Journal of Ankara University Faculty of Medicine

E-ISSN: 1307-5608

Ankara Üniversitesi Tıp Fakültesi mecmuası

Volume/Cilt: 78 Issue/Sayı: 2 June/Haziran 2025

Research Articles / Özgün Makaleler

Case Reports / Olgu Sunumları

Ankara Tıp 78 Yıl

galenos yayınevi

Ankara Üniversitesi
Tıp Fakültesi mecmuası
Journal of Ankara University Faculty of Medicine

Journal of Ankara University Faculty of Medicine is an official journal of the Ankara University Faculty of Medicine.
Ankara Üniversitesi Tıp Fakültesi Mecmuası, Ankara Üniversitesi Tıp Fakültesi'nin resmi yayın organıdır.

Publisher Contact/Yayınevi İletişim
Address/Adres: Molla Gürani Mah. Kaçamak Sk. No: 21/1 34093 İstanbul, Türkiye
Phone/Telefon: +90 (530) 177 30 97 / +90 (539) 307 32 03
E-mail/E-posta: info@galenos.com.tr/yayin@galenos.com.tr **Web:** www.galenos.com.tr
Publisher Certificate Number/Yayıncı Sertifika No: 14521

Publishing Date/Yayın Tarihi: Haziran 2025 / June 2025

E-ISSN: 1307-5608
International scientific journal published quarterly.
Üç ayda bir yayımlanan süreli yayındır.

Ankara Üniversitesi
Tıp Fakültesi
mecmuası
Journal of Ankara University Faculty of Medicine

SCIENTIFIC ADVISORY BOARD/DANIŞMA KURULU

Ankara Üniversitesi
Tıp Fakültesi
mecmuası
Journal of Ankara University Faculty of Medicine

SCIENTIFIC ADVISORY BOARD/DANIŞMA KURULU

Ankara Üniversitesi
Tıp Fakültesi
mecmuası
Journal of Ankara University Faculty of Medicine

SCIENTIFIC ADVISORY BOARD/DANIŞMA KURULU

Ankara Üniversitesi
Tıp Fakültesi
mecmuası
Journal of Ankara University Faculty of Medicine

Please refer to the journal's webpage **(https://www.ankaratipfakultesimecmuasi.net/)** for "Aims and Scope", "Instructions to Authors" and "Ethical Policy".

The editorial and publication process of Journal of Ankara University Faculty of Medicine are shaped in accordance with the guidelines of ICMJE, WAME, CSE, COPE, EASE, and NISO. The journal is in conformity with the Principles of Transparency and Best Practice in Scholarly Publishing.

Journal of Ankara University Faculty of Medicine is indexed in **Tübitak/Ulakbim TR Dizin, EBSCO (Central & Eastern European Academic Source), Gale, ProQuest, CABI, IdealOnline, J-GATE, Hinari, GOALI, ARDI, OARE, AGORA, Türk Medline, Embase** and **Türkiye Atıf Dizini**.

The journal is published electronically.

Owner: Zehra Aycan on behalf of Journal of Ankara University Faculty of Medicine

Chief Editor: Neriman Defne Altıntaş

Ankara Üniversitesi
Tıp Fakültesi
mecmuası
Journal of Ankara University Faculty of Medicine

CONTENTS / İÇİNDEKİLER

Research Articles / Özgün Makaleler

Case Reports / Olgu Sunumları

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2024.45762
J Ankara Univ Fac Med 2025;78(2):87-92

BASIC MEDICAL SCIENCES / TEMEL TIP BİLİMLERİ

Evaluation of Academic Success of Ankara University Faculty of Medicine Students According to the Social Determinants of Health

Ankara Üniversitesi Tıp Fakültesi Öğrencilerinin Akademik Başarılarının Sağlığın Sosyal Belirleyicilerine Göre İncelenmesi

Filiz Ak Azar[1], Elif Nur Çakınberk[2], Melda Doğan[2], Yiğit Yahya İkizler[2], Ece Korkut[2], Ceyda Ceren Dönder[2], Sezin Naz Yıldırım[2], Cevdet Arda Selvi[2], Beyza Doğanay Erdoğan[3]

[1]Ankara University Faculty of Medicine, Department of Family Medicine, Ankara, Türkiye
[2]Ankara University Faculty of Medicine, Ankara, Türkiye
[3]Ankara University Faculty of Medicine, Department of Biostatistics, Ankara, Türkiye

Abstract

Objectives: The objective of this study is to investigate the association between social determinants of health (SDOH) and academic success among preclinical students at Ankara University Faculty of Medicine. We aim to provide insights for policies and practices that promote student well-being and ensure equitable support for academic achievement.

Materials and Methods: A cross-sectional survey design was employed over a period of 18 months, from October 2021 to March 2023. Data was collected through an online survey using Google Forms, including demographic and academic achievement information, and analyzed using statistical tests. Ethical approval was obtained, and a sample of 153 participants was used for analysis.

Results: This study was conducted with 153 preclinical students from Ankara University Faculty of Medicine and evaluated the SDOH. The participants, predominantly Turkish citizens (93.5%) and female (65.4%), had diverse accommodation arrangements, including living with parents (39.9%) or in a dormitory with roommates (32.0%). Factors such as access to healthcare, monthly income, safety, social support, and environmental conditions were assessed. Academic success, measured through a Likert scale, revealed that feeling non-discriminated and receiving psychological support significantly correlated with academic performance. However, other SDOH did not show a significant association with academic success.

Conclusion: While SDOH other than feeling non-discriminated and receiving psychological support did not show significant correlations in our study, further research is needed to explore their impact. Creating a supportive and non-discriminatory environment is essential for the academic success and well-being of medical students.

Keywords: Academic success, academic inventory scale, social determinants of health, medical students

Öz

Amaç: Bu çalışmanın amacı, Ankara Üniversitesi Tıp Fakültesi klinik öncesi öğrencileri arasında sosyal sağlık belirleyicileri (SDOH) ile akademik başarı arasındaki ilişkiyi araştırmak, öğrenci refahını destekleyen politika ve uygulamalara içgörü sağlamak ve akademik başarı için eşit destek sağlama konusunda farkındalıklar sunmaktır.

Gereç ve Yöntem: On sekiz aylık bir süre boyunca, Ekim 2021'den Mart 2023'e kadar kesitsel bir anket tasarımı kullanılmıştır. Veriler, Google Forms aracılığıyla çevrimiçi olarak toplanmıştır ve demografik ve akademik başarı bilgilerini içermektedir. Veriler istatistiksel testler kullanılarak analiz edilmiştir. Etik kurul onayı alınmıştır ve analiz için 153 katılımcı örneği kullanılmıştır.

Address for Correspondence/Yazışma Adresi: Elif Nur Çakınberk, MD
Ankara University Faculty of Medicine, Department of English Medicine, Ankara, Türkiye
E-mail: elifnurcakinberk@gmail.com **ORCID ID:** orcid.org/0000-0003-1072-9068

Received/Geliş Tarihi: 11.06.2023 **Accepted/Kabul Tarihi:** 22.10.2024 **Epub:** 06.05.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025
Cite this article as/Atıf: Ak Azar F, Çakınberk EN, Doğan M, et al. Evaluation of academic success of Ankara University Faculty of Medicine students according to the social determinants of health. J Ankara Univ Fac Med. 2025;78(2):87-92

Bulgular: Ankara Üniversitesi Tıp Fakültesi'ndeki 153 klinik öncesi öğrenci üzerinde yaptığımız çalışmada SDOH incelenmiştir. Katılımcılar, çoğunlukla Türk vatandaşı (%93,5) ve kadın (%65,4) öğrencilerden oluşmaktadır ve aileleriyle birlikte yaşayanlar (%39,9) veya yurtta oda arkadaşlarıyla yaşayanlar (%32,0) gibi farklı konaklama düzenlemelerine sahip oldukları gözlemlenmiştir. Sağlık hizmetlerine erişim, aylık gelir, güvenlik, sosyal destek ve çevresel koşullar gibi faktörler de değerlendirilmiştir. Bir Likert ölçeği aracılığıyla ölçülen akademik başarının ayrımcılık hissetmeme ve psikolojik destek alma ile anlamlı bir şekilde ilişkili olduğu görülmüştür. Ancak diğer SDOH, akademik başarıyla anlamlı bir ilişki göstermemiştir.

Sonuç: Çalışmamızda ayrımcılık hissetmeme ve psikolojik destek alma dışındaki SDOH akademik başarıyla anlamlı bir ilişki göstermemesine rağmen, etkilerini araştırmak için daha fazla çalışmaya ihtiyaç vardır. Tıp öğrencilerinin akademik başarı ve refahını desteklemek için destekleyici ve ayrımcılık yapmayan bir ortamın oluşturulması önemlidir.

Anahtar Kelimeler: Akademik başarı, akademik envanter ölçeği, sağlığın sosyal belirleyicileri, tıp öğrencileri

Introduction

The field of medicine is very demanding both academically and personally. Medical students must balance rigorous coursework with the demands of clinical rotations, research, and other extracurricular activities (1). In order to continue to care about others, we, as students, also need to prioritize our own health and well-being. While the importance of individual health is widely recognized by medical schools and institutions (2), there is still much to be learned about how social determinants of health (SDOH) affect academic success in medical school.

Some academic groups in Türkiye conducted a study of the validity and reliability of Turkish adaptations of the Academic Success Inventory Scale in university students (3). Although not designed specifically for medical students, their study highlights the importance of measuring academic success and the factors that contribute to it. This study provides insights for evaluating and understanding the academic success of medical students.

Social Determinants of Health

SDOH are non-medical factors that contribute to an individual's overall health and well-being (4). Examples of these determinants are education, employment opportunities, housing and access to healthcare (5). These factors can play an important role in determining an individual's overall health. For medical students, SDOH can have a significant impact on academic success.

Studies show that SDOH can influence academic success in different ways. For example, low-income students may have limited access to resources such as textbooks, technology, and tutoring, making it more difficult for them to excel academically (6). Similarly, students without a permanent place to live may find it difficult to balance the search to find and maintain their housing with their studies (7). In addition, students without access to medical care may face health problems that make it difficult to concentrate on school work (8).

This study aims to provide useful insights for policies and practices aimed at promoting student well-being by investigating the relationship between SDOH and academic success in medical students. For example, this research may identify specific areas that require additional support and resources to ensure students have the tools and opportunities they need to succeed academically. This study may also indicate a need for policies and programs that address broader SDOH, such as affordable housing and access to health care.

Medical schools should consider the social determinants of an applicant's health in admission decisions and provide additional resources and support to students who may face SDOH-related challenges. In this way, medical schools can promote student diversity and equity while ensuring that all students receive the support they need to succeed academically. In summary, the relationship between SDOH and medical students' academic success is a complex and multifaceted issue. By exploring this link, this research intends to provide useful insight into policies and practices aimed at promoting student well-being and ensuring that all students receive the support they need to succeed academically. The ultimate goal is to improve the overall health and well-being of medical students and promote equity and diversity in the health profession.

Materials and Methods

Study Design

This study employed a cross-sectional survey design to investigate the association between the SDOH and academic success levels among preclinical students at Ankara University Faculty of Medicine. The study was conducted over a period of 18 months, from October 2021 to March 2023.

Study Population

The present research focuses on the medical student population in Türkiye, with a study sample limited to preclinical students (semester 1, 2, and 3) enrolled in the Ankara University Faculty of Medicine. The study excluded students who were involved in organizing the survey administration, as well as clinical students (semesters 4, 5, and 6). As the clinical and preclinical periods of the medical faculty vary from a psychosocial point of view and should be evaluated seperately, we included

only preclinical students in this study. A seperate on clinical students is recommended. As a result of the power analysis, it was determined that 246 people should be reached. However, due to various limitations, 153 people were included in the study.

Research Hypothesis

The research hypothesis for this study is that a high level of SDOH in Ankara University Faculty of Medicine preclinical students has a positive effect on their academic achievement levels.

