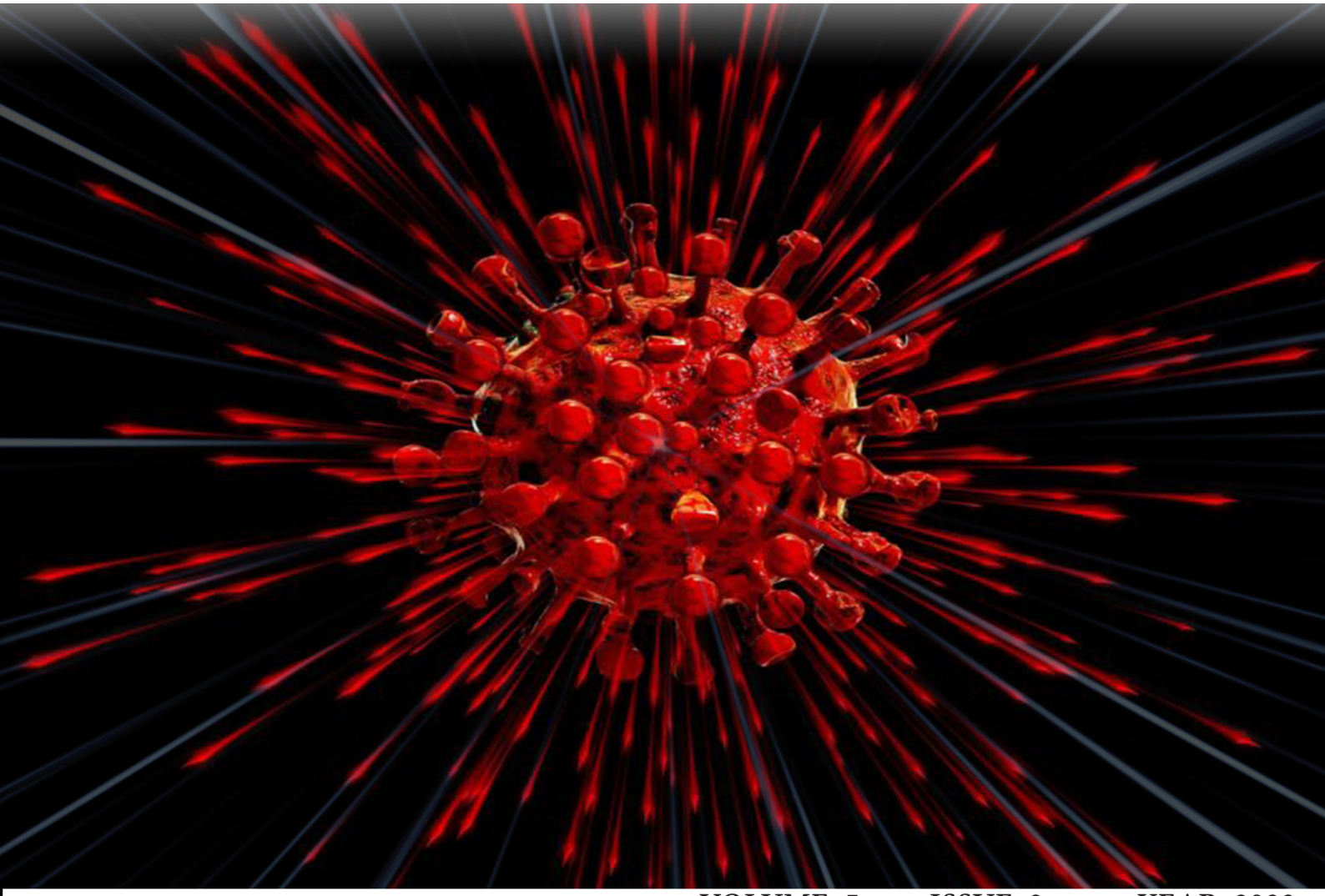
e-ISSN: 2718-0115

ACMJ

Anatolian Current Medical Journal



VOLUME: 5 ISSUE: 2 YEAR: 2023

MHA
MEDIHEALTH ACADEMY

EDITORIAL BOARD

FRANCHISE OWNER

MediHealth Academy Publishing
(***www.medihealthacademy.com***)

DESIGN

Fatih Şamil ULUDAĞ
(fsuludag@medihealthacademy.com)

CORRESPONDENCE ADDRESS

MediHealth Academy Publishing
Emniyet Mah., Yukarı Sk., No: 6/1, Yenimahalle, Ankara, TÜRKİYE
E-mail: mha@medihealthacademy.com
Phone: +90 312 349 77 77

ARTICLE SUBMISSION ADDRESS

https://dergipark.org.tr/tr/journal/2384/submission/step/manuscript/new

https://dergipark.org.tr/en/journal/2384/submission/step/manuscript/new

We are going through a difficult process as a country, first due to the pandemic and then to the earthquakes. In this second issue in 2023, we have received 15 original articles from different fields of medicine, and one interesting case report. Thanks to the close interest of our colleagues in our journal, both the number and quality of our articles are increasing day by day. In 2022, Anatolian Current Medical Journal (ACMJ) entered TR-Dizin ULAKBİM, and strong indexes. We are working hard to further improve the quality of our journal and to enter indexes with higher impact factor.

In this difficult time, we thanks our valuable academicians who contributed as authors, and to everyone who contributed to the journal.

Best Regards

Prof. Aydın ÇİFCİ, MD.
Editor-in-Chief

CONTENTS

Original Article

CONTENTS

Original Article

Case Report

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1233818

Anatolian Curr Med J 2023; 5(2); 80-83

Evaluation of pediatric ophthalmic consultations in a tertiary care university hospital

Ayşe Güzin Taşlıpınar Uzel[1], Özlem Özcanlı Çay[2], Mehmet Murat Uzel[3]

[1]Department of Ophthalmology, Faculty of Medicine, Ufuk University, Ankara, Turkey
[2]Department of Pediatry, Balıkesir City Hospital, Balıkesir, Turkey
[3]Department of Ophthalmology, Faculty of Medicine, Balıkesir University, Balıkesir, Turkey

Cite this article as: Taşlıpınar Uzel AG, Özcanlı Çay Ö, Uzel MM. Evaluation of pediatric ophthalmic consultations in a tertiary care university hospital. Anatolian Curr Med J 2023; 5(2); 80-83.

ABSTRACT

Aim: To characterize the patient groups referred to the ophthalmology clinic from the pediatrics clinic and to determine the frequency of the findings.

Material and Method: The patients consulted to Balıkesir University Eye Clinic by the Pediatrics Clinic were evaluated retrospectively. Patients were divided into rule-out and ocular symptom groups. Reasons for consultation and ocular findings were recorded.

Results: The mean age of 116 patients included in the study was 8.04±4.11 years. Of the patients included in the study, 75 (64.7%) rule-out 41 (35.3%) were in the ocular symptom group. 41 (54.7%) patients in the rule-out group were those who applied for headaches and requested an examination of the fundus and optic disc. Papilledema was detected in 7 (17.1%) patients with headache. Of the patients in the ocular symptom group, 11 (26.8%) were consulted for ocular trauma, 11 (26.8%) for red eye, and 7 (17.1%) for preseptal/orbital cellulitis. Preseptal cellulitis was detected in 4 (57.1%) patients consulted for preseptal/orbital cellulitis. Ocular findings were detected in 10 (91%) patients consulted for trauma. Conjunctivitis was detected in 9 (81.8%) patients who were consulted with red eyes.

Conclusion: In the pediatric age group, ophthalmic consultation is mainly performed due to rule-out. The most common reason is the examination of the fundus of the eye due to headache. It is crucial for pediatric age groups to consult an ophthalmologist by performing an eye and vision examination by a pediatrician in terms of early diagnosis and treatment.

Keywords: Pediatric age group, ophthalmic consultation, headache papilledema, ocular trauma

INTRODUCTION

Ophthalmology consultation for eye involvement in patients admitted to the hospital due to a systemic disease or surgical intervention has a significant place in the daily routine of ophthalmologists. Many systemic diseases progress with ocular findings and may be affected by medical treatment, or ocular involvement may occur after surgical intervention (1-5). Many conditions, such as the general condition and catheterization of inpatients, can affect the optimal eye examination. Bedside examinations can be performed with portable biomicroscopes and Tonopen, which can measure intraocular pressure (6).

The eye is affected by many conditions, such as diabetes mellitus (DM), hypertension, rheumatic diseases and metabolic disorders in the pediatric age group (7-10). Eye involvement may also occur in cases such as headache, infection and trauma (11). Anterior and posterior segment findings of the eye help guide the pediatrician to the correct diagnosis. In addition, regular follow-up of some drugs in terms of eye effects is required (12).

In the literature, eye consultations of inpatient groups were investigated (1,2). In the pediatric age group, there are few studies on this subject (13-15). However, in many cases, including systemic diseases in the pediatric age group, patients are followed up on an outpatient basis. For this reason, we aimed to characterize all patient groups referred from the pediatrics clinic to the ophthalmology clinic through consultation. Thus, we increase awareness of the patient groups followed and treated jointly by pediatricians and ophthalmologists.

MATERIAL AND METHOD

The study was carried out with the permission of Balıkesir University Clinical Researchs Ethics Committee (Date: 04.01.2023, Decision No: 2023/10). All procedures were

Corresponding Author: Özlem Özcanlı Çay, ozlemozcanli@yahoo.com

Received: 13.01.2023 **Accepted:** 23.01.2023

carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients consulted by the Pediatrics Clinic of BalıkesirUniversity Faculty of Medicine Ophthalmology Clinic between January 2020 and December 2022 were included in this retrospective study. Local ethics committee approval was obtained for the study, and the study was conducted in accordance with the Declaration of Helsinki.

Patients under 18 who were referred to the eye clinic with a consultation note after being examined by a pediatrician were included in the study. Patients with missing medical records and patients referred for screening for retinopathy of prematurity (ROP) were excluded from the study.

Age, gender, the reason for consultation, full ophthalmological examination findings and diagnosis of all patients were recorded. Consultations were divided into two groups: rule-out group (headache, systemic diseases, hereditary syndromes, etc.) and ocular symptom and sign group (red eye, diplopia, ocular trauma, etc.).

Data analysis was performed using SPSS 21.0. Study data were expressed as frequency, percentage, mean, and standard deviation.

RESULTS

A total of 161 pediatric patient consultations were identified between the analyzed dates. After excluding 31 patients consulted for ROP screening and 14 patients with missing medical records, 116 patients were included in the study. Of the patients, 48 (41.4%) were female, 68 (58.6%) were male, and the mean age was 8.04±4.11 years.

Seventy-five (64.7%) of the patients included in the study were in the rule-out group. 41 (54.7%) of this group's patients requested an examination of the fundus and optic disc due to headache. Papilledema was detected in 7 (17.1%) patients with headache. 16 (21.3%) patients included examination for ocular findings in patients with a known or suspected syndrome. In the group of patients with the syndrome, 3 (20%) patients were required to have eye scans due to microcephaly/macrocephaly, and 3 (20%) patients for suspected neurofibromatosis. Other causes included trisomy 18, down syndrome, and Wilson's disease. In one patient, chorioretinitis was detected in the baby due to rubella in the mother. Diabetes mellitus, rheumatic diseases and collagen tissue diseases, and consultations due to eye scans due to drug (topiramate) use were among other causes. **Table 1** shows the reasons for consultation and the frequency of ocular findings in the rule-out group.

Table 1. Reasons for consultation and frequency of ocular findings in the rule-out group

Reason	Presence of ocular findings
Headache	7/41
Syndrome	3/16
Suspected trauma	0/1
Other	2/17

Forty-one (35.3%) patients included in the study were those consulted for ocular signs and symptoms. Of these patients, 11 (26.8%) were consulted for ocular trauma, 11 (26.8%) for red eye, and 7 (17.1%) for preseptal/orbital cellulitis. Preseptal cellulitis was detected in 4 (57.1%) patients consulted for preseptal/orbital cellulitis. Ocular findings were detected in 10 (91%) patients consulted for trauma. Eye globe perforation was found in 2 trauma patients, corneal epithelial defect in 4, corneal foreign body in 3, and conjunctival abrasion in 1 patient. Conjunctivitis was detected in 9 (81.8%) patients who were consulted with red eyes. The most common cause was adenoviral keratoconjunctivitis. Other reasons for consultation included low vision, strabismus, ptosis, and dizziness. **Table 2** shows the reasons for consultation due to ocular signs and symptoms and the frequency of eye involvement.

Table 2. Reasons for consultation and frequency of ocular findings in the ocular symptom and sign group

Reason	Presence of ocular findings
Preseptal/orbital cellulitis	4/7
Trauma	10/11
Red eye	9/11
Diplopia	0/1
Other	6/11

DISCUSSION

In this study, the reasons and findings of the children referred to the eye department by the pediatrician were investigated. According to the results of our study, patients were mainly consulted to evaluate eye involvement in disease. Children who applied mostly because of headache were consulted for fundus examination. In the patient group with any ocular finding, the patient was primarily consulted because of red eye and preseptal/orbital cellulitis.

Ophthalmic consultations are essential in diagnosing some diseases and follow-up of eye involvement in some systemic diseases. There are very few studies in the literature about eye consultation of patients in the pediatric age group (13-15). These studies addressed eye consultations of pediatric inpatients. We also evaluated outpatients in our study. Many systemic diseases are also followed as outpatients.

In our study, we observed that most patients were consulted for rule out. This was consistent with other studies as well (13-15). In our study, the most common reason for consultation in the rule-out group was headache. In case of increased intracranial pressure, scanning the fundus for papilledema is very helpful in the diagnosis (11). Papilledema was detected in 17.1% of these children. In other studies, the rule-out group's most common reason for consultation was eye screening for systemic diseases (13-15). This difference may be due to the size of the hospital's pediatric service and the inclusion of only inpatients in other studies. The second most common reason for consultation in the rule-out group in our study was to screen for eye involvement of various syndromes. Trisomy 18, Down syndrome, neurofibromatosis, Marfan's disease, Wilson's disease, and microcephaly/macrocephaly were diseases in this group. Some findings, such as pallor in the optic disc, Lisch nodules, kayser-Fleischer ring, and lens subluxation, can be found as ocular findings in these diseases (16-18). In our study group, no ocular findings were detected in the patients referred for this purpose. In our study, 21.3% of patients were consulted due to systemic diseases. These diseases included type 1 DM, collagen tissue diseases, rheumatic diseases and Behcet disease. Although diabetic retinopathy (DR) is not as prevalent in children as in adults, it is known that DR develops in 6% of children with type 1 DM (19). Chorioretinitis was detected in a newborn whose mother had rubella in the rule-out group.

In our study, 35.3% of patients included ophthalmic consultation of patients with ocular symptoms or signs. The patients were primarily consulted because of trauma and red eye. Eye findings were detected in 91% of the patients referred for trauma, and 81.8% of the patients consulted for red eye. Naturally, the patients whose ocular findings were detected by the pediatrician had a higher rate of ocular involvement than the rule-out group. In the study of Güngör et al. (13) in inpatients children, the red eye was the second most common reason for consultation, and the most common reason was conjunctivitis. In our study, conjunctivitis was the most common cause of red eye. In addition, uveitis, herpetic keratoconjunctivitis and ocular rosacea were other causes. Consultation of patients evaluated by pediatricians due to trauma to the ocular region regarding possible eye injuries is significant. In this way, there may be a chance to apply early treatment to injuries that will be ignored by the child and his family because they do not cause severe symptoms. In our study, the corneal epithelial defect was the most common finding in patients consulted due to ocular trauma. Follow-up of these patients with appropriate treatment also prevents permanent corneal opacities. 57.1% of the patients consulted for preseptal/orbital cellulitis were evaluated as preseptal cellulitis. Daily follow-up of these patients is critical in terms of early treatment change in the progression of orbital cellulitis (20). Other reasons for consultation in the ocular symptom and finding group are low vision, dizziness or diplopia, strabismus and ptosis. With a correct visual examination by the pediatrician, refractive errors can be detected earlier, and possible amblyopia can be prevented. This group of patients must be referred to an ophthalmologist, as amblyopia can also occur in cases of strabismus and ptosis.

The most important limitation of our study is that it is a cross-sectional retrospective study. We cannot comment on the development of ocular findings, especially in children with chronic diseases. Another limiting factor is that the study was single-center. However, considering that only inpatient consultations are not evaluated and that many systemic diseases are followed up on an outpatient basis, it is valuable in terms of being the first study to evaluate the eye consultations of pediatric patients with this method.

CONCLUSION

Ophthalmic consultation by a pediatrician is very important in planning the diagnosis and treatment of various systemic diseases in the pediatric age group and in the early diagnosis and treatment of possible eye diseases that are not aware of by the family and the child. In this regard, combined studies of pediatricians and ophthalmologists may prevent irreversible vision loss.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Balıkesir University Faculty of Medicine Clinical Researches Ethics Committee (Date: 04.01.2023, Decision No:2023/10)

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Carter K, Miller KM. Ophthalmology inpatient consultation. Ophthalmology 2001; 108: 1505-11.
2. Grewal DS, Gabr H. Inpatient ophthalmology consultations. Med Clin North Am 2021; 105: 563-76.
3. Peragallo J, Biousse V, Newman NJ. Ocular manifestations of drug and alcohol abuse. Curr Opin Ophthalmol 2013; 24: 566-73.
4. Kara-Junior N, Espindola RF, Valverde Filho J, et al. Ocular risk management in patients undergoing general anesthesia: an analysis of 39,431 surgeries. Clinics (Sao Paulo) 2015; 70: 541-3.
5. Mendel E, Stoicea N, Rao R, et al. Revisiting postoperative vision loss following non-ocular surgery: a short review of etiology and legal considerations. Front Surg 2017; 4: 34.
6. Yamamoto LG, Young DA. Tonometry methods in the pediatric emergency department. Pediatr Emerg Care 2010; 26: 678-83.
7. Palejwala NV, Yeh S, Angeles-Han ST. Current perspectives on ophthalmic manifestations of childhood rheumatic diseases. Curr Rheumatol Rep 2013; 15: 341.
8. Davison JE. Eye involvement in inherited metabolic disorders. Ther Adv Ophthalmol 2020; 12: 2515841420979109.
9. Di Marco E, Aiello F, Lombardo M, et al. A literature review of hypertensive retinopathy: systemic correlations and new technologies. Eur Rev Med Pharmacol Sci 2022; 26: 6424-43.
10. Kırboğa K, Uçar M, Sarp Ü, Arıcı MK. Romatizmal hastalıklarda göz tutulumu. Bozok Tıp Derg 2015; 5: 51-5.
11. Sergott RC. Headaches associated with papilledema. Curr Pain Headache Rep 2012; 16: 354-8.
12. Lim HW, Oh SY. Ocular manifestations of pediatric systemic disease. Hanyang Med Rev 2016; 36: 182-5.
13. Güngör A, Özmen S, Sezgin Ersoy A, et al. Evaluation of ophthalmology consultations of inpatients in a tertiary pediatric hospital. J Dr Behcet Uz Child Hosp 2019; 9: 114-8.
14. Patel SH, Park S, Rosenberg JB. Comparison of Pediatric and adult ophthalmology consultations in an Urban Academic Medical Center. J Pediatr Ophthalmol Strabismus 2017; 54: 17-21.
15. Hasan SJ, Yen KG, Parghi CR, Castanes MS, Edmond JC. The frequency of ocular abnormalities in inpatient pediatric ophthalmology consultations. J Pediatr Ophthalmol Strabismus 2008; 45: 85-9.
16. Kannauje PK, Pandit VR, Wasnik PN, Das P, Venkatesan N. Wilson's disease: diagnosis in novel way. Cureus 2021; 13: e18650.
17. Bouirig K, Cherkaoui LO. Nodules de Lisch: marqueur ophtalmologique de la neurofibromatose de type 1. Pan Afr Med J 2022; 42: 108.
18. Rodrigo BJ, Paulina LL, Francesc Mde R, Eduardo TT, Alejandro N. Intraocular lens subluxation in Marfan syndrome. Open Ophthalmol J 2014; 8: 48-50.
19. Bratina N, Auzanneau M, Birkebaek N, et al. Donaghue KC; Australasian Diabetes Data Network (ADDN) Study Group, the Prospective Diabetes Follow-up Registry (DPV) initiative, Danish National Diabetes Registry (DanDiabKids), National Pediatric Diabetes Audit (NPDA), Region Marche Registry for Diabetes, Diabeter Diabetes Database, Slovenian Childhood Diabetes Registry, SEARCH for Diabetes in Youth Study. Differences in retinopathy prevalence and associated risk factors across 11 countries in three continents: A cross-sectional study of 156,090 children and adolescents with type 1 diabetes. Pediatr Diabetes 2022; 23: 1656-64.
20. Santos JC, Pinto S, Ferreira S, et al. Pediatric preseptal and orbital cellulitis: a 10-year experience. Int J Pediatr Otorhinolaryngol 2019; 120: 82-8.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1214890

Anatolian Curr Med J 2023; 5(2); 84-90

Evaluation of extremity and pelvis traumas admitted to the emergency department before and during the pandemic; with laboratory, embolism and mortality data

Burak Demirci, Abuzer Coşkun

Department of Emergency Medicine, Istanbul Bağcılar Training and Research Hospital, University of Health Sciences, Istanbul, Turkey

Cite this article as: Demirci B, Coşkun A. Evaluation of extremity and pelvis traumas admitted to the emergency department before and during the pandemic; with laboratory, embolism and mortality data. Anatolian Curr Med J 2023; 5(2); 84-90.

ABSTRACT

Aim: The purpose of this study was to determine the forms of trauma, demographic features, embolism status and mortality of patients who presented to the emergency department due to extremity and pelvis trauma before and during the pandemic period.

Material and Method: This retrospective study included 319 patients, who presented to the emergency department due to trauma between January 1, 2019, and December 31, 2020. The associations between embolism and mortality after trauma, as well as COVID-19, were investigated.

Results: The mean age of the 319 patients was 55.11±19.02 years, the distribution was 19-90 years and 133 (41.7%) were women. It was determined that 171 (53.7%) of the trauma patients were in the pre-pandemic period and 148(46.3%) were in the pandemic period. Embolism was detected in 19 (11.1%) cases before the pandemic and in 35 (23.6%) cases during the pandemic (p=0.003). Pre-pandemic mortality was observed in 10(5.8%) cases, and in pandemic 21 (14.2%) cases (p=0.010). While embolism was present in 22 (71%) cases in the mortality group, it was not observed in 9(29%) cases (p=0.001).

Conclusion: COVID-19 infection and pandemic can adversely affect the incidence of trauma, embolism and mortality. Embolism and mortality rates have increased significantly with the effects of COVID-19 during the pandemic period.

Keywords: COVID-19, embolism, emergency department, extremity traumas, mortality

INTRODUCTION

The coronavirus epidemic started at the end of 2019 and continued throughout 2020 (1). Admissions to pandemic hospitals were affected by many different parameters during this period (2). Turkey's first official case was detected in March 2020; and from that date to December 2020, more than 2 million cases were diagnosed with COVID-19 (3). Patients may develop varying degrees of respiratory failure, cardiovascular complications, secondary infections, thromboembolic events, and inflammatory complications.

Trauma affects all age groups, especially young people, and can cause serious labor loss. All kinds of trauma patients apply to emergency services, and extremity and pelvis traumas constitute a substantial group among these applications. Approximately 33 million musculoskeletal traumas occur each year, 20 million of which are fractures. Pelvic trauma occurs in 3% of skeletal injuries and is associated with serious complications (4-6). Both these traumas and the complications that may develop after them are very important in terms of morbidity and mortality.

Due to coronavirus disease 2019 (COVID-19), the effects of the pandemic are now being studied in every medical field. Although the infectious agent and pandemic had no direct impact on trauma, they had indirect effects.

It is already known that embolism poses an increased risk in trauma patients. While planning the study, we wondered how the incidence of extremity and pelvis trauma, which is a frequent reason for admission to the emergency department, is affected by the pandemic process, and how the history of COVID-19 positivity affects the development of embolism and mortality risks in these trauma cases.

This study aimed to compare the incidence of emergency admission, embolism development, morbidity and mortality in patients with extremity and pelvic trauma before and after the pandemic. It is anticipated to

Corresponding Author: Burak Demirci, drburakdemirci@hotmail.com

Received: 05.12.2022 **Accepted:** 24.01.2023

contribute to the literature by determining the effects of the COVID-19 pandemic due to social closures and the increased tendency to thrombosis caused by the infection that causes it, on the distribution of extremity and pelvic trauma cases and the subsequent complication process.

MATERIAL AND METHOD

Ethics

The study was carried out with the permission of Medipol University Noninvasive Clinical Researches Ethics Committee (Date: 14.10.2021, Decision No: 1001). All procedures complied with the ethical norms of the institutional and national committees responsible for human experiments and the Helsinki Declaration. Due to the retrospective design of the investigation, no written informed permission forms were acquired from patients. The corresponding author certifies, on behalf of all authors, that there are no conflicts of interest.

Study Design and Population

This retrospective analysis included 319 individuals over the age of 18 who accessed emergency treatment for trauma between January 1, 2019 and December 31, 2020. The first year was defined as the pre-pandemic period, and the following year as the pandemic period. Patients with upper extremity, lower extremity and pelvis trauma who applied to our hospital during these time periods were screened. Among the cases, those over the age of 18, who applied with a history of falling from a height (>1meter) , gunshot injury and traffic accident were included in the study. In this way, Age, gender, laboratory, trauma localization, trauma type, embolism and mortality data were evaluated. Minor home and play accidents, related incisions, additional thorax, neck, head and abdominal traumas were excluded from the study as they may affect the outcome of the study with other complications. Apart from these, patients who did not have COVID-19 disease, whose polymerase chain reaction test was negative, or who had 3 months past the COVID-19 infection disease during the pandemic period were not included in the research. The reason for this was to see the direct effects of COVID-19 infection by excluding cases who did not have COVID-19 infection during the pandemic period. While the effect of the pandemic was evaluated in the comparison of the pandemic process and the pre-pandemic period in terms of the admissions of trauma patients, the effect of COVID-19 on other laboratory, embolism and mortality results was evaluated.

Patients who applied to the emergency department due to fall, traffic accident, and gunshot injury, had upper extremity, lower extremity, and pelvis trauma, and had hemogram, biochemistry, D-Dimer, C-reactive protein (CRP), and sedimentation tests studied in the emergency clinic were included. Patients with missing data on the type of injury, clinical, laboratory or imaging findings in the hospital data recording system were excluded from the study.

The patients were divided into two groups as pre-pandemic and pandemic periods. According to the trauma types, three groups were determined as falling from a height, traffic accident, and gunshot injury. For upper extremity trauma patients with the following forms of injury were included; " clavicle, proximal humerus, distal humerus, humerus shaft, radius head and neck, monteggia, Radius + ulna shaft, colles, hand bone, and multiple upper extremity fractures". For pelvic traumas, following forms of injury were included " sacrum, iliac wing, acetabulum, symphysis pubis, and common pelvis fracture". For lower extremity traumas following forms of injury were included as "proximal femur, distal femur, femur shaft, patella, proximal tibia, tibia shaft, tibia-fibula, fibula, distal tibia, foot bone, multiple lower extremity fractures". In addition, two groups were determined according to post-traumatic mortality and development of embolism.

In the study, individuals with excellent and moderate general conditions were reviewed in the trauma emergency unit, while those with bad coma scores and awareness levels were evaluated in the emergency critical resuscitation room. The proper care was initiated for individuals who required fluid and blood resuscitation, and forensic forms of these patients were made and administered to those without tetanus vaccine. All patients were logged into the hospital's automation system and patient files. Our hospital's registration structure incorporates diagnoses, admission dates, contact information, and demographic, clinical, and laboratory data.

Statistical Analysis

This study's data were analyzed using the SPSS 20 (SPSS Inc., Chicago, IL, USA) software platform. For continuous variables, descriptive statistics were reported as mean±standard deviation or median (minimum-maximum), and for nominal variables, as number of cases and percentage (%). To investigate the differences between the groups, the Mann-Whitney U Test and Kruskal-Wallis Test were utilized. Chi-square analysis was used to investigate the associations between nominal variable groupings. The linear relationship between the variables was analyzed using a Pearson correlation. A boxplot study of age, mortality, trauma, pre-pandemic, and pandemic periods was undertaken. In analyzing the data, values below the significance threshold of 0.05 were determined statistically significant.

RESULTS

The mean age of the 319 patients who applied was 55.11±19.02 years; distribution was 19-90 years, 133(41.7%) were women. Of the trauma patients, 171(52%) were admitted before the pandemic, and 158(48%) during the pandemic period. Age (p=0.293) and gender (p=0.262) were not associated with pandemic and pre-pandemic referrals. Blood glucose 142.99±55.18mg/dL (p=0.028), white blood cell (WBC) 12.70±3.79 x103/UL (p=0.001), hemoglobin 13.04±2.51 g/dL (p=0.001), and hematocrit %39.33±7.34 (p=0.001), varied significantly between the admission periods. Whereas, platelet, D-dimer, sedimentation, and CRP groups were found to be significant (p=0.001). Evaluation of the pre-pandemic and pandemic groups with variables; 68 (39.8%) of 171 patients before the pandemic and 65 (43.9%) of 148 patients during the pandemic period were women. Falls from height and traffic accidents were equal to 145 cases in both groups, and firearm injuries were detected in 29 cases. Gunshot injuries were also close to each other, with 13 and 16 cases. Of all cases, 272 (85.3%) had upper extremity, 123 (38.6%) pelvis, 294 (92.2%) lower extremity trauma pathology. There was no significant change in injury localizations before and during the pandemic. Among post-traumatic groups, 19 (11.1%) cases of embolism were identified prior to the pre-pandemic, compared to 35 (23.6%) during the pandemic (p=0.003). Before the pandemic, mortality was identified in 10 (5.6%) individuals, and in 21 (14.2%) during the pandemic (p=0.010, **Table 1**).

Table 1. Evaluation of age, gender, laboratory, trauma localization, trauma type, embolism and mortality data in pandemic and pre-pandemic periods.

	Period			
	All Patients	Pre-pandemic	Pandemic	p value
	mean±SD	mean±SD	mean±SD	
Age, year	55.11±19.02	54.26±17.89	56.10±20.28	0.293
Labaratory finding				
Glucose, mg/dL	142.99±55.18	135.32±41.09	151.86±66.98	0.028
WBC, $\times10^3$/UL	12.70±3.79	11.81±3.76	13.71±3.57	0.001
Hemoglobin, g/dL	13.04±2.51	13.72±2.25	12.26±2.57	0.001
Hemotocrit, %	39.33±7.34	41.27±6.63	37.10±7.51	0.001
Platelet, $\times10^3$/UL	251.40±77.02	276.03±67.03	222.95±78.21	0.001
D-dimer, ng/mL	394.05±185.33	344.05±153.41	451.83±202.03	0.001
Sedimentation, mm/h	28.84±20.29	22.20±11.93	36.51±24.02	0.001
CRP, mg/dL	19.24±23.47	13.48±15.97	25.88±28.52	0.001
	n(%)	n(%)	n(%)	
Gender				0.262
Female	133 (41.7)	68 (39.8)	65 (43.9)	
Male	186 (58.3)	103 (60.2)	83 (56.1)	
Trauma Type				0.594
Fall from height	145 (45.5)	78 (45.6)	67 (45.3)	
Traffic accident	145 (45.5)	80 (46.8)	65 (43.9)	
Gunshot injury	29 (9)	13 (7.6)	16 (10.8)	
Trauma Localization				
UE				0.843
No	47 (14.7)	28 (16.4)	19 (12.8)	
Yes	272 (85.3)	143 (83.6)	129 (87.2)	
PV				0.361
No	196 (61.4)	110 (64.4)	86 (58.1)	
Yes	123 (38.6)	61 (38.6)	62 (35.6)	
LE				0.718
No	25 (7.8)	15 (8.8)	10 (6.8)	
Yes	294 (92.2)	156 (91.2)	138 (93.2)	
Embolism				
No	265 (83.1)	152 (88.9)	113 (76.4)	0.003
Yes	54 (16.9)	19 (11.1)	35 (23.6)	
Mortality				0.010
No	288 (90.3)	161 (94.2)	127 (85.8)	
Yes	31 (9.7)	10 (5.8)	21 (14.2)	
TOTAL	319 (100)	171 (100)	148 (100)	

SD: Standard Deviation, WBC: White Blood Cell, CRP: C-reactive protein, UE: Upper Extremity, PV: Pelvis, LE: Lower Extremity, p:Statistical significance (<0.05)

While the mean age of the survival group was 52.59±17.63 years, it was 78.51±15.37 years in the mortality group (p=0.001). Twenty-one (67.7%) of 31 cases with mortality were male. When the mortality status of the pre-pandemic and pandemic groups is evaluated; while it was insignificant with gender, the mortality rate increased with increasing age. Glucose level, WBC, hemoglobin, hematocrit, platelet, D-dimer, sedimentation, and CRP values were associated with mortality (p= 0.001). Mortality was detected in 31 (9.7%) of 319 patients (p=0.001). While there were 16 (51.6%) mortality cases due to falling from a height and 15 (48.4%) mortality cases due to traffic accidents, there was no death due to firearm injuries. When mortality was evaluated according to the traumatic pathology region, it was seen that the region of pelvis and lower extremity traumas had a significant relationship with mortality (p=0.001). While there was no embolism in 9 (29%) cases with mortality, embolism was present in 22 (71%) cases (p=0.001, **Table 2**).

Table 2. Evaluation of age, gender, laboratory, trauma localization, trauma type, embolism and mortality data in pandemic and pre-pandemic periods.

	Mortality		
	No	Yes	p value
	mean±SD	mean±SD	
Age, year	52.59±17.63	78.51±15.37	0.001
Labaratory finding			
Glucose, mg/dL	137.22±45.64	196.66±95.11	0.001
WBC, $\times10^3$/UL	12.28±3.59	16.54±3.43	0.001
Hemoglobin, g/dL	13.40±2.22	9.68±2.53	0.001
Hematocrit, %	40.27±6.64	30.59±7.87	0.001
Platelet, $\times10^3$/UL	258.32±74.25	187.16±73.54	0.001
D-dimer, ng/mL	355.96±146.63	747.90±122.84	0.001
Sedimentation, mm/h	25.06±15.33	63.99±26.45	0.001
CRP, mg/dL	14.80±16.42	60.42±36.27	0.001
	n(%)	n(%)	
Gender			0.177
Female	123 (42.7)	10(32.3)	
Male	165(57.3)	21(67.7)	
Trauma Type			0.044
Fall from height	129(44.8)	16(51.6)	
Traffic accident	130(45.1)	15(48.4)	
Gunshot injury	29(10.1)	0(0)	
Trauma Localization			
UE			0.134
No	46(16)	1(3.2)	
Yes	242(84)	30(96.8)	
PV			0.001
No	195(67.7)	1(3.2)	
Yes	93(32.3)	30(96.8)	
LE			0.001
No	25(8.7)	0	
Yes	263(92.3)	31(100)	
Embolism			0.001
No	279(96.9)	9(29)	
Yes	9(3.1)	22(71)	
TOTAL	288(100)	31(100)	

SD: Standard Deviation, WBC: White Blood Cell, CRP: C-reactive protein, UE: Upper Extremity, PV: Pelvis, LE: Lower Extremity, p:Statistical significance (<0.05)

DISCUSSION

Understanding the epidemiology of trauma enables accurate estimation of morbidity and mortality. As a result, risk groups are identified, clinical treatment is facilitated, and trauma team coordination is facilitated. Fractures of the skeletal system and associated soft tissue changes are the most common type of injury in trauma patients. The emergency department's primary goals for extremity injuries are to define life-threatening, extremity-threatening injuries, to manage extremity injuries in conjunction with other injuries, to determine whether extremity injuries require surgical management, and to manage simple fractures, dislocations, and soft tissue injuries (7). Potentially life-threatening extremity injuries are mainly; active bleeding from major vessels, severe crush injuries, severe open fractures, proximal amputation and multiple proximal extremity fractures. Extremity-threatening extremity injuries are arterial injury or occlusion, compartment syndrome, open fracture, limited crush injuries, and joint dislocations. In addition, mortality is quite common due to complications that develop after trauma, not directly related to trauma (7).

Venous thromboembolism (VTE) is a clinicopathological event in which deep vein thrombosis (DVT) and pulmonary embolism (PE) occur together (8). The frequency of VTE after major trauma is between 10-60%, and the risk of VTE increases up to 13 times in trauma patients. It is a known fact that VTE and mortality rates are higher in patient groups who are being followed up in trauma and intensive care units as immobile compared to other patient groups (9).

The obtained data show that coagulopathy has an important place in the pathogenesis of COVID-19 infection. COVID-19 causes a tendency to thrombosis in both the venous and arterial systems with the activation of the coagulation system by several risk factors such as increased inflammation, platelet activation, endothelial dysfunction and stasis in the blood flow due to immobilization. Coagulopathy seems to be related to the severity of the disease, its pathogenesis is not yet known, and it is thought to occur as a result of a "thromboinflammation" process (10-12)

All this information encouraged us to evaluate the rates of admission to the emergency department, development of embolism, laboratory results and mortality rates of extremity and pelvis trauma cases of pre-pandemic and pandemic periods.

In the study of Öztürk et al. (13) on patients with upper extremity trauma, when the distribution of the cases according to gender and age was examined, it was seen that male patients (n=58) were more than female patients

(n=24) by 71%, and the age range of the patients was mostly between 14-44 years. The mean age was 30.6 years in the study of Srivastava et al. (14) and 32.4 years in the study of Helmi et al (15). Our study also consisted of patients who showed characteristics before and during the pandemic, with a mean age of 55 years and 58.3% male. The fact that the male population is high and they are more active has led to a higher number of male patients.

The elderly population's developmental pattern of trauma is distinct from that of the general population. Traffic accidents are the leading cause of general body trauma worldwide. Age is a risk factor for traffic accidents. The elderly's diminished reflexes and sensations are the primary contributors to the occurrence of such accidents. The most common cause of trauma in our country, accounting for 60-66 percent, is traffic accidents. This is followed by falls (20%), assault (8%), stab wounds (6-8%), and firearm injuries (4%) (16). In some studies, falls are the first cause of trauma in the elderly population, followed by motor vehicle accidents (17). While data were collected in our study, the most common cause of trauma was traffic accidents, followed by falls from height.

Although we evaluated trauma patients in pandemic and pre-pandemic period, we also evaluated the change in laboratory results of two groups in the study. Infection markers such as white blood cell (WBC), sedimentation and C-reactive protein (CRP) are expected to be high in cases of COVID-19, which is already an infectious process. Studies have also shown the relationship between these values and mortality (18). Other reported main laboratory parameters included decreased platelet, lymphocyte, total protein levels, and increased D-dimer, creatinine, and creatine kinase levels (19). Rostami et al. found a significant relationship between D-dimer levels and mortality in their study (20). Yalcin et al. reported the possibility of hereditary thrombophilia with prolonged or newly emerging D-dimer elevation in COVID-19 disease with mild-to-moderate symptoms (21). Similarly, in our study, WBC, CRP, and sedimentation values were found to be high and associated with mortality in the pandemic group. Also, D-dimer was found to be high in the pandemic group and was found to be significantly associated with mortality. We believe that the increase in embolism cases in the study may be correlated with this process.

It has been reported that 10% of deaths worldwide are due to trauma injuries. 3% of all deaths in Turkey occur due to trauma. Again, according to these data, the most common cause of death as a result of trauma is motor vehicle accidents, with 26% of these deaths occurring in young people between the ages of 20-35 and 74% in males (22). In the study of Başoğlu et al. (23) on a blunt multi-trauma patient group, the mortality rate was 16.2%. While the mortality rate was 25% in the study of Helmi et al. (15) on traffic accidents, it was 8.9% in the study of MacLeod et al. (24). Similarly, in the study of Wladis et al. (25), no statistically significant difference was found between the genders in terms of mortality rates. Mortality was found in 31 (9.7%) cases in our study. Mortality was observed in 10 (5.8%) patients in the pre-pandemic group and 21 (14.2%) patients during the pandemic period. Mortality cases in falls from height and traffic accidents were close to each other. Various studies show that the mortality rate in the elderly trauma population varies between 10% and 34% (26,27). 28% of all deaths due to trauma are cases over 65 years of age (26). In our study, the mean age of mortality group was 78 years and there was no significant difference between gender. As in similar studies, falls were detected in the first line of traumas over the age of 75.

COVID-19 has been noted for coagulopathy associated with an increased incidence of DVT and PE. As it is well known, immobility, inflammatory state, and changes in coagulation mechanisms cause DVT and PE (28). In a study of 388 COVID-19 patients in Italy, a thromboembolic event developed in 28 (7.7%) of all patients, 8 (27.6%) of intensive care patients, and 20 (6.4%) of service patients (28). An important factor that worsens the prognosis in COVID-19 cases is the increased probability of developing PE (29). In our study, although pulmonary embolism cases increased despite decreasing trauma numbers, it also seems to have contributed to a significant increase in mortality.

As a result, it is thought that pelvis and extremity traumas decreased numerically during the pandemic period, and this may be due to the decrease in trauma cases due to social restrictions. Despite the decreasing number of traumas, the increase in mortality rates and embolism detections during the pandemic can be explained by the negative contribution of COVID-19 to the process with coagulopathy.

When all these are evaluated, we can say that the pandemic has an indirect effect on the number of traumas to decrease numerically, but that the COVID-19 infection significantly increases the incidence of embolism and mortality by contributing to the thrombotic process with the mechanisms we mentioned. Therefore, although this is always a necessity, care should be taken in terms of embolism, especially in cases of trauma concurrent with COVID-19 infection, and the necessary prophylactic treatment process should be applied in this regard. In this respect, we think that embolism and related mortality will decrease if care is taken and foresighted and necessary prophylaxis is provided in these cases.

One of the study's limitations is that the data were collected retrospectively from a single center, and the data ranges for some patient groups were limited. Another limitation is the loss of patient information and follow-up data after treatment. To maintain a balance in the age and comorbidity distributions, patient selection close to these data points can also be considered a form of limitation.

CONCLUSION

In trauma patients, we can indicate that the presence of old age and COVID-19 infection increase the risk of pulmonary embolism and mortality. The fact that COVID-19 infection increases the risk of developing coagulopathy plays a role in this situation. Additionally, this can be explained by an unintentional reduction in the priority placed on trauma in the provision of health services during the pandemic period, as well as the elective prolongation of necessary procedures. We believe that numerous additional comprehensive studies are necessary to ascertain the pandemic's impact on health services and survival in terms of trauma and internal pathologies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medipol University Noninvasive Clinical Researches Ethics Committee (Date: 14.10.2021, Decision No: 1001).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Birkmeyer JD, Barnato A, Birkmeyer N, Bessler R, Skinner J. The impact of the COVID-19 pandemic on hospital admissions in the United States. Health Affairs 2020; 39: 2010-7.
2. Nourazari S, Davis SR, Granovsky R, et al. Decreased hospital admissions through emergency departments during the COVID-19 pandemic. Am J Emerg Med 2021; 42:203-10.
3. Turkish Health Ministry, https://covid19.saglik.gov.tr/ (Access Date: December 01, 2022)
4. GBD 2016 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 333 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet 2017; 390: 1260-344.
5. Brunett PH, Cameron PA. Trauma. In: Tintinalli JE, Stapczynski JS, Ma OJ, Cline DM, Cydulka RK, Meckler GD, eds. Tintinalli's Emergency Medicine A Comprehensive Study Guide. 7th ed. New York, NY: Mc Graw Hill; 2011: 1671-6.
6. Arvieux C, Thony F, Broux C, et al. Current management of severe pelvic and perineal trauma. J Visc Surg 2012; 149: e227-38.
7. DiMaggio CJ, Avraham JB, Lee DC, Frangos SG, Wall SP. The epidemiology of emergency department trauma discharges in the United States. Acad Emerg Med 2017; 24: 1244-56
8. Sarıkaya S. Approach to the patient with extremity trauma in the emergency department. J Clin Develop 2008; 21: 90-100.
9. Kefer MP. Initial evaluation and management of orthopedic injuries . Cline DM, Ma O, Cydulka RK, Meckler GD, Handel DA, Thomas SH. Eds. Tintinalli's Emergency Medicine Manual, 7e. McGraw Hill. 2012: 843-6.
10. Bikdeli B, Madhavan MV, Jimenez D, et al. Global COVID-19 Thrombosis Collaborative Group, endorsed by the ISTH, NATF, ESVM, and the IUA, supported by the ESC Working Group on pulmonary circulation and right ventricular function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020; 75: 2950-73.
11. Cannegieter SC, Klok FA. COVID-19 associated coagulopathy and thromboembolic disease: Commentary on an interim expert guidance. Res Pract Thromb Haemost. 2020; 4: 439-45.
12. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. Blood 2020; 135: 2033-40.
13. Öztürk Ş, Sevim KZ. The retrospective analysis and the demographics of upper extremity injury patients and their problems in the first 24 hours after operation. Med Bull Sisli Etfal Hosp 2020; 54: 67–72.
14. Srivastava AR, Kumar S, Agarwal GG, Ranjan P. Blunt abdominal injury: Serum ALT-A marker of liver injury and a guide to assessment of its severity. Injury 2007; 38: 1069-74.
15. Helmi I, Hussein A, Ahmed AH. Abdominal trauma due to road traffic accidents in Qatar. Injury 2001; 32: 105-8.
16. Thal ER, Rochon RB. Inner-city trauma centers. Financial burdens or community saviors? Surg Clin North Am 1991; 71: 209-19.
17. Liberman M, Mulder DS, Sampalis JS. Increasing volume of patients at level I trauma centres: Is there a need for triage modification in elderly patients with injuries of low severity? Can J Surg 2003; 46: 446-52.
18. Bindal A, Patmano M, Cansun F. Laboratory markers used to predict mortality in severe COVID-19. Ann Med Res 2022; 29: 545–9.
19. Y Salamanna F, Maglio M, Landini MP, Fini M. Platelet functions and activities as potential hematologic parameters related to Coronavirus Disease 2019 (Covid-19). Platelets 2020; 31: 627-32.
20. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol 2020; 13: 1265-75.
21. Yalçın KS, Yücetürk H, Kasapoğlu B, Kekilli M. The relationship between extended D-dimer elevations and hereditary thrombophilia in COVID-19 patients. J Med Palliat Care 2022; 3: 147-151.
22. Kirkpatrick JR, Youmans RL. Trauma index. An aide in the evaluation of injury victims. J Trauma 1971; 11: 711-4.
23. Başoğlu A, Akdağ AO, Celik B, Demircan S. Thoracic trauma: an analysis of 521 patients. TJTES 2004; 10: 42-6.

24. MacLeod J, Lynn M, McKenney MG, Jeroukhimov I, Cohn SM. Predictors of mortality in trauma patients. Am Surg 2004; 70: 805-10.
25. Wladis A, Boström L, Nilsson B. Injuries and mortality in motorcycle and moped accidents in Sweden 1987-1994. Advanced age and male sex are risk factors of fatal moped and motorcycle accidents. Lakartidningen 2003; 100: 1238-41.
26. Ma OJ, DeBehnke DJ. Geriatric trauma. In: Tintinalli J, Kelen GD, Stapcznski JS, eds. Emergency Medicine, A Comprehensive Study Guide. 5th ed. New York, NY: McGraw-Hill; 1999:1623-7.
27. Richmond TS, Kauder D, Strumpf N, Meredith T. Characteristics and outcomes of serious traumatic injury in older adults. J Am Geriatr Soc 2002; 50: 215-22.
28. Klok FA, Kruip MJHA, van der Meer NJM, et al. Confirmation of the high cumulative incidence of thrombotic complications in critically ill ICU patients with COVID-19: An updated analysis. Thromb Res 2020; 191: 148–50.
29. Rindi LV, Al Moghazi S, Donno DR, Cataldo MA, Petrosillo N. Predictive scores for the diagnosis of Pulmonary Embolism in COVID-19: A systematic review. Int J Infect Dis. 2022; 115: 93-100.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1240036

Anatolian Curr Med J 2023; 5(2); 91-96

The role of ADC histogram analysis in the diagnosis of pediatric malignant lymphadenopathy

Turgut Seber[1], Tuğba Uylar Seber[1], Elif Aktaş[1], Fatma Türkan Mutlu[2], Veysel Gök[2], Şuayip Keskin[3], Fatoş Tekelioğlu[4], Erdem Arzu Taşdemir[4]

[1]Department of Radiology, Kayseri City Education and Research Hospital, Kayseri, Turkey
[2]Department of Pediatric Hematology and Oncology, Kayseri City Education and Research Hospital, Kayseri, Turkey
[3]Department of Pediatric Health and Diseases, Kayseri City Education and Research Hospital, Kayseri, Turkey
[4]Department of Medical Pathology, Kayseri City Education and Research Hospital, Kayseri, Turkey

Cite this article as: Seber T, Uylar Seber T, Aktaş E, et al. The role of ADC histogram analysis in the diagnosis of pediatric malignant lymphadenopathy. Anatolian Curr Med J 2023; 5(2); 91-96.

ABSTRACT

Aim: Lymphadenopathy (LAP) is one of the most common daily practice clinical findings in children. LAPs that involve more than one region and do not decrease with treatment are a significant cause of anxiety for clinicians and families. In this occurence, ultrasonography, which is the primary imaging method, is insufficient in some cases. Our aim is to make histopathological predictions with apparent diffusion coefficient (ADC) histogram analysis.

Material and Method: A total of thirty-one patients, seventeen male and fourteen female, who underwent magnetic resonance imaging and were diagnosed histopathologically (with tru-cut or excisional biopsy) were included in our study. Magnetic resonance imagings were evaluated retrospectively.

Results: We could not differentiate lymphoma (when considered as a single group), granulomatous LAP and reactive lymphoid hyperplasia with an ADC histogram analysis ($p>0.05$). However, when the lymphoma subgroups were evaluated separately, we could only distinguish Burkitt's lymphoma (with ADCmin values) from other pathologies ($p<0.05$). The optimal cut-off value distinguishing Burkitt's lymphoma from other groups was 245×10^{-6} mm²/sec in receiver operating characteristic curve analysis (AUC 0.981, sensitivity 75%, specificity 93%, PPV 67%, NPV 93%). As in recent studies, we did not find significant differences in ADC histogram analysis values of reactive lymphoid hyperplasia, granulomatous LAPs and lymphomas (when considered as a single group). However, when the lymphoma subgroups were considered separately, we were able to distinguish Burkitt's lymphoma from other subgroups and granulomatous LAP, reactive lymphoid hyperplasia with the ADCmin value.

Conclusion: The ADCmin value in pediatric LAPs may contribute to the diagnosis of Burkitt's lymphoma.

Keywords: Lymphadenopathy, pediatric, magnetic resonance imaging, histogram analysis, apparent diffusion coefficient

INTRODUCTION

Lymphadenopathy (LAP) is a common clinical finding in children and results from the infiltration in lymph nodes with phagocytic or malignant cells or the proliferation of normal lymphoid elements. In most patients, the cause can be identified with a careful history and a complete physical examination. Since infections are the most common cause, the majority of children are given empirical antibiotic therapy first (1). If the lymph nodes do not regress in size or if they increase in size and number within 4 to 6 weeks, and there are systemic complaints, laboratory and imaging methods are used to determine the underlying cause (2). Ultrasound is the most suitable initial imaging method, as it does not contain ionizing radiation. Computed tomography and magnetic resonance imaging (MRI) are usually complementary and contribute to the diagnosis when required.

It has been reported that diffusion-weighted imaging (DWI) is effective in distinguishing benign and malignant lymph nodes, and can help conventional sequences (3, 4). Our aim was to minimize data loss with apparent diffusion coefficient (ADC) map histogram analysis (HA) and to prevent individual-dependent subjective assessment (5, 6).

MATERIAL AND METHOD

The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 29.09.2022, Decision No: 706). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Corresponding Author: Turgut Seber, turgutseber@hotmail.com

Received: 20.01.2023 **Accepted:** 05.02.2023

Thirty-one children were retrospectively re-evaluated, between December 2019 and January 2022. We obtained the clinical information and MRIs of the subjects from the hospital records and the PACS system.

Study Patients

The patients consisted of seventeen boys and fourteen girls, with a mean age of thirteen years and a range of 4 to 17. All subjects were undergoing MRI and diagnosed histopathologically with tru-cut or excisional biopsy.

MRI Technique

All MRI examinations were performed on a 3T MRI (Magneatom Skyra; Siemens Healthcare, Erlangen, Germany) using a body matrix 8-channels flex coil and 20 channels neck coil, depending on the localization of lymph nodes. Intravenous sedation (ketamine 1 mg/kg) was performed for two children who were six and seven years old, in order to prevent motion artifacts. All subjects had standard sequences (including T1 and T2 weighted turbo spin-echo, contrast-enhanced T1 turbo spin-echo) with DWI and ADC map. Interleaved multi-shot (IMS) echo-planar imaging (EPI) DWI sequences were acquired using 2 b values (b=0–1000 sec/mm²) and 3 orthogonal (x, y, z) diffusion directions. ADC was the mean diffusivity. The acquisition parameters of DWI were as follows: FOV=120×120 mm; matrix size 128×128; slice thickness=4 mm; voxel size=0.9×0.9×4 mm; distance factor=0%; TR=6600 msn; TE=87 msn; turbo factor=128; number of excitations=3; integrated parallel acquisition technique factor=2. ADC maps were pixel-based and postprocessed, with a mono-exponential calculation from DWI.

Imaging Evaluation

Volumetric HA was performed for lymph nodes on the ADC map. Lymph nodes were drawn separately in each slice with a free-hand 3D volume of interest. Necrotic areas were excluded from the volume of interest. The quantitative ADC values (mean [ADCmean], median [ADCmedian], mode [ADCmode], minimum [ADCmin], maximum [ADCmax], kurtosis, skewness, P10 [10th percentile ADC], P25 [25th percentile ADC], P75 [75th percentile ADC], P90 [90th percentile ADC]) were obtained separately for each region and statistically compared with the histopathology. Analyses and evaluations were performed on a Syngo Via (Software Version VA30A, Siemens AG, Germany) Workstation by a pediatric radiologist (T.S.) with seven years of experience in pediatric radiology.

Statistical Analyses

The distribution of histogram parameters was normal with the "Kolmogorov–Smirnov" test. The "One Way Anova" test was used to compare each parameter with the histopathology in the groups. Receiver operating characteristic (ROC) curve analyses were used to determine the potential diagnostic performance. All statistical analyses were performed using the SPSS software (version 22.0; SPSS Inc., Chicago, IL, USA). In all analysis, $p<0.05$ was taken to indicate statistical significance.

RESULTS

The study population consisted of thirty-one patients (seventeen boys and fourteen girls, age range of 4 to 17 years, with a mean age of 13 years). There were no significant differences in sex or age distribution between the groups (p=0.5 and p=0.8, respectively).

Histopathological diagnoses of LAPs are reactive lymphoid hyperplasia (n=7), granulomatous LAP (GL) (n=7), nodular sclerosing HL (n=5), Burkitt's lymphoma (BL) (n=4), anaplastic large cell NHL (n=4) and mixed cellular HL (n=4).

With HA, the differentiation of lymphoma (when considered as a single group), GL and RLH was not statistically significant ($p>0.05$). When lymphoma subgroups were considered separately, only the ADCmin values of BL were found to be significantly lower than other pathologies (**Table 1**, **Figure 1**). The optimal cut-off value distinguishing BL from other groups was 245×10^{-6} mm²/sec in ROC curve analysis (AUC 0.981, sensitivity 75%, specificity 93%, PPV 67%, NPV 93%) (**Figure 2**). The long and short axis of lymph nodes were significantly larger in lymphoma compared to other groups (p=0.005), and there was no significant difference between RLH and GL (p=0.13) (**Table 2**, **Figure 3**). Cut-off values distinguishing lymphoma from other groups were 31 mm for the long axis (AUC 0.899, sensitivity 88%, specificity 86%, PPV 88%, NPV 86%), 21.5 mm for the short axis in ROC curve analysis (AUC 0.868, sensitivity 82%, specificity 79%, PPV 87%, NPV 80%) (**Figure 4**).

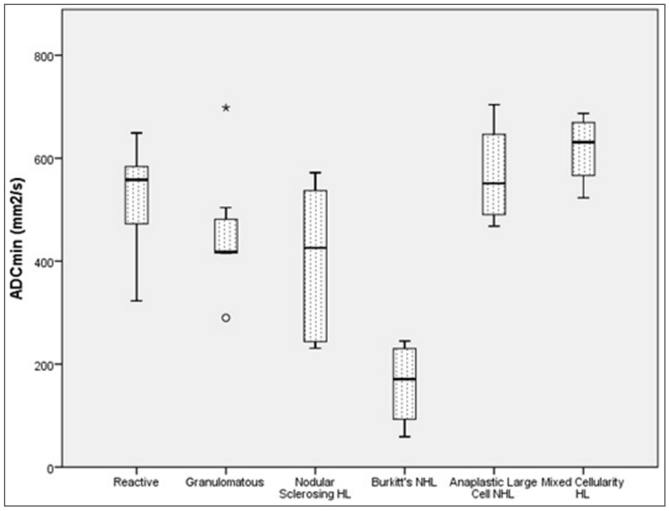


Figure 1. Box- and- Whisker plot showing the distribution of groups according to ADCmin

(ADC apparent diffusion coefficient, HL Hodgkin's lymphoma, Min minimum, NHL non-Hodgkin's lymphoma)

Table 1. Distribution of histopathologies according to ADCmin values

Histopathology	N (%)	Mean±SD	Min.-Max.	95% CI	P value (differentiation from Burkitt's Lymphoma)
Reactive LH	7 (22.6%)	520±112	323-649	416-624	0.001
Granulomatous LAP	7 (22.6%)	457±124	290-698	342-572	0.005
Nodular Sclerosing HL	5 (16.1%)	402±159	231-572	231-600	0.05
Burkitt's Lymphoma	4 (12.9%)	161±84	59-245	59-245	---------
Anaplastik Large cell NHL	4 (12.9%)	568±103	468-704	468-704	0.001
Mixed Cellularity HL	4 (12.9%)	618±70	523-687	523-687	0.001
Total	31(100%)				

(ADC apparent diffusion coefficient, HL Hodgkin's lymphoma, LAP lymphadenopathy, LH lymphoid hyperplasia Max maximum, Min minimum, N number of cases, NHL non-Hodgkin's lymphoma, SD standard deviation; The unit of values is 10^{-6}×mm²/sec)

Table 2. Shows the distribution of the short and long axes of the lymph nodes according to the groups

Histopathology	N (%)	Short axis	Long axis
		Min.-Max. (Mean±SD) [95% CI]	Min.-Max. (Mean±SD) [95% CI]
Reactive LH	7 (22.6%)	5 – 14 mm (8.43±2.99) [5.66 – 11.2]	10 – 22 mm (14.43±4.27) [10.47 – 18.38]
Granulomatous LAP	7 (22.6%)	6 – 35 mm (19.14±10.97) [8.99 – 29.29]	10 – 51 mm (27.14±16.32) [12.05 – 42.24]
Nodular Sclerosing HL	5 (16.1%)	19 – 60 mm (39±17.29) [17.53 – 60.47]	32 – 74 mm (53±16.88) [32.04 – 73.96]
Burkitt's Lymphoma	4 (12.9%)	22 – 42 mm (29±9.45) [13.96 – 44.04]	33 – 55 mm (40.25±10.04) [24.27 – 56.23]
Anaplastik Large cell NHL	4 (12.9%)	21 -33 mm (26.5±5.19) [18.23 – 34.77]	30 -54 mm (39.5±10.24) [23.19 – 55.81]
Mixed Cellularity HL	4 (12.9%)	16 – 43 mm (29.25±11.5) [10.95 – 47.55]	27 – 67 mm (43.5±17.13) [16.23 – 70.77]
Total	31 (100%)		

(CI confidence interval, HL Hodgkin's lymphoma, LAP lymphadenopathy, LH lymphoid hyperplasia, Max maximum, Min minimum, NHL non-Hodgkin's lymphoma, SD standard deviation)

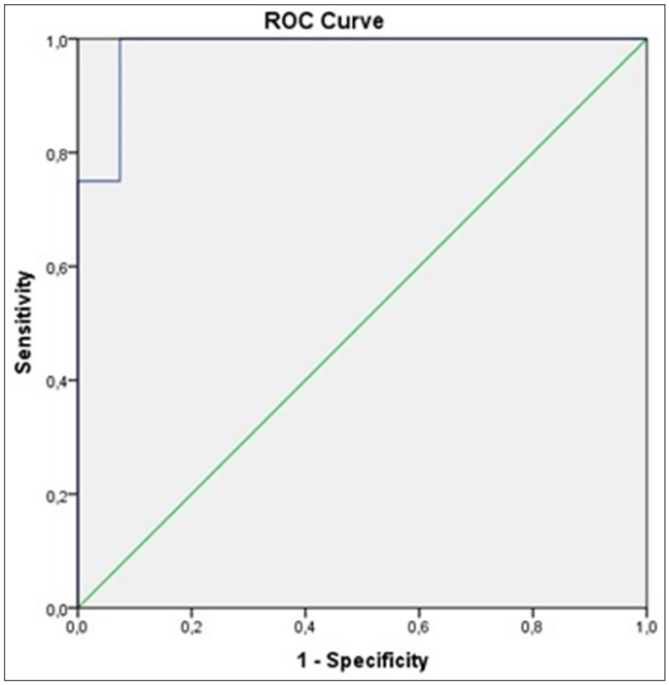


Figure 2. ROC curve analysis showing the differentiation of Burkitt's lymphoma from other lymphoma subgroups and pathologies according to ADCmin values.

