previously undergone appendectomy surgery. 64,20% (62) of the patients had RDB, 63,20% (61) had constipation, and 32,10% (31) had anosmia. The NMS frequencies of the patients are listed in Table 1.

Table 1.

Demographic data of patients, age of disease onset, duration of disease, disease type, disease stage, total levodopa doses, appendectomy, prodromal stage symptoms and rates of non-motor symptoms

		Min-Max	Median	Avg.±sd/n-%	
Age		38,0-89,0	66,0	64,0 ±10,3	
Gender	Male			50	51,8%
	Female			47	48,2%
Educational Status	Not Literate			7	7,5%
	Literate			3	2,8%
	Primary school			64	66,0%
	Middle school			10	10,4%
	High school			11	11,3%
	University			2	1,9%
Age of Disease Onset	< 50			22	23,6%
	50-70			61	62,3%
	≥ 70			14	14,2%
Age of Disease Onset		37,0 - 83,0	59,0	58,2 ± 10,1	
Disease Duration	< 5 years			42	43,4%
	5-10 years			29	30,2%
	> 10 years			26	26,4%
Disease Duration		1,00-26,00	5,00	6,65 ± 5,33	
UPDRS		5,00-76,00	21,00	26,41 ± 16,01	
HY		1,00-5,00	2,00	2,01 ± 0,99	
Daily Total Levodopa Dose		138,0-1600,0	687,5	705,4 ± 376,6	
Disease Type	Tremor Dominant Type			38	39,6%
	Akinetic Rigid Type			49	50,9%
	Mixed Type			10	9,4%

		Min-Max	Median	Avg.±sd/n-%	
Disease Stage	Mild			31	32,1%
	Moderate			30	31,1%
	Advanced			36	36,8%
Daily Total Levodopa Dose Coefficient	< 400 mg			24	24,5%
	400-800 mg			34	35,8%
	800-1200 mg			29	30,2%
	1200-2000 mg			10	9,4%
Appendectomy				12	13,2%
RBD				62	64,2%
Constipation				61	63,2%
Anosmia				31	32,1%
Excessive Daytime Sleepiness				61	63,2%
Depression				5	5,7%
Orthostatic Hypotension				10	10,4%
Forgetfulness				37	38,7%
Hallucinations				23	24,5%
Anxiety				58	60,4%
Apathy				56	57,5%
Sleep problem				58	60,4%
Pain				56	57,5%
Frequent Urination				62	64,2%
Dizziness				24	25,5%
Fatigue				60	62,3%

Min: Minimum, Max: Maksimum, Avg: Average, Sd:Standart deviation, RBD: REM sleep behavior disorde

There was no significant difference (p >0,05) between the rates of appendectomy, prodromal stage symptoms, and NMS between genders (Table 2).

When the NMS rates according to the disease stage were examined, only forgetfulness, dreaming and fatigue were found to be statistically significantly (p<0,05) lower in mild-stage PD patients than in the moderate and severe stages. No significant correlation was found between other NMSs and disease stages (Table 3).

4.DISCUSSION

PD is the second most common neurodegenerative disease.[3,10] Although the exact cause is unknown, the prevalence of PD has been increasing rapidly in the last few decades. There are currently more than 6 million patients with PD worldwide, and according to the global burden of disease study conducted in 2016, this figure is predicted to double to 12 million in 2040.[11]

Studies to date have shown that there are multiple NMS accompanying motor symptoms in PD. NMS can be seen in every stage of the disease, starting from the prodromal stage. In a review published by Pfeiffer in 2015, it was stated that 100% of PD patients had at least one NMS. Since NMS is very common and responds well to treatment, it is of great importance to raise awareness among clinicians and to question them in all patients.[12] In a study conducted in 2008, anxiety was reported

Table 2.

Mean UPDRS and H&Y scores, and rates of appendectomy, prodromal stage symptoms, and non-motor symptoms by gender

	Male			Female			p	
	Avg.±sd/n-%		Median	Avg.±sd/n-%		Median		
UPDRS	Severe Stage		21,0	26,3 ± 17,3		20,00	0,699	m
HY			2,00	2,01 ± 1,10		2,00	0,739	m
Appendectomy	6	42,9%	4	28,6%	4	28,6%	0,619	X^2
RBD	15	25,0%	19	31,7%	26	43,3%	0,132	X^2
Constipation	17	27,9%	21	34,4%	23	37,7%	0,466	X^2
Anosmia	12	40,0%	9	30,0%	9	30,0%	0,476	X^2
Excessive Daytime Sleepiness	19	30,6%	23	37,1%	20	32,3%	0,192	X^2
Depression	2	40,0%	1	20,0%	2	40,0%	0,851	X^2
Orthostatic Hypotension	3	27,3%	4	36,4	4	36,4%	0,902	X^2
Forgetfulness	3	8,6%	14	40,0%	18	51,4%	0,001	X^2
Hallucinations	2	8,3%	6	25,0%	16	66,7%	0,001	X^2
Anxiety	16	26,7%	21	35,0%	23	38,3%	0,319	X^2
Apathy	14	25,0%	16	28,6%	26	46,4%	0,069	X^2
Sleep problem	17	28,8%	20	33,9%	22	37,3%	0,639	X^2
Pain	13	23,2%	18	32,1%	25	44,6%	0,072	X^2
Frequent Urination	17	27,4%	23	37,1%	22	35,5%	0,188	X^2
Dizziness	6	23,1%	8	30,8%	12	46,2%	0,436	X^2
Fatigue	13	22,0%	22	37,3%	24	40,7%	0,028	X^2

^{m} Mann-whitney u test / $^{X^2}$ Chi-square test (Fischer test)
Avg: Average, Sd: Standart deviation, RBD: REM sleep behavior disorder

Table 3.

Table 3. Frequency of non-motor symptoms by disease stage

	Mild Stage		Moderate Stage		Severe Stage		p	
Appendectomy	6	42,9%	4	28,6%	4	28,6%	0,619	X^2
RBD	15	25,0%	19	31,7%	26	43,3%	0,132	X^2
Constipation	17	27,9%	21	34,4%	23	37,7%	0,466	X^2
Anosmia	12	40,0%	9	30,0%	9	30,0%	0,476	X^2
Excessive Daytime Sleepiness	19	30,6%	23	37,1%	20	32,3%	0,192	X^2
Depression	2	40,0%	1	20,0%	2	40,0%	0,851	X^2
Orthostatic Hypotension	3	27,3%	4	36,4	4	36,4%	0,902	X^2
Forgetfulness	3	8,6%	14	40,0%	18	51,4%	0,001	X^2
Hallucinations	2	8,3%	6	25,0%	16	66,7%	0,001	X^2
Anxiety	16	26,7%	21	35,0%	23	38,3%	0,319	X^2
Apathy	14	25,0%	16	28,6%	26	46,4%	0,069	X^2
Sleep problem	17	28,8%	20	33,9%	22	37,3%	0,639	X^2
Pain	13	23,2%	18	32,1%	25	44,6%	0,072	X^2
Frequent Urination	17	27,4%	23	37,1%	22	35,5%	0,188	X^2
Dizziness	6	23,1%	8	30,8%	12	46,2%	0,436	X^2
Fatigue	13	22,0%	22	37,3%	24	40,7%	0,028	X^2

X^2 Chi-square test (Fischer test) RBD: REM sleep behavior disorder

to be the most common NMS with a frequency of 66% in PD patients.[13] The most common NMS in our study was frequent urination with 64.2%. Anxiety was detected with a frequency of 60.4%. In an article published in 2012, it was reported that NMS is more common in females.[14] In another study, it was reported that excessive daytime sleepiness was observed more frequently in the male.[15] In our study, unlike the literature, no significant difference was found between the genders.

When studies comparing NMS with disease stage are reviewed, it is stated that the frequency of NMS increases in severe stage. In particular, studies have reported that forgetfulness, excessive daytime sleepiness, depression, and apathy are more common in severe stages.[16,17] In another study conducted with newly diagnosed mild stage PD patients, it was stated that all patients had at least one NMS. In the same study, anxiety was the most common NMS in patients with newly diagnosed PD.[18] In our study, when we looked at the NMS rates according to the disease stage, we found that only forgetfulness, hallucinations, and fatigue were statistically significantly lower in patients with mild stages than in the moderate and severe stages. We did not find a significant relationship between other NMS and disease stages. We think that if the study is repeated with larger patient populations, the relationship between NMS and disease stage can be exposed more accurately.

The fact that NMS is seen from the prodromal stage is also important in terms of identifying the patient group at risk for PD. It is stated in the literature that if patients with symptoms of constipation, anosmia-hyposmia, RBD, and depression can be followed up with imaging methods showing dopaminergic neuron loss, there may be a chance for early diagnosis of PD.[6] For this reason, it is of great importance to raise awareness for NMS.

In conclusion, NMS consists of many neuropsychiatric, autonomic, and sensory symptoms that can be seen in every stage of disease from the prodromal to the severe stage, and they increase the disability caused by the motor findings of PD and decrease the quality of life. Therefore, it is important to question, detect and treat NMS in every patient with PD. The small number of patients and the absence of a prodromal stage group are the limitations of our study. Larger, multicenter longitudinal studies including patients in prodromal stages are warranted.

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Research Article/ Araştırma Makalesi

Tıp Fakültesi 4. 5. ve 6. Sınıf Öğrencilerinin Farmakovijilans Hakkında Bilgi, Tutum ve Davranışları

Knowledge, Attitudes, and Behaviors About Pharmacovigilance of Medical Faculty 4th, 5th, and 6th Grade Students

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Amaç: Farmakovijilans, advers ilaç reaksiyonları (AİR) başta olmak üzere ilaçla ilgili sorunların tespit edilmesi, yorumlanması ve önlenmesi ile ilgili bilimsel çalışmalardır. AİR bir ilaca karşı gelişen zararlı ve beklenmeyen cevap olarak tanımlanmaktadır. AİR'nın saptanması ve takibi, mortalite ve morbidite oranlarını artırması, iş gücü kaybı gibi sonuçlar nedeniyle önemlidir. Bu çalışmada tıp fakültesi 4. 5. ve 6. sınıf öğrencilerinin; farmakovijilans ve AİR konusundaki farkındalığını, bilgi ve görüşlerini belirleyerek farmakovijilans uygulamalarına ilişkin görevlerine yeterince hazırlıklı olup olmadıklarının incelenmesi amaçlanmıştır.

Yöntem ve Gereçler : Bu çalışma gözlemsel, kesitsel ve tanımlayıcı tipte 2022-2023 tarihleri arasında Sağlık Bilimleri Üniversitesi Gülhane Tıp Fakültesinde yapılmıştır. Öğrencilere, çalışma hakkında bilgi verilerek, Microsoft Forms uygulaması üzerinden anketi doldurmaları sağlanmıştır. Kullanılan anket ile tıp fakültesi öğrencilerinin demografik özellikleri, farmakovijilans ve AİR'na yönelik bilgi, tutum ve uygulamaları değerlendirilmiştir.

Bulgular: Çalışmaya katılan öğrenci sayısı 338'dir. Öğrencilerin %70'i farmakovijilansın tanımına doğru cevap vermiştir. %38'i Türkiye'de bir Farmakovijilans Merkezi'nin (TÜFAM) olduğunu ve %58'i Türkiye'de AİR izlenmesinden sorumlu kurumunun TÜFAM olduğunu ifade etmektedir. Öğrencilerinin %87,2'si AİR bildiriminin gerekli olduğunu düşünürken %26'sı hastanede farmakovijilans irtibat noktasının olduğunu bilmektedir. Öğrencilerin %81,6'sı AİR bildiriminin profesyonel bir yükümlülük olduğunun farkındadır. Öğrencilerin %53,5'i farmakovijilansın tıp fakültesi eğitiminde ayrıntılı olarak ele alınması gerektiğini belirtirken yalnızca %14'ü farmakovijilansın eğitimi müfredatında yeterli şekilde yer aldığını ifade etmektedir.

Sonuç: Çalışmamızda tıp fakültesi öğrencilerinin farmakovijilansa yönelik bilgi, tutum ve uygulamalarında eksiklikler olduğu gösterilmiştir. Bu eksikliklerin giderilmesi için tıp fakültesi eğitim müfredatında farmakovijilans ve AİR bildirimi ile ilgili düzenlemelerin yapılması ve ilgili hastanelerin farmakovijilans irtibat noktaları ve TÜFAM'ın bu konuda aktif rol oynamaları önemlidir.

Anahtar Kelimeler: Tıp öğrencisi, Farmakovijilans, İstenmeyen ilaç reaksiyon, Tıp eğitimi

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Purpose: Pharmacovigilance is characterized as scientific studies related to the detection, interpretation, and prevention of drug-related problems, especially adverse drug reactions (ADRs). ADR is defined as a harmful and unintended response to a drug. Detection and monitoring of ADR is important due to consequences such as increased mortality and morbidity rates and loss of workforce. In this study, we aimed to determine whether the 4th, 5th, and 6th year medical faculty students are sufficiently prepared for their duties regarding pharmacovigilance practices by determining their awareness, knowledge, and opinions about pharmacovigilance and ADR.

Method: This observational, cross-sectional, and descriptive study was conducted between 2022-2023 at Gülhane Faculty of Medicine, University of Health Sciences. Students were informed about the study and were asked to fill out the survey via Microsoft Forms application. The demographic characteristics of medical faculty students, their knowledge, attitudes, and practices toward pharmacovigilance and ADR were evaluated.

Results: 338 students participated in the study. While 70% of the students answered correctly to the definition of pharmacovigilance, 38% stated that there is a Pharmacovigilance Center (Turkish Pharmacovigilance Center-TÜFAM) in Turkey and 58% stated that the institution responsible for monitoring ADRs in Turkey is TÜFAM. While 87.2% of the students think that ADR notification is necessary, 26% know that there is a pharmacovigilance contact point in the hospital. 81.6% of the students are aware that reporting ADR is a professional obligation. While 53.5% of the students stated that pharmacovigilance should be discussed in detail in medical school education, only 14% stated that pharmacovigilance was adequately included in the curriculum.

Conclusion: Our study showed that medical faculty students have deficiencies in their knowledge, attitudes, and practices toward pharmacovigilance. To resolve these deficiencies, it is important that regulations regarding pharmacovigilance and ADR notification be made in the medical faculty education curriculum and that the pharmacovigilance contact points of the relevant hospitals and TÜFAM must play an active role in this regard.

Keywords: Medical student, Pharmacovigilance, Adverse drug reaction, Medical education

EXTENDED ABSTRACT

Background

Pharmacovigilance is the science of detecting, interpreting, and preventing drug-related problems, including adverse drug reactions (ADRs). They are one of the leading causes of morbidity and mortality worldwide, making their detection and management crucial for public health.

Healthcare professionals play a crucial role in pharmacovigilance and ADR reporting. However, studies indicate a deficiency in their knowledge and awareness of these responsibilities. Addressing this issue is imperative for ensuring the proficient reporting of ADRs. National-level regulations should be implemented to enhance spontaneous ADR notifications. The Thalidomide disaster in 1961 marked the initiation of pharmacovigilance systems worldwide, and ongoing research continues to contribute to this field.

In a Netherlands-based research initiative, the implementation of the Junior-Adverse Drug Event Managers (J-ADEMs) unit, comprising medical school students, revealed enhanced competency in effectively managing adverse drug events. Participants in this unit demonstrated superior proficiency in both addressing immediate situations and undertaking the necessary steps for the formulation of ADR reports compared to their peers who did not engage in this specialized program. Furthermore, an investigation into physicians' awareness, knowledge, and opinions regarding pharmacovigilance and ADR reporting in our country has identified insufficient awareness and knowledge among physicians and nurses. Conse-

quently, there is a recognized need for heightened awareness among medical professionals, including doctors and medical students, regarding the pivotal role of pharmacovigilance to facilitate spontaneous ADR notifications.

Research Purpose

This study aims to assess the professional competencies of 4th, 5th, and 6th-year medical faculty students in pharmacovigilance. It seeks to gather information on their awareness, knowledge, and thoughts about pharmacovigilance and ADR. This research marks the first measurement of medical faculty students' knowledge levels in pharmacovigilance in Turkiye. The objective is to implement practices that enhance awareness and knowledge about ADR reporting and pharmacovigilance before entering the medical profession.

Methodology

This observational study, conducted at Gülhane Faculty of Medicine, University of Health Sciences, between 2022-2023, aimed to assess pharmacovigilance and adverse drug reaction (ADR) knowledge, attitudes, and practices among 338 medical faculty students. The study, approved by the SBU Gülhane Faculty of Medicine Clinical Research Ethics Committee (protocol no: 2021/9), utilized Microsoft Forms to collect data from the entire student population without sampling. Participants provided informed consent, and their anonymous responses were gathered and evaluated. The survey, comprising 26 questions, explored demographic characteristics, knowledge, attitudes, and practices related to ADR and pharmacovigilance. Descriptive statistics, mean±SEM, and Kruskal Wallis-H Test were employed for analysis using Graph Pad Prism Version 5. The chi-square test determined statistical significance ($p < 0.05$) for categorical data.

Findings

338 students participated in the study. While 70% of the students answered correctly to the definition of pharmacovigilance, 38% stated that there is a Pharmacovigilance Center (Turkish Pharmacovigilance Center-TÜFAM) in Turkiye and 58% stated that the institution responsible for monitoring ADRs in Turkiye is TÜFAM. While 87.2% of the students think that ADR notification is necessary, 26% know that there is a pharmacovigilance contact point in the hospital. 81.6% of the students are aware that reporting ADR is a professional obligation. The number of students who stated that there should be a pharmacovigilance contact point in every hospital is 183 (57%). Among 4th-grade students, 21.3% acknowledged witnessing adverse drug reactions (ADRs), with only 2.7% (n=6) actively reporting such incidents. In the case of 5th-grade students, 18.2% claimed to have encountered ADRs, with 3.6% (n=3) reporting them. Notably, 45.8% of 6th-grade students acknowledged witnessing ADRs; however, none of them reported having submitted ADR reports. While 53.5% of the students stated that pharmacovigilance should be discussed in detail in medical school education, only 14% stated that pharmacovigilance was adequately included in the curriculum.

Conclusions

Our study showed that medical faculty students have deficiencies in their knowledge, attitudes, and practices toward pharmacovigilance. In the section where the level of knowledge about pharmacovigilance and ADR is evaluated, similar to the studies conducted, it was observed that more than half of the medical faculty students who participated in the survey answered correctly to information questions such as the definition and purpose of pharmacovigilance, the definition of ADR and that drugs subject to additional monitoring should

carry an inverted black triangle emblem. In previous studies conducted in Turkiye, the fact that this rate was higher among doctors (77%), nurses (45%) and pharmacy students (75%) show that medical faculty students have insufficient knowledge about this subject. Based on this, it has been concluded that ADR reporting and pharmacovigilance training for students during their medical school education, especially during their hospital internship period, is not sufficient.

A substantial majority of surveyed students (87%) recognize reporting ADR as a professional obligation, aligning with findings from other studies. Additionally, 85% believe that suspected ADRs should prompt discontinuation of the drug and/or treatment with an alternative medicine. Moreover, 75% are aware of the necessity to report ADRs, indicating that medical faculty students possess the requisite knowledge, awareness, and a sense of responsibility to actively engage in ADR reporting. Approximately 10-15% of 4th, 5th, and 6th-year medical school students state that they received training on ADR notification. This result is a shallow rate for physician candidates who will soon start their clinical practice. One of the important outcomes of this study is that 4th-grade (n=6) students reported more ADRs than 5th (n=3) and 6th (n=0) students and 6th-grade students did not report any ADRs despite encountering more ADRs.
As a result of this study, it was determined that although medical faculty students who will soon start their careers are aware of the importance of reporting ADRs, their knowledge about how to report ADRs and where to send the reports is insufficient. Although there is international recognition of the importance of pharmacovigilance and ADR reporting, it is thought that insufficient attention is given to this in clinical or teaching practice. This underscores the need for heightened attention and concerted efforts to enhance the understanding and competencies of medical students in the field of pharmacovigilance.

1.GİRİŞ

Farmakovijilans, advers ilaç reaksiyonları (AİR) başta olmak üzere ilaçla ilgili sorunların tespit edilmesi, yorumlanması ve önlenmesi ile ilgili bilimsel çalışmalardır ve ilaçların güvenli ve doğru şekilde kullanımı açısından son derece önemlidir.[1] AİR bir ilacın kullanımı sonucu gelişen zararlı ve amaçlanmayan cevap olarak tanımlanmaktadır. AİR uluslararası farmakoepidemiyolojik verilere göre halk sağlığını olumsuz yönde etkileyen nedenlerden biridir[2]. AİR nedeniyle mortalite ve morbidite oranlarının artması, hastanede yatış sürelerinin uzaması ve iş gücü kaybı gibi durumların neden olduğu ekonomik sonuçlar toplumu ilgilendirmekte ve çözülmesi önemli olan bir sağlık problemi olarak değerlendirilmektedir.[2–4] Bu nedenle AİR'nın tespiti ve izlenmesi ilaç güvenliği açısından son derece önemlidir.[5]

Sağlık çalışanları tarafından spontan AİR bildirimi farmakovijilansın temel bileşenlerinden biridir.[2] Spontan AİR bildirimlerinin artması için, ulusal düzeyde düzenlemeler oluşturulmalıdır. 1961 yılında gerçekleşen Talidomid faciası ülkelerde farmakovijilans sistemlerinin oluşturulması için bir başlangıç olup bu konuyla ilgili çeşitli çalışmalar devam etmektedir. Ülkemizde ise farmakovijilansla ilgili ilk yönetmelik 2005 yılında yayınlanmış, sonuncu yönetmelik ise 2014 yılında yürürlüğe girmiştir.[6]

Farmakovijilans ve AİR bildirimi sağlık çalışanları için mesleki bir yükümlülük olup, dikkatle değerlendirilmesi gereken bir konudur, ancak yapılan çalışmalar sağlık çalışanlarının farmakovijilans ile ilgili bilgi düzeyleri ve AİR rapor etme farkındalığının yeterli olmadığını göstermektedir.[5,7] Hemşirelere yönelik yapılan bir çalışmada; farmako-

vijilans hakkında bilgi, tutum ve uygulamalarda eksiklikleri olduğu, hemşireler tarafından yapılan AİR bildirimlerinin ise yetersiz olduğu saptanmıştır.[8] Seçilmiş üç eczacılık fakültesinin öğrencilerinde yapılan bir anket çalışmasında farmakovijilans konusunda eğitim alan öğrencilerin bilgi düzeylerinin ve farkındalıklarının yüksek olduğu ancak AİR bildirimi konusunda bilgilerinin yetersiz olduğu bulunmuştur.[9] Hekimlerin farmakovijilans konusunda aktif rol oynaması ve bilgi düzeylerinin artması AİR bildirimlerinin artmasını yönünde önemli bir adımdır.

Hollanda'da yapılan bir çalışmada tıp fakültesi öğrencileri tarafından Öğrenci- Advers İlaç Olay Yönetim (Junior-Adverse Drug Event Managers (J-ADEMs)) birimi oluşturulmuştur. Bu öğrenciler AİR raporları hazırlanması sürecinde hem durumu yönetme hem de gerekli basamakları uygulama konusunda bu birime katılmayan öğrencilerine göre daha yetkin olarak bulunmuşlardır.[10] Hindistan'da yapılan bir çalışmada tıp fakültesi öğrencilerinin farmakovijilans hakkında bilgi seviyelerinin düşük olduğu, AİR bildirimlerinin yetersiz olmasının nedeni olarak ise farkındalık eksikliği, neyin rapor edileceğine ilişkin yanlış anlamalar olduğu saptanmıştır.[11] Ülkemizde hekimlerin farmakovijilans ve AİR bildirimi hakkında farkındalık, bilgi ve görüşlerini inceleyen bir çalışma tespit edilmiş olup, bu araştırmada hekimlerin ve hemşirelerin farkındalıklarının ve farmakovijilans hakkında bilgilerinin yeterli olmadığı bildirilmiştir. AİR spontan bildirimlerinin düşük olma sebebi hekimlere göre, ulusal farmakovijilans sisteminin bilinmemesi iken, hemşirelerde ise AİR'lerin spontan raporlanma ihtiyacının bilinmemesinden kaynaklanmakta olduğu saptanmıştır. Aynı zamanda bu çalışmada hemşirelerin AİR ile karşılaşma sıklığı hekimlere göre daha düşük olmasına rağmen, bildirim oranının hekimlere göre daha fazla olduğu bulunmuştur.[5] Bu nedenle doktorlarda ve tıp fakültesi öğrencilerinde farmakovijilansın önemi hakkında farkındalık yaratmak spontan AİR bildirimleri için önemlidir.

Bu çalışmada tıp fakültesi 4. 5. ve 6. sınıf öğrencilerinin; farmakovijilans ve AİR konusundaki farkındalığını, bilgi düzeylerini ve uygulama ile ilgili düşüncelerini belirleyerek farmakovijilans uygulamalarına ilişkin mesleki yeterlilikleri hakkında bilgi sahibi olunması amaçlanmıştır. Ayrıca ülkemizde ilk kez tıp fakültesi öğrencilerinin farmakovijilans hakkında bilgi düzeyleri ölçülecek olup; AİR rapor etme ve farmakovijilans konusunda, hekimlik mesleğine başlamadan önce, farkındalık sağlanması ve bilgi düzeyinin yükselmesine yönelik uygulamaların artması hedeflenmiştir.