Variables of the Study

The independent variables of this study are social determinants affecting the health of Ankara University Medical Faculty students, including economic stability, access to health services and quality of healthcare that could be accessed neighborhood and built environment, and social and community context. The dependent variable is the success levels determined by the individual evaluations of the students according to items such as general academic skill, internal motivation/confidence, perceived instructor efficacy, concentration, external motivation/future, socializing, career decidedness, lack of anxiety, personal adjustment, and external motivation/current.

Survey Plan

The survey was administered using an online platform, specifically Google Forms, which was distributed to the student participants through various digital channels. Prior to accessing the survey, participants were required to provide their informed consent by agreeing to the terms outlined in a consent form. Only those who had given their explicit consent were able to proceed to the questionnaire, ensuring that all participants had provided informed consent to participate in the research.

In the initial segment of the survey, data pertaining to the students' demographic, social, behavioral, and economic backgrounds was gathered through the implementation of polar questions. The second segment of the study aimed to assess the academic achievement levels of the participants, utilizing the seven-point Likert-type "Academic Achievement Inventory Scale for University Students", originally developed by Prevatt et al. (9) and adapted into Turkish by Orçanlı et al (3). This instrument has demonstrated cross-cultural applicability and has undergone rigorous psychometric testing for validity and reliability in Türkiye. Prior to use in the present study, ethical approval and permissions for the utilization of the aforementioned scale were obtained from the owners through formal correspondence.

Statistical Analysis

Numerical data has been summarized using median (minimum-maximum) and mean ± standard deviation, while frequency and percentage, n (%), was used for categorical data. Mann-Whitney U test has been done during data analysis. SPSS v.15 was used for data analysis, and $p<0.05$ was considered statistically significant. Due to various limitations, the data of 153 participants has been used.

Ethics Committee Approval

Ethical approval for the study was obtained from the Ankara University Faculty of Medicine Ethics Committee for Student Research (decision no.: E-72189195-050.03.04-775372, date: 02.01.2023).

Literature Review

The importance of understanding the relationship between SDOH and the academic success of medical students is widely recognized. Several studies have addressed this issue, revealing how SDOH influence academic performance.

The World Health Organization (WHO) recognizes the impact of social determinants on health in its charter and policy documents (10). They emphasize the need to address these determinants to improve overall health outcomes. WHO's comprehensive perspective provides a fundamental understanding of the influence of social determinants on the academic success of medical students (10).

WHO also emphasizes the importance of SDOH in its online resources (4). This resource provides an overview of various social determinants and their impact on health outcomes. Understanding these determinants is important for examining their impact on the academic success of medical students.

Survey of this study has been developed as an "Academic Success Inventory" for college students (9). This has practical implications for assessing and promoting academic success. Although this study did not specifically target medical students, it highlights the relevance of measuring academic success and the implications of supporting the student's educational journey. The development and practical implications of this scale are also applicable to the medical school environment. Some studies (11,12) emphasize the need to consider the underlying causes of SDOH. They argue that addressing these root causes is essential to promoting overall health and well-being. This perspective provides a basis for understanding the influence of social determinants on the academic success of medical students.

The relationship between unconscious bias and clinical judgment by medical students is well investigated (11). This research reveals the existence of racial and social class biases that can affect how students are evaluated and supported in their academic pursuits. Understanding these biases is critical to creating an equitable learning environment that promotes academic success for all students.

Insights into gender inequality in academia is also provided (13). This study highlights the gender gap in scientific research

and the importance of addressing this gap to promote academic success and gender equality. This research is important for medical students because it highlights the need for gender-responsive policies and support systems that promote equal opportunity.

In summary, the reviewed literature highlights the importance of understanding the SDOH and their impact on the academic success of medical students. These studies highlight the need to address root causes, adopt appropriate assessment tools, and consider the wider social context, including global health crises. By understanding and addressing these factors, medical schools can promote student well-being, diversity, equity, and overall academic success. WHO resources provide comprehensive information and perspectives on the SDOH and serve as valuable references for further research in this area.

Results

A total of 153 students studying at Ankara University Faculty of Medicine in the preclinical years took part in our questionnaire. Out of the participants 34.6% (n=53) were male and 65.4% (n=100) were female. The mean age of the participants was 19.87. 93.5% were Turkish citizens and 6.5% were foreign citizens. The distribution of the participants' accommodation conditions are demonstrated in Table 1.

The SDOH of the participants were asked through 11 questions that aimed to evaluate their conditions in a precise and effective manner after thorough research on the topic.

It was found that, 148 of the 153 students were able to access basic healthcare services when they were ill. One hundred fifteen of them believed their monthly income was sufficient for access to healthy food, appropriate clothing, transportation, educational materials, and accommodation and 85 students believed their monthly income did not hinder them from having a social life and hobbies. One hundred and twenty nine students were not required to work part-time because their income was sufficient for them. One hundred forty-five of the students could provide appropriate heating for the place where they accomodated and 143 felt safe in the place where they accomodated. One hundred twenty-four of them said that they had a sufficient internet connection and 102 were not bothered by noise in the place where they accomodated. One hundred and nine students were satisfied with the size of the space they had in the place where they accomodated and 136 did not feel discriminated in their environment. One hundred thirty eight students had people in their environment (family, friends, etc.) who provided them the necessary psychological support.

Table 1: Distribution of the participants' accommodation conditions

Variables	n (%)
With a relative	4 (2.6)
At home (with my parents)	61 (39.9)
At home [with flatmate (s)]	21 (13.7)
At home (by myself)	11 (7.2)
Dormitory [with roommate (s)]	49 (32.0)
Dormitory (by myself)	7 (4.6)
Total	**153 (100)**

For the calculation of the academic success of the participants, which were measured through the likert scale mentioned above, we used the sum of the numerical values after recoding the reverse coded questions. The points were given from 1 to 7, 1 being "I completely disagree" and 7 being "I completely agree".

After the given answers by each participant were added up, those who had a higher score were considered more successful. Out of these results, the minimum was 115 points, the maximum was 248 points, and the mean was 180 points.

For the comparison of the SDOH and academic success, the Mann-Whitney U test was used, in order to compare the two independent variables. In this paper, all of the SDOH were individually compared with the academic success, and out of those, it was found that the following SDOH had a statistically significant correlation with academic success: "I do not feel discriminated in my environment" (p=0.32). The median of the students' achievements who did not feel discriminated in their environment was higher than the median of those who felt discriminated. This shows us that there is a positive relationship with the "I don't feel discriminated in my environment" statement and students' total score of success which can be seen in Figure 1.

For the statement "There are people in my environment (family, friends, etc.) who will provide me the necessary psychological support" (p=0.14), the median of the achievements of students who received sufficient psychosocial support from their environment was higher than the median of those who did not receive this support. This shows us that there is a positive relationship with the "There are people in my environment (family, friends, etc.) who will provide me with the necessary psychological support" statement and students' total score of success which can be seen in Figure 2.

The other SDOH that we compared with the academic success were not found to have a significant correlation. The statement "I can access basic healthcare services when I am ill" had a p-value of 0.648. "I believe my monthly income is sufficient for healthy food, appropriate clothing, transportation, educational materials, and accommodation" had a p-value of 0.097. "I believe my monthly income does not hinder me from having a social life and hobbies" had a p-value of 0.155 "I am not required to work part-time because my income is sufficient for me" had a p-value of 0.390 "I can heat the place where I

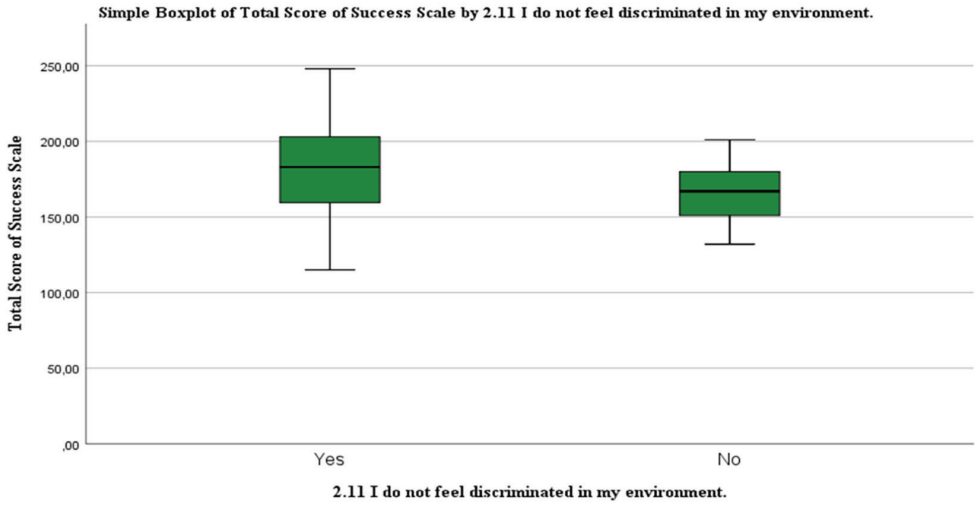

Figure 1: Simple boxplot of "Total Score of Success Scale" by "I do not feel discriminated in my environment"

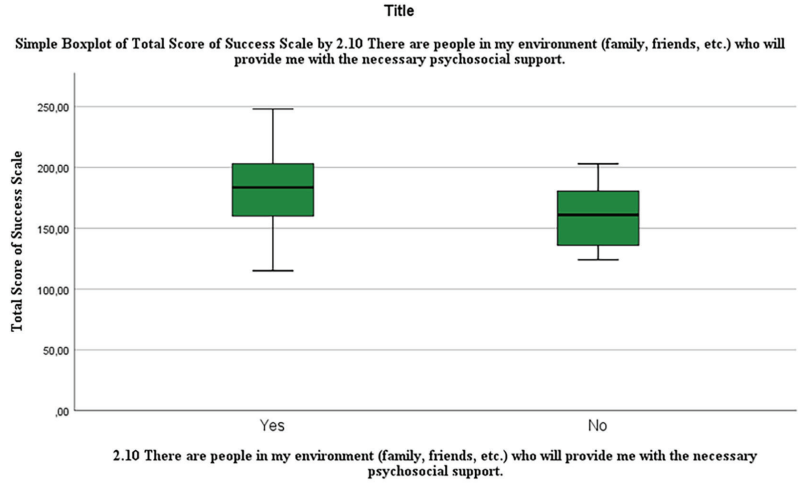

Figure 2: Simple boxplot of "Total Score of Success Scale" by "There are people in my environment (family, friends, etc.) who will provide me with the necessary psychological support"

accommodate" had a p-value of 0.167 "I feel safe in the place where I accommodate" had a p-value of 0.229 "The internet connection in the place where I accommodate is sufficient" had a p-value of 0.125 "I am not bothered by noise in the place where I accommodate" 0.197 "I am satisfied with the size of the space I have in the place where I accommodate" had a p-value of 0.074. As all of these were not lower than p=0.05, they were accepted as not statistically significant correlations.

Discussion

The results of our research on investigating the "relationship between the academic achievement of Ankara University Faculty of Medicine preclinical students and the SDOH" show that students who are not discriminated by their environment and that have people around them who provide them with all kinds of psychological support, have a positive affect on their academic success.

We see that it is very important for medical students to have someone around them who provides them with all kinds of psychological support, especially during stressful periods of their intensive education life. Another factor that also has an important place is discrimination. Of course, just as every individual is different, so is every medical school student. And the duty of a human being is to ignore these differences and treat each person equally under equal conditions. As we can see in our results, non-discrimination and equal behavior of each student positively affects their academic success.

On the other hand, we see that we cannot reach any significant value about the relationship between academic success and other factors in the SDOH. However, the fact that

we could not reach a significant value does not mean that the academic success of any student is not affected by these factors. For example, it is especially important for a student to feel safe where they live. Because the safer a person feels in their environment, the more comfortable they feel mentally. Feeling mentally comfortable also makes it easier to focus on the lessons. This indirectly affects academic success positively. However, since our study is limited to a certain group of students, the significance that we could not achieve may be obtained in other studies.

Study Limitations

As the surveys are based on individuals' opinions, may contain bias and results can vary.