(ADC apparent diffusion coefficient, Min minimum)

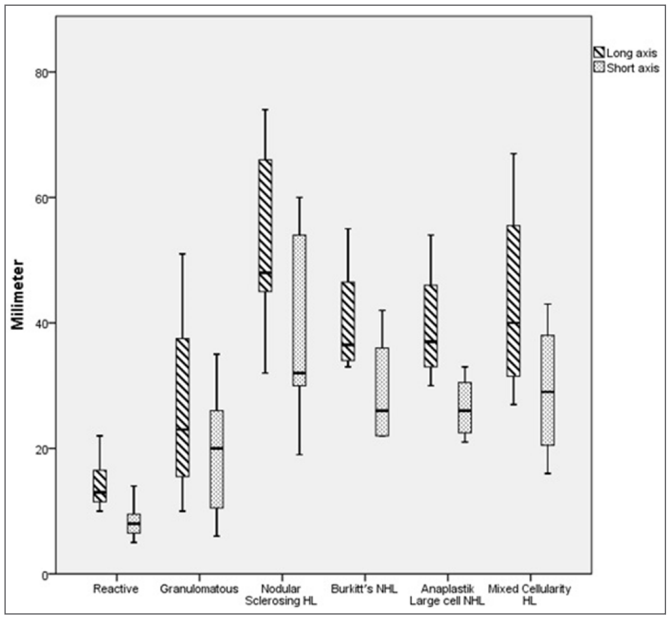


Figure 3. Box and Whisker plot graph showing the distribution of the groups according to the short and long axes

(HL Hodgkin's lymphoma, NHL non-Hodgkin's lymphoma)

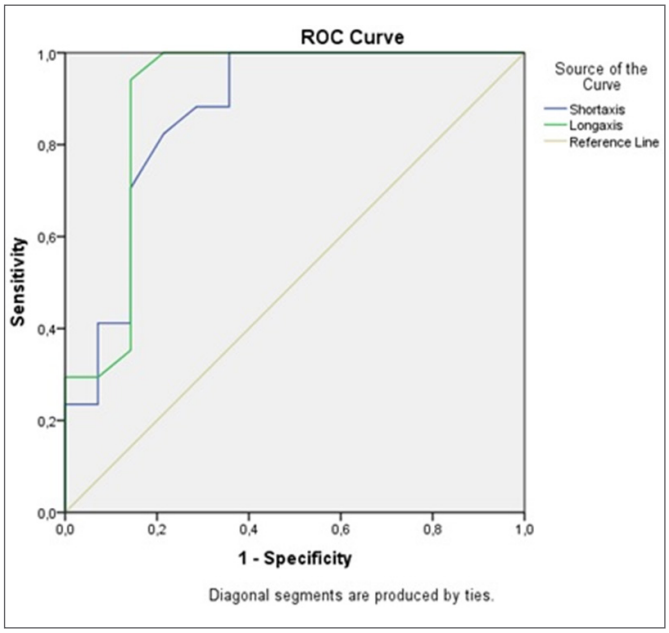


Figure 4. ROC curve analysis showing the differentiation of lymphoma from other groups according to the short and long axes of the lymph nodes

DISCUSSION

DWI visualizes the differences in movement of water between cells in the tissues. Cellular tissues (e.g., lymph nodes) give a high signal, while less cellular tissues have a low signal. Thus, lymph nodes can be easily distinguished from the surrounding tissues. Diffusion can be measured by the ADC map obtained from DWI, which allows tissue characterization and is easily reproducible (7-9). Clinicians can easily identify possible causes of LAP by history and physical examination and rarely require imaging. In these situations, it is crucial for the radiologist to recognize the normal cervical lymph nodes, and report nodal features of specific infections, inflammatory conditions and neoplasms, to assist clinicians in treatment.

RLH is a benign nodular lesion histopathologically characterized by marked proliferation of non-neoplastic polyclonal lymphocytes, that form follicles with active germinal centers. GL is divided into infectious and non-infectious (10). Infectious GL is divided into suppurative and non-suppurative.The suppurative type was not included in our study because it contained central abscess or necrosis (**Figure 5**). The non-infectious type mostly consists of berylliosis, sarcoidosis and sarcoidosis-like reactions (11). In this type, central abscess or necrosis is very rare and is usually caused by tuberculosis and Bacillus Calmette-Guerin (BCG) lymphadenitis. Low ADC values, which can be confused with malignancy, can be observed in RLH and GL (4,12-14).

Studies of ADC-HA in lymph nodes have generally been performed on adults and are aimed at differentiating lymphoma from squamous cell carcinoma metastasis (5,15) and nasopharyngeal carcinoma (16,17). Our study, for its part, was carried out in children with no known diseases and isolated LAP in different body parts, which we meet frequently in our daily practice. We did not have a patient with a diagnosis of squamous cell carcinoma. Therefore, he is not in our study group.

Lymphoma constitutes 10 to 15% of all childhood malignancies. There are two types, HL and NHL: the latter is more common and BL is the most common subtype of NHL in children (40%), whereas it is the least subtype in adults (**Figures 6** and **7**). The sporadic variant is associated with abdominal involvement (18,19). It can be localized or has a diffuse infiltrative pattern. It is an aggressive tumor with a doubling time of 24 to 48 hours. Therefore, early diagnosis and treatment are life-saving (airway obstruction and spinal cord compression are important causes of mortality and morbidity). MRI is very valuable in diagnosis because of its high soft tissue contrast. DWI makes a significant contribution to conventional sequences in the diagnosis of lymphoma (20).

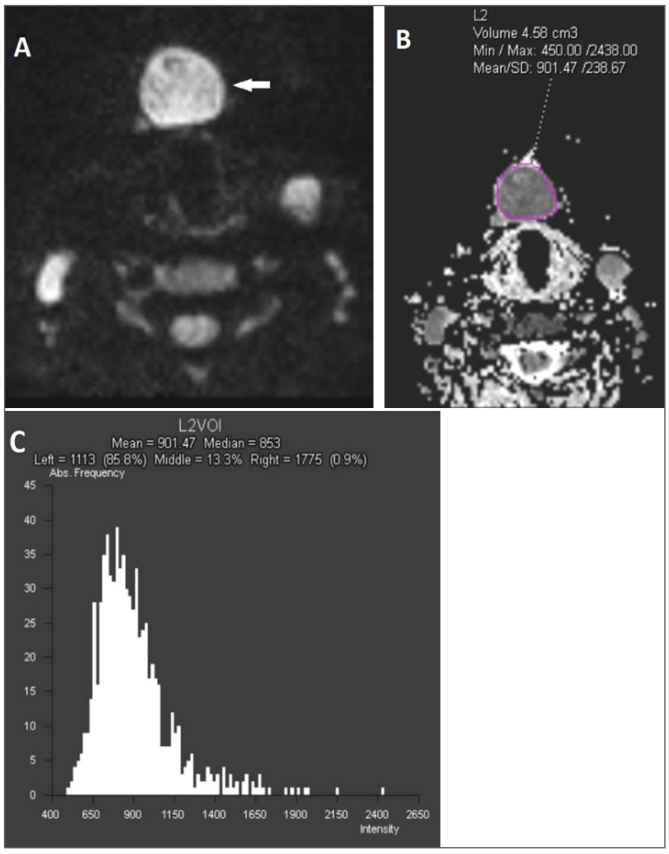


Figure 5. A 15-year-old girl had a lymphadenopathy (arrow) in the submental region (level 1A) that did not decrease in size with treatment (DWI [A], ADC map [B]). Histogram plot (C) was obtained from the lymphadenopathy. Histopathological result was consistent with granulomatous lymphadenopathy.

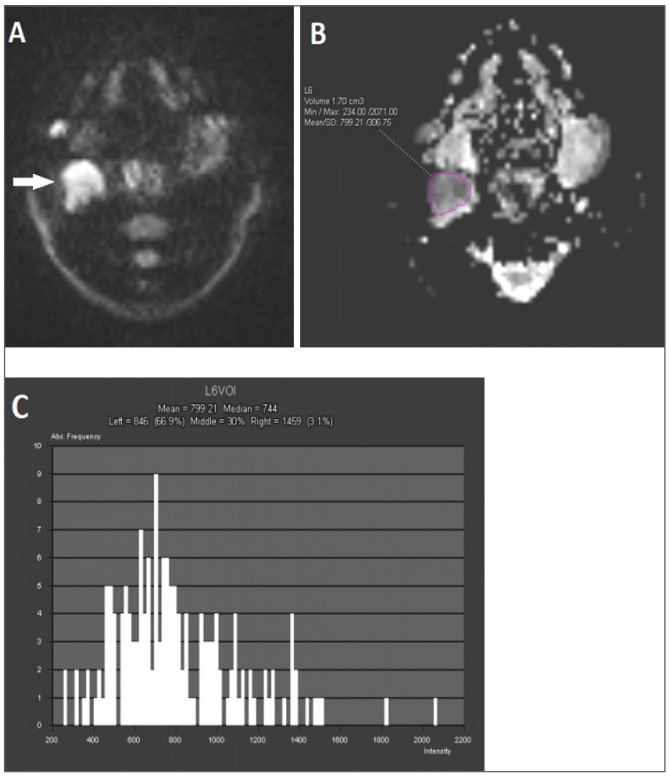


Figure 7. 10-year-old boy had a lymphadenopathy (arrow) with diffusion restriction (DWI [A], ADC map [B]) in the right submandibular region (level 2A). Histogram plot (C) was obtained from the lymphadenopathy. Histopathological result was consistent with Burkitt's lymphoma.

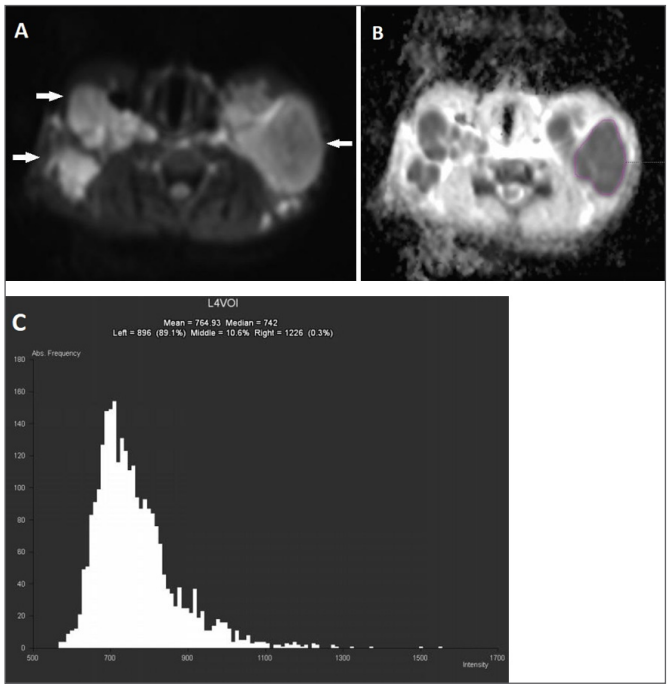


Figure 6. 13-year-old boy had multiple lymphadenopathies (arrows) with diffusion restrictions (DWI [A], ADC map [B]) in the bilateral anterior-posterior cervical chain (level 4-5B). Histogram plot (C) was obtained from large lymphadenopathy at left level 5B. Histopathological result was consistent with classical HL (nodular sclerosing type).

Early studies of DWI in lymph nodes reported significant differences in mean ADC values between lymphoma and normal lymph nodes (3,21-23). However, subsequent studies have found that mean ADC values overlap in pathological and normal lymph nodes (24,25). In some studies about mediastinal lymph nodes, ADC values were found to be significantly lower in lymphoma than in sarcoidosis (26,27). Differentiation of lymphoma subgroups (NHL, HL) could not be achieved in most studies (14,28,29). In these studies, only mean, min and max ADC values were obtained without HA. As in recent studies, we found no significant differences in the ADC-HA of RLH, GLs and lymphomas. However, when the subgroups of lymphoma were considered separately, we were able to distinguish BL from other subgroups and GL, RLH via the ADCmin value. ADCmin values of BL were found to be significantly lower than other pathologies.

CONCLUSION

ADCmin value in pediatric LAPs may contribute to the diagnosis of BL.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 29.09.2022, Decision No: 706).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgements: We would like to thank the Medical Specialty Education Committee for their permission. The English in this document has been checked by J.Y.B, who is native English speaker and professional editor. We thank him for his contributions.

REFERENCES

1. Nield LS, Kamat D. Lymphadenopathy in children: when and how to evaluate. Clin Pediatr (Phila) 2004; 43: 25–33.
2. Tower RL, Carmitta BM. Lymphadenopathy. In: Kliegman RM, Stanton BF, St Geme JW, Schor NF (eds). Nelson Textbook of Pediatrics (20th ed). California, 2016: 2413-15.
3. Abdel Razek AA, Soliman NY, Elkhamary S, Alsharaway ML, Tawfik A. Role of diffusionweighted MR imaging in cervical lymphadenopathy. Eur Radiol 2006; 16: 1468-77.
4. Vandecaveye V, De Keyzer F, Vander Pooten V, et al. Head and neck squamous cell carcinoma: value of diffusion-weighted MR imaging for nodal staging. Radiology 2009; 251: 134-46.
5. Wang YJ, Xu XQ, Hu H, et al. Histogram analysis of apparent diffusion coefficient maps for the differentiation between lymphoma and metastatic lymph nodes of squamous cell carcinoma in head and neck region. Acta Radiol 2018; 59: 672-80.
6. De Paepe KN, De Keyzer F, Wolter P, et al. Improving lymph node characterization in staging malignant lymphoma using first-order ADC texture analysis from whole-body diffusion-weighted MRI. J Magn Reson Imaging 2018; 48: 897-906.
7. Le Bihan D. Molecular diffusion nuclear magnetic resonance imaging. Magn Reson Q 1991; 7: 1-30.
8. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: applications and challenges in oncology. AJR Am J Roentgenol 2007; 188: 1622-35.
9. Donners R, Blackledge M, Tunariu N, Messiou C, Merkle EM, Koh DM. Quantitative whole-body diffusion- weighted MR imaging. Magn Reson Imaging Clin N Am 2018; 26: 479-94.
10. Chang KL, Arber DA, Gaal KK, Weiss LM. Lymph nodes and spleen. In: Silverberg SG, DeLellis RA, Frable WJ, LiVolsi VA, Wick MR, editors. Silverberg's Principles and practice of surgical pathology and cytopathology. Volume 1. New York: Churchill Livingstone; 2006: 507–607
11. Brincker H. Sarcoid reactions in malignant tumours. Cancer Treat Rev 1986; 13: 147-56.
12. ElSaid NA, Nada OM, Habib YS, et al. Diagnostic accuracy of diffusion weighted MRI in cervical lymphadenopathy cases correlated with pathology results. Egypt J Radiol Nuclear Med 2014; 45: 1115-25.

13. Nomori H, Mori T, Ikeda K, et al. Diffusion-weighted magnetic resonance imaging can be used in place of positron emission tomography for N staging of nonsmall cell lung cancer with fewer false-positive results. J Thorac Cardiovasc Surg 2008; 135: 816-22.
14. Abdel Razek AA, Gaballa G, Elashry R, Elkhamary S. Diffusion-weighted MR imaging of mediastinal lymphadenopathy in children. Jpn J Radiol 2015; 33: 449-54.
15. Vidiri A, Minosse S, Piludu F, et al. Cervical lymphadenopathy: can the histogram analysis of apparent diffusion coefficient help to differentiate between lymphoma and squamous cell carcinoma in patients with unknown clinical primary tumor? Radiol Med 2019; 124: 19-26.
16. Lian S, Zhang C, Chi J, Huang Y, Shi F, Xie C. Differentiation between nasopharyngeal carcinoma and lymphoma at the primary site using whole-tumor histogram analysis of apparent diffusion coefficient maps. Radiol Med 2020; 125: 647-53.
17. Song C, Cheng P, Cheng J, Zhang Y, Xie S. Value of apparent diffusion coefficient histogram analysis in the differential diagnosis of nasopharyngeal lymphoma and nasopharyngeal carcinoma based on readout-segmented diffusion-weighted imaging. Front Oncol 2021; 11: 632796.
18. Molyneux EM, Rochford R, Griffin B, et al. Burkitt's lymphoma. Lancet 2012; 379: 1234-44.
19. Thomas AG, Vaidhyanath R, Kirke R, Rajesh A. Extranodal lymphoma from head to toe: part 1, the head and spine. AJR Am J Roentgenol 2011; 197: 350–6.
20. Gu J, Chan T, Zhang J, Leung AY, Kwong YL, Khong PL. Whole-body diffusion-weighted imaging: the added value to whole-body MRI at initial diagnosis of lymphoma. AJR Am J Roentgenol 2011; 197: W384–91.
21. Kwee TC, Ludwig I, Uiterwaal CS, et al. ADC measurements in the evaluation of lymph nodes in patients with non-Hodgkin lymphoma: feasibility study. MAGMA 2011; 24: 1-8.
22. Holzapfel K, Duetsch S, Fauser C, Eiber M, Rummeny EJ, Gaa J. Value of diffusion-weighted MR imaging in the differentiation between benign and malignant cervical lymph nodes. Eur J Radiol 2009; 72: 381-7.
23. Perrone A, Guerrisi P, Izzo L, et al. Diffusion-weighted MRI in cervical lymph nodes: differentiation between benign and malignant lesions. Eur J Radiol 2011; 77: 281-6.
24. De Paepe K, Bevernage C, De Keyzer F, et al. Whole-body diffusion-weighted magnetic resonance imaging at 3 Tesla for early assessment of treatment response in non-Hodgkin lymphoma: a pilot study. Cancer Imaging 2013; 13: 53-62.
25. Wu X, Nerisho S, Dastidar P, et al. Comparison of different MRI sequences in lesion detection and early response evaluation of diffuse large B-cell lymphoma--a whole-body MRI and diffusion-weighted imaging study. NMR Biomed 2013; 26: 1186-94.
26. Santos FS, Verma N, Marchiori E, et al. MRI-based differentiation between lymphoma and sarcoidosis in mediastinal lymph nodes. J Bras Pneumol 2021; 47: e20200055.
27. Sabri YY, Kolta MFF, Khairy MA. MR diffusion imaging in mediastinal masses the differentiation between benign and malignant lesions. Egypt J Radiol Nucl Med 2017; 48: 569–80.
28. Sabri YY, Nossair EZB, Assal HH et al. Role of diffusion weighted MR-imaging in the evaluation of malignant mediastinal lesions. Egypt J Radiol Nucl Med 2020; 51: 1-16.
29. Sabri YY, Ewis NM, Zawam HE, Khairy MA. Role of diffusion MRI in diagnosis of mediastinal lymphoma: initial assessment and response to therapy. Egyptian Journal of Radiology and Nuclear Medicine 2021; 52: 1-11.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1240882

Anatolian Curr Med J 2023; 5(2); 97-101

Determination of antibiotic resistance rates of *Escherichia coli* and *Klebsiella pneumoniae* isolates, which are the causative agents of urinary tract infection in pregnant women

Süheyla Aydoğmuş[1], Esra Kaya Kılıç[2]

[1]Clinic of Obstetrics and Gynaecology, Ankara Training and Research Hospital, University of Health Sciences, Ankara, Turkey
[2]Clinic of Infectious Diseases and Clinical Microbiology, Ankara Training and Research Hospital, University of Health Sciences Ankara, Turkey

Cite this article as: Aydoğmuş S, Kaya Kılıç E. Determination of antibiotic resistance rates of *Escherichia coli* and *Klebsiella pneumoniae* isolates, which are the causative agents of urinary tract infection in pregnant women. Anatolian Curr Med J 2023; 5(2); 97-101.

ABSTRACT

Aim: Urinary tract infections are common infections during pregnancy. Infections seen during pregnancy have a spectrum ranging from asymptomatic bacteriuria to cystitis, pyelonephritis and, urosepsis. In this study, it was aimed to determine the antibiotic resistance rates of *Escherichia coli* (*E. coli*) and *Klebsiella pneumoniae* (*K. pneumoniae*) isolates isolated from urinary cultures of pregnant women who applied to the Ankara Training and Research Hospital.

Material and Method: The identification and antibiotic susceptibility of *E. coli* and *K. pneumoniae* isolates isolated from urinary samples of pregnant women who applied to the Ankara Training and Research Hospital between January 2021 and December 2022 were investigated with VITEK-2 (Biomerioux, France) fully automated system, and the presence of extended-spectrum beta-lactamase (ESBL) was investigated by combined disc diffusion method. The obtained data were analysed retrospectively.

Results: Bacterial growth was detected in 1090 (1.2%) out of a total of 8923 urine samples over a two-year period. 480 (4.4%) of the microbial agents reproducing in urine culture were *E. coli* and 105 (0.96%) were *K. pneumoniae*. The rate of extended-spectrum beta-lactamase (ESBL) in *E. coli* strains was 16.04% (77/480), and the rate of ESBL in *K. pneumoniae* strains was 20.9% (22/105). Resistance rates of amoxicillin-clavulanic acid, ceftriaxone, phosphomycin, ciprofloxacin, piperacillin-tazobactam, nitrofurantoin, imipenem, meropenem, ertapenem in ESBL negative *E. coli* strains were 15.9%, 8.82%, 20%, 11.1%, 5.88%, 0%, 0%, 0% and 0%, respectively. Resistance rates of amoxicillin-clavulanic acid, ceftriaxone, phosphomycin, ciprofloxacin, piperacillin-tazobactam, nitrofurantoin, imipenem, meropenem, ertapenem in ESBL positive *E. coli* strains were determined as 66.5%, 100%, 2.2%, 33.8%, 11.5%, 0%, 0%, 0% and, 0%, respectively. Resistance rates of amoxicillin-clavulanic acid, ceftriaxone, phosphomycin, ciprofloxacin, piperacillin-tazobactam, nitrofurantoin, imipenem, meropenem, ertapenem in ESBL negative *K. pneumoniae* strains were 53%, 100%, 12.5%, 28.5%, 2.2%, 3.5%, 0%, 0% and, 4.5%, respectively. Resistance rates of amoxicillin-clavulanic acid, ceftriaxone, phosphomycin, nitrofurantoin, ciprofloxacin, piperacillin-tazobactam, imipenem, meropenem, ertapenem in ESBL positive *K. pneumoniae* strains were 62.5%, 100%, 12.5%, 35%, 28.5%, 22.7%, 0%, 0% and, 4.5%, respectively.

Conclusion: According to the antibiotic susceptibility data in our hospital, phosphomycin or carbapenems may be preferred due to the low resistance rate in the empirical treatment of *E. coli*-related urinary tract infections in pregnant women. In the treatment of urinary tract infections due to *K. pneumoniae*, phosphomycin, piperacillin-tazobactam or carbapenems may be preferred due to low resistance rates.

Keywords: Pregnancy, urinary tract infection, *Escherichia coli*, *Klebsiella pneumoniae*, extended-spectrum beta-lactamase, antibiotic susceptibility

INTRODUCTION

Urinary tract infections are more common in women than men. Most urinary tract infections in women are asymptomatic urinary tract infections. While more than 60% of women have urinary tract infections throughout their lives, 10% of women may have urinary tract infections every year (1).

Anatomical and physiological changes during pregnancy are predisposing factors for urinary tract infections. The increase in uterine dimensions with pregnancy, facilitates urinary tract infections by causing stasis in the dilatation of urinary flow in the ureter and bladder with the effect of progesterone. Glucosuria, urine osmolality and changes in urine pH during pregnancy are also factors that predispose to urinary tract infections (2,3).

Escherichia coli (*E. coli*) is the most common cause of urinary tract infections in society and hospitals (4-6). Antibiotic resistance rates in *E. coli* strains may differ between countries, geographical regions and hospitals (2,4-7).

The main urinary tract infections seen in pregnant women are asymptomatic bacteriuria, cystitis, pyelonephritis. The most common cause of urinary tract infection in pregnant women is *E. coli* (2,3,8,9). While

Corresponding Author: Süheyla Aydoğmuş, suheylaaydogmus@gmail.com

Received: 23.01.2023 **Accepted:** 07.02.2023

asymptomatic bacteriuria seen during pregnancy should be treated, asymptomatic bacteriuria that can be seen in non-pregnant women does not need to be treated (10).

In this study, it was aimed to determine the antibiotic resistance rates of *E. coli* and *Klebsiella pneumoniae* (*K. pneumoniae*) bacteria isolated from the urine cultures of pregnant women who applied to Ankara Training and Research Hospital and to determine the appropriate empirical antibiotic treatment options.

MATERIAL AND METHOD

No human or animal material was used. It is the study of antibiotic resistance in bacteria. It does not require an ethics committee decision. Institutional approval has been obtained.

Urine samples of pregnant women who applied to Ankara Training and Research Hospital between January 2021 and December 2022 were incubated in 5% sheep-blooded agar and eosin methylene blue (EMB) agar medium with quantitative culture method at 37 ° C for 18-24 hours under aerobic conditions. Samples with single species and 105 colony forming units (CFU) reproduction in urine culture were evaluated. Only *E. coli* and *K. pneumoniae* isolates were included in the study. Identification and antibiotic susceptibility of *E. coli* and *K. pneumoniae* isolates isolated from urine samples were investigated with VITEK-2 (Biomerioux, France) fully automated system, and the presence of extended-spectrum beta-lactamase (ESBL) was investigated by the double-disc synergy method.

Double-Disc Synergy Test

For the test, bacterial suspension was prepared from colonies in fresh bacterial culture equal to 0.5 McFarland turbidity and transplanted into Mueller-Hinton Agar plaque. Three antibiotic discs [aztreonam (30 µg), ceftriaxone (30 µg), ceftazidime (30 µg)] were placed 20 mm away from the center of the amoxicillin-clavulanic acid (20/10 µg) disc and incubated at 37°C for 24 hours (11,12). Antibiotic susceptibilities of isolated *E. coli* and K. pneumonia strains were evaluated according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria (13). The obtained data were analysed retrospectively. Antibiotic resistance rates were calculated as %.

RESULTS

Results: Bacteria grew in 1090 (1.2%) of a total of 8923 urine samples over a two-year period. 480 (4.4%) of the factors reproducing in urine culture were *E. coli* and 105 (0.96%) were *K. pneumoniae*. The rate of extended-spectrum beta-lactamase (ESBL) in *E. coli* strains was 16.04% (77/480), and the rate of ESBL in *K. pneumoniae* strains was 20.9% (22/105).

In our study, phosphomycin, ceftriaxone and piperacillin-tazobactam resistance rates were found to be high in ESBL negative *E. coli* strains in pregnant women, while amoxicillin-clavunate, ciprofloxacin and piperacillin-tazobactam resistance rates were found to be high in ESBL positive *E. coli* strains, respectively. High resistance to ceftriaxone, amoxicillin-clavulanate, ciprofloxacin, and ertapenem were detected in ESBL negative *K. pneumoniae* strains, respectively, while high resistance to amoxicillin-clavulanate, nitrofurantoin, ciprofloxacin, and piperacillin-tazobactam was detected in ESBL positive *K. pneumoniae* strains, respectively.

ESBL rate and resistance rates to various antibiotics in *E. coli* and *K. pneumoniae* strains isolated from pregnant patients are shown in **Table**.

DISCUSSION

Urinary tract infections such as cystitis and pyelonephritis, especially asymptomatic bacteriuria, are the most common infections during pregnancy (1-3).

The Infectious Diseases Society of America (IDSA), the UK National Screening Committee and numerous international associations recommend urine culture screening during pregnancy and treatment of urinary tract infections, including asymptomatic bacteriuria (2,10,14).

Studies have reported that bacterial colonization of the urinary system during pregnancy may cause undesirable conditions due to renal infection, intrauterine growth retardation and preterm birth risks (10,15). In approximately 25% of the patients, asymptomatic bacteriuria may progress to symptomatic urinary tract infection (16).

Table. ESBL rate and resistance rates to various antibiotics in *E. coli* and *K. pneumoniae* strains isolated from pregnant patients (%)

Bacteria/antibiotic resistance rate	AMC	CRO	CIP	FF	NT	TZP	IMP	MEM.	ETP
ESBL negative *E. coli*, n:403	15.9	8.82	11.1	20	0	5.88	0	0	0
ESBL positive *E. coli*, n:77	66.5	100	33.8	2.2	0	11.5	0	0	0
ESBL negative *K. pneumoniae*, n:83	53	100	28.5	12.5	3.5	2.2	0	0	4.5
ESBL positive *K. pneumoniae*, n:22	62.5	100	28.5	12.5	35	22.7	0	0	4.5

(*) AMC: Amoxicillin/clavulanic acid, CRO: ceftriaxone, CIP: ciprofloxacin. NT: Nitrofurantoin, FF: Phosphomycin, TZP: Piperacillin-tazobactam, IMP: Imipenem, MEM: Meropenem, ETP: Ertapenem

Treatment of asymptomatic bacteria during pregnancy reduces the risk of pyelonephritis, hypertension and preterm birth in the mother. Second and third-generation cephalosporins, fosfomycin, nitrofurantoin, and sulfonamides at term in the treatment of urinary system infections during pregnancy, and piperacillin-tazobactam and carbapenems can be used in the treatment of infections caused by resistant Gram-negative bacteria (1). Increased antibiotic resistance in *E. coli* and *K. pneumoniae* isolates, which cause urinary tract infections, is an important problem in recent years (4-7).

E. coli is the most common cause of urinary tract infection in society, hospitals, pregnant women, and adults (1-9). In recent years, the increase in antibiotic resistance rates in *E. coli* and *K. pneumoniae* strains, the causative agent of urinary tract infection, has been an important problem (4,5). The increase in antibiotic resistance rates makes it difficult to choose in empirical antibiotic treatment and causes the failure of treatment (1,2,5,11). In international guidelines, it has been recommended to determine local antibiotic resistance rates in the selection of empirical antibiotic treatment and not to use antibiotics with a resistance rate of more than 20% in empirical treatment (1,2,17).

In a meta-analysis study, the resistance rate of trimethoprim-sulfamethoxazole (TMP-SMZ) in *E. coli* strains was reported to be approximately 30% in China and South Korea, and above 15% in Europe and Mediterranean regions. It has been reported that the reason for the low TMP-SMZ resistance rate in Europe may be due to the low prescription of this drug (7).

Rosana et al. (9) In a study conducted on pregnant women in Indonesia, asymptomatic bacteriuria was detected in 10.5% of 715 pregnant women. The most common causes of urinary tract infection were determined as *E. coli* (26.7%), *K. pneumoniae* (20%) and Streptococcus agalactiae (9.3%), respectively. In the study, no phosphomycin resistance was detected in ESBL positive *E. coli* isolates, while resistance to trimethoprim/sulfamethoxazole was reported at 40% and piperacillin-tazobactam at 20%. In the study, no side effects were observed in pregnant women and new-borns who started phosphomycin with the diagnosis of urinary tract infection, and it was reported that phosphomycin was an appropriate option in the treatment of pregnant women.

In our study, 25% resistance was detected in ESBL-negative *E. coli* isolates and 2.2% resistance was detected in ESBL-positive *E. coli* isolates, while 11.1% resistance was detected in ESBL-negative *E. coli* isolates for piperacillin-tazobactam, and no resistance was detected in ESBL-positive *E. coli* isolates.

Lee et al. (8) reported urinary tract infection in 8.9% (4.4% symptomatic urinary tract infection, 4.5% asymptomatic bacteriuria) of pregnant women in a study conducted in Bangladesh. In the study, the frequency of urinary tract infection factors were reported as *E. coli* (38%), staphylococci (23%), *Klebsiella* species (spp.) (12%) and Group B streptococci (5.3%), respectively. In the study, ceftriaxone resistance was reported as 21.1%, trimethoprim/sulfamethoxazole (TMP/SMZ) resistance as 37.3% and nitrofurantoin resistance as 0.8% in *E. coli* strains. In the same study, ceftriaxone resistance was reported as 11.4% nitrofurantoin resistance as 25.7% and TMP/SMZ resistance as 2.8% in *Klebsiella* spp.

The bacteria that secrete the extended-spectrum beta-lactamase enzyme (ESBL) the most are *E. coli* and *K. pneumoniae*. Turkey is one of the countries where infections due to ESBL-producing *E. coli* and *K. pneumoniae* isolates are common all over the world.

In the Hitit University's multi-center study conducted by Gür et al. (18), ESBL rates in *E. coli* and *Klebsiella pneumoniae* isolates were reported as 42% and 41.4%, respectively. In our study, the ESBL rates we found in *E. coli* and *Klebsiella pneumoniae* isolates were 16.04% and 20.9%, respectively, and were lower than the rates reported by Gür et al. In the study of Gür et al., no imipenem resistance was detected in *E. coli* strains, while ciprofloxacin resistance was reported to be 58%. In the same study, imipenem resistance was reported as 3.1% and ciprofloxacin resistance as 17.8% in *K. pneumoniae* isolates.

In our study, no resistance to imipenem, meropenem and ertapenem was detected in *E. coli* isolates, and the resistance rate to ciprofloxacin was determined as 11.1% in ESBL negative *E. coli* isolates and 33.8% in ESBL positive *E. coli* isolates. In our study, ESBL positive and ESBL negative *K. pneumoniae* isolates showed 4.5% resistance to carbapenem group, while no resistance to imipenem and meropenem was detected. In ESBL positive and ESBL negative *K. pneumoniae* isolates, ciprofloxacin resistance was determined as 28.5%.

In studies conducted in our country, ciprofloxacin resistance rates in *E. coli* strains have been reported between 36.5% and 43%, and phosphomycin resistance rates have been reported between 4-15% (19-23).

Avcıoğlu et al. (21) In their retrospective study on 1466 *E. coli* isolates, they reported resistance to amoxicillin/clavulanic acid by 42%, nitrofurantoin and phosphomycin by 4%, ciprofloxacin by 41%, and imipenem by 2%. In our study, unlike this study, no imipenem resistance was detected in *E. coli* strains, while our quinolone resistance rate was lower than the rate reported in this study.

Bayram et al. (22) found ESBL positivity in 30% of the strains in their study on 375 *E. coli* strains. In the study, no imipenem and meropenem resistance was detected in ESBL-positive and ESBL-negative *E. coli* strains; ESBL-positive and ESBL-negative *E. coli* strains reported resistance to phosphomycin at 15% and 5%, respectively; and nitrofurantoine at 18% and 10%. In our study, no nitrofurantoin resistance was detected in ESBL positive and ESBL negative *E. coli* strains, while resistance to phosphomycin was found in ESBL positive and ESBL negative *E. coli* strains by 2.2% and 20%, respectively.

Tekin et al. (23) In their in vitro study on 3279 *E. coli* strains, they detected phosphomycin resistance in ESBL positive *E. coli* strains by 5.7%, while they did not report resistance in ESBL negative *E. coli* strains. In the same study, the ciprofloxacin resistance rate in *E. coli* strains was reported as 58.9%.

In our study, the ciprofloxacin resistance rates we found in ESBL positive and ESBL negative *E. coli* isolates were 33.8% and 11.1%, respectively, and were lower than the resistance rates in the studies conducted in our country. This may be due to the fact that quinolone group antibiotics cannot be used in pregnant women because they are contraindicated.

Asgın et al. (2) In their study on pregnant women diagnosed with urinary tract infection in Karabuk province, they reported that the most frequently isolated bacteria from urine culture were *E. coli* (567), Streptococcus agalactiae (11%) and *K. pneumoniae* (9%), respectively. In the study, ESBL rate in *E. coli* and *K. pneumoniae* strains was reported as 8% and 13%, respectively. In this study, the ESBL rate reported in *E. coli* and *K. pneumoniae* strains was lower than the rates reported by Gür et al. (18).

Aşgın et al. (2) reported phosphomycin resistance in *E. coli* and *K. pneumoniae* strains as 3% and 17%, nitrofurantoin resistance as 3% and 8%, ciprofloxacin resistance as 5% and 0%, amoxicillin/clavulanic acid resistance as 53% and 92%, respectively. In the study, it was reported that phosphomycin and nitrofurantoin were appropriate options due to the low resistance rates in the treatment of urinary tract infections in pregnant women in Karabük province.

In our study, ceftriaxone, phosphomycin and carbapenems may be preferred due to the low resistance rate in the empirical treatment of urinary tract infections due to ESBL negative *E. coli*n pregnant women in our hospital. In the treatment of infections due to ESBL positive *E. coli*, phosphomycin may be preferred due to low resistance rates, and phosphomycin and carbapenems may be preferred due to lack of resistance. Piperacillin-tazobactam, nitrofurantoin and ertapenem may be preferred in the treatment of urinary tract infections due to ESBL negative *K. pneumoniae* due to low resistance rates, and imipenem and meropenem may be preferred due to the absence of resistance. In the treatment of urinary tract infections due to ESBL positive *K. pneumoniae*; ertapenem and phosphomycin can be used due to low resistance rates, and imipenem and meropenem can be used due to lack of resistance.

One limitation of our study was that it was not known whether *E. coli* and K.pneumoniae strains were community- acquired or nosocomial.

CONCLUSION

As a result, determining the distribution of urinary tract infection factors and antibiotic susceptibility in pregnant women will guide clinicians in the initiation of appropriate empirical treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: No human or animal material was used. It is the study of antibiotic resistance in bacteria. It does not require an ethics committee decision. Institutional approval has been obtained.

Informed Consent: No human or animal material was used. It is the study of antibiotic resistance in bacteria. It does not require an informed consent.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Sobel JD, Brown P. Urinary tract infections. In: Bennet JE, Dolin R, Blaser MJ, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases 9th edi. 2020. p. 962-989 e4.
2. Aşgın N, Eroğlu S, Çakmaklıoğulları EK. Gebelikte üriner sistem infeksiyonlarının ampirik tedavisinde hangi antibiyotikler ilk seçenek olmalıdır? ANKEM Derg 2018; 32: 94-102
3. İnci M, İnci M, Davarcı M. Gebelikte görülen üriner sistem enfeksiyonları ve tedavisi. Turk Urol Sem 2011; 2: 124-6.
4. Tandogdu Z, Wagenlehner FM. Global epidemiology of urinary tract infections. Curr Opin Infect Dis 2016;29: 73-9.
5. Fasugba O, Gardner A, Mitchell BG, Mnatzaganian G. Ciprofloxacin resistance in community- and hospital-acquired *Escherichia coli* urinary tract infections: a systematic review and meta-analysis of observational studies. BMC Infect Dis 2015; 15: 545.

6. Mancini A, Pucciarelli S, Lombardi FE, Barocci S, Pauri P, Lodolini S. Differences between community- and hospital-acquired urinary tract infections in a tertiary care hospital. New Microbiol 2020; 43: 17-21.
7. Lee DS, Lee SJ, Choe HS. Community-acquired urinary tract ınfection by *Escherichia coli* in the era of antibiotic resistance. Biomed Res Int 2018; 2018: 7656752.
8. Lee AC, Mullany LC, Koffi AK, et al. Urinary tract infections in pregnancy in a rural population of Bangladesh: population-based prevalence, risk factors, etiology, and antibiotic resistance. BMC Pregnancy Childbirth 2019; 20: 1.
9. Rosana Y, Ocviyanti D, Halim M, et al. Urinary tract ınfections among Indonesian pregnant women and ıts susceptibility pattern. Infect Dis Obstet Gynecol 2020; 2020: 9681632.
10. Ghouri F, Hollywood A, Ryan K. Urinary tract infections and antibiotic use in pregnancy - qualitative analysis of online forum content. BMC Pregnancy Childbirth 2019; 19: 289.
11. Genç S, Dündar D. *Escherichia coli* ve *Klebsiella pneumoniae* suşlarında GSBL üretiminin saptanmasında VITEK- 2 otomatize sistemi ile çift disk sinerji testinin karşılaştırılması. Türk Mikrobiyol Cem Derg 2015; 45: 36-40.
12. Gülay Z. Antibiyotiklere direnç mekanizmaları ve çözüm önerileri: beta-laktamlara ve karbapenemlere direnç. Hastane Infeks Derg 2001; 5: 210-29.
13. European Committee on Antimicrobial Susceptibility Testing (EUCAST). EUCAST Clinical Breakpoint Table Version 10.0, Valid From 2020-01-01. Basel: EUCAST, 2020. http://www.eucast. org/clinical_breakpoints
14. Luu T, Albarillo FS. Asymptomatic bacteriuria: prevalence, diagnosis, management, and current antimicrobial stewardship ımplementations. Am J Med 2022; 135: 236-44.
15. Matuszkiewicz-Rowińska J, Małyszko J, Wieliczko M. Urinary tract infections in pregnancy: old and new unresolved diagnostic and therapeutic problems. Arch Med Sci 2015; 11: 67–77.
16. de Rossi P, Cimerman S, Truzzi JC, et al. Joint report of SBI (Brazilian Society of Infectious Diseases), FEBRASGO (Brazilian Federation of Gynecology and Obstetrics Associations), SBU (Brazilian Society of Urology) and SBPC/ML (Brazilian Society of Clinical Pathology/Laboratory Medicine): recommendations for the clinical management of lower urinary tract infections in pregnant and non-pregnant women. Braz J Infect Dis 2020; 24: 110-9.
17. Gupta K, Hooton TM, Naber KG, et al. Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis 2011; 52: 103-20.
18. Gur D, Hascelik G, Aydin N, et al. Antimicrobial resistance in gram-negative hospital isolates: results of the Turkish HITIT-2 Surveillance Study of 2007. J Chemother 2009; 21: 383-9.
19. Keskin BH, Çalışkan E, Kaya S, Köse E, Şahin İ. Üriner sistem enfeksiyonlarında etken bakteriler ve antibiyotik direnç oranları. Turk Mikrobiyol Cemiy Derg 2021; 51: 254-62.
20. Duran H, Çeken N, Kula Atik T. İdrar kültüründen izole edilen *Escherichia coli* ve *Klebsiella pneumoniae* suşlarının antibiyotik direnç oranları: Dört yıllık analiz. Ankem Derg 2020; 34: 41-7.
21. Avcıoğlu F, Behçet M. üriner sistem enfeksiyonu etkeni *Escherichia coli* izolatlarının çeşitli antibiyotiklere direnç oranlarının değerlendirilmesi. Turk Mikrobiyol Cemiy Derg 2020; 50: 172-7.
22. Bayram Y, Eren H, Berktas M. İdrar örneklerinden izole edilen bakteriyel patojenlerin dağılımı ve GSBL pozitif ve negatif *Escherichia coli* suşlarının fosfomisin ve diğer antimikrobiyallere duyarlılık paterni. Ankem Derg 2012; 25: 232-36.
23. Tekin A, Deveci Ö, Dal T, et al. Üropatojen *Escherichia coli* izolatlarına fosfomisin ve bazı antibiyotiklerin in vitro etkinliği. Ankem Derg 2012; 26: 61-8.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1245104

Anatolian Curr Med J 2023; 5(2); 102-110

The effects of extremely low-frequency magnetic field exposure on apoptosis, neurodegeneration and trace element levels in the rat brain

Mehmet Onat Çakıt[1], Gökhan Koca[2], Aylin Akbulut[2], Onur Erdem[3], Serdar Çetinkaya[3], Gaye Umurhan[4], Nur Aydınbelge[2], Meriç Arda Eşmekaya[5], Nihat Yumuşak[6], Ayşe Gülnihal Canseven Kurşun [5], Meliha Korkmaz[2]

[1]Department of Family Medicine, University of Health Sciences, Ankara Training and Research Hospital, Ankara, Turkey
[2]Department of Nuclear Medicine, University of Health Sciences, Ankara Training and Research Hospital, Ankara, Turkey
[3]Department of Pharmaceutical Toxicology, University of Health Sciences Gulhane Faculty of Pharmacy, Ankara, Turkey
[4]Gazi University, Non-ionizing Radiation Protection, Application and Research Center, Ankara, Turkey
[5]Department of Biophysics, Gazi University Faculty of Medicine, Ankara, Turkey
[6]Department of Pathology, Harran University Faculty of Veterinary Medicine, Şanlıurfa, Turkey

Cite this article as: Çakıt MO, Koca G, Akbulut A, et al. The effects of extremely low-frequency magnetic field exposure on apoptosis, neurodegeneration and trace element levels in the rat brain. Anatolian Curr Med J 2023; 5(2); 102-110.

ABSTRACT

Aim: The aim of this study was to investigate the effects of 1mT, 1.5 mT, and 2 mT extremely low-frequency magnetic fields, which were within the limits for public environmental and occupational magnetic field exposure guidelines, on apoptosis, neurodegeneration and trace elements in rat brain cells.

Material and Method: A total of 35 adult male Wistar rats were allocated into four main groups: Group 1 (n=8) was healthy controls; Group 2 (n=9) was exposed to 1 mT extremely low-frequency magnetic field; Group 3 (n=9) was exposed to 1.5 mT extremely low-frequency magnetic field and Group 4 (n=9) was exposed to 2 mT extremely low-frequency magnetic field. All the rats in the exposure groups were exposed to 50 Hz extremely low-frequency magnetic field for 4 hours per day, 5 days per week for 30 days in the Helmholtz coils. After the exposure, rats were sacrificed and rat brains were evaluated for histopathological and immunohistochemical changes as well as about the trace element levels in the brain.

Results: Different levels of exposure to extremely low-frequency magnetic field doses caused increases in Ca levels and increased apoptosis in the rat brain. As the applied extremely low-frequency magnetic field levels increased, so did the apoptosis and Ca levels in the brain tissues.

Conclusion: Extremely low-frequency magnetic field exposure caused neurodegeneration in rat brain tissue, increased apoptosis, and increased Ca concentration. These changes may cause various biological damage, especially cancer in healthy tissues and measures should be taken to minimize extremely low-frequency magnetic field exposure in daily life in terms of protecting public health.

Keywords: Extremely low frequency, electromagnetic field, rat brain, apoptosis, trace elements, neurodegeneration

INTRODUCTION

As a result of the vast amount of currently developing technologies, humans are increasingly exposed to Electromagnetic Fields (EMF). The 0–300 Hz range of this spectrum is called Extremely Low Frequency (ELF). In daily life, almost all electrical devices used at homes and workplaces, particularly transformers and high voltage lines, are the major sources of exposure to ELF, so the general population is exposed to ELF-EMF involuntarily or accidentally (1).

It is now an accepted fact that ELF-EMF affects biological systems, although the mechanism has not yet been clarified. Despite the many studies investigating the biological effects of ELF-EMF, it cannot be claimed to be a potential human carcinogen based on side-effects as the results have been quite contradictory (2).

Programmed cell death or apoptosis, which is one of the most important factors in cancer control, plays an important role in regulating cell population in tissues, and a dysfunction in apoptosis can lead to tumor formation (2,3). Both epidemiological and laboratory studies including leukemia also indicate that, 50 Hz/ 60 Hz EMFs may lead to a number of different adult cancers including brain, lymphoma, nervous system, pharynx and breast

Corresponding Author: Mehmet Onat Çakıt, onatcakit@gmail.com

Received: 01.02.2023 **Accepted:** 18.02.2023

cancers (4,5). Thus, clarifying the factors that may cause apoptosis, which plays a key role in neurodegenerative diseases and tumor pathogenesis, may be of guidance in the prevention and treatment of these diseases.

In vivo and in vitro studies on apoptosis induced by the effect of ELF-EMF have yielded conflicting results. While some studies have shown that ELF-EMF induces apoptosis susceptibility (6), others have shown that it decreases apoptosis (7,8). In a meta-analysis, it was reported that ELF-EMF significantly increased apoptosis in in-vitro studies (2). However, the effects of ELF-EMF on apoptosis in rat brain tissue in vivo have not been well studied.

ELF-EMF exposure may affect the levels of trace elements in serum and various organs by causing various biochemical changes in living cells. In studies with guinea pigs, changes in trace element levels have been found in the serum and other organs. In one study (9), magnesium levels were found to be increased, and Cu, Zn, and Ca levels remained unchanged, while another study (10) reported increased Cu, Zn, Ca and Mg levels in 50 Hz, 2 mT magnetic fields. Therefore, in the literature, there are conflicting results about the levels of trace elements in brain tissue.

In light of these informations, the aim of this study was to investigate the effects of 1mT, 1.5 mT, and 2 mT ELF-EMF. We tried to assess the effects of these magnetic fields which are within the limits for public environmental and occupational magnetic field exposure guidelines, on apoptosis, neurodegeneration, and trace elements in rat brain cells.

MATERIAL AND METHOD

Experimental Animals

All procedures performed in the experimental animal unit were in accordance with the principles of the Guide for the Care and Use of Laboratory Animals (https://www.nap.edu/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals). The Laboratory Animal Care Committee of Ankara Training and Research Hospital reviewed and approved the experimental protocol (Report no: 19.03.2020/609). A total of 35 adult male Wistar rats, each weighing 200-260 g, were used in this experimental study. All the animals were obtained from Gulhane Laboratory Animal Production and Research Center, and the animals were assigned randomly to one of four groups: Group 1 (n=8) was Healthy Controls; Group 2 (n=9) was exposed to 1 mT ELF-MFs; Group 3 (n=9) was exposed to 1.5 mT ELF-MFs and Group 4 (n=9) was exposed to 2 mT ELF-MFs. When selecting these magnetic field levels, the scaling factor was taken in to consideration. The level of magnetic field that a person would be exposed to was estimated by the equivalent animal exposure. One of these methods was the ellipsoid modeling performed when the animal is standing and on four legs in sweat (11). According to this model average value of human:guinea pig scaling factor was calculated as 3.1. According to the calculated scaling factor (3.1), 1 mT, 1.5 mT and 2 mT magnetic field values in the animal correspond to respectively 0,32 mT, 0,48 mT and 0,65 mT in humans.

All the rats in the exposure groups were exposed to 50 Hz ELF-MFs for 4 hours/day, 5 days per week for 30 days, and the exposures were applied between 9.00 am and 1.00 pm. During the exposure, 3 rats were placed in plexiglass cages and then positioned in the center of the Helmholtz coil at a controlled temperature (230C), 65–70% humidity, 12 hours light and 12 hours dark cycle and fed with standard food and water. All the rats were checked twice a day in respect to any changes in health. No restrictions were applied to the animals. During the study, all the rats were fed with standard chow and water ad libitum.

Anaesthesia with Ketamine (50 mg/kg) and Xylazine (5 mg/kg) was administered as intramuscular injections to all of the rats at the end of the last exposure, and all the animals were then sacrificed. Brain tissue samples were taken and frozen in liquid nitrogen and kept at -80°C until electron microscopy and histopathological examinations were performed.

Exposure systems

The ELF-EMF system was developed in Gazi University Faculty of Medicine, Biophysics Laboratory, and it has been described in detail in our previous study (12). EMF (1 mT, 1.5 mT, 2 mT) was produced in the center of an exposure system by means of a circular Helmholtz coils system. This system consisted of a combination of two parallel horizontal flat circular coils 42.75 cm in diameter with a common axis and 21.375 cm apart. Each coil had 154 turns and was constructed of insulated copper wires. EMFs were measured by a NARDA EFA 300 ELF EMFAnalyzer and a related probe at the center of the Helmholtz coils. These measurements were confirmed with a Gaussmeter (Yokogawa, Tokyo, Japan). The environment geomagnetic field in the measurement area was recorded as 0.04 μT.

Histopathologic Evaluation

Tissues were washed overnight in running water to remove the formalin. After routine pathological tissue monitoring, the samples were passed through graded alcohol (50%, 75%, 96%, 100%) and xylol series, and then were embedded in paraffin blocks. Paraffin sections in 5 μm thickness were prepared by Leica RM 2125 RT and the first, third and tenth sections were included in the slides. The preparations were passed through alcohol and xylol

series and were stained with hematoxylin-eosin (HE). All samples were examined under high-resolution light microscopy (Olympus DP-73 camera, Olympus BX53-DIC microscope; Tokyo, Japan). The neurodegeneration parameters evaluated included congestion, Purkinje cells with pyknotic nuclei, granular cells with pyknotic nuclei, neuronophagia, and gliosis. All changes detected in tissue structures were noted and scored according to the previously described grading systems as: 0= none, 1= mild, 2= moderate, and 3= severe (13).

Analysis of Apoptosis in the Brain Tissue

Immunohistochemical procedures

Caspase-3

Immunohistochemical staining was performed with the streptavidin-biotin-peroxidase complex (ABC) method according to the protocol of primary antibodies. Sections of 5μm thickness were taken from the previously prepared paraffin blocks onto the slides with poly-L-lysine and deparaffinized and dehydrated with alcohol and xylol. The sections were treated with citrate buffer (Ph 6.0) in a microwave oven (700 W) for 20 minutes to recover the antigen from the tissues. Then, in order to suppress the peroxidase activity, they were placed in a humid chamber in 0.3% H_2O_2 at room temperature for 15 minutes. Before applying the primary antibody, the tissues were incubated for 20 minutes with 5% normal goat serum for protein suppression. The sections were then incubated with Caspase-3 (1:200, Invitrogen, PA5-16335) primary antibody for 1 h at room temperature. The sections were washed with phosphate buffered saline (PBS) and incubated for 30 minutes in the secondary antibody, and then AEC (3-Amino 9-Ethyl Carbasole, Dako, Glostrup, Denmark) and were chromatographed for 10 minutes to ensure the visibility of the reaction. Hematoxylin was used for background contrast staining. Finally, the sections were passed through alcohol and xylol and closed with entellan.

To assess the caspase immunohistochemistry, 10 fields were chosen randomly and the cytoplasmic staining intensities in the cells were globally scored as 0 for no staining, 1 as weak, 2 as moderate, or 3 as strong staining. In each field, at each intensity, the total number of cells and the number of cells stained were counted. Staining indexes were calculated as follows based on the percentages of the stained nuclei for these three markers: negative: 0 (<1% positive); weak: 1 (1-25% positive); intermediate: 2 (>25–75% positive); and strong: 3 (>75% positive).

TUNEL assay

TUNEL (Terminal Deoxynucleotidyl Transferase mediated Deoxyuridine Triphosphate-dUTP Nick end Labeling) assays were performed according to the manufacturer's catalog procedure (In situ Cell Death Detection Kit, POD, Roche, Germany) to determine apoptosis-related DNA breaks in the rat brain cells. Routine deparaffinization and dehydration with alcohol and xylol were applied to standard 5-μm thick tissue sections on the poly-L-lysine-coated glass slides. Subsequently, sections were incubated for 15 minutes at room temperature in 0.3% H_2O_2 to suppress peroxidase activity. Sections were washed with PBS and incubated with Protein K (20 mg/ml; Roche, Mannheim, Germany) at room temperature and in a humid chamber for 15 minutes. Washed sections were then incubated for 1 h at 37°C in a dark environment in freshly prepared 50 μl of TUNEL reaction mixture (TdT & dUTP) solution. The sections were then coated with 50 μl of anti-fluorescein antibody conjugate POD enzyme homogeneously and incubated for 30 minutes at 37°C. Finally, the washed sections were treated with AEC (3-Amino 9-Ethyl Carbasole, Dako, Glostrup, Denmark) for 10 minutes and then covered with a slide after staining with hematoxylin for background contrast. Immunohistochemical and TUNEL assay scoring were evaluated according to previous studies (14-16).

In the TUNEL assay, which stains all the nuclei, 10 randomly chosen areas under the microscope were used. In each area of observation, the total number of nuclei and the highlighted nuclei were counted. Staining indexes were calculated as follows based on the percentages of the stained nuclei for these three markers: negative: 0 (<1% positive); weak 1 (1-25% positive); intermediate: 2 (>25–75% positive); and strong: 3 (>75% positive).

Detection of Trace Elements in the Brain

Reagents

All aqueous solutions were prepared with deionized water obtained using an ultra-pure water system (Aqua Nova Hepta Distillated, resistivity 0.34 MΩ-cm, Kristianstad, Sweden). HNO_3 (65%) and H_2O_2 (30%) from Merck supra-pure grade (Darmstadt, Germany) were used for digestion of the samples and dilution. Plastic bottles, autosampler cups, Teflon vessels, vials for collecting samples, and glassware were cleaned by soaking in HNO_3 (10% v/v) for a day, rinsing four times with ultra-pure water, and drying in an oven at 40°C. All prepared solutions were stored in high-density polypropylene bottles. Stock standard solutions of analytes (1 g/L each) were obtained from Merck. Mixed standard solutions were freshly prepared by diluting the stock standard solutions to the desired calibration ranges in 0.2% HNO_3.

Apparatus

An Inductively Coupled Plasma Mass Spectrometry (ICP-MS) method with a Thermo Scientific ICAP Q Series (Bremen, Germany) was used for element

analysis. Digestion was carried out using Milestone Ethos Up, High-Performance Microwave Digestion System (Serisole, Italy).

Analytical procedures

The samples were analyzed using an in-house validated and accredited method based on ICP-MS using microwave acid digestion. Briefly, 30 mg tissue samples were weighed and then the samples were dried using a magnetic mixer with a heating plate. The dried samples were transferred into a Teflon vessel and digested with 3 mL 65% HNO_3 and 1 mL 30% H_2O_2. Digestion conditions for the microwave system were applied as 15 minutes at 200°C rising (max power), 15 min at 200°C waiting (max power), and 15 min cooling to 80°C. After the cooling process, the total volume of the digested samples were made up to 10.0 mL with 0.2% HNO_3. Digested samples were introduced to ICP-MS for element determination. The operation parameters for the investigated elements were set as recommended by the manufacturer (**Table 1**).