2. GEREÇ ve YÖNTEMLER

2.1.Araştırma Planı

Bu çalışma gözlemsel, kesitsel ve tanımlayıcı tipte 2022-2023 tarihleri arasında Sağlık Bilimleri Üniversitesi Gülhane Tıp Fakültesinde yapıldı. SBÜ Gülhane Tıp Fakültesi Klinik Araştırmalar Etik Kurulu tarafından onaylanmıştır (protokol no:2021/9). Veriler toplanırken örneklem seçilmeden tüm evrene (338 tıp fakültesi öğrencisi) Microsoft Forms uygulaması üzerinden ulaşılarak, anket uygulanmadan önce çalışma hakkında gerekli bilgi verilmiştir. Ankete katılmayı kabul eden öğrenciler anketin içerisinde yer alan çalışmanın amacını ve istedikleri zaman çekilme haklarını açıklayan gönüllü bilgilendirilmiş katılım formu sorusuna onay vererek anketi tamamlamış olup, ankette katılımcının ad ve soyadı belirtilmeden verilerin anonim toplanması sağlanmıştır. Öğrencilerin yanıtları Microsoft Forms üzerinden toplanarak gerekli değerlendirmeler yapılmıştır.

2.2.Verilerin Toplanması

Çalışmada kullanılan anket, literatürün kapsamlı bir şekilde gözden geçirilmesinden sonra oluştu-

rulmuştur.[5,12] Anket, tıp fakültesi öğrencilerinin demografik özelliklerini, farmakovijilans ve AİR'ye yönelik bilgilerini, tutumlarını ve uygulamalarını değerlendirmek üzere tasarlanmıştır. Çalışma anketi tıp fakültesi öğrencilerinin demografik özellikleri ile ilgili 3 soru, AİR ve farmakovijilans bilgi düzeyleri ile ilgili 12 soru (her doğru cevap için 1, yanlış cevap için 0 puan verildi), AİR ve farmakovijilans ile ilgili tutumlarını ölçmek için 7 soru (bir veya daha fazla doğru yanıtlı çoktan seçmeli olarak tasarlanmıştır) ve AİR ve farmakovijilans ile ilgili uygulamalarını değerlendirmek amacıyla 4 soru (bir veya daha fazla doğru yanıtlı çoktan seçmeli olarak tasarlanmıştır) olmak üzere toplam 26 sorudan oluşturmaktadır.

2.3.İstatiksel Analiz

Çalışma bulgularını açıklamak için tanımlayıcı istatistikler kullanılmıştır. Sürekli ve kategorik değişkenleri tanımlamak için ortalama ± ortalamanın standart hatası (OSH) ve frekans (%) kullanılmıştır. Anketin bilgi kısmı 12 puandan oluşmaktadır ve sonuçlar ortalama±SEM olarak sunulmuştur. 4. sınıf, 5. sınıf ve 6. sınıf arasındaki karşılaştırmalar Kruskal Wallis-H Testi ile analiz edilmiştir. Kategorik veriler için ki-kare testi kullanılmış ve $p<0.05$ değeri istatistiksel olarak anlamlı kabul edilmiştir. Tüm istatistiksel analizler Graph Pad Prısm Version 5 programı kullanılarak yapılmıştır.

3.BULGULAR

3.1.Tıp Fakültesi 4. 5. ve 6. Sınıf Öğrencilerinin Sosyodemografik Özellikleri

Çalışmaya katılan toplam öğrenci sayısı 338'dir. Öğrencilerin 321'i (%95) sorulara yanıt verirken, yanıt veren öğrencilerin %58'i erkek (n=186) ve %42'si kadındır (n=135). Yaş ortalaması 22,6 olan öğrencilerin yaklaşık %66'sı 4. sınıf, %26'sı 5. sınıf, %8'si 6. sınıf öğrencisidir. SBÜ Gülhane Tıp Fakültesi 4.,5. ve 6. Sınıf öğrencilerinin sosyodemografik özellikleri tablo halinde verilmiştir (Tablo 1).

Tablo 1.

SBÜ Gülhane Tıp Fakültesi 4.,5. ve 6. Sınıf öğrencilerinin sosyodemografik özellikleri

	Kişi sayısı (n)	Sıklık (%)
Cinsiyet		
Kadın	135	%42
Erkek	186	%58
Yaş		
19-23 yaş	174	
24-28 yaş	147	
Sınıf		
4. sınıf	215	% 66
5. sınıf	82	%26
6. sınıf	24	% 8

3.2.Tıp Fakültesi 4. 5. ve 6. Sınıf Öğrencilerinin AİR ve Farmakovijilans ile İlgili Bilgi Düzeyleri

Bilgi bölümünden aldıkları toplam puan 4. sınıflar için (5,9±0,1), 5. sınıfların için (5,2±0,2) ve 6. sınıflar için ise (6,1±0,3) olarak bulunmuştur. 4., 5. ve 6. sınıf bilgi puanları arasında istatiksel olarak anlamlı bir fark saptanmamıştır (Kruskal – Wallis testi: $p=0.3679$). Çalışmaya katılan öğrencilerin %70'i farmakovijilansın tanımına doğru cevap vermiştir. Daha önce farmakovijilans terimini duyan 134 4. sınıf öğrencisi, 52 5. sınıf öğrencisi, 16 6. sınıf öğrencisinin tamamı farmakovijilans tanımını doğru bilirken, 4. sınıf öğrencilerinin %55'i, 5. sınıf öğrencilerinin %59'u 6. sınıf öğrencilerinin %70'i farmakovijilansın en önemli amacının ilaç güvenliğini belirlemek olduğunu bildirmiştir. 4. sınıfların 141 kişi ciddi advers ilaç reaksiyonunun tanımını bilirken bu sayı 5. sınıflar için 44, 6. sınıflar için 19'dur. Tıp fakültesi öğrencilerinin %38'i Türkiye'de bir Farmakovijilans Merkezi'nin (TÜFAM) olduğunu ve Türkiye'nin AİR'leri uluslararası merkezlerle paylaştığını belirtirken bu öğrencilerin sadece %58'i Türkiye'de AİR'lerin izlenmesinden sorumlu kurumunun TÜFAM olduğunu bilmiştir. Ek izlemeye tabi ilaçların ters siyah üçgen amblemi taşıması gerektiği bilgisine 4. sınıf-

ların %72'si, 5. sınıfların %59'u, 6. sınıfların %45'i sahiptir.

Çalışmaya katılan öğrencilerin %87,2'si AİR bildiriminin gerekli olduğunu düşünürken yalnızca %26'sı hastanede bir farmakovijilans irtibat noktasının olduğunu bilmektedir. Bununla birlikte öğrencilerin %47,3'ü hastanede AİR'leri bildirmekten sorumlu sağlık çalışanlarının doktor, eczacı, diş hekimi ve hemşire olduğunu ifade etmektedir. Ciddi AİR tanımını sırasıyla; 4. sınıfların %60,4'ü, 5. sınıfların %50'si, 6. sınıfların %70,8'i, AİR bildirim süresinin 15 gün olduğunu ise 4. sınıfların %13,4'ü, 5. sınıfların 15,8'i, 6. sınıfların %25'i doğru olarak bilmiştir.

Tıp fakültesi öğrencilerinin farmakovijilans ile ilgili bilgi düzeylerini ölçmeye yönelik sorulara verdikleri yanıtlar tablo halinde verilmiştir (Tablo 2).

Tablo 2.

SBÜ Gülhane Tıp Fakültesi 4., 5. ve 6. Sınıf öğrencilerinin farmakovijilans ile ilgili bilgi düzeylerini ölçmeye yönelik sorular ve verilen yanıtlar

	4. sınıf		5. sınıf		6. sınıf		p*
	n	%	n	%	n	%	
Daha önce "Farmakovijilans" terimini duydunuz mu?							
Evet	163	75,8	67	81,7	23	95,8	0,3535
Hayır	25	11,6	6	7,3	0	0	
Hatırlamıyorum	26	12,1	9	11	1	4,2	
	1 boş	0,5					
Aşağıdakilerden hangisi "Farmakovijilans" tanımı için en uygun seçenektir?							
İlaç ruhsat aldıktan sonra advers ilaç reaksiyonlarının tipini ve ortaya çıkma sıklığını belirleyen çalışma alanı	23	10,7	9	11	6	25	0,1860
Hastanelerde advers ilaç reaksiyonu oluşumlarını izleyen çalışma alanı	9	4,2	2	2,4	1	4,2	
Advers etkilere yatkınlık faktörlerini belirleme çalışmaları	1	0,5	1	1,2	0	0	
Advers etkilerin veya ilaçla ilgili diğer problemlerin belirlenmesi, değerlendirilmesi, anlaşılması ve önlenmesine ait faaliyetler ve çalışma alanı	164	76,3	54	65,9	17	70,8	
Fikrim yok	18	8,4	14	17,1	0	0	
			1 boş	1,2			
Farmakovijilansın en önemli amacı nedir?							
İlaç güvenliğini belirlemek	120	55,8	49	59,8	17	70,8	0,3418
Advers ilaç reaksiyonlarının insidansını hesaplamak	20	9,3	10	12,2	2	8,3	
Advers ilaç reaksiyonları için kolaylaştırıcı faktörleri belirlemek	7	3,3	3	3,7	1	4,2	
Önceden tanınmayan advers ilaç reaksiyonlarını tanımlamak	66	30,7	19	23,2	4	16,7	
	2 boş	0,9	1 boş	1,2			

Tablo 2.

SBÜ Gülhane Tıp Fakültesi 4., 5. ve 6. Sınıf öğrencilerinin farmakovijilans ile ilgili bilgi düzeylerini ölçmeye yönelik sorular ve verilen yanıtlar

	4. sınıf		5. sınıf		6. sınıf		p*
	n	%	n	%	n	%	
Türkiye'de farmakovijilans Merkezi var mı?							
Evet	84	39,1	28	34,1	13	54,2	0,2086
Hayır	2	0,9	0	0	0	0	
Olabilir	79	36,7	33	40,2	4	16,7	
Bilmiyorum	50	23,3	21	25,6	7	29,2	
Türkiye'de advers ilaç reaksiyonlarının izlenmesinden hangi kurum sorumludur?							
Türkiye Farmakovijilans Derneği	31	14,4	12	14,6	1	4,2	0,8724
Türkiye İlaç ve Tıbbi Cihaz Kurumu	45	20,9	21	25,6	8	33,3	
TÜFAM (Türkiye Farmakovijilans Merkezi)	112	52,1	40	48,8	12	50	
Türk Tabipleri Birliği	13	6	0	0	1	4,2	
Böyle bir kurum bulunmamaktadır	11	5,1	9	11	2	8,3	
	3 boş	1,4					
Türkiye advers ilaç reaksiyonlarına ait bildirimleri uluslararası olarak paylaşıyor mu?							
Evet	84	39,1	25	30,5	10	41,7	0,3484
Hayır	3	1,4	3	3,7	1	4,2	
Olabilir	73	34	37	45,1	8	33,3	
Bilmiyorum	54	25,1	17	20,7	5	20,8	
	1 boş	0,5					
Ek izlemeye tabi ilaçlar aşağıdaki amblemlerden hangisini taşımaktadır?							
Siyah kare	14	6,5	10	12,2	3	12,5	0,0094*
Üçgen	28	13	17	20,7	4	16,7	
İçi boş kare	13	6	4	4,9	5	20,8	
Ters siyah üçgen	155	72,1	49	59,8	11	45,8	
	5 boş	2,3	2 boş	2,4	1 boş	4,2	
Hastanenizde farmakovijilans irtibat noktası var mı?							
Evet	60	27,9	16	19,5	8	33,3	0,2400
Hayır	5	2,3	1	1,2	0	0	
Henüz kurulmamış	4	1,9	65	79,3	16	66,7	
Bilmiyorum	144	67					
	2 boş	0,9					
Advers ilaç reaksiyonu'larının bildiriminin gerekli olduğunu düşünüyor musunuz?							
Evet	194	90,2	65	79,3	21	87,5	0,0406*
Hayır	4	1,9	1	1,2	1	4,2	
Olabilir	7	3,3	6	7,3	2	8,3	
Bilmiyorum	7	3,3	10	12,2			
	3 boş	1,4					

Tablo 2.

SBÜ Gülhane Tıp Fakültesi 4., 5. ve 6. Sınıf öğrencilerinin farmakovijilans ile ilgili bilgi düzeylerini ölçmeye yönelik sorular ve verilen yanıtlar

	4. sınıf		5. sınıf		6. sınıf		p*
	n	%	n	%	n	%	
Aşağıdakilerden hangisi/hangileri ciddi bir advers ilaç reaksiyonudur? * (birden fazla seçenek işaretlenebilir)							
Ölüm ve/veya hayati tehlike	202	93,9	71	86,5	24	100	0,9922
Hastaneye yatış/hastanede yatış süresinin uzaması	153	71,1	50	60,9	18	75	
Önemli ve kalıcı sakatlığa veya iş görmezliğe neden olmak	182	84,6	70	85,3	24	100	
Konjental anomali ve /veya doğumsal defekt	170	79,0	63	76,8	23	95,	
	4 boş	1,8	1 boş	1,2			
Bir hastanede advers ilaç reaksiyonlarını bildirmekten sorumlu sağlık çalışanları kimlerdir? * (birden fazla seçenek işaretlenebilir)							
Doktor	209	97,2	81	35,1	24	31,6	0,9806
Hemşire	123	57,2	44	19	15	19,7	
Eczacı	145	67,4	50	21,6	20	26,3	
Diş hekimi	138	64,2	56	24,2	17	22,4	
Yaşanan bir advers ilaç reaksiyonunu kaç gün içerisinde ilgili kuruma bildirmelisiniz?							
1 gün	62	28,8	23	28	3	12,5	0,3135
7 gün	102	47,4	33	40,2	12	50	
15 gün	29	13,5	13	15,9	6	25	
28 gün	17	7,9	11	13,4	3	12,5	
	5 boş	1,9	2 boş	2,4			
*χ^2 test							

3.3.Tıp Fakültesi 4. 5. ve 6. Sınıf Öğrencilerinin Farmakovijilans ile İlgili Tutumları

Tıp fakültesi öğrencilerinin %81,6'sı AİR bildiriminin profesyonel bir yükümlülük olduğunun farkındadır. AİR şüphesi olduğunda öğrencilerin %85'i ilacın kesilmesi ve/veya alternatif ilaç ile tedavi edilmesi gerektiğini, %75,7'si AİR bildiriminin yapılması gerektiğini ifade etmiştir.

4. sınıf öğrencilerinin %26,5'i, 6. sınıf öğrencilerinin %12,5'i, 5. sınıf öğrencilerin ise sadece %8,5'i AİR bildirimi konusunda eğitim aldığını bildirmektedir. Öğrencilerin %53,5'i farmakovijilansın tıp fakültesi eğitiminde ayrıntılı olarak ele alınması gerektiğini belirtirken yalnızca %14'ü farmakovijilansın tıp fakültesi eğitimi müfredatında yeterli şekilde yer aldığını belirtmektedir.

Her hastanede farmakovijilans irtibat noktasının olması gerektiğini ifade eden öğrencilerin sayısı 183'tür (%57). 4.,5. ve 6. sınıf öğrencileri tarafından AİR raporlamasında caydırıcı faktör olarak en çok seçilen cevaplar, AİR meydana gelip gelmediğine karar vermenin zor olması (%71) ve AİR bildirmek için yeterli zamanın olmaması (%41,4) olarak saptanmıştır. Bununla birlikte öğrencilerin %17,1'i bildirim yapmanın ücret karşılığının olmamasını ve %16,5'i ise bildirilmeyen sadece bir

vakanın AİR veri tabanını zaten etkilemeyebileceğini düşündüklerini bildirim yapmamalarına sebep olarak göstermişlerdir.

SBÜ Gülhane Tıp Fakültesi 4.,5., ve 6. sınıf öğrencilerinin farmakovijilans ile ilgili tutumlarını gösteren bulgular tablo halinde verilmiştir (Tablo 3).

Tablo 3.

SBÜ Gülhane Tıp Fakültesi 4., 5. ve 6. Sınıf öğrencilerinin farmakovijilans ile ilgili tutum sorularına verdiği yanıtlar

	4. sınıf		5. sınıf		6. sınıf		p*
	n	%	n	%	n	%	
Advers ilaç reaksiyonlarının bildiriminin sizin için profesyonel bir yükümlülük olduğunu düşünüyor musunuz?							
Evet	176	81,9	64	78	22	91,7	0,4671
Hayır	7	3,3	2	2,4	0	0	
Olabilir	22	10,2	9	11	1	4,2	
Bilmiyorum	8	3,7	7	8,5	1	4,2	
	2 boş	0,9					
Advers ilaç reaksiyonlarından şüphelenildiğinde ne yapılmalıdır? *(birden fazla seçenek işaretlenebilir)							
İlaç kesilmeli ve/veya alternatif ilaç ile tedavi edilmeli	174	80,9	67	81,7	21	87,5	0,7394
İlaç kesilmeli ve/veya doz azaltılmalı	84	39,1	32	39	12	50	
Nedensellik belirlenmeli	106	49,3	36	43,9	16	66,7	
Advers ilaç reaksiyonu'ları bildirilmeli	130	60,5	59	72	19	79,2	
	2 boş	0,9	1 boş	1,2			
Advers ilaç reaksiyonu'nunu nasıl rapor edeceğiniz konusunda hiç eğitim aldınız mı?							
Evet	57	26,5	7	,5	3	12,5	0,0002*
Hayır	91	42,3	49	59,8	19	79,2	
Hatırlamıyorum	64	29,8	26	31,	2	8,3	
	3 boş	1,4					
Farmakovijilansın tıp fakültesi eğitiminde ayrıntılı olarak ele alınması gerektiğini düşünüyor musunuz?							
Evet	120	55,8	38	46,3	15	62,5	0,4302
Hayır	10	4,7	7	8,5	1	4,2	
Olabilir	73	34	31	37,8	8	33,3	
Bilmiyorum	10	4,7	6	7,3	0	0	
	2 boş	0,9					
Farmakovijilans tıp fakültesi eğitimi müfredatında yeterli şekilde yer aldığını düşünüyor musunuz?							
Evet	40	18,6	2	2,4	1	4,2	0,0001*
Hayır	82	38,1	45	54,9	19	79,2	
Olabilir	48	22,3	19	23,2	4	16,7	
Bilmiyorum	43	20	16	19,5	0	0	
	2 boş	0,9					

Her hastanede farmakovijilans irtibat noktası kurulmasına ilişkin fikriniz nedir?							
Her hastanede olmalı	135	62,8	40	48,8	8	33,3	0,053
Bir şehirde bir tane yeterli	12	5,6	6	7,3	2	8,3	
Her hastanede gerekli değil	34	15,8	15	18,3	5	20,8	
Hastanelerdeki yatak sayısına göre değişir	32	14,9	19	23,2	9	37,5	
	2 boş	0,9	2 boş	2,4			
Aşağıdaki faktörlerden hangileri sizi yaşanan bir advers ilaç reaksiyonunu bildirmekten vazgeçirir? * (birden fazla seçenek işaretlenebilir)							
Bildirim yapmanın ücret karşılığının olmaması,	34	15,8	15	6,5	6	7,9	0,5857
Advers ilaç reaksiyonunu bildirmek için yeterli zamanın olmaması,	77	35,8	38	16,5	18	75	
Bildirilmeyen tek bir vaka advers ilaç reaksiyonunu veri tabanını zaten etkilemeyebilir	32	14,9	11	4,8	6	25	
Advers ilaç reaksiyonlarının meydana gelip gelmediğine karar vermenin zor olması	152	70,7	60	73,2	19	79,2	
	10 boş	4,7	3 boş	3,7			
*χ2 test							

3.4.Tıp Fakültesi 4. 5. ve 6. Sınıf Öğrencilerinin Farmakovijilans ile İlgili Uygulamaları

AİR'ler hakkında bilgi edinmek için öğrenciler çoğunlukla ilaç bilgi formu/prospektüs (%70,7) kullandıklarını belirtirken, doktor/eczacıya danışmak (%61) ikinci tercih ettikleri yöntem olmuştur. 4. sınıfların %21,3 si bugüne kadar AİR gördüğünü belirtirken yalnızca %2,7'si (n=6) AİR bildirimi yapmıştır. 5. sınıfların %18,2'si bugüne kadar AİR gördüğünü belirtirken %3,6'sı (n=3) AİR bildirimi yapmıştır. 6. sınıfların ise %45,8'i bugüne kadar AİR gördüğünü belirtirken hiçbiri AİR bildirimi yapmadığını ifade etmektedir. Daha önce advers etki bildirim formunu görenlerin oranı ise 4. sınıflar için %20, 5. sınıflar için %8,5, 6 sınıflar için ise %8,3'tür.

4.,5. ve 6. sınıf tıp fakültesi öğrencilerinin farmakovijilans ile ilgili uygulamalarına yönelik sorulara verdikleri yanıtlar tablo halinde verilmiştir (Tablo 4).

4.TARTIŞMA

Bu çalışmada SBÜ Gülhane Tıp Fakültesi 4., 5. ve 6. sınıf öğrencilerinin farmakovijilans ve AİR hakkında bilgi, tutum ve uygulamaları araştırılmıştır. Bu çalışmanın birinci bulgusu ulusal farmakovijilans sistemi tarafından kendilerine verilen sorumlulukları yerine getirmek için tıp fakültesi 4., 5. ve 6. sınıf öğrencilerinin bilgi düzeylerinin istenilen seviyede olmadığıdır.

Bu çalışma sonucunda hekimlik mesleğine yakın zamanda başlayacak olan tıp fakültesi öğrencilerinin AİR raporlanmasının önemi hakkında farkındalığa sahip olmasına rağmen, AİR bildiriminin nasıl yapılacağı ve raporların nereye iletileceği hakkındaki bilgisinin yetersiz olduğu saptanmıştır. Farmakovijilans ve AİR raporlamasının önemine dair uluslararası bir kabul olmasına rağmen, buna klinik veya öğretim uygulamalarında yeterli önemin verilmediği düşünülmektedir. Bu son derece istenmeyen bir durumdur ve tıp fakültesi öğrencilerinin farmakovijilans hakkındaki bilgi ve becerilerini geliştirmek için daha fazla çaba göste-

Tablo 4.

SBÜ Gülhane Tıp Fakültesi 4., 5. ve 6. Sınıf öğrencilerinin farmakovijilans uygulamaları ile ilgili sorularına verdiği yanıtlar

	4. sınıf		5. sınıf		6. sınıf		p*
	n	%	n	%	n	%	
Advers ilaç reaksiyonlarını tanımlamak için hangi yöntemleri kullanıyorsunuz? * (birden fazla seçenek işaretlenebilir)							
İnternet kaynakları	127	59,1	45	54,9	15	62,5	0,9883
İlaç bilgi formu/prospektüs	153	71,2	55	67,1	19	79,2	
Doktor/Eczacıya danışmak	134	62,3	44	53,7	18	75	
Üretici firmaya danışmak	52	24,2	21	25,6	6	25	
Hiçbiri	29	13,5	11	13,4	3	12,5	
	4 boş	1,9	4 boş	4,9			
Bugüne kadar hiç advers ilaç reaksiyonu gördünüz mü?							
Evet	46	21,4	15	18,3	11	45,8	0,0008*
Hayır	118	54,9	35	42,7	9	37,5	
Olabilir	29	13,5	21	25,6	2	8,3	
Bilmiyorum	18	8,4	9	11	2	8,3	
	4 boş	1,9	2 boş	2,4			
Advers Etki Bildirim Formunu hiç gördünüz mü?							
Evet	43	20	7	8,5	2	8,3	0,042*
Hayır	141	65,6	57	69,5	20	83,3	
Olabilir	22	10,2	5	6,1	1	4,2	
Bilmiyorum	6	2,8	12	14,6	1	4,2	
	3 boş	1,4	1 boş	1,2			
Bugüne kadar kaç tane "Advers Etki Bildirim Formu" doldurdunuz?							
Hiç	207	96,3	78	95,1	24	100	0,6337
1-2	6	2,8	3	3,7	0		
	2 boş	0,9	1 boş	1,2			
*χ2 test							

rilmelidir.