Conclusion

In order for medical students to have good academic success and at the same time to be healthy both in their educational life and in the future, they should be given psychological support by the people around them and all kinds of discrimination should be prevented. Other factors among the SDOH should also be investigated to show whether they have an impact on academic success.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ankara University Faculty of Medicine Ethics Committee for Student Research (decision no.: E-72189195-050.03.04-775372, date: 02.01.2023).

Informed Consent: The participants were informed about the anonymisation of the data and voluntary participation, and their written consent was taken.

Acknowledgements

We would like to thank our biostatistics consultant, Associate Professor Beyza Doğanay Erdoğan, for her precious contributions to the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.A.A., E.N.Ç., M.D., Y.Y.İ., E.K., C.C.D., S.N.Y., C.A.S., Concept: F.A.A., E.N.Ç., M.D., Y.Y.İ., E.K., C.C.D., S.N.Y., C.A.S., B.D.E., Design: F.A.A., E.N.Ç., M.D., Y.Y.İ., E.K., C.C.D., S.N.Y., C.A.S., B.D.E., Data Collection or Processing: E.N.Ç., M.D., Y.Y.İ., E.K., C.C.D., S.N.Y., C.A.S., Analysis or Interpretation: E.N.Ç., M.D., E.K., B.D.E., Literature Search: Y.Y.İ., C.A.S., Writing: E.N.Ç., M.D., Y.Y.İ., E.K., C.C.D., S.N.Y., C.A.S.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: This study received no financial support.

References

1. Al-Halabi B, Marwan Y, Hasan M, et al. Extracurricular research activities among senior medical students in Kuwait: experiences, attitudes, and barriers. Adv Med Educ Pract. 2014;5:95-101.
2. Izadnegahdar R, Correia S, Ohata B, et al. Global health in Canadian medical education: current practices and opportunities. Acad Med. 2008;83:192-198.
3. Orçanlı K, Bekmezci M, Boztoprak H. Adaptation of Academic Success Inventory Scale for College Students to Turkish: validity and reliability study. OPUS International Journal of Society Researches, 2021;17:3999-4026.
4. World Health Organization. Social determinants of health. [Internet]. 2022. Available from: https://www.who.int/health-topics/social-determinants-of-health#tab=tab_1
5. Gnanapragasam SN, Astill Wright L, Pemberton M, et al. Outside/inside: social determinants of mental health. Ir J Psychol Med. 2023;40:63-73.
6. Kurmanova A, Kozhayeva S, Ayupova G, et al. University students' relationship with technology: psychological effects on students. World Journal on Educational Technology: Current Issues. 2022;14:1225-1233.
7. Nelson D, Misra K, Sype G. et al. An analysis of the relationship between distance from campus and GPA of commuter students. Journal of International Education Research. 2016;12:37-46
8. Strolin-Goltzman J. The relationship between school-based health centers and the learning environment. J Sch Health. 2010;80:153-159.
9. Prevatt F, Li H, Welles T, et al. The academic success inventory for college students: scale development and practical implications for use with students. Journal of College Admission. 2011;26-31.
10. World Health Organization. Constitution of the World Health Organization. Basic Documents. Forty. [Internet]. 2006. Available from: https://www.who.int/docs/default-source/documents/publications/basic-documents-constitution-of-who.pdf
11. Haider AH, Sexton J, Sriram N, et al. Association of unconscious race and social class bias with vignette-based clinical assessments by medical students. JAMA. 2011;306:942-951.
12. Shen H. Inequality quantified: Mind the gender gap. Nature. 2013;495:22-24.
13. Braveman P, Gottlieb L. The social determinants of health: it's time to consider the causes of the causes. Public Health Rep. 2014;129(Suppl 2):19-31.

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2025.78608
J Ankara Univ Fac Med 2025;78(2):93-105

BASIC MEDICAL SCIENCES / TEMEL TIP BİLİMLERİ

In Vivo Effects of Exogenous BDNF Administration on AMPA Receptors in the Dentate Gyrus of Female Rats

Eksojen BDNF Uygulamasının Dişi Sıçan Dentat Girus AMPA Reseptörüne *In Vivo* Etkisi

Burcu Sırmatel Bakrıyanık[1,2], Çiğdem Özer[3], Cemile Merve Seymen[4]

[1]*Ankara University Institute of Health Sciences, Department of Interdisciplinary Neuroscience, Ankara, Türkiye*
[2]*Gazi University Neuroscience and Neurotechnology Center of Excellence, Ankara, Türkiye*
[3]*Gazi University Faculty of Medicine, Department of Physiology, Ankara, Türkiye*
[4]*Gazi University Faculty of Medicine, Department of Histology and Embryology, Ankara, Türkiye*

Abstract

Objectives: Previous *in vitro* studies have demonstrated that brain-derived neurotrophic factor (BDNF) modulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) expression and the trafficking of synaptic AMPA receptors (AMPARs). However, it is not known whether exogenous BDNF administration similarly regulates AMPAR trafficking *in vivo*. This study aims to elucidate this unknown aspect. Additionally, considering that BDNF and estrogen have similar effects in the brain and may interact through their cellular mechanisms, the study also aims to explore the outcomes of BDNF administration in female rats.

Material and Methods: For this purpose, female Long-Evans rats in the same estrus phase were divided into the experimental group (EG, n=5) and the control group (CG, n=5). In the EG, recombinant BDNF protein (4 µg/day) was administered to the right hippocampus via osmotic minipumps for 7 days, while the CG received phosphate-buffered saline (4 µg/day) under the same conditions. The Morris Water Maze (MWM) test was employed for assessing learning and memory. AMPAR levels in the left and right hippocampi were examined using immunohistochemical methods, and the intensity patterns were evaluated using H-scoring.

Results: Although no significant behavioral differences were observed between the groups in the MWM task ($p>0.05$), H-scoring results revealed that BDNF treatment significantly increased GluR1 subunit immunoreactivity in the right hippocampus of the EG compared to the CG ($p\leq0.001$). Notably, GluR1 H-score levels were also significantly increased in the left hemisphere, which was not directly infused with BDNF.

Conclusion: This study demonstrates that long-term BDNF administration increases AMPAR levels in the hippocampus *in vivo*. While this increase has behavioral implications for spatial learning and memory in female rats, further research is needed to explore the full extent of these effects.

Keywords: AMPA receptor, long-term potentiation, brain-derived neurotrophic factor, learning and memory, synaptic plasticity

Öz

Amaç: Önceki *in vitro* araştırmalar, beyin türevli nörotrofik faktörün (BDNF) α-amino-3-hidroksi-5-metil-4-izoksazol propiyonik asit (AMPA) ekspresyonunu ve sinaptik AMPA reseptörlerinin (AMPAR) trafiğini modüle ettiğini göstermiştir. Ancak, eksojen BDNF uygulamasının *in vivo* ortamda AMPAR trafiğini benzer şekilde düzenleyip düzenlemediği bilinmemektedir. Bu çalışma, bu bilinmeyeni aydınlatmayı amaçlamaktadır. Ayrıca BDNF ve östrojenin beyinde benzer etkilere sebep olması ve hücresel mekanizmalarının birbirini etkilemesi nedeniyle dişilere BDNF uygulamanın sonuçlarını gözlemlemek de hedeflenmiştir.

Gereç ve Yöntem: Aynı estrus evresindeki dişi Long-Evans sıçanları, deney grubu (DG, n=5) kontrol grubu (KG, n=5) olarak ayrılmıştır. DG sağ hipokampüslerine BDNF proteini (4 µg/gün), KG grubu sıçanlarınkine ise fosfat tamponlu salin (4 µg/gün), ozmotik minipompalar vasıtasıyla

Address for Correspondence/Yazışma Adresi: Prof. MD. Çiğdem Özer,
Gazi University Faculty of Medicine, Department of Physiology, Ankara, Türkiye
E-mail: cigdemozer@gazi.edu.tr **ORCID ID:** orcid.org/0000-0002-2705-4522

Received/Geliş Tarihi: 16.07.2024 **Accepted/Kabul Tarihi:** 28.02.2025 **Epub:** 12.05.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025
Cite this article as/Atıf: Sırmatel Bakrıyanık B, Özer Ç, Seymen CM. *In vivo* effects of exogenous BDNF administration on AMPA receptors in the dentate gyrus of female rats. J Ankara Univ Fac Med. 2025;78(2):93-105

intrahipokampal olarak 7 gün boyunca verilmiştir. Öğrenme ve bellek görevleri için Morris Su Labirenti (MWM) testi uygulanmıştır. Sol ve sağ hipokampal AMPAR seviyeleri immünohistokimyasal yöntemle incelenmiş ve yoğunluk deseni H-skorlama yapılarak değerlendirilmiştir.

Bulgular: Genel olarak davranış deneyi açısından gruplar arasında anlamlı farklılık gözlenmemesine rağmen H-skor sonuçlarına göre BDNF uygulaması DG'nin sağ ($p \leq 0,001$) hipokampusunda KG'ye kıyasla AMPAR alt birimi GluR1'in immünoreaktivitesini önemli ölçüde artırmıştır. Hatta GluR1 H-skor seviyeleri infüzyon alanı olmayan sol hemisferde de anlamlı olarak yükselmiştir ($p \leq 0,001$).

Sonuç: Bu çalışma, uzun süreli BDNF uygulamasının hipokampusta AMPAR seviyelerini artırdığını *in vivo* olarak göstermektedir. Bu artışın dişi sıçanlardaki mekansal öğrenme ve bellek sürecine davranışsal yansımaları olmakla birlikte anlamlı etkileri için ileri araştırmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: AMPA reseptörü, uzun-dönem potansiyasyon, beyin türevli nörotrofik faktör, öğrenme ve bellek, sinaptik plastisite

Introduction

Memory is a complex cognitive function based on synaptic plasticity. Long-term potentiation (LTP), a fundamental mechanism of synaptic plasticity, has been widely explored in hippocampal neurons, where it plays a crucial role in memory formation (1,2). LTP progresses through three distinct stages: Short-term potentiation, early-LTP (E-LTP), and late-LTP (L-LTP). The first two phases involve modifications of pre-existing proteins, whereas L-LTP depends on the activation of transcription factors and protein synthesis, allowing sustained synaptic strengthening (3,4). Glutamatergic excitatory synapses and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are essential for LTP in the hippocampus. Specifically, the regulation of AMPAR synaptic trafficking is crucial for the long-term encoding of synaptic activity (5,6). AMPARs are tetrameric receptors composed of combinations of four distinct subunits: GluR1, GluR2, GluR3, and GluR4. In the adult hippocampus, there are two dominant types of AMPARs: Those formed by "GluR1 and GluR2" and those formed by "GluR3 and GluR2" (5). Among these subunits, the GluR1 subunit is particularly important for synaptic plasticity and LTP (7,8).

As essential modulators of synaptic plasticity, neurotrophins are a group of secreted proteins involved in neuronal survival and function (9,10). Brain-derived neurotrophic factor (BDNF) is essential for neuron differentiation and survival, and unlike other members of this family, it has a broad distribution in the adult brain and hippocampal subregions. BDNF plays a crucial role in regulating activity-dependent changes in synaptic structure and function. BDNF is postulated to potentiate synaptic responsiveness to tetanic stimulation, thereby facilitating E-LTP induction, while orchestrating synaptic vesicle dynamics through modulation of synaptic protein phosphorylation and spatial redistribution (11). Genetic and pharmacological interrogations of BDNF and its cognate receptor Tyrosine kinase B (TrkB) underscore its indispensable role in both the initiation and sustenance of L-LTP (12,13). In hippocampal slices derived from BDNF-deficient mice, the perturbation in LTP induction was ameliorated upon reinstatement of *BDNF* gene expression (14). These findings suggest that endogenous BDNF is necessary for various stages of LTP. Moreover, to better understand its functions and mechanisms in this process, and how it alters extrinsic modulation of synaptic plasticity and memory, numerous studies have explored exogenous BDNF applications (15-20). Studies focusing on its effects on AMPARs have shown that BDNF modulates AMPAR expression by regulating specific phosphorylation pathways (21,22). Similarly, studies in hippocampal and cortical neuron cultures have revealed that BDNF increases AMPAR levels in both the membrane (23,24) and synaptic pools (25,26). It was also noted that BDNF treatment in cortical cultures was found to significantly elevate AMPAR levels, particularly enriching GluR1- and GluR2-bearing subunits (27). These findings set the stage for further exploration of how AMPAR modulation by BDNF contributes to synaptic plasticity and memory formation.