Table 1. Instrument operating parameters for ICP-MS.

Parameter	Value
Peristaltic pump speed	40 rpm
Pump tubing	orange/green tubing for both carrier (sample) and internal standard
Nebulizer	PFA-ST
Interface cones	Nickel
RF Power	1550 W
Cool gas flow	14 L/min
Auxiliary gas flow	0.8 L/min
Nebulizer gas flow	0.97 L/min
Number of sweeps	20
Dwell Times	0.001 - 0.02 ms
Replicates per analysis	3

A mixed standard solution of Mg, Ca, Cu, Zn, and Se was used for calibration procedures (**Table 2**). The investigated element levels in the brain samples were expressed as µg/g for Mg, Ca, Cu, and Zn and as ng/g for Se (**Table 3**).

Statistical Analyses

Data obtained in the study were analyzed statistically using the Statistical Package for Social Sciences (SPSS) v.15.0 software (SPSS Inc, Chicago, IL, USA). Mean and standard deviation values were calculated. Data were analyzed using the Kruskal-Wallis test, One-way analysis of variance (ANOVA) and non-parametric tests (Mann Whitney U test). Bonferroni correction was used for the Kruskal Wallis and Mann Whitney U-test post hoc. Descriptive statistics were used to determine the continuous variables and frequency distributions for categorical variables. In all analyses, a value of $p<0.05$ was considered statistically significant.

RESULTS

Histopathological Results

The percentage of histopathological grading of neurodegeneration parameters including congestion, Purkinje cells with pycnotic nuclei, granular cells with pycnotic nuclei, neuronophagia, and gliosis are presented on the graphs (**Figure 1**). The congestion rate was significantly higher in groups 2 (1mT), 3 (1.5 mT) and 4 (2 mT) compared to the control group ($p < 0.01$). The levels of Purkinje cells with pycnotic nuclei, granular cells with pycnotic nuclei and neuronophagia were similar in groups 1(control) and 2 (1 mT) ($p > 0.05$) while they were significantly higher in groups 3 (1.5 mT) and 4 (2 mT) ($p < 0.01$). The histopathological grades were increased as the ELF-EMF dose exposure increased (**Figure 1**).

Table 2. Concentrations of elements used for calibration procedures.

	Mg (mg/L) concentration	Ca (mg/L) concentration	Cu (mg/L) concentration	Zn (mg/L) concentration	Se (µg/L) concentration
Calibration Blank	0.0	0.00	0	0	0
Standard 1	0.4	0.25	1	2	20
Standard 2	0.6	0.50	2	4	40
Standard 3	0.8	1.00	4	8	60
Standard 4	1.2	2.00	8	16	80
Standard 5	1.5	4.00	16	32	100
Correlation Coefficient	0.996	0.998	0.998	0.999	0.999

Table 3: The effects of ELF-EMF exposure on Mg, Ca, Cu, Zn and Se levels in the rat brains

	Group 1 (Control) (n=8)	Group 2 (10G) (n=9)	Group 3 (15G) (n=9)	Group 4 (20G) (n=9)
Tissue Dilution (mg/10ml)	63.0±23.88	44.62±20.17	53.75±19.17	56.58±16.29
Mg (µg/g)	446.51±237.88	580.56±67.42	456.61±84.76	674.25±345.17
Ca (µg/g)	278.19±110.04	490.16±179.91	298.53±130.54	628.58±210.98
Cu (µg/g)	8.47±3.95	15.65±13.1	10.38±3.74	11.14±5.76
Zn (µg/g)	14.46±10.68	18.69±4.0	17.74±7.04	19.53±8.19
Se (µg/g)	293.40±98.46	402.13±167.12	327.59±110.84	350.98±170.52

For Mg, Cu, Zn, Se, $p>0.05$ for all groups. For Ca, Group 1-2 p=0.011, Group 1-3 p=0.963, Group 1-4 p=0.002, Group 2-3 p=0.011, Group 2-4 p=0.190, Group 3-4 p=0.008

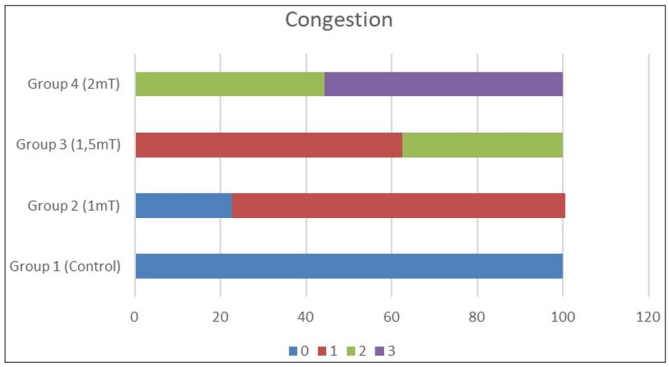


Figure 1a. The level of congestion of the groups

Group 1-2 p=0.002, Group 1-3 p<0.001, Group 1,4 p<0.001, Group 2-3 p=0.074, Group 2-4 p<0.001, Group 3-4 p=0.002,

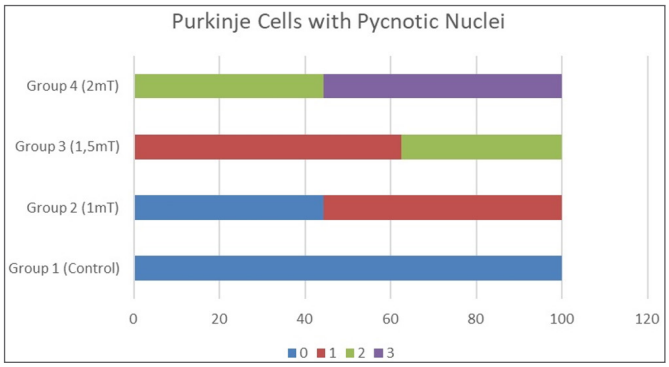


Figure 1b: The levels of Purkinje cells with pycnotic nuclei of the groups

Group 1-2 p=0.059, Group 1-3 p<0.001, Group 1-4 p<0.001, Group 2-3 p=0.021, Group 2-4 p<0.001, Group 3-4 p=0.002.

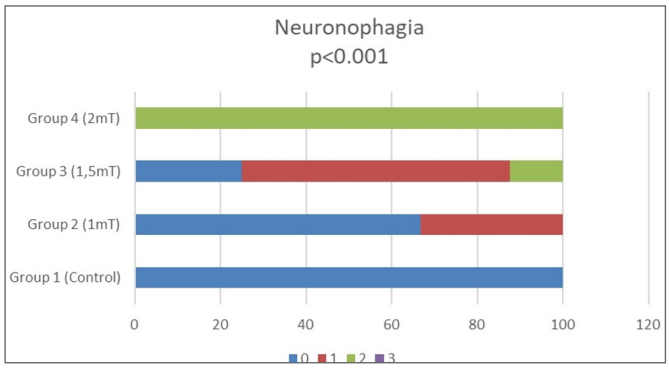


Figure 1c: The level of granular cells with pycnotic nuclei of the groups

Group 1-2 p=0.059, Group 1-3 p<0.001, Group 1-4 p<0.001, Group 2-3 p=0.046, Group 2-4 p<0.001, Group 3-4 p=0.004,

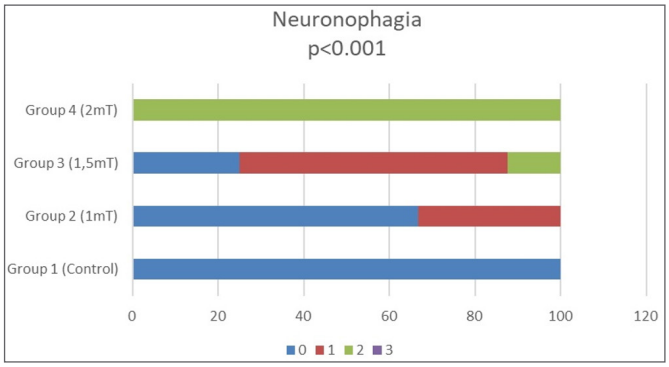


Figure 1d: The level of the neuronophagia of the groups

Group 1-2 p=0.277, Group 1-3 p=0.01, Group 1-4 p<0.001, Group 2-3 p=0.114, Group 2-4 p<0.001, Group 3-4 p=0.001,

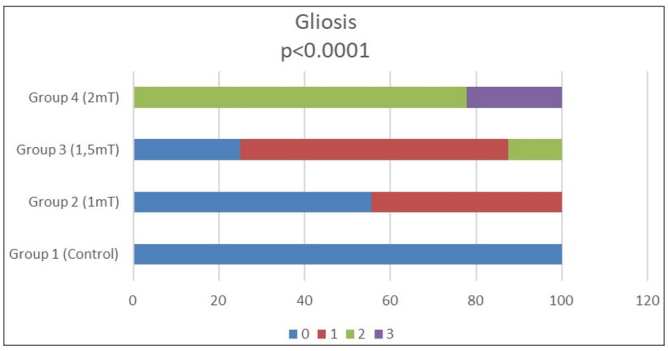


Figure 1e: The gliosis level of the groups

Group 1-2 p=0.139, Group 1-3 p=0.01, Group 1-4 p<0.001, Group 2-3 p=0.236, Group 2-4 p<0.001, Group 3-4 p=0.001,

Figure 1: The percentage of histopathological grading of neurodegeneration parameters were shown on the graphs. The neurodegeneration parameters of the histopathological analysis of brain tissues with 0 indicating no staining, 1 weak, 2 moderate, and 3 strong staining.

Immunohistochemical analysis

The immunohistochemical analysis including the percentage analysis of caspase-3 and TUNEL positivity are presented on the graphs for all groups, with 0 for no staining, 1 as weak, 2 as moderate, or 3 as strong staining (**Figure 2**). Caspase-3 positivity was statistically higher in groups 3 (1.5mT) and 4 (2mT) than in group 1 (control) and group 2 (1mT) and TUNEL positivity was statistically higher in group 2 (1mT), group 3 (1.5mT) and 4 (2mT) than in group 1 (control) (**Figure 2**). Caspase-3 and TUNEL positivity was determined to increase as the ELF-EMF dose exposure increased.

Histopathological sections of brain tissues of the groups are shown in **Figure 3** (a, b, c, d showing HE; e, f, g, h showing Caspase-3 staining and i, j, k, l showing TUNEL staining)

Brain Mg, Ca, Cu, Zn, and Se Levels

The Mg, Ca, Cu, Zn, and Se levels in the brain samples are shown in **Table 3**. There was a significant increase in Ca levels in Group 2 (1mT), Group 3 (1.5mT), and Group 4 (2mT) than in the control group. Brain Ca levels increased as the ELF-EMF dose exposure increased. There were no significant differences between the control and ELF-EMF-exposed groups in terms of Mg, Cu, Zn, and Se levels.

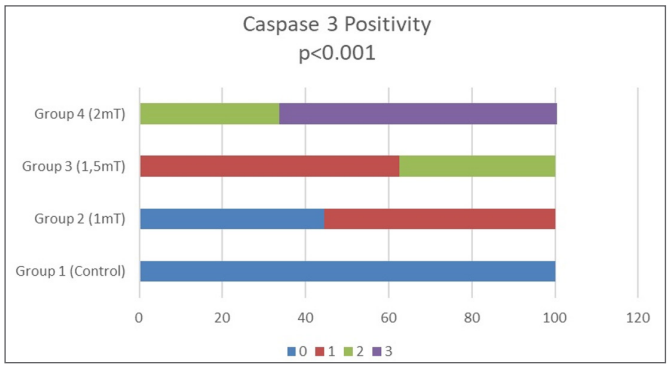


Figure 2a: The caspase 3 positivity of the groups

Group 1-2 p=0.059, Group 1-3 p<0.001, Group 1-4 p<0.001, Group 2-3 p=0.01, Group 2-4 p<0.001, Group 3-4 p=0.001

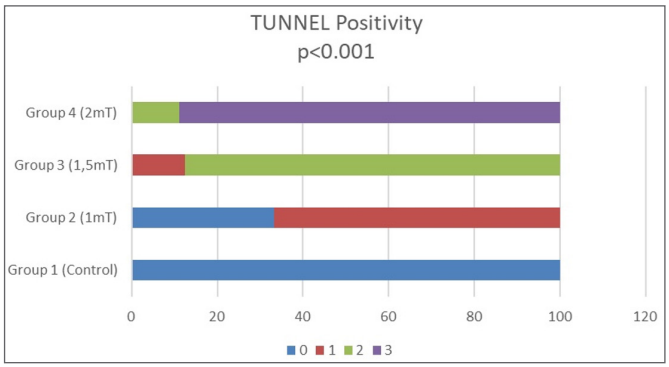


Figure 2b: The TUNNEL Positivity of the groups

Group 1-2 p=0.021, Group 1-3 p<0.001, Group 1-4 p<0.001, Group 2-3 p=0.001, Group 2-4 p<0.001, Group 3-4 p<0.001,

Figure 2: Immunohistochemical procedures; caspase 3 and TUNNEL positivity.

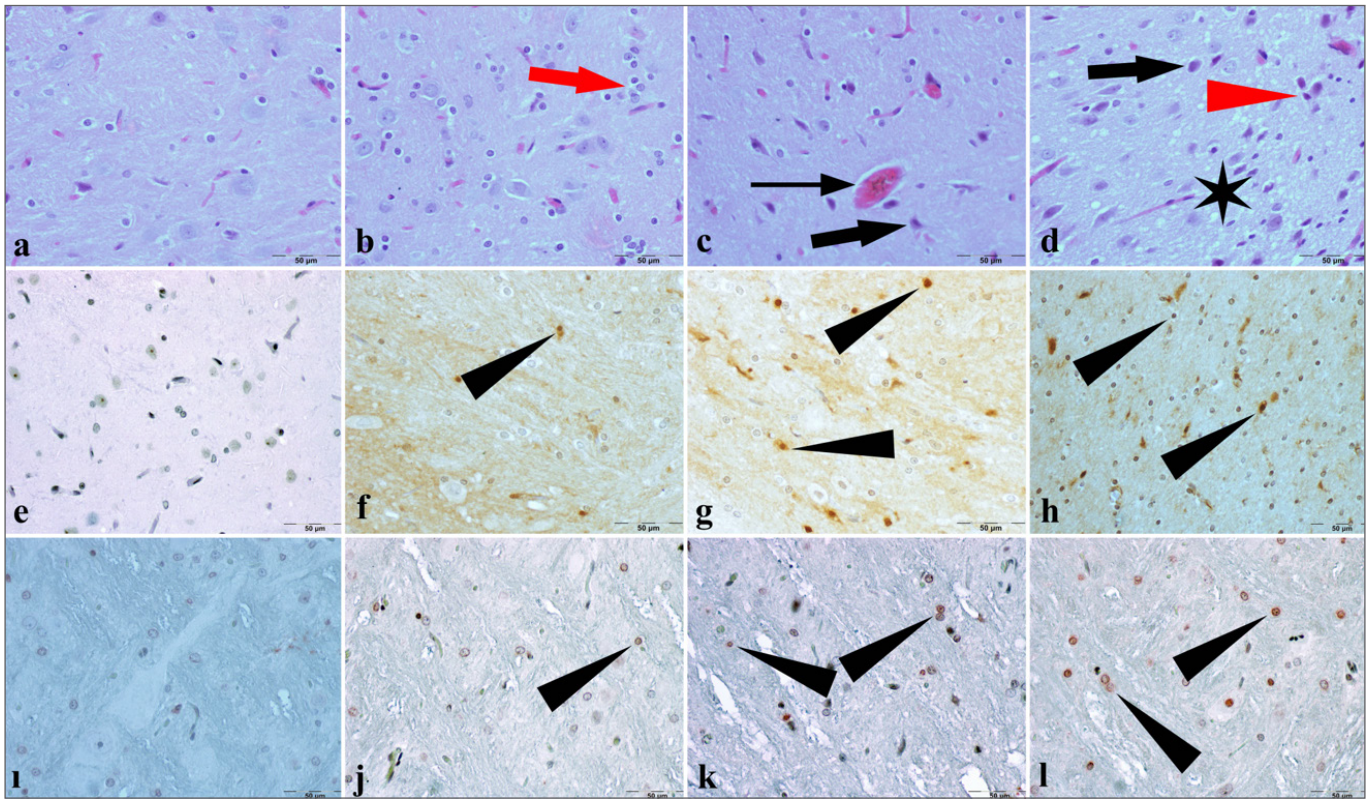


Figure 3: Representative photomicrographs for all groups stained with HE and immunohistochemistry.
a, e, i: control (group 1), b, f, j : group 2 (10G), c, g, k : group 3 (15G), d, h, l : group 4 (20G)
(a), (e) : immunonegative
(b): red arrow shows gliosis
(c): thin arrow shows congestion, thick arrow shows picnosis
(d): arrow shows picnosis, red arrowhead shows neuronophagia, star shows spongiosis (demyelination)
(f), (g), (h), (j), (k), (l): black arrowheads show immunopositive apoptosis
a, b, c, d showing HE, e, f, g, h showing Caspase-3 staining and i, j, k, l showing TUNEL staining. Scale bar: 50 µm.

DISCUSSION

The results of this study demonstrated that different levels of exposure to ELF-EMF doses applied 4 hours a day for 30 days caused increases in Ca levels and increased apoptosis in the rat brain. As the applied ELF-EMF levels increased, the neurodegeneration levels, apoptosis levels and Ca levels in the brain tissues also increased. But there was no significant effect in terms of Mg, Cu, Zn, and Se levels in the rat brain.

The caspases are essential molecules of cellular processes such as inflammation, proliferation, and differentiation, and they can be activated both by intrinsic and extrinsic pathways (17). The TUNEL assay method has been utilized to show the apoptosis-related DNA strand breaks produced by DNA fragmentation (19). Yumusak et al. (18) reported that caspase-3 and TUNEL levels were significantly increased in stressed cells, which confirmed the pathological mechanism underlying apoptosis. In the current study, considering the significant increase

in TUNEL and caspase-3 levels, DNA breaks and damage and increased apoptosis were found in cells exposed to ELF-EMF. It was shown that ELF-EMF caused neurodegeneration in rat brain tissue, and this neurodegeneration increased in severity as the ELF-EMF dose increased. Caspase-3 and TUNEL levels increased as the ELF-EMF dose increased, indicating apoptosis.

Apoptosis plays a vital role in normal tissue homeostasis throughout the life of multicellular organisms, starting with embryogenesis. There are conflicting results in studies about the effects of ELF-EMF on apoptosis in cells. Basille et al. (19) reported that 50 Hz ELF-EMF decreased the rate of apoptosis in melanoma cells by increasing the levels of anti-apoptotic factors (BAG3). Kurian et al. (20) showed that 60 Hz. ELF-EMF decreased the rate of apoptosis in rat myocardial cultures by increasing the anti-apoptotic protein (Bcl-2) levels, leading to a decrease in caspase-3 activity. In a study by Kim et al. (21), it was reported that in TUNEL staining, germ cells showed a significantly higher apoptotic rate in exposed mice than sham controls and in another study (22), apoptotic cells were reported to increase as the duration and dose increased.

ELF-EMF can cause various biochemical changes in cell membranes and tissues by causing changes in ion permeability. Various animal experiments have investigated how trace elements are affected by ELF-EMF in the brain and various organs. In one of these studies, Erdem et al. (9) applied intermittent or continuous 50 Hz and 1.5 mT ELF-EMF to guinea pigs and found an increase in Mg levels in the brain, but no difference in Cu, Zn, and Ca levels. In another study, Ülkü et al. (23) reported that exposure of 500 μT ELF-EMF for 10 months at 2 hours per day caused a decrease in Ca, Mg, and Zn levels in the ribs of rats. Canseven et al. (10) showed that when guinea pigs were exposed to ELF-EMF at 50 Hz, 2mT, 5 days, 4 hours a day, Ca concentration increased in the brain tissue and the plasma. Gmitrova et al. (24) reported that when guinea pigs were exposed to ELF-EMF at 50 Hz, 3 mT, 5-6 days, 1 hour a day, the Ca concentration increased and the Mg concentration decreased in the brain. In these studies, the effect of EMF can be seen to vary according to the frequency and amplitude of the EMF, and properties of the applied areas. These differences in results may be due to experimental parameters, exposure period, application period during the day, and analysis methods (25). In the current study, it was observed that the Ca concentration increased in the brain tissue of the groups exposed to 50 Hz, 1 mT, and 2mT ELF-EMF for 4 hours a day for 30 days, but even though there was an increase in Mg, Cu, Zn, and Se levels, they did not reach a statistically significant level. It can be considered that these ELF-EMF levels may cause changes in the amounts of trace elements in the brain tissue, but they did not reach statistically significant levels due to the small number of rats in the groups. As far as can be observed from other studies and the current study, it can be speculated that Ca can cause an imbalance in the element composition in the tissues through Ca channels. This may be a risk factor that can cause impaired brain function.

Ca ion is involved in various immunological, endocrinological, and neurological events. Ionic balance is vital, especially in the microenvironment of the central nervous system. Calcium, a key mediator of intracellular signaling and an important factor in determining cell fate, is influenced by EMF. ELF-EMFs have been reported to increase the expression of presynaptic calcium channels in the presynaptic terminal which promotes the release of synaptic vesicles (26). Disruption in intracellular homeostasis of Ca ion is also the first step of lethal injury caused by acute oxidative stress. Ca ions are also very important in the modulation of the effects of the magnetic field in cells. It is thought that magnetic field exposure can cause free ion movement, especially Ca movement, and oscillations, and the occurrence of fluctuations in this normal ionic balance changes normal cell behavior and cell membrane behavior (27). Alterations in Ca homeostasis affect many cellular processes, including apoptosis. Sheikh et al. (28) reported that perturbation in intracellular Ca concentrations, especially increased mitochondrial Ca levels, is responsible for apoptotic triggering. Stratton et al. (29) reported that pulsed ELF-EMF causes transient plasma membrane damage in human monocytic leukemia cells, which leads to calcium influx, and as a result, it increases the tendency to apoptosis by increasing microvesicle release. The changes in Ca level can be considered to have contributed to the neurodegeneration and increased apoptosis that was determined histopathologically in this study.

The mammal brain is protected from harmful molecules by the blood-brain barrier. There is evidence that EMF exposure increases the permeability of the blood-brain barrier (30). However, while in one study it was reported that ELF-EMF had an effect on the blood-brain barrier in diabetic rats and had no effect on an intact barrier, in another study (32), it was observed that the amount of Ca was increased in the cerebrospinal fluids of cows exposed to 60 Hz, 30μT ELF-EMF, which could be associated with increased permeability in the blood-brain barrier. Similarly, in the current study, it was thought that the increased Ca levels in the rat brain tissue may be associated with increased blood-brain barrier permeability.

Lai et al. (32) found that a magnetic field of 60 Hz. for 2 hours at 0.1-0.5 mT caused single- and double-strand breaks in DNA, and the severity of these breakages increased as the exposure time increased. Acute

magnetic field exposure also increases apoptosis and necrosis in rat brain cells. Akdağ et al. (33) reported that for 10 months and 2 hours per day, 100-500 μT did not increase apoptosis, evaluated with active-caspase-3 immunohistochemical staining, but it created toxic effects in the rat brain by increasing oxidative stress and reducing the antioxidant defense system. In addition to these controversial studies on oxidative stress and apoptosis, it is necessary to draw attention to two more studies that investigated why ELF-EMF increases apoptosis in some cells and reduces or does not affect others. One of these studies was conducted by Oda et al., (34) investigating the effect of 50 Hz ELF-EMF on immature cerebellar granule neurons, and it was seen to have prevented apoptosis and increased survivability. It was concluded that ELF-EMF could be a potential tool by which neuronal death or survival could be manipulated. In another study conducted by Falone et al., (35) it was stated that a 50 Hz magnetic field could be a risk factor for oxidative stress-based nervous system pathologies by weakening antioxidant defense mechanisms in the aged rat brain. It is an interesting finding that ELF-EMF protects immature neurons from apoptosis while leading mature neurons to apoptosis. Furthermore, in immature and developing neurons, Ca has a mainly apo-protective role, whereas in fully mature and established neurons, Ca plays an apo-inducing role (36). In the light of these pieces of information, the use of mature rats in the current study may explain their predisposition to apoptosis and neurodegeneration in the presence of high Ca level caused by the applied ELF-EMF. However, a limitation of this study is that oxidative stress was not evaluated in the rat brain tissue.

CONCLUSION

The results of this study showed that ELF-EMF exposure caused neurodegeneration in rat brain tissue, increased apoptosis, and increased Ca concentration. Although it is not possible to adapt the results of this study directly to humans, it can be considered that these changes may cause various biological damage, especially cancer, in healthy tissues and measures should be taken to minimize ELF-EMF exposure in daily life in terms of protecting public health.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Ankara Training and Research Hospital The Laboratory Animal Care Ethics Committee (Date: 19.03.2020, Decision No:609)

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgement: Electromagnetic field measurement devices used in this study were supplied by the grant from Gazi University Research Foundation, No. 31/2002-07

REFERENCES

1. Kim JH, Lee JK, Kim HG, et al. Possible Effects of Radiofrequency Electromagnetic Field Exposure on Central Nerve System. Biomol Ther (Seoul) 2019; 27: 265-75.
2. Mansourian M, Marateb HR, Vaseghi G. The effect of extremely low-frequency magnetic field (50-60 Hz) exposure on spontaneous apoptosis: The results of a meta-analysis. Adv Biomed Res 2016; 5: 141.
3. Fadeel B, Orrenius S, Zhivotovsky B. Apoptosis in human disease: A new skin for the old ceremony? Biochem Biophys Res Commun 1999; 266: 699–717.
4. Byus CV, Pieper SE, Adey R. The effects of low-energy 60 Hz environmental electromagnetic fields upon the growth related enzyme ornithine decarboxylase. Carcinogenesis 1987; 8: 1385–9.
5. Frey A, On the Nature of Electromagnetic Field Interactions with Biological Systems. Landes Company, Medical Intelligence Unit, R.G, Austin, TX. 1994.
6. Nie Y, Du L, Mou Y, et al. Effect of low frequency magnetic fields on melanoma: Tumor inhibition and immune modulation. BMC Cancer 2013; 13: 582.
7. Garip AI, Akan Z. Effect of ELF-EMF on number of apoptotic cells; correlation with reactive oxygen species and HSP. Acta Biol Hung 2010; 61: 158-67.
8. Basile A, Zeppa R, Pasquino N, et al. Exposure to 50 Hz electromagnetic field raises the levels of the anti-apoptotic protein BAG3 in melanoma cells. J Cell Physiol 2011; 226: 2901–7.
9. Erdem O, Akay C, Cevher SC, et al. Effects of Intermittent and Continuous Magnetic Fields on Trace Element Levels in Guinea Pigs. Biol Trace Elem Res 2018; 181: 265-71.
10. Canseven AG, Seyhan N, Aydın A, et al. Effects of ambient ELF magnetic fields: variations in electrolyte levels in the brain and blood plasma. Gazi Medical Journal 2005; 16: 121-7.
11. Canseven A, Seyhan N. Ellipsoid Models for Human and Guinea Pigs Exposed to Magnetic Fields, IEEE.
12. Canseven AG, Seyhan N. Design, installation and standardization of homogeneous magnetic field systems for experimental animals. IFMBE Proceedings, Vol. 11. Prague: IFMBE, ISSN 1727–1983. In: Hozman J, Kneppo P, editors. Proceedings of the 3rd European Medical & Biological Engineering Conference (EMBEC 2005). Prague, Czech Republic 2005: 2333-8.
13. Luna LG. Manual of histologic staining methods of the armed forces. Institute of Pathology. New York: Blakiston, 1968; pp 1-46.
14. Turbin DA, Leung S, Cheang MCU, et al. Automated quantitative analysis of estrogen receptor expression in breast carcinoma does not differ from expert pathologist scoring: A tissue microarray study of 3,484 cases. Breast Cancer Res Treat 2008; 110: 417–26.
15. Detre S, Saccani Jotti G, Dowsett M. A "quickscore" method for immunohistochemical semiquantitation: validation for oestrogen receptor in breast carcinomas. J Clin Pathol 1995; 48: 876–8.

16. Koca G, Singar E, Akbulut A, et al. The effect of resveratrol on radioiodine therapy-associated lacrimal gland damage. Curr Eye Res 2020; 8: 1-10.
17. Shalini S, Dorstyn L, Dawar S, et al. Old new and emerging functions of caspases. Cell Death Differ 2015; 22: 526–39.
18. Yumusak N, Sadic M, Yucel G, et al. Apoptosis and cell proliferation in short-term and long-term effects of radioiodine-131-induced kidney damage: an experimental and immunohistochemical study. Nucl Med Commun 2018; 39: 131-9.
19. Basile A, Zeppa R, Pasquino N, et al. Exposure to 50 Hz electromagnetic field raises the levels of the anti-apoptotic protein BAG3 in melanoma cells. J Cell Physiol 2011; 226: 2901-7.
20. Kurian MV, Hamilton L, Keeven J, et al. Enhanced cell survival and diminished apoptotic response to simulated ischemia-reperfusion in H9c2 celss by magnetic field preconditioning. Apoptosis 2012; 17: 1182-96.
21. Kim YW, Kim HS, Lee JS, et al. Effects of 60 Hz 14 μT magnetic field on the apoptosis of testicular germ cell in mice. Bioelectromagnetics 2009; 30: 66-72.
22. Kim HS, Park BJ, Jang HJ, et al. Continuous exposure to 60 Hz magnetic fields induces duration and dose dependent apoptosis of testicular germ cells. Bioelectromagnetics 2014; 35: 100-7.
23. Ulku R, Akdag MZ, Erdogan S, et al. Extremely low-frequency magnetic field decreased calcium, zinc and magnesium levels in costa of rat. Biol Trace Elem Res 2011; 143:359-67.
24. Gmitrova A, Ivanco I, Gmitrov J, et al. Biological effects of magnetic field on laboratory animals. J Bioelectricity 1988; 7: 123-4.
25. Garcia-Sancho J, Montero m, Alvarez J, et al. Effects of extremely low frequency electromagnetic fields on ion transport in several mammalian cells. Bioelectromagnetics 1994; 15: 579-88.
26. Sun ZC, Ge JL, Guo B, et al. Extremely low frequency electromagnetic fields facilitate vesicle endocytosis by ıncreasing presynaptic calcium channel expression at a central synapse. Sci Rep 2016; 6: 21774.
27. Santini MT, Ferrante A, Rainaldi G, et al. Extremely low frequency (ELF) magnetic fields and apoptosis: a review. Int J Radiat Biol 2005; 81: 1-11.
28. Sheikh MS, Huang Y. TRAIL death receptors, Bcl-2 protein family, and endoplasmic reticulum calcium pool. Vitam Horm 2004; 67: 169-88.
29. Stratton D, Lange S, Inal JM. Pulsed extremely low-extremely low-frequency magnetic fields stimulate microvesicle release from human monocytic leukaemia cells. Biochem Biophys Res Commun 2013; 430: 470-5.
30. Nittby H, Grafström G, Eberhardt JL, et al. Radiofrequency and extremely low-frequency electromagnetic field effects on the blood-brain barrier. Electromagn Biol Med 2008; 27: 103-26.
31. Burchard JF, Nguyen DH, Block E. Macro- and trace element concentrations in blood plasma and cerebrospinal fluid of dairy cows exposed to electric and magnetic fields. Bioelectromagnetics 1999; 20: 358-64.
32. Lai H, Singhh NP. Magnetic-field induced DNA strand breaks in brain cells of the rat. Environ Health Perspect 2004; 112: 687-94.
33. Akdag MZ, Dasdag S, Ulukaya E, et al. Effects of extremely low-frequency magnetic field on caspase activities and oxidative stress values in rat brain. Biol Trace Elem Res 2010; 138: 238-49.
34. Oda T, Koike T. Magnetic field exposure saves rat cerebellar granule neurons from apoptosis in vitro. Neurosci Lett 2004; 22; 365: 83-6.
35. Falone S, Mirabilio A, Carbone MC, et al. Chronic exposure to 50Hz magnetic fields causes a significant weakening of antioxidant defence systems in aged rat brain. Int J Biochem Cell Biol 2008; 40: 2762-70.
36. Toescu EC. Apoptosis and cell death in neuronal cells: where does Ca^{2+} fit in? Cell Calcium 1998; 24: 387-403.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1245399

Anatolian Curr Med J 2023; 5(2); 111-119

Patient satisfaction, sexual function and decision regret in use of levonorgestrel releasing intrauterine device

Canan Satır Özel[1], Gökçem İnanç Karaman[2], Ergül Demirçivi[2], Oğuz Devrim Yardımcı[1], Mustafa Çakır[3], Abdulkadir Turgut[2]

[1]Department of Obstetrics and Gynecology, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul Medeniyet University, İstanbul, Turkey
[2]Department of Obstetrics and Gynecology, Faculty of Medicine, İstanbul Medeniyet University, İstanbul, Turkey
[3]Department of Public Health, Faculty of Medicine, İstanbul Medeniyet University, İstanbul, Turkey

Cite this article as: Satır Özel C, İnanç Karaman G, Demirçivi E, Yardımcı OD, Çakır M, Turgut A. Patient satisfaction, sexual function and decision regret in use of levonorgestrel releasing intrauterine device. Anatolian Curr Med J 2023; 5(2); 111-119.

ABSTRACT

Aim: Abnormal uterine bleeding is a common condition. The etiological cause and treatments are diverse. Levonorgestrel intrauterin device (LNG-IUD) can be used to treat abnormal uterine bleeding. It has been shown to reduce the amount of bleeding in patients with menorrhagia and increase hemoglobin (Hb) and hematocrit (Hct) values. The aim is to investigate the effects of LNG-IUD on Hb, Hct, bleeding pattern, and its effect on sexual function, decision regret, and menorrhagia effects according to the etiologic cause.

Material and Method: Our study included patients who underwent LNG-IUD implantation and had been using it for over six months. Patients with a history of postmenopausal or adolescent bleeding, hematologic or oncologic diseases, and a history of drug use that may cause coagulation disorders were excluded. Patients were grouped according to their indications as polyp (n=26), adenomyosis (n=16), leiomyoma (n=27), hyperplasia (n=18), and non-structural causes (n=81). Hb and Hct values were examined before and after the application, and bleeding patterns were questioned. Participants were administered Menorrhagia Impact Questionnaire (MIQ), Arizona Sexual Experience Scale and Decision Regret Scale.

Results: 168 patients were included in our study. The average duration of LNG-IUD use was 627.0±319 days and the average age was 43.4±6.1 years. The frequency of bleeding (number of bleedings per year) was 18.0±8.0 before LNG-IUD application and 7.8±8.0 after treatment ($p<0.001$), and bleeding duration was 11.5±9.5 days before application and 4.8±6.2 days after application ($p<0.001$). The number of pads used per day was 7.7±3.9 before the application and 1.1±1.4 after the application ($p<0.001$). While the average Hb value was 11.2±2.0 and Hct value was 34.8±5.1 (n=112) before LNG-IUD application, the average hemogram value was 12.9±1.6 and Hct value was 39.3±4.1 (n=66) after application and a statistically significant increase was observed in Hb and Hct values ($p<0.01$). When the groups were compared according to the indication, there was no significant difference in the average number of days of LNG-IUD use, total Arizona score, number of individuals with sexual dysfunction according to the Arizano score and decision regret score.

Conclusion: LNG-IUD in treating patients with abnormal uterine bleeding increases Hb and Hct values and decreases the bleeding frequency, duration, and daily pad use. LNG-IUD use did not make a difference in sexual functions and decision regret according to the etiologic cause.

Keywords: Bleeding pattern, decision regret, levonorgestrel IUD, sexual function

INTRODUCTION

Abnormal uterine bleeding (AUB), defined as deviation from normal menstrual parameters, is one of the most common reasons for hospital admission in women of reproductive age. It is observed with a prevalence of 10-30% in reproductive age (1). With a frequency of 24 to 38 days, lasting less than 8 days, regular (cycle variation: ≤7 to 9 days), without intermenstrual bleeding and bleedings with normal volume of flows are defined as normal menstrual bleeding (2). AUB has been shown to affect women's sexual life, is associated with psychological morbidity, and affects social, professional and family life (1). AUB symptom can be treated surgically or medically according to its etiological cause. Combined oral contraceptives (COC), progestin-only methods, tranexamic acid, NSAIDs are the main medical treatment methods. Levonorgestrel intrauterine device (LNG-IUD)

Corresponding Author: Canan Satır Özel, drcanansatirozel@gmail.com
Received: 31.01.2023 **Accepted:** 27.02.2023

is one of the medical treatment options in AUB and can be used in many indications (3). Endometrial ablation treatments, LNG-IUD, and hysterectomy have been found to improve the quality of life in AUB compared to pre-treatment (1). Anemia due to AUB can often occur. Improvement in hematologic parameters is also expected with the treatments used. A 7.5% increase in average hemoglobin (Hb) and 68.8% increase in serum ferritin values were reported in 6 months of LNG-IUD use compared to basal (4). In summary, in addition to symptomatic improvement, an increase in hemogram values and psychosocial improvement is expected in patients treated for AUB. In addition, patients' rates of benefit from treatments may vary according to the indication and according to different treatment modalities in the same indication. We aim to investigate the difference in decision regrets, satisfaction, and sexual function in women using LNG-IUD according to the etiologic cause.

MATERIAL AND METHOD

The study was carried out with the permission of Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Researches Ethics Committee (Date: 30/03/2022, Decision No: 2022/0195). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients who applied to our hospital with AUB and underwent LNG-IUD between January 2019 and January 2022 were identified retrospectively. Patients who had been using the LNG-IUD for at least 6 months during the reproductive period were included in our study. We excluded patients who discontinued treatment in less than 6 months, those who planned to become pregnant, patients with postmenopausal bleeding or adolescent age, patients with hematologic or oncologic diseases causing additional bleeding-coagulation problems, thrombolytic drug users, non-native Turkish speakers, and those who refused to participate.

Patients were grouped according to the FIGO (PALM, COEIN) classification system developed to standardize terminology; polyp, adenomyosis, leiomyoma, hyperplasia, and non-structural causes (5). Participants were administered the Menorrhagia Impact Questionnaire (MIQ), the Arizona Sexual Experience Scale, and the Decision Regret Scale. Hemogram, Hematocrit (Hct) values of the patients before LNG-IUD insertion and hemogram, Hct values taken within 6-12 months after the procedure were scanned from the hospital database. The patients were questioned in terms of menstrual parameters before and after the procedure (number of bleeding per year, duration of bleeding, number of pads used daily). In addition, the number of times the patients bleed per year was defined as the annual bleeding frequency. The total number of days with bleeding in a year was calculated by multiplying the bleeding frequencies by the number of days with each bleeding.

Arizona sexual experience scale: It was developed to quantify sexual dysfunction by aiming to evaluate sexual functions by excluding sexual orientation and relationship with a partner (6). The scale consists of 5 questions, and the score of the question is between 1-6. The total score is between 5 and 30. High scores indicate sexual dysfunction. If the total score is 19 or higher, or if the score of an area is 5 or higher, or if the score is 4 or higher in any 3 areas, it is considered sexual dysfunction. There are separate scales for women and men. The scale adapted to the Turkish language was used in the study (7). The scale includes questions that examine sexual drive, psychological arousal, physiological arousal (vaginal lubrication), the capacity to reach orgasm, and the feeling of satisfaction as a result of orgasm. In our study, the cut-off point for sexual dysfunction was taken as 19.

Menorrhagia impact questionnaire (MIQ): It was developed to measure the effect of menstrual blood loss on quality of life. It consists of subjective measurement of blood loss, social and physical activity, and restriction of work life. It consists of 7 items of which 6 of the items are scored. The first item consists of 4 points, and the second and fourth items consist of a 5-point response scale. The fifth item is the open-ended response, in which the person is asked to describe the restriction of a particular activity. In the sixth item, the change in bleeding is asked to be evaluated as the same, better or worse than before. In the seventh item (described as item 6c in the original form), it is questioned whether the change in the amount of bleeding is significant (8).

Decision regret scale: It is a one-dimensional and five-item scale that evaluates patients' regrets after receiving a medical procedure or health service (9). Participants are asked to reflect on specific treatment decisions made and indicate how much they agree or disagree with the statements, ranging from 1 ("strongly agree") to 5 ("strongly disagree"). Scoring consists of averaging the 5 items. From this average, 1 is subtracted and multiplied by 25 to convert to a score ranging from 0-100. High scores show more regret. If the total score is 0, it indicates that there is no regret, and if it is 100, it indicates that there is high regret. In our study, the adapted and validated version of the questionnaire in the Turkish language was used and the scale is shown in the **Appendix** (10).

Appendix-1. Decision Regret Scale - Validated and Adapted to Turkish				
Örnek Araç: Karar Pişmanlık Ölçeği **Karar Pişmanlık Ölçeği** Lütfen [Doktor, Cerrah, Hemşire, Sağlık Personeli, vb.] ile konuştuktan sonra verdiğiniz _____ kararı ile ilgili düşünün. Lütfen nasıl hissettiğinizi 1'den (tamamen katılıyorum) 5'e (tamamen katılmıyorum) kadar bir numarayı çembere alarak gösterin.				
1. Doğru karardı.				
1	2	3	4	5
Tamamen katılıyorum	Katılıyorum	Ne katılıyorum ne katılmıyorum	Katılmıyorum	Tamamen katılmıyorum
2. Aldığım karardan pişmanım.				
1	2	3	4	5
Tamamen katılıyorum	Katılıyorum	Ne katılıyorum ne katılmıyorum	Katılmıyorum	Tamamen katılmıyorum
3. Eğer tekrar yapmak zorunda olsaydım, yine aynı kararı alırdım.				
1	2	3	4	5
Tamamen katılıyorum	Katılıyorum	Ne katılıyorum ne katılmıyorum	Katılmıyorum	Tamamen katılmıyorum
4. Kararım bana çok zarar verdi.				
1	2	3	4	5
Tamamen katılıyorum	Katılıyorum	Ne katılıyorum ne katılmıyorum	Katılmıyorum	Tamamen katılmıyorum
5. Kararım akıllıcaydı.				
1	2	3	4	5
Tamamen katılıyorum	Katılıyorum	Ne katılıyorum ne katılmıyorum	Katılmıyorum	Tamamen katılmıyorum

Statistical Analysis

Statistical analyses were performed in the SPSS 22.0 statistical package program. As statistical analysis, in the descriptive findings section, categorical variables were presented with a number, percentage, and continuous variables with average±standard deviation and median (smallest, largest value). Pearson's Chi-square test was used to compare categorical variables; the Kolmogorov-Smirnov test was used to examine the suitability of the data for normal distribution in the comparison of the variables specified by the measurement, Paired t-test was used to compare two repetitive measurements suitable for normal distribution, Wilcoxon test was used to compare two repetitive measurements suitable for normal distribution, and Kruskal-Wallis test was used to compare more than two independent groups. The statistical significance level was taken as $p<0.05$ in the analysis.

RESULTS

279 patients were reached from the hospital records, the study was explained in clear language by teleconference, and 168 patients who verbally approved participation and were currently undergoing treatment were included in the study, 121 patients could not be included in the study (35 hysterectomized, 31 discontinued treatment, 21 failed to insert, 20 IUDs have resulted with expulsion, 10 patients refused to participate, 4 non-native speakers of Turkish). Based on the examination records and ultrasonography findings, patients were grouped by indication as Group 1 (Polyp) (n=26), Group 2 (Adenomyosis) (n=16), Group 3 (Leiomyoma) (n=27), Group 4 (Hyperplasia) (n=18) and Group 5 (non-structural causes) (n=81).

The demographic data of all participants (n=168) are summarized in **Table 1**. The average duration by LNG-IUD use of the participants was 627.06±319.6 days, and the average age was 43.4±6.1 years. From the hospital records, Hb and Hct values of 112 patients before and 66 patients after treatment with LNG-IUD could be reached among all participants. Hb, Hct values and bleeding parameters before and after LNG-IUD were compared and shown in **Table 2**. It was found that Hb and Hct values were statistically significantly higher after treatment ($p<0.001$ for two variables), while bleeding frequency, bleeding time and the number of pads used were lower ($p<0.001$ for three variables).

The groups were compared in terms of the number of days of LNG-IUD use, the total score of the Arizona Sexual Experience Scale, the number of individuals with sexual dysfunction, and decision regrets, and there was no statistically significant difference between the groups (**Table 3**). It was determined that the groups were not statistically different in terms of the number of days using LNG-IUD, total Arizona Sexual Experience Scale score, and decision regret score (p; 0.350; 0.680; 0.400, respectively). While the decision regret score of 90 people among all participants was 0, only one participant in Group 5 was calculated as 100.

The groups were compared with the Menorrhagia Impact Questionnaire and shown in **Table 4**. No statistical difference was observed in the groups in terms of concepts except MIQ-5 in the table. In the groups, the majority of the participants described the amount of blood loss as "mild", the restriction of work, physical and social activity as "none", and the change in the amount of bleeding was significant. None of the participants stated that the amount of bleeding was higher. To the open-ended response of "List of Behaviors Restricted by MIQ-5 Bleeding Reason", which was not included in the table, 1 patient in Group 2 said that she could not do sports, 1 patient in Group 3 said that she could not go to work, and 1 patient said that she could not walk.

Table 1. Demographic Data of the Participants

	n (%)
Age	
Average±standard deviation	43.4±6.1
Median (min; max)	44 (min:27; 58)
Gravida	
Average±standard deviation	3.0±1.5
Median (min; max)	3.0 (0; 8)
Parity	
Average±standard deviation	2.2±1.1
Median (min; max)	2 (0; 7)
NSD	
Average±standard deviation	1.5±1.4
Median (min; max)	2 (0; 7)
C/S	
Average±standard deviation	0.7±0.9
Median (min; max)	0 (0; 4)
Abortion	
Average±standard deviation	0.2±0.5
Median (min; max)	0 (0; 4)
D&C	
Average±standard deviation	0.3±0.7
Median (min; max)	0 (0; 3)
Ectopic Pregnancy	
0	167 (99.4)
1	1 (0.6)
Chronic Diseases	
No	109 (64.9)
Anemia	3 (1.8)
DM	8 (4.8)
HT	12 (7.1)
Hypothyroidism	16 (9.5)
Other	20 (11.9)
Drug Use	
None	117 (69.6)
Yes	51 (30.4)
Smoking	
No	96 (57.1)
Yes	72 (42.9)
BMI	
<18.5	1 (0.6)
18.5-24.9	57 (33.9)
25-29.9	65 (38.7)
≥30	45 (26.8)
Mean Hemoglobin Level Before LNG-IUD	11.2±2.0
Mean Hemoglobin Level After LNG-IUD	12.9±1.6
Average LNG-IUD Time (Days)	627.06±319.6

(%): percentage of columns

Table 2. Hemoglobin, Hematocrit, Annual Bleeding Frequency, Number of Bleeding Days, Daily Pad Usage Difference Before and After Treatment with LNG-IUD

	Before LNG-IUD	After LNG-IUD	p
Hemoglobin g/dl (n)	11.2±2.0 (n=112)	12.9±1.6 (n=66)	<0.001*
Hematocrit (%) (n)	34.8±5.1 (n=112)	39.3±4.1 (n=66)	<0.001*
Annual bleeding frequency n#	18.0±8.0 (n=168)	7.8±8.0 (n=168)	<0.001**
Bleed duration days (n)	11.5±9.5 (n=168)	4.8±6.2 (n=168)	<0.001**
Number of pads used per day (n)	7.7±3.9 (n=168)	1.1±1.4 (n=168)	<0.001**

*Paired t-test * * Wilcoxon test #Indicates how many times the patient has experienced bleeding in a year

The groups were compared in terms of Hb, Hct changes, bleeding parameters and the total number of bleeding days per year which are shown in **Table 5**. Hb and Hct increases were observed in all groups after the procedure compared to before the procedure. The highest average Hb (12.0±1.0) and Hct (37.1±2.2) values before the procedure were observed in the adenomyosis group, but the increase in Hb (13.6±0.6) and Hct (41.0±1.1) after the procedure was not statistically significant only in this group (p values for Hb and Hct were 0.087 and 0.632, respectively). In all other groups, the increase in Hb and Hct was statistically significant. It was observed that the number of pads used in all groups, the frequency of bleeding, and the total number of bleeding days per year decreased statistically significantly. A decrease in the number of days in each bleeding period was observed in all groups, but the decrease in the adenomyosis group was not statistically significant, while it was statistically significant in other groups.

Table 3. Comparison of Average Treatment Time, Arizona Sexual Experience Scale and Decision Regret Score by Indication Groups

Groups	Mean number of days of lng-iud use	Total arizona sexual experience scale score	Number of people with sexual dysfunction according to the arizona sexual experience scale score n (%)	Decision regret score
Group 1 (Polyp) (n=26)	703.7±316.7	12.9±6.8	4 (20.0)	11.1±17.1
Group 2 (Adenomyosis) (n=16)	653.1±312.6	13.4±5.5	-	12.5±21.1
Group 3 (Leiyomyoma) (n=27)	680.7±297.2	15.2±4.9	3 (15.0)	13.8±17.5
Group 4 (Hyperplasia) (n=18)	509.5±294.0	15.5±2.3	2 (10.0)	9.7±15.1
Group 5 (Non-structural causes) (n=81)	605.5±331.5	14.2±5.4	11 (55.0)	19.5±25.2
p	0.350***	0.680***	0.608****	0.400***

* * * Kruskal Wallis test * * * * Chi-square test (%) column percentage

Table 4. Comparison of Menorrhagia Impact Questionnaire by Indication Groups

	Group 1 (Polyp) (n=26) n (%)	Group 2 (Adenomyosis) (n=16) n (%)	Group 3 (Leiyomyoma) (n=27) n (%)	Group 4 (Hyperplasia) (n=18) n (%)	Group 5 (Non-Structural Causes)(n=81) n (%)	Total (n=168)
MIQ-1 (Detection of amount of blood loss)						
1-Mild	23 (88.4)	14 (87.5)	22 (81.4)	16 (88.8)	74 (91.3)	149 (88,6)
2-Medium	2 (7.6)	2 (12.5)	3 (11.1)	2 (11.1)	7 (8.6)	16 (9.5)
3-High	1 (3.8)	0 (-)	2 (7.4)	0 (-)	0 (-)	3 (1.7)
4-Very high	0	0	0	0	0	
			p= 0.423			
MIQ-2 (Restriction of outdoor and indoor works)						
1-None	24 (92.3)	14 (87.5)	24 (88.8)	18 (100)	78 (96.2)	158 (94.0)
2-Very low	1 (3.8)	0 (-)	0 (-)	0 (-)	2 (2.4)	3 (1.7)
3-Medium	1 (3.8)	2 (12.5)	2 (7.4)	0 (-)	1 (1.2)	6 (3.5)
4-Quite A lot	0 (-)	0 (-)	1 (3.7)	0 (-)	0 (-)	1 (0.5)
5-Extreme	0	0	0	0	0	
			p= 0.301			
MIQ-3 (Restriction of physical activity)						
1-None	24 (92.3)	14 (87.5)	24 (88.8)	18 (100)	78 (96.2)	158 (94.0)
2-Very low	1 (3.8)	0 (-)	0 (-)	0 (-)	2 (2.4)	3 (1.7)
3-Medium	1 (3.8)	2 (12.5)	2 (7.4)	0 (-)	1 (1.2)	6 (3.5)
4-Quite a lot	0 (-)	0 (-)	1 (3.7)	0 (-)	0 (-)	1 (0.5)
5-Extreme	0	0	0	0	0	
			p= 0.301			
MIQ-4 (Restriction of social activity)						
1-None	24 (92.3)	14 (87.5)	24 (88.8)	18 (100)	78 (96.2)	158 (94.0)
2-Very low	1 (3.8)	2 (12.5)	0 (-)	0 (-)	2 (2.4)	5 (2.9)
3-Medium	1 (3.8)	0 (-)	2 (7.4)	0 (-)	1 (1.2)	4 (2.3)
4-Quite a lot	0 (-)	0 (-)	1 (3.7)	0 (-)	0 (-)	1 (0.5)
5-Extreme	0	0	0	0	0	
			p= 0.182			
MIQ-6 (Evaluation of change in bleeding amount)						
0-Pretty much the same	0 (-)	1 (6.2)	3 (11.1)	0 (-)	3 (3.7)	7 (4.1)
1-Almost the same	0 (-)	0 (-)	0 (-)	0 (-)	3 (3.7)	3 (1.7)
2-There is very little decrease	0	0	0	0	0	
3-A little less	0 (-)	1 (6.2)	1 (3.7)	0 (-)	1 (1.2)	3 (1.7)
4-Mediary less	2 (7.6)	0 (-)	0 (-)	0 (-)	0 (-)	2 (1.1)
5-Significantly less	4 (15.3)	3 (18.7)	2 (7.4)	7 (38.8)	19 (23.4)	35 (20.8)
6-Much less	9 (34.6)	6 (37.5)	14 (51.8)	8 (44.4)	38 (46.9)	75 (44.6)
7-So much less	11 (42.3)	5 (31.2)	7 (25.9)	3 (16.6)	17 (20.9)	43 (25.5)
			p= 0.087			
MIQ-7 (Significance of change in bleeding amount)						
0-No	1 (3.8)	1 (6.2)	4 (14.8)	0 (-)	5 (6.1)	11 (6.5)
1-Yes	25 (96.1)	15 (93.7)	23 (85.1)	18 (100)	76 (93.8)	157 (93.4)
			p= 0.329			

(%): percentage of columns

Table 5. Comparison of the Groups with LNG-IUD Before and After Treatment in Terms of Hemogram, Hematocrit, Bleeding Parameters

Groups (column)	Mean Hb before LNG-IUD	Mean Hb after LNG-IUD	Hb difference	Mean Hct before LNG-IUD	Mean Hct after LNG-IUD	Hct difference	Pads before LNG-IUD	Pads after LNG-IUD	Pad number difference
Group 1 (Polyp)	10.9±2.5	12.4±2.0	3.1±1.7	34.0±6.1	38.8±5.0	8.4±3.9	7.8±4.4	1.0±1.5	6.8±4.4
p	0.030*			0.019*			<0.001**		
Group 2 (Adenomyosis)	12.0±1.0	13.6±0.6	2.3±0.5	37.1±2.2	41.0±1.1	5.1±2.3	8.0±3.7	0.8±0.8	7.1±4.2
p	0.087*			0.632*			0.001**		
Group 3 (Leiyomyoma)	10.6±2.2	12.9±2.0	1.5±1.4	33.4±5.1	39.4±5.1	4.3±3.3	9.0±3.5	1.6±2.2	7.3±4.3
p	0.004*			0.003*			<0.001**		
Group 4 (Hyperplasia)	11.5±1.8	12.9±1.2	1.0±0.7	35.7±4.9	39.5±3.3	4.0±2.4	8.3±4.1	1.1±1.4	7.2±3.6
p	0.001*			0.010*			<0.001**		
Group 5 (Non-Structural Causes)	11.3±2.0	12.9±1.6	1.3±2.6	34.9±5.1	39.2±3.9	2.4±3.1	7.0±3.8	1.0±1.0	6.0±3.8
P	<0.001*			<0.001*			<0.001**		

*paired t-Test * * Wilcoxon Test

Table 5. Continued

Groups (column)	Mean frequency before LNG-RIA	Mean frequency after LNG-RIA	Frequency difference	Mean bleeding day before LNG-RIA	Mean bleeding day after LNG-RIA	Bleeding day difference	Mean total number of bleeding days per year before LNG-RIA	Mean Total number of bleeding days per year after LNG-RIA	Mean total number of bleeding days per year difference
Group 1 (Polyp)	17.5±7.3	8.4±7.2	9.0±10.3	11.2±5.2	3.8±5.5	7.4±7.0	157.5±81.2	74.0±98.2	83.5±139.9
p	0.001			<0.001			0.008		
Group 2 (Adenomyosis)	17.1±7.2	6.8±9.4	10.3±12.5	14.2±21.1	6.0±8.5	8.2±22.0	170.8±73.3	53.6±83.2	117.2±128.5
p	0.018			0.086			0.007		
Group 3 (Leiyomyoma)	19.0±8.9	8.9±8.2	9.8±9.8	10.7±4.0	5.2±5.2	5.4±6.5	188.5±96.8	58.4±76.9	130.1±102.0
p	<0.001			0.001			<0.001		
Group 4 (Hyperplasia)	19.0±11.3	7.6±6.6	11.3±13.6	16.3±13.8	7.1±8.4	9.2±12.7	213.0±94.7	51.8±54.9	161.2±111.3
p	0.004			0.010			<0.001		
Group 5 (Non-structural causes)	17.9±7.3	7.5±8.3	10.3±10.2	10.2±6.7	4.2±5.6	5.9±8.8	183.0±83.2	62.8±80.3	120.1±100.3
p	<0.001			<0.001			<0.001		

Wilcoxon Test

DISCUSSION

The use of LNG-IUD in the treatment of patients with abnormal uterine bleeding provided an increase in Hb and Hct values compared to pre-treatment, while bleeding frequency, bleeding time, the number of bleeding days per year and daily pad use decreased. In the treatment of LNG-IUD, there was no difference in sexual functions and decision regret according to etiological cause, and low regret scores were observed.

LNG-IUDs (Mirena® Bayer Healtcare Pharmaceuticals, Pittsburgh, PA, USA) release 20 mcg/day of LNG for 5 years and contain 52 mg in total (11). Apart from the contraceptive effect, it has also been shown to provide effective treatment in clinical conditions such as heavy menstrual bleeding, anemia, dysmenorrhea, endometriosis, pain associated with adenomyosis, premenstrual syndrome, endometrial hyperplasia due to progesterone (12,13). LNG-IUD provides its effect on the endometrium by reducing proliferation and increasing apoptosis. Loss of secretory activities of epithelial glands and inhibition of proliferative activities of the endometrium causes significant impairment in cyclic activity 1 month after insertion (14). As a result, they cause thinning in the functional layer of the endometrium. They show their main effects by creating atrophy in the endometrium and reducing the response to estrogen. LNG-IUD has been shown in many clinical studies to reduce bleeding duration and menstrual blood loss by inhibiting endometrial proliferation. It was found that there was no change in systemic hemostatic and fibrinolytic system parameters in menorrhagic patients before treatment, except for the decrease in urokinase plasminogen activator receptor (u-PAR) in the 1st, 2nd, 3rd, and 6th months of treatment, and there was no change in tissue-type plasminogen activator (t-PA) or urokinase plasminogen activator (u-PA) levels in endometrial samples taken, but a significant increase was observed in u-Par, plasminogen activator inhibitor (PAI)-1 and PAI-2 levels. Thus, it has been shown that bleeding improves only by inhibiting endometrial fibrinolytic activity without systemic (15). In the first year of LNG-IUD use, a decrease in the amount of menstrual bleeding was reported in 90% of women and a decrease in dysmenorrhea symptoms in 30% (16). LNG-IUD has been shown to increase Hb concentration by 8.6 g/L compared to basal at 12 months of use (17). In patients with severe menstrual bleeding, LNG-IUD has been shown to significantly reduce the amount of menstrual bleeding by approximately 105 ml and has been recommended as a first-line treatment (18).