Farmakovijilans ve AİR hakkında bilgi düzeyinin değerlendirildiği bölümde, yapılan çalışmalarla benzer olarak ankete katılan tıp fakültesi öğrencilerin yarısından fazlası farmakovijilansın tanımı ve amacı, AİR tanımı ve ek izlemeye tabi ilaçların ters siyah üçgen amblemi taşıması gerektiği gibi bilgi sorularına doğru yanıt verdikleri görülmüştür.[5,11,13,14] Ancak öğrencilerin sadece 38'i Türkiye'de kurulan ulusal farmakovijilans sisteminden haberdar olduğunu belirtmiştir. Türkiye'de daha önce yapılan çalışmalarda bu oranın doktorlarda (%77) hemşirelerde (%45) ve eczacılık öğrencilerinde (%75) daha yüksek olması tıp fakültesi öğrencilerinin bu konu hakkında bilgilerinin eksik olduğunu göstermektedir.[5,9] Bundan yola çıkarak tıp fakültesi eğitimi süresince özellikle hastanede staj dönemindeki öğrencilerin AİR bildirimi ve farmakovijilans eğitiminin yeterli olmadığı sonucuna ulaşılmıştır.[5,8,9] Türkiye'de yapılan benzer çalışmalarda eczacılık öğrencilerinin bu sorulara doğru

yanıt verme oranının daha yüksek olmasına rağmen doktorların ve hemşirelerin doğru yanıt verme oranı benzer olarak bildirilmiştir.9 Rauniyar ve ark.'nın yaptığı çalışmada ise ulusal AİR izlenmesi ile ilgili sorulara tıp fakültesi 3. sınıf öğrencilerinin yaklaşık %29'u doğru yanıt vermiştir.[15] Bu sonuçlar doktorların ve doktor adaylarının farmakovijilans eğitiminde AİR bildirimi ile ilgili sorumluluklar konusunun daha fazla yer alması gerektiğini düşündürmektedir.

Bu çalışmanın sonuçları, ankete katılan öğrencilerin AİR bildiriminin öneminin farkında olduğunu ancak AİR bildirimi ve yerel farmakovijilans bildirim merkezleri ile ilgili bilgi düzeylerinin yeterli olmadığını düşündürmektedir. Nijerya'da yapılan bir çalışmada tıp fakültesi öğrencileri arasında AİR bildiriminin yapılmasının gerekli olduğunu belirtenlerin oranı %89 iken, hastanede bir farmakovijilans irtibat noktası olduğunu bilenlerin oranı %11 olarak saptanmıştır.[16] Çalışmamızın sonuçları bu veriler ile benzerlik gösterirken doktorlar ve hemşireler ile yapılan çalışmalarda ise AİR bildirimi ile ilgili bilgi düzeyi daha yüksek olarak raporlanmıştır.[17] Bu veriler tıp fakültesi eğitiminde ulusal ve uluslararası farmakovijilans irtibat noktaları ile ilgili konuların eğitim müfredatına daha çok dahil edilmesinin gerekliliğini vurgulamaktadır.

Ankete katılan öğrencilerin çoğunluğu (%87) AİR bildiriminin profesyonel bir yükümlülük olduğunun farkındadır ve bu oran yapılan çalışmalarla benzer olarak saptanmıştır.[15,16] Ayrıca AİR şüphesi olduğunda öğrencilerin %85'i ilacın kesilmesi ve/veya alternatif ilaç ile tedavi edilmesi gerektiğini, %75,7'si AİR bildiriminin yapılması gerektiğini bilmesi tıp fakültesi öğrencilerinin AİR bildiriminde ve AİR ile ilgili tutumlarında aktif rol alabilecek bilgi düzeyine ve sorumluluk bilincine sahip olduklarını göstermektedir.

Tıp fakültesi eğitiminde 4., 5. ve 6. sınıf öğrencilerinin yaklaşık %10-15'i AİR bildirimi konusunda eğitim aldığını belirtmektedir. Bu sonuç yakında klinik uygulamasına başlayacak olan hekim adayları için oldukça düşük bir orandır. Yapılan çalışmalarda tıp fakültesi öğrencileri için bu oranlar benzerken eczacılık öğrencilerinde ve hemşirelerde bu oranlar daha yüksek olarak gözlenmektedir.[5,8,18,19] Ankete katılan öğrencilerin yaklaşık yarısı farmakovijilansın tıp fakültesi eğitiminde ayrıntılı olarak ele alınması gerektiğini belirtirken yalnızca %14'ü farmakovijilansın tıp fakültesi eğitimi müfredatında yeterli şekilde yer aldığını düşünmektedir. Malezya ve Nijerya'da yapılan benzer çalışmalarda öğrencilerin farmakovijilans eğitiminin tıp fakültesi eğitim müfredatında yeterince yer almadığını düşündükleri gösterilmiştir.[16] Bu çalışmanın tek bir tıp fakültesinde yapılmış olması konu hakkında genelleme yapılmasını kısıtlasa da çıktılarımızın diğer çalışmalarla benzer olması farmakovijilans ve AİR bildirimi hakkında bilgi düzeyinin yetersiz olduğu ve bunun nedenlerinin araştırılarak gerekli düzenlenmelerin yapılmasının önemini ortaya koymaktadır.

Çalışmamızda AİR raporlanmasında en çok seçilen caydırıcı faktör, AİR meydana gelip gelmediğine karar vermenin zor olmasıdır (%71). Rauniar ve ark.'nın yaptığı çalışmada ise en çok seçilen caydırıcı faktör AİR raporlanmasının nasıl yapılacağı konusundaki bilgi eksikliği olarak bildirilmiştir.[15] Yapılan bir çalışmada doktorlar arasında en çok seçilen caydırıcı faktör AİR raporlanmasının nasıl yapılacağı konusundaki bilgi eksikliği olarak belirtilirken hemşirelerde ise caydırıcı faktör olarak en çok AİR gelişip gelişmediğine karar vermede zorluk yaşamaları olarak belirtilmiştir.[5,8,20] Bu veriler AİR bildirim sayılarının az olmasının altında yatan temel nedenlerinden birinin bilgi eksikliği olduğunu düşündürmektedir.

Çalışmaya katılan tıp fakültesi öğrencileri AİR raporlanması hakkında kaynak olarak en çok ilaç bilgi formu/prospektüse ve doktor/eczacıya danışmayı tercih etmişlerdir. Ergün ve ark. da yaptığı çalışmada doktorlar ve hemşirelerin AİR raporlanması hakkında kaynak olarak, sıklıkla interneti ve ilaç bilgi formunu tercih ettiklerini belirtmişlerdir.[5]

4. sınıf (n=6) öğrencilerinin 5. (n=3) ve 6. (n=0) sınıf öğrencilerine göre daha fazla AİR bildirimi yaptığı 6. sınıfların ise daha fazla AİR ile karşılaşmasına rağmen hiç bildirim yapmaması bu çalışmanın önemli çıktıları arasındadır. Yapılan benzer çalışmalarda tıp fakültesi öğrencilerinin AİR bildirim sayısı Nijeryada 4, Malezyada 1, Kuzey Hindistan'da ise 37 olarak raporlanmıştır.[14,16] Çalışmamızda AİR bildirim sayılarının bu kadar düşük olmasının nedeni tıp fakültesi öğrencilerinin farmakovijilans irtibat noktasını bilmiyor olmaları ile advers etki bildirim formunu gören öğrencilerin oranının oldukça (yaklaşık %15) düşük olması olabilir. Bu veriler ışığında tıp fakültesi öğrencilerinin farmakovijilans uygulamalarında hem bilgi eksikliği hem de pratik eksikliği olduğu dikkat çekmektedir. Yapılan diğer çalışmalarda olduğu gibi bizim çalışmamızda da tıp fakültesi öğrencileri AİR bildirimlerinin önemli olduğu belirtmesine rağmen AİR raporlama oranı düşüktür.[21] Bu nedenle tıp fakültesi eğitiminin özellikle 4,5, ve 6. sınıfı gibi pratik becerilerinin geliştirildiği sınıflarda farmakovijilans ve AİR raporlanmasına dair eğitimlerin müfredatta yeterli şekilde yer alması ve stajlarda bu konudaki uygulamalarla öğrencilere klinik beceri kazandırılması önem arz etmektedir. Hollanda Farmakovijilans Merkezi Lareb ile iş birliği içinde, dijital dersler ve bir AİR ödevinden oluşan bir eğitim paketi geliştirilerek Hollanda da bulunan tıp fakültelerinin kullanımına sunulmuştur. Ayrıca tıp müfredatına (zorunlu) bir AİR raporlama ödevi dahil edilerek farmakovijilans uygulamalarının ve bilgisinin artırılması hedeflenmiştir.[22] Farmakovijilans eğitimi ile hastalıkları tedavi etmede önemli bir yeri olan ilaçların hem daha etkin bir şekilde kullanılması hem de ilaç maliyetleri için ayrılan bütçenin olumlu şekilde azalması sağlanabilir. Bunun için de diğer sağlık personellerinde olduğu gibi doktorların ve doktor adaylarının farmakovijilans ve AİR bildirimi ile ilgili eğitimlerinin aktif olarak denetlenmesi ve Türkiye'deki tüm tıp fakültelerinin müfredatında yeterli şekilde yer alması büyük önem arz etmektedir.

Bu çalışmanın ana kısıtlılığı, anketin ön çalışma ile hazırlanamamasıdır. Bununla birlikte, ön değerlendirmeler (ilgili yapıyı belirlemek için gerekli literatür taraması) ve geliştirme sürecinin birçok adımı (yapının boyutsallığının belirlenmesi, anket formatının belirlenmesi, soru formatının belirlenmesi, maddelerin geliştirilmesi, soru formu uzunluğu) yapılmıştır. Araştırmanın diğer sınırlılıkları bildirilen AİR sayısıyla ilgili olarak kişilerin cevabına güvenmek, diğer fakültelerin (eczacılık ve hemşirelik) katılımının olmaması ve ankete katılan öğrenciler arasında her sınıf için yakın sayılarda kişinin ankete katılmamış olmasıdır. Bu nedenle literatürdeki benzer yayınların sonuçları ile bulgularımız desteklenmiştir.

Sonuç olarak çalışmamızda bir tıp fakültesi 4.,5. ve 6. sınıf öğrencilerinin farmakovijilansa yönelik bilgi, tutum ve uygulamalarında eksiklikler olduğunu gösterilmiştir. Bu eksikliklerin giderilmesi için tıp fakültesi eğitim müfredatında farmakovijilans ve AİR bildirimi ile ilgili düzenlemelerin yapılması ve bu eğitimlerin sürekliliğinin sağlanması ve ilgili üniversitelerin farmakovijilans irtibat noktaları ve TÜFAM'ın bu konuda aktif rol oynaması önemlidir. Bu katılım ile AİR bildirimlerinin artması; eczacı, hemşire gibi diğer sağlık personelleri ile ilacı reçete edecek olan doktor ve doktor adaylarının da bu konuda bilgi düzeylerinin ve farmakovijilans

uygulama becerilerinin artması sağlanacaktır.

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Bu makale ile ilgili herhangi bir çıkar çatışması bulunmamaktadır.

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Research Article/ Araştırma Makalesi

Sağlıkla İlgili Bölümlerde Öğrenim Gören Öğrencilerde Geleneksel ve Tamamlayıcı Tıp Uygulamaları ve Takviye Edici Gıda Kullanımı Deneyimleri ile Fiziksel Aktivite ve Vücut Farkındalığı Arasındaki İlişkilinin İncelenmesi: Kesitsel Çalışma

Investigation of the Relationship Between Traditional and Complementary Medicine Practices and Supplementary Food Use Experiences and Physical Activity and Body Awareness Among Students Studying in Health-Related Departments: A Cross-Sectional Studys

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Amaç: Bu çalışmanın amacı, sağlıkla ilgili bölümlerde öğrenim gören öğrencilerin geleneksel ve tamamlayıcı tıp (GETAT) uygulamalarına ve takviye edici gıda kullanımına ilişkin deneyimlerini belirlenmek ve bu değişkenler ile fiziksel aktivite ve vücut farkındalığı arasındaki ilişkiyi incelemektir.

Yöntem ve Gereçler: Çalışmanın çevrimiçi anket linki bir devlet üniversitenin sağlıkla ilgili bölümlerinde öğrenim gören ön lisans ve lisans öğrencilerine gönderildi. Çevrimiçi anket formu demografik bilgiler, GETAT ve takviye edici gıda deneyimlerine ilişkin sorular, Uluslararası Fiziksel Aktivite Anketi-Kısa Formu (UFAA-KF), Vücut Farkındalık Anketini (VFA) içermekteydi. Anketi dolduran 186 katılımcının (150 kadın, 36 erkek) verileri analiz edildi.

Bulgular: Katılımcıların %34,6'sı (n=65) GETAT uygulamaları ve %25,3'ü (n=47) takviye edici gıda deneyimlemişti. En sık deneyimlenen GETAT uygulamaları %22 (n=41) masaj, %10,8 (n=20) meditasyon ve %9,7 (n=18) bitkisel tedavi; en sık kullanılan takviye edici gıda %17,2 (n=32) D vitamini, %14 (n=26) B-12 vitamini ve %7 (n=13) C vitaminiydi. Katılımcıların %68,3'ü (n=127) inaktif, %8,1'i (n=15) minimal aktif ve %23,7'si (n=44) çok aktifti ve VFA skoru ortalama 93,53±15,84'tü. GETAT uygulamaları deneyimleri ile takviye edici gıda kullanımı ile fiziksel aktivite ve vücut farkındalık düzeyleri arasında ilişki saptanmadı (p>0,05).

Sonuç: Sağlık hizmet sağlayıcılarında da GETAT uygulamaları ve gıda takviyeleri kullanımındaki artış sağlıkla ilişkili bölümlerin müfredatına bu uygulamaların entegre edilmesi gerekliliğini ortaya koymaktadır. Ayrıca sağlıkla ilgili bölümlerde öğrenim gören öğrencilerin sağlıklı yaşam tarzı davranışlarının arttırılması konusunda farkındalıkları arttırılabilir.

Anahtar Kelimeler: Besin destekleri, Geleneksel tıp, Öğrenciler, Tamamlayıcı tedaviler

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Purpose: The aim of this study is to determine the experiences of the students studying in health-related departments regarding traditional and complementary medicine TCAM practices and use of dietary supplements, and to examine the relationship between these variables and physical activity and body awareness.

Method: The online questionnaire link of the study was sent to associate and undergraduate students studying in health-related departments of a state university. The online questionnaire included questions about demographic information, items about TCAM and dietary supplements, International Physical Activity Questionnaire-Short Form (IPAQ-FF), Body Awareness Questionnaire (BAQ). The data of 186 students (150 females, 36 males) who completed the questionnaire were analyzed.

Results: A total of 34.6% (n=65) of the participants experienced TCAM applications and 25.3% (n=47) had dietary supplementation experience. The most commonly experienced TCAM practices were 22% (n=41) massage, 10.8% (n=20) meditation, and 9.7% (n=18) phytotherapy; the most commonly used supplements were vitamin 17.2% (n=32) D, 14% (n=26) vitamin B-12, and 7% (n=13) vitamin C. 68.3% (n=127) of the participants were inactive, 8.1% (n=15) were minimally active, and 23.7% (n=44) were very active, with a mean BAQ score of 93.53±15.84. There was no relationship between the experiences of TCAM practices, use of dietary supplements, and physical activity and body awareness ($p>0.05$).

Conclusion: The increase in the use of TCAM practices and dietary supplements in health care providers reveals the necessity of integrating these practices into the curriculum of health-related departments. In addition, the awareness of students studying in health-related departments about increasing healthy lifestyle behaviors could be increased.

Keywords: Complementary therapies, Dietary supplements, Students, Traditional medicine

EXTENDED ABSTRACT

Background

Providing courses containing fundamental information on alternative treatment approaches and nutrition to students in health-related disciplines is crucial. This facilitates not only their understanding of various treatment methodologies but also empowers them to make informed health choices and guide future patients who opt for these modalities. This study aims to determine the experiences of students enrolled in health-related departments regarding traditional and complementary medicine (TCAM) practices and supplement utilization, and to examine the relationship between these variables and physical activity and body awareness.

Method

This cross-sectional and descriptive study included undergraduate and associate degree students enrolled in health-related departments at a state university. The survey comprised two sections: in the first part, the demographic data of the participants were questioned (age, gender, body mass index, department, and class), and the second part consists of questions about their previous TCAM experiences. This section encompassed a broad spectrum of TCAM applications, including meditation, acupuncture, chiropractic, homeopathy, cupping, dry needle, massage, leech therapy, herbal treatment, hypnosis, reflexology, neural therapy, etc. and the use of supplements such as vitamin D, vitamin C, B-12, multivitamin, omega 3-6, folic acid, collagen, magnesium, sports performance enhancers, slimming products, etc. In addition, the International Physical Activity Questionnaire-Short Form (IPAQ-SF) and Body Awareness Questionnaire (BAQ) were used to evaluate the level of physical activity and body awareness, respectively.

Results

A total of 186 students, 150 female and 36 male, with an average age of 21.26±3.46 years, participated in the study. 34.6% (n=65) of the participants had previous TCAM application experience. The average number of TCAM experiences was 1.88±1.21 (range: 1-7). 25.3% (n=47) of the participants were using supplements. The average number of supplements used was 2.26±1.36 (range: 1-6).

Among TCAM practices experienced by participants, massage was the most commonly reported at 22% (n=41), followed by meditation at 10.8% (n=20), and herbal therapy at 9.7% (n=18). Acupuncture, chiropractic treatment, cupping, and dry needling were each experienced by 3.8% (n=7) of participants. Leech therapy, hypnosis, reflexology, and neural therapy were less frequently reported, with each being experienced by 1.6% to 1.1% of participants, respectively.

The dietary supplements used by participants were as follows: vitamin D was the most prevalent at 17.2% (n=32), followed by vitamin B-12 at 14% (n=26), and vitamin C at 7% (n=13). Multivitamins were reported by 4.8% (n=9) of participants, while magnesium and Omega 3/6 were each used by 3.8% (n=7). Additionally, folic acid and sports performance enhancers, including protein powder, glutamine, and L-carnitine, were each reported by 2.2% (n=4) of participants. Iron and other food supplements were each used by 1.6% (n=3), while collagen and propolis were each reported by 0.5% (n=1) of participants.

The IPAQ-SF score of the participants was 1213.83±2174.71 (range: 0-14265). Classification based on physical activity level revealed that 68.3% (n=127) were inactive, 8.1% (n=15) were minimally active, and 23.7% (n=44) were very active. The average BAQ score was 93.53±15.84 (range: 37-126). It was determined that the physical activity and body awareness levels of the participants did not change based on their experiences with TCAM applications and dietary supplement usage ($p>0.05$). Furthermore, no statistically significant relationship was observed between the number of TCAM practices experienced and physical activity ($p=.462$) or body awareness levels ($p=.190$). Similarly, there was no significant relationship found between the variety of supplements used and physical activity ($p=.449$) or body awareness levels ($p=.329$).

Conclusion

This study aimed to investigate the experiences of students enrolled in health-related departments concerning TCAM applications and their usage of dietary supplements and to reveal the relationship of these variables with physical activity and body awareness. It was found that 34.6% of the students had TCAM application experience, while 25.3% reported using dietary supplements. Among the TCAM practices, massage, meditation, and herbal therapy were the most frequently experienced. Similarly, the most commonly used dietary supplements were vitamin D, vitamin B-12, and vitamin C. No significant relationship was observed between students' experiences with TCAM applications, their usage of supplements, and their physical activity and body awareness levels. In this study, 68.3% of the participants were classified as physically inactive, while 8.1% were minimally active Additionally, participants had a medium level of body awareness. The lack of relationship between the variables could be attributed to the relatively low levels of physical activity among participants and their moderate level of body awareness. This suggests a potential need to enhance awareness among students enrolled in health-related departments and encourage the adoption of healthy

lifestyle behaviors. The curriculum in health-related departments, which predominantly focuses on traditional Western medicine, may influence students' beliefs and perceptions regarding the utilization of TCAM. Despite widespread reported use of TCAM among undergraduate students, it's noteworthy that students in health-related departments such as medicine, pharmacy, dentistry, nursing, and midwifery have experienced TCAM applications on themselves. Considering the significant role healthcare providers play in evaluating the TCAM applications utilized by patients and addressing inquiries related to these methods, receiving education on these practices and personally experiencing and researching them can help mitigate undesirable side effects and TCAM-drug interactions. While the utilization of TCAM methods, including among healthcare professionals, is becoming more prevalent in society, their clinical efficacy remains a subject of controversy, with scientific data being relatively insufficient. The findings of this study indicate that fundamental knowledge of TCAM methods should be incorporated into the curriculum of healthcare professionals, and their effectiveness should be substantiated by scientific research. Furthermore, future studies could explore the relationship between healthy lifestyle behaviors and the utilization of TCAM and dietary supplements. This may enhance healthcare providers' understanding of patients utilizing these approaches and facilitate the integration of different methods into patient care. The increasing prevalence of TCAM applications and dietary supplements among healthcare providers highlights the necessity of incorporating these practices into the curriculum of health-related departments. Moreover, enhancing awareness among students enrolled in such departments about promoting healthy lifestyle behaviors could yield significant benefits.

1.GİRİŞ

Geleneksel ve tamamlayıcı tıp (GETAT) tanımlamaları dinamik şekilde değişime uğramış ve uğramakta; tanımlamadaki zorluklara rağmen, tamamlayıcı, alternatif, geleneksel veya bütünleştirici olarak tanımlanan tedavilerin dünya çapında kullanımı giderek yaygınlaşmaktadır.[1] Türkiye'de GETAT "fiziksel ve ruhsal hastalıklardan korunma, bunlara tanı koyma, iyileştirme veya tedavi etmenin yanında sağlığın iyi sürdürülmesinde de kullanılan, farklı kültürlere özgü teori, inanç ve tecrübelere dayalı, izahı yapılabilen veya yapılamayan bilgi, beceri ve uygulamaların bütünü, Batı tıbbını destekleyici ve tamamlayıcı yöntemler" olarak tanımlamakta[2] ve bu uygulamaların kullanım oranı %60,5 ile %65,8 arasında bildirilmektedir.[3-4] Takviye edici gıdalar ise Tarım ve Orman Bakanlığı tarafından "normal beslenmeyi takviye etmek amacıyla, vitamin, mineral, protein, karbonhidrat, lif, yağ asidi, amino asit gibi besin öğelerinin veya bunların dışında besleyici veya fizyolojik etkileri bulunan bitki, bitkisel ve hayvansal kaynaklı maddeler, biyoaktif maddeler ve benzeri maddelerin konsantre veya ekstraktlarının tek başına veya karışımlarının, kapsül, tablet, pastil, tek kullanımlık toz paket, sıvı ampul, damlalıklı şişe ve diğer benzeri sıvı veya toz formlarda hazırlanarak günlük alım dozu belirlenmiş ürünler" olarak tanımlanmakta[5] ve Türkiye'de kullanım oranı %35,2-%60 arasında değişmektedir.[6,7]

Yaşam tarzı coğrafi, ekonomik, siyasi, kültürel ve dini faktörler arasında şekillenen bir yoldur.[8] Daha sağlıklı bir yaşam tarzına sahip kişiler spiritüel ve doğal terapileri yaşam biçimlerinin bir parçası olarak görme eğilimde olabilirler. Önceki çalışmalar yaşam tarzları daha sağlıklı olan kişilerin meditasyon, yoga, beslenme terapileri ve akupunktur gibi GETAT uygulamaları[9] ve takviye edici gıda[11] kullanma olasılıklarının daha yüksek olduğunu bildirmektedir. Ayrıca bu uygulamaları kullanan

yetişkinlerin kullanmayanlara göre, düzenli fiziksel aktivite ve egzersiz yapma ihtimallerinin de önemli ölçüde daha fazla olduğu saptanmıştır.[9,10] Aynı zamanda düzenli egzersiz yapanların egzersiz rutinlerinin bir parçası olarak da gıda takviyeleri kullandıkları bilinmektedir.[11] Beden farkındalığı içsel vücut duyumlarına dikkati odaklamayı ve bunların farkındalığını içermekte ve bedenin bilişsel bir temsili olan beden imgesi ile oldukça yakın ilişkilidir.[12] Geleneksel ve tamamlayıcı terapiler vücutla ilişkili algıları subjektif olarak değiştirme, vücut imajına ilişkin bilişleri düzenleme, beden-zihin bağlantısını geliştirme, benlik saygısını geliştirme ve olumsuz duyguları hafifletme yeteneğine sahip olabilir.[13] Ayrıca fiziksel aktivite artışının beden farkındalığını olumlu yönde etkileyebileceği,[14] egzersizin olumlu vücut imajında artış sağladığı da gösterilmiştir.[15]

Sağlıkla ilişkili bölümlerde alternatif tedavi yaklaşımları ve beslenmeyle ilgili temel bilgileri içeren derslerin öğrencilere sunulması, öğrencilerin farklı tedavi yaklaşımları hakkında bilgi sahibi olmasının yanı sıra hem kendi sağlık kararlarını almaları hem de gelecekte sağlık hizmet sağlayıcısı olarak bu yaklaşımları kullanan hastalarını yönlendirebilmeleri açısından önemlidir. Bu çalışmanın amacı, (a) sağlıkla ilgili bölümlerde öğrenim gören öğrencilerin GETAT uygulamaları ile ilgili deneyimleri ile takviye edici gıda kullanımlarının belirlenmesi, (b) bu değişkenler ile fiziksel aktivite ve vücut farkındalık düzeyleri arasındaki ilişkilinin incelenmesidir.