Among these, the activation of estrogen receptor beta (ERβ), a nuclear receptor for the hormone estrogen, has been implicated in the regulation of AMPAR GluR1 subunit expression (28). Estrogen is known to modulate cognitive processes and hippocampal structure and function through interactions with ERα, ERβ nuclear receptors, and ER-like proteins on the plasma membrane (29,30). Selective ERβ agonists, when administered *in vivo*, have been demonstrated to increase the expression of AMPAR GluR1 and postsynaptic density protein 95 (PSD-95), a postsynaptic scaffolding protein critical for the regulation of AMPAR trafficking. Furthermore, ERβ activation has been reported to alter synaptic architecture by influencing dendritic branching, dendritic spine morphology, and density in the hippocampal CA1 and dentate gyrus regions (28). It was found that spatial memory performance was significantly enhanced by both the activation of ERβ and the administration of estradiol. Furthermore, functional overlap was revealed in the examination of the effects of estrogen and BDNF on the central nervous system, indicating that the influence of estrogen on the hippocampus is analogous to that of BDNF (31). There is evidence suggesting that estradiol can induce BDNF expression (32,33), and estrogen receptors have been found to colocalize with neurons expressing BDNF and TrkB (34). However, some studies report that elevated endogenous estrogen levels correlate with reduced BDNF mRNA levels (35,36), while others observe no significant effect of estrogen (37). Consequently, the mechanisms that contribute to the inconsistent findings concerning estrogen-BDNF interactions remain unclear, highlighting the necessity for additional research.

Although many findings suggest that exogenous BDNF administration modulates AMPAR trafficking, it remains uncertain whether similar stimulation occurs in an *in vivo* setting or what effects it has specifically on female rats. To address this gap, the first part of our study involved the infusion of recombinant BDNF protein into the right hippocampal dentate gyrus of female rats using osmotic minipumps, differing from traditional single injection studies. This approach aimed to observe the *in vivo* effects of unilateral intrahippocampal BDNF administration on the levels of AMPAR GluR1 subunits in the dentate gyrus. In the second part of the study, the Morris Water Maze (MWM) task, a well-established model for measuring spatial learning and memory (38), was employed to investigate the impact of the administered protein on spatial memory.

Materials and Methods

This study was supported by the Gazi University Scientific Research Projects Coordination Unit under grant number 01/2017-26 and approved by the Gazi University Local Ethics Committee for Animal Experiments (decision number: E.28661, date: 16.08.2017).

Animals

In this study, we utilized adult female Long-Evans rats (n=10), each weighing between 200-250 g. The animals were obtained from the Gazi University Laboratory Animals Breeding and Experimental Research Center (GUDAM). All procedures involving the rats were conducted in the designated laboratory settings of GUDAM. Prior to inclusion in the study, vaginal smears were collected to confirm that the animals were in the estrus phase, characterized by baseline levels of estrogen and progesterone (39). Throughout the experiment, vaginal smears were periodically monitored. The rats, all in the same phase, were randomly assigned to two groups: the control group (CG, n=5) and the experimental group (EG, n=5).

Each rat was housed individually in a controlled laboratory environment, ensuring unrestricted access to food and water. The housing conditions included a stable 12:12 hour light-dark cycle and a maintained temperature of 24±2 °C. Behavioral tests were conducted during the light phase. In the EG, recombinant BDNF protein (4 µg/day) was infused into the right hippocampal dentate gyrus via osmotic minipumps for 7 days. In contrast, phosphate-buffered saline (PBS) was infused into the CG rats. Aside from this difference, all other experimental procedures were applied equally to the animals in both groups (Figure 1a).

Implantation of Osmotic Minipumps and Stereotactic Surgery

One day prior to stereotactic surgery, osmotic minipumps (ALZET 1007D, Alza Scientific Products, Palo Alto, CA) were filled with recombinant human BDNF protein (140 µg dissolved in 0.1 M PBS; 4 µg/day per animal; ProSpec, Israel) for the EG and PBS (BioShop, Canada) for the CG. The pumps were then incubated overnight in sterile PBS and set to operate at a flow rate of 0.5 µl/hour for seven days. The appropriate BDNF dose was determined based on the study by Mamounas et al. (40).

Intrahippocampal surgery was performed using a stereotaxic apparatus (Stoelting, USA) under anesthesia with a combination of 10% Ketamine and 2% Xylazine (75-90 mg/kg Ketamine+5-8 mg/kg Xylazine, intramuscular). Infusion cannula (ALZET Brain Infusion Kit 2, Alza Scientific Products, Palo Alto, CA) were implanted into the right dentate gyrus. Based on the Paxinos and Watson (41) atlas, coordinates for the dentate gyrus were determined using bregma as the reference point: -3.8 mm AP, 2.0 mm ML, and -3.2 mm dorsoventral. Prior to initiating the experimental procedure, the accuracy of these coordinates was confirmed in a separate rat using a Hamilton syringe with methylene blue (Figure 1c). The infusion cannula were secured to the skull with dental cement, fixed with machine screws, and connected to the osmotic minipumps. The minipumps were placed in a subcutaneous pocket between the scapula bones

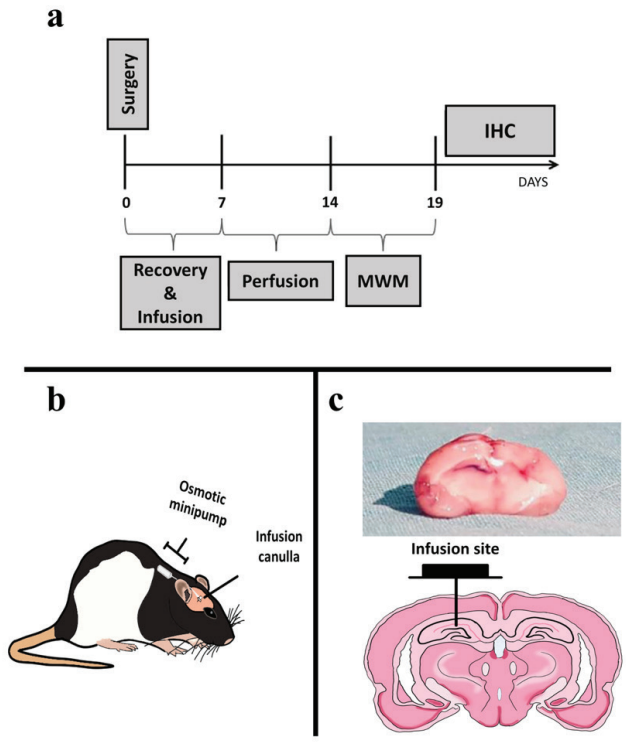

Figure 1: A) A diagram illustrating the overall experimental flow; day 0 symbolizes the start of the experiment, which is the day of the stereotactic surgery. **B)** A schematic representation of the osmotic minipump and infusion cannula implanted into the rat's body. **C)** Right dentate gyrus; infusion area for the EG with BDNF and for the CG with PBS.

MWM: Morris Water Maze, EG: Experimental group, CG: Control group, BDNF: Brain-derived neurotrophic factor, PBS: Phosphate buffered saline

(Figure 1b). After the seven-day infusion period, a seven-day perfusion phase followed to allow for the full diffusion of the administered substances into the hippocampus and to observe their long-term effects. During this perfusion phase, the incision sites were also allowed to heal. Upon completion of the perfusion, the MWM spatial memory task was initiated (Figure 1).

Spatial Memory Task: Morris Water Maze

Cognitive function, specifically learning and memory, was evaluated using the MWM paradigm (42). The maze consists of a tank filled with water, made opaque with black food coloring, measuring 140 cm in diameter and 45 cm in depth. The tank was placed in a room with standard lighting and surrounded by fixed visual cues. The space was conceptually segmented into four distinct quadrants, labeled as star, triangle, pentagon, and circle. A hidden platform was positioned in the center of the triangle quadrant, 2 cm below the water surface. The experiments were recorded using an appropriate camera and software system.

The task consists of two phases: The acquisition phase and the probe test. The acquisition phase spans four days, with four trials per day, aiming to teach the rats the location of the hidden platform using fixed visual cues. At the beginning of each trial, rats were introduced into the maze from varying starting locations and allowed up to 90 seconds to reach the platform. If a rat was unable to locate the platform within this timeframe, it was gently guided by the researcher. Once on the platform, each rat was allowed to remain for 30 seconds to explore the surroundings.

During the acquisition phase, key behavioral metrics, including escape latency, traveled distance, and swimming speed, were systematically recorded. After completing this phase, a probe test was administered, in which the platform was removed, allowing the rats to explore the maze freely for 90 seconds. Throughout this test, multiple parameters were assessed, including the duration spent in each quadrant, swimming speed, the frequency of crossings over the former platform location, time allocation between the center and periphery, and total distance traveled.

Immunohistochemical Analysis

After completing the MWM task, the animals were sacrificed via cardiac puncture under deep anesthesia. Following extraction, brain hemispheres were briefly rinsed with saline and immersed in 10% neutral formaldehyde for at least 72 hours to facilitate immunohistochemical (IHC) analysis. Paraffin-embedded tissue blocks were then prepared using standard histological techniques, from which 4 µm-thick cross-sections were obtained (43).

Following deparaffinization and rehydration, antigen retrieval was achieved using heat in the presence of EDTA (pH: 8.0). To suppress endogenous peroxidase activity, tissue sections were incubated with a 3% hydrogen peroxide solution, followed by serum blocking (Lot: 1754084A, LifeTech, Waltham, MA) for 15 minutes to enhance epitope stability. Subsequently, samples were exposed to a primary antibody specific for anti-glutamate AMPAR 1 (ab31232, Abcam, Cambridge, UK; 1:200 dilution in PBS) at room temperature for 90 minutes. After thorough rinsing with PBS (pH: 7.4), sections were treated with a biotinylated secondary antibody and streptavidin-peroxidase complex (Lot: 1754084A, LifeTech, Waltham, MA) for 10 minutes. The antibody-antigen interaction sites were visualized using 3,3'-diaminobenzidine (DAB; Lot: 38703, DAB Chromogen/Substrate Kit, ScyTek). Finally, slides underwent counterstaining with Harris' Hematoxylin, sequential dehydration in ethanol, clearance with xylene, and permanent mounting with balsam.

Staining intensity and density of anti-glutamate receptor 1 (AMPA Subtype) were analyzed in the dentate gyrus of the right and left hemispheres using a Leica DM4000B light microscope equipped with a DFC280 camera and LAS software (Leica, Wetzlar, GermanyA semi-quantitative evaluation system was employed to categorize staining intensity on a graded scale: 0 (absence of staining), 1 (faint staining), 2 (mild to moderate staining), 3 (moderate staining), 4 (moderate to intense staining), and 5 (pronounced staining). Immunoreactivity scores were independently assessed by two blinded evaluators, who were unaware of the experimental conditions. The H-score was computed using the formula H-score = ΣPi (i + 1), where "i" represents the staining intensity (ranging from 0 to 5), and "Pi" corresponds to the proportion of cells exhibiting each intensity level. Scoring was conducted independently by two investigators.

Statistical Analysis

In this study, MP4 format videos obtained from the MWM task were converted into PNG format images for frame-by-frame analysis. For this purpose, the open-source multimedia processing software FFmpeg was utilized (44). The positions of the rats in the converted PNG images were labeled using the open-source labeling software "LabelMe" (45). The data obtained from the labeled images were analyzed using a custom code written in the Python language (46). To evaluate performance during the acquisition phase of the MWM task, the following metrics were measured: Escape latency, time spent in the center, center distance (the distance the animal traveled in the central area of the maze), peripheral distance, mean cumulative distance (the mean total distance traveled by the animal until reaching the platform), and mean speed. For the probe test phase, the time spent in each quadrant and the number of crossings at the

location of the hidden platform, which served as an indicator of the learning process, were recorded.