Similar to hysterectomy, treatment with LNG-IUD increased Hb in patients with adenomyosis, while a significant increase was observed in average Hb values at 6 and 12 months compared to pre-treatment (19). Similarly, in our study, it was observed that LNG-IUD significantly increased Hb and Hct values after treatment, and a significant increase was observed in average Hb and Hct values after treatment in all groups except adenomyosis. The average duration of treatment in patients with adenomyosis was 653.1±312.6 days, and no statistical difference was observed in average Hb values compared to pre-treatment. This may be due to the high level of Hb in this group in the pre-treatment period.

Most of the endometrial polyp and LNG-IUD studies were conducted in the patient group using tamoxifen. In these patients, LNG-IUD was shown to be risk-reducing for the development of polyps and endometrial hyperplasia only according to monitoring (endometrial surveillance), and OR was calculated as 0.22 and 0.13, respectively (20). After hysteroscopic polypectomy, 3.47% polyp recurrence was observed in the treatment with LNG-IUD and 15.96% in the group without any treatment (21). Although treatment with LNG-IUD has reduced the risk of polyp and hyperplasia in risky groups, it has also been reported that an asymptomatic patient who has been using LNG-IUD for contraception for 46 months develops endometrial carcinoma based on polyp, which was detected on routine examination (22). In a pilot study in which patients with hysteroscopic evidence of endometrial polyp were followed up until the day of polypectomy without treatment or with LNG-IUD, polyp was 37% in the LNG-IUD group and 80% in the control group, the absolute risk reduction was 43% and RR was 0.46 (23). We cannot comment on polyp recurrence after treatment with LNG-IUD in patients who developed AUB due to polyps because our study was not designed that way. However, in this group, while the sexual life scale and decision regret were similar to other etiological causes, there were significant differences in Hb, Hct, the number of pads used, and the number of bleeding days after treatment. It is clear that more studies are needed on the use of LNG-IUD in the treatment of polyps.

Leiomyomas are the most common uterine tumors, and they come in a wide range of sizes (24). They may be asymptomatic or may cause bleeding, compression symptoms and pain. LNG-IUD is recommended to reduce the amount of bleeding in the symptomatic treatment of leiomyomas (25). In addition, when there is no detectable pathology, LNG-IUD is recommended as the first option in the treatment of heavy menstrual bleeding in myomas below 3 cm and not distorting the cavity and in adenomyosis (3). It was shown that patients with an average pre-treatment myoma volume of 22 mm3 had a significant increase in Hb and Hct values in the sixth month of treatment with LNG-IUD compared to the pre-treatment and third month of treatment, and a significant decrease in the Pictorial Blood Loss Assessment score. The average Hb value before treatment was 10.7±1.2, 11.5±0.9 in the third month and 12.3±0.8 in the sixth month. However, no difference was observed in the uterus and myoma size (27). In our study, while the average treatment duration of the leiomyoma group was 680.7±297.2 days, similarly, a significant increase in Hb, Hct, and a significant decrease in bleeding parameters were observed, and it was shown that LNG-IUD provided benefit in AUB due to leiomyoma. Regret of treatment is also low in this group.

In women with severe menstrual bleeding, more satisfaction and treatment adherence were reported, which was not significant in the use of LNG-IUD compared to other medical treatments (28). Female sexual dysfunction decreased from 87.4% to 47.4% in the sixth month of LNG-IUD treatment with AUB bleeding (29). In a randomized study of 236 patients comparing hysterectomy and LNG-IUD in the treatment of menorrhagia, hysterectomy was found to increase sexual satisfaction and reduce sexual problems at the sixth and twelfth months. In the fifth year, partner satisfaction increased. On the other hand, there was no difference in sexual satisfaction and sexual problems in the LNG-IUD group. At 12 months, partner satisfaction declined significantly and remained low for 5 years. Results in favor of hysterectomy were found in the study (30). In our study, the number of people with sexual functions and sexual dysfunction was similar in the groups with similar treatment duration. The average Arizona sexual experience score was low in the groups, and it was observed that there was no sexual dysfunction. However, since the sexual status of the individuals before the treatment is not known, the benefit of the treatment cannot be commented on. In the study groups, it can be said that the regret rates from the treatment are low and the satisfaction is high. In the phase-3 study conducted on other forms of LNG-IUD releasing 8 and 13 mcg/day, more than 90% treatment satisfaction, satisfaction with more than 70% menstrual patterns and user preference were reported (31). Similar to our study in the literature, we did not find a study in which regret from LNG-IUD treatment was measured. Our study will contribute to the literature in terms of measuring the LNG-IUD treatment decision. It can be inspiring for similar studies.

We did not evaluate cost-effectiveness in our study. However, LNG-IUD is recommended as an alternative to hysterectomy in treatment, especially in abnormal uterine bleeding, which is one of the most common causes of hysterectomy in the perimenopausal period, and it has been shown to be 3 times more cost-effective than hysterectomy (32). LNG-IUD treatment was found to be cost-effective in patients with severe menstrual bleeding (33). In the 10-year follow-up, it was less costly than hysterectomy and the quality of life increased in the first 5 years in both methods (34).

The limitations of the study were that it was retrospective and we could not evaluate the sexual functions and effects of menorrhagia in patients before the procedure. It is the first study to evaluate the decision regarding LNG-IUD.

CONCLUSION

As a result, it was observed that there was no difference in sexual functions, decision regrets and menorrhagia effects in people using LNG-IUD on an indicative basis, and patients were highly satisfied with the treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Researches Ethics Committee (Date: 30/03/2022, Decision No: 2022/0195).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Liu Z, Doan Q, Blumenthal P, Dubois RW. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. Value Health 2007; 10: 183–94.
2. Fraser IS, Critchley HOD, Broder M, Munro MG. The FIGO recommendations on terminologies and definitions for normal and abnormal uterine bleeding. Semin Reprod Med 2011; 29: 383–90.
3. Heavy menstrual bleeding: assessment and management. National Institute for Health and Care Excellence (NICE), Clinical Guidelines Vol. 29, 2018, London.
4. Kaunitz AM, Bissonnette F, Monteiro I, Lukkari-Lax E, DeSanctis Y, Jensen J. Levonorgestrel-Releasing Intrauterine System for heavy menstrual bleeding improves hemoglobin and ferritin levels. Contraception 2012; 86: 452–457.
5. Munro MG, Critchley HOD, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011; 113: 3–13.
6. McGahuey CA, Gelenberg AJ, Laukes CA, et al. The Arizona sexual experience scale (ASEX): reliability and validity. J Sex Marital Ther 2000; 26: 25–40
7. Soykan A. The reliability and validity of Arizona sexual experiences scale in Turkish ESRD patients undergoing hemodialysis. Int J Impot Res 2004; 16: 531–4.
8. Bushnell DM, Martin ML, Moore KA, Richter HE, Rubin A, Patrick DL. Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life. Curr Med Res Opin 2010; 26: 2745–55.
9. Brehaut JC, O'Connor AM, Wood TJ, et al. Validation of a decision regret scale. Med Decis Making 2003; 23: 281–92.
10. Telatar T G, Satır Özel C, Turgut A, Kınlı O. Turkish version methodological validation study of the Decision Regret Scale. Ethiopian J Health Development 2021; 35: 362–6.
11. Luukkainen T, Allonen H, Haukkamaa M, Lähteenmäki P, Nilsson CG, Toivonen J. Five years' experience with Levonorgestrel-Releasing IUDs. Contraception 1986; 33: 139–48.
12. Xiao BL, Zhou LY, Zhang XL, Jia MC, Luukkainen T, Allonen H. Pharmacokinetic and pharmacodynamic studies of levonorgestrel-releasing intrauterine device. Contraception 1990; 41: 353–62.
13. Bahamondes L, Valeria Bahamondes M, Shulman LP. Non-contraceptive benefits of hormonal and intrauterine reversible contraceptive methods. Hum Reprod Update 2015; 21: 640–51.
14. Silverberg SG, Haukkamaa M, Arko H, Nilsson CG, Luukkainen T. Endometrial morphology during long-term use of levonorgestrel-releasing intrauterine devices. Int J Gynecol Patholson 1986; 5: 235–41.
15. Koh SCL, Singh K. The effect of levonorgestrel-releasing ıntrauterine system use on menstrual blood loss and the hemostatic, fibrinolytic/inhibitor systems in women with menorrhagia. J Thromb Haemost 2007; 5: 133–8.
16. Fedele L, Bianchi S, Raffaelli R, Portuese A, Dorta M. Treatment of adenomyosis-associated menorrhagia with a levonorgestrel-releasing intrauterine device. Fertil Steril 1997; 68: 426–9.
17. Endrikat J, Shapiro H, Lukkari-Lax E, Kunz M, Schmidt W, Fortier M. A Canadian, multicentre study comparing the efficacy of a levonorgestrel-releasing intrauterine system to an oral contraceptive in women with idiopathic menorrhagia. J Obstet Gynaecol Can 2009; 31: 340–7.
18. Bofill Rodriguez M, Dias S, Jordan V, et al. Interventions for heavy menstrual bleeding; overview of Cochrane reviews and network meta-analysis. Cochrane Database Syst Rev 2022; 5: CD013180.
19. Ozdegirmenci O, Kayikcioglu F, Akgul MA, et al. Comparison of levonorgestrel intrauterine system versus hysterectomy on efficacy and quality of life in patients with adenomyosis. Fertil Steril 2011; 95: 497–502.
20. Romero SA, Young K, Hickey M, Su HI. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Cochrane Database Syst Rev 2020; 12: CD007245.
21. Wang Y, Yang M, Huang X, Li X, Lin E, Feng Y. Prevention of benign endometrial polyp recurrence using a Levonorgestrel-releasing Intrauterine System in premenopausal patients: a retrospective cohort study. J Minim Invasive Gynecol 2020; 27: 1281–6.

22. Kuzel D, Mara M, Zizka Z, Koliba P, Dundr P, Fanta M. Malignant endometrial polyp in woman with the levonorgestrel intrauterine system - a case report. Gynecol Endocrinol 2019; 35: 112–4.
23. Chowdary P, Maher P, Ma T, Newman M, Ellett L, Readman E. The role of the Mirena intrauterine device in the management of endometrial polyps: a pilot study. J Minim Invasive Gynecol 2019; 26: 1297–302.
24. Bulun SE. Uterine fibroids. N Engl J Med 2013; 369: 1344–55.
25. American College of Obstetricians and Gynecologists committee on Prcatice Bulletins-Gynecology, Management of symptomatic uterine leiomyomas. Obstet Gynecol 2021; 137: e100–e15.
26. Senol T, Kahramanoglu I, Dogan Y, Baktiroglu M, Karateke A, Suer N. Levonorgestrel-releasing intrauterine device use as an alternative to surgical therapy for uterine leiomyoma. Clin Exp Obstet Gynecol 2015; 42: 224–7.
27. Chen S, Liu J, Peng S, Zheng Y. LNG-IUS vs. medical treatments for women with heavy menstrual bleeding: a systematic review and meta-analysis. Front Med (Lausanne) 2022; 9: 948709.
28. Turan G, Bahat PY, Cetin BA, Peker N. The effect of a levonorgestrel-releasing intrauterine device on female sexual function. J Obstet Gynaecol (Lahore) 2021; 41: 269–74.
29. Halmesmäki K, Hurskainen R, Teperi J, et al. The effect of hysterectomy or levonorgestrel-releasing intrauterine system on sexual functioning among women with menorrhagia: a 5-year randomised controlled trial. BJOG 2007; 114: 563–8.
30. Gemzell-Danielsson K, Apter D, Hauck B, et al. The effect of age, parity and body mass index on the efficacy, safety, placement and user satisfaction associated with two low-dose Levonorgestrel Intrauterine Contraceptive Systems: subgroup analyses of data from a Phase III trial. PLoS One 2015; 10: e0135309.
31. Hurskainen R, Teperi J, Rissanen P, et al.Clinical outcomes and costs with the levonorgestrel-releasing intrauterine system or hysterectomy for treatment of menorrhagia: randomized trial 5-year follow-up. JAMA 2004; 291: 1456–63.
32. Blumenthal P D, Dawson L, Hurskainen R. Cost-effectiveness and quality of life associated with heavy menstrual bleeding among women using the levonorgestrel-releasing intrauterine system. Int J Gynaecol Obstet 2011; 112: 171–8.
33. Heliövaara-Peippo S, Hurskainen R, Teperi J et al. Quality of life and costs of levonorgestrel-releasing intrauterine system or hysterectomy in the treatment of menorrhagia: a 10-year randomized controlled trial. Am J Obstet Gynecol 2013; 209: 535.e1-535.e14.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1232318

Anatolian Curr Med J 2023; 5(2); 120-124

Investigating the effects of the COVID-19 pandemic on obstetric anesthesia and perioperative outcomes in cesarean section surgery

Leyla Kutlucan, Ömer Faruk Altaş, Nimet Şenoğlu

Department of Anesthesiology, Faculty of Medicine, Bakırçay University, İzmir, Turkey

Cite this article as: Kutlucan L, Altaş ÖF, Şenoğlu N. Investigating the effects of the COVID-19 pandemic on obstetric anesthesia and perioperative outcomes in cesarean section surgery. Anatolian Curr Med J 2023; 5(2); 120-124.

ABSTRACT

Aim: In the literature, studies comparing the preferred anesthesia methods and related parameters in obstetric anesthesia during the pandemic period with the pre-pandemic period are limited. I n this study, primarily in patients who gave birth by cesarean section before and during the COVID-19 (Coronavirus disease 19) pandemic; It was aimed to evaluate the anesthesia method, postoperative complications, length of hospital stay, clinical urgency of the patients and ASA (American Society of Anesthesiologists) scores. In addition, in patients who underwent cesarean section with positive and negative PCR (Polymerase Chain Reaction) tests during the COVID-19 pandemic; It was aimed to evaluate the anesthesia method, postoperative complications, hospital stay, clinical urgency of the cases and ASA scores.

Material and Method: In this retrospective, single-center study, we noted down and compared types of cesarean section (elective or emergency), anesthesia techniques (spinal, spinal+epidural, or general anesthesia), and patients' ages, ASA scores, PCR test results, postoperative complications (e.g., pneumonia, excessive postpartum bleeding), and lengths of hospital stay.

Results: We carried out this study with the data of 2,406 women, 1,458 of whom gave birth before the pandemic. The findings revealed that the rate of developing complications, the length of hospital stay, the number of patients with an ASA score of 3 and above, and the use of spinal anesthesia significantly increased during the pandemic. Moreover, 182 women were COVID-19-positive among a total of 948 applicants during the pandemic. Although the ASA scores and complication rates were significantly higher among those with a positive PCR test result, the length of hospital stay was similar between the patients by their PCR test results.

Conclusion: Our findings revealed a significant decrease in spinal + epidural anesthesia, which was frequently adopted before, in cases with cesarean section during the pandemic. Spinal anesthesia was mostly used alone. Despite increased complication rates in PCR-positive patients with higher ASA scores undergoing cesarean section, we concluded no significant change in the length of hospital stay. In cases of increased risk of infection and transmission (e.g., pandemic), neuraxial blocks may be preferred as an anesthesia technique to minimize the risk of infection in emergency obstetric operations. It should also be noted that the risk of developing postoperative complications always be high during pandemics.

Keywords: COVID-19, cesarean section, regional anesthesia, American Society of Anesthesiologists scores, postoperative complications

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19), having first appeared in Wuhan - China in December 2019, poses a severe risk to mothers and infants, as many patient groups. In this sense, it was highly recommended to adopt regional anesthesia instead of general anesthesia in gynecological surgeries, as in many surgical procedures after the World Health Organization (WHO) declared COVID-19 as a pandemic as of March 2020 (1-7). Regional anesthesia may bring the following advantages in any pandemic: (1) prevention of inhalation and, thus, the reduction of the risk of transmission to healthcare staff, (2) reduced use of personal protective equipment (PPE; e.g., masks with filters), (3) cost savings, (4) fewer impacts on immune function, and (5) early discharge (8-14).

The scholarly interest seems to have missed the impacts of national/international anesthesia guidelines on the rates of general and regional anesthesia for cesarean section during the pandemic. Moreover, the literature hosts a paucity of research on changes in anesthesia techniques in delivery operations compared to the pre-pandemic periods (15-18). The present study, primarily in patients who gave birth by cesarean section before and during the COVID-19 (Coronavirus disease 19) pandemic; it was

Corresponding Author: Leyla Kutlucan, leylakutlucan@hotmail.com

Received: 12.01.2023 **Accepted:** 28.02.2023

aimed to evaluate the anesthesia method, postoperative complications, length of hospital stay, clinical urgency of the patients and ASA (American Society of Anesthesiologists) scores. In addition, in patients who underwent cesarean section with positive and negative PCR (Polymerase Chain Reaction) tests during the COVID-19 pandemic; it was aimed to evaluate the anesthesia method, postoperative complications, hospital stay, clinical urgency of the cases and ASA scores.

MATERIAL AND METHOD

The Non-Invasive Clinical Research Ethics Committee of Izmir Bakircay University granted ethical approval to this retrospective, single-center study (No.: 393-373 dated 11.17.2021). All procedures were carried out in accordance with the ethical rules and principles of the Declaration of Helsinki.

We carried out this study on the data of 2,406 patients aged 18 years and older who underwent cesarean section before the pandemic (March 2019 - March 2020; Group 1; n=1.458) and during the pandemic (April 2020 - April 2021; Group 2; n= 948) in Izmir Bakircay University, Medical Faculty, Cigli Training and Research Hospital. However, we did not consider the data of cases with normal delivery and missing records. We noted down the nature of the operation (elective or emergency), anesthesia techniques, postoperative complications (e.g., pneumonia, excessive postpartum bleeding), and the patients' ages, ASA scores, PCR test results, and lengths of hospital stay.

While nasal and throat swamp samples were obtained from all cases for COVID-19 screening before cesarean section during the pandemic, the patients were taken for surgery without waiting for their PCR test results in only emergency cases. Besides, anesthesia procedures were performed as follows: (1) the patient was taken for spinal anesthesia after the L3-4 spinal space was localized and marked in the sitting position. Then, the skin was washed with antiseptic solutions, and 10 mg bupivacaine was injected into the subarachnoid space with a 25G spinal needle. (2) In spinal + epidural anesthesia, the skin was washed with an antiseptic solution in the sitting position. Next, the epidural space was identified from the L3-4 or L4-5 space with an 18-gauge Tuohy needle with the loss-of-resistance technique. Then, a 25-gauge spinal needle was passed through the Tuohy needle, and 10 mg of bupivacaine was administered into the subarachnoid space. Finally, the spinal needle was withdrawn, and the epidural catheter from the Tuohy needle was inserted 3-4 cm into the epidural space. In the postoperative period, analgesia was administered with the help of an epidural catheter (3). Preoxygenation was administered to patients prior to general anesthesia, and induction was ensured with propofol, rocuronium bromide, and fentanyl. Following induction, As maintenance, maintenance was provided with 50% O2/air and 1 MAC sevoflurane.

The data were presented using descriptive statistics. We resorted to the Kolmogorov–Smirnov test to check the normality of distribution. Accordingly, while performing independent samples t-test to make a pair-wise comparison of the normally distributed data, we used the Mann-Whitney U test to make the comparison above for the data without normal distribıtion. Moreover, we compared the categorical variables using Pearson's chi-square test with Fisher's exact test. We performed all statistical analyses on the IBM SPSS 22.0 program and considered a p-value < 0.05 to be statistically significant.

RESULTS

We evaluated the data of 2.406 patients undergoing cesarean section before (Group 1; n=1.458) and during the pandemic (Group 2; n=948). The groups had a mean age of 29.63±0.28 and 29.42±0.36 years, respectively, and we could not find a significant difference between the groups by age (p=0.09) (**Table 1**).

We found the mean length of hospital stay to be 2.20±0.03 days in Group 1 and 2.29±0.05 in Group 2 and discovered that Group 2 was hospitalized significantly longer ($p < 0.05$) (**Table 1**). Besides, the patients in Group 2 developed significantly more complications than those in Group 1 (n=19 vs. 13; $p < 0.05$). However, the groups did not significantly differ by emergency cesarean section. While 915 (62.8%) cases in Group 1 were taken for an emergency cesarean section, it was 613 (64.7%) in Group 2 (p=0.363). There were significantly more patients with an ASA score of 3 and above who underwent cesarean section in Group 2 (n=45; 4.7%) when compared to Group 1 (n=24; 1.6%) ($p < 0.05$) (**Table 1**).

Table 1. Comparison of the research parameters before and during the pandemic

	Group 1 (n=1.458)	Group 2 (n=948)	p
Age (years)	29.63±0.28	29.42±0.36	0.09
Emergency / Elective cesarean section	915 / 543	613 / 335	0.363
Patients with an ASA score of 3 and above	24 (1.6%)	45 (4.7%)	*0.001
Patients developing complications	13 (0.9%)	19 (2.0%)	*0.027
Length of hospital stay (days)	2.20±0.03	2.29±0.05	*0.044

*p < 0.05, Group 1: Pregnant women undergoing cesarean section before the pandemic Group 2: Pregnant women undergoing cesarean section during the pandemic

The numbers of patients receiving spinal anesthesia, spinal and epidural anesthesia, and general anesthesia before the pandemic were found to be 744 (51%), 675 (46.3%), and 39

(2.7%), respectively. When it comes to the mid-pandemic period, these numbers became 690 (72.8%), 213 (22.5%), and 45 (4.7%), respectively. In this regard, we concluded significant differences between anesthesia techniques in pre- and mid-pandemic periods ($p < 0.05$) (**Table 2**).

Table 2. Comparison of the anesthesia techniques adopted before and during the pandemic

Anesthesia technique	Group 1 (n=1.458)	Group 2 (n=948)
Spinal	744 (51%)	690 (72.8%)
Spinal+epidural	675 (46.3%)	213 (22.5%)
General	39 (2.7%)	45 (4.7%)

Group 1: Pregnant women undergoing cesarean section before the pandemic
Group 2: Pregnant women undergoing cesarean section during the pandemic

The PCR test result came positive for 182 patients (Group A) and negative for 766 patients (Group B) in Group 2. While the mean age of Group A was 28.47±0.85 years, it was 29.25±0.40 years in Group B. Nevertheless, we did not find a significant difference between the patients in the said groups by age (p=0.142). There was also no significant difference between the groups by the length of hospital stay (M=2.39±0.19 vs. 2.27±0.05; p=0.465). While eight patients (4.4%) developed complications (e.g., pneumonia and excessive postpartum bleeding) in Group A, we detected complications among 11 patients (1.4%) in Group B, and the rate of complication development was significantly higher in those with a positive PCR test result ($p < 0.05$). Although the groups did not significantly differ by the type of cesarian section (elective or emergency; p=0.095), there were significantly more cases with an ASA score of 3 in Group A (n=16; 8.8%) than in Group B (n=26; 3.4%) ($p < 0.05$; **Table 3**). Finally, the groups did not significantly differ by anesthesia technique applied (p=0.251; **Table 4**).

Table 3. Comparison of the patients with positive and negative PCR test results

	Group A (n=182)	Group B (n=766)	p
Age (years)	28.47±0.85	29.25±0.40	0.142
Emergency / Elective cesarean section	108 / 74	505 / 261	0.095
Patients with an ASA score of 3 and above	16 (8.8%)	26 (3.4%)	*0.005
Patients developing complications	8 (4.4%)	11 (1.4%)	*0.017
Length of hospital stay (days)	2.39±0.19	2.27±0.05	0.465

*p < 0.05, Group A: Patients testing positive for COVID-19
Group B: Patients testing negative for COVID-19

Table 4. Comparison of the anesthesia techniques adopted in cases with positive and negative PCR test results

Anesthesia technique	Group A (n=182)	Group B (n=766)
Spinal	126 (69.2%)	564 (73.6%)
Spinal+Epidural	49 (26.9%)	164 (21.4%)
General	7 (3.8%)	38 (5.0%)

Group A: Patients testing positive for COVID-19
Group B: Patients testing negative for COVID-19

DISCUSSION

We carried out this retrospective, single-center study to investigate anesthesia technique, postoperative complications, length of hospital stay, clinical urgency, and ASA (American Society of Anesthesiologists) scores among patients who gave birth by cesarean section before and during the pandemic. Our findings revealed that the patients undergoing cesarean section during the pandemic had significantly more complications and prolonged hospitalization. The disease status of 182 COVID-19-positive cases, some of whom had clinical lung-related findings, may have contributed to their complications (e.g., pneumonia) and length of hospital stay. In the subgroup analysis, COVID-19-positive cases also had more complications and an ASA score of 3 and above than healthy subjects. However, it still remains covered if the findings above are associated with the impacts of COVID-19 on the respiratory system or with patient characteristics. We discovered a significant decrease in the preference for spinal + epidural anesthesia; instead, spinal anesthesia was mostly adopted in cesarean section operations during the pandemic. Due to the extended close contact with patients in spinal+epidural anesthesia, the tight protection measures in the pandemic may have significantly hindered the use of this technique. On the other hand, since general anesthesia had already been a less-adopted technique in cesarean sections than regional techniques, there was no significant difference between anesthesia techniques applied before and during the pandemic.

As expected, pneumonia was significantly prevalent in cases testing positive for COVID-19. However, we could not conclude a significant difference between the groups by the length of hospital stay, which may be because patients were discharged earlier to prevent transmission and reserve available beds primarily for severe COVID-19 patients. Moreover, the COVID-19-positive patients had significantly higher ASA scores. While spinal anesthesia was significantly more adopted among all patients the pandemic period, there was no significant difference in the management of anesthesia between the two groups, which is thought to be because operations may have been initiated immediately after swab samples were taken, but PCR test results came out later.

The literature offers limited findings on the clinical courses of patients undergoing cesarean section during the pandemic, anesthesia techniques applied, postoperative complications, and their ASA scores and lengths of hospital stay. Moreover, the previous research usually associated changes in such cases only with the anesthesia technique adopted (16-20). In their study, Korkusuz et al. investigated the mid-pandemic anesthesia preferences of 140 pregnant women with a cesarean delivery at least

once under general anesthesia before the pandemic (18). Their findings showed that 50.7% of the subjects preferred regional anesthesia during the pandemic due to mostly contagion anxiety. Yet, we included all pregnant women undergoing cesarean section regardless of their previous preference for a specific anesthesia technique. In addition, we evaluated types of cesarean section (elective or emergency) and the patients' ASA scores, complications, and lengths of hospital stay.

Binyamin Y and his colleagues included a total of 413 pregnant women receiving elective cesarean section before (n=205) and during the pandemic (n=208) (17). The researchers performed their study in a region where conservative Bedouins are widely settled and general anesthesia is preferred more in cesarean delivery. Their results demonstrated that the cesarean delivery rate with neuraxial anesthesia significantly increased compared to before the pandemic thanks to informing the patients and their relatives well about the possible outcomes of anesthesia techniques. However, it was noted that they investigated a particular group with a small number of pregnant women and that epidural anesthesia was performed on few patients. Although spinal and spinal + epidural anesthesia were widely used techniques in our hospital before and during the pandemic, spinal + epidural anesthesia was preferred significantly less during the pandemic. Ay N et al. evaluated anesthesia techniques, maternal outcomes, and clinical courses among 107 COVID-19-positive patients undergoing cesarean section during the pandemic (19). While spinal anesthesia was adopted for 85 patients, 22 received general anesthesia. The authors also explored the impacts of COVID-19 on the patients and noted that the pregnant should be examined and operated on by experienced teams due to the higher risk of mortality or admission to the intensive care unit among COVID-19-positive and symptomatic pregnant women .

Keita H et al. reported the clinical, obstetric, and anesthesia results of 126 COVID-19-positive or suspicious pregnant women referred to 18 tertiary maternity units (20). About half (52%) of the patients with a distressed general condition underwent cesarean section, 40% gave premature birth, and 86% received neuraxial anesthesia. The authors found COVID-19 to be associated with significant maternal morbidity. In another study, Bhatia K et al. compared anesthesia techniques among 2.480 cases of cesarean delivery in six maternity units during the pandemic with those among 2.555 cesarean deliveries in a similar period before the pandemic (16). Their results revealed a significant decrease in general anesthesia in cesarean delivery cases during the pandemic. In addition, there was a slight increase in the preference for cesarean delivery compared to vaginal delivery, but the difference was not significant. In our study, we discovered no significant change in the preference for general anesthesia despite a significant increase in spinal anesthesia and a decrease in spinal + epidural anesthesia.

The retrospective design of this study may pose a limitation to our findings, but it should be noted that we scrutinized an issue with varying parameters and a relatively larger sample size. In addition, we discovered no mortality among the cases included in this study.

CONCLUSION

We concluded that anesthesia techniques with a lower risk of contagion seem to have been preferred more in cesarean sections during the pandemic. In addition, we determined that postoperative complications and the average length of hospital stay increased during the pandemic.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Izmir Bakircay University Non-Invasive Clinical Research Ethics Committee (Date: 11.17.2021, Decision No: 393-373).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Bampoe S, Odor PM, Lucas DN. Novel coronavirus SARS-CoV-2 and COVID-19. Practice recommendations for obstetric anaesthesia: what we have learned thus far. International Journal of Obstetric Anesthesia 2020; 43: 1–8.
2. Uppal V, Sondekoppam RV, Lobo C, Kolli S, Kalagara H, Edra F. Practice recommendations on neuraxialanesthesia and peripheral nerve blocks during the COVID-19 pandemic. In ASRA/ESRA COVID-19 Guidance for Regional Anesthesia; ASRA Society: Gujarat, India, 2020; Volume 31.
3. Uppal V, Sondekoppam R, Landau R, El-Boghdadly K, Narouze S, Kalagara HKP. Neuraxial anaesthesia and peripheral nerve blocks during the COVID-19 pandemic: a literature review and practice recommendations. Anaesthesia 2020; 75: 1350–63.
4. Bauer ME, Chiware R, Pancaro C. Neuraxial procedures in COVID-19–positive parturients: a review of current reports. Anesthesia and Analgesia 2020; 131: e22–e24.

5. Herman JA, Urits I, Kaye AD, Urman RD, Viswanath O. COVID-19: obstetric anesthesia care considerations. J ClinAnesth. 2020; 65: 109885.
6. Guasch E, Brogly N, Gilsanz F: COVID in obstetrics: labor analgesia and cesarean section. Curr Opin Anaesthesiol 2021; 34: 62–8.
7. Velly L, Gayat E, Quintard H, et al. Guidelines: anaesthesia in the context of COVID-19 pandemic. Anaesth Crit Care Pain Med 2020; 39: 395-415.
8. Macfarlane AJR, Harrop-Griffiths W, Pawa A. Regional anaesthesia and COVID-19: first choice at last? British J Anaesthesia 2020; 125: 243–7.
9. Peng PWH, Ho P-L, Hota SS. Outbreak of a new coronavirus: what anaesthetists should know. Br J Anaesth 2020; 124: 497–501.
10. Lewis D. Is the coronavirus airborne? Experts can't agree. Nature 2020; 580: 175.
11. Zhong Q, Liu YY, Luo Q, et al. Spinal anaesthesia in patients with coronavirus disease 2019 and possible transmission rates in anaesthetists: retrospective, single centre, observational cohort study. Br J Anaesth 2020; 124: 670-5.
12. Cook T, Harrop-Griffiths W. Kicking on while it's still kicking off - getting surgery and anaesthesia restarted after COVID-19. Anaesthesia 2020; 75: 1273-7.
13. Lockhart SL, Duggan LV, Wax RS, Saad S, Grocott HP. Personal protective equipment (PPE) for both anesthesiologists and other airway managers: principles and practice during the COVID-19 pandemic. Can J Anesth 2020; 67: 1005-15.
14. Smiley R. Spinal anaesthesia and COVID-19 transmission to anaesthetists. Comment on Br J Anaesth 2020; 124: 670-5. Br J Anaesth 2020; 125: e247-e248.
15. Dixon T, Bhatia K, Columb M. The SARS-CoV2 effect. An opportunity to decrease general anaesthesia rate for caesarean section? British Journal of Anaesthesia 2020; 125: e324–e326.
16. Bhatia K, Columb M, Bewlay A, et al. The effect of COVID-19 on general anaesthesia rates for caesarean section. A cross-sectional analysis of six hospitals in the north-west of England. Anaesthesia 2021; 76: 312- 9.
17. Binyamin Y, Heesen P, Gruzman I, et al.. A retrospective investigation of neuraxialanesthesia rates for elective cesarean delivery before and during the SARS-CoV-2 pandemic. Isr Med Assoc J 2021; 23: 408-11.
18. Korkusuz M, Et T. Did the COVID-19 pandemic change the anaesthesia preferences of pregnant women for caesarean section? Turk J Anaesthesiol Reanim 2022; 50: 416-23.
19. Ay N, Akyol D, Koyan Karadeniz GN, Çelik M, Gümüş Özcan F. Anesthesia management in cesarian section in pregnant patients with COVID-19 diagnoses. Med Bull Haseki 2022; 60: 447-52.
20. Keita H, James A, Bouvet L, et al. Clinical, obstetrical and anaesthesia outcomes in pregnant women during the first COVID-19 surge in France: a prospective multicentre observational cohort study. Anaesth Crit Care Pain Med 2021; 40: 100937.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1249691

Anatolian Curr Med J 2023; 5(2); 125-129

Comparison of scar outcomes of alar base and columella using irradiated polyglactin 911: a single-blind study

Mehmet Emrah Ceylan[1], Ömer Taşkın Yücel[2]

[1]Head and Neck Surgery, Department of Otolaryngology, Isparta Davraz Yaşam Hospital, Isparta, Turkey
[2]Head and Neck Surgery, Department of Otolaryngology, Hacettepe University, Ankara, Turkey

Cite this article as: Ceylan ME, Yücel ÖT. Comparison of scar outcomes of alar base and columella using irradiated polyglactin 911: a single-blind study. Anatolian Curr Med J 2023; 5(2); 125-129.

Abstract

Aim: The formation of scars on the face after open septorhinoplasty (SRP) with alar base reduction may disturb the patient due to cosmetic concerns. This study aimed to compare scar outcomes of the columella and alar base in patients undergoing SRP.

Material and Method: Twenty-seven patients who underwent alar base reduction during primary open SRP were divided into two groups according to the intervened area as the Columella (CLM) group (n=27) and the Alar Base (AB) group (n=27). Irradiated polyglactin 911 was used in all patients. The modified Stony Brook Scar Evaluation Scale (SBSES) and a questionnaire form were used to measure scar outcomes and patient satisfaction. Columellar and alar base scar outcomes were compared.

Results: Patient satisfaction and scar outcomes were better in the CLM group. There was no significant difference, except for the first month total SBSES scores, between the CLM and AB groups. There was no significant difference in patient questionnaire scores between groups. In the early period, there were more signs of inflammation in the alar base than in the columella, without statistical significance.

Conclusion: Patient satisfaction and scar outcomes in the columellar area were favorable. Scar outcome on the alar base was statistically significantly worse than columella in the early period. There was no statistically significant difference between both areas in the long-term. Irradiated rapid vicryl can be used for closure of the alar base and columella, considering its advantages and disadvantages, in patients undergoing open septorhinoplasty with alar base reduction.

Keywords: Polyglactin 911, rhinoplasty, cicatrix, surveys and questionnaires, septorhinoplasty

INTRODUCTION

Open septorhinoplasty (SRP) provides perfect surgical exposure with direct visualization and facilitates precise maneuvers. However, residual columellar incision scars or possible deformities due to scar formation are the main disadvantages of this technique. Scar formation is influenced by factors such as incision and closure method, as well as postoperative care (1-4). Previous studies have shown that absorbable sutures can be used safely in the columella without any long-term cosmetic concerns or an increased infection risk (5-7).

Alar base reduction is usually performed during SRP when the interalar distance surpasses the intercanthal distance or when the lateral portion of the ala extends significantly beyond the alar-facial groove (8). Although prolene suture is traditionally used, (1-3,8) some surgeons prefer continuing with the same absorbable suture in the alar base following columellar closure since it cuts costs and removes the need for suture removal. However, there are distinct anatomical differences between the alar base and the columellar area, such as the presence of sebaceous glands, the extent of adjacent muscles, and skin thickness. Because of these differences in anatomy, patients who have SRP with alar base reduction may end up with different scar outcomes.

To the best of the author's knowledge, there is no study in the literature comparing the scar outcomes of the alar base and columella. This study aimed to examine the scar outcomes of the columella and alar base in patients who underwent primary SRP using irradiated polyglactin 911 (rapid vicryl) in the early and long-term healing periods.

MATERIAL AND METHOD

The study was carried out with the permission of Süleyman Demirel University Clinical Researches Ethics Committee (Date: 23/12/2021, Decision No: 23/357). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Corresponding Author: Mehmet Emrah Ceylan, mrhcyln@gmail.com

Received: 13.02.2023 **Accepted:** 01.03.2023

Study Population and Design

This single-center, retrospective study was carried out in Davraz Yaşam Hospital ear, nose, and throat clinic between June 2019 and December 2021. Each patient provided written informed consent for all diagnostic and treatment procedures. A portrait consent form was obtained from the patient whose photographs were used.

Patients who had alar base reduction during initial open SRP were retrospectively searched and invited to the clinic by phone for a follow-up visit. The study comprised 27 patients who responded to the invitation, consented to participate in the study, and had postoperative photographic documentation at the first and twelve months. Revision cases and cases where the nostril sill was cut out were not included. The patients were divided into 2 groups based on the intervention area: Columella (CLM) and Alar Base (AB). The senior author conducted all operations and closures, and irradiated polyglactin 911 (Vicryl Rapid TM 6/0; Ethicon Inc., Somerville, NJ, USA) was used. Follow-ups were performed on postoperative day 7, one, six, and twelve months afterward. Before surgery and at follow-ups after surgery, all patients were photographed in the same way, from six different angles, using the same professional camera (Olympus Imaging Corp., Shinjuku, Tokyo, Japan), lens (Sigma Corp., Kawasaki, Japan), and double para flash (TT560 Speedlite, Neewer, Shenzhen, China).

Methods for Evaluation

At their scheduled follow-up visit, all of the patients were asked to use a satisfaction survey to rate their alar base and columellar scars after surgery for subjective evaluation (9) (**Table 1**).

Table 1. Satisfaction Survey

'How do you feel about your scar in the alar base/columellar region after rhinoplasty?		'Did you need to cover this scar?	
I am completely dissatisfied	1	Always	1
I am dissatisfied	2	Frequently	2
I am indifferent	3	Occasionally	3
I am satisfied	4	Extremely uncommon	4
I am extremely satisfied	5	Never	5
0 worst/10 best			

For objective evaluation another ENT specialist, who was blinded to the study, used the Modified Stony Brook Scar Evaluation Scale (SBSES) (10) (**Table 2**) to evaluate the first and twelfth-month photographs of the alar base and columella in all patients. Scars received a 0 or 1 score for the presence or absence of the following characteristics: elevation or depression, notching, hatching, and overall look. The color was assessed on a scale of 0 (worst) to 2 (best). Patient questionnaires and one- and twelve-month modified SBSES scores were examined.

Table 2. Modified Stony Brook Scar Evaluation Scale

Scar category	Points
Height	
Depressed or elevated from surrounding skin	0
Flat	1
Color	
Darker than surrounding skin (Hyperpigmentation)	0
Slightly Darker than surrounding skin (Slight pigmentation)	1
Same color or lighter	2
Notching	
Present	0
Absent	1
Hatching	
Present	0
Absent	1
Overall appearance	
Poor	0
Good	1
Total scar score: sum of individual scores; range, 0 (worst) to 6 (best).	

Surgical Technique

After local anesthetic injection (1% lidocaine with 1:100,000 epinephrine) for hemostasis, an inverted 'V' incision and bilateral marginal incisions were made at the narrowest level of the columella with a No. 15 blade in all patients. Lateral columellar incisions were made close to the posterior 1/3 projection of the medial crus and joined with the marginal incisions of the lateral crus (**Figure 1**). Columellar incisions were closed with 12 full-thickness simple stitches (11). In all cases, a modified Weir incision was made in the alar base, with the lateral incision positioned at the level of the alar-facial groove, and wedge resection was performed. (**Figure 1**). Simple interrupted sutures were utilized to close the wound margins after bipolar cauterization. All patients were told to apply hydrogen peroxide and mupirocin ointment twice daily for seven days to avoid crusting. Sutures in the alar base and columella weren't trimmed soon, and no patients were advised to use external scar-revision prescriptions following surgery. There were also no patients with hypertrophic scars or keloids.

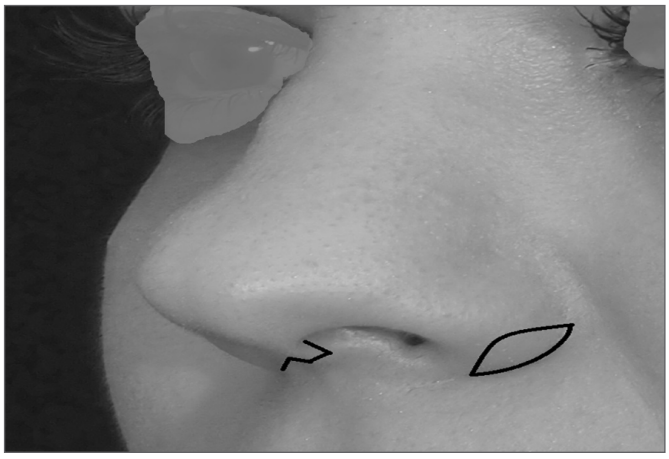


Figure 1. Inverted 'V' incision on columella and Modified Weir incision on the alar-facial groove.

Statistical Analysis

The SPSS version 25 program was used for statistical analysis (IBM Corp., Armonk, NY, USA). Continuous data were represented by the mean standard deviation (SD), whereas categorical variables were represented by n and frequency. The Kolmogorov-Smirnov and Shapiro-Wilk tests were utilized to test the normality of continuous variables. The Independent Sample T-test was used in the comparison of the two groups for variables which is normally distributed. The Mann-Whitney U test was used in the comparison of the two groups for variables which is not normally distributed. A p-value <0.05 was accepted as statistically significant. The Chi-Square test or Fisher's exact test (when chi-square test assumptions do not hold due to low expected cell counts), where appropriate, was used to compare these proportions in different groups.

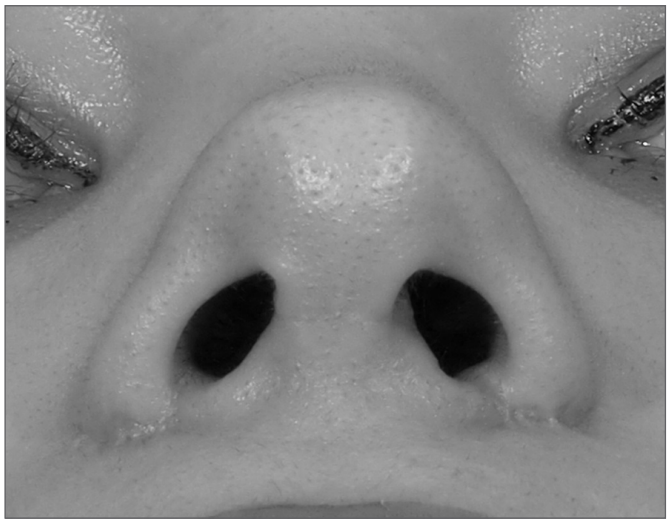


Figure 2. Noticeable notching in the alar base and acceptable scar in columella at 12. months follow-up.

RESULTS

Three (11%) of 27 patients were male and 24 (89%) were female. The mean age was 25±7.1 (range, 18 to 54). Since the outcomes were not affected by age and gender variables in this study, these variables were not analyzed statistically. The mean time to the patient questionnaire was 16.07±4.79 months.

The mean patient questionnaire total score was 9.11±1.01 and 8.37±2.23 in the CLM group and AB group, respectively (**Table 3**). There was no statistically significant difference in the patient questionnaire scores between groups (p=0.639). The mean total SBSES scores regarding the intervened area were 5.40±0.50 and 4.62±1.15 at one month and 5.62±0.49 and 5.07±1.27 at twelve months in the CLM group and AB group, respectively. The power analysis of the studied parameters in this study was the lowest at 80% and the highest at 99% percent, given the all variables.

Table 3. Patient questionnaire according to the intervened area

Scar Questionnaire	Alar Base	Columella	p
Satisfaction	3.88±1.25	4.40±0.69	0.248
Need to hide	4.40±1.06	4.70±0.60	0.431
Total score	8.37±2.23	9.11±1.01	0.639
Questionnaire time	16.07±4.79 months		

There was a statistically significant difference in total SBSES scores between the columella and the alar base in the first month. However, there was no statistically significant difference between the groups at twelve months, Detailed SBSES scores for the groups are given in **Table 4**. Infection, dehiscence, or significant wideness of the scar were not seen in either intervened area.

Table 4. Modified Stony Brook Scar Evaluation Scale outcomes of columella and alar base

SBSES	Columella n (%) Month 1	Alar Base n (%) Month 1	p	Columella n (%) Month 12	Alar Base n (%) Month 12	p
Height						
Depressed / elevated	0 (0)	3 (11)	0.236	2 (7)	2 (7)	--
Flat	27 (100)	24 (89)	0.236	25 (93)	25 (93)	1.000
Discoloration						
Hyperpigmentation	0	1	1,000	0	0	--
Slight pigmentation	16 (59)	22 (81)	0.074	3 (11)	5 (19)	0.704
Same color or lighter	11 (41)	5 (19)	0.074	24 (89)	22 (81)	0.704
Notching						
Present	0 (0)	5 (19)	0.51	5 (19)	9 (33)	0.214
Hatching						
Present	0 (0)	4 (15)	0.111	0 (0)	2 (7)	0.491
Overall appearance						
Poor	0 (0)	2 (7)	0.491	0 (0)	7 (26)	0.010
SBSES Group						
Moderate	0 (0)	4 (15)	0.111	0 (0)	7 (26)	0.010
Good	27 (100)	23 (85)	0.111	27 (100)	20 (74)	0.010
SBSES Score	**(mean±sd)**			**(mean±sd)**		
Total	5 (5-6)	5 (2-6)	0.005	PG 6 (5-6)	PP 6 (3-6)	0.333

SBSES: Stony Brook Scar Evaluation Scale, sd: Standart deviation

DISCUSSION

In the current study, the total SBSES score of the alar base was low in the first month with a statistically significant difference. However, there was no statistically significant difference in long-term total SBSES and patient questionnaire scores between groups. The reason for the low total SBSES score in the alar base in the first month was thought to be that slight pigmentation was higher in the alar base. At 12 months, as the wound matured, the difference in slight pigmentation decreased, and the total SBSES score of the alar base increased. Nevertheless, the total SBSES score in the alar base was still low, predicting poor outcomes, but there was no statistically significant difference between the two groups.

In this study, scar outcomes of the alar base and columella were compared in patients undergoing SRP using irradiated rapid vicryl sutures. To the best of the authors' knowledge, this is the first study to compare the scar outcomes of the alar base and columella in the literature. The outcomes of this study support the findings of the recent study that compared the effects of rapid vicryl and polypropylene use on scar results in the alar base and reported poor outcomes in the alar base (10).

According to Kriedel et al. (8), denser sebum glands in the alar-facial groove may contribute to poor scarring of Weir incisions by predisposing to epithelial cysts and micro-abscess formation during the healing process. The depressor septi nasi muscle has been reported to cause a notch effect on the columellar scar by creating tension on the incision edges (13). There are numerous muscles that may cause similar tension in the alar base. The dilatator naris muscle and the alar portion of the nasalis muscle attach directly to the alar skin and the levator labii superioris partially to the vestibular skin of the nasal vestibule (13,14) According to Daniel et al. (14), the alar base is a dynamic structure integrated with the nasal superficial musculoaponeurotic system and even the entire facial musculature. In addition, Parell et al. (15) reported that there may be an increase in wound tension in scar tissue on a bone structure. The edges of the alar base excision may be more prone to traction than the columella due to the various surrounding muscles and bone structure beneath. Due to the structural differences mentioned above, patients undergoing alar base reduction may have worse scar outcomes compared to those in the columellar area. Nevertheless, despite lower scores, there was no statistically significant difference in the notching between the groups in this study, but the number of notching increased in both groups as the wound matured at the 12th month. In addition, there was a statistically significant difference in terms of overall appearance between groups in the long-term. When photographs of patients with notching in the columella and alar base were examined, the notching was less noticeable at the level of columellar corner stitches but more numerous and noticeable along the alar base incision line. Multiple notches along the incision line may have caused the poor 12th month overall appearance.

It is reported that the use of irradiated rapid vicryl resulted in low inflammation and local reactions with favorable long-term aesthetic results on facial skin wounds (15-18). It is also easy to tie and absorbable, which makes the patient feel less pain and saves time in the clinic (9,15). However, because of its structural features, it may tend to promote infection and cause inflammation. Furthermore, there is one study in the literature that shows that using irradiated rapid vicryl in the inframammary area caused discoloration and scar hypertrophy that lasted up to a year (19). The inflammatory symptoms in the current study were compared by grading color changes in the early and long-term periods between intervened areas. There was difference a in the discoloration at one month postoperatively without statistical significance. More signs of inflammation were detected in the alar base compared to the columella in the early healing period. This finding indicates that scar outcomes may be variable due to structural differences in the alar base and columellar area in the early healing period.

Following a conservative approach with fundamental surgical concepts such as right-angle precise skin cuts, eversion of the wound margins during the closure, and attentive postoperative care may result in favorable scar results. In order to avoid hatching, stitches should not be overly tight. Notching may be a result of carrying the modified Weir incision into the deep muscle layer, as reported by Kriedel et al. (8) Antibiotic ointment and thorough cleansing of clusters should be applied after surgery.

The main strength of this study is that it uses subjective and single-blinded objective methods over the short and long-term healing periods. This study is valuable as it contributes to the literature and increases awareness that a single type of suture material may not yield good outcomes in all regions where it is applied. The study's main limitations are its limited sample size and retrospective nature. Further large-scale, prospective, randomized studies are required to reach more accurate findings on this topic.

CONCLUSION

This study demonstrates that patient satisfaction and scar outcomes in the columella were favorable. Further, irradiated rapid vicryl can be recommended in columellar closure owing to its potential advantages of having a good cosmetic outcome, causing less patient discomfort, and shortening the follow-up time required to remove the sutures.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Süleyman Demirel University Clinical Researches Ethics Committee (Date: 23/12/2021, Decision No: 23/357).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Hudise JY, Aldhabaan SA, Nassar RS, Alarfaj AM. Evaluation of scar outcome after alar base reduction using different surgical approaches. J Oral Maxillofac Surg 2020; 78: 2299.e1-2299.e8.
2. Warner JP, Chauhan N, Adamson PA. Alar soft-tissue techniques in rhinoplasty: algorithmic approach, quantifiable guidelines, and scar outcomes from a single surgeon experience. Arch Facial Plast Surg 2010; 12: 149-58.
3. Carniol ET, Adamson PA. Surgical Tips for the Management of the Wide Nasal Base. Facial Plast Surg 2018; 34: 29-35.
4. Aksu I, Alim H, Tellioğlu AT. Comparative columellar scar analysis between transverse and inverted-V incision in open rhinoplasty. Aesthetic Plast Surg 2008; 32: 638-40
5. Sajid MS, McFall MR, Whitehouse PA, Sains PS. Systematic review of absorbable vs non-absorbable sutures used for the closure of surgical incisions. World J Gastrointest Surg 2014; 6: 241-7.
6. Aldhabaan S, Hudise JY, ALqarny M, Alarfaj A. Catgut versus polypropylene sutures for transcolumellar incision closure in open rhinoplasty: a retrospective cohort study. Cureus 2020; 12: e9769.
7. Kilavuz AE, Bayram AA, Serin GM. Comparison of absorbable and nonabsorbable sutures in columellar incision closure in rhinoplasty and their effects to postoperative scar. Facial Plast Surg 2017; 33: 661-4.
8. Kridel RW, Castellano RD. A simplified approach to alar base reduction: a review of 124 patients over 20 years. Arch Facial Plast Surg 2005; 7: 81-93.
9. Erol O, Buyuklu F, Koycu A, Jafarov S, Gultekin G, Erbek SS. Comparison of rapid absorbable sutures with nonabsorbable sutures in closing transcolumellar incision in septorhinoplasty: short-term outcomes. Aesthetic Plast Surg 2020; 44: 1759-65.
10. Ceylan ME, Balıkçı HH. Comparison of scar outcomes of alar flare region using absorbable and non-absorbable sutures: a single-blind study. Braz J Otorhinolaryngol 2022; 88: 133-9.
11. Inanli S, Sari M, Yanik M. A new consideration of scar formation in open rhinoplasty. J Craniofac Surg 2009; 20: 1228-30.
12. Gamboa M, Shayani P, Schmid R, Bobadilla E, Blackwell S. Anatomic basis of notch deformity in open rhinoplasty. Ann Plast Surg 2003; 50: 282-5.
13. Rohrich RJ, Hoxworth RE, Thornton JF, Pessa JE. The pyriform ligament. Plast Reconstr Surg 2008; 121: 277-81.
14. Daniel RK, Glasz T, Molnar G, Palhazi P, Saban Y, Journel B. The lower nasal base: an anatomical study. Aesthet Surg J 2013; 33: 222-32.
15. Parell GJ, Becker GD. Comparison of absorbable with nonabsorbable sutures in closure of facial skin wounds. Arch Facial Plast Surg 2003; 5: 488-90.
16. Gazivoda D, Pelemiš D, Vujašković G, Djurdjević S. Influence of suturing material on wound healing - An experimental study on dogs. Vojnosanit Pregl 2015; 72: 397-404.
17. Brackeen AR, Wells MJ, Freed JM. Irradiated polyglactin 910 (Vicryl Rapide) for placement of full-thickness skin grafts. Dermatol Surg 2005; 31: 1707-9.
18. Gartti-Jardim EC, de Souza AP, Carvalho AC, Pereira CC, Okamoto R, Magro Filho O. Comparative study of the healing process when using Vicryl®, Vicryl Rapid®, Vicryl Plus®, and Monocryl® sutures in the rat dermal tissue. Oral Maxillofac Surg. 2013; 17: 293-8.
19. Niessen FB, Spauwen PH, Kon M. The role of suture material in hypertrophic scar formation: Monocryl vs. Vicryl-rapide. Ann Plast Surg 1997; 39: 254-60

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1249896

Anatolian Curr Med J 2023; 5(2); 130-137

Relationship between contrast media-induced nephropathy and CANLPH score in patients with ST-segment elevation myocardial infarction

Birsen Doğanay, Özlem Özcan Çelebi

Department of Cardiology, Ankara City Hospital, Ankara, Turkey

Cite this article as: Doğanay B, Özcan Çelebi Ö. Relationship between contrast media-induced nephropathy and CANLPH score in patients with ST-segment elevation myocardial infarction. Anatolian Curr Med J 2023; 5(2); 130-137.

ABSTRACT

Aim: Contrast-induced nephropathy (CIN), a significant complication of percutaneous coronary intervention (PCI), is related to increased morbidity and mortality. It has been suggested that inflammation plays an important role in the development of CIN. This study aimed to investigate the prognostic role of the CANLPH score, a new indicator of inflammation, in predicting CIN and in-hospital mortality among patients with ST-segment elevation myocardial infarction (STEMI) undergoing PCI.

Material and Method: This retrospective study included 1475 patients with STEMI undergoing PCI. CIN was defined as a 25% or 0.5 mg/dL increase in serum creatinine compared to the baseline value within 48 h after PCI. The preprocedural modified Mehran score was calculated for each patient. The CANLPH score was derived from the cut-off points of the platelet/lymphocyte ratio, neutrophil/lymphocyte ratio, and platelet/hemoglobin ratio to predict CIN.

Results: The mean age of the patients was 62.0±14.3 years and the majority were male (69.8%). The incidence of CIN was determined as 11.5%. Multivariable regression analysis showed that increased CANLPH score (OR=4.49, p<0.001) and increased modified Mehran score (OR=1.27, p<0.001) were independent predictors of CIN. The threshold value of the CANLPH score in predicting CIN was >1 with 73.5% sensitivity and 78.2% specificity and it exhibited better diagnostic performance than other inflammatory indices in predicting CIN and in-hospital mortality.

Conclusion: Prior to planned PCI, the CANLPH score has superior diagnostic performance in predicting CIN and mortality, and it may guide decisions about preventive measures and treatments.

Keywords: Biomarkers, contrast-induced nephropathy, inflammation, myocardial infarction

INTRODUCTION

Contrast-induced nephropathy (CIN), a significant complication of percutaneous coronary intervention (PCI) in cases of myocardial infarction (MI), is related to increased morbidity and mortality (1). CIN is defined as the sudden deterioration of kidney functions due to contrast media within 48 h following the procedure, after excluding other factors that may also cause renal failure (2). Although the development of CIN is associated with some etiological factors such as advanced age, renal failure, anemia, diabetes mellitus, hypotension, and conjunctive heart disease, its pathophysiology is still unknown (3).

The toxic effects of contrast agents, oxidative damage, and inflammation are important mechanisms in the pathophysiology of CIN (4). Previous studies have demonstrated that inflammatory indicators such as the ratio of C-reactive protein (CRP) to albumin (CAR), the neutrophil/lymphocyte ratio (NLR), the platelet/lymphocyte ratio (PLR), the platelet/hemoglobin ratio (PHR), and the systemic immune-inflammation index (SII) are strong predictors of CIN and mortality (5-10). The CANLPH score, which was created using the cut-off points of the CAR, NLR, and PHR, has been proposed as a comprehensive model of nutritional status and systemic inflammation (11). In limited studies involving different disease groups such as cancer and acute coronary syndrome, an increased CANLPH score was a strong predictor of mortality (11,12). To the best of our knowledge, no previous studies have evaluated the relationship between CANLPH scores and CIN in patients with acute coronary syndrome.

Considering the relationship between inflammation and the development of CIN (13), we hypothesized that the CANLPH score, a comprehensive combination of inflammation markers, could be an important prognostic marker. This study aimed to investigate the prognostic role of the CANLPH score in predicting CIN and in-hospital mortality among patients with ST-segment elevation myocardial infarction (STEMI) undergoing PCI.

Corresponding Author: Birsen Doğanay, doganay.brsn@gmail.com

Received: 10.02.2023 **Accepted:** 08.03.2023

MATERIAL AND METHOD

This retrospective study included patients with STEMI who underwent PCI in Ankara City Hospital Cardiology Clinic between March 2019 and March 2022. The study was carried out with the permission of Ankara City Hospital Clinical Researches Ethics Committee (Date: 02.11.2022, Decision No: E1-22-3008) and was carried out in accordance with relevant ethical guidelines and the Declaration of Helsinki (revised in 2013, Brazil). The need for informed consent was waived by the local ethics committee due to the retrospective design.