2.GEREÇ ve YÖNTEMLER

2.1.Araştırma ve Yayın Etiği

Bu kesitsel ve tanımlayıcı anket çalışmasının evrenini bir devlet üniversitesinin sağlıkla ilgili bölümlerinde öğrenim gören öğrencileri oluşturmuştur. Araştırma kapsamına alınan bölümlerdeki (Fizyoterapi ve Rehabilitasyon Fakültesi, Sağlık Bilimleri Fakültesi, Tıp Fakültesi ve Meslek Yüksek Okulları) öğrencilerden örneklem seçimine gidilmemiş çalışmaya katılmayı kabul eden 186 gönüllü lisans ve ön lisans öğrencisi ile çalışma gerçekleştirilmiştir. Çalışma Helsinki Deklarasyonu Prensiplerine uygun olarak gerçekleştirildi ve etik kurul onayı Pamukkale Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan (Tarih: 15.11.2022, Sayı: 16) alındı.

Öğrencilerin kendileri üzerinde GETAT uygulamaları deneyimlerini, takviye edici gıda kullanımlarını, fiziksel aktivite ve vücut farkındalık düzeylerini sorgulamak üzere araştırmacılar tarafından hazırlanan çevrimiçi anket formu sınıf haberleşme grupları (WhatsApp LLC, California, USA) aracılığıyla gönderildi. Çevrimiçi anket formunun ilk bölümünde katılımcılara çalışma hakkında bilgi verilerek gönüllü onamları alındı ve çalışmaya katılmayı kabul eden 186 öğrencinin verileri analiz edildi.

2.2.Veri Toplama Araçları

Kişisel bilgi formu 2 bölümden oluşmaktadır. İlk bölüm öğrencilerin demografik verilerini (yaş, cinsiyet, vücut kitle indeksi, öğrenim görmekte olduğu bölüm ve sınıf), ikinci bölüm önceki GETAT deneyimlerini sorgulayan sorulardan oluşmaktadır. Bu bölümde, GETAT uygulaması (meditasyon, akupunktur, karyopraktik, homeopati, hacamat, kuru iğne, masaj, sülük tedavisi, bitkisel tedavi, hipnoz, refleksoloji, nöral terapi vb.) ile takviye edici gıda kullanımı (D vitamini, C vitamini, B-12 vitamini, multivitamin, omega 3-6, folik asit, kollajen, magnezyum, sportif performans arttırıcılar, zayıflatıcı ürünler vb.) deneyimi ve tercih edilen uygulama türleri hakkında verileri içeren sorular yer almaktadır.

Uluslararası Fiziksel Aktivite Anketi-Kısa Formu (UFAA-KF) katılımcıların fiziksel aktivite düzeyi-

nin belirlenmesi amacıyla kullanıldı. 7 maddeden oluşan UFAA-KF'nin Türkçe geçerlilik ve güvenilirliği Saglam ve ark. tarafından yapılmıştır. Fiziksel aktivite düzeyi yürüme (3.3 MET), orta şiddetli aktivite (4.0 MET) ve şiddetli aktivitelerin (8.0 MET) süre (dakika) ve frekans (günler) bilgileri ile hesaplanmaktadır. Aktivitenin MET değeri, dakika cinsinden süre ve yapılan gün sayısı çarpılarak toplam skor elde edilmektedir. Çok aktif kategorisi minimum 1500 MET-dk/hafta skoru olan haftada haftada en az 3 gün şiddetli aktivite yapan veya minimum 3000 MET-dk/hafta skoru olan haftada 7 gün yürüme, orta şiddetli veya şiddetli aktivite kombinasyonuna sahip bireyleri içermektedir. Minimal aktif kategorisi haftada en az 3 gün, günde en az 20 dakika şiddetli aktivite yapan, haftada en az 5 gün orta şiddetli aktivite yapan veya her gün en az 30 dakika yürüyen, minimum 600 MET-dk/hafta skoru olan haftada en az 5 gün yürüme, orta şiddetli veya şiddetli aktivite kombinasyonuna sahip bireyleri içermektedir. İnaktif grup ise bu iki koşulu sağlamayanlardır.[16]

Vücut Farkındalık Anketi (VFA) katılımcıların vücut farkındalık düzeyinin değerlendirilmesi için kullanıldı. Türkçe uyarlaması Karaca ve Bayar tarafından yapılmıştır. Anket vücut döngüleri ve ritimlerine duyarlılık, normal işleyişteki küçük değişiklikleri tespit etme ve bedensel reaksiyonları tahmin etme yeteneği gibi vücutla ilgili durumları belirlemeyi amaçlayan 18 madde ve 4 alt bölümden oluşmaktadır. Alınabilecek en düşük puan 18, en yüksek puan 126'dır ve yüksek skorlar vücut farkındalığındaki artışı gösterir.[17]

2.3.İstatistiksel Analizler

Verilerin istatistiksel analizleri SPSS 24.0 (IBM Corp. Released 2016. IBM SPSS Statistics for Mac, Version 24.0. Armonk, NY: IBM Corp.) paket program ile yapıldı. Tanımlayıcı istatistikler yüzde, ortalama±standart sapma ve minimum-maksimum değer olarak verildi. Katılımcıların fiziksel aktivite ve vücut farkındalık düzeylerinin GETAT uygulamaları deneyimleri ve takviye edici gıda/vitamin kullanımına göre karşılaştırılması amacıyla Mann-Whitney U testi kullanıldı. Deneyimlenen GETAT uygulamaları sayısı ve kullanılan takviye edici gıda çeşitliliği ile fiziksel aktivite ve vücut farkındalık düzeyleri arasındaki ilişki Spearman korelasyon analizi ile incelendi. $p<0,05$ istatistiksel olarak anlamlı kabul edildi.

3.BULGULAR

Çalışmaya yaş ortalamaları 21,26±3,46 yıl olan, 150 kadın, 36 erkek toplam 186 öğrenci katıldı. Araştırmaya fizyoterapi ve rehabilitasyon fakültesinden 87 (%46,8), terapi ve rehabilitasyon bölümünden 85 (%45,7) ve sağlıkla ilgili diğer bölümlerden 14 (%7,5) öğrenci katıldı. Katılımcıların kişisel bilgi formu verilerinin dağılımı Tablo 1'de gösterildi.

Katılımcıların %34,6'sı (n=65) daha önce GETAT uygulaması deneyimi olduğunu belirtti. Bu katılımcıların ortalama deneyimlediği GETAT sayısı 1,88±1,21 (aralık: 1-7) idi. Katılımcıların %25,3'ü (n=47) ise takviye edici gıda kullandığını belirtti. Kullanılan takviye edici gıda sayısı ortalama 2,26±1,36 (aralık: 1-6) idi. GETAT uygulamaları arasında en çok deneyimlenen uygulamalar sırası ile %22 (n=41) masaj, %10,8 (n=20) meditasyon, %9,7 (n=18) bitkisel tedavi, %3,8 (n=7) akupunktur, %3,8 (n=7) kayropraktik tedavi, %3,8 (n=7) hacamat, %3,8 (n=7) kuru iğne, %1,6 (n=3) sülük, %1,6 (n=3) hipnoz, %1,6 (n=3) refleksoloji ve %1,1 (n=2) nöral terapi idi (Şekil 1). Kullanılan takviye edici gıdalar ise sırasıyla %17,2 (n=32) D vitamini, %14 (n=26) B-12 vitamini, %7 (n=13) C vitamini, %4,8 (n=9) multivitamin, %3,8 (n=7) magnezyum, %2,2 (n=4) Omega 3/6, %2,2 (n=4) folik asit, spor performans arttırıcılar %2,2 (n=4) (protein tozu, glutamin, L-karnitin vb.), %1,6

(n=3) demir, %1,6 (n=3) gıda takviyeleri, %0,5 (n=1) Kollajen ve %0,5 (n=1) propolis idi (Şekil 2). Katılımcıların UFAA-KF skoru 1213,83±2174,71'di (aralık: 0-14265) ve katılımcılar fiziksel aktivite düzeyine göre sınıflandırıldığında %68,3'ü (n=127) inaktif, %8,1'i (n=15) minimal aktif ve %23,7'ü (n=44) çok aktifti (Şekil 3). Katılımcıların VFA skoru ortalama 93,53±15,84'tü (aralık: 37-126).

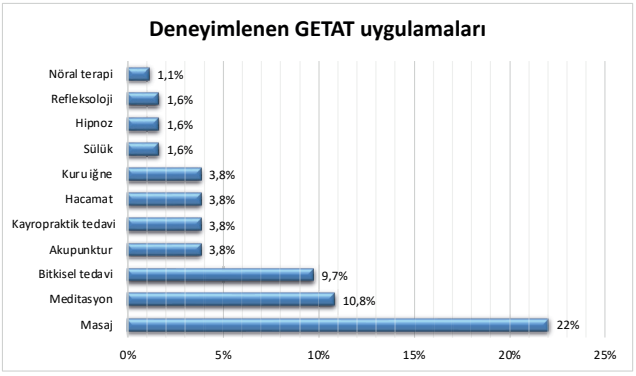
Tablo 1.

Öğrencilerin demografik verileri

	Ort ± SS	Min-Max
Yaş	21,26±3,46	17-39
Vücut kitle indeksi	22,49±4,13	15,84-46,57
	n	%
Cinsiyet		
Kadın	150	80,6
Erkek	36	19,4
Program		
Lisans	87	46,8
Önlisans	99	53,2
Sınıf		
1	69	37,1
2	44	23,7
3	16	8,6
4	53	28,5
5	4	2,2
Bölüm		
Fizyoterapi ve rehabilitasyon fakültesi	87	46,8
Hemşirelik bölümü	8	4,3
Tıp fakültesi	4	2,2
Terapi ve rehabilitasyon bölümü	85	45,7
Tıbbi hizmetler ve teknikler bölümü	2	1,1
n: öğrenci sayısı, %: yüzde		

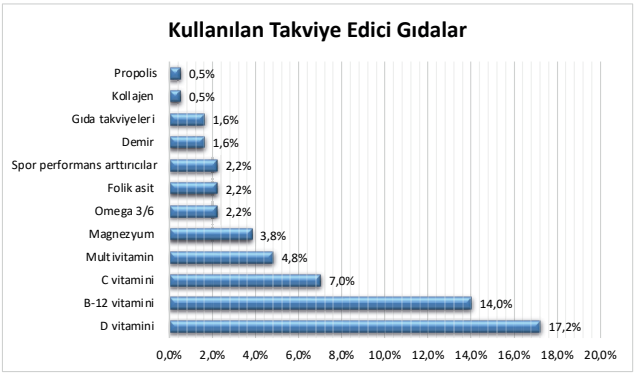
Şekil 1.

Deneyimlenen GETAT uygulamaları



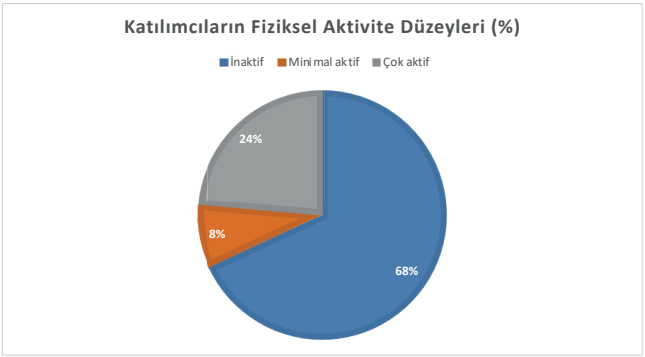
Şekil 2.

Kullanılan takviye edici gıdalar



Şekil 3.

Katılımcıların fiziksel aktivite düzeyine göre sınıflandırılması



Katılımcıların fiziksel aktivite ve vücut farkındalık düzeylerinin GETAT uygulamaları deneyimleri ile takviye edici gıda kullanımına göre değişiklik göstermediği saptandı (p>0,05) (Tablo 2). Deneyimlenen GETAT uygulamaları sayısı ile fiziksel aktivite (p=,462) ve vücut farkındalık düzeyleri (p=,190) arasında; kullanılan takviye edici gıda çeşitliliği ile

Tablo 2.

Öğrencilerin fiziksel aktivite ve vücut farkındalık düzeylerinin GETAT uygulamaları deneyimleri ve takviye edici gıda kullanımına göre karşılaştırılması

	GETAT deneyimi			Takviye edici gıda kullanımı		
	Evet Ort±SS (n=65)	Hayır Ort±SS (n=121)	p	Evet Ort±SS (n=47)	Hayır Ort±SS (n=139)	p
UFAA-KF	1117,15±1703,68	1273,41±2427,58	0,501	945,22±1708,88	1311,27±2320,55	0,324
VFA	95,77±14,52	92,33±16,44	0,204	91,60±15,37	94,19±16,00	0,236

Tablo 3.

Deneyimlenen GETAT uygulamaları sayısı ve kullanılan takviye edici gıda çeşitliliği ile fiziksel aktivite ve vücut farkındalık düzeyleri arasındaki ilişki

	Deneyimlenen GETAT uygulamaları sayısı		Kullanılan takviye edici gıda çeşitliliği	
	r	p	r	p
UFAA-KF	,063	,462	-,065	,449
VFA	,097	,190	-,072	,329

fiziksel aktivite (p=,449) ve vücut farkındalık düzeyleri (p=,329) arasında istatistiksel olarak anlamlı ilişki saptanmadı.

4.TARTIŞMA

Bu çalışmada, sağlıkla ilgili bölümlerde öğrenim gören öğrencilerin GETAT uygulamaları ile ilgili deneyimleri ile takviye edici gıda kullanımlarını incelemek ve bu değişkenlerin fiziksel aktivite ve vücut farkındalığı ile ilişkisini ortaya koymak amaçlandı. Öğrencilerin %34,6'sının GETAT uygulaması deneyimine sahip olduğu, %25,3'ünün takviye edici gıda kullandığı saptandı. En sık deneyimlenen GETAT uygulamaları masaj, meditasyon ve bitkisel tedavi iken; en sık kullanılan takviye edici gıdalar D vitamini, B-12 vitamini ve C vitamini idi. Öğrencilerin GETAT uygulamaları ile ilgili deneyimleri, takviye edici gıda kullanımları ile fiziksel aktivite ve vücut farkındalık düzeyleri arasında ilişki saptanmadı.

Türkiye'de ve dünyada GETAT uygulamaları ve gıda takviyeleri kullanımına olan ilgi artışının pek çok nedeni vardır. Bireyler algılanan yarar ve güvenlik, erişilebilirlik, bütünsel ve girişimsel olmayan yaklaşımları içermesi, arkadaşlar, aile ve sosyal ağlar gibi kitle iletişim araçlarından etkilenme, diğer tedavilerden memnuniyetsizlik, çaresizlik gibi amaçlarla GETAT uygulamalarını;[1,18] sağlığı koruma ve geliştirme, hastalıkların tedavisi, zindelik ve performansı arttırma, bağışıklık sistemini güçlendirme, kilo kaybı gibi sebeplerle de takviye edici gıda kullanımını tercih edilebilmektedir.[19] Bununla birlikte beslenmenin sağlığın korunmasındaki rolü konusunda artan farkındalık ve günümüz gıdalarının vitamin bakımından yetersiz olduğuna dair yaygın inanışlar[20], sentetik ilaçlardan daha doğal, sağlıklı ve güvenli olduklarının düşünülmesi ve hekim reçetesi olmadan kolaylıkla temin edilebilmeleri de gıda takviyelerine olan ilginin ve tüketimin hızla artışına yol açmıştır.[21] Dünya Sağlık Örgütü'ne üye ülkelerin %88'i bitkisel ilaçlar, akupunktur, yoga, yerel terapiler gibi geleneksel ve tamamlayıcı müdahaleleri kullan-

makta ve kullanım oranları ile kullanılan yöntemler ülkeler arasındaki kültürel özelliklere, inançlara, yaşam tarzına göre farklılık göstermektedir.[22]
Sağlıkla ilişkili bölümlerdeki öğrencilerin müfredatlarının geleneksel Batı tıbbına dayalı olması öğrencilerin GETAT kullanımına ilişkin inanç ve algılarını kaçınılmaz biçimde etkileyebilir. Bununla birlikte lisans öğrencilerinde bu uygulamaların kullanımı oldukça yaygın olarak bildirilmiş; tıp fakültesi ve eczacılık,[23] diş hekimliği,[24] hemşirelik ve ebelik[25] gibi sağlıkla ilgili bölümlerde öğrenim gören öğrencilerin GETAT uygulamalarını kendileri üzerinde deneyimledikleri rapor edilmiştir. Sağlık hizmet sağlayıcılarının hastaların mevcut kullandığı GETAT yöntemlerini değerlendirme ve bu uygulamalara ilişkin soruları yanıtlamada önemli rol oynadığı düşünüldüğünde, bu uygulamalar hakkında eğitim almaları, uygulamaları kendilerinin deneyimlemiş ve araştırmış olmaları istenmeyen yan etkileri ve GETAT-ilaç etkileşimlerini azaltabilir.[18,25] Bu çalışmada katılımcıların %34,6'sı GETAT uygulaması deneyimlediğini %25,3 ise takviye edici gıda kullandığını belirtti. Genel popülasyondaki artışın yanı sıra sağlık profesyonellerinde de GETAT uygulamaları ve gıda takviyeleri kullanımındaki artış sağlıkla ilişkili bölümlerin müfredatına bu uygulamaların entegre edilmesi gerekliliğini ortaya koymaktadır. Ayrıca sağlık ile ilişkili bölümlerdeki öğrencilerin GETAT hakkındaki bilgileri genellikle arkadaşlar/akrabalar, internet, televizyon ve diğer sağlık profesyonellerinden edindikleri ve bu bilgilerin yanıltıcı olabileceği göz önüne alındığında[26,27] bu uygulamaların kanıta dayalı potansiyel faydaları, etkinliği, güvenliği ve yan etkilerini içeren derslerin müfredatta yer alması önemlidir. Böylelikle sağlık hizmeti sağlayıcılarının bu yaklaşımları kullanan hastaları daha iyi anlamasına ve farklı yaklaşımları hasta bakımına dahil etmesine olanak sağlanabilir.

Türkiye'de sağlıkla ilgili bölümlerde öğrencilerin deneyimlediği GETAT uygulamaları sıklıkla bitkisel tedavi, kupa uygulaması, akupunktur, hipnoz, sülük olarak bildirilmiştir.[27-29] Bu çalışmada en sık tercih edilen üç yöntem masaj, meditasyon, bitkisel tedavi idi. Bu yöntemlerin daha fazla deneyimlenmiş olmasının nedeni Sağlık Bakanlığı "Geleneksel ve Tamamlayıcı Tıp Uygulamaları Yönetmeliği" kapsamında kabul gören uygulamalar arasında yer almaları nedeniyle yaygın kullanılıyor olmaları olabilir. Ayrıca D, B-12 ve C vitamini de en sık tercih edilen gıda takviyeleriydi ve bu sonuç aile hekimliği polikliniklerine başvuran sağlık personeli dışındaki 18-65 yaş aralığındaki genel popülasyonla da uyumluydu.[30] D vitamini eksikliği ve vitamin B12 yetersizliğinin ülkemizde de sık görülüyor olması kullanım sıklığındaki artışın nedeni olabilir.[31,32]

Mevcut çalışmada fiziksel aktivite ve vücut farkındalık düzeyi ile GETAT uygulamaları deneyimleri ve takviye edici gıda kullanımı arasında ilişki saptanmadı. Bununla birlikte literatürde yetişkin GETAT kullanıcılarının daha fazla egzersiz yapma, obezite olasılığında azalma,[33] daha fazla sebze, daha az yağ veya lipid tüketimi[34] gibi sağlıklı yaşam tarzı davranışları gösterdikleri saptanmıştır. Aynı şekilde gıda takviyesi kullananların dengeli beslenmeye çalışmak, düzenli egzersiz yapmak, sağlıklı kiloyu korumak gibi sağlıklı alışkanlıkları benimseme olasılıklarının daha yüksek olduğu bildirilmiştir.[10] Ayrıca fiziksel aktivitedeki artış beden farkındalığını da olumlu yönde etkileyebilir.[14] Ancak çalışmamızda katılımcıların %68,3'ü fiziksel olarak inaktif ve %8,1'i minimal aktifti. Vücut farkındalıkları ise orta düzeyde idi. Değişkenler arasında ilişki saptanmamış olmasının nedeni katılımcıların fiziksel aktivite düzeylerinin oldukça düşük olması ve vücut farkındalıklarının da orta düzeyde olması olabilir. Sağlıkla ilişkili bölümler-

de öğrenim gören öğrenciler sağlıklı yaşam tarzı davranışlarının arttırılması konusunda farkındalıkları arttırılmalı ve teşvik edilmelidir.

Tek bir üniversiteden veri toplanması ve katılımcıların öğrenim gördükleri bölümlerin homojen dağılmaması çalışmamızın kısıtlılıklarıdır. Ayrıca katılımcıların bu yöntemleri deneyimleme sebeplerini sorgulamadık. GETAT ve takviye edici gıda kullanımı herhangi bir hastalık durumunda geleneksel Batı tıbbı uygulamalarının tamamlayıcısı olarak kullanabilirken, koruyucu sağlık hizmetleri kapsamında sağlıklı yaşam tarzının bir parçası olarak da kullanılabilir. Bu sebeple gelecek çalışmalarda katılımcıların bu uygulamaları deneyimleme sebeplerinin araştırılması da önemlidir. İleri çalışmalarda sağlıklı yaşam tarzı davranışları ile GETAT ve takviye edici gıda kullanımı arasındaki ilişki incelenebilir.

5.SONUÇ

Öğrencilerin yaklaşık üçte biri daha önce GETAT uygulamasını deneyimlediğini, dörtte biri ise takviye edici gıda kullandığını bildirdi. GETAT uygulamaları içerisinden en çok tercih edilen yöntemler masaj, meditasyon ve bitkisel tedavi iken takviyelerden ise D vitamini, B-12 vitamini ve C vitamini idi. Bu yöntemlerin sağlık profesyonelleri de dahil olmak üzere toplumda kullanımı giderek yaygınlaşsa da klinik etkinliği hala tartışmalı ve bilimsel veriler nispeten yetersizdir. Bu çalışma sonucunda GETAT yöntemlerine ilişkin temel bilgilerin sağlık profesyonellerinin müfredatına entegre edilmesi ve etkinliklerinin bilimsel çalışmalarla desteklenmesi gerektiğini düşündürmektedir.[35] Buna ek olarak ileri çalışmalarda sağlıklı yaşam tarzı davranışları ile GETAT ve takviye edici gıda kullanımı arasındaki ilişkiyi incelenebilir.

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Yazar Katkıları

Çalışma Konsepti / Tasarımı

[RS, NB, İG]; Veri Toplama: [RŞ, İG]; Veri Analizi/Yorumlama: [RŞ, NB, İG]; Yazı Taslağı: [RŞ, İG]; Teknik Destek / Malzeme Desteği: [RŞ, NB, İG]; İçeriğin Eleştirel İncelemesi: [NB]; Literatür Taraması: [RŞ, NB, İG].

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Research Article/ Araştırma Makalesi

Percutaneous Endoscopic Gastrostomy Experience: Early and Late Complications

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Purpose: This study retrospectively evaluated the early and late complications of patients who had a percutaneous endoscopic gastrostomy (PEG) tube placed, discussed complication frequency of different diseases and finally pointed on some advices to reduce complications.

Method: The study was conducted with 99 patients who had a PEG tube placed in the endoscopy unit of a training and research hospital. Patients' age, gender, diagnosis, types of early and late complications, and complication development rates were evaluated.

Results: Mean age of the patients was 70.42±16.75(18-94) years and 48.50% were male. Early complications occurred in 11.10%, of which 6.05% were bleeding at the entry site of the PEG tube, and 5.05% were peristomal infection. 39.40% of the patients had late complications, including tube dislodgement in 18%, infection in 8.10%, aspiration pneumonia in 7.10% and other complications in 6%. No complications were observed in 51.50% of the patients, and early or late complications were observed in 48.50% of the patients. 2% of the patients had both early and late complications. The incidence of late complications was significantly higher in patients with Alzheimer's disease (p=0.027).

Conclusion: In the follow-up of patients who had a PEG tube placed in the previous six months, the most common early complication was bleeding in 6.05%, and the most common late complication was tube dislodgement in 18%. Despite its potential complications, the PEG tube is a safe method for long-term enteral feeding. Alzheimer patients are at risk for late complications more than other diseases.