The data were analyzed using the Jeffrey's Amazing Statistics Program (47). Repeated measures analysis of variance (ANOVA) was utilized for the evaluation of MWM behavioral data and IHC H-score data. Multiple comparisons were assessed using the post-hoc Tukey test or the Holm test. An independent samples t-test was employed solely for group comparisons. Descriptive statistics were presented as means and standard deviations, with differences considered statistically significant at $p<0.05$.

Results

MWM Task Results

In the acquisition phase of the MWM experiment, the effects of the group, trial, and day variables on escape latencies (the time taken to find the hidden platform) were analyzed using repeated measures ANOVA. The main effect of days on escape latencies was found to be significant [F (3,12): 7.965, p=0.003, η^2=0.238], while the interaction between day and group was not significant [F (3,12): 0.789, p=0.523, η^2=0.456]. Similarly, although the main effect of trials was significant [F (3,12): 7.583, p=0.004, η^2=0.083], the interaction between trial and group was not significant [F (3,12): 3.184, p=0.063, η^2=0.035; Figure 2a, Table 1]. Regarding the time spent in the center, neither the main effects of days [F (3,12): 0.489, p=0.696, η^2=0.016] nor trials [F (3,12): 0.246, p=0.862, η^2=0.007] were found to be significant, nor was the interaction between day and group [F (3,12): 1.464, p=0.274, η^2=0.049; Figure 2b]. All effects related to distances traveled in the center were similarly not significant (Figure 2c). For distances traveled in the periphery, both day [F (3,12): 6.658, p=0.007, η^2=0.217] and trial main effects [F (3,12): 5.940, p=0.010, η^2=0.041] were significant; however, group interactions were not significant [$F_{day*group}$ (3,12): 0.383, p=0.767, η^2=0.012; $F_{trial*group}$ (3,12): 0.471, p=0.708, η^2=0.003; Figure 2d]. The main effects of days and trials on mean cumulative distance were significant [F (3,12): 6.415, p=0.008, η^2=0.131; F (3,12): 5.555, p=0.013, η^2=0.042], while group interactions remained non-significant [$F_{day*group}$ (3,12): 1.000, p=0.426, η^2=0.020; $F_{trial*group}$ (3,12): 1.188, p=0.356, η^2=0.009; Figure 2e]. When examining the effects on mean swimming speed, only the main effect of days was found to be significant [F (3,12): 4.210, p=0.030, η^2=0.107], with the Holm test indicating that the speed on day 4 was statistically significantly lower than on Day 1 (p=0.004; Figure 4a, Table 1).

During the probe phase of the MWM task, the duration spent in each quadrant did not exhibit a statistically meaningful variation between the two groups [$F_{quadrant*group}$ (3, 12): 1.262, p=0.31, η^2=0.092; Figure 3a, Table 2]. Similarly, while the EG demonstrated a greater frequency of crossings at the

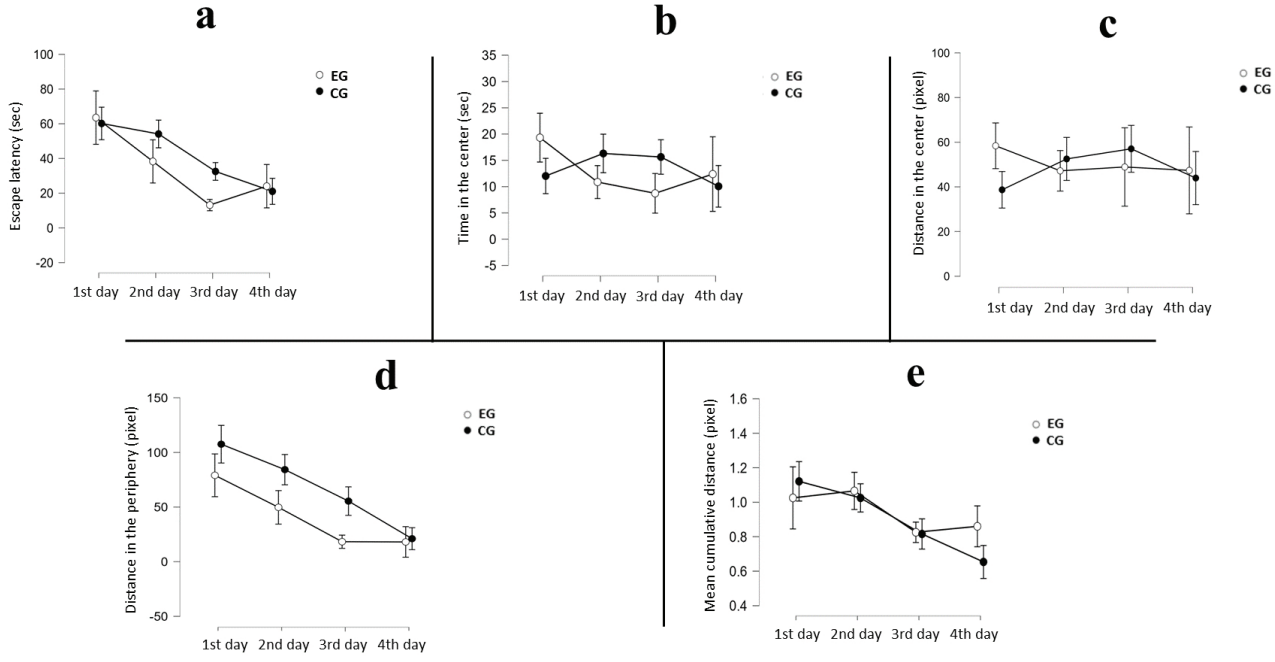

Figure 2: Daily findings of the Morris Water Maze task during the acquisition phase for the groups; **a)** shows mean escape latency times, **b)** mean time spent in the center of the tank, **c)** mean distances traveled in the center of the tank, **d)** mean distances traveled in the periphery of the tank, and **e)** mean cumulative distance traveled

EG: Experimental group, CG: Control group

former platform location, this trend did not reach statistical significance[t(8): 1.968, p=0.085, Cohen's d=1.244; Figure 3b, Table 3]. The two groups showed comparable results in terms of time allocation within the center [t(8): 0.673, p=0.520, Cohen's d=0.647; Figure 3c, Table 3], distance covered in the central region [t(8): 1.280, p=0.236, Cohen's d=0.682; Figure 3d, Table 3], distance traveled along the periphery [t(8): -1.520, p=0.167, Cohen's d=-0.961; Figure 3e, Table 3], and overall cumulative distance [t(8): 0.613, p=0.557, Cohen's d=0.388; Figure 3f, Table 3]. However, akin to the acquisition phase, a statistically robust difference was detected between the groups in terms of mean swimming speed [t(8): -3.466, p=0.008, Cohen's d=-2.192; Figure 4b, Table 3], with the EG exhibiting a notably lower swimming speed than the CG.

Immunohistochemistry Findings

The molecular, granular cell, and polymorphic layers of the dentate gyrus region were observed in the dentate gyrus examinations conducted on the right and left hemispheres of the CG (Figures 5a and 6a). In high magnification examinations of this group, immunoreactivity for the "AMPAR GluR1 subunit" was predominantly observed in a small number of granular neurons within the granular cell layer and in some neurons of the polymorphic layer. It was determined that this immunoreactivity

Table 1: The results of the ANOVA analysis conducted to evaluate the performance of both groups on various behavioral measures during the acquisition phase of the Morris Water Maze task

		Repeated-measures ANOVA					
	Mean ± Standard deviation	Sum of squares	*df*	Mean square*	*F*	p	η^2
Escape latency							
Main effect of days (sec)	36.89±15.73 sec	23566.641	3.000	7855.547	7.965	0.003***	0.238
Days x Groups interaction		2334.570	3.000	778.190	0.789	0.523	0.024
Main effect of trials (sec)	37.6±19.49 sec	8213.693	3.000	2737.898	7.583	0.004***	0.083
Trials x Groups interaction		3448.380	3.000	1149.460	3.184	0.063	0.035
Time spent in the center							
Main effect of days (sec)	14.01±2.32 sec	238.026	3.000	79.675	0.489	0.696	0.016
Days x Groups interaction		715.227	3.000	238.409	1.464	0.274	0.049
Main effect of trials (sec)	14.08±5.35 sec	95.965	3.000	31.988	0.246	0.862	0.007
Trials x Groups interaction		1023.655	3.000	341.218	2.629	0.098	0.070
Distance traveled in the center							
Main effect of days (px)	50.32±2.17 px	588.929	3.000	196.310	0.138	0.935	0.005
Days x Groups interaction		2511.396	3.000	837.132	0.598	0.634	0.020
Main effect of trials (px)	50.62±15.02 px	424.988	3.000	141.663	0.162	0.920	0.003
Trials x Groups interaction		8527.323	3.000	2842.441	3.255	0.060	0.067
Distance traveled in the periphery							
Main effect of days (px)	47.89±28.39 px	68103.016	3.000	22701.005	6.658	0.007***	0.217
Days x Groups interaction		3913.324	3.000	1304.441	0.383	0.767	0.012
Main effect of trials (px)	49.49±35.85 px	12834.172	3.000	4278.057	5.940	0.010**	0.041
Trials x Groups interaction		1016.941	3.000	338.980	0.471	0.708	0.003
Cumulative distance							
Main effect of days (px)	0.92±0.15 px	1.611	3.000	0.537	6.415	0.008***	0.131
Days x Groups interaction		0.251	3.000	0.084	1.000	0.426	0.020
Main effect of trials (px)	0.93±0.22 px	0.515	3.000	0.172	5.555	0.013**	0.042
Trials x Groups interaction		0.110	3.000	0.037	1.188	0.356	0.009
Swimming speed							
Main effect of days (px/sec)	1.01±0.21 px/sec	4.092	3.000	1.364	4.210	0.030**	0.107
Days x Groups interaction		0.661	3.000	0.220	0.681	0.581	0.017
Main effect of trials (px/sec)	1.03±0.31 px/sec	0.488	3.000	0.163	1.944	0.176	0.013
Trials x Groups interaction		0.451	3.000	0.150	1.799	0.201	0.012

Significance levels are indicated as p<0.05 and p<0.01. *Type III mean square, **p<0.05, ***p<0.01
sec: Second, px: Pixel, ANOVA: Analysis of variance

was present in the cell membrane and the cytoplasm (Figures 5b and 6b).

In the dentate gyrus examinations of the left hemisphere of the EG, moderate immunoreactivity was observed, particularly in neurons of the granular and some polymorphic layers. It was determined that this immunoreactivity was present in the cell membrane and the cytoplasm. Neurons showing immunoreactivity for the AMPAR GluR1 subunit demonstrated a range of effects from moderate to severe in the polymorphic cell layers compared to the neurons in the granular cell layer (Figures 7a and b).