Study Population

A total of 2894 STEMI patients undergoing PCI (angioplasty or stent implantation) within 12 h of the onset of their chest pain were assessed retrospectively. STEMI was defined following the fourth universal definition of MI (14) with management procedures being aligned with the latest guidelines of the European Society of Cardiology (15). A total of 1349 patients who did not meet the inclusion criteria were excluded. Exclusion criteria were a history of any systemic inflammatory or autoimmune disease, uncontrolled hypertension or uncontrolled diabetes mellitus, anemia of inflammation, history of MI or decompensated heart failure, thyroid dysfunction, liver diseases, active hepatitis, malignancy, renal failure, history of anti-inflammatory or chronic corticosteroid or nephrotoxic drugs, sepsis, emergency or elective coronary artery bypass graft following an angiography procedure, major bleeding, pregnancy or delivery within the last 90 days, and missing clinical data. After the exclusion process, 1475 patients were included in this study.

Analysis of Patient Data

The hospital's electronic information system and patient files were used to gather demographic and clinical data. Blood samples were taken at the time of admission and during follow-up and were measured using a Beckman Coulter LH 780 device (Mervue, Galway, Ireland). Levels of hemoglobin (photometrically), platelets (impedance method), C-reactive protein (immunoturbidimetric method), albumin (bromocresol green method), triglycerides and total cholesterol (enzymatic colorimetric method), and high-density lipoprotein (homogeneous enzymatic colorimetric method) were determined. The Friedewald formula was used to determine low-density lipoprotein levels. Inflammation indices were calculated as follows: PLR=platelets/lymphocytes; NLR=neutrophils/lymphocytes; PHR=platelets/hemoglobin; SII=neutrophils × platelets/lymphocytes; CAR=CRP/albumin. The CANLPH score was derived from the cut-off points of the CAR, NLR, and PHR to predict CIN (11). In this context, the threshold values of CAR, NLR and PHR in predicting CIN were determined by Youden index method in ROC Curve analysis (**Figure 1**). For each index, patients below the threshold value were given 0 points, while patients above the threshold value were given 1 point. The CANLPH score for each patient was obtained by summing the points.

Two experienced cardiologists collected echocardiographic data immediately following PCI in the coronary intensive care unit using the Vivid 7 Dimension Cardiovascular Ultrasound System (General Electric Vingmed, Horten, Norway). The modified Simpson method was used to determine the left ventricular ejection fraction (LVEF).

Coronary Angiography

Angiographic data were analyzed in the cardiac catheterization laboratory. Patients undergoing PCI through the femoral artery were given a non-ionic low osmolality contrast medium (Omnipaque, 350 mg/mL; GE Healthcare, Cork, Ireland). Before the procedure, a loading dose of 300 mg of aspirin, 180 mg of ticagrelor, or 600 mg of clopidogrel was given. After visualizing the arterial anatomy, heparin (100 U/kg) was administered. Administration of glycoprotein IIb/IIIa was at the operator's discretion. Thrombolysis in myocardial infarction (TIMI) classification was also performed.

After PCI, each patient was admitted to the intensive care unit and therapy was sustained with 100 mg of aspirin, 90 mg of ticagrelor, or 75 mg of clopidogrel twice a day. The decision to concurrently use beta-blockers, angiotensin-converting enzyme inhibitors, or statins was made based on the latest guidelines (15). For patients who had good general condition, oral fluid intake began 90 min after the procedure. All patients were followed with blood pressure measurements, electrocardiogram monitoring, and assessment of blood samples.

Definitions end Endpoint

In repeated measurements, blood pressure of >140/90 mmHg or use of antihypertensive drugs was defined as hypertension, and a fasting plasma glucose level of ≥126 mg/dL or use of antidiabetic drugs was defined as diabetes mellitus. Hypotension was defined as systolic blood pressure of <80 mmHg for at least 1 h necessitating inotropic support with drugs or an intra-aortic balloon pump within 24 h following the procedure. CIN was defined as a 25% or 0.5 mg/dL increase in serum creatinine compared to the baseline value within 48 h after PCI (16). The primary endpoint was defined as the development of CIN and the secondary endpoint was in-hospital mortality.

The preprocedural modified version of Mehran score was calculated as previously described (5 points for hypotension, 5 points for intra-aortic balloon pump insertion, 5 points for congestive heart failure, 5 points for age >75 years, 3 points for anemia, 3 points for diabetes mellitus, 4 points for chronic kidney disease) (17).

Modified Mehran score was classified according to risk categories as low (score ≤2), moderate (score 3-8), high (score 8-12), and very high (score ≥13) (17).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Based on the results of the Kolmogorov-Smirnov test, normally distributed numerical data were presented as mean±standard deviation and non-normally distributed variables were presented as median values (25th-75th quartiles). For comparisons between groups, the Student t-test and Mann-Whitney U test were used according to the normality of the distribution. Categorical variables were expressed as numbers and percentages, and comparisons between groups were evaluated with Chi-square and Fisher exact tests. Multivariable logistic regression analysis was performed to identify any possible independent predictors of CIN. Receiver operating characteristic (ROC) curve analysis was performed to evaluate diagnostic performance. Values of $p<0.05$ were considered statistically significant.

RESULTS

The mean age of the 1475 patients included in this study was 62.0±14.3 years, the majority of them were male (69.8%), and the incidence of CIN was 11.5%. The baseline characteristics of the patients are reported in **Table 1**. The rates of diabetes mellitus and hypertension were higher in the group with CIN than the group without CIN while the mean LVEF level was lower (47.1±6.8% vs. 49.2±7.0%, $p<0.001$). The median cardiac troponin I level was higher in the group with CIN (58.2 vs. 41.3 ng/L, $p=0.030$). The levels of glucose, leukocytes, CRP, and albumin also significantly differed between the groups ($p<0.05$). All inflammatory index values were higher in the group with CIN than the group without CIN. The median modified Mehran score was higher in the CIN group (5.5 vs. 3, $p<0.001$). Other angiographic and procedural features did not differ between groups (**Table 1**).

Angiographic and procedural characteristics are presented in **Table 2**. The rate of three-vessel disease was higher in the group with CIN than the group without CIN (25.3% vs. 17.4%, $p=0.014$). The in-hospital mortality rate was higher in the group with CIN than the group without CIN (27.1% vs. 11.3%, $p<0.001$) (**Table 2**).

Variables associated with CIN (Tables 1 and 2) were considered as potential confounding factors. Among these factors, the components of the modified Mehran score and the CANLPH score were not included in the regression analysis due to multicollinearity. Multivariable regression analysis showed that the CANLPH score (OR=4.49, 95% CI=3.51-5.74, $p<0.001$) and the modified Mehran score (OR=1.27, 95% CI=1.20-1.35, $p<0.001$), as well as hypertension and number of diseased vessels, were independent predictors of CIN (**Table 3**).

The diagnostic performance of the inflammatory indices in predicting CIN is shown in **Figure 1**. The threshold value of the CANLPH score in predicting CIN was >1 with 73.5% sensitivity and 78.2% specificity and it exhibited better diagnostic performance than other inflammatory indices (**Figure 1A**). It also showed better diagnostic performance than other inflammatory indices in predicting mortality (**Figure 1B**). Increases in the CANLPH score (**Figure 1C**) and modified Mehran score (**Figure 1D**) were associated with a higher risk of mortality. A higher CANLPH score was also associated with a higher modified Mehran score (**Figure 2A**). The distribution of the endpoints according to stratified CANLPH and modified Mehran risk scores is shown in **Figure 2B**.

DISCUSSION

This study was the first to evaluate the prognostic value of the CANLPH score in cases of STEMI. The main findings of the study were as follows: 1) Increased CANLPH score was an independent predictor of CIN. 2) The CANLPH score exhibited superior diagnostic performance compared to the modified Mehran score and other inflammatory indices in predicting CIN. 3) The CANLPH score was associated with an increased risk of mortality.

The incidence of CIN in the current study was 11%, consistent with the prevalence rates (6-15%) reported by previous meta-analysis studies (18-20). Preprocedural factors such as advanced age, comorbidities, which are the components of the modified Mehran score, are important factors increasing the incidence of CIN (17, 21). On the other hand, it is suggested that the inflammatory milieu predisposes patients to the development of CIN (22, 23). Additional risk factors such as uncontrolled hypertension and uncontrolled diabetes mellitus, anemia of inflammation, renal failure, liver diseases, sepsis, autoimmune diseases, use of nonsteroidal anti-inflammatory drugs, and high-osmolality contrast media may contribute to inflammation and the risk of CIN (24). In this study, we excluded patients with additional risk factors to evaluate the effect of inflammation on CIN more objectively and the PCI procedure applied for these patients involved the use of low-osmolality contrast media. In addition, a previous study reported that the preprocedural modified Mehran score showed close diagnostic performance compared to the original Mehran score in predicting CIN (17, 25). Therefore, we used the preprocedural modified Mehran score to estimate the risk of preprocedural CIN, consistent with the current study design.

Table 1. Baseline characteristics of patients with STEMI

Variables	All population n=1475	CIN (+) n=170	CIN (-) n=1305	p
Baseline characteristics				
Age, years	62.0±14.3	64.4±13.8	61.7±14.4	0.023
Male gender, n (%)	1029 (69.8)	114 (67.1)	915 (70.1)	0.414
Diabetes mellitus, n (%)	398 (27.0)	90 (52.9)	308 (23.6)	<0.001
Hypertension, n (%)	524 (35.5)	78 (45.9)	446 (34.2)	0.003
Current smoker, n (%)	900 (61.0)	107 (62.9)	793 (60.8)	0.584
Systolic BP, mm Hg	123.3±18.1	115.6±19.2	124.6±17.0	<0.001
Diastolic BP, mm Hg	76.5± 12.9	74.6±12.6	76.8±13.1	0.038
Heart rate, bpm	77.2±13.4	76.2±14.2	77.3±13.2	0.311
LVEF, %	48.9±7.0	47.1±6.8	49.2±7.0	<0.001
Symptom to balloon time, min	291.0±48.8	288.5±43.7	291.3±49.0	0.478
Door to balloon time, min	43.1±7.6	42.5±8.7	43.1±7.4	0.331
Laboratory Findings				
Cardiac troponin I, ng/L	42.3 (33.2-52.4)	58.2 (44.4-65.1)	41.3 (30.2-50.5)	0.030
Glucose, mg/dL	110 (96-137)	128.5 (107-175)	108 (96-131)	<0.001
Hemoglobin, g/dL	13.7±1.6	13.0±1.8	13.8±1.6	<0.001
eGFR, mL/min/1.73m²	94.6±25.0	92.7±26.1	94.8±24.9	0.312
White blood cell, $\times10^3/\mu L$	10.1±2.9	11.3±2.8	9.7±2.9	<0.001
Neutrophil, $\times10^3/\mu L$	6.6 (5.1-8.4)	8.2 (6.6-10.3)	6.4 (4.9-8.1)	<0.001
Lymphocyte, $\times10^3/\mu L$	2.2 (1.6-2.8)	1.8 (1.4-2.3)	2.2 (1.6-2.9)	<0.001
Platelet, $\times10^3/\mu L$	235.1±64.6	273.4±83.2	230.1±60.0	<0.001
Total cholesterol, mg/dL	192.5±40.8	195.5±47.8	192.2±39.7	0.318
HDL, mg/dL	40.0±8.5	40.9±7.8	39.8±8.6	0.187
LDL, mg/dL	120.1±31.5	120.7±29.7	120.0±31.7	0.791
Triglyceride, mg/dL	132 (107-177)	132 (106-173)	132 (107-177)	0.386
C-reactive protein, mg/L	7 (3.5-13.2)	16 (7-24.2)	6.6 (3.4-11.7)	<0.001
Albumin, g/dL	3.9±0.4	3.7±0.4	3.9±0.4	<0.001
Creatinine, mg/dL	0.9±0.3	0.9±0.3	0.9±0.2	0.495
NLR	2.9 (2-4.7)	4.9 (3.1-6.4)	2.8 (2.0-4.4)	<0.001
PLR	108 (80-146)	150 (112-179)	103 (78-138)	<0.001
PHR	16.6 (13.7-20.3)	20.0 (16.4-25.1)	16.2 (13.5-19.7)	<0.001
SII	658 (443-1098)	1202 (786-1603)	626 (432-986)	<0.001
CAR	1.8 (0.9-3.6)	4.4 (1.7-6.8)	1.6 (0.8-3.0)	<0.001
CANLPH score	1 (0-2)	2 (1-3)	1 (0-2)	<0.001
0, n (%)	426 (28.9)	4 (2.4)	422 (32.2)	<0.001
1, n (%)	640 (43.4)	41 (24.1)	599 (45.9)	<0.001
2, n (%)	321 (21.8)	67 (39.4)	254 (19.5)	<0.001
3, n (%)	88 (6.0)	58 (34.1)	30 (2.3)	<0.001
Modified Mehran score	3 (0-4)	3 (0-4)	5.5 (3-8)	<0.001
Low risk, n (%)	587 (39.8)	569 (43.6)	18 (10.6)	<0.001
Medium risk, n (%)	772 (52.3)	670 (51.3)	102 (60.0)	<0.001
High risk, n (%)	103 (7.0)	65 (5.0)	38 (22.4)	<0.001
Very high risk, n (%)	13 (0.9)	1 (0.1)	12 (7.1)	<0.001

Continues variables are reported mean±SD or median (IQR). Categorical variables are reported n (%). Abbreviations: BP, blood pressure, CAR, C-reactive protein to albumin ratio; CIN, contrast-induced nephropathy; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index.

Table 2. Angiographic and procedural characteristics and distribution of in-hospital mortality

Variables	All population n=1475	CIN (+) n=170	CIN (-) n=1305	p
Culprit lesion, n (%)				0.900
LAD	675 (45.8)	75 (44.1)	600 (46.0)	
LCX	211 (14.3)	25 (14.7)	186 (14.3)	
RCA	589 (39.9)	70 (41.2)	519 (39.8)	
Number of diseased vessels, n (%)				0.014
1	740 (50.2)	70 (41.2)	670 (51.3)	
2	465 (31.5)	57 (33.5)	408 (31.3)	
3	270 (18.3)	43 (25.3)	227 (17.4)	
Preprocedural TIMI grade <3, n (%)	1420 (96.3)	165 (97.1)	1255 (96.2)	0.564
Postprocedural TIMI grade <3, n (%)	40 (2.7)	5 (2.9)	35 (2.7)	0.999
GP IIb/IIIa Ri use, n (%)	681 (46.2)	80 (47.1)	601 (46.1)	0.805
Contrast medium volume, mL	200 (150-250)	250 (150-250)	200 (150-250)	0.155
Stent length, mm	19.3±6.4	20±7.2	19.2±6.3	0.131
Stent diameter, mm	3.1±0.4	3.1±0.3	3.1±0.4	0.882
Antiplatelet treatment, n (%)				0.830
Klopidogrel	1455 (98.6)	168 (98.8)	1287 (98.6)	
Ticagrelol	20 (1.4)	2 (1.2)	18 (1.4)	
Hypotension, n (%)	88 (6.0)	32 (18.8)	56 (4.3)	<0.001
In-hospital mortality, n (%)	147 (10.0)	57 (33.5)	90 (6.9)	<0.001
Follow-up time, days	25 (12-30)	19 (11-30)	27 (12-33)	<0.001

Continues variables are reported mean±SD or median (IQR). Categorical variables are reported n (%). Abbreviations: CIN, contrast-induced nephropathy; GP IIb/IIIa Ri, glycoprotein IIb/IIIa receptor inhibitor; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

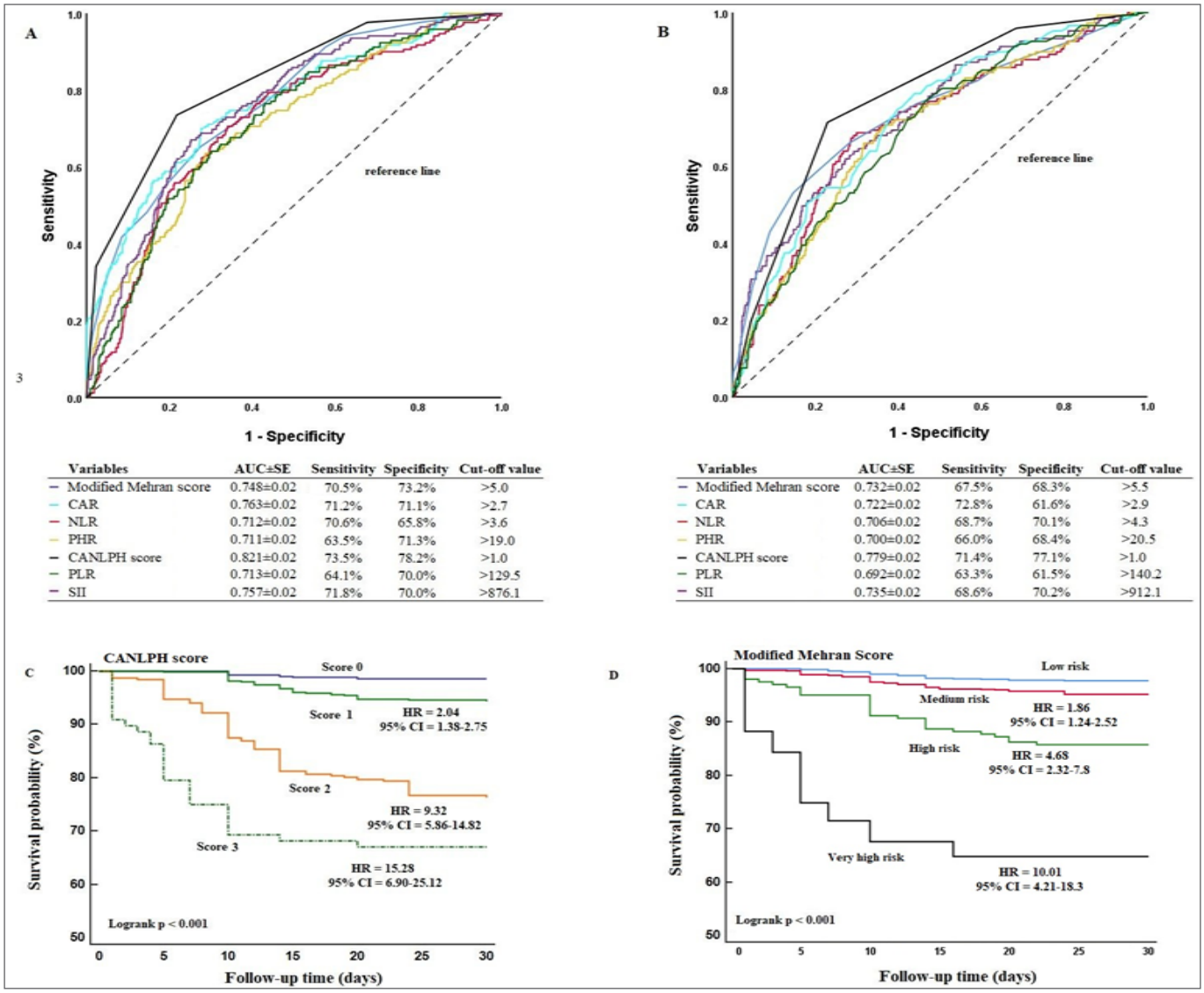


Figure 1. Diagnostic performance of the CANLPH score in predicting CIN (A) and in-hospital mortality (B). Risk of in-hospital mortality according to the classification of CANLPH score (C) and modified Mehran score (D).

Table 3. Independent predictors of contrast induced nephropathy

Variables	Univariable			Multivariable		
	OR	95% CI	p	OR	95% CI	p
Hypertension	1.63	1.18-2.25	<0.001	1.48	1.08-2.20	0.047
LVEF	0.96	0.94-0.98	<0.001	-	-	-
Cardiac troponin I	1.06	1.01-1.14	0.045	-	-	-
Glucose	1.03	1.01-1.06	<0.001	-	-	-
White blood cell	1.17	1.11-1.23	<0.001	-	-	-
Modified Mehran score	1.33	1.26-1.40	<0.001	1.27	1.20-1.35	<0.001
CANLPH score	5.21	4.12-6.60	<0.001	4.49	3.51-5.74	<0.001
Number of diseased vessels						
1	ref			ref		
2	1.34	0.92-1.93	0.12	1.55	0.98-2.42	0.060
3	1.81	1.21-2.73	<0.001	2.07	1.26-3.40	0.004
					Nagelkerke R2=0.410, p<0.001	

Mehran score and CANLPH components were not included in the regression analysis. Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio.

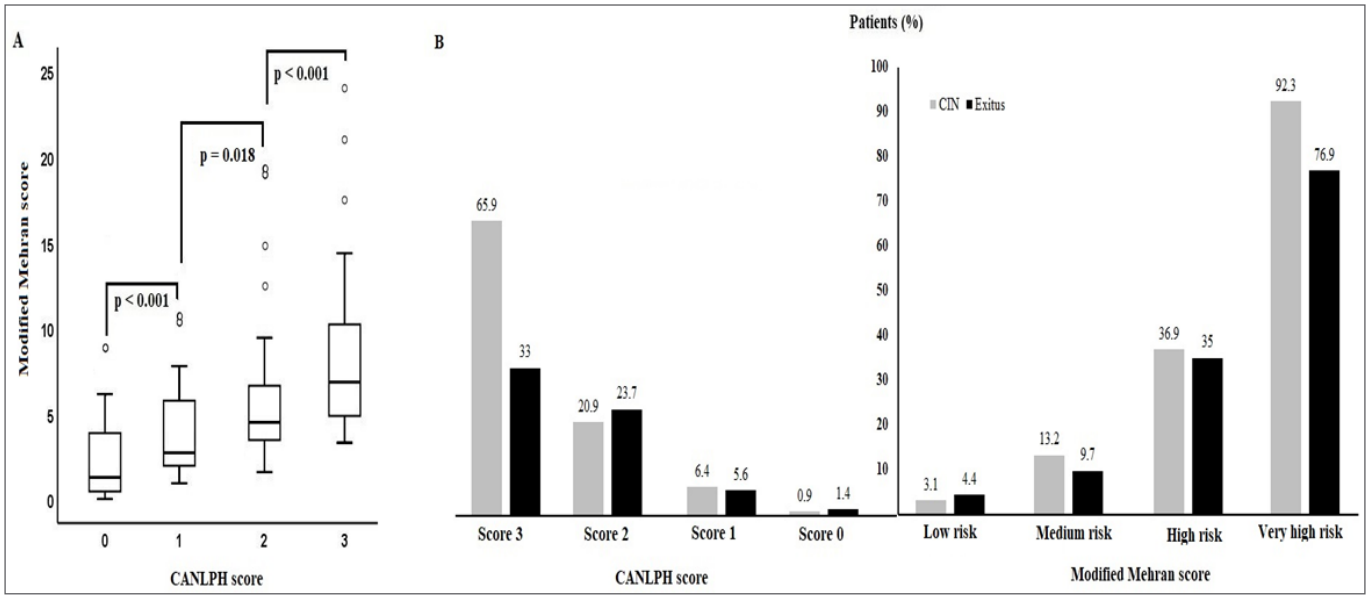


Figure 2. A) Distribution of modified Mehran score by CANLPH score. B) Distribution of endpoints by classified CANLPH and modified Mehran scores

How the inflammatory response triggered by the immune system following STEMI responds to contrast media and its contribution to the development of CIN remains a mystery. A decrease in hemoglobin levels following STEMI is the cause of tissue hypoxia and the triggering of the immune system (7). Contrast media can rapidly alter renal hemodynamics, leading to renal hypoxia injury. Increased reactive oxygen species and oxidative stress can cause an excessive inflammatory response (23). Subsequently, leukocyte activation can induce CRP expression and decrease the levels of albumin, a negative acute-phase reactant (26). Contrast media toxicity causes damage to the renal vascular endothelium and tubular epithelial cells, resulting in increased apoptosis and necrosis (27). This chain of events can exacerbate kidney damage by causing an adverse response of the immune system to the contrast medium.

Experimental studies have demonstrated that inflammatory cytokines, macrophages, and neutrophils increase following contrast media administration, resulting in acute tubular injury (28-30). Therefore, inflammation markers in blood parameters can be an important screening tool in the early risk estimation of CIN. Moreover, combined indices, which can be obtained inexpensively and easily from blood parameters, can better reflect the inflammatory status compared to their components (31). Previous studies in patients undergoing PCI reported that elevated values of the NLR, PLR, and CAR indices at the time of hospital admission were independent predictors of CIN (5-8). Recent studies have shown that the SII obtained from leukocyte subparameters is an essential indicator of the inflammatory response triggered by the immune system and exhibits significant diagnostic accuracy in detecting CIN (9, 10, 31). In addition, the capacity of these indices to predict CIN was not limited to patients undergoing PCI. Previous studies have reported that CRP or SII levels were exhibited significant diagnostic performance

in predicting CIN in patients after carotid artery angiography (32, 33). However, the CANLPH score was found to be a better predictor with stronger diagnostic performance compared to the SII. This may be related to the CANLPH score's more extensive inflammatory parameters compared to the components of the SII.

The CANLPH score was first studied by Komura et al. (11) in patients with renal cell carcinoma and it was reported to be an independent predictor of mortality. In the following years, Abacioglu et al. (12) reported that it is an essential predictor of in-hospital mortality in patients undergoing coronary artery bypass grafting and exhibited similar diagnostic performance compared to the European System for Cardiac Operative Risk Evaluation II score. The current research both expands on the literature to date and presents new findings on the prognostic role of the CANLPH score. Firstly, multivariable regression analysis showed that a one-unit increase in the CANLPH score, an independent predictor of CIN, increased the risk of CIN by 4.49-fold. Secondly, in predicting both CIN and in-hospital mortality, the CANLPH score had superior diagnostic performance with a lower rate of false negatives and false positives compared to other markers of inflammation and the modified Mehran score. Compared to the modified Mehran score, which includes preprocedural risk factors, the CANLPH score may be an important variable in predicting CIN before PCI. Thirdly, a gradual increase in the CANLPH score was associated with a higher risk of in-hospital mortality. Therefore, the CANLPH score may be an important screening tool in determining CIN and in-hospital mortality in cases of STEMI.

The present study has some critical limitations. Firstly, it had a retrospective and single-center design. Secondly, proinflammatory cytokines before PCI and inflammation parameters during PCI and in follow-up were not evaluated. The variability in inflammation during the hospital stay could have explained CIN further. Finally, we could not evaluate the effects of potential risk factors for CIN, such as drugs used for comorbid conditions and diuretics, antibiotics, and other nephrotoxic agents used during hospitalization.

CONCLUSION

The CANLPH score predicted CIN and in-hospital mortality with superior diagnostic performance compared to other inflammation indices. Before PCI, the CANLPH score can contribute to the application of the preprocedural modified Mehran score in predicting CIN and it may guide choices regarding preventive measures and treatments. It may be an important screening tool in identifying patients at high risk of experiencing CIN and in-hospital mortality following PCI.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Clinical Researches Ethics Committee (Date: 02.11.2022, Decision No: E1-22-3008).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Sgura FA, Bertelli L, Monopoli D, et al. Mehran contrast-induced nephropathy risk score predicts short- and long-term clinical outcomes in patients with ST-elevation-myocardial infarction. Circ Cardiovasc Interv 2010; 3: 491-8.
2. Mohammed NM, Mahfouz A, Achkar K, Rafie IM, Hajar R. Contrast-induced Nephropathy. Heart Views 2013; 14: 106-16.
3. Chong E, Poh KK, Liang S, Tan HC. Risk factors and clinical outcomes for contrast-induced nephropathy after percutaneous coronary intervention in patients with normal serum creatinine. Ann Acad Med Singap 2010; 39: 374-80.
4. Kusirisin P, Chattipakorn SC, Chattipakorn N. Contrast-induced nephropathy and oxidative stress: mechanistic insights for better interventional approaches. J Transl Med 2020; 18: 400.
5. Altiparmak IH, Tanriverdi Z, Tascanov MB, et al. C-reactive protein/albumin ratio as a novel predictor of contrast induced nephropathy in patients with stable angina pectoris. Angiology 2022; 74: 189-96.
6. Butt K, D'Souza J, Yuan C, et al. Correlation of the neutrophil-to-lymphocyte ratio (NLR) and Platelet-to-lymphocyte ratio (PLR) with contrast-induced nephropathy in patients with acute coronary syndrome undergoing percutaneous coronary interventions. Cureus 2020; 12: e11879.
7. Bao K, Huang H, Huang G, et al. Platelet-to-hemoglobin ratio as a valuable predictor of long-term all-cause mortality in coronary artery disease patients with congestive heart failure. BMC Cardiovasc Disord 2021; 21: 618.
8. Kocas C, Yildiz A, Abaci O, et al. Platelet-to-lymphocyte ratio predicts contrast-induced nephropathy in patients with non-st-segment elevation acute coronary syndrome. Angiology 2015; 66: 964-8.
9. Karauzum I, Karauzum K, Hanci K, Gokcek D, Kalas B, Ural E. The utility of systemic immune-inflammation index for predicting contrast-induced nephropathy in patients with st-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. Cardiorenal Med 2022; 12: 71-80.
10. Bagci A, Aksoy F, Bas HA. Systemic immune-inflammation index may predict the development of contrast-induced nephropathy in patients with st-segment elevation myocardial infarction. Angiology 2022; 73: 218-24.

11. Komura K, Hashimoto T, Tsujino T, et al. The CANLPH score, an integrative model of systemic inflammation and nutrition status (SINS), predicts clinical outcomes after surgery in renal cell carcinoma: data from a multicenter cohort in Japan. Ann Surg Oncol 2019; 26: 2994-3004.
12. Abacioglu OO, Yildirim A, Koyunsever NY, Ucak HA, Abacioglu S. Relationship between CANLPH score and in-hospital mortality in patients undergoing coronary artery bypass grafting. Biomark Med 2021; 15: 1659-67.
13. Wei X, Chen H, You Z, et al. Nutritional status and risk of contrast-associated acute kidney injury in elderly patients undergoing percutaneous coronary intervention. Clin Exp Nephrol 2021; 25: 953-62.
14. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). Glob Heart 2018; 13: 305-38.
15. Ibanez B, James S, Agewall S, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018; 39: 119-77.
16. Moro AB, Strauch JGN, Groto AD, Toregeani JF. Creatinine level variation in patients subjected to contrast-enhanced tomography: a meta-analysis. J Vasc Bras 2021; 20: e20200161.
17. Blanco A, Rahim F, Nguyen M, et al. Performance of a pre-procedural Mehran score to predict acute kidney injury after percutaneous coronary intervention. Nephrology (Carlton) 2021; 26: 23-9.
18. Lutz ME. Women, work, and preventive health care: an exploratory study of the efficacy of HMO membership. Women Health 1989; 15: 21-33.
19. Yang Y, George KC, Luo R, et al. Contrast-induced acute kidney injury and adverse clinical outcomes risk in acute coronary syndrome patients undergoing percutaneous coronary intervention: a meta-analysis. BMC Nephrol 2018; 19: 374.
20. Wang W, Qu W, Sun D, Liu X. Meta-analysis of effect of renin-angiotensin-aldosterone system blockers on contrast-induced nephropathy. J Renin Angiotensin Aldosterone Syst 2020; 21: 1470320320919587.
21. Abellas-Sequeiros RA, Raposeiras-Roubin S, Abu-Assi E, et al. Mehran contrast nephropathy risk score: Is it still useful 10 years later? J Cardiol 2016; 67: 262-7.
22. Oweis AO, Alshelleh SA, Daoud AK, Smadi MM, Alzoubi KH. Inflammatory milieu in contrast-induced nephropathy: a prospective single-center study. Int J Nephrol Renovasc Dis 2018; 11: 211-5.
23. Li Y, Ren K. The Mechanism of Contrast-Induced Acute Kidney Injury and Its Association with Diabetes Mellitus. Contrast Media Mol Imaging 2020; 2020: 3295176.
24. Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. Eur Heart J 2012; 33: 2007-15.
25. Rahim F, Nguyen M, Quach S, Guduru S, Abusaada K. Performance of a Pre-Procedural Mehran Score to Predict Acute Kidney Injury After Percutaneous Coronary Intervention. Circulation 2018; 138: A12186-A.
26. Tourki B, Halade G. Leukocyte diversity in resolving and nonresolving mechanisms of cardiac remodeling. FASEB J 2017; 31: 4226-39.
27. Caiazza A, Russo L, Sabbatini M, Russo D. Hemodynamic and tubular changes induced by contrast media. Biomed Res Int 2014; 2014: 578974.
28. Lu Z, Cheng D, Yin J, et al. Antithrombin III Protects Against Contrast-Induced Nephropathy. EBioMedicine 2017; 17: 101-7.
29. Wang F, Yin J, Lu Z, et al. Limb ischemic preconditioning protects against contrast-induced nephropathy via renalase. EBioMedicine 2016; 9: 356-65.
30. Li Y, Shi D, Zhang H, et al. The application of functional magnetic resonance imaging in type 2 diabetes rats with contrast-induced acute kidney injury and the associated innate immune response. Front Physiol 2021; 12: 669581.
31. Kelesoglu S, Yilmaz Y, Elcik D, et al. Systemic immune inflammation index: a novel predictor of contrast-induced nephropathy in patients with non-ST segment elevation myocardial infarction. Angiology 2021; 72: 889-95.
32. Kelesoglu S, Yilmaz Y, Elcik D, et al. C-reactive protein to albumin ratio as a predictor of contrast-induced nephropathy after carotid angiography. Angiology 2022: 33197221135950.
33. Yilmaz Y, Kelesoglu S, Kalay N. A Novel predictor of contrast-induced nephropathy in patients with carotid artery disease; the systemic immune inflammation index. Angiology 2022; 73: 781-7.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1250769

Anatolian Curr Med J 2023; 5(2); 138-142

The frequency of co-positivity of anti-smooth muscle antibody and anti-nuclear antibodies and their contribution to the diagnosis of autoimmune hepatitis

Neval Yurttutan Uyar

Department of Microbiology and Clinical Microbiology, Faculty of Medicine, Mehmet Ali Aydınlar Acıbadem University, İstanbul, Turkey

Cite this article as: Yurttutan Uyar N. The frequency of co-positivity of anti-smooth muscle antibody and anti-nuclear antibodies and their contribution to the diagnosis of autoimmune hepatitis. Anatolian Curr Med J 2023; 5(2); 138-142.

ABSTRACT

Aim: Autoimmune hepatitis (AIH) is a chronic disease observed especially in women. The International Autoimmune Hepatitis Group recommends scoring systems for diagnosis using clinical and laboratory data. All scoring systems gave points to autoantibodies as anti-nuclear antibody (ANA) and anti-smooth muscle antibody (SMA) positivity. This study investigates the impact of the co-positivity of the ANA and SMA antibodies on the autoimmune hepatitis diagnosis.

Material and Method: We monitored 78 autoimmune liver disease (autoimmune hepatitis, AIH) suspected patients with positive SMA antibody and then further tested for ANA between 2014 and2021. SMA test was screened at 1/40 and 1/100 titers and patients who were positive were taken to further dilution. The ANA test was screened at a titer of 1/40 and 1/160, a positive result was found to be repeated with advanced dilutions. All patients' autoantibody scores of simplified AIH diagnostic system were calculated.

Results: Seventy eight patients with positive SMA antibodies screened for ANA test with 1/40 and 1/160 titer, only 2 patients was found to be negative. The most frequently observed ANA pattern is cytoplasmic linear fibrils (68%). The 95% ANA positive results was examined at a screening titer of 1/160. The 95% SMA positive results was found at a screening titer of 1/100. The autoantibody scores of 76 patients were +2, patient's scores were +1.

Conclusion: SMA antibody positivity is accompanied by a high rate of ANA antibody positivity but the co-positivity didn't effect diagnostic score systems. On the other the co-positivity could be a sign of another associated autoimmune diseases.

Keywords: Anti-smooth muscle antibody, anti-nuclear antibodies, autoimmune hepatitis

INTRODUCTION

Autoimmune hepatitis (AIH) was first identified as chronic hepatitis in young women in 1951 and was characterized in the USA a short time later (1, 2). In 1956, by discovering its association with anti-nuclear antibodies (ANA), lupoid hepatitis was created (3). The emergence of immuno-fluorescence assay (IFA), radio-immunno assay method (RIA), enzyme-linked immunosorbent assay (ELISA), molecular methods, and cloning techniques allowed the identification of hepatocellular auto antigen in AIH (**Table 1**). Characterizing the humoral and cellular immune systems in patients and animal models of autoimmune liver disease has improved knowledge (1, 4-7).

IAH is divided into two main groups:

i. Type 1 AIH (AIH-1); related with anti-nuclear antibody (ANA) and/or anti-smooth muscle antibody (SMA) positivity.

ii. Type 2 AIH (AIH-2); related with anti-liver kidney microsomal antibody type 1 (anti-LKM1), anti-LKM3 and/or anti-liver cytosol antibody type 1 (anti-LC1) positivity.

Both genetic and environmental factors are thought to be influential in etiology. An immune response targeting liver autoantigens is believed to initiate and sustain liver damage (1, 7).

Various scoring systems prepared by the International Autoimmune Hepatitis Group are used to diagnose autoimmune hepatitis. The most commonly "revised Scoring System" and "simplified scoring system" used. Both scoring systems gave points to ANA and SMA positivity (8).

1-Revised International Autoimmune Hepatitis Group Modified Scoring System:

Corresponding Author: Neval Yurttutan Uyar, nevaluyar@gmail.com

Received: 13.02.2023 **Accepted:** 14.03.2023

The revised original scoring system is a diagnostic method to ensure the systematic evaluation of patients. This scoring system was based on 12 clinical components, originally used developed as a tool for scientific purposes. Though the revised original diagnostic criteria were incorporated into clinical diagnosis of AIH, it is a very complex score system, and even including a variety of parameters of questionable value, it is difficult for wider applicability in routine clinical practice.

ANA, SMA, and LKM autoantibodies. On the diagnosis of autoimmune hepatitis when the total reaches ≥17 points (8).

2- To simplify the use of revised original diagnostic scoring system, the IAIHG defined simplified diagnostic criteria for routine clinical practice in 2008. The simplified score system is a reliable and simple tool to establish and exclude the diagnosis of AIH more frequently in liver diseases concurrent with immune manifestations, it was purely meant for clinical purposes. The simplified score system has superior specificity and accuracy comparing to the original revised scoring system, but only includes four clinical components, and no treatment response in the scoring system, it is generally accepted that simplified score system has a lower sensitivity (**Table 1**) (8).

Table 1. The simplified AIH diagnostic score system (*Sum of points achieved for all autoantibodies (maximum 2 points))

	Clinical feature	Results	Scores
1	ANA or SMA	≥1:40 by IIF	+1
	ANA or SMA	≥1:80 by IIF	+2*
	Anti-LKM1 (alternative to ANA and SMA)	≥1:40 by IIF	+2*
	Anti-SLA (alternative to ANA, SMA and anti-LKM1)	Positive	+2*
2	IgG	>UNL	+1
		>1.1 UNL	+2
3	Liver histology	AIH	+1
		Typical AIH	+2
		Atypical AIH	0
4	Absence of viral hepatitis	Yes	+2
		No	0
Total scores		≥6: probable AIH ≥7: definite AIH	

This study investigates the co-positivity of the ANA and SMA antibodies used to diagnose autoimmune hepatitis and their contribution to the diagnosis of autoimmune hepatitis.

MATERIAL AND METHOD

The study was carried out with the permission of Atadek, Acibadem University Medical Faculty Clinical Researches Ethics Committee (Date: 2022, Decision No: 19-05). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Clinical Sample Selection

From fifty-one (51) different primary, secondary and tertiary health care centers in seven geographical regions of Turkey, blood samples are sent to our central clinical laboratory (Acibadem Labmed, Istanbul, TR) for ANA and SMA testing. All ANA and SMA analyzes were performed in the central microbiology laboratory. The selection of patients, testing procedures, and follow-up period decayed for eight years between 2014 and 2021.

This study included 78 patients monitored for suspected autoimmune liver disease, with positive SMA antibody and ordered for an ANA test.

ANA and SMA test studies

SMA tests were studied using the RLKs–Rat wrapped (Rat/Monkey) (Aesku, Wendelshei, Germany) kit on a Helmed IFA systems (Aesku) device using the IFA method. The slides were evaluated by two IIFA microscopist (one experienced laboratory technician and microbiology specialist) under a Led Immunofluorescence Microscope (Motic, Hong Kong). In case of incompatibility between the two readings, the SMA test was repeated with the Euro plus LKS Mosaic kit (Euroimmun, Lübek, Germany) the patients who were screened at 1/40 and 1/100 titers, and positive patients were diluted at 1/320, 1/1000, and 1/3200 titers.

The ANA tests were performed using Helios automated IFA systems (Aesku, Wendelsheim, Germany) and HEp-2 Standard kit (Factory, Country?). The images of the ANA slides were taken using Helios automated IFA systems, added to the report through a Laboratory Information System (LIS), and then stored. In October, two IIFA microscopist (one experienced laboratory technician and microbiology specialist) examined the slides using a Led Immunofluorescence Microscope (Motic, Hong Kong). In the case of discordance between two readings, an ANA test was repeated using Mosaic HEP20-10/Liver (Monkey) (Euroimmun, Lüebeck, Germany). The patients who were screened at titers of 1/40 and 1/160 and positive were diluted at titers of 1/320, 1/1000, and 1/3200.

Simplified AIH diagnostic score system

All patients' simplified AIH diagnostic system scores were sorted from their files.

RESULTS

The demographic analysis of 78 patients is summarized in **Table 2**.

Table 2. Demographic information of the patients'

	SMA Positive (n: 78)
Gender	Female n:65 (83.33%)
Age, years	46.8 (15-89)

(Abbreviations: SMA: Smooth muscle Antibody)

The ANA results of SMA-positive patients (pattern and titers) are presented in **Table 3**. Cytoplasmic linear fibrillary pattern was found to be positive most frequently (68%). After that, homogeneous (13.2%), cytoplasmic reticular (7.5%), spotted (2.5%), and nucleolar (1.3%) were found, respectively (**Figure 1**).

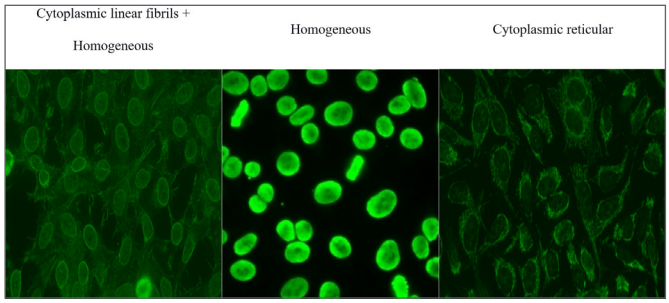


Figure 1: The captured pictures of 3 most common ANA patterns.

Table 3. Distribution of SMA-positive patients and their ANA patterns at a titer of 1/160. (Abbreviations: ANA: Anti-Nuclear antibody, SMA: Smooth muscle Antibody)

ANA Patterns	Number and percentage of patients
Cytoplasmic linear fibrils	53 (68.0%)
Homogeneous	10 (13.2%)
Cytoplasmic reticular	6 (7.5%)
Negative	6 (7.5%)
Speckled	2 (2.5%)
Nucleolar	1 (1.3%)

The patient, whose 6 ANA tests were negative, repeated the ANA test at a titer of 1/40 again. Homogeneous cytoplasmic linear fibrillary patterns were observed in 3 patients, linear fibrillary patterns were observed in 1 patient, and two patients were found to be negative at both titers.

In the ANA screening test of 78 SMA-positive patients performed at a titer of 1/160, 72 were found positive and received +2 points from autoantibodies score of simplified AIH diagnostic system. Six patients whose ANA test was negative, the ANA test was repeated at a titer of 1/40, and 4 patients were found positive and received +1 points from autoantibodies score of simplified AIH diagnostic system. Of the patients with a positive SMA test, 76 were positive at 1/100 titer positive and received +2 points from autoantibodies score of simplified AIH diagnostic system. And two were positive at 1/40 titer positive and received +1 points from autoantibodies score of simplified AIH diagnostic system (**Figure 2**) (**Table 4**).

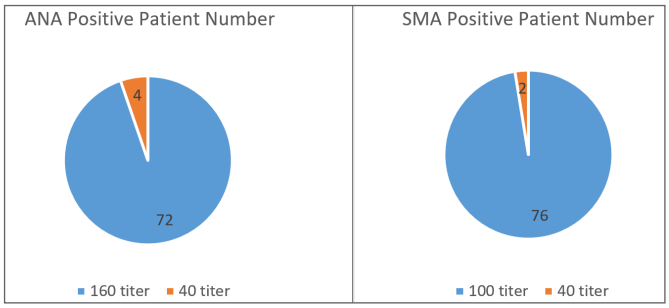


Figure 2: Titers of SMA and ANA tests positive. Abbreviations: ANA: Anti-Nuclear antibody, SMA: Smooth muscle Antibody (1:160, 1:40, 1:100 titers).

Table 4. Distribution of co-positivity of ANA- SMA and autoantibodies scores of simplified AIH diagnostic score system.

SMA/ ANA Screening Titers	Number and percentage of patients	simplified AIH diagnostic score (points achieved for all autoantibodies)
SMA positive 1/100 ANA positive 1/160	72	+2
SMA positive 1/100 ANA positive 1/40	2	+2
SMA positive 1/100 ANA negative	2	+2
SMA positive1/40 ANA positive1/40	2	+1

Distribution of the co-positivity, their titers, number of patients and autoantibodies score of Simplifed AIH diagnostic system were summarized at **Table 3**.

We calculated autoantibodies scores of simplified AIH diagnostic system. Scores received from single antibody couldn't increase by co-positivity.

DISCUSSION

Autoimmune hepatitis is a disease of exactly unknown cause that occurs in women of all ages and races. The diagnosis is made according to laboratory criteria, including clinical and specific autoantibodies (9, 10, 11). Autoimmune hepatitis (AIH) is an immuno-inflammatory liver disease with a non-self-limiting clinical course in which immunosuppressive agents are required in most affected patients (1, 12).

In recent years, the molecular targets of most autoantibodies-related associated diseases have been identified and characterized. The recent autoimmune disease diagnostic criteria clarified the place of autoantibodies in the diagnosis (13, 14).

Scoring systems including various clinical and laboratory data are used to diagnose autoimmune hepatitis. The "revised Scoring System" and the "simplified scoring system" prepared by the International Autoimmune Hepatitis Group are frequently used. ANA, SMA, LKM, and SLA are the autoantibodies used in scoring (1, 15).

It is common more than one autoantibody to appear together simultaneously in autoimmune diseases.

More than one autoantibody may also coincide in autoimmune hepatitis disease. 20-40% of the patients with AIH had another associated autoimmune or auto inflammatory disease (concomitant autoimmune diseases (CAIDs) (16).

Gergenli et al. (17) found an association in 35% of the patients, 12% had vitiligo, 6% had celiac disease, 6% had juvenile idiopathic arthritis, 6% had Familial Mediterranean Fever (FMF), and one patient had both type-1diabetes mellitus and Hashimoto thyroiditis (HT) .

Gökçe et al. (18) represented a case with atypical celiac patient with AIH. The patients had SMA + celiac autoantibodies and gave rapid responses to treatment.

Gencdal et al. (19) recommend to check AIH patients for celiac. 8.7% of patients in the AIH group were serologically and histologically diagnosed with celiac disesase.

Ordering multiple autoantibody tests used for diagnostic scoring together in patients with suspected autoimmune hepatitis, and their co-positivity is often observed (8).

The ANA international consensus pattern (ICAP: a sub-division of the American College of Rheumatology (ACR)) and the European Autoimmunity Standardization Initiative/immunology Union of international associations (EASI/IUIS) reached a consensus on reporting the ANA patterns. In contrast, for ANA cytoplasmic/mitotic apparatus patterns do not imply a clear position on the reporting ANA as negative or positive result (20-24).

In our study, of the 78 SMA-positive patients, 76 tested positive in the ANA test. Of the 76 ANA pattern positives, 75% are related to cytoplasmic patterns. The co-positivity of ANA and SMA were high but the co-positivity didn't effect diagnostic score systems, since sum of points achieved for all autoantibodies restricted to maximum 2 points. On the other the co-positivity could be a sign of another associated autoimmune or auto inflammatory disease (concomitant autoimmune diseases (CAIDs)).

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Atadek, Acibadem University Medical Faculty Clinical Researches Ethics Committee (Date: 2022, Decision No: 19-05).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Manns M, Lohse AW, Vergani D. Autoimmune hepatitis – Update 2015. Journal of Hepatology 2015; 62: 100– 11.
2. Waldenstrom J. Liver, blood proteins and food proteins. DTSH Z Verdau Stoffwechselkr 1952; 12: 113- 21.
3. Mackay JR, Taft LI, Crowling DC. Lupoid hepatitis. Lancet 1956; 271: 1323- 6.
4. Kirk AP, Jain S, Pocock S, Thomas HC, Sherlock S. Late results of the Royal Free Hospital prospective controlled trial of prednisolone therapy in hepatitis B surface antigen negative chronic active hepatitis. GUT 1980; 21: 78- 63.
5. Muratori P, Granito A, Quarneti C, et al. Autoimmune hepatitis in Italy: the Bologna experience. J Hepatol 2009; 50: 1210- 8.
6. Liberal R, Longhi ms, Mieli-Vergani G, Vergani D. Pathogenesis of autoimmune hepatitis. Best Pract Res Clin Gastroenterol 2011; 25: 653- 64.
7. Donaldson PT. Genetics of liver diease: immunogenetics and disease pathogenesis. Gut 2004; 53: 599- 608.
8. Alvarez F, Berg PA, Bianchi L, et al. International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol 1999; 31: 929- 38.
9. Ma Y, Bogdanos DP, Hussain MJ, et al. Poly-clonal T-cell responce to cytochrome P45OID6 are associated with disease activity in autoimmune hepatitis type2. Gastroenterology 2006; 130: 868- 82.
10. Mack CL, Adams D, Assis DN, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American Association for the Study of Liver Diseases. Hepatology 2020; 72: 671- 722.
11. Kim BH, Choi HY, Ki M, Kim KA, Jang ES, Jeong SH. Population based prevalence, incidence, and disease burden of autoimmune hepatitis in South Korea. PLoS One 2017; 12: e0182391.
12. Takahashi A, Arinaga-Hino T, Ohira H, et al. Autoimmune hepatitis in Japan: trends in a nationwide survey. J Gastroenterol 2017; 52: 631- 40.
13. Tanaka A, Mori M, Matsumoto K, Ohira H, Tazuma S, Takikawa H. Increase trend in the prevalence and male-to-female ratio of primary biliary cholangitis, autoimmune hepatitis, and primary sclerosing cholangitis in Japan. Hepatol Res 2019; 49: 881- 9.
14. Lee YM, Teo EK, Ng TM, Khor C, Fock KM. Autoimmune hepatitis in Singapore: a rare syndrome affecting middle-aged women. J Gastroenterol Hepatol 2001; 16: 1384- 9.
15. Hurlburt KJ, McMahon BJ, Deubner H, Hsu-Trawinski B, Williams JL, Kowdley KV. Prevalence of autoimmune liver disease in Alaska natives. Am J Gastroenterol 2002; 97: 2402- 7.
16. Werner M, Prytz H, Ohlsson B, et al. Epidemiology and the initial presentation of autoimmune hepatitis in Sweden: a nationwide study. Scand J Gastroenterol 2008; 43: 1232- 40.
17. Gerenli N, Çeltik Ç. Mode of presentation and association of autoimmune diseases in children with autoimmune hepatitis. Genel Tıp Derg 2022: 32: 95- 101.
18. Gölçe S, Durmaz Ö, Çeltik Ç et al. Atipik Celiac Hastası ve eşlik eden otoimmun hepatit. Balkan Med J 2009: 3: 273- 276.

19. Gencdal G, Meral C, Azarsız E, et al. Prevalence of coeliac disease in autoimmune liver disease and priamry biliary cholangitis. Çağdaş Tıp Derg 2018: 8: 295- 8.
20. Agmon-Levin N, Damoiseaux J, Kallenberg C, et al. International recommendations for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. Ann Rheum Dis 2014; 73: 17–23.
21. Damoiseaux J, Mühlen C, Torre I, et al. International consensus on ANA patterns (ICAP): the bumpy road towards a consensus on reporting ANA results. Autoimmune Highlights 2016; 7: 1- 8.
22. Solomon DH, Kavanaugh AJ, Schur PH. Evidence-based guidelines for the use of immunologic tests: antinuclear antibody testing. Arthritis Rheu. 2002; 47: 434– 44.
23. Chan E.K.L., Damoiseaux J, de Melo Cruvinel, et al. Report on the second International Consensus on ANA Pattern (ICAP) workshop in Dresden 2015. Lupus 2016; 25: 797- 804.
24. Meroni PL, Schur PH. ANA screening: an old test with new recommendations. Ann Rheum Dis 2010; 69: 1420– 2.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1241530

Anatolian Curr Med J 2023; 5(2); 143-147

The effect of proton pump inhibitor use on the biodistribution of FDG in patients undergoing ^{18}F FDG PET/CT imaging

İhsan Kaplan[1], Yunus Güzel[1], Canan Can[1], Cihan Gündoğan[1], Mehmet Serdar Yıldırım[2], Ferat Kepenek[1], Bekir Taşdemir[3], Halil Kömek[1]

[1]Department of Nuclear Medicine, Diyarbakır Gazi Yaşargil Training and Research Hospital, Sağlık Bilimleri University, Diyarbakır, Turkey
[2]Department of Internal Medicine, Diyarbakır Gazi Yaşargil Training and Research Hospital, Sağlık Bilimleri University, Diyarbakır, Turkey
[3]Department of Nuclear Medicine, Faculty of Medical, Dicle University, Diyarbakır, Turkey

Cite this article as: Kaplan İ, Güzel Y, Can C, et al. The effect of proton pump inhibitor use on the biodistribution of FDG in patients undergoing ^{18}F FDG PET/CT imaging. Anatolian Curr Med J 2023; 5(2); 143-147.

ABSTRACT

Aim: In this study, we aimed to investigate the effects of proton pump inhibitors (PPIs) administered shortly before intravenous (iv) F-18 fluorodeoxyglucose (FDG) injection on the physiological FDG uptake in the gastrointestinal tract (GIS) of patients undergoing F-18 FDG positron emission tomography/computed tomography (PET/CT) for oncological purposes.

Material and Method: We retrospectively evaluated 350 patients who underwent ^{18}F-FDG PET/CT in our clinic between November 2020 and June 2021. Among these, 178 patients were given iv PPIs before the scan and the remaining 172 patients with similar characteristics were not. FDG uptake in the gastrointestinal tract was analyzed visually and quantitatively.

Results: The mean age of the patients was 51.7±15 years. There was no significant difference between the two groups in terms of age and gender. Quantitative evaluation revealed that the FDG uptakes in the stomach, duodenum, ileum, and transverse colon and their ratio to hepatic uptake were significantly lower in the group receiving iv PPIs ($p<0.05$). In visual evaluation, gastric and ileal uptake were significantly lower in the intravenous PPI group ($p<0.05$).

Conclusion: Our findings indicate that intravenous administration of a PPI before FDG PET/CT imaging can decrease the FDG uptake in the gastrointestinal tract. We think that this practice can reduce false positive findings in the gastrointestinal system and help identifying gastric and intestinal cancers by reducing background activity.

Keywords: Positron emission tomography, proton pump inhibitor, physiological uptake, gastrointestinal tract

INTRODUCTION

^{18}F-FDG PET/CT is a non-invasive diagnostic tool that shows metabolic activity in target tissues and is used to obtain quantitative parameters (1,2). FDG PET/CT is a valuable imaging tool for diagnosis, staging, evaluation of response to treatment and prognosis in oncology (3,4).

Recommended for imaging infection/inflammation as well as cancer diseases (5, 6). In addition, variable degrees of physiological FDG uptake may occur in the brain, salivary glands, thyroid, muscles, GIS, urinary system, adrenal gland, uterus, ovary, adipose tissue, muscles, spleen, and bone marrow (7-9).

FDG uptake may increase in the stomach, small and large intestines physiologically, in benign diseases or due to drug use (10-13). Gastric distention (drinking water) and use of iv buscopan were found to be effective in reducing FDG uptake in the stomach, and oral omeprazole in small and large intestines (14,15). Suspected focal or diffuse FDG uptake in the GIS requires endoscopic examination to rule out malignancy or to accurately stage malignant disease. The operations performed cause cost and time loss.

In this study, we aimed to examine the effect of using iv proton pump inhibitor on the physiological involvement of GIS before ^{18}F-FDG PET/CT imaging.

MATERIAL AND METHOD

The study was carried out with the permission of Diyarbakır Training and Research Hospital Ethics Committee (Date: 21.04.2022, Decision No: 72). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Corresponding Author: İhsan Kaplan, drihsankaplan@hotmail.com

Received: 23.01.2023 **Accepted:** 15.03.2023

Three hundred and fifty patients who had no prior history of gastrointestinal symptoms or oral PPI use and underwent ^{18}F-FDG PET/CT in our clinic between November 2020 and June 2021 were retrospectively included in our study. One hundred and seventy-eight patients received an iv PPI (40 mg of pantoprazole) one hour before the FDG injection. One hundred and seventy-two patients with similar demographic characteristics and diagnoses, who also don't have a history of oral or iv PPI use, were included in the control group. Patients with a history of abdominal surgery, using oral antidiabetic drugs, or using stomach drugs (antiacids, H2 receptor blockers, and PPIs) for any reason were excluded from the study.

^{18}F-FDG PET/CT imaging protocol

All patients were asked to fast and cease iv glucose intake at least six hours before FDG imaging. Blood glucose was confirmed to be ≤ 140 mg/dL using fingerstick method, and 3.5-5.5 MBq/kg of ^{18}F-FDG was intravenously injected. One hour after the injection, CT images (120 kV, 80 mAs/slice, 700 mm transaxial FOV, no gap, 64x0.625 mm collimation, pitch 1.4, 0.5 s rotation time, 3.3 mm slice thickness, 512x512 matrix) from the vertex to the middle of the thigh were obtained using the Discovery IQ 4 ring 20-cm axial FOV PET/CT device (GE Healthcare, Milwaukee, WI, USA) in the supine position. Then, PET images were obtained at 2.5 minutes per bed position (3D FOV 20 cm, ordered subset expectation-maximization algorithm [OSEM] 5 iterations/12 subset, full width at half maximum [FWHM] 3 mm).

Evaluation of Images

All ^{18}F-FDG PET/CT images were evaluated by two nuclear medicine specialists with at least 10 years of experience using Advantage Workstation software version AW 4.7 (GE Healthcare Milwaukee, WI, USA). FDG uptake was assessed both visually and quantitatively in the liver, stomach (cardia, fundus, body, antrum, and pylorus), duodenum, jejunum, ileum, ascending colon, transverse colon, descending colon, sigmoid colon, and rectum separately. In visual assessment, uptakes were scored as grade 1 (uptake<liver), grade 2 (uptake=liver), and grade 3 (uptake > liver). In quantitative assessment, maximum standardized uptake value (SUVmax) of the gastrointestinal segments and their ratio to hepatic SUVmax were calculated.

Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, United States) program was used for statistical analyses. Normality of univariate data was evaluated using Shapiro-Wilk and Kolmogorov-Smirnov test. Descriptive statistics (mean, standard deviation, minimum, median, and maximum) were used to define continuous variables. Mann-Whitney U test was used to compare two independent and non-normally distributed groups. Visual data was analyzed with chi-squared test. $p < 0.05$ was considered statistically significant.