Keywords: Enteral feeding, Percutaneous endoscopic gastrostomy, Early complications, Late complications

1.INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) is the procedure of inserting a tube directly into the stomach through the abdominal wall to provide nutritional support to patients who have a functional gastrointestinal tract but cannot be fed orally and require long-term enteral feeding.[1] The PEG tube was first used by Gauderer and Ponsky in 1980.[2] PEG is preferred because it does not require surgery, the tube can be used for a long time, and it is cheaper than other feeding methods.[3,4,5] In the literature, the rate of minor complications after PEG tube placement has been reported as 8-30%, and the rate of major complications as 1-4%.[6] Some complications occur immediately, while others develop when the gastrostomy tract matures. Minor complications of the PEG tube include wound infection, buried bumper syndrome (BBS), tube occlusion, tube edge leakage, and tube dislodgement. Major complications are bleeding, necrotizing fasciitis, perforation, ileus, gastrocolic fistula and aspiration pneumonia.[6]

Elderly patients with comorbidities and infections appear to be at higher risk of developing complications.7 Most complications are minor, but major complications, in rare cases, can result in death.[4] Early recognition of complications provides fast

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and effective treatment.[8]

In the literature, studies have been conducted mostly on minor and major complications in patients with PEG tube placed.[9,10] A study in Italy evaluated patients who underwent PEG tube placement for early and late complications.[11] There have been few studies in our country that evaluate early and late PEG complications together.[12]

This study was conducted to evaluate the types and rates of early and late complications associated with PEG tube.

2.MATERIALS and METHODS

2.1.Ethical Statements

Ethics committee approval was obtained before starting the study. (Health Sciences University, Ümraniye Training and Research Hospital Ethics Committee, meeting date: 24 November 2022, decision number: 01/353). All procedures involving human participants comply with ethical standards set by the institutional and national research committee. and the Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

The study was carried out with 99 adult patients who underwent PEG in an endoscopy unit of a training and research hospital between 01.01.2022 and 30.06.2022. The patients' age, diagnosis, demographic characteristics, early and late complications were evaluated in the study. Complications that developed within the first 1 week after PEG tube placement were considered as early complications, and those that developed between 8 days and 3 months were considered as late complications. Early and late complications were recorded retrospectively from patient files. In addition, the caregivers of the patients were called by phone and were asked about any records of hospitalization associated with PEG tubes in different hospitals in the last 3 months.

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software was used for statistical analysis. Descriptive statistical methods (mean, standard deviation, median, frequency, percentage, minimum, maximum) were used to evaluate the study data. The fit of the quantitative data to normal distribution was tested with the Shapiro-Wilk test and graphical examinations. The Mann-Whitney U test was used for comparisons between two groups of quantitative variables that did not show normal distribution. Pearson chi-square test and Fisher-Freeman-Halton exact test were used to compare qualitative data. Statistical significance was set at $p<0.05$.

3.RESULTS

Of the 99 patients included in the study, 48.50% were male and 51.50% were female. Their mean age was 70.42±16.75 (18-94) years. PEG placement indications were dementia in 11.10%, malignancy in 14.10%, Alzheimer's disease in 19.20%, stroke in 27.30% and other (drowning, cardiac arrest, dyspnea and trauma) in 28.30% (Table 1).

Table 1.

Distributions of Descriptive Characteristics (n=99)

			n (%)
Gender	Male		48 (48.50)
	Female		51 (51.50)
Diagnosis	Dementia		11 (11.10)
	Alzheimer		19 (19.20)
	Malignancy		14 (14.10)
	Stroke		27 (27.30)
	Other		28 (28.30)
Age (year)	Mean±Sd	70.42±16.75	
	Median (Min-Max)	75 (18-94)	

Early complications were found in 11.10% of the patients participating in the study. Considering all the patients, bleeding was found in 6.05% of the patients and infection was found in 5.05% as an early complication (Table 2).

Table 2.

Distribution of Complications (n=99)

		n (%)
Early Complication	No	88 (88.90)
	Yes	11 (11.10)
	Bleeding	6 (6.05)
	Peristomal infection	5 (5.05)
Late Complication	No	60 (60.60)
	Yes	39 (39.40)
	Peristomal infection	8 (8.10)
	PEG tube dislocation	18 (18.20)
	Aspiration pneumonia	7 (7.10)
	PEG tube occlusion	1 (1)
	PEG tube perforation	1 (1)
	Buried bumper syndrome	2 (2)
	Peristomal leakage	2 (2)
Early or Late Complication	No	51 (51.50)
	Yes	48 (48.50)
Early and Late Complication	No	97 (98)
	Yes	2 (2)

39.40% of the patients had late complications. Considering all patients, late complications were PEG tube dislodgement in 18.20%, infection in 8.10%, aspiration pneumonia in 7.10%, buried bumper syndrome in 2%, peristomal leakage in 2%, PEG tube occlusion in 1% and PEG tube perforation in 1% (Table 2).

51.50% of the patients participating in the study had no complications compared to 48.50% with early or late complications. 2% had both early and late complications (Table 2).

There was no statistically significant difference between the gender, age and diagnosis of the patients according to the incidence of early complications ($p>0.05$). A statistically significant difference was found between patients'diagnoses according to the late complication incidence. Late complication rate was higher in Alzheimer's disease than other diagnoses ($p<0.05$) (Table 3).

Table 3.

Comparison of Descriptive Characteristics by Late Complications (n=99)

		Late Complications		p
		No (n=60)	Yes (n=39)	
Gender	Male	32 (53.30)	16 (41)	[a]0.231
	Female	28 (46.70)	23 (59)	
Diagnosis	Dementia	8 (13.30)	3 (7.70)	
	Alzheimer	7 (11.70)	12 (30.80)	[b]0.027*
	Malignancy	6 (10)	8 (20.50)	
	Stroke	17 (28.30)	10 (25.60)	
	Other	22 (36.70)	6 (15.40)	
Age (year)	Mean±Sd	69.48±16.66	71.87±17.02	[c]0.376
	Median (Min-Max)	71.50 (21-92)	77 (18-94)	

[a]Pearson Chi-Square Test
[b]Fisher Freeman Halton Test
[c]Mann Whitney-U Test
*p<0,05

4.DISCUSSION

PEG is indicated in patients who need long-term nutritional support, have a functional gastrointestinal tract, but have insufficient oral nutritional intake.[1] Minor and major complications can be seen in patients who are fed enterally with a PEG tube. These complications cause frequent hospitalizations, malnutrition and delay in the healing process.[6]

In our study, which we carried out to examine early and late complications in patients who had a PEG tube placed, patients' mean age was similar to the previous related studies in the literature.[1,9,13,14] Indications for PEG tube placement include cerebrovascular diseases, amyotrophic lateral sclerosis, Alzheimer's disease, dementia and head-neck cancers.[5,8,13,14] When the PEG tube placement diagnoses of the cases were examined in the study, it was seen that 27.30% stroke, 19.20% Alzheimer's, 14.10% malignancy, 11.10% dementia and 28.30% other diagnoses. In a study by Cortes et al. examining PEG tube placements in neurological diagnoses, 33.30% were due to cerebrovascular disease.[13] Alsaeed et al. examined caregivers' experiences of enteral feeding at home and found that PEG tube was placed in 48% of the patients as a result of stroke.[15] In the study by Coşkun and Arı (2019) evaluating the short and long-term results of PEG tubes, 84.40% of PEG tube placements was due to neurological diseases, other indications were multi-trauma, malignancy and septicaemia.[9] The diagnoses of the patients in our study were similar to those in the previous studies.

4.1.Early Complications

In our study, 11.10% of the patients experienced early complications, which included bleeding and infection. Post-procedural bleeding is a rare complication of PEG tube placement. Patients with coagulation disorders and using anticoagulants are at risk for bleeding.[16] An incidence of bleeding up to 2.50% has been reported after the procedure.[17] In our study, bleedings occurred in 6.05% of the patients but were not major bleedings that required transfusion. In the study of Stenberg et al. examining PEG tube complications, minor bleeding was reported in 2% of the cases.[7] Our high rates of bleeding complication result may be due to the use of anticoagulants for ahigh number of patients with neurological diagnoses.

The most common PEG tube-related complication is peristomal infection with an incidence of 5-25%.[18] Patients with diabetes, obesity, malnutrition, corticosteroid and immunosuppressive therapy are at risk for developing peristomal infection.[19] In our study, 5.05% of the patients had peristomal infection as an early complication (8.10% in late complications). In a study by Boland et al. examining the complications of home enteral fed patients, 46% of the subjects had stoma site infections.[20] In their study evaluating the major complications of PEG tubes, Keji et al. reported wound infection in 9.30% of the cases.[21] In another study by Demirci et al. evaluating PEG applications, peristomal infection developed in 3.50% of thepatients.[23] Our PEG tube peristomal infection findings were similar to the literature.

4.2.Late Complications

In our study, late complications occurred in 39.40% of the patients and included peristomal infection, PEG tube dislodgement, aspiration pneumonia, PEG tube occlusion, PEG tube perforation, BBS, and peristomal leakage. The most common tube-related complications were accidental removal of the PEG tube which may occur during patient care or when the patient pulls it off unintentionally (for example in dementia or delirium).[1] PEG tube dislodgement occurred in 18.20% of the patients in our study. Alivizatos et al. reported PEG tube dislodgement in their study 45.10% examining the long-term complications related to the feeding tube.[23] In the study of Boland et al., PEG tube dislodgement occurred in 24%of the cases.[20] Accidental PEG tube dislodgement in our study was found to be similar to the literature.

The causes of peristomal leaks include infections, gastric hypersecretion, malnutrition, immunodeficiency, and diabetes.[17] In our study, 2% of the patients had a leaking PEG tube. Kenji et al. not-

ed peristomal leakage in 2.10% of their subjects.[21] In a study by Çelik et al. examining the results of patients who had a PEG tube placed, peristomal leakage developed in 3.90%.[10] Peristomal leakage results in our study were also similar to the literature.

Aspiration pneumonia can occur as a result of feeding in supine position, neurological impairment, advanced age and the bolus feeding method. In our study, aspiration pneumonia occurred in 7.10% of the patients compared with 0.80% reported by Kenji et al.[21] and 1.20% by Demirci et al.[23] Our result may be associated with the high number of patients with neurological disorders, the frequent preference of bolus feeding (because of the high cost of pump sets), and the fact that the patient is not given a 30-degree sitting position during feeding.

BBS is seen in approximately 1% of patients with PEG tubes and is a serious complication.[24] In our study, BBS was seen in 2% of the patients compared with 0.30% reported by Kenji et al.[21] and 0.60% reported by Demirci et al.[22] The PEG tube care of two patients who developed BBS was performed by the health personnel in the nursing home in our study, suggesting that the nursing home health personnel do not receive adequate training on PEG care. Our results are similar to the literature, and patients with a PEG tube should be followed closely.

PEG tube occlusion can be seen after enteral feed (hypercaloric nutrition products) and drug administration. As preventive measures, feeding should be intermittent, and the tube should be flushed with 30-60 ml of water regularly before and after drug administration and every four hours in case of continuous (infusion) feeding. PEG tube occlusion has been reported to be between 23 and 35% in the literature.[17] In our study, PEG tube occlusion occurred in 1% of the patients. Boland et al. observed PEG tube occlusion in 30%.[20] In a study by Kartal et al. examining PEG tube complications and outcomes, occlusion of the PEG tube was reported as 2.70%.[25] Based on the results obtained in this study, it can be said that caregivers understood well, the training they received on the necessary precautions to prevent the tube from clogging.

5.CONCLUSION and SUGGESTIONS

In our study, early complications were bleeding and peristomal infection and late complications were PEG tube dislodgement, infection, aspiration pneumonia, BBS, PEG tube leaking, PEG tube occlusion, and PEG tube perforation.

Early and late complications of PEG tube were found to be consistent with the literature. Complications can be prevented by correct positioning of the external plate, good PEG placement technique and evidence-based care interventions in addition to clearly identifying the need for PEG.

To reduce complications, we recommend that caregivers should be given training at frequent intervals, education should be supported by audio-visual tools such as video-DVD, and the educator should observe the caregiver at least once while PEG dressing.

Conflict of interest statement

The authors declared that there was no conflict of interest.

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Ethics approval

The research followed the ethical guidelines established by the Helsinki Declaration and its

later revisions, or those of an equivalent kind. This study was approved by the ethics committee of Umraniye Training and Research Hospital in 24 November 2021 with the letter numbered B.10.1.TKH.4.34.H.GP.0.01/353.

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Research Article/ Araştırma Makalesi

Effectiveness of Platelet Markers in Estimating the Amount of Intraoperative Bleeding in Vertebra Surgery

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Purpose: One of the most important steps in perioperative bleeding management is the predetermination of the patient at risk. Even if there is no hemostatic abnormality in vertebral surgery, which is a major surgery, severe bleeding can be encountered and many perioperative blood transfusions might be required. In this study; we investigated the effectiveness of preoperative mean platelet volume (MPV), platelet distribution width (PDW), plateletcrit (PCT), mean platelet volume lymphocyte count ratio (MPVLR), and platelet count to lymphocyte count ratio (PLR) values in predicting the amount of intraoperative bleeding in patients who will undergo vertebral surgery.

Method: Preoperative MPV, PDW, PCT, MPVLR, PLR values and demographic data such as gender, age, ASA score and body mass index (BMI) were recorded in patients scheduled for vertebral surgery in the neurosurgery clinic. In addition, the duration of surgery, the number of vertebral transpedicular screwing and laminectomy levels as surgical procedure were recorded. The amount of intraoperative bleeding was obtained by calculating the amount of blood accumulated in the aspirator and the amount of blood in the sponges during the operation.

Results: Of the 63 patients included in the study, 60.3% (n=38) were female and 39.7% (n=25) were male. The mean age of the patients was 54.7 ± 11 years and the mean BMI was 29.6 ± 4.6. No correlation was found between the amount of bleeding and gender, age, MPV, PDW, PCT, MPVLR, or PLR values. A significantly high correlation was found between amount of bleeding and BMI, duration of surgery, and the number of transpedicular screwing segments.

Conclusion: Platelet markers do not appear to have an effect on the amount of bleeding. However; as the BMI increases, the duration of surgery prolongs and the number of transpedicular screw segments increases for which the amount of bleeding increases.

Keywords: Intraoperative bleeding amount, Mean platelet volume, Mean platelet volume lymphocyte ratio, Platelet distribution width, Plateletcrit, Platelet lymphocyte ratio

1.INTRODUCTION

Perioperative bleeding is an undesirable but inevitable complication of surgery. Bleeding control in the surgical field or insufficiency in hemostatic pathways are the two main causes of perioperative bleeding. One of the most important steps in perioperative bleeding management is the early identification of the patient at risk.

Coagulation tests and platelet counts are the parameters examined for preoperative evaluation before major surgery. Mean platelet volume (MPV, which indicates the size of platelets), platelet distribution width (PDW, which shows the size heterogeneity of platelets), plateletcrit (PCT, which is the percentage of platelets in circulation), MPV/lymphocyte count ratio (MPVLR), and platelet count/lymphocyte count ratio (PLR) are parameters that provide information about platelet functions.

As far as we know to date, there are no studies in the literature examining platelet markers as a predictor for intraoperative surgical bleeding in vertebra surgeries. In this study, we aimed to investigate the effectiveness of preoperative MPV,

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PCT, PDW, MPVLR and PLR values for predicting the amount of intraoperative bleeding in patients undergoing vertebra surgery.

2.MATERIALS and METHODS

This prospective, clinical observational study was conducted at Sakarya University Training and Research Hospital in accordance with the Declaration of Helsinki, after receiving approval from the Sakarya University Faculty of Medicine Non-Interventional Ethics Committee on November 9, 2020 (decision no: 71522473/050.01.04/566).

2.1.Patient Selection and Exclusion Criteria

Patients between the ages of 18 and 65 years who were classified by the American Society of Anesthesiologists (ASA) to fall within I–III risk groups and who would undergo elective surgery for lumbar vertebra stabilization, were included in our study. Those who declined to participate in the study, patients under 18 years and over 65 years old, patients in the ASA IV and higher risk groups, with a body mass index (BMI) of 35 and above, with low platelet count (<150,000) or diagnosed with platelet dysfunction, those who received anticoagulant or used antiplatelet drugs, who had previous vertebral surgery, patients with more than five segments of surgical level, and patients with liver failure and chronic renal failure were excluded from the study. Patients who met the inclusion criteria were identified from surgery lists. A day before the surgery, the patients were visited at the neurosurgery clinic. Written informed consent was obtained from patients who were informed about the study and agreed to participate. The study was conducted with a single surgical team to ensure standardization.

2.2.Collection of Data

Patient demographic data was collected for the study: age, gender, ASA score, height, weight, and BMI were recorded. MPV, PCT, PDW, PLR and MPV-LR values obtained from the hemogram sample taken in the ward before the operation was recorded. The total surgery time from the beginning to the end and the number of vertebral instruments and laminectomy levels performed as surgical procedures were recorded.

2.3.Calculation of Bleeding Amount

The total amount of bleeding that occurred during the surgery was calculated. First, the amount of aspirated blood was calculated by subtracting the amount of washing solution in the graduated bottles used in the surgical area from the amount accumulated in the aspirator at the end of the surgical procedure. In addition, at the end of the surgical procedure, the amount of blood collected in the sponges was calculated by subtracting the total dry sponge weight from the total weight of the bloody sponges used. In the weighing calculation, the average density of the blood (plasma + blood cells) was taken as 1060 kg/m3, and each gram on the precision scale was considered as 1 milliliter.[1]

2.4.Anesthesia Management

After the patients were taken to the operating room, peripheral venous cannulation was performed and 0.9% NaCl infusion was started. Electrocardiogram (ECG), pulse oximetry (SpO2), and noninvasive arterial blood pressure monitoring were performed on the patients for routine monitoring. Anesthesia induction was achieved intravenously with 2 mg/kg propofol (2%), 2 mcg/kg fentanyl, and 0.6 mg/kg rocuronium. After sufficient muscle relaxation was achieved, intubation was performed with a spiral-cuffed endotracheal tube (ETT). Neuromuscular blockade in patients was maintained with rocuronium at doses of 0.15 mg/kg at 30–45 minute intervals. Anesthesia was maintained with sevoflurane and an oxygen and air gas mixture with a minimum alveolar con-

centration (MAK) value of 1, with was performed using remifentanil infusion at a dose range of 0.05–0.25 mcg/kg/min. Approximately 30 minutes before terminating anesthesia, 1 mg/kg tramadol and 1 g paracetamol were administered intravenously for postoperative analgesic treatment. After the surgery was completed, the sevoflurane vaporizer was turned off. The effect of the neuromuscular agent was antagonized with 2 mg/kg sugammadex and when patient breathing was at an adequate volume, they extubated and taken to the postoperative recovery unit.

2.5.Statistical Analysis

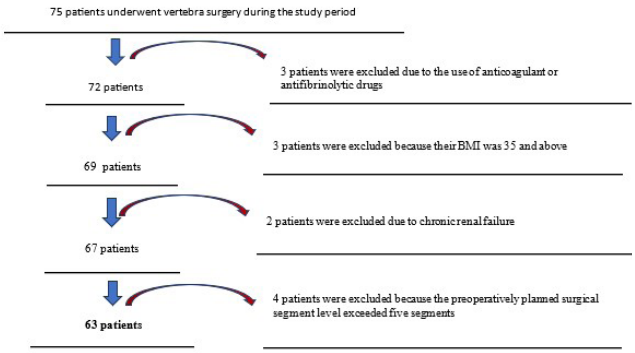
The SPSS 20 software program was used for statistical analysis of the data. Qualitative data were expressed as numbers and percentages. Quantitative data were expressed as mean and standard deviation was given. The correlation of quantitative data was evaluated with the Pearson correlation test. Normality test of continuous data was performed with Kolmogorov–Smirnov test. Comparison of repeated measurements of continuous variables was made with Student's t-test. Factors related to the total amount of bleeding were investigated by correlation test. Factors associated with the amount of intraoperative bleeding were examined by linear regression analysis. In all tests, the statistical significance level was taken as $p<0.05$. The minimum sample size required to detect an effect size of 0.4 between the two variables of interest with an $\alpha=0.05$ type 1 error and 80% power under the H0:p=0 hypothesis, was found to be 46 patients using G.Power-3.1.9.2.

3.RESULTS

In our study, a total of 75 patients who underwent surgery for vertebra stabilization at the neurosurgery clinic of Sakarya Training and Research Hospital were evaluated. The data from 63 patients were analyzed, three patients were excluded from the study due to the use of anticoagulant or antifibrinolytic drugs, three patients were excluded because their BMI was 35 and above, two patients were excluded because of existing chronic renal failure, and four patients were excluded because the preoperative planned surgical segment level exceeded five segments (Figure 1).

Figure 1.

Workflow diagram



Demographic data and platelet parameters of the patients are given in Table 1. The average amount of intraoperative bleeding in the patients was 298.73 ± 170.3 ml (60–920). The number of transpedicular screw segments and laminectomies performed as surgical interventions for vertebra stabilization and the amount of bleeding are given in Table 2.

The relationship between the amount of bleeding and the number of transpedicular screw segments was analyzed. Patients who underwent one and two segment transpedicular screw procedures lost 213 ± 95 ml of blood, and patients who underwent three segments or more transpedicular screw procedures lost 420 ± 180 ml of blood. The amount of bleeding was found to increase significantly in patients who underwent transpedicular screw procedures of three segments or more ($p=0.002$; Figure 2).

Table 1.

Demographic data and platelet parameters of the patients

Values are given as mean ± standard deviation, n, and percentage. n=number of patients. cm=centimeters. min=minutes. kg=kilogram. BMI=body mass index. MPV=mean platelet volume. PDW=platelet distribution width. PCT=Plateletcrit. MPVLR=mean platelet volume/lymphocyte count ratio. PLR=platelet count/lymphocyte count ratio.

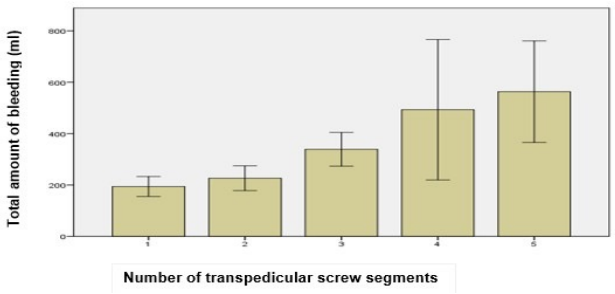
Total number of patients (n)	63
Gender, n (%)	
Female	38 (60.3%)
Male	25 (39.7%)
ASA, n (%)	
I	7 (11.1%)
II	31 (49.2%)
III	25 (39.7%)
Age (year)	54.0 ± 11.0
Size (cm)	161.6 ± 21.8
Weight (kg)	79.0 ± 12.0
BMI (kg/m^2)	29.2 ± 4.6
Surgery duration (min)	125.3 ± 28.6
MPV	8.5 ± 1.3
PDW	18.2 ± 1.1
PCT	0.21 ± 0.06
MPVLR	4.0 ± 2.0
PLR	113.9 ± 46.7

The relationship between the amount of bleeding and the number of transpedicular screw segments was analyzed. Patients who underwent one and two segment transpedicular screw procedures lost 213 ± 95 ml of blood, and patients who underwent three segments or more transpedicular screw procedures lost 420 ± 180 ml of blood. The amount of bleeding was found to increase significantly in patients who underwent transpedicular screw procedures of three segments or more (p=0.002; Figure 2).

When examining the demographic data of the patients and the amount of bleeding, no significant correlation was found between gender and age and the amount of bleeding (p=0.93 and p=0.16, respectively). A significant and moderate correlation was detected between BMI and the amount of bleeding (p <0.01; Table 4). When the relationship between platelet markers and bleeding amount was evaluated; no correlation was found between MPV (p=0.83), PDW (p=0.12), PCT (p=0.13), MPVLR (p=0.49), and PLR (p=0.83) values and the amount of bleeding (Table 3). On the contrary, a significantly high correlation was detected with the duration of surgery and the number of transpedicular screw segments, and a moderate correlation was detected with the number of laminectomies (p<0.01; Table 4).

Figure 2.

Relationship between total bleeding amount and number of transpedicular screw segments. Values are the mean and error bars represent standard deviation (95% CI).



To examine the factors associated with the amount of intraoperative bleeding, linear regression analysis was performed between the amount of bleeding and factors with moderate or a high degree correlation. BMI (p<0.01, β=0.22), surgical time (p<0.01, β=0.40), and number of transpedicular screw segments (p<0.01, β=0.37) were associated with the amount of bleeding. The effect of the number of laminectomies on the amount of bleeding was not found to be significant according to linear regression analysis (p=0.882, β=0.01; Table 5).

Table 2.

Distribution of bleeding amount according to surgery type and level

		n (%)	Amount of bleeding (ml)		
			Mean ± SD	Minimum (ml)	Maximum (ml)
Number of transpedicular screw segments	1	15 (23.8%)	194 ± 70	60	300
	2	22 (34.9%)	226 ± 108	90	475
	3	15 (23.8%)	339 ± 118	170	580
	4	5 (7.9%)	493 ± 220	270	720
	5	6 (9.5%)	563 ± 188	370	920
Laminectomy	0	5 (7.9%)	225 ± 197	60	500
	1	23 (36.5%)	229 ± 105	90	580
	2	28 (44.4%)	326 ± 151	95	700
	3	5 (7.9%)	369 ± 201	235	720
	4	2 (3.2%)	712 ± 293	505	920
Values are given as mean ± standard deviation, n, and percentage. n=number of patients. SD=standard deviation. ml=milliliter.					

Table 3.