The most intense immunoreactivity for the AMPAR GluR1 subunit was observed in the dentate gyrus of the right hemisphere of the EG. In the examinations conducted in this region, it was noted that the immunoreactivity for the AMPAR GluR1 subunit in the cell membrane and cytoplasm of neurons in both the granular and polymorphic cell layers varied from severe to very severe. The most significant finding was that

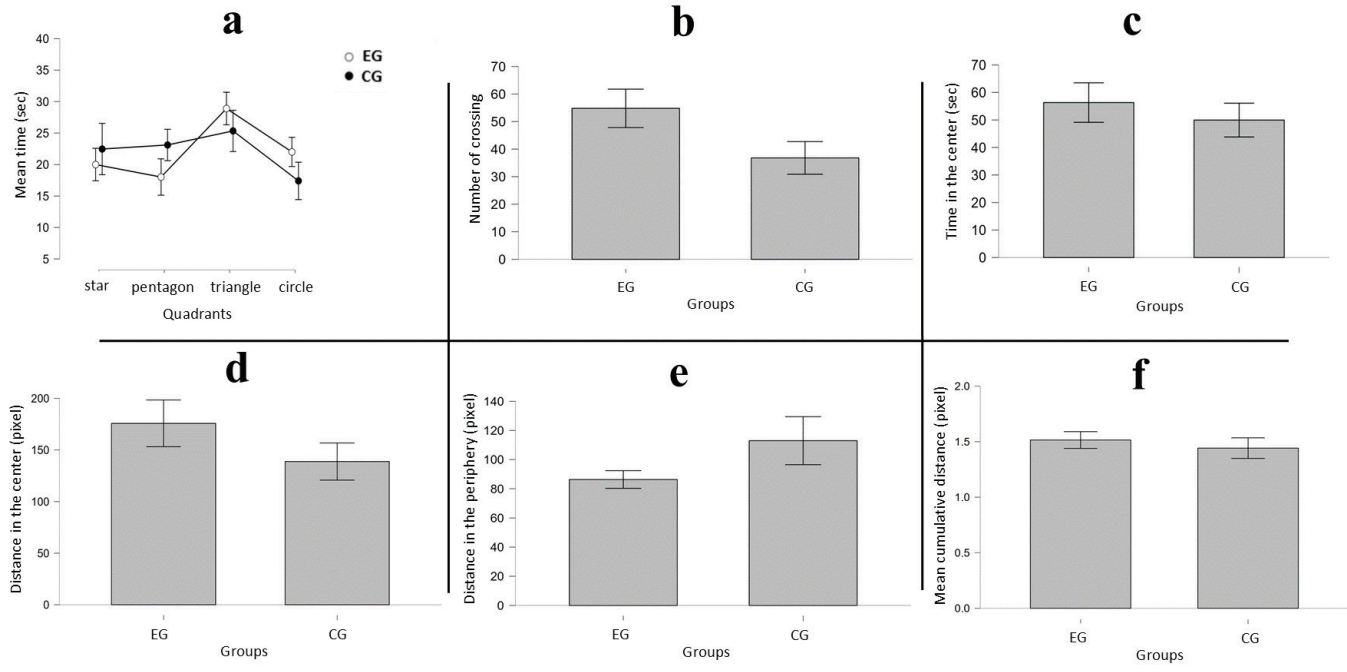

Figure 3: Findings from the testing phase of the Morris Water Maze task for the groups; **a)** mean time spent in quadrants, **b)** mean number of crossings at the location of the previously hidden platform throughout the test, **c)** mean time spent in the center of the tank, **d)** mean distance covered in the center of the tank, **e)** mean distance covered in the periphery of the tank, and **f)** mean cumulative distance covered.
EG: Experimental group, CG: Control group

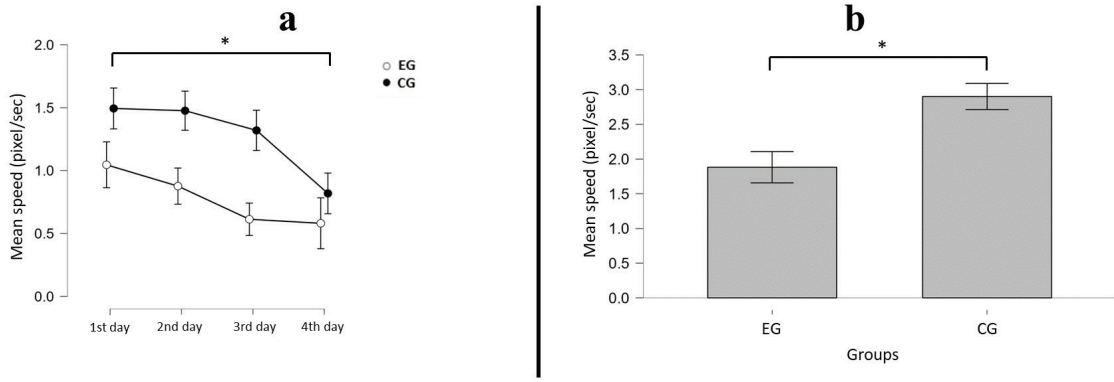

Figure 4: The mean swimming speeds of the groups are shown during, **a)** the days of the acquisition phase and **B)** the probe test phase of the Morris Water Maze task. The significant difference observed between the days, as determined by the post-hoc Holm test, was found to be due to the speed difference between the 1st and 4th days of the acquisition phase (p=0.04). *Indicates significant comparisons at p<0.05 level

the number of cells exhibiting immunoreactivity in the right hemisphere of this group was greater than that of the other group. Additionally, unlike the CG, particularly intense immunoreactivity was observed in the neuronal extensions extending towards the molecular layer (ML) of the dentate gyrus in this group (Figures 8a and b).

The distribution and intensity of AMPAR GluR1 subunit IHC staining in the dentate gyrus of both groups' right and left hemispheres were evaluated using the H-scoring method (Table 4). When comparing the H-scores of the EG in the right and left hemispheres with those of the CG, a significant increase was observed in both hemispheres [right hippocampus: t(6): 112.715, p≤0.001, Cohen's d=71.287; left hippocampus: t(6): 68.259, p≤0.001, Cohen's d=43.171, Figure 9, Table 5]. Additionally, the H-score of the EG left hemisphere was found to be significantly lower than that of the right hemisphere [t(6): -45.163, p≤0.001, Cohen's d=−28.117].

Table 2: The results of the repeated measures ANOVA and post-hoc comparisons for the time spent in quadrants (star, pentagon, triangle and circle) during the probe trial phase of the Morris Water Maze task for both groups

			Repeated-measures ANOVA					
		Mean ± Standard deviation	Sum of squares	*df*	Mean square*	*F*	p	η^2
Main effect of quadrants		22.16±3.37 sec	340.520	3.000	113.507	2.617	0.074	0.190
Quadrants x Groups interaction			164.292	3.000	54.764	1.262	0.310	0.092
			Post-hoc comparisons					
				Mean difference	*SE*	*t*	Cohen's d	p (Holm)
Experimental group								
Quadrant duration	**Mean ± SD**	**Quadrant duration**	**Mean ± SD**					
Star (sec)	20.0±7.25 sec	Pentagon (sec) Triangle (sec) Circle (sec)	18.02±6.09 sec 28.9±7.51 sec 22.01±3.66 sec	1.982 -8.901 -2.005	3.675 3.675 3.675	0.539 -2.422 -0.546	0.314 -1.409 -0.318	1.000 0.161 1.000
Pentagon (sec)	18.02±6.09 sec	Triangle (sec) Circle (sec)	28.9±7.51 sec 22.01±3.66 sec	-10.883 -3.988	3.675 3.675	-2.961 -1.085	-1.723 -0.631	0.071 0.898
Triangle (sec)	28.9±7.51 sec	Circle (sec)	22.01±3.66 sec	6.895	3.675	1.876	1.092	0.341
Control group								
Star (sec)	22.47±7.74 sec	Pentagon (sec) Triangle (sec) Circle (sec)	23.11±5.18 sec 25.34±6.52 sec 17.41±5.82 sec	-0.644 -2.878 5.059	4.604 4.604 4.604	-0.140 -0.625 1.099	-0.101 -0.451 0.739	1.000 1.000 1.000
Pentagon (sec)	23.11±5.18 sec	Triangle (sec) Circle (sec)	25.34±6.52 sec 17.41±5.82 sec	-2.234 5.703	4.604 4.604	-0.485 1.239	-0.350 0.893	1.000 1.000
Triangle (sec)	25.34±6.52 sec	Circle (sec)	17.41±5.82 sec	7.937	4.604	1.724	1.243	0.662

Significance levels are indicated as p<0.05 and p<0.01. *Type III mean square
SD: Standard deviation, SE: Standard error, sec: Second, ANOVA: Analysis of variance

Table 3: The results of Levene's test for the homogeneity of variances between groups and the Independent Samples t-test for the mean differences between groups for various behavioral parameters during the probe test of the Morris Water Maze task

		Levene's test		Independent Samples t-test			
		F	p	t	*df*	p	SE effect size
	Mean ± SD						
Number of crossings (count)	45.8±16.61 count	0.477	0.509	1.968	8	0.085	0.745
Time spent in the center (sec)	53.14±14.48 sec	0.051	0.827	0.673	8	0.520	0.647
Distance traveled in the center (px)	157.27±47.31 px	0.662	0.439	1.280	8	0.236	0.682
Distance traveled in the periphery (px)	99.67±29.65 px	4.344	0.071	-1.520	8	0.167	0.702
Cumulative distance (px)	1.48±0.18 px	1.347	0.279	0.613	8	0.557	0.644
Swimming speed (px/sec)	2.39±0.69 px/sec	0.019	0.895	-3.466	8	0.008*	0.938**

Significance levels are indicated as p<0.01. *p<0.01, **The effect size is reported using Cohen's d
SD: Standard deviation

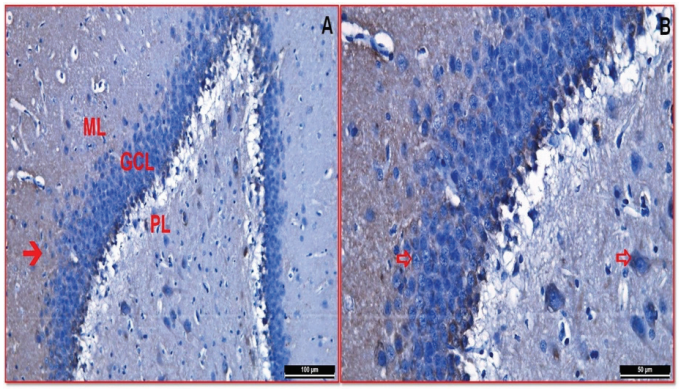

Figure 5: In the AMPAR GluR1 subunit staining of CG left hemisphere (A): →: Dentate Gyrus, ML: Molecular Layer, GCL: Granular Cell Layer, PL: Polymorphic Layer and (B): ⇨: Neurons with weak immunoreactivity
Immunoperoxidase-Hematoxylin; A: 200x, B: 400x, AMPAR: AMPA receptors, CG: Control group

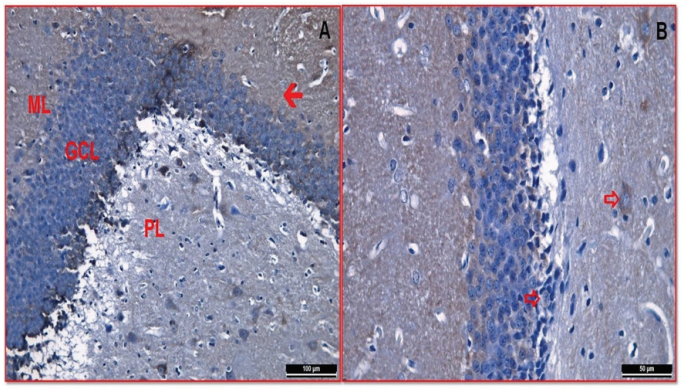

Figure 6: In the AMPAR GluR1 subunit staining of CG right hemisphere (A): →: Dentate Gyrus, ML: Molecular Layer, GCL: Granular Cell Layer, PL: Polymorphic Layer and (B): ⇨: Neurons with weak immunoreactivity
Immunoperoxidase-Hematoxylin; A: 200x, B: 400x, AMPAR: AMPA receptors, CG: Control group

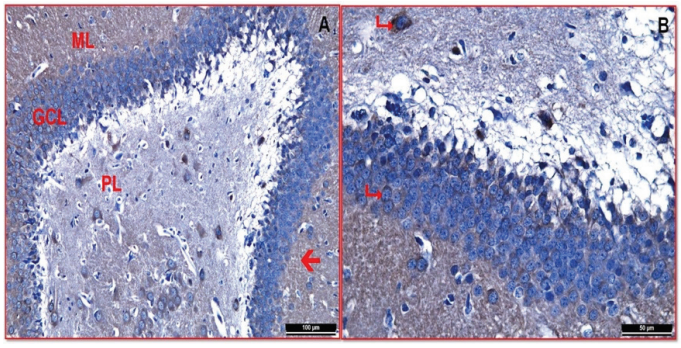

Figure 7: In the AMPAR GluR1 subunit staining of EG left hemisphere (A): →: Dentate Gyrus, ML: Molecular Layer, GCL: Granular Cell Layer, PL: Polymorphic Layer and (B): ↳: Neurons showing moderate immunoreactivity
Immunoperoxidase-Hematoxylin; A: 200x, B: 400x, AMPAR: AMPA receptors, EG: Experimental gorup