RESULTS

The mean age of the patients was 51.7±15 years and the median age was 53 years (18-92). Fifty percent (175) of the patients included in the study were male. There was no significant difference between the two groups in terms of age and gender. The underlying diseases of the PPI group and control group are summarized (**Table 1**).

Table 1. Demographic characteristics and underlying diseases of patients with and without proton pump inhibitors

Patient Groups	PPI Group	Control Group	p value
Male	92	83	0.296
Female	86	89	
Age (range)	52 (20-87)	53.5 (18-92)	0.766
Underlying diseases			
Lung ca	30	37	
Breast ca	28	33	
Malignant lymphoma	18	15	
Head-neck tumors (Thyroid ca, Larynx ca, etc)	14	17	
Cancer of unknown origin	20	3	
Colorectal ca	15	22	
Gynecological ca	15	10	
Stomach ca	11	3	
Multiple myeloma	3	1	
Malignant mesothelioma	5	1	
Male genitourinary ca	6	4	
Small intestine tumors	5	3	
Thymoma	1	1	
Renal cell carcinoma	4	4	
Skin ca (Malignant melanom-Squamous cell carcinoma)	5	1	
Esophagus ca	1	5	
Soft tissue sarcoma	2	3	
Pancreatic ca	1	5	
Hepatocellular carcinoma	0	1	

PPI: proton pump inhibitor, cancer: ca

The SUVmax values measured in the stomach and intestinal segments of the patients with and without intravenous PPI use before the scan, the ratios of these values to the hepatic SUVmax, and the p values obtained are summarized in **Table 2**. FDG uptake in the cardia, fundus, gastric body, duodenum, and transverse colon were significantly lower in the group using iv PPIs ($p=0.011$, $p<0.001$, $p=0.004$, $p<0.001$, and $p=0.003$, respectively).The ratios of cardia/liver, fundus/liver, gastric body/liver, antrum/liver, pylorus/liver, duodenum/liver, and ileum/liver SUVmax were also significantly lower in the iv PPI group ($p<0.001$, $p<0.001$, $p<0.001$, $p=0.006$, $p=0.002$, $p=0.037$, and $p<0.000$, respectively) (**Table 2**).

Visual evaluation revealed that the FDG uptakes in gastric cardia, fundus, body, antrum, pylorus, and ileum were significantly lower in the intravenous PPI group (p=0.0006, p<0.001, p=0.002, p=0.040, and p<0.001, respectively) (**Figure 1** and **2**). No significant difference was observed in other intestinal segments (**Table 3**).

Table 2. Quantitative comparison of patients with and without proton pump inhibitors.

	PPI (+)			PPI (-)			p
	n	Mean+SD	Med (Min-Max)	n	Mean+SD	Med (Min- Max)	
Cardia SUVmax	178	2.5+1.0	2.3(0.6-6.2)	172	2.7+1.0	2.7(0.7-6.7)	0.011
Cardia/Liver SUVmax ratio	178	0.7+0.3	0.6(0.2-1.6)	172	0.8+0.3	0.8(0.2-2.4)	0.000
Fundus SUVmax	178	2.2+1.2	2.2(0.0-7.4)	172	2.8+1.1	2.7(0.5-5.7)	0.000
Fundus/Liver SUVmax ratio	178	0.6+0.3	0.6(0.0-1.9)	172	0.8+0.4	0.8(0.1-2.3)	0.000
Gastric Body SUVmax	178	2.6+1.3	2.5(0.4-6.8)	172	2.9+1.1	2.9(0.6-6.1)	0.004
Gastric Body/Liver SUVmax ratio	178	0.7+0.3	0.7(0.1-1.6)	172	0.9+0.3	0.8(0.2-1.8)	0.000
Antrum SUVmax	178	2.5+1.4	2.2(0.2-6.5)	172	2.5+1.2	2.4(0.5-6.0)	0.242
Antrum/Liver SUVmax ratio	178	0.6+0.3	0.6(0.1-1.8)	172	0.7+0.3	0.7(0.2-1.8)	0.006
Pylorus SUVmax	178	2.4+1.1	2.2(0.7-7.5)	172	2.5+1.1	2.4(0.4-5.5)	0.242
Pylorus/Liver SUVmax ratio	178	0.6+0.3	0.6(0.2-2.5)	172	0.7+0.3	0.7(0.1-1.8)	0.002
Duodenum SUVmax	178	2.6+0.9	2.5(0.9-6.3)	172	2.3+0.8	2.1(0.7-4.7)	0.000
Duodenum/Liver SUVmax ratio	178	0.7+0.2	0.6(0.2-1.5)	172	0.6+0.2	0.6(0.1-1.6)	0.037
Jejunum SUVmax	178	2.9+1.0	2.8(1.1-8.6)	172	2.7+0.8	2.6(0.8-5.4)	0.067
Jejunum/Liver SUVmax ratio	178	0.8+0.3	0.7(0.4-2.5)	172	0.8+0.2	0.8(0.3-1.7)	0.120
Ileum SUVmax	178	3.6+2.3	2.9(1.0-17.7)	172	3.7+2.1	3.3(0.9-16.3)	0.063
Ileum/Liver SUVmax ratio	178	1.0+0.6	0.8(0.2-5.0)	172	1.1+0.6	1.0(0.3-4.3)	0.000
Cecum SUVmax	178	2.8+1.8	2.4(0.5-10.8)	172	2.7+1.9	2.1(0.7-13.3)	0.054
Cecum/Liver SUVmax ratio	178	0.8+0.5	0.6(0.1-2.9)	172	0.8+0.5	0.6(0.2-2.9)	0.519
Asc.Col. SUVmax	178	3.1+2.1	2.4(0.8-13.3)	172	2.8+2.1	2.1(0.7-12.6)	0.067
Asc.Col./Liver SUVmax ratio	178	0.8+0.6	0.7(0.2-3.2)	172	0.8+0.6	0.6(0.2-3.3)	0.728
Trans.Col. SUVmax	178	2.6+1.8	2.2(0.7-12.7)	172	2.6+2.7	1.7(0.5-18.7)	0.003
Trans.Col./Liver SUVmax ratio	178	0.7+0.5	0.6(0.2-2.7)	172	0.7+0.7	0.5(0.2-4.9)	0.153
Desc.Col. SUVmax	178	2.4+1.8	1.9(0.4-13.7)	172	2.4+2.2	1.6(0.5-16.0)	0.195
Desc.Col. /Liver SUVmax ratio	178	0.6+0.5	0.5(0.1-3.9)	172	0.7+0.6	0.5(0.1-4.2)	0.976
Sig. Col. SUVmax	178	3.3+2.3	2.7(0.6-14.2)	172	3.5+2.9	2.8(0.4-23.6)	0.779
Sig. Col. /Liver SUVmax ratio	178	0.9+0.6	0.7(0.2-4.0)	172	1.0+0.8	0.8(0.2-5.5)	0.106
Rectum SUVmax	178	3.0+2.0	2.4(0.7-13.5)	172	2.8+2.2	2.4(0.6-20.5)	0.174
Rectum/Liver SUVmax ratio	178	0.8+0.5	0.7(0.2-3.4)	172	0.8+0.6	0.7(0.2-4.5)	0.831

PPI (+): patients using proton pump inhibitors, PPI (-): patients not using proton pump inhibitors, n: number of cases, SD: standard deviation, Med: median, Min: minimum, Max: maximum, SUVmax: maximum standardized uptake value, Asc.Col: ascending colon, Trans.Col: transverse colon; Desc.Col: descending colon, Sig. Col: sigmoid colon

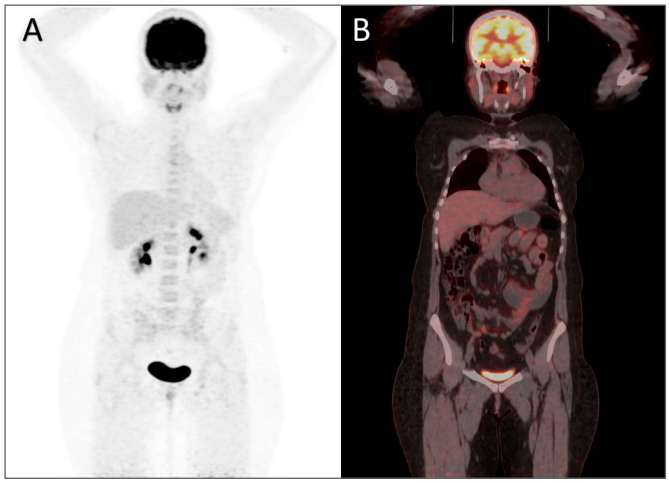


Figure 1. 32 year old woman with breast cancer using iv PPI before imaging; FDG uptake in the stomach and intestines was less than in the liver (Visual score: Grade 1).

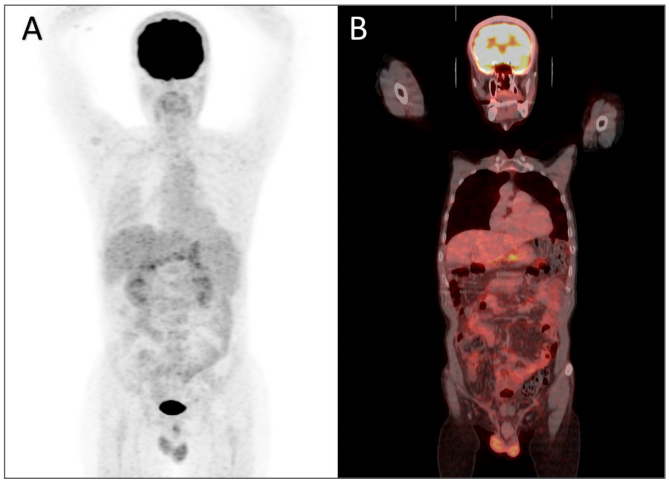


Figure 2. 50 year old man with hepatocellular carcinoma who did not use iv PPI before imaging; FDG uptake in stomach was higher than liver (Visual score: Grade 3).

Table 3. A visual comparison of patients with and without proton pump inhibitors.

	Visual score	PPI (+)	PPI (-)	Total	p
Cardia	1	129	92	221	<0.001
	2	40	61	101	
	3	9	19	28	
Fundus	1	133	93	226	<0.001
	2	37	49	86	
	3	8	30	38	
Gastric Body	1	121	85	206	0.002
	2	43	60	103	
	3	14	27	41	
Antrum	1	129	106	235	0.041
	2	34	51	85	
	3	15	15	30	
Pylorus	1	148	109	251	<0.001
	2	14	47	58	
	3	11	16	21	
Duodenum	1	131	145	282	0.199
	2	31	23	59	
	3	5	4	9	
Jejunum	1	125	114	239	0.600
	2	42	48	90	
	3	11	10	21	
İleum	1	109	63	172	<0.001
	2	36	61	101	
	3	33	44	77	
Cecum	1	129	121	250	0.431
	2	25	20	45	
	3	24	31	55	
Asc.Col.	1	119	118	237	0.810
	2	20	20	40	
	3	39	34	73	
Trans.Col.	1	143	133	276	0.796
	2	14	15	29	
	3	21	24	45	
Desc.Col.	1	142	139	281	0.745
	2	17	15	32	
	3	19	18	37	
Sig. Col.	1	116	92	208	0.062
	2	23	40	63	
	3	39	40	79	
Rectum	1	124	110	234	0.602
	2	29	37	66	
	3	25	25	50	

PPI (+): patients using proton pump inhibitors, PPI (-): patients not using proton pump inhibitors, n: number of cases, SD: standard deviation, Med: median, Min: minimum, Max: maximum, SUVmax: maximum standardized uptake value, Asc.Col: ascending colon, Trans.Col: transverse colon; Desc.Col: descending colon, Sig. Col: sigmoid colon

DISCUSSION

Similar to our study, Yamamoto et al. (15) used iv PPIs in their study on rats. However, probably due to very small size of rats, the measurements were obtained by removing the relevant GI segment of the rats and taking measurements on a gamma counter instead of scanning images on a PET/CT device. In this study, observed no effect of iv PPI use on the physiological FDG uptake in the esophagus and stomach, while the FDG activity in the small intestines and colon were significantly decreased. However, in our study, we observed that the use of iv PPIs decreases the FDG uptake in the duodenum and transverse colon along with many gastric segments. In addition to the SUVmax measurements, we also calculated the GI segment/hepatic SUVmax ratios in our study. This way, a statistically more significant difference was obtained, especially in the stomach segments and ileum. In the study of Yamamoto et al. (15), the change in the stomach may have been overlooked since the ratio of the measurements to the liver could not be evaluated. In our study, no statistical difference was observed in the antrum and pylorus when only the difference in FDG uptake was examined, but the evaluation of the GI segment/liver SUVmax ratio revealed a difference in the antrum and pylorus. In addition, because Yamamoto et al. (15) could not evaluate the ratio of their SUVmax measurements to the liver, a dose difference that could be caused by a possible extravasation of the FDG dose given to the rats could be missed. Yamamoto et al (15). also observed that iv PPIs decreased the FDG uptake in the small intestines and colon. We, on the other hand, divided the small intestine and colon into segments within themselves and found that the use of an iv PPI reduced the FDG uptake in the duodenum, ileum, and transverse colon.

Domeki et al. (16) used oral rabeprazole in a human study and investigated its effect on the physiological FDG uptake in the stomach and colon. Similar to our study, the investigators observed that the PPI significantly reduced the physiological FDG uptake in the stomach and colon, but especially in the stomach. Domeki et al. (16) attributed this impact, which was more evident in the stomach, to the mucosal absorption of the orally administered PPI. However, our study showed that direct mucosal absorption may not be an accurate pathophysiological explanation. As a matter of fact, our study showed that iv PPI administration significantly decreased the physiological FDG uptake, especially in the stomach. Domeki et al. (16) did not evaluate small intestinal segments in their study. They also did not assess the stomach and colon segments separately. Another limitation of that study is that the GI segment/liver SUVmax ratio was not evaluated. In addition, for this study, patients were required to use the PPI orally for 3 nights before the study. Since three days of medication use is required for imaging with oral PPI, it loses its applicability when urgent and early scans are required. IV administration of a PPI before FDG PET/CT, however, is a very practical and reliable method.

In this study, we aimed to identify the effects of intravenous PPI use on the physiological FDG uptake in the stomach and intestines. There are studies in the literature reporting that PPIs exhibit inhibitory activity on intestinal peristalsis with their anticholinergic effects (17, 18). Our findings may be due to this anticholinergic impact of PPIs. However, previous studies have shown that PPIs also have an anti-inflammatory effect (19-21). The decreased FDG uptake observed in the PPI group in our study may be due to suppression of inflammation. Even though we did not include patients with gastric or intestinal symptoms to avoid this bias, we were not able to exclude an inflammatory condition endoscopically. However, considering that the purpose of FDG PET/CT is to distinguish between malignant and benign conditions, even if PPIs have an anti-inflammatory effect, it is obvious that it will contribute to this major purpose.

The limitations of our study are that it is retrospective.

CONCLUSION

Our findings indicate that intravenous administration of a PPI before FDG PET/CT imaging can decrease the FDG uptake in the gastrointestinal tract. We think that this practice can reduce false positive findings in the gastrointestinal system and help identifying gastric and intestinal cancers by reducing background activity.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Diyarbakır Training and Research Hospital Ethics Committee (Date: 21.04.2022, Decision No: 72).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Boellaard R, Delgado-Bolton R, Oyen WJ, et al. European Association of Nuclear Medicine (EANM). FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015; 42: 328-54.
2. Howard BA, Wong TZ. ^{18}F-FDG-PET/CT imaging for gastrointestinal malignancies. Radiol Clin North Am 2021; 59: 737-53.
3. de Geus-Oei LF, van der Heijden HF, Corstens FH, Oyen WJ. Predictive and prognostic value of FDG-PET in nonsmall-cell lung cancer: a systematic review. Cancer 2007; 110: 1654-64.
4. Jayaprakasam VS, Paroder V, Schöder H. Variants and pitfalls in PET/CT imaging of gastrointestinal cancers. Semin Nucl Med 2021; 51: 485-501.
5. Jamar F, Buscombe J, Chiti A, et al. EANM/SNMMI guideline for ^{18}F-FDG use in inflammation and infection. J Nucl Med 2013; 54: 647-58.
6. Pijl JP, Nienhuis PH, Kwee TC, Glaudemans AWJM, Slart RHJA, Gormsen LC. Limitations and pitfalls of FDG-PET/CT in infection and inflammation. Semin Nucl Med 2021; 51: 633-45.
7. Abouzied MM, Crawford ES, Nabi HA. ^{18}F-FDG imaging: pitfalls and artifacts. J Nucl Med Technol 2005; 33: 145-55
8. Shreve PD, Anzai Y, Wahl RL. Pitfalls in oncologic diagnosis with FDG PET imaging: physiologic and benign variants. Radiographics 1999; 19: 61-77.
9. Wang X, Koch S. Positron emission tomography/computed tomography potential pitfalls and artifacts. Curr Probl Diagn Radiol 2009; 38: 156-69.
10. Pilkington P, Lopci E, Adam JA, Kobe C, Goffin K, Herrmann K. FDG-PET/CT variants and pitfalls in haematological malignancies. Semin Nucl Med 2021; 51: 554-71.
11. Koppula BR, Fine GC, Salem AE, et al. PET-CT in clinical adult oncology: III. gastrointestinal malignancies. Cancers (Basel) 2022; 14: 2668.
12. Shmidt E, Nehra V, Lowe V, Oxentenko AS. Clinical significance of incidental [18 F]FDG uptake in the gastrointestinal tract on PET/CT imaging: a retrospective cohort study. BMC Gastroenterol 2016; 16: 125.
13. Kousgaard SJ, Thorlacius-Ussing O. Incidental colorectal FDG uptake on PET/CT scan and lesions observed during subsequent colonoscopy: a systematic review. Tech Coloproctol 2017; 21: 521-9.
14. Le Roux PY, Duong CP, Cabalag CS, Parameswaran BK, Callahan J, Hicks RJ. Incremental diagnostic utility of gastric distension FDG PET/CT. Eur J Nucl Med Mol Imaging 2016; 43: 644-53.
15. Yamamoto F, Nakada K, Zhao S, Satoh M, Asaka M, Tamaki N. Gastrointestinal uptake of FDG after N-butylscopolamine or omeprazole treatment in the rat. Ann Nucl Med 2004; 18: 637-40.
16. Domeki Y, Yamazaki E, Matsuura A, Kitajima K, Murakami K, Kato H. Effects of a proton pump inhibitor on the physiological accumulation of fluoro-2-deoxy-D-glucose (FDG) in FDG-positron emission tomography. Surg Today 2012; 42: 927-33.
17. Okabe S, Takagi K, Inoue K. Effect of NC-1300-O-3 on healing of acetic acid-induced gastric ulcers in rats. Jpn J Pharmacol 1993; 62: 25–33.
18. Suzuki M, Nakamura M, Mori M, Miura S, Tsuchiya M, Ishii H. Lansoprazole inhibits oxygen-derived free radical production from neutrophils activated by Helicobacter pylori. J Clin Gastroenterol 1995; 20: 93–6.
19. Yoshida N, Yosikawa T, Tanaka Y, Fujita N, Kassai K, Naito Y. A new mechanism for anti-inflammatory actions of proton pump inhibitors-inhibitory effects on neutrophil-endothelial cell interactions. Aliment Pharmacol Ther 2000; 14: 74–81.
20. Wandall JH. Effects of omeprazole on neutrophil chemotaxis, super oxide production, degranulation and translocation of cytochrome b-245. Gut 1992; 33: 617–21.
21. Suzuki M, Mori M, Fukumura D, et al. Omeprazole attenuates neutrophil-endothelial cell adhesive interaction induced by extract of *Helicobactor pylori*. J Gastroenterol Hepatol 1999; 14: 27–31.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1259439

Anatolian Curr Med J 2023; 5(2); 148-152

A new prognostic marker in small cell lung cancer: red cell distribution width ratio of hemoglobin

Figen Öztürk Ergür, Ayperi Öztürk

Department of Chest Disease, Ankara Atatürk Chest Diseases and Thoracic Surgery Training and Research Hospital, University of Health Sciences, Ankara, Turkey

Cite this article as: Öztürk Ergür F, Öztürk A. A new prognostic marker in small cell lung cancer: red cell distribution width ratio of hemoglobin. Anatolian Curr Med J 2023; 5(2); 148-152.

ABSTRACT

Aim: The ratio of hemoglobin (Hb) to red cell distribution width (RDW) (HRR) has been defined as an effective prognostic factor in various cancer types. The aim of this study is to investigate the prognostic role of HRR value in small cell lung cancer (SCLC).

Material and Method: A total of 1039 patients diagnosed with SCLC between 2010-2021 were included in the study. After exclusion of 199 patients without positron emission tomography-computerized tomography (PET-CT), age, gender, additional disease histories, smoking history, pathological stages, survival status, disease progression times, treatments applied, first hemoglobin obtained after diagnosis, red cell distribution width and ratios, and other laboratory parameters of 840 patients were recorded. The log-rank test and the Cox proportional hazards model were used to identify predictors of mortality.

Results: A total of 840 patients were included in the study. The median overall survival (OS) and the progression-free survival (PS) times of the patients were 9 months, and 7 months, respectively. The cut-off value for HRR was determined 0.580 (sensitivity 78.73%, specificity 37.88%). In this study, each one-unit increase in HRR reduces death and survival by 1.6 times detected, and it was revealed that HRR had a statistically significant effect on OS and PS. When the patients were divided into two as limited and extensive disease, there was a statistically significant difference between the groups in terms of OS (12-6 months) and PS (10-6 months), but no significant difference was found in terms of HRR between these two groups.

Conclusion: HRR is an easily accessible, inexpensive parameter that can be used as a prognostic marker in patients with SCLC.

Keywords: HRR, SCLC, survival, prognosis

INTRODUCTION

Small cell lung cancer (SCLC) constitutes approximately 15-20% of all lung tumors (1). It has a poor prognosis due to its faster tumor replication time and thus the early development of distant metastases. Although SCLC responds dramatically to chemotherapy and radiotherapy, overall survival (OS) and progression-free survival (PS) of patients are adversely affected due to tumor resistance or recurrence within one year (2).

In recent years, numerous studies have examined the prognosis of SCLC. A few molecular markers such as Glasgow prognostic score(3), alkaline phosphatase (ALP) (4) and lactate dehydrogenase (LDH) level (5), serum P53 antibody (6) have been confirmed to be associated with mean survival in patients with SCLC; however, these molecular markers are of limited use due to the complex and expensive detection methods thereof. Therefore, it is of great importance to identify more economical, useful, and effective biomarkers to evaluate the prognosis of patients with SCLC.

It was reported that hemoglobin (Hb) value, which reflects the degree of anemia, may be an independent predictor of prognosis in solid organ tumors and hematological malignancies such as lymphoma and multiple myeloma (7). Red cell distribution width (RDW) is an important complete blood count (CBC) parameter used in the diagnosis and differential diagnosis of various types of anemia. It was shown to be closely associated with poor prognosis in cardiovascular and oncological diseases (8,9). High RDW values are associated with an indicator of poor prognosis in patients with lung cancer, breast cancer, esophagus and kidney cancer (10-13). Wherefore Hg and RDW values are affected by many non-neoplastic conditions alone the Hb/RDW ratio (HRR) may be a more independent marker (14).

There are few studies on SCLC due to both the lack of new treatment regimens and simple and effective prognostic factors to evaluate the prognosis (15). In this study, it was aimed to determine that the HRR value, which is an easily

Corresponding Author: Figen Öztürk Ergür, figturk@gmail.com

Received: 02.03.2023 **Accepted:** 17.03.2023

measurable, repeatable, and inexpensive parameter, is an independent prognostic factor for OS and PS, with the number of patients we think may be sufficient considering this deficiency.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences, Ankara Atatürk Sanatoryum Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.02.2023, Decision No: 2661). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

SCLC patients diagnosed at Ankara Atatürk Sanatoryum Training and Research Hospital between January 2010 and January 2021 were included in the study. Inclusion criterias are: (i) histopathologically diagnosed SCLC; (ii) adequate imaging data for computed tomography (CT), magnetic resonance imaging device (MRI), and PET-CT tumor staging; (iii) no previous antitumor therapy including radiotherapy, chemotherapy, immunotherapy, and targeted therapy; (iv)routine findings of blood analysis and blood biochemistry, hospital-based laboratory test results. Exclusion criteria are: (i) patients younger than 18 years of age; (ii) patients with non-small cell lung carcinoma; (iii) patients with a secondary malignancy; (iv) patients with comorbid infections, inflammatory diseases, lymphoproliferative diseases, additional diseases such as chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD), diabetes mellitus (DM) affecting the RDW value.

1039 SCLC patients were screened. 199 patients who had no PET-CT were excluded from the study, and 840 patients were included in the study. The study was designed retrospectively, no written informed consent form was obtained from patients.

Clinical Data

Clinical data such as age, gender, smoking history, staging, treatment regimens (chemotherapy, radiotherapy), adjuvant therapy, neoadjuvant therapy, operation], diagnosis time, initial HRR values were recorded. The HRR value was calculated using CBC values as follows: Hb(g/dl)/RDW (%).

Tumor Staging

Tumor staging was based on the eighth edition of the staging criteria published by the International Association for the Study of Lung Cancer (16).

Observation Indicators

The following indicators of observation were used: OS was defined as the time from first treatment to death or last follow-up, while PS was defined as the time from the start of first-line chemotherapy to the date of disease progression or death.

Statistical Analysis

Descriptive statistics (mean, standard deviation, minimum, median, maximum) were used to describe continuous variables. The distribution of continuous variables was examined using a Shapiro-Wilk test, and variables with p-levels under 0.05 were considered to have abnormal distribution. Overall survival and progression-free survival were evaluated by the Kaplan-Meier method. The effect of CBC parameters on survival was examined by Cox Regression analysis. The power of CBC parameters to predict death and progression were examined by A Receiver Operating Characteristic (ROC) analysis.Statistical significance level was determined as 0.05. Analyzes were performed using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; 2021).

RESULTS

199 patients without PET-CT were excluded from the study, and 840 patients were included. The demographic data and clinical characteristics of the patients were shown in **Table 1**. The majority of the patients were male (n=751, 89.4%). The mean age was 62,2 +9,1 years (25-88). 44.2% (371) of the patients were smokers, and the mean number of packs/year was 40. There was no comorbid disease in 57.5% of the patients. When patients were classified according to tumor size, lymph node metastasis, and distant organ metastasis; 70% of them were in the T4 group; 54.7% were in the N3 group, and 59.6% were in M0. The most common organ with metastasis was bone (n=111, 13.2%) (**Table 1**).

The laboratory parameters of the patients are given in **Table 1**. Mean lymphocyte/C-reactive protein (CRP) ratio (LCR) value was 0.5 (0-361), neutrophil/lymphocyte ratio (NLR) value 3.4 (0-12684.7), platelet/lymphocyte ratio (PLR) value 151.4 (20-54187.2) and HRR value 1.0 (0.3-1, 4). The median OS of the patients was 9 months, and the median PS was 7 months. The effects of LCR, NLR, PLR, CRP/Alb, and HRR values on survival were examined. According to statistical analysis, while the significant effect of LCR was only in overall survival (p=0.03) on the other hand HRR was found to be an expressive effect in both OS and PS (p=0.01) (**Table 2**). The cut-off value of HRR was determined by the ROC analysis as <1.08 and is shown in **Figure 1**. Moreover, it was determined as a remarkable result that each one-unit increase in HRR reduces both mortality and progression by nearly 1.6-fold(**Figure 2**).

Table 1: Demographic Data

	n (%)
Gender	
Male	751 (89.4)
Female	89 (10.6)
Age	62.2 (+9.1)*
Smoking	371 (44.2)
Smoking consumption amount (Pack/year)	48.9(+25.5)*
Tumor Size (mm)	71.2+28.7*
T1	50 (6)
T2	110 (13.1)
T3	88 (10.5)
T4	592 (70.5)
N0	43 (5.1)
N1	34 (4)
N2	304 (36.2)
N3	459 (54.7)
M0	501 (59.6)
M1a	103 (12.3)
M1b	236 (28.1)
Metastasis localizations:	
Bone	111 (13.2)
Opposite Lung	22 (2.6)
Liver	16 (1.9)
Surrenal	25(3)
Brain	10 (1.2)
> Two organs	328 (39.1)
Laboratory parameters:	**Med(min-max)**
Hemoglobin	14(6.8-18.5)
Lymphocyte (103)	1.8(0-5.6)
Neutrophil	6.2(0-51.5)
Platelet	277(31-972)
RDW	14.6(11.8-31.2)
Albumin	4.2(1.9-49.2)
CRP (mg/l)	3.3(0-321.1)
LCR	0.5(0-361)
NLR	3.4(0-12684.7)
Platelet/ Albumin	60.8(1-260.6)
PLR	151.4(20-54187.2)
CRP/ Albumin	0.5(0-65.7)
HRR	1.0(0.3-1.4)

CRP: C-reactive protein, HRR: Hemoglobin/ Red cell distribution width ratio LCR: lymphocyte/CRP ratio, NLR: neutrophil/ lymphocyte ratio PLR: Platelet/ lymphocyte ratio RDW: Red cell distribution width, *: Mean ± SD

Table 2. Effect of LCR, NLR, PLT/ALB, HRR Values on OS and PS

	OS			PS		
	p	HR	95% GA	p	HR	95% GA
LCR	0.038	0.997	0.995-1.00	0.079	0.998	0.995-1.00
NLR	0.798	1.00	1.00-1.00	0.686	1.00	1.00-1.00
Platelet/Alb.	0.627	1.00	0.999-1.002	0.203	1.001	0.999-1.003
PLR	0.988	1.00	1.00-1.00	0.877	1.00	1.00-1.00
CRP/Alb.	0.067	1.020	0.999-1.042	0.133	1.017	0.995-1.040
HRR	0.013	0.605	0.406-0.901	0.019	0.624	0.421-0.925

CRP: C-reactive protein, HRR: Hemoglobin/ Red cell distribution width ratio, LCR: lymphocyte/CRP ratio, NLR: neutrophil/ lymphocyte ratio PLR: Platelet/ lymphocyte ratio

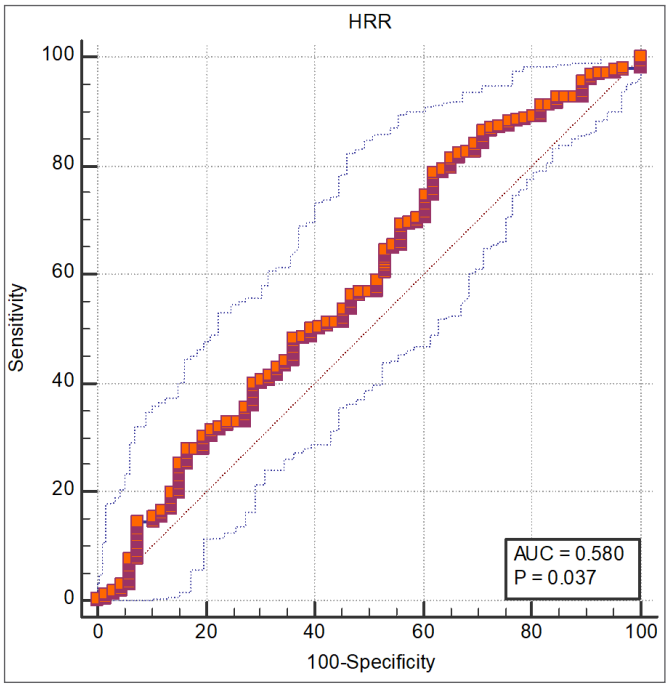


Figure 1: HRR ROC analysis graph

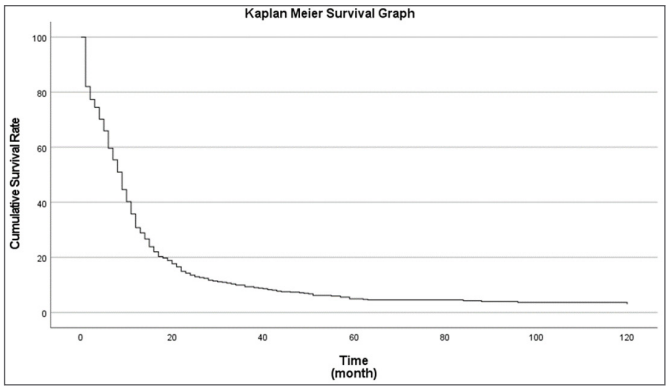


Figure 2: The effect of HRR on OS (Each one-unit increase in HRR reduces mortality by 1.6-fold)

In our study, there was a statistically significant difference between limited and extensive disease in terms of OS (12 /6 months) and PS (10/6 months) (p<0.001), in parallel with the studies performed so far. On the other hand, when laboratory parameters were examined between limited and extensive stages, while there was no difference was found for HRR, but statistically, a significant difference was found for PCR, NLR, and CRP/Alb between the two groups (**Table 3**).

Table 3: Determination of Factors Predicting Progression and Mortality

	AUC	p	Cut-off value	Sensitivity	Specificity
LCR	0.515	0.718	>0.09	83.09	30.77
NLR	0.633	<0.001	>2.93	63.90	63.64
Platelet/Alb.	0.688	<0.001	>39.77	72.08	60.61
PLR	0.581	0.021	>190	34.63	80.30
CRP/Alb.	0.570	0.078	>0.149	77.66	39.39
HRR	0.580	71	<1.08	78.73	37.88

CRP: C-reactive protein, HRR: Hemoglobin/ Red cell distribution width ratio, LCR: lymphocyte/CRP ratio, NLR: neutrophil/ lymphocyte ratio PLR: Platelet/ lymphocyte ratio

DISCUSSION

While the prognosis of patients with non-small cell lung cancer (NSCLC) has greatly improved with recent advances in molecular biology techniques and the advent of targeted drugs and immunotherapy, the survival of patients with SCLC has not changed due to the lack of both new treatment regimens and simple-effective prognostic factors to assess the prognosis. Therefore, it is essential to find new and effective prognostic indicators to improve the prognosis of patients with SCLC. Studies have confirmed that HRR is associated with the prognosis of patients with esophageal (17), head and neck tumors (18), and NSCLC (19), whereas the number of studies on patients with SCLC is very few (20).

Although there are studies showing the prognostic values of RDW and hemoglobin separately in patients with lung cancer, studies showing the prognostic effect of HRR on lung cancer are limited. In the first study conducted with HRR by Sun et al. (17) in 362 patients receiving curative treatment for esophageal cancer, hemoglobin and RDW alone were not found to be significant in terms of survival, while HRR was found to be predictive for overall survival. Bozyaka et al. (19) reported that low HRR value may be an independent predictor factor of overall survival in their study consisting of 153 patients with advanced NSCLC. In another study by Petrella et al. (14) 349 patients with a diagnosis of lung adenocarcinoma who were undergone operation were included in the study. It has been reported that the preoperative HRR value is an effective prognostic factor together with pathological lymph node involvement for disease-free survival in resected patients.

The first study by Wu et al. (20), showing the prognostic importance of HRR in SCLC, was conducted with a total of 146 patients, and the cut-off value for HRR was found to be 0.985. OS was determined as 9 and 17.5 months in the low and high HRR groups, respectively, and PS as 5 and 8.5 months, respectively. Univariate and multivariate analyzes determined that low HRR was an independent predictor of poor prognosis for OS. In our study, the prognostic significance of HRR in SCLC patients was evaluated. Our study was conducted with a larger number of patients (840 patients). OS of the patients was found to be 9 months and PS was found to be 7 months. When the patients were examined according to the determined cut-off value (<1.08), it was found that each one-unit increase in HRR reduced mortality by 1.6-fold, and each one-unit increase in HRR reduced progression by 1.62-fold.

There are studies on NLR and PLR as markers that can be used as prognostic factors in lung cancer (5, 21). However, in our study NLR and PLR values were not statistically significant in relation to OS and PS in SCLC patients.

HRR is a very easy, repeatable and inexpensive test if chronic inflammatory diseases and autoimmune diseases can be excluded. In our opinion, the fact that patients with these diagnoses were not included in our study conducted by screening a very large patient population (1039 patients) increases the importance of our study. While a large number of patients is the other strength of our study, however, there are a few limitations. First, it is a single-center retrospective study, and second, there is no standard cut-off value that can be compared in the literature.

CONCLUSION

Our study shows that HRR value is a prognostic factor and may be predicted survival in SCLC patients. However, prospective studies are needed to show the relationship of HRR with OS and PS as independent factors, considering all the factors affecting the HRR value.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences, Ankara Atatürk Sanatoryum Training and Research Hospital Clinical Researches Ethics Committee (Date: 22.02.2023, Decision No: 2661).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Spigel DR, Socinski MA. Rationale for chemotherapy, immunotherapy, and checkpoint blockade in SCLC: Beyond traditional treatment approaches. J Thorac Oncol 2013; 8: 587–98.
2. Sundstrom S, Bremnes RM, Kaasa S, Aasebo U, Aamdal S. Second-line chemotherapy in recurrent small cell lung cancer. Results from a crossover schedule after primary treatment with cisplatin and etoposide (EP-regimen) or cyclophosphamide, epirubicin, and vincristin (CEV-regimen). Lung Cancer 2005; 48: 251–61.
3. Zhou T, Zhao Y, Zhao S. Comparison of the prognostic value of systemic inflammation response markers in small cell lung cancer patients. J Cancer 2019; 10: 1685–92.

4. Kang EJ, Lee SY, Kim HJ. Prognostic factors and skeletal-related events in patients with small cell lung cancer with bone metastases at the time of diagnosis. Oncology 2016; 90: 103-11.
5. Bremnes RM, Sundstrom S, Aasebo U, Kaasa S, Hatlevoll R, Aamdal S. The value of prognostic factors in small cell lung cancer: Results from a randomised multicenter study with minimum 5 year follow-up. Lung Cancer 2003; 39: 303–13.
6. Zalcman G, Tredaniel J, Schlichtholz B. Prognostic significance of serum p53 antibodies in patients with limited-stage small cell lung cancer. Int J Cancer 2000; 89: 81–6.
7. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. Cancer 2001; 91: 2214-21.
8. Riedl J, Posch F, Königsbrügge O, et al. Red cell distribution width and other red blood cell parameters in patients with cancer: association with risk of venous thromboembolism and mortality. PLoS ONE 2014; 9: 111440.
9. Ellingsen TS, Lappegård J, Skjelbakken T, Brækkan SK, Hansen JB. Impact of red cell distribution width on future risk of cancer and all-cause mortality among cancer patients-The Tromsø Study. Haematologica 2015; 100: 387–9.
10. Ichinose J, Murakawa T, Kawashima M. Prognostic significance of red cell distribution width in elderly patients undergoing resection for non-small cell lung cancer. J Thorac Dis 2016; 8: 3658–66.
11. Seretis C, Seretis F, Lagoudianakis E, Gemenetzis G. Salemis NS. Is red cell distribution width a novel biomarker of breast cancer activity? Data from a pilot study. J Clin Med Res 2013; 5: 121–6.
12. Chen GP, Huang Y, Yang X, Feng JF. A nomogram to predict prognostic value of red cell distribution width in patients with esophageal cancer. Mediators Inflamm 2015; 2015: 854670.
13. Wang FM, Xu G, Zhang Y, Ma LL. Red cell distribution width is associated with presence, stage, and grade in patients with renal cell carcinoma. Dis Markers 2014; 2014: 860419.
14. Petrella F, Casiraghi M, Radice D, et al. Prognostic value of the hemoglobin/red cell distribution width ratio in resected lung adenocarcinoma. Cancers 2021; 13: 710.
15. Wu F, Yang S, Tang X, Liu W, Chen H, Gao H. Prognostic value of baseline hemoglobin-to-red blood cell distribution width ratio in small cell lung cancer: a retrospective analysis. Thorac Cancer 2020; 11: 888–97.
16. Goldstraw P, Chansky K, Crowley J. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. J Thorac Oncol 2016; 11: 39–51.
17. Sun P, Zhang F, Chen C. The ratio of hemoglobin to red cell distribution width as a novel prognostic parameter in esophageal squamous cell carcinoma: a retrospective study from southern China. Oncotarget 2016; 7: 42650–60.
18. Tham T, Olson C, Wotman M. Evaluation of the prognostic utility of the hemoglobin-to-red cell distribution width ratio in head and neck cancer. Eur Arch Otorhinolaryngol 2018; 275: 2869–78.
19. Yakup B, Bediz K, Fatih G. A prognostic parameter in advanced non-small cell lung cancer: the ratio of hemoglobin-to-red cell distribution width. Int J Clin Oncol 2019; 24: 798-806.
20. Wu F, Yang S, Tang X, Liu W, Chen H, Gao H. Prognostic value of baseline hemoglobin-to-red blood cell distribution width ratio in small cell lung cancer: a retrospective analysis. Thorac Cancer 2020; 11: 888–97.
21. Petrella F, Casiraghi M, Radice D, et al. Prognostic value of the hemoglobin/red cell distribution width ratio in resected lung adenocarcinoma. Cancers 2021; 13: 710.
22. Suzuki R, Wei X, Allen PK, Cox JD, Komaki R, Lin SH. Prognostic significance of total lymphocyte count, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio in limited-stage small-cell lung cancer. Clin Lung Cancer 2019; 20: 117–23.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1242763

Anatolian Curr Med J 2023; 5(2); 153-159

New determinants for causal neural mechanism of dry mouth in Parkinson's disease induced by destruction of superior salivatory nucleus, facial nerve, and submandibular gland circuitry: an experimental study

Mete Zeynal

Department of Neurosurgery, Faculty of Medicine, Atatürk University, Erzurum, Turkey

Cite this article as: Zeynal M. New determinants for causal neural mechanism of dry mouth in Parkinson's disease induced by destruction of superior salivatory nucleus, facial nerve, and submandibular gland circuitry: an experimental study. Anatolian Curr Med J 2023; 5(2); 153-159.

ABSTRACT

Aim: Dry mouth has been considered a clinical finding of Parkinson's disease (PD), but we think otherwise. We studied if the olfactory bulbectomy (OBX) might rely on the superior salivatory nucleus (SSN), submandibular ganglia (SMGn), and submandibular glands (SLGl) circuity disruption induced submandibular gland degeneration related dry mouth in rats.

Material and Method: This study was carried out on twenty-six male rats. Five (GI-n=5), six (GII, n=6), and sixteen (GIII, n=15) of them were used as control, SHAM, and OBX groups, respectively, and followed eight weeks. PD-related clinical examinations were done before and after the experiment (1/day), and animals were decapitated. The olfactory bulb volumes (mm^3), degenerated neuron densities of SSN/SMG (n/mm^3 and SMGl follicles volumes were detected serologically. Olfactory bulb volume values and degenerated neuron density values of SSN/SMGn/SMGl follicles volumes were compared statistically.

Results: OBX-applied animals showed anosmia, tremors, rigidity, and memory loss. The mean olfactory bulb volumes (mm^3), degenerated neuron density of SSN (n/mm^3), SMGn (n/mm^3), and follicles volumes of SMGl (cubic micrometer/mm^3) were measured in the order written as; (4.27±0.21), (4±1), (5±2), (81.23±13.34).106 in GI; (3.67±0.33), (14±3), (17±4), (72.45±11.78).106 in GII and (2.91±0.14), (23±5), (29±8), (57.19±11.93).106 in Group III. The mean P values between olfactory bulb volumes, degenerated neuron densities of SSN and SMGn, and salivary follicles volumes were: $p<0.005$ in GI/GII; $p<0.0005$ in GII/GIII; $p<0.0001$ in GI/GIII.

Conclusion: OBX-related olfactory network designalisation may be responsible for SSN/SMGn circuitry degeneration-induced SMGl atrophy-based dry mouth. The OBX-related dry mouth should be considered a causative factor for Parkinson's disease, not a result.

Keywords: Olfactory bulbectomy, salivatory nucleus, submandibular ganglion, facial nerve, salivary gland

INTRODUCTION

Anosmia and ageusia are the most common and frequent nonmotor features of Parkinson's disease (PD) (1). Olfactory involvement usually occurs together with parasympathetic dysautonomia (2). Psychiatric disorders and cognitive problems are also common manifestations (3). The olfactory impulses augment appetite, salivation, and food intake (4). Taste and smell loss decreases salivary secretions (5). The saliva is required for swallowing and digestion. Pavlov reported that classic conditioning could also secrete saliva (6). There is an important relationship between smell, taste, and salivary secretion. Smell disorders cause decreased salivary secretions (7). The odor augments appetite, salivation, and food intake (4). Taste and smell loss decrease in parotid salivary functions (5). The facial nerve modulates parasympathetic innervation of the salivary, lacrimal, and paranasal-oral mucosal glands via postganglionic parasympathetic fibers of the pterygopalatine ganglion (8). Dry mouth, difficulty in slowing, and digestive disorders are troublesome components of PD. Because PD is accompanied by amyloid degeneration of the salivary secretion starting facial, glossopharyngeal, and vagal salivatory nuclei, sympathetic ganglia, and myenteric plexus (8). Facial nerve lesions lead to decreased salivary secretion (9). It has been reported that damage to the olfactory pathways causes the same neuropathological changes in neural nuclei and circuits that are frequent PD (10). If so, dry mouth caused by superior salivary nucleus-

Corresponding Author: Mete Zeynal, dr.metezeynal@gmail.com

Received: 26.01.2023 **Accepted:** 20.03.2023

facial nerve-submandibular gland circuitry disruption induced by olfactory signal loss should be considered the cause of Parkinson's disease, not as a causative agent for Parkinson's disease.

MATERIAL AND METHOD

The study was carried out with the permission of permission of Atatürk University, Faculty of Medicine, Ethics Committee for Animal Experiments (Date: 09.11.2022, Decision No: E-42190979-000-2200225459). All procedures were carried out under ethical rules and principles.

26 Wistar Albino male rats were included in this study. The test subjects were placed in single stainless steel cages at 21°C and cycles of light and dark with appropriate humidity. A standard feeding was given to test subjects for nutrition.

The subjects were divided into three random groups. For pain control balanced, injectable anesthetics were preferred. Isoflurane was applied by a face mask, 0.2 mL/kg of the combined drugs (Ketamine HCL, 150 mg/1.5 mL; Xylazine HCL, 30 mg/1.5 mL; and distilled water, 1 mL) was administered before the surgical procedures. The study groups were; the control group (Group I, n=5), the SHAM group, and (Group II, n=5). Burr holes were made, and olfactory bulbectomy (OBX) was not applied, and the study group, in which bilaterally OBX was done via a micro clamp (Group III, n=16), and all groups were observed for ten weeks. During the ten weeks, all subjects were observed without any medical treatment. They were seen for noticing their vital findings with ten minutes periods two times a day during the experiment. The test subjects' olfactory functions, appetite status, and weight were recorded. After ten weeks of follow-up, all subjects were decapitated under general anesthesia. The total brain structures of all test subjects were stored in 10% formalin solutions for seven days. After cleaning procedures, all tissue specimens underwent histologic evaluation.

The volumes of olfactory bulbs were measured and recorded macro anatomically. Both olfactory bulbs, brainstem, superior salivatory nucleus (SSN), and SLGl sections were stained with GFAP and hematoxylin-eosin. Olfactory bulbs and superior salivary nuclei sections were stereologically analyzed. With olfactory bulb volume values, degenerated neuron densities of the superior salivary nucleus and submandibular ganglion and follicle volumes of the SLGl were compared.

Histopathological Procedures

The olfactory bulbs were sliced in 5 μm thickness at each 30 μm length. Every 28th and 29th, section were sampled to calculate the volume of olfactory bulbs. The fractioner method studies the total number of olfactory bulb glomerulus. Specimen slices were stained with hematoxylin-eosin (H&E) and GFAP methods and examined under a light microscope. To detect the olfactory nerve lesion, portions were taken parallelly to the long axis of the nerves. The same procedures were performed for the SSN to reveal histology.

Stereological Analysis

Stereological methods have a significant role in the estimation of particle density. Stereological methods determine the number of a particle per unit volume by the integral method. Suppose the point taken as a reference in one of two consecutive parallel sections taken from the tissue to be examined at intervals smaller than the diameter of the particle to be estimated is not present. In that case, it is taken as a disector pair and included in the count.

In our study, sections were cut with measurements corresponding to values below the nucleus diameter of the neuron cells to be examined. The physical dissecting method was used. Therefore, 20 sections of 3 microns passing through the plane of the superior salivator nucleus; 20 sections of 5 microns passing through the plane of the ganglion were taken from the SLGl. The physical dissection method was also performed to determine degenerated neurons in the superior salivary nucleus. In Kolmogorov-Smirnov and Shapiro-Wilk tests, there was no normal distribution in all groups ($p<0.05$). The Mann-Whitney-U test was applied to the separately compared groups for independent samples compared in pairs and then analyzed with the Kruskal-Wallis test. For the p-value used for multiple comparisons by dividing 0.05 by six with Bonferroni regulation, a value of $p\leq 0.0098$ was considered significant. Statistically, the p-value was considered significant at the 0.05 level. (Confidence interval 95%). Since the olfactory bulbs resemble an ellipsoid, the volume values were also estimated by the volume formula of the ellipsoid (10). Follicle volumes of the salivary glands were measured with the method Aydin N et al. used to measure the thyroid gland follicle volumes. Data were analyzed using the method (SPSS® for Windows v. 12.0, Chicago, USA). Data analysis consisted of the Kruskal-Wallis and Mann-Whitney U tests. Differences were considered significant at $p< 0.05$.

RESULTS

Anosmia, finger tremors during food selection, rigidity, and loss of memory were seen in OBX-applied subjects. To evaluate the finger tremor sign, which is the typical finding of PD, the subjects were subjected to tests to determine tight-handedness. Tremors more than six times per minute were found to be significant. Histopathological

evaluation of the specimens was demonstrated in **Figures 1-5**. OOBX-applied animals showed anosmia, tremors, rigidity, and memory loss. The mean olfactory bulb volumes (mm³), degenerated neuron density of SSN (n/mm³), SMGn (n/mm³), and follicles volumes of SMGl (cubic micrometer/mm³) were measured in the order written as; (4.27±0.21), (4±1), (5±2), (81.23±13.34).106 in GI; (3.67±0.33), (14±3), (17±4), (72.45±11.78).106 in GII and (2.91±0.14), (23±5), (29±8), (57.19±11.93).106 in Group III. The mean P values between olfactory bulb volumes, degenerated neuron densities of SSN and SMGn, and salivary follicles volumes were: $p<0.005$ in GI/GII; $p<0.0005$ in GII/GIII; $p<0.0001$ in GI/GIII.

In macroscopic evaluation decrease in olfactory bulb volume, obstruction of the ethmoid foramen, thickening and adhesions in the dura and arachnoid membranes inflammatory changes in the subfrontal area was seen. Histopathologically degeneration in glomerules of olfactory bulbs, decrease in glial cell density and interneuronal connections, and inflammatory changes in olfactory bulbs were evaluated. Inflammation, adhesions, thickening in dural structures, and ischemic pathologies were observed. In the analysis of salivatory nuclei, neuronal degeneration such as cytoplasmic and nuclear condensation, pericytoplasmic halo formation, dendritic fragmentation, cellular angulation, and neuronal loss existed. In the control group, minimal, sham mild, study severe changes were observed. Specific findings of the histopathological evaluation were demonstrated in **Figures 1-5**.

In the microscopic analysis of sublingual glands, SSN and sublingual ganglion (SLGn) degenerated neurons were rarely observed in the control group because of postmortal degeneration due to technical reasons. Still, mild degeneration was observed in the SHAM group, and severe degeneration was observed in the study group.

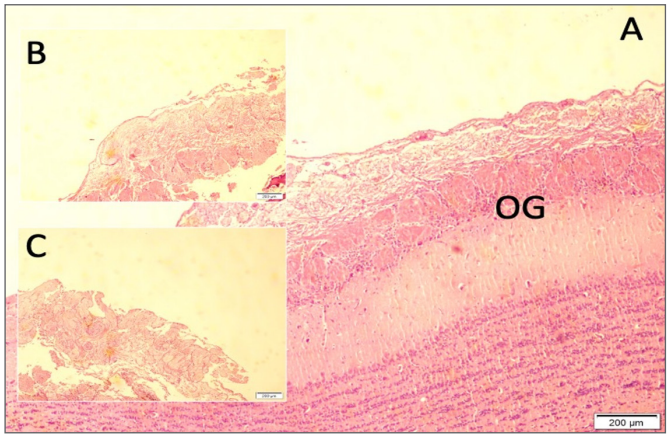


Figure 1. Vertical sections of the olfactory bulb in a normal subject shows the histological structures of the olfactory nerve and the olfactory glomeruli that we examined. A subject from the SHAM group has a partially deformed olfactory bulb (in figure B), and a subject from the study group has a significantly deformed olfactory bulb in figure C (Light Microscope, H&E, 4X magnification/A, B, C).

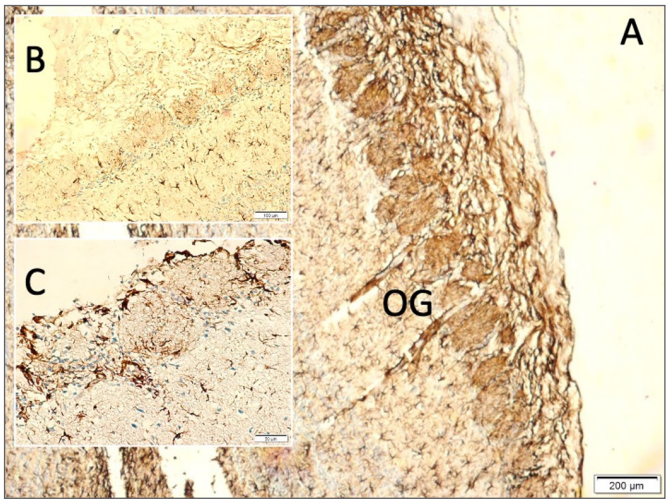


Figure 2. By the immunohistochemical method, Vertical sections of the olfactory bulb in a normal subject show the histological structures of the olfactory nerve and the olfactory glomeruli we examined (in figure-A. A subject from the SHAM group has a partially deformed olfactory bulb in figure B, and a subject from the study group has a significantly deformed olfactory bulb in figure C (LM, GFAP, x4/A, B, C).

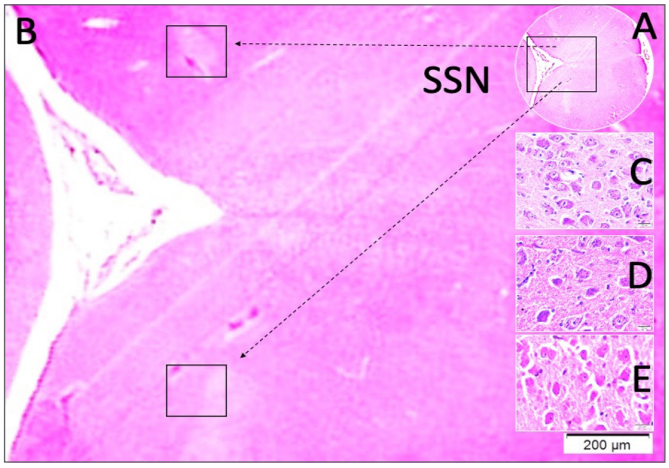


Figure-3. localization of the nucleus salivatory superior (A, B) and normal nucleus neurons (C), moderately degenerated neurons of the SHAM group (D), and highly deformed neurons of the study group are observed in a rat (LM, HE, x4/A; x20/C-E).

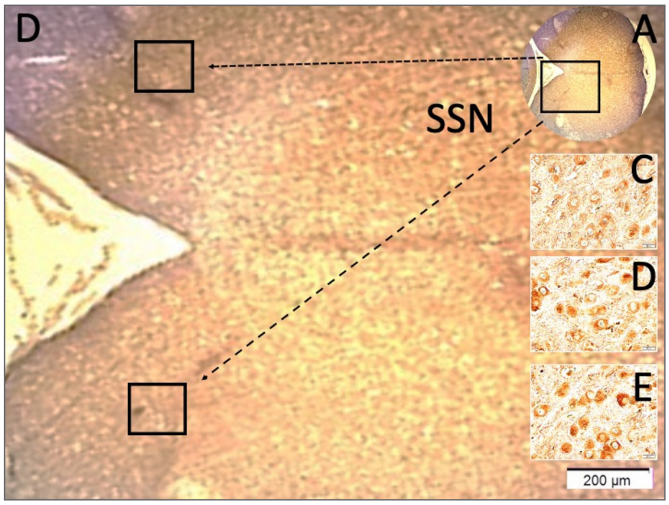
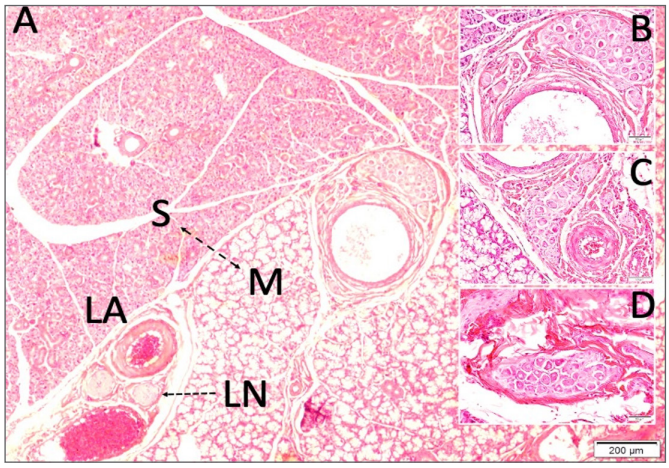


Figure-4. localization of the nucleus salivatory superior (A, B) and normal nucleus neurons (C), mildly degenerated neurons of the SHAM group (D), and highly deformed neurons of the study group are observed in a rat (LM, GFAP, x4/A; x20/C-E).



Fgure-5. In a normal subject, the serous (S) and mucous (M) parts of the submandibular gland, lingual artery branch (LAb), and lingual nerves branch (LNb) are observed. Again, submandibular ganglion in a normal subject; moderately degenerated neurons included SLG in group 2; and high degeneration in neurons included submandibular ganglion belonging to group 3 (LM, H&E, x4/A: x20/BCD).