Correlation of bleeding amount and platelet markers

		MPV	PDW	PCT	MPVLR	PLR
Total amount of bleeding	r	0.03	0.19	0.19	0.09	0.27
	p	0.83	0.12	0.13	0.49	0.83
*p<0.05 Pearson correlation test. MPV=mean platelet volume. PDW=platelet distribution width. PCT=plateletcrit. MPVLR=mean platelet volume/lymphocyte count ratio. PLR=platelet count/lymphocyte count ratio.						

Table 4.

Correlation of bleeding amount and operation characteristics

		Gender	Age	BMI	Duration of surgery	Number of transpedicular screw segments	Number of laminectomies
Total amount of bleeding	r	0.01	0.18	0.46	0.67	0.69	0.47
	p	0.93	0.16	<0.01*	<0.01*	<0.01*	<0.01*
*p<0.05 Pearson Correlation test. BMI=body mass index							

Table 5.

Factors affecting the amount of intraoperative bleeding according to the results of linear regression analysis

	Not standardized		Standardized	T	p value
	β	SD	β		
BMI (kg/m2)	9.65	3.45	0.22	-3.81	<0.01*
Surgery duration	2.39	0.64	0.40	3.69	<0.01*
Number of transpedicular screw segments	52.55	14.77	0.37	3.55	<0.01*
Number of laminectomies	2.83	19.01	0.01	0.14	0.882
β=regression coefficient. BMI=body mass index. SD=standard deviation.					

4.DISCUSSION

Although no correlation was found between the amount of intraoperative bleeding and MPV, PDW, PCT, MPVLR, and PLR values, a correlation was observed between the duration of surgery and the number of transpedicular screw segments applied and the amount of bleeding. Additionally, while no correlation was found between gender and age and the amount of bleeding, a significant correlation was found between high BMI and the amount of bleeding.

We examined all of these parameters in our study separately and in relation to studies in the literature that address situations that are prone to intraoperative bleeding or coagulation. Evaluating our findings based on the results of studies on susceptibility to intraoperative bleeding or coagulation might be important to understand the relationship to the existing literature. We believe that such a comparison might help to better understand the findings of our current study and also allow us to identify consistency or differences between information in the literature and our own findings.

It has been shown that male gender is a risk factor for intraoperative bleeding in patients with proximal humerus fractures.[2] Two different studies conducted on patients undergoing vertebra surgery showed that gender did not affect the amount of bleeding.[3,4] Similarly, in our study, no significant difference was detected between male and female patients in terms of the amount of intraoperative bleeding. It has been reported that increasing age correlates with an increase in the amount of bleeding in colon surgery, gastrectomy, and nephrectomy surgeries.[5–6] Furthermore, increasing age is a risk factor for bleeding during bariatric surgeries.[7,8] In patients who underwent retropubic prostatectomy and hepatic resection, age was not associated with the amount of bleeding.[9] Another study reported no correlation between perioperative blood loss and age in patients who underwent percutaneous kyphoplasty due to vertebral fracture.[10] In our study, no relationship was found between the age of the patients and the amount of surgical bleeding. This could be because the age distribution of the patients in our study was not homogeneous and that patients over the age of 65 were excluded from the study. In other studies involving prostatectomy and cystectomy surgeries, BMI has been reported to be a predictive variable in predicting increased blood loss.[11–12] Villavicencio et al. investigated the factors associated with blood loss of 172 patients who underwent vertebra surgery, and reported that patients with a BMI of more than 30 kg/m2 were associated with more intraoperative blood loss.[13] According to the data of a retrospective study on the possible causes of surgical occult bleeding in 143 patients who underwent vertebra surgery, the amount of bleeding increased in patients with a BMI greater than 24 kg/m2.[14] Similar to the results of various studies in the literature, a moderately significant correlation was found between BMI and bleeding amount in our study.

High platelet volume is an important variable in the pathophysiology of thrombosis. Large platelets produce more prothrombotic substances, such as thromboxane A2, B-thromboglobulin, P-selectin, glycoprotein-IIIa, and serotonin compared with normal-sized platelets.[15] For this reason, large volume platelets are more prone to adhesion and aggregation compared with smaller ones. In the literature, high MPV value is accepted as an independent risk factor for different clinical conditions.[16–17] It was observed that patients with pulmonary embolism had higher MPV values than those in the control group without a diagnosis of pulmonary embolism.[18] Increased MPV has been observed in cardiovascular diseases, cerebral

stroke, respiratory diseases, chronic renal failure, and rheumatoid diseases.[20] It has been reported that an MPV 11.6 fL or greater might be an independent risk factor for heart infarction in patients with coronary heart disease and that patients with high MPV have a higher risk of acute stroke than patients with normal MPV values.[19] In the literature, it was seen that high MPV value was associated with susceptibility to coagulation. In our study, no correlation was found between MPV values and the amount of bleeding. More studies are needed to confirm that the MPV value is not effective in predicting the amount of bleeding.

There are various studies in the literature investigating the relationship of PDW value with the prothrombotic process. It has been shown that platelet activity plays a central role in myocardial infarction and that high PDW is associated with prognosis in patients with CAD (coronary artery disease).[20,21] PDW was found to be higher in patients with ST-elevation myocardial infarction (STEMI) compared with those with stable CAD.20 In one study; the PDW value was an independent marker of STEMI in young patients and might reflect the prothrombotic state in this specific population, given that it has been reported that a 1 fL increase in PDW levels corresponds with 13.5% greater likelihood to be associated with STEMI in young people.[21] Also, PCT value, another platelet marker, is an independent marker for STEMI and might reflect the prothrombotic state, especially in the young patient population.[23] In the literature, we see that an increase in PDW and PCT values causes susceptibility to prothrombotic conditions such as myocardial infarction. In our study, we found that PDW and PCT values did not have a positive or negative effect on the amount of bleeding. More studies are needed to determine if these values are not effective in estimating the amount of bleeding.

When we examined the literature, we found that similar to the other platelet markers we discussed in our study, that there are no studies on MPVLR and PLR values regarding the amount of bleeding. Attention has been drawn to the importance of these values in various diseases associated with the thrombotic process. In a study of 266 stroke patients who received intravenous thrombolysis, it was thought that MPVLR could be used as an activity marker for prognosis in acute ischemic stroke patients receiving intravenous thrombolysis.[22] Studies have reported that patients with acute deep vein thrombosis have increased MPVLR and PLR values compared with the control group.[23] Also, patients with retinal vein occlusion had higher PLR values than the control group.[24] A meta-analysis by Wang et al. conducted in 2017, recommended PLR to be used routinely in the prognostic evaluation of pulmonary embolism.[25] Similarly, Telo et al. concluded that the PLR value increased in patients at high risk for acute pulmonary embolism and that the PLR value had an estimated predictive value for 3-month mortality.[26] Although there is no specific study in the literature on whether MPVLR and PLR values are directly related to the amount of bleeding, these markers could be valuable indicators in many diseases and are associated with thrombotic conditions. In our study, we did not detect a relationship between MPVLR and PLR values and the amount of bleeding. Various surgical clinical studies are needed to elucidate whether these values are predictive in estimating the amount of bleeding.

We examined the relationship between surgical time and the number of transpedicular screw segments and the amount of intraoperative bleeding. Zheng et al., in their study involving patients undergoing lumbar spine surgery, reported the number of surgical vertebra segments as a predictive factor in terms of intraoperative blood loss.[27] In

another study, Thompson et al. in their study of 311 patients who underwent vertebra surgery, reported that the amount of bleeding increased as the number of vertebral segments underwent surgery and the surgical time increased.[28] In agreement with similar vertebral surgery studies in the literature, we concluded in our study that the amount of bleeding increases proportionally with the surgical time and the number of transpedicular screw segments.

Our study has some limitations. To ensure standardization, we planned our study to be conducted in a single center and with a single surgical team to eliminate differences in operating room conditions, surgery, and anesthesia protocols. For these reasons, our most important limitation was that we performed a single-center study with a small number of patients. Another limitation was that the number of laminectomy and transpedicular screw segments performed in the patients was not distributed homogeneously.

5.CONCLUSION

We did not detect a correlation between the amount of intraoperative bleeding and patient gender, age, and platelet markers MPV, PCT, PDW, MPVLR, and PLR values. However, with secondary inferences we found that the amount of bleeding increased corresponding to increased patient BMI, surgery time, and the number of transpedicular screw segments applied.

In many clinics around the world; conventional coagulation parameters and platelet counts are first evaluated in terms of bleeding risk during preoperative routine anesthesia evaluation. With this study, we wanted to draw attention to platelet markers that we think are ignored with the aim of gaining a broader perspective during the preoperative evaluation process. Although we did not determine the predictive relationship between platelet markers and the amount of intraoperative bleeding, we believe that many different clinical studies are needed to confirm this.

Ethics Committee Approval

Sakarya University Faculty of Medicine Non-Interventional Ethics Committee November 9, 2020 (decision no: 71522473/050.01.04/566). The study was carried out following the international declaration and guidelines.

Conflict of Interest

No conflict of interest was declared by the authors.

Author Contributions

Concept – SÇ, OP; Supervision – OP, HK, ATT; Materials – SÇ, DC; Data Collection and Processing – SÇ, OP, HK; Analysis and Interpretation – OP, ATT; Writing –SÇ

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Research Article/ Araştırma Makalesi

The Effect of Proximal Femoral Nail and Position in the Femur on Clinical and Radiological Outcomes of Intertrochanteric Fractures

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Purpose: Intramedullary nail treatment for intertrochanteric fractures has gained widespread popularity in recent years. Predisposing factors for mechanical failure of the proximal femoral nail include lag screw position, tip apex distance, reduction quality, and the femoral neck/shaft angle (FNSA). Our study aimed to evaluate the effect of the position of the nail end on the mechanical failure rates and radiological parameters.

Method: The data of 118 patients who underwent proximal femoral nail repair due to intertrochanteric fractures were analyzed between June 2019 and September 2022. The patients were divided into three groups according to the proximal femoral nail end positioning of the femoral canal, and tip apex distance, FNSA, reduction quality, lag screw position, union time, and complications were evaluated on postoperative and follow-up radiographs.

Results: When all patients included in the study were evaluated, cut-out was observed in 9. The cut-out rates were significantly higher in the medial group (n=7, p=0.003). Regarding FNSA, there were statistically significant differences among all three groups (<0.001M-S, M-L, S-L). In the medial group, the superiorly located lag screw, and in the lateral group, the inferiorly located lag screw was higher than in the other groups(p<0.001)

Conclusion: It has been observed that placement of the distal tip of the nail in the canal affects both these parameters and clinical results, and the clinical and radiological results were worse in cases where the distal nail was medial to the canal.

Keywords: Intertrochanteric femur fracture, Proximal femoral nail, Tip apex distance, Reduction

1.INTRODUCTION

The incidence of intertrochanteric fractures is increasing every year.[1] The incidence of intertrochanteric fractures is expected to be 6.3 million in 2050.[2] Intertrochanteric femur fracture (IFF) is a common hip fracture, representing about 31–35% of all hip fractures.[3] In recent years, intramedullary nail treatment for intertrochanteric fractures has gained widespread popularity for treating trochanteric fractures.[4] Intramedullary fixation methods in treating intertrochanteric fractures have increased significantly in the last ten years.[5] Intramedullary fixation methods offer better biomechanical properties than Extramedullary fixation methods.[6] Due to the difficulties in obtaining anatomical reduction and low bone quality, which can result in eventual implant failure and high morbidity and mortality rates associated with geriatric patients, the treatment of unstable intertrochanteric fractures in the elderly has proven problematic.[7] Mechanical complication rates after intramedullary fixation of intertrochanteric fractures are between 2-13%.[8] Among these, lag screw cut out after reduction losses and varus collapse, excessive sliding of the lag screw, are frequently encountered.[9,10] Less frequently, fractures can be seen around the nail.[11] Among the predisposing factors are improper reduction, incorrect positioning of the lag screw, short tip-apex distance (TAD), and femur neck/shaft angle (FNSA)[12,13]. Studies have been conducted on the nail position in the distal femur in intertrochanteric fractures, and these studies are focused on lateral and anterior impingement and its related com-

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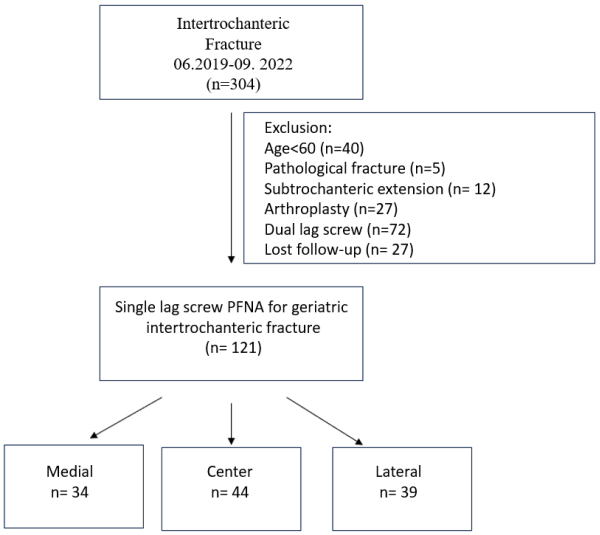
plications.[14,15] Due to proximal femur anatomical variations and canal sizes, difficulties may be encountered during nail application.[16] The nail may not be applied in the desired position. We planned a study to investigate the effect of nail position in the distal femoral canal on the lag screw position, TAD, FNSA, and clinical results.

2.MATERIALS and METHODS

The Institutional Review Board approval was obtained (IRB approval number: 2022-16/149). Retrospective review of consecutive patients aged 60 and above who underwent proximal femoral nailing for IFF in our clinic. Pathological fractures or intertrochanteric fractures with subtrochanteric extension were excluded from the study. Patients who underwent double lag or arthroplasty for intertrochanteric fractures other than proximal femoral nail anti-rotation (PFNA) were excluded from the study. Finally, 121 patients with at least one-year follow-up were included in the study. (Figure 1)

Figure 1.

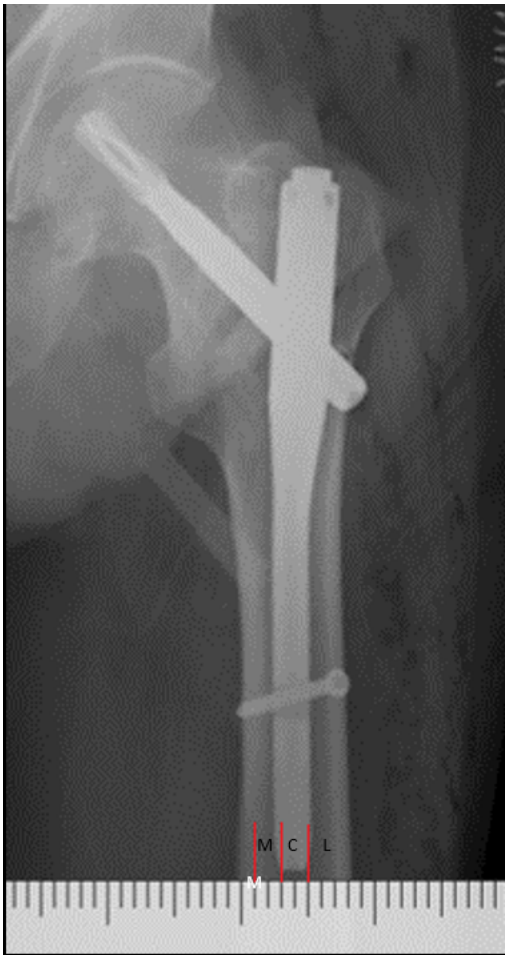
Patients' flow chart



Fracture types are defined according to the AO/OTA classification system.[17] All fractures were stabilized using short PFNA II (Asian version) with a centrum-collum-diaphyseal (CCD) angle of 130°. All surgeries were performed on a traction table, following the manufacturer's guide by one surgeon. 10 mm diameter nails were preferred in all cases. In all cases, nail distal locking was done with one screw. Intraoperative and postoperative radiographs, including anterior-posterior (AP) and lateral radiographs, were reviewed in all cases. The patients were mobilized on the 1st postoperative day, using a walker with as much weight as they could tolerate. Determination of the nail position within the femur on post-operative hip AP plain radiographs. (Figure 2)

Figure 2.

Evaluation of nail distal tip location on the postoperative hip anterior-posterior radiograph



According to the location of the nail at the distal end, it was examined in 3 groups: central, medial,

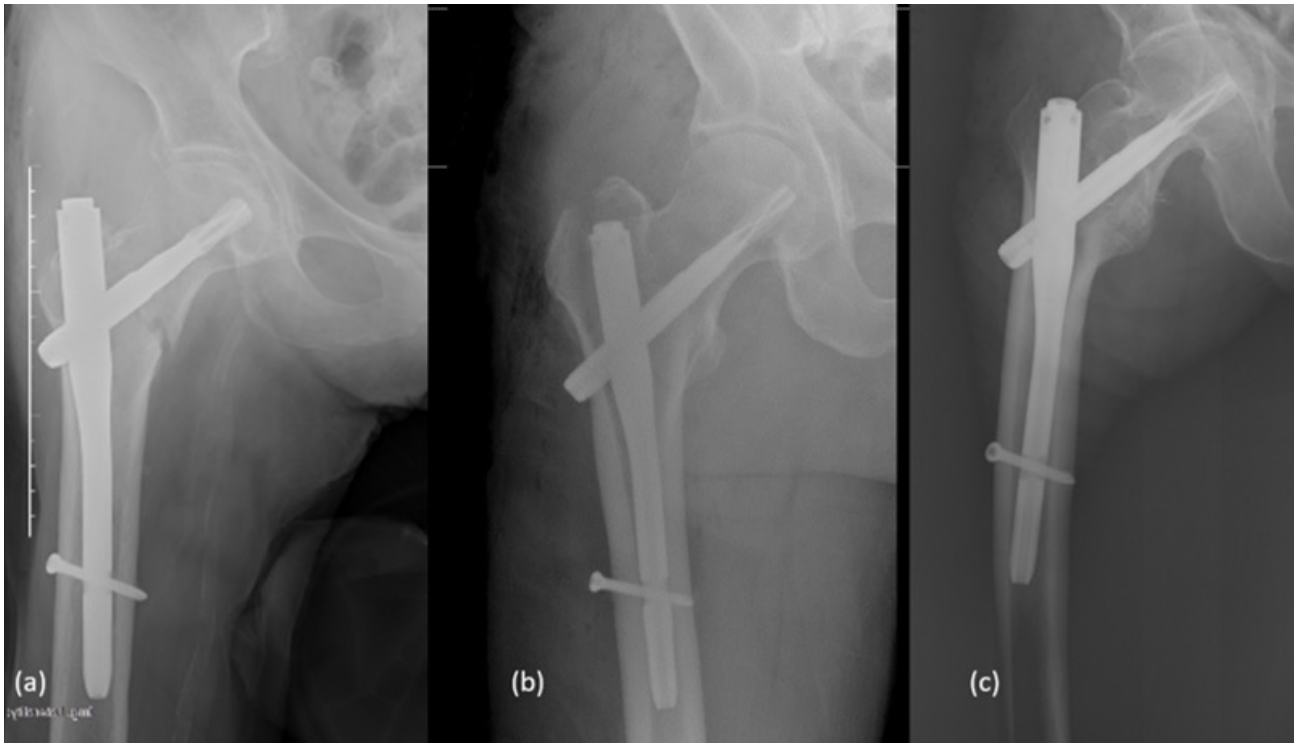
and lateral. (Figure 3) On the second postoperative day, postoperative radiographs were collected at the 1, 6, and 12-month follow-up. All images have been stored in the hospital digital archive, and digital ruler tools were used for measurements. TAD, FNSA, reduction quality, lag screw position, union time, and fractures around the implant were evaluated on postoperative follow-up radiographs. Reduction quality was graded as optimal, acceptable, and unacceptable according to the system of YC Yoon.[18] The lag screw position was assessed on radiographs as described by Cleveland et al.[19] The diameter of the medullary cavity was measured at the isthmus level using the known intramedullary nailing (IMN) diameter to correct measurement. The presence of callus in at least three cortices was interpreted in favor of fracture healing. The absence of pain during walking and the patient's ability to mobilize without support were evaluated as fracture healing. Changes in FNSA during clinical follow-ups were recorded. The data about re-operation needs and indications such as cut-out, implant breakage, fracture around the implant, nonunion, infection, and symptomatic implants were recorded.

2.1.Statistical Analysis

The data collected in the study were analyzed using the IBM SPSS 25.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics such as frequency (%), mean ± standard deviation (SD), and minimum, median, and maximum values were used to present the data. Different statistical tests were utilized for comparisons between the three groups based on the data type. The chi-square test was used for categorical data. The independent t-test was applied to parametric data with a normal distribution, allowing for the comparison of means between three independent groups. On the other hand, the Mann-Whitney U test was used for non-parametric data, which does not assume a normal distribution, and it compares the medians of three independent groups.

Figure 3.

According to the location of the nail end in the distal intramedullary area; (a) medial, (b) central, (c) lateral



3.RESULT

After the exclusion criteria, a total of 118 patients who were operated on for intertrochanteric fractures between June 2019 and September 2022 were included in the study. They were evaluated into three groups: 34 patients in the medial group, 45 in the center group, and 39 in the lateral group. There was no significant difference in demographic data such as age and gender and preoperative baseline data such as AO/OTA classification system.(Table 1) When the FNSA was examined, it was observed that the mean was 124.56±4.54° in the medial group, 130.56±3.20° in the central group, and 132.13±3.47° in the lateral group. There were differences in the FNSA evaluation in all three groups (p<0.001M-S. M-L, S-L). A statistically significant difference was found when the lag screw placement was compared according to the groups (p<0.001). In the medial group, the superiorly located lag screw, and the lateral group, the inferiorly located lag screw was higher than in the other groups. Mean TAD values were 23.59±2.49 in the medial group, 16.62±3.64 in the center group, and 19.05±2.88 in the lateral group (p<0.001). When the groups were evaluated in terms of reduction quality, poor reduction quality was observed in 6 patients in the medial group, one patient in the central group, and two patients in the lateral group, and a statistically high rate of poor reduction quality was observed in the medial group (p=0.004). When the lag screw cut-out rates were examined, they were significantly higher in the medial group (n=7, p=0.003). Three groups were compared in terms of femoral canal width. There was no statistically significant difference between the Medial Group (14.26±0.81), Center Group (14.03±0.70), and Lateral Group (14.11±0.84). (Table 2) When complications were examined, arthroplasty was performed as a result of 7 cut-outs in the medial group, 1 in the central group, and 1 in the lateral group. No difference was observed in all three groups regarding varus displacement that developed without cut-out below 10° in FNSA. While there was no difference in terms of union time in the medial and lateral groups, a difference was observed between the central and medial groups. Union was significantly higher in the medial group over six months than in the central group. Superficial infection was observed in 1 patient in each central and lateral group. The patients were fol-

Table 1.

Demographic and baseline data of patients

Group	Medial Group	Center Group	Lateral Group	p-value
Sex n (%)				
Female	31 (91.20%)	41 (91.10%)	36 (92.30%)	0.977
Male	3 (8.80%)	4 (8.90%)	3 (7.70%)	
Age				
Mean±SD	73.44±6.51	73.60±5.71	73.56±5.14	0.871
Min/Med/Max	65.00/71.50/87.00	65.00/72.00/87.00	65.00/72.00/86.00	
AO/OTA class n (%)				
A1.2	2 (5.90%)	4 (8.90%)	3 (7.70%)	0.941
A1.3	3 (8.80%)	4 (8.90%)	2 (5.10%)	
A2.2	22 (64.70%)	29 (64.40%)	29 (74.40%)	
A2.3	7 (20.60%)	8 (17.80%)	5 (12.80%)	
n: Number, Mean±SD: Mean and standard deviation, Min: Minimum, Med: Median, Max: Maximum, AO/OTA class n: AO/OTA classification number				

Table 2.

Postoperative variables and clinical outcomes comparison between the three groups.