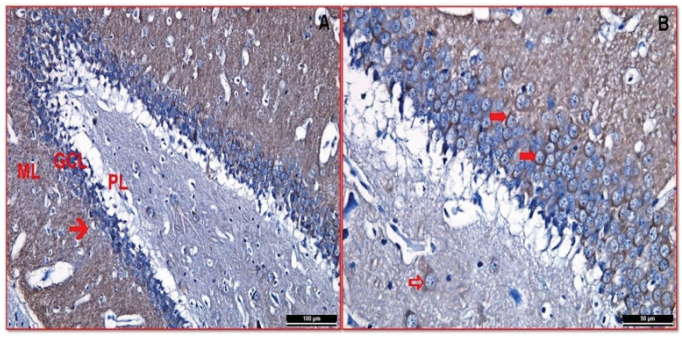

Figure 8: In the AMPAR GluR1 subunit staining of EG right hemisphere (A): →: Dentate Gyrus, ML: Molecular Layer, GCL: Granular Cell Layer, PL: Polymorphic Layer and (B): ➡: Neurons with severe immunoreactivity ⇨: Nerve cell extensions showing immunoreactivity
Immunoperoxidase-Hematoxylin; A: 200x, B: 400x, AMPAR: AMPA receptors, EG: Experimental gorup

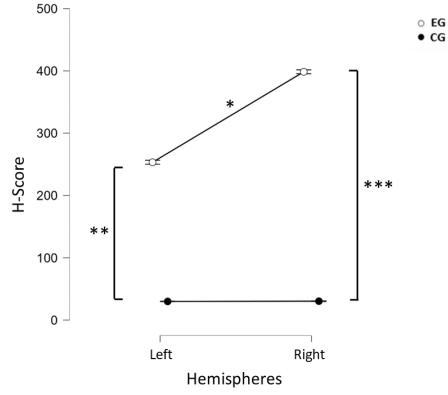

Figure 9: H-score values for the AMPA receptor GluR1 immunoreactivity in the left and right dentate gyrus of the groups. The H-scores were significantly higher in the BDNF-treated right hemisphere of the EG, while both hemisphere scores were found to be significantly elevated compared to the control group
*, **, ***p<0.001; EG: Experimental group

Discussion

Numerous studies investigating the effects of BDNF on neuronal activity and synaptic plasticity have revealed that this protein and its receptors play critical roles in learning and memory processes (3,48). Studies conducted with TrkB or BDNF mutant mice have shown that disruption of BDNF signaling severely negatively affects hippocampal E-LTP and L-LTP (13,14). However, it has also been found that these LTP defects can be reversed with the restoration of gene expression (14). These findings underscore the importance of BDNF in the LTP process. Neuron culture studies aimed at investigating the effect of BDNF on AMPARs served as the fundamental starting point for planning the current study. These studies have shown that BDNF

Table 4: H-score results based on the evaluation of AMPA receptor GluR1 subunit immunoreactivity in the dentate gyrus region obtained from slices of the left and right hemispheres of the groups

Dentate gyrus AMPA receptor GluR1 subunit	Left hemisphere			Right hemisphere		
	Percentage intensity (%)	Staining intensity	H-Score (AU)	Percentage intensity (%)	Staining intensity	H-Score (AU)
CG1	25	0	30.8	20	1	30.6
CG2	15	1	31.2	20	0	31
CG3	20	1	29.9	15	1	32.5
CG4	25	0	29.8	15	1	28.7
CG5	25	0	28	15	1	29
EG1	70	3	250.8	75	4	405
EG2	65	2	250.4	75	5	385.7
EG3	55	3	249.85	70	5	400.8
EG4	70	3	250	75	4	402.3
EG5	70	3	265.45	80	4	398.7

Staining intensity values were categorized on a graded scale: 0 (absence of staining), 1 (faint staining), 2 (mild to moderate staining), 3 (moderate staining), 4 (moderate to intense staining), and 5 (pronounced staining)
CG: Control group, EG: Experimental group, H-score: Histochemical scoring, AU: Arbitrary unit

Table 5: The ANOVA results of the differences in H-score values of the AMPA receptor GluR1 subunit between hemispheres for the experimental groups, as well as post-hoc comparisons between hemispheres and groups

			Repeated-measures ANOVA					
		Mean ± SD	Sum of squares	*df*	Mean square*	*F*	p-value	η^2
Main effect of hemispheres (AU)		111.51±82.36	26506.480	1	26506.480	1025.760	<0.001**	0.054
Hemispheres x Groups interaction			26201.560	1	26201.560	26201.560	<0.001**	0.053
			Post-hoc comparisons - Hemispheres x Groups interaction					
H-score (AU)	**Mean ± SD**	**H-score (AU)**	**Mean ± SD**	**Mean difference**	***SE***	***t***	**Cohen's d**	**p (Tukey)**
EG, left	253.3±6.8	CG, left EG, right CG, right	29.94±1.24 398.5±7.51 30.36±1.55	223.360 -145.200 222.940	3.266 3.215 2.266	68.387 -45.163 68.259	43.252 -28.117 43.171	<0.001** <0.001** <0.001**
CG, left	29.94±1.24	EG, right CG, right	398.5±7.51 30.36±1.55	-368.560 -0.420	3.266 3.215	-112.844 -0.131	-71.369 -0.081	<0.001** 0.999
EG, right	398.5±7.51	CG, right	30.36±1.55	368.140	3.266	112.715	71.287	<0.001**

Significance levels are indicated as p<0.001. *Type III mean square, **p<0.001
CG: Control group, EG: Experimental group, SD: Standard deviation, SE: Standard error, AU: Arbitrary unit, ANOVA: Analysis of variance

modulates AMPAR gene expression (21), increases membrane AMPAR levels (23,24), converts AMPAR-deficient silent synapses into AMPAR-containing synapses (22), enhances the synaptic transmission of AMPARs (25,26), and specifically increases the expression of AMPARs containing GluR1 and GluR2 (27). Moreover, it has been demonstrated that slow and continuous administration of BDNF strengthens the positive effects that support synaptic transmission (17). In this study, in line with the results of these *in vitro* studies in the literature, it was observed that recombinant BDNF protein administered via long-term infusion significantly increased the levels of the AMPAR GluR1 subunit in the right dentate gyrus region compared to the control group (p≤0.001; Figure 9). Additionally, the intense immunoreactivity of AMPAR GluR1 subunits observed in both the synaptic membrane and cytoplasm suggests that BDNF administration may have increased AMPAR levels not only at the membrane receptor level but also in the synaptic vesicle pool (Figure 8). This situation indicates that exogenous BDNF application could support E-LTP by increasing the amount of membrane AMPARs, like the effects observed in neuron cultures, and could even contribute to the formation and maintenance of L-LTP by triggering the production of new AMPARs. Therefore, the findings of our study support the observations from neuron culture studies (25,49). Furthermore, the mentioned neuron culture studies generally reveal the effects of BDNF on the hippocampal tissues of male animals. However, the existence

of certain correlations between the neural effects of BDNF and estrogen (31), the presence of common signaling transduction molecules and transcription factors in the mechanisms of action of both molecules (50-52), and studies indicating estrogen's control over BDNF synthesis in both sexes (34,53,54) raise the question of whether the hippocampal effects of exogenous BDNF application in non-ovariectomized females would be similar to those observed in males. Our findings indicate that the effect demonstrated in terms of AMPAR also operates similarly in female rats, yet the interaction between estrogen and BDNF and their common contributions, especially in LTP and learning and memory processes, contain many unanswered questions that need to be investigated.

One of the other interesting findings of our study is that in the EG rats, the AMPAR GluR1 subunit H-scores for the left dentate gyrus region, showed significantly higher immunoreactivity compared to controls ($p \leq 0.001$; Figure 9, Table 5). This increase in GluR1 subunit levels observed in this hemisphere, where BDNF was not directly administered, suggests that BDNF likely exerts a bilateral effect either through cerebrospinal fluid, local circulation, or a mechanism different from these pathways. A possible explanation for this mechanism could be the fibers originating from the mossy cells located in the polymorphic layer of the dentate gyrus, projecting to some cells in both the ipsilateral and contralateral MLs (55-57). These projections, referred to as associative/commissural projections, are believed to exist in the dentate gyrus of rodents but not in the primate brain (58,59). Moreover, there are studies indicating that these projections are excitatory due to their immunoreactivity to glutamate (60,61). However, the mechanisms underlying the effects of BDNF on these projections that influence both hemispheres need to be clarified in further studies.

Disruptions in BDNF-TrkB signaling have been associated with declines in performance on various learning and memory tasks, such as the radial arm maze (62), contextual fear conditioning (28), and the MWM. Notably, BDNF mutant mice exhibit significant impairments in spatial learning and memory functions (63-65). In our study, the MWM task, used to test spatial reference memory, utilized a circular pool filled with water in a specific room, where spatial fixed cues were placed at levels visible to the rats on the walls of the room. Although the neuroanatomical basis for this is not yet fully elucidated, there is evidence that rats possess a cognitive map representing the spatial characteristics of the testing environment in their hippocampus (66-68), and it is suggested that rats use these spatial cues in forming this representational map. There are few studies investigating the effects of exogenous BDNF application in the MWM task. For example, Cirulli et al. (69) found that intraventricular (ICV) BDNF injections did not affect MWM performance. Similarly, Fischer et al. (70) demonstrated that ICV BDNF application did not alter the MWM performance of aged rats with cholinergic neuron damage. These findings suggest that the method and/or duration of BDNF application may be responsible for these outcomes. TrkB receptors are expressed in both the ventricular ependymal layer and throughout the brain, so ICV BDNF application may have reduced the likelihood of reaching target tissues (71). In another study by Cirulli et al. (72) BDNF was administered as a single injection into the right hippocampus of rats, and after one day of training in the MWM, they evaluated the rats' short-term spatial memory performance. However, they again found no significant difference compared to the control group. This finding suggests that BDNF may play a more critical role in regulating long-term memory than in short-term memory. Therefore, in the present study, we aimed to directly apply BDNF to the right hippocampus through long-term infusion and to test long-term memory in the MWM task. According to our findings, although there was no significant difference between the BDNF group and the control group in the parameters assessed during the acquisition and testing phases of the MWM task (Figures 2-4, Tables 1-3), the EG rats exhibited a relatively better performance trend in the observed parameters. The lack of statistical significance in this trend may be due to the small sample size in the groups for reasons beyond our control; thus, future studies with a larger sample size could yield more consistent results. The fact that the mean swimming speeds of the animals were significantly higher at the beginning of the acquisition phase but slowed down toward the end may reflect a behavioral pattern associated with increased spatial learning. Similarly, the significantly slower swimming of EG rats compared to controls during the testing phase may also be interpreted as a reflecting difference. Another factor contributing to the perception of relatively better spatial memory performance is that the mean number of crossings at the escape platform location for EG rats [mean: 54 $\pm$ standard deviation (SD): 15] was relatively higher compared to controls (mean: 34 $\pm$ SD: 13). However, due to the absence of significant differences in overall performance results, it can be stated that the distinct molecular effects of BDNF application on AMPAR GluR1 subunit levels did not manifest as significant differences at the behavioral level. Nevertheless, some studies indicate that there may be differences in the performance strategies of rats in the MWM task, which could affect the results when evaluating measurement parameters that are considered standard for the task (73). The lack of significant differences in our behavioral findings between the groups may be due to the fact that the spatial memory strategies used by the animals in this study were not specifically assessed. Similarly, we believe it would be beneficial for future studies to evaluate the performance of animals from this perspective.