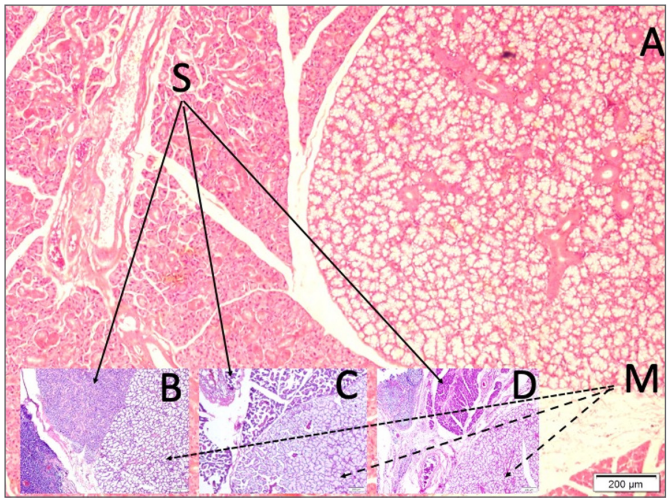


Figure-6. In a normal subject, the serous-mucous parts of a submandibular gland (A-B); moderately degenerated epithelial cells included salivary gland in group 1 (C); and severely high degeneration in epithelial cells included salivary gland submandibular ganglion belonging to group 3 (D)(LM, H&E, x4/A: x20/B, C, D, Serous S, Mucous M)

DISCUSSION

An important anatomical, physiological, and even psychological interaction exists between the senses of smell, taste, and salivary secretion. Smell disorders cause a significant loss in eating habits and quality of life. Changes in odor perception also negatively affect food taste. Olfactory dysfunction dangerously affects taste sensitivity and saliva secretion (7). The odor augments appetite, salivation, and food intake (4). Taste and smell loss decrease parotid salivary functions (5). The secretion of saliva is an important physiological function for swallowing and digestion. Pavlov reported a century ago that saliva in dogs could also be secreted by classical ring-tone conditioning (6). Odor stimuli play an important role in the perception of ingested food flavor. Food-related odors have been shown to induce appetite, salivation, gastric acid, and insulin secretion (11). Olfaction stimulates salivary secretions (12). Olfactory signals start salivary reflexes (13). Olfactory impairment and depression can be seen in the onset of PD motor manifestations (14). Anosmia and ageusia are common nonmotor features of PD (15, 16). Olfactory involvement leads to parasympathetic dysautonomia (2). The amygdala-hippocampal complex is functionally implicated in conditioned olfaction and taste aversion in learning memory and autonomic functions required for food selection, eating, and metabolism (17).

The SSN is the primary parasympathetic center of the submandibular and sublingual salivary glands. Their neurons receive excitatory impulses from facial and glossopharyngeal nerves; inhibitory impulses come from cervical sympathetic (18). The SSN is a part of the reticular formation and is placed between the trigeminal nerve's facial nucleus and spinal nucleus. The salivatory nucleus extends from a level at the facial nucleus's caudal border through the facial nerve's genu (19). The SSN includes neurons that supply the intra-glandular submandibular ganglion. The SSN cells are typical preganglionic autonomic neurons (20). Preganglionic neurons of the SSN receive excitatory inputs from the solitary tract and the central nucleus of the amygdala (21, 22). The SSN innervates the submaxillary and sublingual salivary glands by preganglionic fibers (23). The SSN sends parasympathetic axons to salivary glands (24). The parasympathetic neurons of the SSN controls the parotid and von Ebner salivary glands (25). SSN stimulation causes salivation from sublingual-submandibular glands (26). Stimulation of the chords-lingual nerve evoked saliva secretion from oral glands. Sympathetic nerve stimulation decreased saliva secretion (27).

Facial Nerve - Superior Salivatory Nucleus Relations

The facial nerve includes the motor, sensory and parasympathetic fibers (28). The general visceral motor part gives autonomic parasympathetic innervation to the lacrimal, salivary, and paranasal-oral mucosal glands (29).

When afferent signals from smell, taste, and chewing reach the central nervous system, they initiate salivation from the salivary glands. Fluid salivary secretion generally depends on parasympathetic cholinergic signals, while sympathetic nerves, neuro peptides, and noradrenaline signals salivary secretion. Since the salivary glands have regenerative abilities, The autonomic nerves that innervate them have a role in regeneration, gland development, also maintaining their long-term normal functions. We come across experimental findings that the destruction of the olfactory pathways also negatively affects the sympathetic nervous system.

In previous studies of Aydin et al. SLGl lesions and atrophy was studied in 10 weeks time to establish substanti nigra degeneration. In this study we have studied for 8 weeks time. In this study, we made a more specific examination by also analyzing the superior salivatory nuclei of the facial nerve to investigate the more rational cause of dry mouth. The olfactory bulb sends signals to the superior salivatory nucleus, which is related to the facial nerve, via the olfactory pathways, which sends parasympathetic impulses to the sublingual and submandibular glands, which we focused on in our study, unlike the previous ones. Interruption of the olfactory pathways causes denervation injury in the SSN. This injury also causes denervation injury in sublingual and submandibular glands. Both injuries disrupt secretion production in salivator glands and reveal atrophy, which we analyzed volumetrically, different from other studies.

Olfactory Bulb Lesion Induced Clinico-Histopathological Problems Mimic Parkinson's Disease

Odor stimuli play a major role in the perception of food flavor, appetite, salivation, and release of enzyme and hormone secretion to the metabolism of foods (11). Olfactory bulb lesions lead to substantia nigra degeneration, mammary gland insults, Peyer's patches hyperplasia induced by infections, hypothyroidism, neuropsychiatric disorders, sexual problems, Hirschprung-like disease, and spermatogenesis disorders (10, 30-35). The findings summarized under this title are generally observed in PD. However, the events that caused these findings were recorded as symptoms of PD. According to us, the correct information is that these events started PD. Since the regeneration capacity of olfactory nerves and glands is present, we also observed that the secretory activities returned in some subjects.

Brain Stimulation and Olfaction Relations in Parkinson's Disease

Deep brain stimulation is an effective treatment method to improve motor and olfactory function and odor identification (36, 37). Deep brain stimulation of the subthalamic nucleus may also improve olfaction and constipation (38). Subthalamic and pallidal deep brain stimulation improves the quality of life, motor, and nonmotor (39). Reversible improvement occurs in olfactory dysfunction after subthalamic nucleus stimulation (40). Chronic high-frequency stimulation of the subthalamic nucleus induces neurogenesis in the hippocampus and olfactory bulb and ameliorates mood disorders and olfaction deficits (41). Neuroregeneration occurring in olfactory bulbs can improve the course of alarming findings.

Deep Brain Stimulation and Salivation

Deep brain stimulation ameliorates gastrointestinal dysfunctions (42). Subthalamic nucleus deep brain stimulation is an important option for treating eating, sweating, absorption, metabolism, and excretion disorders (43). Deep brain stimulation also modulates oropharyngeal swallowing process arising from olfactory disorders. We continue to work on how noninvasive olfactory stimulation can be more beneficial than a breakthrough.

Limitation: This study only includes experimental results.

CONCLUSION

OBX-related olfactory network designalisation may be responsible for SSN degeneration, and related dry mouth is the first symptom of PD. Facial nerve pathologies may cause dry mouth. If so, olfactory signal loss induced superior salivatory nucleus-facial nerve-salivary gland circuitry disruption may lead to dry mouth and ageusia, which has not been mentioned in the literature so far. Energy failure due to neurodegeneration in the SSN may be responsible for dry mouth in Parkinson's disease.

Future Insights: This method, which has been examined in the pathology of Parkinson's, may also open up horizons for these mechanisms in treatment. We can predict from our studies that noninvasive olfactory nerve, facial nerve, glossopharyngeal nerve, and trigeminal nerve stimulations can be used in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of permission of Atatürk University, Faculty of Medicine, Ethics Committee for Animal Experiments (Date: 09.11.2022, Decision No: E-42190979-000-2200225459).

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgement: Prof. Dr. Mehmet Dumlu Aydın & Doç. Dr. Sevilay Özmen

REFERENCES

1. Tarakad A, Jankovic J. Anosmia and ageusia in Parkinson's disease. Int Rev Neurobiol 2017; 133: 541-56.
2. Kang P, Kloke J, Jain S. Olfactory dysfunction and parasympathetic dysautonomia in Parkinson's disease. Clin Auton Res 2012; 22: 161-6.
3. Morley JF, Weintraub D, Mamikonyan E, Moberg PJ, Siderowf AD, Duda JE. Olfactory dysfunction is associated with neuropsychiatric manifestations in Parkinson's disease. Mov Disord 2011; 26: 2051-7.
4. Proserpio C, de Graaf C, Laureati M, Pagliarini E, Boesveldt S. Impact of ambient odors on food intake, saliva production and appetite ratings. Physiol Behav 2017; 174: 35-41.
5. Henkin RI, Velicu I. Decreased parotid salivary cyclic nucleotides related to smell loss severity in patients with taste and smell dysfunction. Metabolism 2009; 58: 1717-23.
6. Watanabe H, Mizunami M. Pavlov's cockroach: classical conditioning of salivation in an insect. PLoS One 2007; 2: e529.
7. Zang Y, Han P, Burghardt S, Knaapila A, Schriever V, Hummel T. Influence of olfactory dysfunction on the perception of food. Eur Arch Otorhinolaryngol 2019; 276: 2811-7.
8. Dickson DW. Parkinson's disease and parkinsonism: neuropathology. Cold Spring Harb Perspect Med. 2012; 2(8).
9. Paşahan R, Yardım A, Karadağ MK, Alpaslan A, Aydın MD. Dry mouth caused by facial nerve ischemia due to subarachnoid hemorrhage: an experimental study. World Neurosurg 2021; 154: e488-e94.
10. Aydin MD, Kanat A, Hacimuftuoglu A, Ozmen S, Ahiskalioglu A, Kocak MN. A new experimental evidence that olfactory bulb lesion may be a causative factor for substantia nigra degeneration; preliminary study. Int J Neurosci 2021; 131: 220-7.
11. Yeomans MR. Olfactory influences on appetite and satiety in humans. Physiol Behav. 2006; 87: 800-4.
12. Lee VM, Linden RW. An olfactory-submandibular salivary reflex in humans. Exp Physiol 1992; 77: 221-4.
13. Lee VM, Linden RW. An olfactory-parotid salivary reflex in humans? Exp Physiol 1991; 76: 347-55.
14. Savica R, Rocca WA, Ahlskog JE. When does Parkinson disease start? Arch Neurol 2010; 67: 798-801.
15. Alvarez MV, Grogan PM. Hyposmia in Parkinson's disease. Psychiatry Clin Neurosci 2012; 66: 370.
16. Suchowersky O. Non-motor symptoms and parkinsonism. Can J Neurol Sci 2013; 40: 1-2.
17. Lasiter PS, Deems DA, Glanzman DL. Thalamocortical relations in taste aversion learning: I. Involvement of gustatory thalamocortical projections in taste aversion learning. Behav Neurosci 1985; 99: 454-76.
18. Mitoh Y, Funahashi M, Fujii A, Fujita M, Kobashi M, Matsuo R. Development of inhibitory synaptic transmission to the superior salivatory nucleus in rats. Brain Res 2008; 1191: 47-54.
19. Nicholson JE, Severin CM. The superior and inferior salivatory nuclei in the rat. Neurosci Lett 1981; 21: 149-54.
20. Ng YK, Wong WC, Ling EA. A light and electron microscopical localisation of the superior salivatory nucleus of the rat. J Hirnforsch 1994; 35: 39-48.
21. Li C, Fitzgerald ME, Del Mar N, Reiner A. Disinhibition of neurons of the nucleus of solitary tract that project to the superior salivatory nucleus causes choroidal vasodilation: Implications for mechanisms underlying choroidal baroregulation. Neurosci Lett 2016; 633: 106-11.
22. Takeuchi Y, Fukui Y, Ichiyama M, Miyoshi S, Nishimura Y. Direct amygdaloid projections to the superior salivatory nucleus: a light and electron microscopic study in the cat. Brain Res Bull 1991; 27: 85-92.
23. Way JS. Evidence for the site of the superior salivatory nucleus in the guinea pig: a retrograde HRP study. Anat Rec 1981; 201: 119-26.
24. Matsuo R, Yamamoto T, Kawamura Y. Morphological and functional evaluation of the superior salivatory nucleus in rabbits. Exp Neurol 1980; 68: 147-57.
25. Fukami H, Bradley RM. Biophysical and morphological properties of parasympathetic neurons controlling rats' parotid and von Ebner salivary glands. J Neurophysiol. 2005; 93: 678-86.
26. Eisenman JS. Response of rat superior salivatory units to chorda tympani stimulation. Brain Res Bull. 1983; 10: 811-5.
27. Templeton D, Thulin A. Secretory, motor and vascular effects in the sublingual gland of the rat caused by autonomic nerve stimulation. Q J Exp Physiol Cogn Med Sci 1978; 63: 59-66.
28. Ramos JMJ, Castillo ME, Puerto A. Relationship between prandial drinking behavior and supersensitivity of salivary glands after superior salivatory nucleus lesions in rats. Physiol Behav 2020; 224: 113022.
29. Kim M, Chiego DJ, Jr., Bradley RM. Morphology of parasympathetic neurons innervating rat lingual salivary glands. Auton Neurosci 2004; 111: 27-36.
30. Karadeniz E, Kocak MN, Ahiskalioglu A, et al. Exploring of the unpredicted effects of olfactory network injuries on mammary gland degeneration: a preliminary experimental study. J Invest Surg 2019; 32: 624-31.
31. Firinci B, Caglar O, Karadeniz E, Ahiskalioglu A, Demirci T, Aydin MD. Mysterious effects of olfactory pathway lesions on intestinal immunodeficiency targeting Peyer's patches: The first experimental study. Med Hypotheses 2019; 125: 31-6.
32. Aydin N, Ramazanoglu L, Onen MR, et al. Rationalization of the irrational neuropathologic basis of hypothyroidism-olfaction disorders paradox: experimental study. World Neurosurg 2017; 107: 400-8.
33. Oral E, Aydin MD, Aydin N, et al. How olfaction disorders can cause depression? The role of habenular degeneration. Neuroscience 2013; 240: 63-9.
34. Caglar O, Firinci B, Aydin MD, et al. Disruption of the network between Onuf's nucleus and myenteric ganglia, and developing Hirschsprung-like disease following spinal subarachnoid haemorrhage: an experimental study. Int J Neurosci. 2019; 129: 1076-84.
35. Caglar O, Firinci B, Aydin ME, et al. First emerging evidence of the relationship between Onuf's nucleus degeneration and reduced sperm number following spinal subarachnoid haemorrhage: Experimental study. Andrologia 2021; 53: e14030.
36. Saatçi Ö, Yılmaz NH, Zırh A, Yulug B. The therapeutic effect of deep brain stimulation on olfactory functions and clinical scores in Parkinson's disease. J Clin Neurosci. 2019; 68: 55-61.
37. Cury RG, Carvalho MJ, Lasteros FJL, et al. Effects of subthalamic stimulation on olfactory function in Parkinson disease. World Neurosurg 2018; 114: e559-e64.
38. Kola S, Prichard DO, Bharucha AE, Hassan A. A prospective pilot study of the effects of deep brain stimulation on olfaction and constipation in Parkinson's disease. Clin Neurol Neurosurg 2021; 207: 106774.
39. Dafsari HS, Dos Santos Ghilardi MG, Visser-Vandewalle V, et al. Beneficial nonmotor effects of subthalamic and pallidal neurostimulation in Parkinson's disease. Brain Stimul 2020; 13: 1697-705.
40. Fonoff ET, de Oliveira YS, Driollet S, et al. Pet findings in reversible improvement of olfactory dysfunction after STN stimulation in a Parkinson's disease patient. Mov Disord. 2010; 25: 2466-8.

41. Khaindrava V, Salin P, Melon C, Ugrumov M, Kerkerian-Le-Goff L, Daszuta A. High frequency stimulation of the subthalamic nucleus impacts adult neurogenesis in a rat model of Parkinson's disease. Neurobiol Dis 2011; 42: 284-91.
42. Zibetti M, Torre E, Cinquepalmi A, et al. Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. Eur Neurol 2007; 58: 218-23.
43. Yavasoglu NG, Comoglu SS. The effect of subthalamic deep brain stimulation on autonomic dysfunction in Parkinson's disease: clinical and electrophysiological evaluation. Neurol Res. 2021; 43: 894-9.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1257547

Anatolian Curr Med J 2023; 5(2); 160-167

Advanced age; not a contraindiction for resections of colorectal liver metastasis recurrence

Recep Erçin Sönmez

Department of General Surgery, Göztepe Prof. Dr. Süleyman Yalçın City Hospital, İstanbul Medeniyet University, İstanbul, Turkey

Cite this article as: Sönmez RE. Advanced age; not a contraindiction for resections of colorectal liver metastasis recurrence. Anatolian Curr Med J 2023; 5(2); 160-167.

ABSTRACT

Aim: The influence of advanced age on the outcome of repeat resections performed for colorectal liver metastasis (CLM) is ill-defined. We aimed to evaluate the safety and efficacy of repeat resections performed for the recurrence of CLMs in younger (≤70 years) and elderly patients (70< years), and to define predictive factors of survival.

Material and Method: A prospectively maintained database of a single center including 291 CLM patients between 1998 and 2019 was analyzed retrospectively. Short and long-term outcomes were compared among younger (n=99, 34%) and elderly (n=192, 66%) patient groups who were treated by repeat resections for CLM recurrence.

Results: Although statistically not significant, analysis of different age groups (≤70, 70-75, 75-80, and 80< years) have given similar results in terms of 1, 3, and 5-year survival (p=0.143). Globally curative resection was validated as a determinant factor in the estimation of survival following resections performed for recurrences according to multivariate analysis (p<0.05).

Conclusion: Repeat resections for the recurrence of CLMs in selected elderly patients are reliable with regards to similar survival outcomes achieved compared to their younger counterparts.

Keywords: Colorectal liver metastasis (CLM), liver recurrence, resection, elderly patients

INTRODUCTION

Colorectal cancer (CC) stands for the third most common cancer worldwide and the liver is the most common site of distant organ metastasis with an approximate rate of 35-58% (1-3). Surgery with curative intent is the best treatment option with an average 25-58% rate of 5-year survival (4-6).

Around 60% of the patients experience liver recurrences despite previously done curative-intent resections. Five-year survival rates following resections performed for liver recurrences are 21-88% (7-10). Improvements in treatment methods and growing experience have enabled surgeons to be more confident while performing surgery, and thus have encouraged to perform multiple resections.

Advanced age is one of the main concerns in deciding to perform liver surgery due to the increased risk of certain perioperative complications (11). This becomes more complicated when it is a redo surgery since re-resections are technically more challenging due to the adhesions of the previous surgery, and the liver is prone to bleeding due to increased fragility. Therefore, the management of repeat liver resections in elderly patients demands extra effort and attention to provide certain benefit.

We aimed to analyze and compare short and long-term outcomes following repeat liver resections among younger (≤70 years) and elderly (70< years) patients. The secondary end-point was to define predictive factors of survival after recurrence.

MATERIAL AND METHOD

The study was carried out with the permission of Istanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Researches Ethics Committee (Date: 22.02.2023, Decision No: 2023/0124). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Consecutive patients who were treated at 'Centre Hépato-Biliaire, Paul Brousse Hospital, Villejuif, France,' between 1998 and 2019 were investigated. Relevant ones with a history of resection due to the recurrence of CLM were considered for further analysis. The patients who were managed non-surgically (Transarterial Embolization (TAE), Transarterial Chemoembolization (TACE), Radiofrequency Ablation (RFA), Microwave Ablation

Corresponding Author: Recep Erçin Sönmez, sonmezercin@gmail.com

Received: 28.02.2023 **Accepted:** 22.03.2023

(MWA), SIRT (Selective internal radiation therapy)) or resected by Two-stage Hepatectomy (TSH) or ALLPS (Associated Liver Partition Portal Vein Ligation and Staged-Hepatectomy) were excluded.

Short and long-term outcomes of younger and elderly patients were compared with each other in terms of clinical characteristics, operative, and histopathological features, disease-free (DFS), and overall survival (OS). Different aged groups (≤70, 70-75, 75-80, and 80<years) were compared with each other in terms of 1, 3, and 5-year OS. Obtained results were analyzed to define predictive factors of survival after recurrence.

The terminology used to define the extent of resections was selected according to 'Brisbane Guidelines 2000'. Liver resections that were classified as 'major' represented those with equal to or more than three segments, and the 'limited' resections stated the ones less than three segments.

Preoperative Evaluation and Patient Selection

Included patients were selected from those that were under routine follow-up after initial resections performed for CLM. Detailed evaluations (Abdominopelvic ultrasound (US), computerized tomography (CT), magnetic resonance imagining (MRI), and positron emission tomography (PET) scans, measurement of tumor markers (CEA (Carcinoembryonic antigen) and CA 19-9)) revealed the ones with intra and extra-hepatic recurrences, and also ensured to choose the ones that were feasible for repeat resections.

Those who were considered for surgery were preoperatively evaluated in detail during multi-disciplinary meetings counting in the technically demanding nature of resections because of possible adhesions, increased fragility of the liver due to previous chemotherapy and surgery, advanced age, and associated co-morbidities.

Response to neoadjuvant therapy was determined by CEA levels, radiological assessments on control scans, and histopathological evaluations according to tumor regression grade (TRG) (12). Responses were graded according to a scoring scale between '0' and '5', which the minimum grade ('0') defining the term 'non-assessable, and with an increasing rate of response as the maximum grade ('5') representing the complete response to treatment.

The ones with estimated insufficient future liver remnant (less than 30-40% postoperative remnant liver volume), extra-hepatic site involvement that would not be amenable for curative-intent resection, major vascular proximity, multi nodularity, and large tumor size were treated by preoperative chemotherapy.

Operational Characteristics

Whole abdominal exploration was performed routinely to look for extra-hepatic disease. Afterward, a bi-manual examination and US evaluation of the liver were performed accordingly. Different types of resections (Anatomic or non-anatomic) were selected to achieve complete tumor removal. Patients that would not have sufficient postoperative liver volume were treated with PVE (Portal vein embolization) before the operation to achieve adequate liver hypertrophy. Choice of vascular occlusions (None, selective, total, exclusion) was taken according to the type of resections. Ultrasonic dissectors, intra-operative US, argon beam, and bipolar forceps were used to facilitate the parenchymal dissections as much as possible.

Postoperative Follow-up and O

Postoperative follow-up was accomplished by physical examination, measurement of tumor markers (CEA, CA 19-9), the hepatobiliary US at 1st and every 4 months consecutively; and chest, and abdominal CT scans were performed every 8 months. Postoperative follow-up findings were evaluated based on the type and frequency of complications, and survival outcomes. The severity of complications was assessed according to the 'Dindo-Clavien classification (13).

Study end-points

The primary end-point was to assess repeat liver resections in elderly patients in terms of clinical outcomes when compared to the younger patients. The secondary end-point was to search for clinically relevant parameters, if any, estimating survival outcomes.

Statistical Analysis

The clinical characteristics of the research sample were compared using the x2 tests. For examining the survival probabilities of the patients, the log-rank test of the Kaplan-Meier method was used and compared according to variable factors. Lastly, a univariate analysis was performed among the research sample to identify independent prognostic factors of survival. In the context of research, $p \leq 0.05$ was considered statistically significant. Multivariate analysis was performed to define independent predictive factors of survival for factors with $p \leq 0.1$ in univariate analysis. Statistical analysis of the research was performed using SPSS® version 25.0 (IBM, Armonk, New York, USA).

RESULTS

Between 1998 and 2019, 443 patients were diagnosed with liver recurrence of CLM. Those with history of resection (n=291 (65.7%)) were included in the study, 152 (34.3%) ((n=141; not found eligible for surgery due to the advanced disease or the comorbid conditions) (n=11; missing data)) were excluded from further analysis (**Figure 1**).

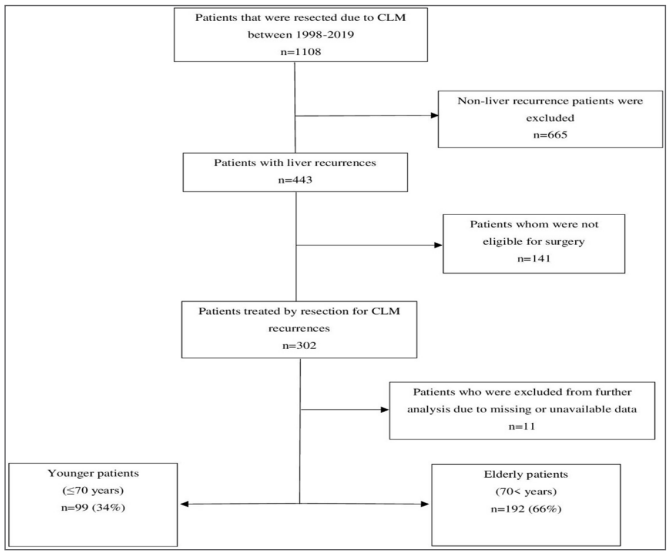


Figure 1. Flow chart

Comparison of Younger and Elderly Groups

The majority of the study population consisted of elderly patients (70< years) (n=192, 66%), and the less were the younger group (≤70 years) (n=99, 34%). The maximum diameter of resected lesions was mostly smaller than 50 mm ((≤70 years; 88.9%) vs (70< years; 83.3%)) (p=0.206). Resections were often limited which involved less than 3 segments for both age groups ((≤70 years; 65.7%) vs (70< years; 66.7%)) (p=0.863). Globally curative resections were achieved substantially in both groups ((≤70 years; 73.7%) vs (70< years; 74%)) (p=0.968). Demonstrations of all clinical characteristics are outlined in **Table 1**.

Of note; younger and elderly patients who were not eligible for resection had no significant differences in terms of tumor characteristics (Tumor size, number, location (lobar/bilobar), extra-hepatic extension), and survival outcomes.

Operative Characteristics

The time interval between initial and secondary resections (performed for recurrence) was longer in elderly patients ((≤70 years; 46.6 months) vs (70< years; 74 months)) (p=0.309). The majority of the patients in both groups were not treated with PVE preoperatively ((≤70 years; 87.9%) vs (70< years; 83.3%)) (p=0.305). Non-anatomic resections were selected more than anatomic and combined (anatomic and non-anatomic simultaneously) resections ((≤70 years; 40.2%) vs (70< years; 39.1%)) (p=0.615). Total pedicular occlusion or intermittent 'Pringle maneuver' was the commonly preferred approach with percentages of 61.6 vs 49.7 for younger and elderly patients in consecutive order (**Table 2**).

Complete necrosis and fibrosis were the dominant histopathological features recorded during microscopic evaluations of resected specimens in both groups (**Table 2**).

Table 1. Comparison of clinical characteristics

	Patients aged ≤70 years (n=99)	Patients aged 70< years (n=192)	P§
Sex			0.256
Male	70 (70.7)	123 (64.1)	
Female	29 (29.3)	69 (35.9)	
Primary tumour			0.723
Colon	75 (75.8)	149 (77.6)	
Rectum	24 (24.2)	43 (22.4)	
Liver metastases at diagnosis			0.191
No. of metastases			
1–3	78 (78.8)	163 (84.9)	
> 3	21 (21.2)	29 (15.1)	
Maximum diameter (mm)			0.206
0–50	88 (88.9)	160 (83.3)	
> 50	11 (11.1)	32 (16.7)	
Location			0.42
Unilateral	43 (43.4)	74 (38.5)	
Bilateral	56 (56.6)	118 (61.5)	
Hepatic resection			0.863
Type of resection			
Limited (< 3 segments)	65 (65.7)	128 (66.7)	
Major (≥ 3 segments)	34 (34.3)	64 (33.3)	
Liver curative resection			0.338
Yes	83 (83.8)	152 (79.2)	
No	16 (16.2)	40 (13.7)	
Globally curative resection			0.968
Yes	73 (73.7)	142 (74.0)	
No	26 (26.3)	50 (26.0)	
Combined treatment modalities to improve resectability			0.349
Yes	14 (14.1)	20 (10.4)	
No	85 (85.9)	172 (89.6)	
Concomitant extrahepatic disease			0.909
Yes	17 (17.2)	34 (17.7)	
No	82 (82.8)	158 (82.3)	
Preoperative chemotherapy			0.484
Yes	68 (68.7)	124 (64.6)	
No	31 (31.3)	68 (35.4)	
Clinical response to last line			0.334
Complete response	5 (10.2)	5 (3.9)	
Partial response	4 (8.2)	15 (11.8)	
Stabilization	13 (26.5)	29 (22.8)	
Disease progression	8 (16.3)	23 (18.1)	
Non-assessable	19 (38.8)	55 (43.3)	
Total no. of cycles			0.081
≤ 6	32 (65.3)	64 (50.4)	
> 6	17 (34.7)	63 ((49.6)	
Postoperative chemotherapy			0.923
Yes	52 (52.5)	102 (53.1)	
No	47 (47.5)	90 (46.9)	

Table 2. Operative and histopathological features

	Patients aged ≤70 years (n=99)	Patients aged 70< years (n=192)	P§
Time interval between operations (months)*	46.6 (189.5)	74 (258.6)	0.309
PVE			0.305
Yes	12 (12.1)	32 (16.7)	
No	87 (87.9)	160 (83.3)	
Type of resection			0.615
Anatomical	19 (20.7)	45 (25.9)	
Non-anatomical	37 (40.2)	68 (39.1)	
Combined	36 (39.1)	61 (35.1)	
Vascular occlusion			0.208
None	14 (19.2)	46 (30.1)	
Selective	6 (8.2)	16 (10.5)	
Total pedicular	45 (61.6)	76 (49.7)	
Vascular exclusion	8 (11)	15 (9.8)	
Intraoperative transfused blood units*	0.6 (1.6)	1.3 (3.5)	0.100
90-day postoperative complications			0.312
Yes	35 (35.4)	61 (31.7)	
No	64 (64.6)	131 (68.3)	
Grade of complications			0.651
0	64 (64.6)	131 (68.3)	
I	3 (3)	2 (1)	
II	16 (16.2)	32 (16.7)	
III	16 (16.2)	26 (13.5)	
IV	0 (0)	1 (0.5)	
Minimal margin of resection	2.7 (5.2)	3.1 (6.5)	0.621
Complete necrosis			0.635
Yes	3 (3)	6 (3.1)	
No	96 (97)	186 (96.9)	
Fibrosis			0.175
Yes	13 (13.1)	17 (8.9)	
No	86 (86.9)	175 (91.1)	
Histology of non tumoral liver			0.363
Normal	19 (28.4)	40 (32)	
Abnormal	48 (71.6)	85 (68)	
Histology of non tumoral liver			0.529
Normal parencymal architecture	52 (60.5)	114 (65.5)	
Congestion	0 (0)	1 (0.6)	
Fibrosis	8 (9.3)	22 (12.6)	
Noduler Hyperlasia	4 (4.7)	3 (1.7)	
Steatosis	18 (20.9)	27 (15.5)	
Other	4 (4.7)	7 (4)	
Last patient status			0.088
Alive	67 (67.6)	110 (57.2)	
Deceased	15 (15.1)	62 (32.2)	
Lost to follow-up	17 (17.1)	20 (10.4)	

Postoperative Morbidity and Mortality

Sixty-four (64.6%) patients in the younger group and 131 (68.3%) in the elderly group didn't have any postoperative complications before discharge. Only 1 (0.5%) patient in the elderly group had grade IV (According to 'Dindo-Clavien classification) complication which was due to liver insufficiency. Postoperative complications were mostly graded II-III in both younger (grade II:16.2% vs grade III:16.2%) and elderly groups (grade II:16.7% vs grade III:13.5%) respectively. Three (3%) patients in the younger group and 2 (1%) in the elderly group had grade I postoperative complications (p=0.651). There was no incidence of mortality recorded for both groups within 90-day postoperative follow-up.

Survival Analysis

Survival analysis of age groups demonstrated similar results for up to 4 years; 73.5%, 73.8%, 73.3%, and 73.3% for those aged ≤70, 70-75, 75-80, and 80< years respectively (p<0.001) (**Figure 2**).

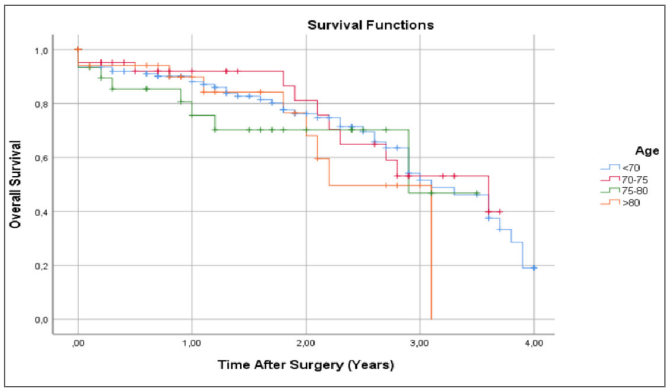


Figure 2. Overall survival according to different age groups (p<0,001 (log rank test))

Predictive Factors of Postoperative Survival

Variances in the origin of tumors according to locations on colon vs rectal didn't show superiority among each other in terms of survival considering 1, 3, and 5-year follow-up (p=0.138) (**Table 3**). The number of liver metastasis had similar impact on survival outcomes among younger and elderly age groups. Differences in tumor diameters (50 mm> vs >50 mm) didn't reach a significant result considering 1, 3, and 5-year survival analysis (p=0.313). Unilobar or bilobar tumoral involvement didn't have an influential role in survival among the study group (**Table 3**). Responses given to chemotherapy have shown marked differences in terms of survival (1, 3, 5-year); such that patients having a complete and partial response to chemotherapy had a clear advantage of survival, particularly for up to 3-year follow-up compared to other groups including stable response, and disease-progression groups (p=0,055).

Table 3. Clinical impact of prognostic factors on 1, 3, and 5-year survival

	No of Patients	1 Year Survival	3 Year Survival	5 Year Survival	P§
Sex					0,223
Male	193	76.9	59.9	40.3	
Female	98	76.4	62.7	48.2	
Age					0.143
<70	185	75	69.5	44.1	
70-75	42	79.3	61.7	37.9	
75-80	30	85	64.3	55	
80<	34	72	60	48	
Primary tumour					0.138
Colon	224	75.3	60.6	51.8	
Rectum	67	78.8	61.5	47.7	
Liver metastases at diagnosis					
No. of metastases					0.212
1–3	241	75.1	61.1	42.4	
> 3	50	81.1	59.5	46.8	
Maximum diameter (mm)					0.313
0–50	248	74.6	60	41.4	
> 50	43	83.8	64.9	40.8	
Location					0.058
Unilateral	117	71.6	54.5	40	
Bilateral	174	79.1	64.9	45	
Hepatic resection					0.108
Type of resection					
Limited (< 3 segments)	193	75.7	61.8	43.9	
Major (≥ 3 segments)	98	77.1	58.6	41.4	
Liver curative resection					0.223
Yes	216	77.5	65.3	48.4	
No	21	80.9	60.3	41.3	
Globally curative resection					0.275
Yes	166	76.0	60.1	43.0	
No	71	80.4	68.2	48.8	
Combined treatment modalities to improve resectability					0.089
Yes	23	79.2	58.3	44.6	
No	257	75.8	61.1	43	
Concomitant extrahepatic disease					0.069
Yes	51	73	56.8	38.6	
No	240	76.8	61.6	34.1	
Preoperative chemotherapy					0.119
Yes	192	74.1	60.1	35.9	
No	99	79.7	62.2	38.4	
Clinical response to last line					0.055
Complete response	10	82.4	66.3	52.2	
Partial response	19	80.1	60.1	49.5	
Stabilization	42	47.1	40.4	34.3	
Disease progression	31	33.3	23.4	20.8	
Non-assessable	74	69.4	53.2	48.1	
Total no. of cycles					0.449
≤ 6	96	65.4	50.6	44.4	
> 6	80	72.9	55.7	51.4	
Postoperative chemotherapy					0.217
Yes	154	83.6	64.7	48.6	
No	137	67.9	56.6	47.2	
Abnormal histology of non-tumoral liver parenchyma					
Steatosis	83	77.6	77.1	60.1	0.287
SOS	24	72.4	60.1	53.5	
CHN	5	64.7	52.3	44.5	
CASH	5	68.4	50.6	42.7	
Normal	167	78.9	73.5	66.1	

Chemotherapy-associated steatohepatitis (CASH), Sinusoidal obstruction syndrome (SOS), Coagulative hemorrhagic necrosis (CHN)

Univariate analysis of independent variables was constituted among different age groups to find out if there can be defined any prognostic or influential factors to estimate postoperative survival. Parameters with p values less than 0.1 on univariate analysis were included in multivariate analysis (**Table 4**). Patients who were not treated by globally curative resections had better 1,3, and 5-year survival patterns on both univariate and multivariate analysis (p=0.031).

Table 4. Univariate and multivariate analysis of prognostic factors for survival after recurrence

	No of Patients	3 Year Survival (%)	UV P§	MV P§
Sex			0,112	-
Male	193	59,9		
Female	98	62,7		
Age			0,108	-
<70	185	69,5		
70-75	42	61,7		
75-80	30	64,3		
80<	34	60		
Primary tumour			0,076	NS
Colon	224	60,6		
Rectum	67	61,5		
Liver metastases at diagnosis			0,233	-
No. of metastases				
1–3	241	61,1		
> 3	50	59,5		
Maximum diameter (mm)			0,086	NS
0–50	248	60		
> 50	43	64,9		
Location			0,072	NS
Unilateral	117	54,5		
Bilateral	174	64,9		
Hepatic resection			0,309	-
Type of resection				
Limited (< 3 segments)	193	61,8		
Major (≥ 3 segments)	98	58,6		
Liver curative resection			0,106	-
Yes	216	65,3		
No	21	60,3		
Globally curative resection			0,072	0,031
Yes	166	60,1		
No	71	68,2		
Combined treatment modalities to improve respectability			0,166	-
Yes	23	58,3		
No	257	61,1		
Concomitant extrahepatic disease			0,057	NS
Yes	51	56,8		
No	240	61,6		
Preoperative chemotherapy			0,107	-
Yes	192	60,1		
No	99	62,2		
Clinical response to last line			0,069	NS
Complete response	10	66,3		
Partial response	19	60,1		
Stabilization	42	40,4		
Disease progression	31	23,4		
Non-assessable	74	53,2		
Total no. of cycles			0,336	-
≤ 6	96	50,6		
> 6	80	55,7		
Postoperative chemotherapy			0,405	-
Yes	154	64,7		
No	137	56,6		
Abnormal histology of non-tumoral liver parenchyma			0,224	-
Steatosis	83	71,1		
SOS	24	60,1		
CHN	5	52,3		
CASH	5	50,6		
Normal	169	73,5		

Chemotherapy-associated steatohepatitis (CASH), Sinusoidal obstruction syndrome (SOS), Coagulative hemorrhagic necrosis (CHN)

Assessment of Chemotherapy-induced Liver Lesions and Clinical Outcomes

The dominant histopathological finding was 'steatosis' in 83 patients, 'sinusoidal obstruction syndrome (SOS)' in 24, 'chemotherapy-associated steatohepatitis (CASH)' in 5, and 'coagulative hemorrhagic necrosis (CHN)' in other 5 respectively. Though statistically non-significant, patients with steatotic liver had superiority among others in terms of survival during 1,3, and 5-year follow-ups. Comparison of chemotherapy-induced liver lesions (CILL) associated with postoperative 90-day morbidity rate has not gained a statistical value. CASH was associated with the lowest OS rates (27,4%) (p=0.005), as patients with CHN had better DFS rates among others (p=0.006). The search for a meaningful association between the number of chemotherapy cycles and resultant effects on liver parenchyma in terms of clinical outcomes didn't end with a significant result (p=0.082).

DISCUSSION

We investigated the clinical outcomes of repeat liver resections for both younger (≤70 years) and elderly (70< years) patients and searched for an upper age limit that would provide non-inferior results in terms of survival compared to the younger patients. The present study demonstrated similar rates of 1,3, and 5-year survival for patients aged ≤70, 70-75, 75-80, and 80< years respectively. Advanced age did not lead to an inferior outcome in terms of survival when surgery was performed for selected patients. Multivariate analysis of several independent parameters revealed the globally curative resections as a significant parameter of survival after recurrence.

The outcome of repeat liver resections is diversely appreciated in the literature. A multi-institutional retrospective study including 170 patients from 20 centers has analyzed repeat resections performed for recurrences of CLM of which 32% of long-term survival was reported in selected patient groups with acceptable rates of morbidity and mortality (14). Ziff et al. (15) presented 32 months of median and 32% 5-year survival for patients with extended repeat liver resections in another study. We have demonstrated similar results for the patient groups constituted by ≤70, 70-75, 75-80, and 80< years of age.

The tumor downstaging after neoadjuvant therapy is a good prognostic factor for the long-term outcome (12). We observed favorable 1,3, and 5-year survival outcomes for those who had complete and/or partial response to neoadjuvant therapies compared to those with stable status or having disease progression. In line with current knowledge, response to neoadjuvant therapy played an influential role in survival for the present study as well. Those being non-responsive or acting in a progressive pattern after neoadjuvant therapy had less favorable outcomes for survival on long-term follow-up.

Some of the chemotherapeutics linked with reversible hepatic parenchymal injury, mentioned as CILLs, are accused of elevating the risk of postoperative morbidity and mortality (16). This clinical entity is commonly divided into two groups according to their histopathological features such as chemotherapy-associated fatty liver diseases (Steatosis and CASH) and sinusoidal injuries (CHN, SOS, and nodular regenerative hyperplasia) (17). Controversy exists in current literature regarding the detrimental role of chemotherapy and associated CILLs over clinical outcomes. Such that, T. Pawlik et al. (18) did not find a clinical association between preoperative chemotherapy and postoperative morbidity and mortality. Whereas, Karoui et al. (19) have demonstrated increased morbidity due to preoperative chemotherapy given to CLM patients. Vauthey et al. (20) have demonstrated an elevated risk of 90-day mortality among CLM patients, particularly for those having steatohepatitis due to oxaliplatin chemotherapy compared to those who didn't have steatohepatitis. We didn't observe any significant clinical association between CILLs and pre-defined independent factors (Diabetes mellitus, BMI, intra-operative blood transfusion) and the total number of chemotherapy cycles given. CASH patients had the least favorable postoperative outcomes among other CILLs, and patients with CHN achieved better DFS rates among other CILLs. An interesting finding was the spontaneous disappearance of most CILLs at secondary resections. Those lesions that appear after chemotherapy may mimic metastatic lesions thus it should be kept in mind to prevent unnecessary struggles and possible interventions (21). A few weeks of the non-chemotherapy interval before surgery most likely will ensure the disappearance of these lesions.

Patients who received surgery combined with adjunct therapies like thermal ablation (RFA, MWA), TACE, TARE, or SIRT had taken similar benefits of 1, 3, and 5-year survival compared to those that were only treated by surgery (p=0.089). Those adjuncts may offer clear advantages such as an increased chance of resectability to achieve R0 resection by decreasing tumor burden before the surgery, also tumor ablative therapies may allow less radical and safe surgeries to be performed (22). Current literature favors surgery over other treatment methods for providing the best survival outcomes (23-25). Alternative therapies should be reserved for unresectable cases that are not eligible for surgery, for palliative purposes, or as a bridging therapy to decrease tumor burden that may have a chance of resection later on in the future.

No clear benefit in terms of survival was stated between unilobar or bilobar involvement of CLM. As in both circumstances, comparable long-term outcomes can be achieved (26,27). In a multicentric ALLPS cohort study published by Petrowsky et al. (28) which included 510 CLM patients from 22 different centers; the size of metastasis and site of involvement (Unilobar vs bilobar) were not found as predictive factors of cancer-specific survival. We achieved close rates of 1, 3, and 5-year survival for patients with unilobar and bilobar involvements consecutively (p=0.058). We may attribute this to successfully performed R0 resections for the majority of the patients independent of unilobar or bilobar involvement. Likewise, we did not observe a significant difference among survival rates for those with different tumor diameters. Complete tumor removal with respect to R0 resection is crucial for optimum survival.

In a similar study from our center, unresectable CLM patients that were given chemotherapy before surgery were compared with upfront resected ones. Even though 38% of the patients that were resected had previously known extra-hepatic site involvements, this demonstrated no clinical impact on survival outcomes (29). Likewise, the presence of concomitant extra-hepatic metastasis didn't have a significant role in the survival rate according to multivariate analysis in our cohort as well.

There was no significant difference in terms of survival between non-anatomic and anatomic liver resections of 288 consecutive patients with CLM recurrences which was previously reported by our team (30). Non-anatomic liver resections offer shorter operative times and less requirement of blood transfusion by leaving more remnant liver volume behind which enables a lower risk of postoperative liver failure compared to anatomic resections as both types of resections provide similar oncological benefits for repeat liver resections of CLM recurrences (31,32). Our findings support performing non-anatomic resections with respect to non-inferior outcomes in all patient groups compared to anatomic resections.

CONCLUSION

This is the first documentation of long-term outcomes of resections performed for liver recurrences of CLMs among both younger and elderly patients. Elderly patients have gained similar 1,3, and 5-year survival rates compared to younger patients following repeat resections. Upper age solely shouldn't be a contradiction in the case of redo surgery as well when well-selected patients are offered for resection. Chemotherapy should be considered at the perioperative setting as the clinical association of CILLs with long-term outcomes should be elucidated with future prospective studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Göztepe Prof. Dr. Süleyman Yalçın City Hospital Clinical Researches Ethics Committee (Date: 22.02.2023, Decision No: 2023/0124).

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

Referee Evaluation Process: Externally peer-reviewed.

Conflicts of interests: The author certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author Contribution: The author declare that he has participated in the design, execution, and analysis of the paper and he has approved the final version.

REFERENCES

1. Chong G, Cunningham D. Improving long-term outcomes for patients with liver metastases from colorectal cancer. J Clin Oncol 2005; 23: 9063–6.
2. Stangl R, Altendorf-Hofmann A, Charnley RM. Factors influencing the natural history of colorectal liver metastases. Lancet 1994; 343: 1405–10.
3. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 2006; 94: 982-99.
4. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004; 239: 818-27.
5. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 1999; 230: 309-21.
6. Zorzi D, Mullen JT, Abdalla EK, et al. Comparison between hepatic wedge resection and anatomic resection for colorectal liver metastases. J Gastrointest Surg 2006; 10: 86-94.
7. Sa Cunha A, Laurent C, Rault A, Couderc P, Rullier E, Saric J. A second liver resection due to recurrent colorectal liver metastases. Arch Surg 2007; 142: 1144-50.
8. Nishio H, Hamady ZZ, Malik HZ, et al. Outcome following repeat liver resection for colorectal liver metastases. Eur J Surg Oncol 2007; 33: 729–34.
9. de Jong MC, Pulitano C, Ribero D, et al. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. Ann Surg 2009; 250: 440–8.
10. Brachet D, Lermite E, Rouquette A, Lorimier G, Hamy A, Arnaud JP. Prognostic factors of survival in repeat liver resection for recurrent colorectal metastases: review of sixty-two cases treated at a single institution. Dis Colon Rectum 2009; 52: 475–83.
11. Brand MI, Saclarides TJ, Dobson HD, Millikan KW. Liver resection for colorectal cancer: liver metastases in the aged. Am Surg 2000; 66: 412-6

12. Rubbia-Brandt L, Giostra E, Brezault C, et al. Importance of histological tumor response assessment in predicting the outcome in patients with colorectal liver metastases treated with neo-adjuvant chemotherapy followed by liver surgery. Ann Oncol 2007; 18: 299-304.
13. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240: 205–13.
14. Fernández-Trigo V, Shamsa F, Sugarbaker PH. Repeat liver resections from colorectal metastasis. Repeat Hepatic Metastases Registry. Surgery 1995; 117: 296-304.
15. Ziff O, Rajput I, Adair R, Toogood GJ, Prasad KR, Lodge JP. Repeat liver resection after a hepatic or extended hepatic trisectionectomy for colorectal liver metastasis. HPB (Oxford) 2014; 16: 212-9.
16. Rubbia-Brandt L, Audard V, Sartoretti P, et al. Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. Ann Oncol 2004; 15: 460-6.
17. Pilgrim CH, Satgunaseelan L, Pham A, et al. Correlations between histopathological diagnosis of chemotherapy-induced hepatic injury, clinical features, and perioperative morbidity. HPB (Oxford) 2012; 14: 333-40.
18. Pawlik TM, Olino K, Gleisner AL, Torbenson M, Schulick R, Choti MA. Preoperative chemotherapy for colorectal liver metastases: impact on hepatic histology and postoperative outcome. J Gastrointest Surg 2007; 11: 860–8.
19. Karoui M, Penna C, Amin-Hashem M, et al. Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases. Ann Surg 2006; 243: 1-7.
20. Vauthey JN, Pawlik TM, Ribero D, et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 2006; 24: 2065-72.
21. You SH, Park BJ, Kim YH. Hepatic Lesions that Mimic Metastasis on Radiological Imaging during Chemotherapy for Gastrointestinal Malignancy: Recent Updates. Korean J Radiol 2017; 18: 413-26.
22. Abdalla EK, Vauthey JN, Ellis LM, et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg 2004; 239: 818-27.
23. Viganò L, Capussotti L, Majno P, et al. Liver resection in patients with eight or more colorectal liver metastases. Br J Surg 2015; 102: 92-101.
24. Simmonds PC, Primrose JN, Colquitt JL, Garden OJ, Poston GJ, Rees M. Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 2006; 94: 982-99.
25. Petrowsky H, Gonen M, Jarnagin W, et al. Second liver resections are safe and effective treatment for recurrent hepatic metastases from colorectal cancer: a bi-institutional analysis. Ann Surg 2002; 235: 863-71.
26. Omichi K, Shindoh J, Cloyd JM, et al. Liver resection is justified for patients with bilateral multiple colorectal liver metastases: A propensity-score-matched analysis. Eur J Surg Oncol 2018; 44: 122-9.
27. Fukami Y, Kaneoka Y, Maeda A, et al. Bilobar versus unilobar multiple colorectal liver metastases: a propensity score analysis of surgical outcomes and recurrence patterns. J Hepatobiliary Pancreat Sci 2017; 24: 153-60.
28. Petrowsky H, Linecker M, Raptis DA, et al. First long-term oncologic results of the ALPPS procedure in a large cohort of patients with colorectal liver metastases. Ann Surg 2020; 272: 793-800.
29. Adam R, Delvart V, Pascal G, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 2004; 240: 644-58.
30. Wicherts DA, de Haas RJ, Salloum C, et al. Repeat hepatectomy for recurrent colorectal metastases. Br J Surg 2013; 100: 808-18.
31. Viganò L, Torzilli G, Troisi R, et al. CLISCO group. Minor hepatectomies: focusing a blurred picture: analysis of the outcome of 4471 open resections in patients without cirrhosis. Ann Surg 2019; 270: 842-51.
32. Mise Y, Aloia TA, Brudvik KW, Schwarz L, Vauthey JN, Conrad C. Parenchymal-sparing hepatectomy in colorectal liver metastasis improves salvageability and survival. Ann Surg 2016; 263: 146-52.

Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1252898

Anatolian Curr Med J 2023; 5(2); 168-176

An examination of the relationship between self-compassion, temperament types and cognitive flexibility according to deceiving tendency

Onur Okan Demirci[1], Kahraman Güler[2]

[2]Department of Psychology, Administravite and Social Sciences, Faculty of Economics, Istanbul Gelişim University, Istanbul, Turkey
[1]Department of Psychology, Faculty of Science and Literature, Doğus University, Istanbul, Turkey

Cite this article as: Güler K, Demirci OO. An examination of the relationship between self-compassion, temperament types and cognitive flexibility according to deceiving tendency. Anatolian Curr Med J 2023; 5(2); 168-176.

ABSTRACT

Aim: The aim of this study was to examine self-compassion, temperament types and cognitive flexibility characteristics of individuals residing in Istanbul, Turkey aged between 18 and 45 years who never cheated and who cheated at least once.

Material and Method: The sample of this study consists of 85 individuals who never cheated and 91 individuals who cheated at least once, residing in Istanbul, Turkey aged between 18 and 45 years. The sample was selected by using simple random sampling. The sample was administered Sociodemographic Form, Deception Tendency Scale (DTS), Self-Compassion Scale (SCS), Temperament Evaluation of Memphis, Pisa, Paris, San Diego-Autoquestionnaire (TEMPS-A) and Cognitive Flexibility Scale (CFS). First, it was checked whether there was a normal distribution or not. For this, skewness and kurtosis values were checked. This study was carried out by the relational screening model, one of the quantitative research methods. Statistical evaluations were analyzed using SPSS (Statistical Package for Social Sciences) 25.0.

Results: The results of this study showed that there was a significant difference between self-compassion components: self-judgment, common humanity, isolation, and over-identification scores of individuals with and without tendency to deceive ($p<.05$). There was a positive relationship between psychological flexibility and romantic relationship quality ($p<.05$). Individuals without tendency to deceive scored higher on self-compassion, self-judgment, isolation, and over-identification compared to individuals with tendency to deceive ($p<.05$). There was a significant difference between cognitive flexibility scores of individuals with and without tendency to deceive ($p<.05$).

Conclusion: The results of the study revealed the importance of the cognitive flexibility.

Keywords: Deceiving, self-compassion, temperament types, cognitive flexibility

INTRODUCTION

Although sexual intercourse outside of marriage or relationship is not widely approved by societies, not everyone is monogamous. Many people experience non-relational sexual intercourse while they are married or in a relationship (1). Cheating can be defined as the deterioration of the agreement and trust between individuals in a close relationship, through emotional, sexual, or romantic involvement of a different person (2). According to Carnes (3), children who are exposed to cheating in their families have a higher risk of cheating in later ages. Moultrup (4) explains this by children taking their family relationships as a model. Wiederman (5) shows that, as a common feature of studies on cheating, the percentage of men having extramarital affairs is much higher than women. Kinsey, Pomeroy, Martin and Gebhard (6) found that 36% of married men and 25% of married women cheat on their spouses (7). Whisman, Gordon and Chatay (8) stated in their research that neurotic personality structure, religious belief of the person, and pregnancy process are important predictors of sexual infidelity. In another study supporting this research revealed that individuals with high impulsivity cannot resist an opportunity that the desire in this direction may bring, and the potential to evaluate potential sexual opportunities can increase (9).

The concept of self-compassion was created based on Eastern psychology (10). Compassion is an emotion that one feels in the face of other people's pain and distress (11). As people's self-compassion level increases, they

Corresponding Author: Onur Okan Demirci, oo_demirci@yahoo.com

Received: 18.02.2023 **Accepted:** 25.03.2023

can understand that they and others deserve attention and love, and they can balance their own needs and the needs of others in their relationships (12). Self-compassionate individuals strengthen their self-confidence by getting rid of destructive thoughts and emotional traps, while also reducing their depression and anxiety (13). Studies have shown that self-compassionate individuals get more satisfaction from life and self-compassion undertakes a preventive task against negative emotional states such as depression, anxiety, and stress (14).

Although there are differences in terms of personality traits, it can be said that there are two main factors that determine personality in general. These are: Hereditary traits (temperament) and character traits (character) (15).

In the literature, there are studies examining the relationship between self-related variables such as self-esteem, self-efficacy and self-awareness and psychological well-being. It is clear that the concept of self-compassion may also be one of the variables in current research (16). For this reason, the relationship between psychological symptoms and the ability of individuals to understand and show compassion for themselves and others has become an important focus in recent studies.

It is stated that individuals structure the world according to their own thoughts and act in this direction. Cognitions are acquired through an individual's interaction with others. However, the individual may form inflexible, over-generalized, and dysfunctional cognitions during these experiences (17). Cognitive flexibility can also be considered as an individual's ability to adapt to certain situations and to move from one thought to another, or to approach different problems with multi-dimensional strategies (18). Martin, Anderson and Thweatt (19) stated that individuals with cognitive flexibility feel secure to communicate in challenging situations. While cognitive flexibility shows a positive relationship with being non-combatant and tolerant, it shows a negative relationship with verbal aggression. In addition, the literature revealed that cognitive flexibility, which can be defined as the ability to adapt to new situations (20), has a significant relationship with self-compassion (21). As the cognitive flexibility of individuals increases, their level of adaptation also increased (22). Additionally, individuals with cognitive flexibility believe that they have the right to forgive themselves because they think that they do not have a single path but have access to alternative options (23). Self-compassion reduces self-criticism, self-doubt, excessive feelings of isolation, and over-identification (22) and increases psychological functioning and adjustment (21). Overall, these findings reveal that cognitive flexibility may have a predictive role on self-compassion.

Aim of the study

The aim of this study was to examine self-compassion, temperament types and cognitive flexibility characteristics of 85 individuals who never cheated and 91 individuals who cheated at least once, residing in Istanbul, Turkey aged between 18 and 45 years. The aim of this research is to show whether there is a differentiation between the variables of depressive temperament, cyclothymic temperament, hyperthymic temperament, irritable temperament, anxious temperament, self compassion, self-kindness, self-judgment, common humanity, isolation, over-identified, mindfullness, cognitive flexibility in those who have and those who do not have a tendency to deceive. The study was carried out on the basis that it may be useful for mental health professionals to act by understanding whether working with these variables shows a difference in clients with a tendency to deceive.

MATERIAL AND METHOD

The study was carried out with the permission of Istanbul Aydın University Social Sciences Ethics Committee (Date: 09.06.2021, Decision No: 2021/07). All procedures were carried o ut in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Research Model

This study was conducted using the comparative survey method, one of the relational survey models.

Research Universe and Sample

The sample of this study consists of 85 individuals who never cheated and 91 individuals who cheated at least once, residing in Istanbul, Turkey aged between 18 and 45 years. The sample was selected by using simple random sampling. While determining the cheating and non-cheating groups in this study, we determined this by asking those who did not take the demographic form and those who cheated at least once. Accordingly, the groups were divided. The sample size was calculated with the "G. Power-3.1.9.4" programme with a 95% confidence interval before data collection. Since there is no similar study in the literature, the effect size standardised by Cohen (24) was taken as a reference. Accordingly, in this study, the minimum number of samples was determined as 128 with an effect size of 0.50, alpha value of 0.05 and theoretical power of 0.80. Informations are listed below:

T tests-means:	Difference between two independent means (two groups)	
Analysis:	A priori: Compute required sample size	
Input:	Tail(s)	= Two
	Effect size d	= 0.5
	α err prob	= 0.05
	Power (1-β err prob)	= 0.80
	Allocation ratio N2/N1	= 1
Output:	Noncentrality parameter δ	= 2.8284271
	Critical t	= 1.9789706
	Df	= 126
	Sample size group 1	= 64
	Sample size group 2	= 64
	Total sample size	= 128

Data Collection

Tools were distributed to 176 participants. It took an average of 20 minutes to fill data collection tools and there were no breaks between them. While participants were answering data collection tools, they were ensured to be in a suitable environment without noise. Statistical evaluations were analyzed using SPSS 25.0 package program. Before starting the analyses, it is first checked whether the scales meet the assumption of normal distribution. At this control stage, the skewness and kurtosis values of the scales are examined. These values include the reference range of -2 +2 (25). As a result of this evaluation, parametric tests were preferred.

Pearson correlation analysis was used to test the relationship between the measurement tools, and Independent Groups t-test was used to compare the groups with and without deception tendency according to the scale scores. Independent Samples T-Test, which is a parametric test, is performed to test whether there is a significant difference between the means of a dependent quantitative variable of two independent groups. The assumptions for performing this test are that the sample is randomly selected from the population, the variable data whose averages are at least in the interval scale to be compared show normal distribution characteristics in both groups, the two groups are independent of each other, and the variances of the groups are expected to be equal (26; 27; 28). All assumptions were found to be fulfilled.

Data Collection Tools

Sociodemographic Form, Deception Tendency Scale (DTS), Self-Compassion Scale (SCS), Temperament Evaluation of Memphis, Pisa, Paris, San Diego-Autoquestionnaire (TEMPS-A) and Cognitive Flexibility Scale (CFS) were used as data collection tools in the study.

Sociodemographic Form: It is a personal data form consisting of age, gender, marital status, and educational status.

Deception Tendency Scale (DTS): It was developed based on the general views of social exchange theory (29). It is a 30-item five-point Likert type scale developed by Polat (29) to measure the tendency of married individuals to deceive. To determine the scale's reliability, Cronbach's Alpha and two-half reliability were tested. The results showed that both reliability indices were .95 for Cronbach's Alpha and.95 for two-half reliability.