	Medial Group	Center Group	Lateral Group	P value
Femoral canal width (mm)				
Mean±SD	14.26±0.81	14.03±0.70	14.11±0.84	0.313
Min/Med/Max	12.50/14.40/15.90	12.50/14.10/15.70	12.50/13.90/15.70	
Femur neck/shaft angle				
Mean±SD	124.56±4.54	130.56±3.20	132.13±3.47	<0.001
Min/Med/Max	115.00/125.00/132.00	120.00/130.00/137.00	122.00/132.00/139.00	<0.001$^{M\text{-}C.\ M\text{-}L}$
Tip apex distance				
Mean±SD	23.59±2.49	16.62±3.64	19.05±2.88	<0.001
Min/Med/Max	19.00/23.50/28.00	11.00/15.00/26.00	14.00/19.00/24.00	<0.001$^{M\text{-}C.\ M\text{-}L}$ 0.026C-L
Reduction quality				
Poor	6(17.60%)	1(2.20%)	2(5.10%)	0.004
Optimal	10(29.40%)	29(64.40%)	26(66.70%)	
Acceptable	18(52.90%)	15(33.30%)	11(28.20%)	
Lag screw position at the coronal plane				
İnferior	1(2.90%)	9(20.0%)	16(41.0%)	<0.001
Central	25(73.50%)	34(75.60%)	22(56.40%)	
Superior	8(23.50%)	2(4.40%)	1(2.60%)	
Lag screw position at the sagittal plane				
Posterior	7(20.60%)	7(15.60%)	8(20.50%)	0.928
Central	24(70.60%)	35(77.80%)	29(74.40%)	
Anterior	3(8.80%)	3(6.70%)	2(5.10%)	
Union time				
>6 month	3(8.80%)	2(4.40%)	4(10.30%)	0.018$^{M\text{-}C}$
<6 month	24(70.60%)	42(93.30%)	34(87.20%)	
Varus collapse <10 degrees without cut-out				
No	33(97.10%)	43(95.60%)	36(92.30%)	0.634
Yes	1(2.90%)	2(4.40%)	3(7.70%)	
Cut-out				
No	27(79.40%)	44(97.80%)	38(97.40%)	0.003
Yes	7(20.60%)	1(2.20%)	1(2.60%)	

Mean±SD: Mean and standard deviation, Min: Minimum, Med: Median, Max: Maximum, M: Medial, C: Center, L: Lateral, M-C: Medial – Center, M-L: Medial – lateral, C-L: Central - Lateral

lowed up with dressing and antibiotics. In the lateral group, a revision nail was applied to the patient due to a nail breakage in one patient. Data related to complications are given in Table 3.

Table 3.

Complications

Complication	Medial Group	Center Group	Lateral Group
Cut-Out	7 (19.40%)	1 (2.20%)	1 (2.50%)
Nail breakage	-	-	1 (2.50%)
Superficial infection	-	1 (2.20%)	1 (2.50%)

4.DISCUSSION

As a result of our study, fixation failure rates were significantly higher in cases where the distal tip of the nail was located medially (p=0.003). In patients where the distal end of the nail was medial, it was observed that the lag screw was placed superiorly at a higher rate compared to the other groups(p<0.001). When the reduction quality was evaluated, the poor reduction was higher in the medial group than in the other groups (p=0.004). No implant-related fracture was observed in any group due to the distal tip placement of the nail. The overall failure rate was 7.6% when all groups were evaluated together. Failure developed because of cut-out after progressive varus collapse. When the literature is examined, it is observed that the failure rates vary between 3-14%.[20] It is thought that the reason why the position of the lag screw is superior in the medial group is the superior orientation of the guide wire applied for the lag screw because of the medial placement of the nail end in the ao, even if anatomical reduction is achieved. Another reason for the order of the lag screw in the superior position in the medial group is the medial orientation of the nail after lateral entry and the deterioration of reduction due to the lateral entry point. As a result of the research, lateral entry constitutes a risk factor for mechanical failure in proximal femoral nail applications for intertrochanteric fracture.[20-22] When the FNSA was compared, the mean FNSA was found to be 124.56±4.54 degrees in the medial group. We think that the reason for the low FNSA in the medial group is the impingement of the nail in the medial cortex due to the lateral entry point and then the displacement of the fracture line into the varus by the effect of the lever. Jiamton et al. observed that fracture reduction losses occurred during nail application when the lateral entry point was preferred for proximal femoral nail application.[23] Even if the anatomical reduction was achieved during the operation, opening, and varus collapse in the fracture line associated with the wrong entry point were shown during nail application.[24] In the surgical treatment of femoral intertrochanteric fractures, failure rates have been shown to increase significantly in cases where FNSA was restored below 125°.[25] Mean FNSA was 124.56±4.54° in the medial group, and cut-out was observed in 7 patients. In the lateral and center groups, the FNSA was 132.13±3.47 and 130.56±3.20, respectively. In treating intertrochanteric fractures, fixation of the FNSA in the normal or slightly valgus position is recommended.[26,27] Lag screw placement in the inferior position in the coronal plane was found to be significantly higher in the lateral group. As a result of the research, there is a consensus that the ideal position of the lag screw is the center.[28] In addition, it has been shown that the inferior-center placement of the lag screw gives clinically and radiologically similar results to the center-center placement.[29] Fixation failure after cut-out in the lateral and central groups was observed only in 1 case in both groups, and no statistically significant difference was observed. In particular, after computational and biomechanical experimental studies, it has been shown that the inferior positioned lag screw applied from the denser inferior calcar region is mechanically superior.[30,31] Although the TAD dis-

tance was higher in the lateral group (19.05±2.88) due to the inferior-located lag screw compared to the medial group (16.62±3.64), no clinical difference was observed. It has been shown that inferior-positioned lag screws give equal or even better results than center-placed screws, even if the TAD distance is higher than 25mm.[29,31,32] In all cases included in the study, a single-size nail was applied. It has been shown that nail sizes do not affect clinical and radiological results, regardless of canal diameter. [33]

There are some limitations of this study. Retrospective nature of the study. Another limitation is the small study population due to follow-up losses. Changes in femoral bowing, which will affect the placement of the femoral nail in the femur, were not evaluated. Again, the analysis did not assess parameters such as the weight and height of the patients that would affect the femoral bowing.

5.CONCLUSION

There are many factors affecting the prognosis of intertrochanteric fractures. Among these factors, femur neck shaft angle, lag screw position, and TAD are frequently used. It has been observed that the placement of the nail end in the femur affects both these parameters and clinical results. It has been observed that the desired radiological parameters and clinical outcomes are better in cases where the nail distal is central and lateral. In addition, it was observed that the clinical and radiological results were worse in cases where the distal nail was medial in the canal. Cases where the nail distal is medial have been associated with a false entry point.

Conflict of interest statement

The authors declared that there was no conflict of interest during the preparation and publication of this article.

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Ethics Approval

This study was approved by Faculty of Medicine Clinical Research Ethics Committee (06.09.2022/2022-16/149). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. All participants gave their written informed consent to participate in the study.

Authors' Contributions

MFÇ: Data Curation, Methodology, Literature search, Writing – Original Draft , Writing – Review & Editing.

LH: Data Curation, Literature search, Writing – Original Draft . Supervision, Visualization.

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Research Article/ Araştırma Makalesi

Comparison of the Damage Results of Bullet and Pellet Ammunition in Firearm Injuries Causing Bone Fractures in the Extremities

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Purpose: The spectrum of firearm injuries (FI) is broad and challenging for physicians in terms of diagnosis and treatment. The bullets and pellet ammunition used in FI exhibit different ballistic patterns and cause quite different damage to the body. The aim of this study was to compare the outcomes of bullet and pellet injuries causing bone fractures in the extremities.

Method: The files of patients who were injured in their extremities due to civilian FI between 2016 and 2020 and who were followed up by the orthopedic clinic due to bone fractures were retrospectively analyzed. Age, gender, injured extremity, presence of infection, presence of vascular injury, presence of nerve injury, total number of operations, length of hospital stay and permanent sequelae were evaluated. Cases with missing files were excluded from the study. Evaluation criteria were compared under two main headings for bullet and pellet ammunition types.

Results: There were a total of 40 cases with a mean age of 43.5 years. The mean follow-up period was 41.5(24-61) months. 39 of the cases were male and 1 was female. There were 28 bullet injuries and 12 pellet injuries. Thirty-two of the cases were lower extremity injuries and 8 were upper extremity injuries. There were significant differences between ammunition type and number of operations (p=0.032). The length of hospital stay was significantly higher in the pellet group (p=0.024, p=0.024. Overall, 12.5% infection, 10% vascular damage, 17.5% nerve damage and 30% permanent sequelae occurred as a result of treatments. There were no significant differences between the groups in terms of infection, vascular injury, nerve injury and permanent sequelae.

Conclusion: It was concluded that pellet injuries require longer hospital stays and a higher number of surgeries compared to bullet injuries.

Keywords: Firearm injury, bullet, pellet, fracture, nerve damage

1.INTRODUCTION

The range of firearms injuries (FI) caused by bullets and pellets is quite broad, making diagnosis and treatment difficult for physicians.[1] FIs can range in severity from minor soft tissue injuries to vascular, nerve, and organ damage, and even death.[2,3] In FIs, the extremities are among the most affected areas.[3-5] Although the severity of the injury depends on the energy transmitted to the tissues rather than the type of weapon employed, the bullet's velocity, diameter, shape, orbital stability, and weight affect this energy.[2,5,6]

In FI, only a single bullet or ammunition containing multiple pellets may be fired at the target.[2] Typically, a single bullet is used as ammunition in pistols.[2] Shotguns often use capsule ammunition consisting of a large number of small pellets for hunting.[7,8] Shotgun bullets behave uniquely and exhibit complex ballistic patterns because they are composed of a variable number of small metal balls that disperse after leaving the gun.[9,10] Consequently, the evaluation of pellet injuries differs from that of bullet injuries.[1] There are few clini-

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cal studies on this subject and the debate continues.[5,11,12]

The aim of this study was to compare the clinical effects and treatment processes of bullet and pellet injuries in civilian FI causing bone fracture in the extremity and to reveal the differences.

2.MATERIAL and METHODS

The study was designed retrospectively. Ethics committee approval for the study was obtained from the scientific research ethics committee with the number 2022/264. The level of evidence for this study is level IV.

The files of the patients who were admitted to the emergency department of our hospital between 2016 and 2020 with extremity fractures due to FI and followed up by the orthopedics clinic were analyzed. Control examinations were performed and informed consent was obtained. Patients' age, gender, injured extremity, presence of infection, presence of vascular injury, presence of nerve injury, total number of operations, length of hospital stay, follow-up period, and presence of permanent sequelae formation criteria were collected and analyzed.[13] Patients with no missing data in their files were included in the study. The results of the values analyzed under two headings as bullet and pellet injury groups were compared statistically.

2.1.Patient Management

The Emergency Room handled the initial emergency management following the injury. Patients underwent physical examination, blood tests, and x-ray assessment. A consultation with an orthopedic surgeon was then requested. Patients underwent emergency surgery or ward hospitalization as needed. Bullets or pellets encountered during surgery or palpable during debridement are removed. No further removal or exploration was performed. Patients who had completed their orthopedic treatments were discharged. If there were any additional complaints or complications during the control examinations, the necessary operations or interventions were conducted out.

2.2.Statistical Analysis

Categorical variables were expressed as numbers (%) while continuous variables were expressed as median (range). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine whether continuous variables conformed to a normal distribution. The Man-Whitney U test was used to compare continuous variables between the two groups, and the Fisher Exact test was used to compare categorical variables. A $p < 0.05$ was considered statistically significant. The statistics were calculated using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

3.RESULTS

The study was performed in 40 cases with a mean age of 43.5 years. 39 of the patients were male and 1 was female. There were 28 bullet injuries and 12 pellet injuries. Of the cases, 32 were lower extremity injuries and 8 were upper extremity injuries. In the bullet group, lower extremity injuries were more common and upper extremity injuries were less common ($p=0.039$). The mean follow-up period was 41.5(24-61) months. Detailed general characteristics are shown in table 1. Case examples are shown in figures 1 and 2.The average hospital stay was 10(1-43) days. Those in the pellet group had significantly longer hospital stay when compared to the bullet group ($p=0.024$).

There was a statistically significant difference between ammunition type and number of operations ($p=0.032$). The effects of bullet and pellet injuries at similar sites on the ankle are shown in figures 3 and 4. The rate of one operation was higher in the

bullet group and the rate of multiple operations was higher in the pellet group. Figure 5 shows the excision of the remaining pellets in a patient four months after discharge due to discomfort. In this case some pellets were removed from the tendon sheath.

Nerve injuries occurred in a total of 7 patients, 4 in the bullet group and 3 in the pellet group. Of these injuries, 3 were related to the radial nerve, 1 to the median nerve, 2 to the peroneal nerve and 1 to the sciatic nerve. There was no significant difference between the groups in terms of nerve injuries. There was a significant difference in nerve injury rates between extremities (p=0.020). There were 4 (50%) nerve injuries in the upper extremity and 3 (9.4%) in the lower extremity. Two posterior tibial arteries, one anterior tibial artery, and one ulnar artery were injured. There was no significant difference between extremities in vascular injury (p=1). Table 2 shows the rates of vascular and nerve injury amongst the patients. In terms of infection, vascular injury and permanent sequelae, there was no significant difference between the

Table 1.

General characteristics

Characteristic	Total n=40 (%) median (range)	Bullet n=28 (%) median (range)	Pellet n=12 (%) median (range)	p
Age	43.5 (15-73)	43 (15-73)	48 (32-62)	0.124
Gender				1
Male	39 (97.5)	27 (96.4)	12 (100)	
Female	1 (2.5)	1 (3.6)	0	
Extremity				0.039
Upper	8 (20)	3 (10.7)	5 (41.7)	
Lower	32 (80)	25 (89.3)	7 (58.3)	
Permanent sequel	12 (30)	8 (28.6)	4 (33.3)	1
Infection	5 (12.5)	2 (7.1)	3 (25)	0.149
Vascular Damage	4 (10)	2 (7.1)	2 (16.7)	0.570
Nerve Damage	7 (17.5)	4 (14.3)	3 (25)	0.410
Numer of Surgeries	1 (1-4)	1 (1-4)	1 (1-4)	0.032
1	27 (67.5)	22 (78.6)	5 (41.7)	
2-4	13	6 (21.4)	7 (58.3)	
Length of hospital stay (days)	10 (1-43)	10(1-30)	13.5(4-43)	0.024

Table 2.

Characteristics of vascular and nerve damage

Characteristic	Extremity (n)		P
Number of injured nerves (%)	4 (50)	3 (9.4)	
Injured Nerves (n)	Radial (3) Median (1)	Peroneal (2) Sciatic (1)	0.020
Number of injured vessels (%)	1(12.5)	3(9.4)	1.000
Name of vessels (n)	Ulnar(1)	Posterior tibial (2) Anterior tibial (1)	0

groups (p=0.149, p=0.570, p=1). Overall, 12.5% infection, 10% vascular damage, 17.5% nerve damage and 30% permanent sequelae occurred as a result of treatments.

Figure 1.

Femur fracture due to bullet injury (A:Bullet entry hole, B:Femur radiograph after fracture, C,D:Femur radiographs after surgery, E:Femur radiograph after union)

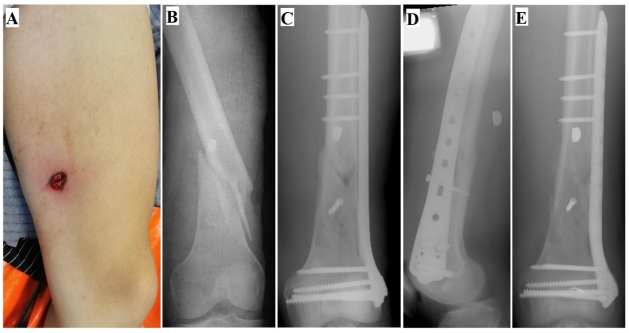


Figure 2.

Cruris injury and tibia fracture after pellet injury (A: View of injury site, B:Fluoroscopy image of tibia fracture and many pellets, C:After external fixator surgery)

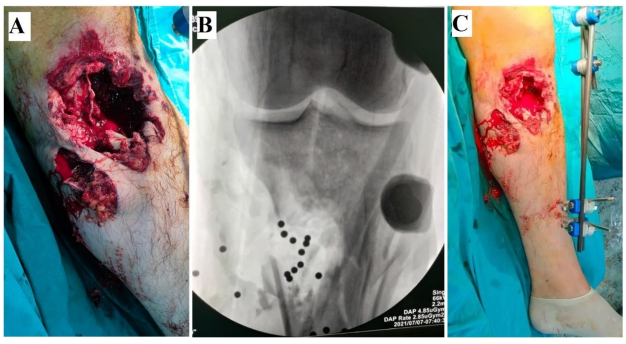


Figure 3.

Talus fracture caused by an ankle gunshot wound (A:Bullet entry hole, B:Computed tomography Horizontal section showing the course of the bullet, C:Computed tomography sagittal section showing talus fracture, D,E: Postoperative anterior posterior and lateral radiographs)

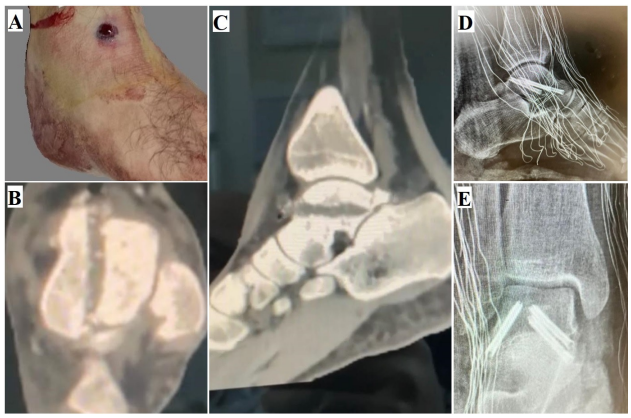


Figure 4.

Gunshot wound to the ankle with pellet (A: Ankle injury site, B: Ankle radiograph after pellet injury, C: Radiograph after ankle arthrodesis surgery, D: Radiograph after union)

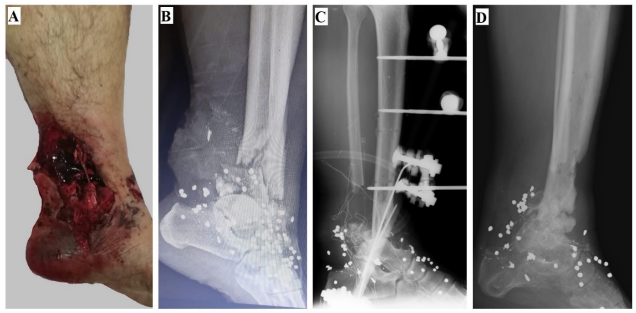
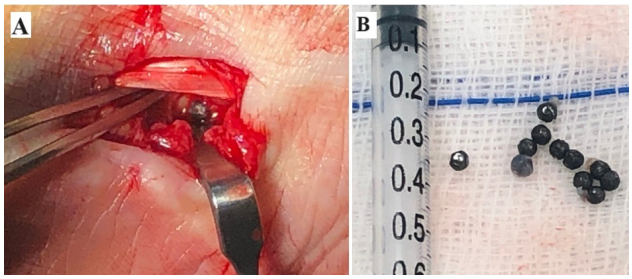


Figure 5.

The pellet that remained in the peroneus longus tendon sheath after a birdshot injury and the pellets removed from the same foot



4.DISCUSSION

When we compared the cases with single surgery and cases with multiple surgeries, it was determined that multiple surgeries were performed significantly in the pellet group. The fact that 78.6% of bullet injuries underwent a single operation in the treatment process after FI, while 58% of the pellet group underwent more than one operation is another indicator of the difference in severity of injury. In addition, a significant difference was observed in the duration of hospitalization. Therefore, it can be considered that the cost and morbidity expectation for pellet injury will be higher. According to the literature, shotgun injuries have significantly higher mortality and morbidity compared to bullet injuries.[1,14,15] Mortality in pellet injuries has been reported as 20-38%, 17% and morbidity as 38%.[1,14] Mortality in bullet injuries has been reported as 5-12%, 4% and morbidity as 17%.[1,15] Despite the results showing that the severity of injury was higher in the buckshot group, no difference was found between the groups in terms of infection rate, nerve injury, vascular injury and permanent functional sequelae in our study. In other words, in order to achieve the same recovery rate as the bullet group, the pellet group underwent more surgeries and stayed in the hospital longer. Despite all the advances, a morbidity rate as high as 30% reveals the importance of FI injuries.

Consistent with the literature, the majority of our cases (97.5%) were male.[1,5,12,16] In a study of FIs with extremity injuries, 75% of injuries were reported to involve the lower extremities.[17] In a study evaluating FI patients who underwent orthopedic surgery, 53.7% had lower extremity injuries, 37.1% had upper extremity injuries, and 9.2% had both lower and upper extremity injuries.[16] Similarly, 80% of the cases in our study were lower extremity injuries. This result may be due to the limb size difference, or it may be due to the fact that the weapon may have been fired for injury rather than fatal damage.

Although capillaries are susceptible to rupture in FI, they are extremely resistant to damage unless the large arteries are directly struck.[2,7] Although large nerve trunks are also susceptible to neuropraxia, they are usually not completely damaged, similar to vessels.[2,7] Burg et al. reported a nerve injury rate of 16.8%, with the deep peroneal nerve being the most affected (38%).[17] Tokyay et al. reported the incidence of vascular and nerve injury as 5.5% and 11.1% (3 radial, 1 ulnar, 1 median, 1 peroneal), respectively.[16] In another study examining low-energy lower extremity FI cases, the rates of vascular injury, nerve injury, and acute infection were 6.1%, 1.4%, and 5.3%, respectively.[18] In a study of civilian upper extremity FI, the rate of nerve injury in patients with fractures was reported to be 43.1%, with ulnar, median, radial, and brachial plexus injuries reported, in order of frequency.19 In a study evaluating high-energy upper extremity war injuries, the ulnar and radial nerves were reported to be frequently injured.[12] In the same study, 46.8% nerve injury, 12.9% artery injury and 37.1% infection rate were concluded.[12] In our study, 12.5% infection, 10% vascular damage, 17.5% nerve damage were determined in all cases. There was also no significant difference between the two groups in terms of vascular and nerve injuries. In terms of the number of nerve injuries, 3 radial nerve, 2 peroneal nerve, 1 median nerve, and 1 sciatic nerve injuries are generally similar to the values in the literature. However, there was a significantly higher risk of nerve damage in the upper extremity injury rate. The fact that the upper extremity has less soft tissue support and the bone and nerve neighborhoods are relatively closer may have increased the rate of nerve injury. For these reasons, the physician performing neu-

rologic examination in the emergency department should be more meticulous especially in upper extremity FI.

4.1.Limitations

Our study is limited by its retrospective design and small sample size. On a topic such as FI, whose treatment and outcomes are debatable, there is a need for in-depth studies involving a greater number of cases.

5.CONCLUSION

There are many differences in the damage and expectation of the treatment process when comparing bullet and pellet ammunition in an extremity FI with bone fracture. In this study, it was concluded that soft tissue damage would be high in pellet injury, the hospital stay would be longer and more than one operation would most likely be required during the treatment process. These injuries can result in a significant proportion of permanent sequelae. In addition, if the upper extremity is affected in FI cases, nerve damage can be seen at a high rate, so special attention should be paid during the first examination.

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Olgu Sunumu / Case Report

Anjioödem ile Karıştırılan Nefrotik Sendrom: Olgu Sunumu

Nephrotic Syndrome Confused with Angioedema: Case Report

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Özet: Nefrotik sendrom yaygın ödem, masif proteinüri ve hipoalbuminemi ile karakterize, sıklıkla 2-6 yaşlarında oluşan bir sendromdur. Genellikle gün içinde azalan periorbital ödem nedeniyle bu hastalar yanlışlıkla alerjik hastalık tanısı almaktadır. Daha önceden bilinen takipli hastalığı olmayan, bilateral hidrosel ve inguinal herni nedeniyle ameliyatı planlanan, operasyon öncesi değerlendirmede gözlerinde bilateral şişlik farkedilen 4 yaş 9 aylık erkek hasta, anjioödem ön tanısı ile çocuk immünoloji alerji bölümüne konsülte edildi. Göz kapakları ödemli, bilateral pretibial gode bırakan ödem ve skrotumda bilateral translüminasyon gösteren şişlik olan hastanın diğer muayeneleri normaldi. Laboratuvar incelemesinde: Albumin: 1.6g/dl, Sedimentasyon:76 mm/saat, C3:1,23 mg/dl, ve C4: 0,24 mg/dl. İdrarda: dansite: 1051, protein: +++, protein/kreatinin 17,8 mg/mg idi. Hem nefrotik sendrom hem de anjioödem göz kapaklarında, genital bölgede ciddi ödem oluşturur. Bu nedenle laboratuvar tetkikleri, klinik bulgular, dikkatli muayene ayırıcı tanı için yeterlidir. Çalışmamızda alerjik anjioödem ön tanılı nefrotik sendrom olgusunu sunmayı amaçladık.

Anahtar Kelimeler: Anjioödem, Hipoalbuminemi, Nefrotik sendrom

Abstract: Nephrotic syndrome is characterized by diffuse edema, massive proteinuria and hypoalbuminemia. It usually occurs between the ages of 2-6. Due to periorbital edema these patients are mistakenly diagnosed with allergic disease. A 4-year-old 9-month-old male patient, who had no known disease under follow-up, was admitted to the pediatric surgery service due to bilateral hydrocele and inguinal hernia, was planned to be operated on, and bilateral swelling in his eyes was noticed in the preoperative evaluation, was consulted to the pediatric immunology-allergy department. His general condition was good, his skin turgor was normal, his eyelids were edematous. There was bilateral pretibial pitting edema and bilateral transluminated swelling in the scrotum. In laboratory examination: Albumin: 1.6g/dl, Sedimentation:76 mm/hr, C3:1.23 mg/dl, and C4: 0.24 mg/dl. In urine: density: 1051, protein: +++, protein/creatinine was 17.8 mg/mg. Both nephrotic syndrome and angioedema cause severe edema of the eyelids and genital area. Therefore, laboratory tests, clinical findings and careful examination are sufficient for differential diagnosis. In our study, we aimed to present a case of nephrotic syndrome with a prediagnosis of allergic angioedema.

Keywords: Angioedema, Hypoalbuminemia, Nephrotic syndrome

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EXTENDED ABSTRACT

Background

Angioedema, known as fluid accumulation under the skin and mucosa, may have many different pathogenesis. Different treatments should be applied to different pathologies. We present our patient who was consulted to the pediatric allergy clinic due to bilateral angioedema around the eyes, but it evolved into a very different path than allergy.

Purpose

We aim to diversify the differential diagnoses of clinicians in angioedema cases, which are frequently encountered in daily practice, to make the correct diagnosis for the right patient, to prevent the wrong treatment by making the wrong diag-

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nosis, and to avoid delays in the right treatment.

Case

A 4-year-old and 9-month-old male patient, who was hospitalized at the pediatric surgery clinic to be operated on due to hydrocele, was consulted to the pediatric allergy clinic due to bilateral swelling around the eyes before the operation. The patient was transferred to the pediatric allergy service. Angioedema was not accompanied by urticaria, and it was learned from his history that a similar swelling had occurred around the eyes a month before. Pheniramine maleate was administered intravenously to the patient. It was observed that there was no response to treatment within 24 hours. It was also noteworthy that pitting edema occurred in the patient's legs. When examined to investigate the etiology of angioedema, the patient was found to have massive proteinuria and associated hypoalbuminemia (Albumin: 1.6 g/dl, Sedimentation: 76 mm/hr, C3: 1.23 mg/dl, and C4: 0.24 mg/dl. In spot urine: density: 1051, protein: +++, protein/creatinine was 17.8 mg/mg). The patient was referred to the pediatric nephrology department. The patient showed a dramatic response to steroid treatment during follow-up, and his edema regressed.

Discussions

Swelling caused by fluid accumulation under the skin or mucosa is called angioedema and may occur in any body part, including the eyes, lips, and extremities. These swellings may occur as a result of different pathogenesis.

The pathophysiology of angioedema may include allergic (histamine-mediated), acquired (bradykinin-mediated), and systemic diseases. Histaminergic angioedema is the most common type of angioedema. For this reason, the first diagnosis that comes to the mind of clinicians who encounter a case of angioedema is histaminergic angioedema. It is often accompanied by urticaria and responds well to antihistamine treatment, and it is not expected to last for days.

Hereditary angioedema (HAE), one of the other causes of angioedema, is an autosomal dominant inherited, bradykinin-mediated angioedema that progresses with attacks. The disease progresses with isolated angioedema attacks and can be fatal if laryngeal involvement occurs. HAE is not accompanied by urticaria, does not respond to antihistamine treatment, and regression of angioedema takes time. Treatment includes disease-specific agents such as bradykinin receptor antagonists and C1 esterase inhibitors. It should be kept in mind in the differential diagnosis of patients presenting with isolated angioedema.

Among systemic diseases, right heart failure and nephrotic syndrome are the ones that should come to mind. Treating these diseases, which cause fluid leakage outside the vessels through different mechanisms, should be directed toward the underlying pathology. Bilateral involvement in the eye is expected, and pitting edema in the extremities is more suggestive of systemic disease. Angioedema caused by systemic diseases does not respond to antihistamine treatment.

In nephrotic syndrome, hypoalbuminemia occurs as a result of massive protein loss from the kidney. As a result, fluid leaks out of the vein. It occurs mainly in the lower extremities and around the eyes due to gravity. Unlike allergic angioedema, it is expected to occur bilaterally, causes pitting, and is not accompanied by urticaria. It causes severe anxiety in families. These patients primarily apply to the emergency department. It is mistaken for allergic angioedema, and due to mislabeling, treatment is delayed, or even the wrong treatment is

applied. When angioedema is encountered, clinicians should also examine the extremities and note the presence of a pit. Our patient had no edema in the lower extremities at the first examination, but it occurred during the follow-up. We think that this situation is due to deepening hypoalbuminemia. Corticosteroids are used in the treatment of nephrotic syndrome. Our patient also responded well clinically to steroid treatment.

Conclusions

Our case report emphasizes that the most common cause should always be in our minds, but further examination should be performed in cases of angioedema that do not respond to treatment, along with other warning signs such as unresponsiveness to antihistamine treatment, long-term continuation, accompanied by systemic findings.

1.GİRİŞ

Nefrotik sendrom, yaygın ödem, masif proteinüri ve hipoalbuminemi ile karakterize bir sendromdur.[1] Nefrotik sendrom, çocukluk yaş grubunda etyolojisi ve patogenezisi tam anlamı ile bilinmeyen (idiyopatik) ve yalnız böbrekteki bozukluklarla karakterize bir hastalıktır. Sıklıkla 2-6 yaşları arasında başlar.[2] İdiopatik nefrotik sendromun yanında, etyo-patogenezi net olarak belirlenmiş ve sekonder nefrotik sendrom olarak gruplandırdığımız (enfeksiyonlara, diyabete, toksinlere, malign hastalıklara sekonder gibi) ise çocuklarda daha nadir gözlenir.[1]

Genellikle gün içinde azalan periorbital ödem nedeniyle bu hastalar yanlışlıkla alerjik veya diğer nedenlere bağlı olduğu düşünülen anjioödem tanısı almaktadır.[3-5] Çalışmamızda alerjik anjioödem ön tanısıyla çocuk allerji polikliniğine yönlendirilen fakat nefrotik sendrom tanısı alan olgu sunulmaktadır.

2.GEREÇ ve YÖNTEMLER

2.1.Araştırma ve Yayın Etiği

2.1.1.Olgu

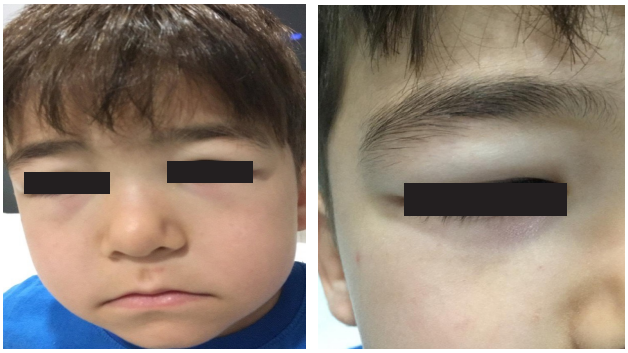
Daha önceden bilinen hastalığı olmayan, bilateral hidrosel ve inguinal herni nedeniyle çocuk cerrahi servisine yatışı yapılarak ameliyatı planlanan, operasyon öncesi değerlendirmede gözlerinde bilateral şişlik fark edilen 4 yaş 9 aylık erkek hasta, anjioödem ön tanısı ile çocuk immünoloji alerji bölümüne konsülte edildi.

Hastanın anamnezinden 1 ay önce de benzer şekilde 3-4 gün süren göz kapağında şişlik şikâyeti olduğu öğrenildi. Özgeçmişinde sık üst solunum yolu enfeksiyonu geçirme öyküsü olan hastanın, soygeçmişinde sağlam sağlıklı abi ve kız kardeşi olduğu, anne babası arasında birinci derece kuzen evliliği olduğu öğrenildi.

Fizik muayenesinde genel durumu iyi, deri turgor ve tonusu doğal, göz kapakları ödemli idi (resim 1 a,b). Vücut ağırlığı: 27 kg (90-97p) ve boy: 120cm (90-97p) idi. Solunum sesleri doğal, kalp sesleri ritmik, nabız 100/dak, tansiyon 90/55 mmHg, batın yumuşak, karaciğer 2 cm ele geliyordu. Cilt muayenesinde ürtiker, purpura ve döküntü yoktu. Bilateral pretibial bölgede gode bırakan ödem ve skrotumda bilateral translüminasyon gösteren şişlik mevcuttu.

Resim 1a. b.

Bilateral göz kapaklarında ödem.



Laboratuvar incelemesinde; üre: 24mg/dl, kreatinin: 0,19 mg/dl, AST: 31 U/l, ALT: 14 U/l, albumin: 1.6g/dl, Na+: 134 mEq/L, K+: 4.1 mEq/L, CRP:<3,3 mg/dl, sedimentasyon: 76 mm/saat, lökosit: 6.890/mm3, nötrofil: 1.690/mm3, Hb: 13,1g/dl, platelet: 379.000/mm3 idi. İdrar incelemesinde; pH:6.0, dansite: 1051, protein: 3+, C3: 1,23 mg/dl ve C4: 0,24 mg/dl idi. Yaşına uygun yapılan deri prik testi ve alerjene spesifik immünglobülin E değerlendirmeleri de normal sınırlar içinde saptandı. Batın ultrasonografi: karaciğer boyutları artmış (116 mm), sağ subhepatik sağ parakolik-retroperineal alanda sıvı kolleksiyonları izlenmektedir.

3.TARTIŞMA

Ödem, sıvı birikiminin vücut ağırlığının %3-5'ini geçtiğinde fark edilebilir. İlk olarak göz kapaklarında şişlik şeklindedir. Yerçekimine bağlı olarak gün içinde yer değiştirir. Ödem gözlerden başlayıp, bacakların ön yüzüne ve kalçaya doğru yayılır. Genellikle gün içinde değişen periorbital ödem nedeniyle bu hastalık yanlışlıkla alerjik hastalık tanısı alır. Hastamızda da periorbital ödem saptandı. Allerjik anjioödem ön tanısı ile yatırılıp ileri tetkikleri alındı. Feniramin intravenöz olarak uygulandı. Fakat tedaviye beklenen cevap alınamayınca ayırıcı teşhise giren diğer nedenler düşünüldü.[4-7]

Allerjik bir nedene bağlı olmayan (non-allerjik) anjioödemler tekrarlayan fakat nedeni açıklanamayan, 24 saatten uzun süre devam eden, anti-histaminiklere cevap vermeyen, ürtikerin eşlik etmediği, bazen larenks ödemi veya barsak ödemi sonucu kolik tarzında karın ağrısı gelişebilen ödemlerdir.[6] Bunlar arasında ilk akla gelen, C1 esteraz inhibitör (C1-INH) eksikliğine bağlı oluşan herediter anjioödem (HAÖ)' dir. Cilt, barsak submukozası ve üst solunum yollarını tutar; kaşıntı ve ürtiker olmadan tekrarlayan anjioödem ataklarıyla süren otozomal dominant geçiş gösteren bir hastalıktır. Nadir görülmesine rağmen acil serviste atak tedavisinde gecikmeler yaşanabilmektedir.[3]

Hastamızda olduğu gibi, non-allerjik ödemlerde dikkat edilmesi gereken bir diğer konu da, ödem eğer bilateral ise-her iki tarafı tutuyorsa-, gode bırakıyorsa, daha yaygın tutulum gösteriyorsa (aynı anda göz, pretibial bölge ve sırtın alt kısmında tutulum vb.) ve alerjik anjioödem tedavisine cevabı yoksa bu olgularda sistemik bir (böbrek, kalp, karaciğer vb.) hastalığa bağlı ödem olduğu düşünülmelidir.[2,6,7]

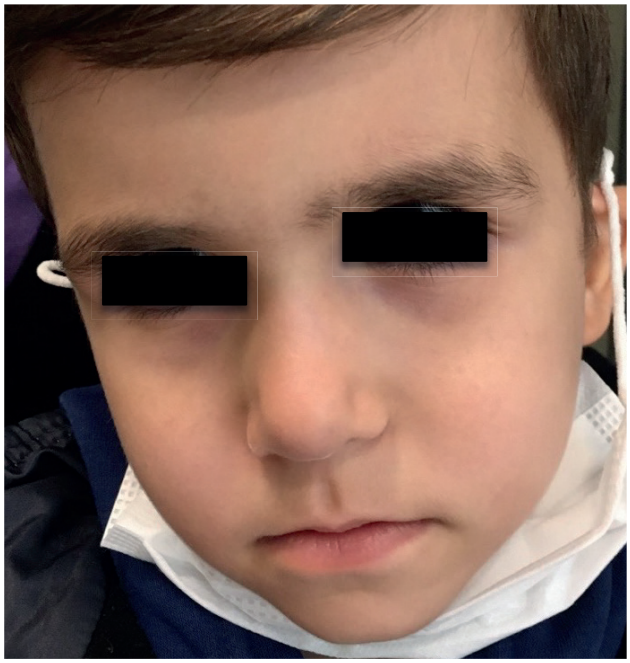
Nefrotik sendrom genellikle minör enfeksiyonlar, seyrek olarak da böcek ısırıkları, arı sokması sonrasında gelişir. Çocuklar genellikle hafif ödem tablosundadır. İlk olarak periorbital ve pretibial ödem saptanır. Genellikle gün içinde değişen periorbital ödem nedeniyle bu hastalık yanlışlıkla alerjik hastalık tanısı alır. Zamanla asit, plevral efüzyon, genital ödem gelişebilmektedir. İştahsızlık, karın ağrısı, halsizlik en sık rastlanan bulgulardır. Ayırıcı tanıda protein kaybettiren enteropati, karaciğer yetmezliği, kalp yetmezliği, akut ya da kronik glomerülonefrit, hipotiroidizm bağlı ödem, protein malnütrisyonu düşünülmektedir. Bu hastalığın önemli özelliği hipertansiyon ve makroskopik hematüri (eşlik eden nefritik sendromu) olmamasıdır.[2] Nefrotik sendromlu çocuk hastalarda kan basıncı sıklıkla normal sınırlardadır, ancak %5-15 olguda yüksek bulunmaktadır. Şiddetli ödem durumlarında solunum sıkıntısı, göbek, kasık fıtığı ortaya çıkabilir. Vakamızda tansiyon normal sınırda, ama hepatosplenomegali ve batında serbest sıvı izlenmişti. Bu hastalarda enfeksiyonlara eğilim artmış olup deri ve akciğer enfeksiyonları gelişebilir. Arteriyal ve venöz trombozlar görülebilir. Karında biriken sıvının (asit) yaptığı gerginliğe bağlı olarak karın ağrısı da görülebilmektedir.[1,2]

Vücut ağırlığı ve boyu (büyümesi) normal olan, malnütrisyon, hipotiroidizm olmayan ve kardiyak

patolojisi bulunmayan hasta nefrotik sendrom açından ileri tetkikleri alındı. İleri tetkikler değerlendirildiğinde, hastamızda da total protein/albümin düşüklüğü (hipoproteinemi / hipoalbuminemi), 3+ proteinüri (masif proteinüri), allerji (antihistaminik) tedavisine cevapsızlık, alerjik testlerin negatif bulunmasıyla hastamızda çocukluk çağında nefrotik sendroma yol açan sistemik böbrek hastalığı düşünülüp ileri tetkik ve tedavi için uygun merkeze gönderildi. Orada da ön tanımız doğrulanıp hastada çocuklarda nefrotik sendromun en sık nedeni olan minimal change (değişiklik) hastalığı düşünülüp literatüre uygun şekilde Prednisolon tedavisi başlanılmıştır ve tedavi sonrası ödem gerilemiştir (resim 2).

Resim 2.

Prednizolon tedavi esnasında bilateral göz kapaklarında ödemin azaldığı görülmektedir.



Kişisel 8 yıllık çocuk allerji deneyimimizde, 3 çocuk periorbital ödem nedeniyle alerjik anjioödem şüphesi ile bize gönderilmiş ya da konsülte edilmiş fakat tedaviye cevapsızlık ve ileri tetkiklerle minimal change hastalığı doğrulanmış ve tedavi verilmiştir.[8,9] Nadir de olsa, çocuk uzmanı hekimler tarafından nefrotik sendroma bağlı ödem, alerjik anjiyoödem ile karıştırılabilmektedir. Erişkinlerde de, akkiz anjiyoödem[10], ACE (angiotensin converting enzyme) inhibitörü kullanımı[11] gibi tablolar akla gelmelidir. Yine literatürde idiyopatik membranöz glomerulonefrite bağlı nefrotik sendrom tablosunun da, herediter anjioödemli bir hastada geliştiği bildirilmiştir.[12]

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Olgu Sunumu / Case Report

Impulse Control Problems Following Bariatric Surgery and Extrapyramidal Adverse E ects with Fluoxetine: A Case Report

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Abstract: Although bariatric surgery is an effective method used in the treatment of obesity today, many psychiatric difficulties are detected when patients are evaluated biopsychosocially during the pre-and postoperative periods. Especially when surgery is used in patients with eating disorders, different addiction problems and impulse control disorders may arise afterward. We present a clinical case of a patient with increased obsessive-compulsive symptoms, various impulsive control problems, and bulimia nervosa starting after bariatric surgery. Another feature that made this case interesting was the extrapyramidal adverse effects that occurred after fluoxetine treatment used for her psychiatric treatment. Our aim, thus, was to contribute to the literature by discussing psychiatric problems evolving after bariatric surgery and the rare adverse effect of fluoxetine.

Keywords: Bariatric surgery, Fluoxetine, Obesity, Sialorrhea, Trichotillomania, Obsessive compulsive disorder

1.INTRODUCTION

Although bariatric surgery is efficient for losing weight, it can bring different psychosocial difficulties.[1,2] Some studies suggested that different addictions or impulse control disorders could emerge in patients after surgery.[3,4] Conversely, some studies reported that cognitive functions improved after bariatric surgery and increased cognitive control corresponds with decreased impulsive symptoms.[5]

Selective serotonin reuptake inhibitors (SSRI) are used for the treatment of many psychiatric disorders such as mood disorders, anxiety disorders, obsessive-compulsive disorders, and eating disorders.[6] and their effects and adverse effects are well known.[7] Rarely, these well-known drugs can cause extrapyramidal symptoms (EPS).[8] Among the SSRIs, paroxetine, sertraline, and fluoxetine have been reported for inducing EPS.[9] When fluoxetine is used with dopamine-blocking agents, the risk of developing EPS increases.[10]

In this case, we present a patient with new onset bulimia nervosa, worsening impulse control problems, and recurrence of her obsessive-compulsive disorder after bariatric surgery. In addition, we discuss the adverse effects of the treatment that was used for psychiatric diagnoses. We aimed to illustrate the importance of detailed evaluation of symptom profiles in different clinical conditions like bariatric surgery and rare possible adverse effects that may arise when using medications to treat them under these circumstances.

2.CASE REPORT

D.T., a 46-year-old married housewife, and mother of two children was admitted to our psychiatry outpatient clinic with the symptoms of worries about gaining weight, disliking her body, insom-

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nia, irritability, skin picking-hair pulling, and having obsessions about symmetry and dirt-contamination.

In her psychiatric history, the patient presented to the hospital with symptoms such as anhedonia, and loss of interest, which started after her father's death in 2007. She was diagnosed as having major depression and was prescribed fluoxetine (dosage unknown). Due to the lack of a pharmacotherapeutic response, sertraline, venlafaxine, and paroxetine treatments were used, respectively and non-significant improvement with pharmacotherapy was achieved (dosage unknown). Besides that, the patient reported increased intolerance and irritability, therefore duloxetine treatment was initiated (30 mg/day). During the same period, she described dirt, contamination, symmetry obsessions, and over-cleaning and tidying/ordering the house (compulsions). Duloxetine was titrated to 90 mg/day and used for 10 years.

Also, in her psychiatric history, the patient reported that she underwent bariatric surgery in 2017, and after surgery, she had fear of gaining weight, had obsessive control over her weight, excessive eating episodes, and self-induced vomiting 2-3 times a week. She still was misusing laxatives and she had a negative body image even though her BMI was within normal limits. She started to exhibit hair-pulling and skin-picking behaviors. Duloxetine treatment was discontinued, and fluoxetine treatment was started at 20 mg/day considering the insufficient information about effective duration-dose use in the past and the efficacy profile.

She presented to the hospital 3 days after initiating the fluoxetine with sialorrhea and difficulty in speaking. Her vital signs were stable during the examination. The patient was using no other medication. In her mental status examination, cognitive functions were normal, her mood was anxious with restricted affect. In her thought process, her associations were normal, there were worries about gaining weight, disturbances in body shape, and contamination-symmetry obsessions in her thought content. Motor activity was normal. She had no impairment of intelligence and no perception abnormalities. In physical examination, bradymimia and hypersalivation were identified. There was no rigidity and no cog wheeling. Her cerebellar and cranial nerve examinations were also normal. The results of blood analysis, electrolytes, and miscellaneous tests were within reference ranges. The patient's prolactin level was 46.35 ng/mL. After discontinuing the fluoxetine treatment, the hypersalivation and bradymimia dramatically regressed and disappeared. The patient's follow-up prolactin test result was 10.5 ng/mL.

3.DISCUSSION

The case we report has different features from many perspectives. The patient's depressive and obsessive symptoms before bariatric surgery were treated with a noradrenergic antidepressant. Besides that, she presented with many psychiatric symptoms, of which impulsivity was at the forefront after bariatric surgery, and EPS was experienced as an adverse effect with a serotonergic agent that was chosen for the treatment of these problems. As is known, fluoxetine is an antidepressant that is approved for the treatment of bulimia nervosa and obsessive-compulsive disorder. Also, fluoxetine is commonly preferred for impulse control disorders.[11,12]

EPS is seen with many pharmacotherapeutic agents, but usually with first-generation antipsychotics. Among the antidepressants, there are more reports about SSRIs causing EPS than the tricyclic antidepressant group.[13] However, some

studies showed no significant differences between SSRIs, imipramine, and other antidepressants.[14] Among the SSRIs, EPS is most seen commonly with fluoxetine; paroxetine and sertraline have also been associated with EPS.[9,15] There are no certain risk factors related to EPS; however, older age; female sex; use of concomitant drugs such as anti-psychotics; and neurologic illness such as Parkinson's disease, which particularly affects basal ganglions, could be related to increased risk for EPS.[14]

The neuro-pathophysiologic mechanism for SSRI-induced EPS is still not properly understood. The extrapyramidal system involuntarily contributes to providing balance and muscular tone by the muscular regulation system.[16] Neurotransmitters such as dopamine, serotonin, acetylcholine, and GABA play an important role in this regulation.[17] 5HT2A receptors in basal ganglia may lead to adverse effects; increased serotonin activation can cause EPS by inhibiting both the nigrostriatal and tubero-infindibular dopaminergic neuronal pathways.[8,18] In this case, the patient's initial increased prolactin levels and subsequent decrease in prolactin following the discontinuation of fluoxetine can be explained by the effects on the dopaminergic pathways. It is also noteworthy that movement disorders that occur with SSRIs are more common in the literature; hypersalivation was prominent in our case. Case reports have established that SSRI-induced EPS could diminish following the discontinuation of drug or dosage modification.[13] Similar to the literature, in our case, EPS effects regressed and disappeared after discontinuing the drug.

Another remarkable point in our case was the start of bulimia nervosa symptoms and trichotillomania after the gastric bypass procedure the patient in 2017. The term food addiction has been proposed to help explain the increasing spread of obesity over the last 30 years.[19] Studies have shown changes in neurotransmitter networks, including dopaminergic and opioidergic systems associated with overeating behavior.[20] In altered reward sensitivity and food-related attentional biases, binge eating disorder may be defined as an impulsive/compulsive disorder.[21] Neuroimaging research has proposed there are corticostriatal circuitry changes observed in binge eating disorder similar to the changes in function in the prefrontal, insular, and orbitofrontal cortices and striatum in substance use disorder.[21] Furthermore, the role of the dopaminergic system is being investigated in eating, alcohol, and substance use and whether there is a possible association between them.[4,22]

In the literature, there are studies supporting the idea that patients who have undergone bariatric surgery may develop a new addiction or impulse control disorder instead of a 'food addiction,' depending on how the addiction is defined[3]. Authors have reported an increased frequency of eating disorders, skin picking, trichotillomania, kleptomania, non-paraphilic compulsive sexual behaviors, compulsive shopping, pathologic gambling, pathologic internet use, compulsive exercise, and especially alcohol use disorder following bariatric surgery, but this is still an area to be researched[3,4]. Impulse control disorders or behavioral addictions may also be common in patients who undergo bariatric surgery because obesity is associated with increased impulsivity and decreased impulse control.[3,23] Additionally, despite significant weight loss after bariatric surgery, persisting dissatisfaction with body shape is commonly reported, especially by women.[24]

The case we present contributes to the literature about the psychiatric symptomatology that can be seen after bariatric surgery. The symptoms that

occurred after bariatric surgery in the presented case are a good example of additional diagnoses and problems that might occur in clinical practice, albeit rarely. It is important to remember that patients' past treatment and surgery history may be related to the current psychiatric symptoms and should be investigated in detail. Undetermined mechanisms and risk factors may play a role in the occurrence of fluoxetine-induced EPS adverse effects. An integrated treatment plan should be formed in case management, and care should be taken in terms of adverse effects in follow-up.

3.1.Declarations

Ethics approval and consent to participate

Patient confidentiality has been strictly observed. For this type of study ethical approval is not required. Written informed consent to participate was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for publication.

Competing interests

No potential conflict of interest was reported by the authors.

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Authors' contributions

All listed authors have participated sufficiently in the design and writing of the manuscript.

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