Self-Compassion Scale (SCS): It was developed by Neff (10). The subscales' respective internal consistency reliability coefficients were found to be.78,.77,.80,.79,.75, and.81. It was discovered that the test-retest reliability coefficients were.88,.88,.80,.85,.85, and.88, respectively and adapted into Turkish by Akın Ü, Akın A and Abacı (30). It consists of 26 items and 6 subscales: self-kindness, self-judgment, common humanity, isolation, mindfulness, over-identification. It is a five-point Likert type scale. Test-retest reliability values ranged from.56 to.69, while internal consistency coefficients ranged from.72 to.80. Adjusted item-total correlations varied from.48 to.71, and a t-test revealed significant differences between the means of each item's upper 27% and lower 27% points.

Temps-A: It was developed by Akiskal (31) and adapted into Turkish by Vahip, Kesebir, Alkan, Yazıcı, Akiskal K and Akiskal H (32). It onsists of 100 items and 5 subscales: depressive, cyclothymic, hyperthymic, irritable, and anxious. In Akiskal's study two internal consistency measures coefficient and item-total correlations were used to evaluate the TEMPS-reliability. The internal consistency coefficients of TEMPS-A were 0.91 for cyclothymic temperament subscale, 0.81 for depressive temperament subscale, 0.77 for irritability, 0.76 for hyperthymic temperament, and 0.67 for anxious temperament. In the study of Vahip et al., test-retest reliability ranged from 0.73 to 0.93 and Cronbach-Alpha coefficients from 0.75 to 0.84.

Cognitive Flexibility Scale (CFS): It was developed by Dennis and Vander Wal (33) to measure the ability of individuals to produce alternative, harmonious, appropriate, and balanced thoughts in the face of difficult situations. It was adapted into Turkish by Gülüm and Dağ (34). It consists of 20 items and 2 subscales. It is a five-point Likert type scale. In Dennis and Vander Wal's studies, the Cronbach alpha value of the Alternatives subscale was 0.91 in the first and last measurements. The Cronbach's alpha values of the control subscale were 0.86 in the first measurement and 0.84 in the last measurement (33). In the adaptation study, the two-factor structure of the original scale was confirmed. The Cronbach's alpha value for the total score was calculated as 0.90, 0.89 for the alternatives sub-dimension and 0.85 for the control sub-dimension (34).

RESULTS

Of the participants without tendency to deceive; the average age was 30 (SD=8), and minimum age was 18, maximum age was 45 (**Table 1**).

Of the participants with tendency to deceive; the average age was 30 (SD=7), and minimum age was 18, maximum age was 45 (**Table 1**).

Table 1. Descriptive Statistics of Age

	n	Min	Max	M	SD
Participants without tendency to deceive	85	18	45	30	8
Participants with tendency to deceive	91	18	45	30	7

There was a significant difference between hyperthymic temperament scores of participants without tendency to deceive (M=10.42, SD=4.69) and participants with tendency to deceive (M=11.93, SD=4.81); t (174)=-2.11, p=0.037 (**Table 2**).

There was a significant difference between irritable temperament scores of participants without tendency to deceive (M=3.40, SD=3.35) and participants with tendency to deceive (M=5.26, SD=3.93); t (174)=3.37, p=0.001 (**Table 2**).

There was a significant difference between anxious temperament scores of participants without tendency to deceive (M=6.14, SD=5.12) and participants with tendency to deceive (M=8.08, SD=5.12); t (174)=-2.50, p=0.013 (**Table 2**).

There was a significant difference between self-compassion scale scores of participants without tendency to deceive (M=3.52, SD=0.57) and participants with tendency to deceive (M=3.17, SD=0.66); t (174)=3.69, p=0.000 (**Table 2**).

There was a significant difference between self-judgment scores of participants without tendency to deceive (M=3.94, SD=0.67) and participants with tendency to deceive (M=3.51, SD=0.85); t (169.42)=3.68, p=0.000 (**Table 2**).

There was a significant difference between common humanity scores of participants without tendency to deceive (M=3.03, SD=0.85) and participants with tendency to deceive (M=2.68, SD=0.86); t (174)=2.67, p=0.008 (**Table 2**).

There was a significant difference between isolation scores of participants without tendency to deceive (M=3.84, SD=0.81) and participants with tendency to deceive (M=3.41, SD=1.08); t (166.17)=2.99, p=0.003 (**Table 2**).

Table 2. T-test results of comparison of deceiving tendency in TEMPS-a temperament scale, self-compassion scale, cognitive flexibility scale scores

		n	M	SD	t	df.	p
Depressive Temperament	Participants without tendency to deceive	85	5.06	3.02	-1.92	174	0.057
	Participants with tendency to deceive	91	6.01	3.52			
Cyclothymic Temperament	Participants without tendency to deceive	85	7.28	4.87	-1.81	174	0.072
	Participants with tendency to deceive	91	8.60	4.83			
Hyperthymic Temperament	Participants without tendency to deceive	85	10.42	4.69	-2.11	174	0.037*
	Participants with tendency to deceive	91	11.93	4.81			
Irritable Temperament	Participants without tendency to deceive	85	3.40	3.35	-3.37	174	0.001*
	Participants with tendency to deceive	91	5.26	3.93			
Anxious Temperament	Participants without tendency to deceive	85	6.14	5.12	-2.50	174	0.013*
	Participants with tendency to deceive	91	8.08	5.12			
Self-Compassion Scale	Participants without tendency to deceive	85	3.52	0.57	3.69	174	0.000*
	Participants with tendency to deceive	91	3.17	0.66			
Self-Kindness	Participants without tendency to deceive	85	3.00	0.83	1.61	174	0.110
	Participants with tendency to deceive	91	2.79	0.85			
Self-Judgment	Participants without tendency to deceive	85	3.94	0.67	3.68	169.42	0.000*
	Participants with tendency to deceive	91	3.51	0.85			
Common Humanity	Participants without tendency to deceive	85	3.03	0.85	2.67	174	0.008*
	Participants with tendency to deceive	91	2.68	0.86			
Isolation	Participants without tendency to deceive	85	3.84	0.81	2.99	166.17	0.003*
	Participants with tendency to deceive	91	3.41	1.08			
Over-Identification	Participants without tendency to deceive	85	3.78	0.79	2.39	174	0.018*
	Participants with tendency to deceive	91	3.46	0.93			
Mindfulness	Participants without tendency to deceive	85	3.26	0.90	0.26	174	0.793
	Participants with tendency to deceive	91	3.22	0.92			
Cognitive Flexibility Scale	Participants without tendency to deceive	85	56.00	7.44	3.40	174	0.001*
	Participants with tendency to deceive	91	51.92	8.41			

*p<0.05 Used anaylze: Independent Samples T-Test

There was a significant difference between over-identification scores of participants without tendency to deceive (M=3.78, SD=0.79) and participants with tendency to deceive (M=3.46, SD=0.93); t (174)=2.39, p=0.018 (**Table 2**).

There was a significant difference between cognitive flexibility scale scores of participants without tendency to deceive (M=56.00, SD=7.44) and participants with tendency to deceive (M=51.92, SD=8.41); t (174)=3.40, p=0.001 (**Table 2**).

Between deceiving tendency scale and depressive temperament (r(176)=.16, p<.05), cyclothymic temperament (r(176)=.16, p<.05), irritable temperament (r(176)=.27, p<.01), anxious temperament (r(176)=.22, p<.01) were found to be pozitively correlated. Between deceiving tendency scale and self compassion scale (r(176)=-.32, p<.01), self-judgment (r(176)=-.30, p<.01), common humanity (r(176)=-.21, p<.01), isolation (r(176)=-.28, p<.01), mindfulness (r(176)=-.24, p<.01), and cognitive flexibility scale (r(176)=-.27, p<.01) were found to be negatively correlated. (**Table 3**).

Between depressive temperament and self compassion scale (r(176)=-.46, p<.01), self-kindness (r(176)=-.23, p<.01), self-judgment (r(176)=-.38, p<.01), isolation (r(176)=-.46, p<.01), mindfulness (r(176)=-.48, p<.01), over-identified (r(176)=-.26, p<.01), and cognitive flexibility scale (r(176)=-.36, p<.01) were found to be negatively correlated. (**Table 3**).

Between cyclothymic temperament and self compassion scale (r(176)=-.41, p<.01), self-judgment (r(176)=-.46, p<.01), isolation (r(176)=-.47, p<.01), and mindfulness (r(176)=-.54, p<.01) were found to be negatively correlated. (**Table 3**).

Between hyperthymic temperament and self-kindness (r(176)=.18, p<.05), over-identified (r(176)=.23, p<.01), and cognitive flexibility scale (r(176)=.36, p<.01) were found to be positively correlated. (**Table 3**).

Between irritable temperament and self compassion scale (r(176)=-.43, p<.01), self-kindness (r(176)=-.18, p<.05), self-judgment (r(176)=-.47, p<.01), isolation (r(176)=-.37, p<.01), mindfulness (r(176)=-.44, p<.01), over-identified (r(176)=-.23, p<.01 and cognitive flexibility scale (r(176)=-.16, p<.05) were found to be negatively correlated. (**Table 3**).

Between anxious temperament and self compassion scale (r(176)=-.47, p<.01), self-judgment (r(176)=-.45, p<.01), isolation (r(176)=-.51, p<.01), mindfulness (r(176)=-.57, p<.01), over-identified (r(176)=-.18, p<.05), and cognitive flexibility scale (r(176)=-.30, p<.01) were found to be negatively correlated. (**Table 3**).

Between cognitive flexibility scale and self compassion scale (r(176)=.31, p<.01), self-kindness (r(176)=.28, p<.01), self-judgment (r(176)=.23, p<.01), common humanity (r(176)=.22, p<.01), isolation (r(176)=.19, p<.05), mindfulness (r(176)=.24, p<.01), and over-identified (r(176)=.38, p<.01) were found to be positively correlated. (**Table 3**).

Limitations

This study has some limitations. Since the scales used in the study are self-report scales, we assume that the participants are objective when they answering the scales. The sincerity of the participants during the scale answering phase may vary. The presence of 176 participants in the study is seen as a limitation. It was also assumed that the participants filled in the scales sincerely.

Table 3. Pearson corelation results between deceiving tendency scale, TEMPS-A temperament scale, self compassion scale, cognitive flexibility scale scores

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Deceiving tendency scale	1													
2. Depressive temperament	.16*	1												
3. Cyclothymic temperament	.16*	.63**	1											
4. Hyperthymic temperament	.10	-.25**	.09	1										
5. Irritable temperament	.27**	.32**	.55**	.30**	1									
6. Anxious temperament	.22**	.66**	.68**	-.03	.52**	1								
7. Self compassion scale	-.32**	-.46**	-.41**	.09	-.43**	-.47**	1							
8. Self-kindness	-.15	-.23**	-.08	.18*	-.18*	-.12	.73**	1						
9. Self-judgment	-.30**	-.38**	-.46**	.04	-.47**	-.45**	.77**	.33**	1					
10. Common humanity	-.21**	-.13	.06	.06	-.10	-.05	.60**	.75**	.15*	1				
11. Isolation	-.28**	-.46**	-.47**	.00	-.37**	-.51**	.81**	.32**	.70**	.23**	1			
12. Mindfulness	-.24**	-.48**	-.54**	.05	-.44**	-.57**	.73**	.29**	.63**	.08	.65**	1		
13. Over-identified	-.04	-.26**	-.04	.23**	-.23**	-.18*	.52**	.71**	.21**	.64**	.14	.22**	1	
14. Cognitive flexibility scale	-.27**	-.36**	-.12	.36**	-.16*	-.30**	.31**	.28**	.23**	.22**	.19*	.24**	.38**	1

*p<0.05 Used anaylze: Pearson Corellation Analyze

DISCUSSION

The aim of this study was to examine self-compassion, temperament types and cognitive flexibility according to deceiving tendency.

There was no study in the literature that examined the relationship between deceiving and temperament types. In this respect, a significant difference was found between hyperthymic, irritable, and anxious temperament scores of individuals with and without tendency to deceive. Individuals with tendency to deceive got higher hyperthymic, irritable, and anxious temperament scores. Temperament is an important personality trait that shows the emotional aspect and there are different temperament types. Hyperthymic temperament is characterized by positive, happy, social, confident, creative, practical personality traits, less need for sleep, and leadership features (35). This temperament also has other features such as meddling in other people's affairs, seeking stimulant, or having random sexual intercourse (36). Considering these features, individuals with hyperthymic temperament may have problems in not meeting the needs of love, belonging and secure attachment in a romantic relationship. Anxious temperament is characterized by avoidance of social environments and close relationships with people, shyness, fear of losing support, and hypersensitivity to criticism and disapproval. Mostly pessimism, rarely well-being is observed. There are other features such as being easily angered and impulsive, contemplating, criticizing, complaining, and approaching people even when not wanted (37). Therefore, individuals with anxious temperament may tend to abandon or deceive in order to cope with the fear of losing the people who are important to them. Irritable temperament and cyclothymic temperament have some features in common. However, Irritable temperament differs from cyclothymic by its high energy and low-level empathy. These individuals approach situations with suspicion and critical thinking (35). Irritable temperament is characterized by being pessimistic, easily angered, dysphoric, judgmental, having many complaints and undesirable humor (36). Based on this information, it is considered that individuals with irritable temperament will have a high tendency to deceive.

A significant difference was found between self-compassion scores of individuals with and without tendency to deceive. Individuals without tendency to deceive scored higher on self-compassion compared to individuals with tendency to deceive. Self-compassion refers to being open to painful experiences and personal failings, accepting these experiences and failings as a natural part of being human being instead of ignoring them (38). Gilbert and Irons (37) stated that self-compassion increases individuals' well-being as it helps individuals to be more sensitive in their interpersonal relationships. Bibi (39) stated that the relationship between self-compassion and marital adjustment is significant, and that the individual's well-being, self-criticism and over-identification are important predictors of marital adjustment. Wispe (40) defined compassion as being aware of another's pain and trying to do what is necessary to alleviate that pain. Onaylı (41) mentioned that cognitive assessment, self-compassion, rumination, and forgiveness have important roles in coping with negative emotional reactions to deceiving, and that therapists can help deceived clients to cope with rumination, strengthen their self-compassion, and improve their ability to forgive. Based on this information, it is considered that individuals without tendency to deceive are more self-compassionate.

A significant difference was found between cognitive flexibility scores of individuals with and without tendency to deceive. Individuals without tendency to deceive scored higher on cognitive flexibility compared to individuals with tendency to deceive. Due to the high cognitive flexibility of individuals who do not have a tendency to deceive, it is thought that they can look from the perspective of others and do not cheat on their partners. Thompson (42) revealed in his study that being able to see from the perspective of others and establish an empathetic relationship with them requires having a certain level of cognitive flexibility.

According to the study of Solmus (43), individuals with secure attachment style show more commitment, satisfaction and closeness to the relationship and invest more than individuals with insecure attachment style. Yumbul (44) examined the effects of attachment styles on tendency to deceive and showed that people with secure attachment have lower deceiving tendencies than people with insecure attachment. Based on these findings, it can be said that the cognitive flexibility of individuals with a tendency to deceive is low. Attachment styles are one of the important factors that determine the cognitive flexibility level of individuals. Individuals' ability to establish social relationships affects their development of cognitive flexibility (45). Thus, individuals who have weak social relationships have low levels of cognitive flexibility. Overall, attachment styles seem to be quite effective in determining communication motivation and deceiving tendency in romantic relationships (29).

Between deceiving tendency scale and depressive temperament, deceiving tendency scale and cyclothymic temperament, deceiving tendency scale and irritable temperament, deceiving tendency scale and anxious temperament were found to be pozitively correlated. A positive correlation was found between the increase in deceiving tendency and depressive temperament, cyclothymic temperament, irritable temperament and anxious temperament. The absence of any study in the field

between deceiving tendency and temperament shows the importance of investigating the subject. The result of the study indicates that individuals with depressive, irritable, anxious temperament may be more prone to deceiving, and it is thought that considering this situation for mental health professionals may be beneficial in increasing the foresight against clients.

Between deceiving tendency scale and self compassion scale, deceiving tendency scale and self-judgment, deceiving tendency scale and common humanity, deceiving tendency scale and isolation, deceiving tendency scale and mindfulness, deceiving tendency scale and cognitive flexibility scale were found to be negatively correlated. The results show that individuals with self-compassion, self-judgement, common humanity, mindfulness, and cognitive flexibility decrease their tendency to deceive as these characteristics increase. It has been observed that the cognitive flexibility of people who forgive cheating is higher than those who are not prone to cheating (46). In another study, this ability to forgive was found to be the same for the person himself, and people with high cognitive flexibility were more likely to forgive themselves than those with low cognitive flexibility (47). From this point of view, it is possible to say that cognitive flexibility and other functional characteristics are negatively correlated with the tendency to cheat, as a predictable result. This situation seems to indicate that individuals who are cognitively flexible, can evaluate themselves realistically, and therefore approach their personal characteristics more rationally, may be less prone to deceiving. It is thought that these results will be useful for mental health professionals working in the field. Because it is thought that developing the characteristics in individuals with a tendency to cheat will be useful in dealing with this situation.

Between depressive temperament and self compassion scale, depressive temperament and self-kindness, depressive temperament and self-judgment, depressive temperament and isolation, depressive temperament and mindfulness, depressive temperament and over-identified, depressive temperament and cognitive flexibility scale were found to be negatively correlated. It is seen that the depressive temperament, which indicates that the individual is pessimistic, more introverted, physically limited, and has less enjoyment from life, is negatively related to self-compassion, self-kindness, self-judgment, isolation, awareness, over-identification and cognitive flexibility. This result will help to see the deficiencies in someone with depressive temperament.

Between cyclothymic temperament and self compassion scale, cyclothymic temperament and self-judgment, cyclothymic temperament and isolation, cyclothymic temperament and mindfulness were found to be negatively correlated. In cyclothymic temperament, there are both manic and depressive symptoms, the person experiences dull thoughts and emotions, and the sensation of exhaustion usually takes center stage along with hypomanic features (48). For this reason, it is seen that the negative relationship between cyclothymic temperament and self-compassion, self-judgment, isolation and mindfulness is in accordance with the expected results.

Between hyperthymic temperament and self-kindness, hyperthymic temperament and over-identified, hyperthymic temperament and cognitive flexibility scale were found to be positively correlated. It is known that hyperthymic temperament, which causes intense emotion, has a facilitating effect on mood disorders (49). This trait, which suggests that the person has trouble managing their feelings, is believed to have a bad impact on self-kindness, over-identification, and cognitive flexibility as an anticipated outcome.

Between irritable temperament and self compassion scale, irritable temperament and self-kindness, irritable temperament and self-judgment, irritable temperament and isolation, irritable temperament and mindfulness, irritable temperament and over-identified, irritable temperament and cognitive flexibility scale were found to be negatively correlated. The negative relationship between irritable temperament and self-compassion, self-kindness, self-judgment, isolation, mindfulness, over-identification and cognitive flexibility emerges as a predictable result based on the appearance of irritable personality traits.

Between anxious temperament and self compassion scale, anxious temperament and self-judgment, anxious temperament and isolation, anxious temperament and mindfulness, anxious temperament and over-identified, anxious temperament and cognitive flexibility scale were found to be negatively correlated. The negative relationship between anxious temperament and self-compassion, self-judgment, isolation, mindfulness, over-identification and cognitive flexibility emerges as a result suitable for anxious temperament characteristics.

Between cognitive flexibility scale and self compassion scale, cognitive flexibility scale and self-kindness, cognitive flexibility scale and self-judgment, cognitive flexibility scale and common humanity, cognitive flexibility scale and isolation, mindfulness, cognitive flexibility scale and over-identified were found to be positively correlated. Cognitive flexibility has features such as coping with unexpected situations, having problem-solving strategies, coping with stress or having skills such as critical thinking (50). From this point of view, it is a predictable result that there is a positive correlation between variables such as self-compassion, self-kindness, self-judgment, common humanity, isolation, mindfulness and over-identification, and cognitive flexibility.

CONCLUSION

In general, it is seen that cognitive flexibility has a positive relationship with functional temperament characteristics, while the tendency to deceive has a negative relationship. This situation emerges as a predictable result when looking at the nature of the variables. Due to the low availability of such studies in the literature, it is thought that the study will contribute to the literature.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of İstanbul Aydın University Social Sciences Ethics committee (Date: 09.06.2021, Decision No: 2021/07).

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

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Sprecher S. Social exchange theories and sexuality the use of theory in research and scholarship on sexuality. J Sex Res 1998; 1: 32-43.
2. Hall JH, Fincham FD. Relationship dissolution following infidelity: The roles of attributions and forgiveness. J Soc Clin Psychol 2006; 25: 508-22.
3. Carnes P. Out of the shadows. Minneapolis: CompCare Publishers; 1983.
4. Moultrup D. Husbands, wives & lovers: The emotional system of the extramarital affair. New York: Guilford Press; 1990.
5. Wiederman MW. Extramarital sex: Prevalence and correlates in a national survey. J Sex Res 1997; 2: 167-74.
6. Kinsey A, Pomeroy W, Martin C, Gebhard P. Sexual behavior in the human female. Philadelphia: Saunders; 1953.
7. Drigotas SM, Barta W. The cheating heart: Scientific explorations of infidelity. Curr Dir Psychol Sci 2001; 5: 177-80.
8. Whisman MA, Gordon KC, Chatav Y. Predicting sexual infidelity in a population-based sample of married individuals. J Fam Psychol 2007; 2: 320-24.
9. Buss DM, Shackelford TK. Susceptibility to infidelity in the first year of marriage. Journal of Research in Personality 1997; 2: 193-221.
10. Neff KD. Self-compassion: An alternative conceptualization of a healthy attitude toward oneself. Self and Identity 2003; 2: 85-102.
11. Goetz JL, Keltner D, Simon-Thomas E. Compassion: an evolutionary analysis and empirical review. Psychol bull 2010; 3: 351-74.
12. Yarnell L M, Neff KD. Self-compassion, interpersonal conflict resolutions, and well-being. Self and Identity 2013; 2: 146-59.
13. Neff K, Germer, C. Self-compassion and psychological. The Oxford Handbook of Compassion Science, 371; 2017.
14. Yağbasanlar O. A conceptual glance: self-compassion. Eğitim ve Öğretim Araştırmaları Derg 2017; 2: 88-101.
15. Alkahtanı AH, Abu-Jarad I, Sulaiman M, Nikbin D. The impact of personality and leadership styles on leading change capability of malaysian managers. Australian J Business Management Res 2011; 2: 70-99.
16. Korkmaz, B. Öz-duyarlık: psikolojik belirtiler ile ilişkisi ve psikoterapide kullanımı. Psikiyatride Güncel Yaklaşımlar 2018; 1: 40-58.
17. Cormier S, Cormier B. Interviewing strategies for helpers. Pasific Grove (California): Brooks/Cole Publishing Company; 1997.
18. Stevens AD. Social problem-solving and cognitive flexibility: Relations to social skills and problem behavior of at-risk young children (Unpublished doctoral thesis). Available from ProOuest Dissertations and Theses database; 2009.
19. Martin MM, Anderson CM, Thweatt KS. Aggressive communication traits and their relationship with the cognitive flexibility scale and the communication flexibility scale. J Soc Behav Pers 1998; 3: 34-45.
20. Carroll DJ, Blakey E, FitzGibbon L. Cognitive flexibility in young children: Beyond perseveration. Child Development Perspectives 2016; 4: 211–5.
21. Neff KD, Kirkpatrick KL, Rude SS. Self-compassion and adaptive psychological unctioning. J Res Pers 2007; 41: 139-54.
22. Neff KD, Hsieh Y, Dejitthirat K. Self-compassion, achievement goals, and coping with academic failure. Self and Identity 2005; 4: 263-87.
23. Martin MM, Staggers SM, Anderson CM. The relationships between cognitive flexibility with dogmatism, intellectual flexibility, preference for consistency, and self-compassion. Communication Research Reports 2011; 3: 275-80.
24. Cohen J. Quantitative methods in psychology: A power primer. Psychological Bulletin, 1992; 112(1): 155-9.
25. Hahs-Vaughn DL, Lomax R.G. Statistical Concepts A First Course. Routledge: New York; 2020.
26. Can, Abdullah. SPSS ile Bilimsel Araştırma Sürecinde Nicel Veri Analizi, 7. Baskı, Pegem Akademi, Ankara; 2019.
27. Büyüköztürk, Şener. Sosyal Bilimler Için Veri Analizi El Kitabı, 11. Baskı, Pegem Akademi, Ankara; 2010.
28. Field, Andy. Discovering Statistics Using SPSS, (Third Edition), Sage Publications Ltd., London; 2009.
29. Polat D. Examining the relationship between martial adjustment, infidelity tendency and conflict tendency among married couples according to some variables. Ankara Üniversitesi Sosyal Bilimler Enstitüsü. [Postgraduate thesis]; 2006.
30. Akın Ü, Akın A, Abacı R. Self-compassion scale: The study of validity and reliability]. Hacettepe Üniversitesi Eğitim Fakültesi Dergisi 2007; 33: 1-10.
31. Akiskal HS. In: Robins L, Barrett, J (Eds.). Validating affective personality types: In the validity of psychiatric diagnosis. Raven Press 1989; 217-27.
32. Vahip S, Kesebir S, Alkan M, Yazıcı O, Akiskal KK, Akiskal HS. Affective temperaments in clinically-well subjects in Turkey: initial psychometric data on the TEMPS-A. J Affect Disord 2005; 85: 113-25.
33. Dennis JP, Vander Wal JS. The cognitive flexibility inventory: Instrument development and estimates of reliability and validity. Cognitive Therapy and Research 2010; 34: 241-53.
34. Gülüm İV, Dağ İ. The Turkish adaptation, validity and reliability study of the repetitive thinking questionnaire and cognitive flexibility inventory. Anadolu Psikiyatri Derg 2012; 13: 216-23.

35. Sayin A, Aslan S. The relationship between mood disorders and temperament character and personality. Türk Psikiyatri Dergisi 2005; 16: 276–83.
36. Akiskal HS. Validating 'hard'and 'soft' phenotypes within the bipolar spectrum: continuity or discontinuity. J Affect Disord 2003; 1: 1-5.
37. Gilbert, P, Irons, C. Focused therapies and compassionate mind training for shame and self-attacking. In Compassion (pp. 263-325). Routledge; 2005.
38. Cormier S, Cormier B. Interviewing strategies for helpers. Pasific Grove (California): Brooks/Cole Publishing Company; 1997.
39. Bibi S, Masood S, Ahmad M, Bukhari S. Effect of self-compassion on the marital adjustment of Pakistani adults. Foundation University Journal of Psychology 2017; 2: 52-66.
40. Wispé L. The psychology of sympathy. Springer Science & Business Media; 1991.
41. Onaylı S. Emotional reactions to infidelity: examining the roles of self-compassion, forgiveness, rumination and cognitive appraisal (Doctoral Thesis). Middle East Technical University; 2019.
42. Thompson LY, Snyder CR, Hoffman L, Michael ST, Rasmussen HN, Billings LS. Forgiveness of self, others, and situations. J Pers 2005; 73: 313-59.
43. Solmuş T. Romantic attachment (II): Relational variables and process. Türk Psikoloji Bülteni 2003; 9: 99-208.
44. Yumbul, C, Cavusoglu, S, Geyimci B. The effect of childhood trauma on adult attachment styles, infidelity tendency, romantic jealousy and self-esteem. Procedia Social Behav Sci 2010; 5: 1741-45.
45. Bilgin M. Some variables predicting cognitive flexibility. Çukurova Üniversitesi Eğitim Fakültesi Derg 2009; 3: 142-52.
46. Flanigan, B. Forgivers and the unforgivable, Exploring Forgiveness, Wisconsin: The University of Wisconsin Press; 1998.
47. Gueta, K. Self-forgiveness in the recovery of israeli drug-addicted mothers: a qualitative exploration. J Drug Issues 2013; 43: 450-67.
48. Kuloğlu M, Çayköylü A, Albayrak Y. Siklotimik bozukluk. Klinik Psikiyatri Derg 2007; 10: 216-22.
49. Demirpençe D, Guliyev EI, Gurbuz HGA. Afektif mizaç özelliklerinin duygu düzenleme zorluklarında etkisi. Klinik Psikiyatri Derg 2021; 24: 350-8.
50. Çuhadaroğlu, A. Bilişsel esnekliğin yordayıcıları. Cumhuriyet Int J Educ 2013; 2: 86-101.

Case Report

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1234563

Anatolian Curr Med J 2023; 5(2); 177-179

Idiopathic axillary web syndrome: a case-based review of an unusual disorder

İsa Cüce[1], Sinem Kübra Konca[2], Rıdvan Yıldızhan[3], İbrahim Halil Kafadar[4], Hüseyin Demir[5]

[1]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Erciyes University, Kayseri, Turkey·
[2]Department of Physical Medicine and Rehabilitation, Bünyan State Hospital, Kayseri, Turkey
[3]Department of Physical Medicine and Rehabilitation, Zile State Hospital, Tokat, Turkey
[4]Department of Orthopaedics and Traumatology, Faculty of Medicine, Erciyes University, Kayseri, Turkey
[5]Department of Physical Medicine and Rehabilitation, Medikal Palas Private Hospital, Kayseri, Turkey

Cite this article as: Cüce İ, Konca SK, Yıldızhan R, Kafadar İH, Demir H. Idiopathic axillary web syndrome: a case-based review of an unusual disorder. Anatolian Curr Med J 2023; 5(2); 177-179.

ABSTRACT

Axillary web syndrome (AWS), which frequently develops following axillary lymph node dissection, can also be caused by several other conditions, such as infection or strenuous exercise. In recent years, idiopathic cases have also been reported. We report the case of a 27-year-old female who presented with pain, tension and a taut rope-like structure in the left armpit area. She also had a limited shoulder range of motion in abduction and forward flexion. We diagnosed the patient with idiopathic AWS based on a detailed clinical history and manifestations. The patient completely recovered without any sequelae by therapeutic interventions, including nonsteroidal anti-inflammatory drugs and physical therapy. Through a systematic review of the literature, four additional cases of idiopathic AWS were identified. This study aimed to investigate the similarities and differences between idiopathic and typical AWS cases.

Keywords: Axillary web syndrome, idiopathic, physical therapy

INTRODUCTION

Axillary web syndrome (AWS) is a skin disorder characterized by a visible taut cord within the axillary skin, usually detected by inspection and/or palpation. This cord often originates in the axilla and can extend to the elbow, forearm, and even the hand. In symptomatic cases, the most common complaints include pain, feeling of tension, and a limited range of motion (ROM) of the shoulder joint (1).

AWS is commonly known as a complication that occurs after axillary lymph node dissection (ALND), with an incidence rate of 6%–86% following ALND. AWS usually develops in the early postoperative period, but it is likely to occur several months or years later and even recur (2). The most common indication for ALND is breast cancer, followed by melanoma. In such patients, AWS, despite being a self-limiting disorder, induces additional morbidity (1). Apart from ALND, cases of AWS due to causes such as granulomatous inflammation after folliculitis or epidermal inclusion cysts have also been reported (3,4).

In recent years, four interesting cases of AWS that were apparently "idiopathic" and had no attributable cause have been reported around the world (5-8). In this report, we present the clinical characteristics and treatment of an idiopathic AWS case in light of the few idiopathic cases reported in the literature.

CASE

A 27-year-old, normal-weight female engineer was admitted to our clinic with complaints of pain and tension in the left armpit, which had started approximately three weeks earlier, and a taut rope-like structure in the left armpit area, which she had noticed one week earlier. The pain started in the left armpit, spread to the medial forearm, and increased with overhead activities. Her visual analogue scale (VAS) pain score was 7 (0=no pain; 10=worst pain) at the time of admission. She had no history of trauma, surgery, rash, or infection in the axillary region. Close examination revealed a non-erythematous subcutaneous cord-like structure originating in the left axillary region and extending from the medial to the middle portion of the left arm (**Figure 1**). There were no signs suggestive of infection in the axillary region, and there were no skin lesions or lymphadenopathy. The neurological examination was normal, and peripheral

Corresponding Author: İsa Cüce, icuce@erciyes.edu.tr

Received: 15.01.2023 **Accepted:** 24.02.2023

pulses were palpable, with equal volume in both upper extremities. Active and passive shoulder abduction and forward flexion were limited to 120°, while other movements were within normal limits. The last part of her left elbow extension was mildly painful (2/10 VAS scale). Laboratory parameters (complete blood count [CBC], biochemical parameters, tumor markers, serology, erythrocyte sedimentation rate [ESR], and C-reactive protein [CRP]) were within normal ranges. No biceps tendon pathology or muscle tear was detected on a shoulder ultrasound (US) examination. Left upper extremity Doppler US was negative for superficial or deep venous thrombosis.

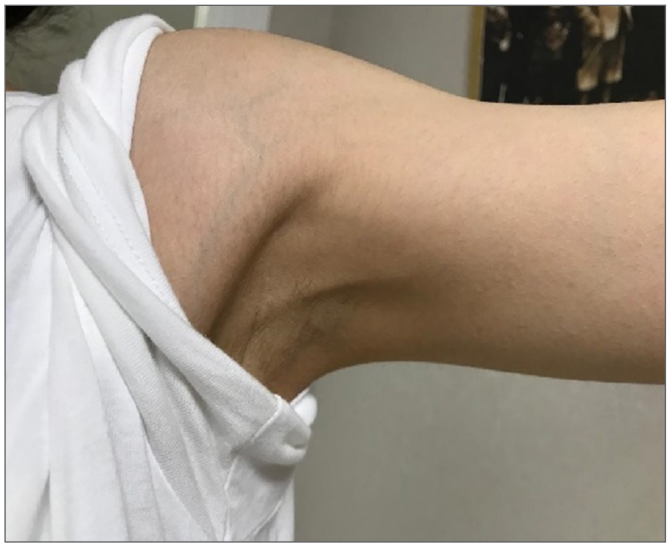


Figure 1. Idiopathic AWS, a band-like structure extending from the axilla to the antecubital fossa in the left arm.

Based on these signs and symptoms, the patient was diagnosed with idiopathic AWS and was initiated on oral meloxicam (7.5 mg/day) and topical nimesulide. She also received concurrent physical therapy five times per week for two weeks. Physical therapy interventions comprised superficial heat therapy, therapeutic ultrasound, transcutaneous electrical nerve stimulation (TENS) treatment, axillary myofascial release, and ROM and stretching exercises. The patient was then provided with an individualized, written, daily home exercise program, which was prescribed for the next 20 days.

The patient was seen for follow-up one month later. She reported that her shoulder pain had almost ceased (1/10 VAS scale), and the subcutaneous cord had completely disappeared. Additionally, her shoulder and elbow ROM were within normal limits without pain or discomfort. Informed consent was obtained from this patient.

DISCUSSION

In this case report, we describe the clinical features, diagnostic approach, and management of a patient with idiopathic AWS. To date, there have been only four reported cases of idiopathic AWS similar to that of our patient in the world (5-8) (**Table 1**). In the other four cases, the duration of symptoms ranged from two days to two months, and three of these cases presented with typical symptoms of AWS, such as a feeling of tension and pain in the axillary region, as in our patient (5,6,8). Interestingly, the remaining patient—a 67-year-old female AWS patient in France—had neuropathic-like upper extremity pain complaints, such as stinging, burning, and itching, and the patient's cord in the axillary region occurred later during follow-up (7).

Potential risk factors associated with the development of AWS after ALND include low body mass index, young age, more aggressive and extensive surgery, radiotherapy or chemotherapy, and hypertension (9). In the four cases reported in the literature, the ages of the patients ranged from 29 to 67 years, and no associated risk factors, including the factors mentioned above, were identified in the patient histories and physical examinations (5-8). Although the exact pathogenesis of AWS remains unclear, it has been reported that the processes occurring secondary to varying degrees of damage in veins following ALND, particularly in lymphatic vessels, and the processes occurring during the tissue healing phases, particularly during the proliferative phase, are effective in the formation of a visible taut cord (1,10). Moskovitz et al. (11) evaluated a large cohort of AWS patients and reported that a patient with stage IV invasive breast cancer and fixed axillar metastasis developed AWS due to the

Table 1. Summary of five cases of "idiopathic" AWS

Author	Age (yr) / Sex	Affected upper extremity	Symptom duration	Symptoms	Baseline pain severity	Management
Demir Y. et al., 2017	40 / M	Right	2 days	Shoulder pain, limitation of ROM in shoulder	VAS : 8	Oral analgesics, exercise, and physiotherapy
Tetik B. et al., 2019	41 / M	Right	2 weeks	Feeling of tension and pain in the axillary region	-	Oral-topical analgesics, exercise, and physiotherapy
Puentes Gutiérrez AB et al., 2020	67 / F	Right	2 months	Sense of itching, and stinging in the axillary region	LANSS : 14	Shoulder stretching exercises and massage
Dündar Ahi E. et al., 2022	29 / F	Left	3 days	Shoulder pain, limitation of ROM in shoulder	VAS : 5	Oral analgesics, exercise, physiotherapy, and massage
Cüce İ. et al., 2023	27 / F	Left	3 weeks	Feeling of tension and pain in the axillary region	VAS : 7	Oral-topical analgesics, exercise, and physiotherapy

ROM: Range of motion, VAS: Visual Analogue Scale, LANSS: The Leeds Assessment of Neuropathic Symptoms and Signs Scale.

disruption of normal lymphatic flow despite undergoing no surgery. In contrast, in the patient reported by Lee et al., the cord developed following the emergence of an epidermal inclusion cyst and consisted of band-like fibrotic tissue, with no accompanying lymph duct or sclerosing veins observed (4).

The diagnosis of AWS is easily made by patient-reported symptoms, visual inspection, and palpation of the cord in the axilla, upper extremity, or trunk (1). US can be used alongside physical examination for diagnosis, but its contribution is controversial in the context of visualizing the structure of the cord (12). Ahi et al. (8) reported in a case of idiopathic AWS that the cord was visualized as a hypoechoic band under the skin with US.

Management of AWS comprises physical therapy-based conservative treatment aimed at relieving pain and restoring full ROM, as well as education and medication. Additionally, it is known that AWS may resolve spontaneously without any treatment (1,9). Nevertheless, physical therapy may provide faster resolution of the cord than patients experience when they do not receive physical therapy (2). In a prospective study, 56 patients with AWS underwent physical therapy, and at the assessment 3 months after ALND, 54 had complete recovery, and 2 had residual signs of the disease (13). To our knowledge, there is not yet a definitive guide for the scope and duration of physical therapy in AWS. Physical therapy management of AWS often includes manual therapy, therapeutic exercises for restoration of ROM restrictions in the affected shoulder joint, and physical modalities, such as heat or cold therapy. According to our understanding of the literature, all of these interventions can be delivered safely, especially in idiopathic AWS cases.

CONCLUSION

It should be recognized that AWS may rarely develop idiopathically, regardless of undergoing ALND. Accordingly, an extensive awareness of the development of idiopathic AWS is essential since it can be easily diagnosed by clinical evaluation alone. However, additional diagnostic tools may be required for differential diagnosis. The clinical signs, symptoms, and management of idiopathic cases are similar to those of typical AWS cases that develop after ALND.

ETHICAL DECLARATIONS

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying image.

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

REFERENCES

1. Yeung WM, McPhail SM, Kuys SS. A systematic review of axillary web syndrome (AWS). J Cancer Surviv 2015; 9: 576-98.
2. Koehler LA, Haddad TC, Hunter DW, et al. Axillary web syndrome following breast cancer surgery: symptoms, complications, and management strategies. Breast Cancer (Dove Med Press) 2019; 11: 13-9.
3. Zhang Q, Tan C. Axillary web syndrome following granulomatous inflammation after folliculitis. Eur J Dermatol 2016; 26: 314-5.
4. Lee KC, Chang YW, Chen CP. Axillary web syndrome following epidermal inclusion cyst: a case report and literature review. Clin Exp Dermatol 2019; 44: 64-6.
5. Demir Y, Güzelküçük Ü, Kesikburun S, et al. A rare cause of shoulder pain: axillary web syndrome. Turk J Phys Med Rehabil 2017; 63: 178-80.
6. Tetik B, Songür K, Aşkın A. Aksiller web sendromu: omuz ağrısının gözden kaçan nedeni. Cukurova Medical Journal 2019; 44: 255-9.
7. Puentes Gutiérrez AB, García Bascones M, Puentes Gutiérrez R, et al. [Idiopathic axillary web syndrome]. Rehabilitacion (Madr) 2020; 54: 68-72.
8. Dündar Ahi E, Ozen S, Saraçgil Coşar SN. Idiopathic Axillary Web Syndrome: A Case Report on a Rare Entity. J PMR Sci 2022; 25: 119-22.
9. Dinas K, Kalder M, Zepiridis L, et al. Axillary web syndrome: Incidence, pathogenesis, and management. Curr Probl Cancer 2019; 43: 100470.
10. Koehler LA, Hunter DW. Lymphspiration: The Axillary Web and Its Lymphatic Origin. Lymphology 2016; 49: 185-91.
11. Moskovitz AH, Anderson BO, Yeung RS, et al. Axillary web syndrome after axillary dissection. Am J Surg 2001; 181: 434-9.
12. Mullen LA, Harvey SC. Review of axillary web syndrome: What the radiologist should know. Eur J Radiol 2019; 113: 66-73.
13. Torres Lacomba M, Mayoral Del Moral O, Coperias Zazo JL, et al. Axillary web syndrome after axillary dissection in breast cancer: a prospective study. Breast Cancer Res Treat 2009; 117: 625-30.

PUBLICATION RULES, PUBLICATION POLICY, GENERAL PRINCIPLES AND SUBMISSION RULES

AUTHOR GUIDELINES

Anatolian Current Medical Journal (ACMJ) is a refereed, open access and periodical publication. The articles published according to the journal's writing rules are accepted through the **DergiPark** system. All numbers are available at our https://dergipark.org.tr/en/pub/acmj/archive web address and **Dergipark** web page for free. Our purpose is to provide high-quality scientific articles for diseases' diagnosis and treatment having appropriate innovations internationally. It is a scientific medical journal published four times (**January, April, July, October**) a year. The articles coming as a refereed journal are primarily evaluated in terms of common rules conformity with the standard requirements defined by the **Committee of International Medical Journal Editors** (www.icmje.org) in biomedical articles. You can access all of the articles published in our journal electronically, read and download from our web site (https://dergipark.org.tr/en/pub/acmj). Our goal is to make sure that your colleagues send the decision and publishing process of publications that we send to you in the shortest possible time. We would like to emphasize that we are always open to suggestions and constructive criticisms to raise the quality of our publication, and that we will show the necessary sensitivity to the statements in this regard. The **English** name of the journal will be used in the article operating system and citations.

Anatolian Current Medical Journal (ACMJ) It is a scientific, internationally refereed journal that publishes retrospective/prospective clinical and laboratory studies, interesting case presentations, invited collections, editorial letters, original images, short reports and surgical technical articles about every branch of medicine. The language of the journal is **English**. Articles are accepted in English. Sent for evaluation to be published or published articles in another journal or not written in accordance with the journal's rules are not accepted for evaluation. The editor, co-editor and publisher do not take any responsibility for the articles published in the journal.You can access all of the articles published in our journal electronically, read and download from our web site: https://dergipark.org.tr/en/pub/acmj.

JOURNAL NAME

Anatolian Current Medical Journal

ABBREVIATION OF JOURNAL NAME

Anatolian Curr Med J / ACMJ

CORRESPONDENCE ADDRESS

Manuscripts should be sent by e-mail by the responsible author, after registering with **DergiPark**, by going to https://dergipark.org.tr/en/journal/2384/submission/step/manuscript/new.

ARTICLE GENERAL WRITING RULES

All scientific responsibility of the manuscripts belongs to the author (s). The editor, co-editor and publisher do not accept any responsibility for the articles published in the journal.

EDITORIAL PRE-CONTROL EVALUATION

Manuscripts sent to the **Anatolian Current Medical Journal (ACMJ)** are evaluated in terms of format and plagiarism. Manuscripts that do not conform to the format are sent back to the author responsible for evaluation. Spelling rules should be reviewed to avoid such a waste of time. All manuscripts submitted for publication are evaluated by two or more domestic/foreign referees. The evaluation of the articles is made considering the scientific importance and originality. Manuscripts that are accepted for publication can be rearranged by the editorial board without informing the authors. After the article is submitted to the journal or accepted for publication, the order of names cannot be changed, author name cannot be added or removed.

SCIENTIFIC AND ETHICAL RESPONSIBILITY

The editorial and the publication processes of **Anatolian Current Medical Journal (ACMJ)** are shaped in accordance with the guidelines of the World Association of Medical Editors (**WAME**), the Committee on Publication Ethics (**COPE**), the International Council of Medical Journal Editors (**ICMJE**), the Council of Science Editors (**CSE**), the European Association of Science Editors (**EASE**) and National Information Standards Organization (**NISO**). The journal conforms to the Principles of Transparency and Best Practice in Scholarly Publishing (doaj.org/bestpractice).

The protocol for clinical research articles must be approved by the **Ethics Committee**. In all studies conducted on humans, the "Material and Method" section was approved by the relevant committee or the **Helsinki Declaration of Principles** (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/). It should be stated in the text that all persons included in the study signed the Informed Consent Form. The articles submitted to the **ACMJ** will be deemed to have been conducted in accordance with the **Helsinki Declaration of Principles**, and have received ethical and legal permissions and will not be held responsible. If "Animal" was used in the study, the authors stated in the Materials and Methods section of the article that they protect animal rights in accordance with the principles of the **Guide for the Care and Use of Laboratory Animals** (www.nap.edu/catalog/5140.html), and that they have received approval from the ethics committees of their institutions. it is difficult. In case reports Informed Consent an should be obtained from patients regardless of the identity of the patient. If the **Ethics Committee Approval** is required in the article; the received document should be sent with the article. The article should be passed by the authors for **academic plagiarism prevention program**. It is the authors' responsibility to ensure that the article complies with the ethical rules.

All manuscript submissions should be scanned for plagiarism research and then uploaded to the journal system. In the event of alleged or suspected research misconduct, e.g., plagiarism, citation manipulation, and data falsification/ fabrication, the Editorial Board will follow and act in accordance with the **COPE** guidelines. See **Guidance from the Committee on Publication Ethics** (**COPE**).

Each individual listed as an author should fulfill the authorship criteria recommended by the International Committee of Medical Journal Editors (ICMJE- www.icmje.org). The **ICMJE** recommends that authorship should be based on the following 4 criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) Drafting the work or revising it critically for important intellectual content; (3) Final approval of the version to be published; (4) Agreement to be accountable of all aspects of the work in ensuring that questions related to the accuracy or the integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he/she had done, an author should be able to identify which co-authors are responsible for the specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

All those designated as authors should meet all of the four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria should be acknowledged and thanked on the title page of the article. If the editorial board suspects that someone who does not meet the authorship requirements has been added as a writer, the article will be rejected without further investigation.

ACMJ requires and encourages the authors and the individuals who involved in the evaluation process of submitted manuscripts to disclose any existing or potential conflicts of interests, including financial, consultant, and institutional, that might lead to the potential bias or a conflict of interest. Any financial grants or other supports received for the submitted study from individuals or institutions should be disclosed to the Editorial Board. To disclose a potential conflict of interest, the **ICMJE Potential Conflict of Interest Disclosure Form** should be filled in and submitted by all of the contributing authors. Cases of the potential conflict of interest of the editors, authors, or reviewers are being resolved by the journal's Editorial Board within the scope of **COPE** and **ICMJE** guidelines. The Editorial Board of the journal handles all of the appeal and complaint cases within the scope of COPE guidelines. In such cases, authors should get in direct contact with the editorial office to regard their appeals and complaints. When needed, an ombudsperson may be assigned to resolve cases that cannot be resolved internally. The Editor in Chief is the final authority in the decision-making process for all of the appeals and complaints. When submitting a manuscript to the **ACMJ**, authors should accept to assign the copyright of their manuscript to the **ACMJ**. If authors rejected for publication, the copyright of the manuscript will be assigned back to the authors. When using previously published content including figures, tables, or any other material in both of the print and electronic formats, authors must obtain permission from the copyright holder. Legal, financial and criminal liabilities in this regard belong to the author(s). Statements or opinions expressed in the manuscripts published in the **ACMJ** reflect the views of the author(s) and not the opinions of the editors, the editorial board, or the publisher; the editors, the editorial board, and the publisher disclaim any responsibility or liability for such materials. The final responsibility in regard to the published content rests with the authors.

ARTICLE IS NOT PUBLISHED ELSEWHERE

Each author should indicate to the editor on the presentation page that part or all of the manuscript is not published elsewhere and is not in the process of being evaluated in another journal at the same time. Oral or poster presentations presented at congresses should be indicated on the title page with the name of the congress, place and date. All responsibility for the articles published in the journal (ethics, scientific, legal, etc.) belongs to the authors.

COPYRIGHT TRANSFER FORM

Copyright Transfer Form (https://dergipark.org.tr/en/journal/2384/file/3854/download) can be obtained from the link. In the native language of the manuscript should be filled in must be sent on-line when loading. According to the 1976 Copyright Act, all kinds of publication rights of articles accepted for publication belong to the publisher.

WRITING LANGUAGE CONTROL

The publication language of the journal is **English**. English articles and Abstract should be checked by a professional linguist before being submitted. The spelling and grammatical errors in the manuscript are corrected by our English language consultant and editorial committee.

STATISTICS EVALUATION

All prospective, experimental and retrospective research articles should be evaluated in terms of statistics (if required by the statistical expert) and indicated by appropriate planning, analysis and reporting.

ACCEPTANCE OF PUBLISHING

After the approval of the editors and referees, the publication date of the article is taken into consideration. A Doi number is obtained for each post.

ARTICLE WRITING RULES

Manuscripts are double-spaced with Microsoft Word, and title titles (Abstract, Abstract, Introduction, Materials and Methods, Results, Discussion, References, etc.) are written in 12 pt. 2.5 cm space should be written at the top and bottom. The writing style should be Times New Roman. "System International" (SI) units should be used. Figures, tables and graphs should be referenced in the text. Abbreviations should be given in parentheses where the word first appears. Review should not exceed 4000 words, research articles 4000, case reports 2000, letters to the editor should not exceed 500 words. Pages should be numbered from the abstract page.

SECTIONS OF MANUSCRIPT

1. Presentation to the Editor

This is the article that the author of the article sends to the editor of the journal. In this section, it should be noted that part or all of the article is not published elsewhere and is not in the process of being evaluated in another journal at the same time, "**Material Support and Interest Relationship**" status, language and statistical checks are made.

2. Title Page

The category of the article submitted at the beginning of the page should be indicated (clinical analysis, research article, experimental study, case report, review, etc.). The names and surnames of all authors should be numbered after the superscript and numbered from 1, and they should be added under the names of the institutions, clinics, cities and countries. On the title page, each author's **Orcid ID** should be his/her e-mail address. This page should include the Authorized Author (s), name, full address, telephone and **e-mail** (address information should be indicated in English. Oral or Poster presentations presented at congresses should be indicated on the title page by giving the name, place and date of the congress.

3. Article File

There should be no names of authors and institutions, only this information should be on the title page.

Title: There should be a short and clear title. It should not contain abbreviations. Abstract: English abstracts should be written. In research articles; It should be divided into sections of Aim, Material and Method, Results and Conclusion and should not exceed 400 words. In the review, case reports and the like.

Keywords: A minimum of 3 and a maximum of 6 should be written. Words should be separated by semicolons. Keywords should be submitted in accordance with Subject **Medical Subject Headings (MESH)** (www.nlm.nih.gov/mesh/MBrowser.html).

Figures, Photographs, Tables and Graphics: It should be indicated at the end of the sentence where it is mentioned in the text, should not be placed in the text, and should be added to the end of the text after the references. Abbreviations used should be indicated in the description below. If previously printed figures, pictures, tables and graphics are used, written permission must be obtained and this permission should be stated in the description of figures, pictures, tables and graphics. The article should be passed by the authors for academic plagiarism prevention program. The picture/photo should be in jpeg and at least 300 dpi resolution.

Text Sections: The text samples to be sent for publication are as follows.

Editorial Comment/Discussion: It is the evaluation of the original research articles published by the expert other than the authors. It is published before the articles in the journal.

Research Article: Prospective-retrospective and all kinds of experimental studies can be published. Introduction, Material and Method, Results, Discussion, Conclusion. Abstract (approximately 400 words; aim/introduction, material and method, findings/results and conclusion sections), Introduction, Material and Method, Results, Discussion, Conclusion, Acknowledgments, References.

Review: Can be prepared by invited authors or directly. It can be prepared to include the latest medical literature for any subject that has medical characteristics. Abstract (about 300 words, unpartitioned), titles, references.

Case Report: These are rare or different articles in diagnosis and treatment. It should be supported with sufficient number of photographs and diagrams. Abstract (about 250 words; no section), Introduction, Case report, Discussion, Conclusion.

Letter to the Editor: The articles that are published in the journal within the last year include a maximum of 500 words containing various opinions, experiences and questions of the readers. There are no Title and Abstract sections. The number of references is limited to 5 (max. 10). It should be indicated which article (number, date) is dedicated and at the end there should be the name, institution and address of the author. The answer to the letter is given by the editor or the author (s) of the article and published in the journal.

Education: Scientific articles supported by the latest clinical and laboratory applications that send messages to readers on current issues within the scope of the journal. Abstract (about 200-250 words; no section), related titles, references.

Book Evaluations: Evaluations of national or internationally accepted books of current value within the scope of the journal.

WHAT SHOULD BE INDICATED BEFORE THE RESOURCES

ETHICAL CONSIDERATIONS

Ethics Committee Approval: The study was carried out with the permission of …….... Ethics Committee of ……. (permission granted: ……., decision no: ……).

Informed Consent: All patients signed the free and informed consent form. (If retrospective study; **Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.)

Referee Evaluation Process: Externally peer-reviewed.

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

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

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

Acknowledgements: If any, it should be written before references.

References: References should be written according to the order of arrival. If the number of authors in the source is 6 or less, all authors (surname and first name should be the first letter, the names of the authors should be separated by commas) should be specified; (”et al ”), the name of the article (only the first letter of the sentence and the first letter of the special names will be capitalized), short journal name, year, volume, short page number (15-8, not 15-18) and a space between the punctuation marks. The format used for the manuscript submission should be as specified in Index Medicus (www.icmje.org). The list of references should only include studies that have been published or accepted for publication or have a Doi number. Journal abbreviations should follow the style used in **Cumulated Index Medicus** (http=//www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng.). The number of references should be limited to 40 in research articles, 60 in reviews, 20 in case reports and 5 (max. 10) in letter to the editor. References should be given in parentheses at the end of the sentence just before the period. For example (4,5). The author (s) is responsible for the accuracy of the references. Importance should be given to the synthesis of domestic and foreign sources.

4. Figures and Table Titles

Titles should be written after the references. Each must be submitted as a separate image file (at least 300 dpi resolution, jpg).

After the article is accepted for publication, the first copy of the string will be sent to the responsible author by e-mail. In this text, only the spelling errors will be corrected and no additions or substitutions will be made. The responsible author will notify the editorial center by e-mail of the corrections within 2 days.

SOURCE WRITING EXAMPLES

Excerpt from journals;

Cesur S, Aslan T, Hoca NT, Cimen F, Tarhan G, Cifci A. Clinical importance of serum neopterin level in patients with pulmonary tuberculosis. Int J Mycobacteriol 2014; 3: 15-8 (not 15-18).

Excerpt from the book;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Excerpt from the book, which is the only author and editor;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Excerpt from the book with multiple authors and editors;

Schulz JE, Parran T Jr.: Principles of identification and intervention. In: Principles of Addicton Medicine, Graem AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998: 1-10.

If the editor is also the author of the chapter in the book;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Excerpt from PhD / Undergraduate Thesis;

Kilic C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Excerpt from an internet site;

Site name, URL address, author names, access date should be given in detail.

Giving a Doi number;

Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into the family market in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

For other reference styles, see "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References".

Eder I hereby declare that all or part of the material in this study has not previously been published in any place and is not currently being evaluated elsewhere for publication. electronic submissions and all kinds of pre-declarations.

Sponsorship Statement

Authors should declare, if any, the roles of sponsors of the study:

1. Design of the study 2. Data collection, analysis and interpretation of the results 3. Writing the report

CHECKLIST / CONTROL LIST

The checklist must be complete.

What should be in the article;

—Editor to Presentation Page

—Title Page

- Ethical Status,
- "Conflict of Interest"
- Orcid numbers and author information should be on this page.

—Main Text

—Copyright Transfer Form

1. **Presentation page to the Editor:** It should be written by the responsible author addressed to the editor. Phone and E-mail must be added. The title, short name of the submitted article, 'this work has not been sent to any journal and it is not under consideration and it is authors' own work' should be written in a Conflict of Interest statement'
2. **Title page:** Article titles/Short titles, Authors and Institutions, Corresponding Author's postal address and telephone, **Orcid no** (mandatory since 2019) and **E-mail** addresses of all authors. **Special names and lowercase letters should be used in the title.**
3. **Main pages of the article:** Article Titles/Short Titles, Abstract and Keywords, Article Text, References, Table and Figure Titles, Tables. **This page will not contain author names or institution information.**
4. **Font:** Titles should be "Times New Roman 12 and 12 pt, with 11 pt, double-spaced line spacing and 2.5 cm indentation in all areas.
5. **Abstract**: Abstract should begin with the title ABSTRACT and include the sections "**Introduction/Aim, Material and Method, Findings/Results, Conclusion"**.
6. **Keywords** should be added under the abstract in "**Keywords**", under "**Abstract**". Keywords should be at least 3, at most 6 words, separated by commas, and should be MeSH-compliant.
7. **M**aterial and Method section should indicate the approval of the **Ethics Committee** (it is recommended to include the place, date, ethics committee number). In articles that do not require Ethics Committee Approval, it should be stated that the Approval/Permission of the Institution has been obtained (in order to avoid Conflict of Interest). Related documents should be sent on request. It should be noted that the author (s) is responsible for ethical problems.
8. **S**tatistical terms (such as p, r, α) should **not** be used in the discussion.
9. **"Financial Support/Conflict of Interest Status";** should be stated before the bibliography and "***Acknowledgment***" should be written before the bibliography.
10. **References Representation;** should be as detailed in the spelling rules. Journal's number number "(2)" **is not** in bibliography. In articles with up to six authors, the names of all authors should be written (with the first letter of surname and first name), and for articles with seven or more authors, the first three authors should be cited as et al (et al.). The name of the manuscript should be in the form of sentence usage (**except for special names and first letter**). **The journal should be given a short name.** A space must be left between the punctuation marks after the journal name.
11. **T**ables, Graphs, Pictures and Figures should be placed under a separate title after the bibliography. **Figures/ Images** (at least 300 dpi resolution, must be **jpeg** file) and **Table**s should be submitted as one or more separate files.
12. **Copyright Transfer Form:** Must be filled in the original language of the manuscript. It must be signed by all authors. In the absence of the signature of all authors, the **Corresponding Author** may take responsibility and sign on behalf of all authors.
13. **Similarity rate** (recommended with **Ithenticate**) should be below 20%.