Conclusion

In conclusion, it was found that the chronically administered BDNF protein significantly increased the immunoreactivity of

the AMPAR GluR1 subunit in the right hemisphere of the EG group. Furthermore, this immunoreactivity was observed not only in the cell membrane but also in the cytoplasm due to the transmembrane nature of the receptor. Interestingly, a moderate effect was observed in the left hemisphere, where BDNF was not directly administered.

Ethics

Ethics Committee Approval: This study was approved by the Gazi University Local Ethics Committee for Animal Experiments (decision no: E.28661, date: 16.08.2017).

Informed Consent: In this study, we utilized adult female Long-Evans rats (n=10), each weighing between 200-250 g. The animals were obtained from the Gazi University Laboratory Animals Breeding and Experimental Research Center (GUDAM). All procedures involving the rats were conducted in the designated laboratory settings of GUDAM.

Acknowledgments

We would like to thank the expert and staff members at the Gazi University Laboratory Animal Breeding and Experimental Research Center. We also extend our gratitude to young researcher Batuhan Sözer for his contributions in preparing Python code for data analysis from the video recordings of the MWM task, which facilitated a detailed examination of this aspect of the study.

Footnotes

Authorship Contributions

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

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

Financial Disclosure: This study is supported by the Gazi University Scientific Research Projects Coordination Unit with the decision number 01/2017-26.

References

1. Kandel ER, Schwards JH, Jessel TM, et al. Principles of neural science. 5th ed. New York, USA: McGrow Hill; 2013.
2. Lynch MA. Long-term potentiation and memory. Physiol Rev. 2004;84:87-136.
3. Leal G, Afonso PM, Salazar IL, et al. Regulation of hippocampal synaptic plasticity by BDNF. Brain Res. 2015;1621:82-101.
4. Lu Y, Christian K, Lu B. BDNF: A key regulator for protein synthesis-dependent LTP and long-term memory? Neurobiol Learn Mem. 2008;89:312-323.
5. Anggono V, Huganir RL. Regulation of AMPA receptor trafficking and synaptic plasticity. Curr Opin Neurobiol. 2012;22:461-469.
6. Bramham CR, Messaoudi E. BDNF function in adult synaptic plasticity: the synaptic consolidation hypothesis. Prog Neurobiol. 2005;76:99-125.
7. Jensen V, Kaiser KMM, Borchardt T, et al. A juvenile form of postsynaptic hippocampal long-term potentiation in mice deficienct for the AMPA receptor subunit GluR-A. J Physiol. 2003;553:843-856.
8. Lee HK, Takamiya K, He K, et al. Specific roles of AMPA receptor subunit GluR1 (GluA1) phosphorylation sites in regulating synaptic plasticity in the CA1 region of hippocampus. J Neurophysiol. 2010;103:479-489.
9. Lessmann V. Neurotrophin-dependent modulation of glutamatergic synaptic transmission in the mammalian CNS. Gen Pharmacol. 1998;31:667-674.
10. Lewin GR, Barde Y-A. Physiology of the neurotrophins. Annu Rev Neurosci. 1996;19:289-317.
11. Lewin GR, Carter BR. Neurotrophic factors. In: Lewin GR, Carter BR, authors. Handbook of experimental pharmacology. 49th vol. Berlin, Germany: Springer-Verlag; 2014. s.3-251.
12. Patterson SL, Pittenger C, Morozov A, et al. Some forms of cAMP-mediated long-lasting potentiation are associated with release of BDNF and nuclear translocation of phospho-MAP kinase. Neuron. 2001;32:123-140.
13. Minichiello L, Korte M, Wolfer D, et al. Essential role for TrkB receptors in hippocampus-mediated learning below a certain threshold before behavioral defects become apparent. neuron. 1999;24:401-414.
14. Korte M, Griesbeck O, Gravel C, et al. Virus-mediated gene transfer into hippocampal CA1 region restores long-term potentiation in brain-derived neurotrophic factor mutant mice. Proc Natl Acad Sci U S A. 1996;93:12547-12552.
15. Figurov A, Pozzo-Miller LD, Olafsson P, et al. Regulation of synaptic responses to high-frequency stimulation and LTP by neurotrophins in the hippocampus. Nature. 1996;381:706-709.
16. Kang HJ, Schuman EM. Neurotrophin-induced modulation of synaptic transmission in the adult hippocampus. J Physiol - Paris. 1995;89:11-22.
17. Ji Y, Lu Y, Yang F, et al. Acute and gradual increases in BDNF concentration elicit distinct signaling and functions in neurons. Nat Neurosci. 2010;13:302-309.
18. Xu B, Michalski B, Racine RJ, et al. The effects of brain-derived neurotrophic factor (BDNF) administration on kindling induction, Trk expression and seizure-related morphological changes. Neuroscience. 2004;126:521-531.
19. Scharfman H, Goodman J, Macleod A, et al. Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. Exp Neurol. 2005;192:348-356.
20. Ye Y, Wang G, Wang H, et al. Brain-derived neurotrophic factor (BDNF) infusion restored astrocytic plasticity in the hippocampus of a rat model of depression. Neurosci Lett. 2011;503:15-19.
21. Narisawa-Saito M, Silva AJ, Yamaguchi T, et al. Growth factor-mediated Fyn signaling regulates α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor expression in rodent neocortical neurons. Proc Natl Acad Sci USA. 1999;96:2461-2466.
22. Itami C, Kimura F, Kohno T, et al. Brain-derived neurotrophic factor-dependent unmasking of "silent" synapses in the developing mouse barrel cortex. Proc Natl Acad Sci U S A. 2003;100:13069-13074.
23. Narisawa-Saito M, Iwakura Y, Kawamura M, et al. Brain-derived neurotrophic factor regulates surface expression of α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid receptors by enhancing the N-ethylmaleimide-sensitive factor/GLuR2 interaction in developing neocortical neurons. J Biol Chem. 2002;277:40910.
24. Jourdi H, Iwakura Y, Narisawa-Saito M, et al. Brain-derived neurotrophic factor signal enhances and maintains the expression of AMPA receptor-associated PDZ proteins in developing cortical neurons. Dev Biol. 2003;263:216-230.
25. Caldeira MV, Melo CV, Pereira DB, et al. Brain-derived neurotrophic factor regulates the expression and synaptic delivery of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor subunits in hippocampal neurons. J Biol Chem. 2007;282:12619-12628. Erratum in: J Biol Chem. 2007;282:27556.
26. Li W, Keifer J. BDNF-induced synaptic delivery of AMPAR subunits is differentially dependent on NMDA receptors and requires ERK. Neurobiol Learn Mem. 2009;91:243-249.
27. Jourdi H, Kabbaj M. Acute BDNF treatment upregulates GluR1-SAP97 and GluR2-GRIP1 interactions: implications for sustained AMPA receptor expression. PLoS One. 2013;8:e57124.

28. Liu F, Day M, Muñiz LC, et al. Activation of estrogen receptor-beta regulates hippocampal synaptic plasticity and improves memory. Nat Neurosci. 2008;11:334-343.
29. Woolley CS. Estrogen-mediated structural and functional synaptic plasticity in the female rat hippocampus. Horm Behav. 1998;34:140-8.
30. Levin ER. Cellular functions of plasma membrane estrogen receptors. Steroids. 2002;67:471-475.
31. Scharfman HE, Maclusky NJ. Similarities between actions of estrogen and BDNF in the hippocampus: coincidence or clue? Trends Neurosci. 2005;28:79-85.
32. Zhou J, Zhang H, Cohen R, et al. Effects of estrogen treatment on expression of brain-derived neurotrophic factor and cAMP response element-binding protein expression and phosphorylation in rat amygdaloid and hippocampal structures. Neuroendocrinology. 2005;81:294-310.
33. Allen A, McCarson K. Estrogen increases nociception-evoked brain-derived neurotrophic factor gene expression in the female rat. Neuroendocrinology. 2005;81:193-199.
34. Sohrabji F, Lewis DK. Estrogen-BDNF interactions: implications for neurodegenerative diseases. Front Neuroendocrinol. 2006;27:404-14.
35. Bimonte-Nelson H, Nelson M, Granholm AG. Progesterone counteracts estrogen-induced increases in neurotrophins in the aged female rat brain. Neuroreport. 2004;15:2659-2663.
36. Gibbs R. Levels of trkA and BDNF mRNA, but not NGF mRNA, Fluctuate across the estrous cycle and increase in response to acute hormone replacement. Brain Res. 1998;787:259-268.
37. Cavus I, Duman R, Influence of estradiol, stress, and 5-HT2A agonist treatment on brain-derived neurotrophic factor expression in female rats. Biol. Psychiatry. 2003;54:59-69.
38. Vorhees CV, Williams MT. Morris water maze: procedures for assessing spatial and related forms of learning and memory. Nat Protoc. 2006;1:848-858.
39. Lebron-Milad K, Milad MR. Sex differences, gonadal hormones and the fear extinction network: implications for anxiety disorders. Biol Mood Anxiety Disord. 2012;7:2-3.
40. Mamounas LA, Altar CA, Blue ME, et al. BDNF promotes the regenerative sprouting, but not survival, of injured serotonergic axons in the adult rat brain. J Neurosci. 2000;20:771-782.
41. Paxinos, G, Watson C. The rat brain in stereotaxic coordinates. 4th ed. San Diego, CA, USA: Academic Press Inc; 1998.
42. D'Hooge R, De Deyn PP. Applications of the Morris water maze in the study of learning and memory. Brain Res Rev. 2001;36:60-90.
43. Ünal SG, Take G, Erdoğan D, et al. The effect of di-n-butyl phthalate on testis and the potential protective effects of resveratrol. Toxicol Ind Health. 2016;32:777-790.
44. Tomar, S. Converting video formats with FFmpeg. Linux Journal. 2006;146:10.
45. Wada, K. Image polygonal annotation with Python (polygon, rectangle, circle, line, point and image-level flag annotation). 2018. Available from: https://github.com/wkentaro/labelme
46. van Rossum, Guido. Python Reference Manual. Department of Computer Science [CS]. Centrum voor Wiskunde en Informatica (CWI). Amsterdam; 1995.
47. JASP Team, JASP [Computer software]. Version 0.18.3; 2024. Available from: https://jasp-stats.org/
48. Leal G, Comprido D, Duarte CB BDNF-induced local protein synthesis and synaptic plasticity. Neuropharmacology. 2014;76:639-656.
49. Fortin DA, Srivastava T, Dwarakanath D, et al. Brain-derived neurotrophic factor activation of CaM-kinase kinase via transient receptor potential canonical channels induces the translation and synaptic incorporation of GluA1-containing calcium-permeable AMPA receptors. J Neurosci. 2012;32:8127-8137.
50. Bi R, Broutman G, Foy MR, et al. The tyrosine kinase and mitogen-activated protein kinase pathways mediate multiple effects of estrogen in hippocampus. Proc Natl Acad Sci U S A. 2000;97:3602-3607.
51. Blanquet PR, Mariani J, Derer P. A calcium/calmodulin kinase pathway connects brain-derived neurotrophic factor to the cyclic AMPresponsive transcription factor in the rat hippocampus. Neuroscience. 2003;118:477-490.
52. McEwen BS. Invited review: Estrogens effects on the brain: multiple sites and molecular mechanisms. J. Appl. Physiol. 2001;91:2785-2801.
53. Blurton-Jones M. Kuan PN, Tuszynski MH. Anatomical evidence for transsynaptic influences of estrogen on brain-derived neurotrophic factor expression. J Comp Neurol. 2004;468:347-360.
54. Luine V, Frankfurt M. Interactions between estradiol, BDNF and dendritic spines in promoting memory. Neuroscience. 2013;3:34-45.
55. Laurberg S, Sorensen KE. Associational and commissural collaterals of neurons in the hippocampal formation (hilus fasciae dentate and subfield CA3). Brain Res. 1981;212:287-300.
56. Amaral DG, Scharfman HE, Lavenex P. The dentate gyrus: fundamental neuroanatomical organization (dentate gyrus for dummies). Prog Brain Res. 2007;163:3-22.
57. Matteo Egger, Wenshu Luo, Natalia Cruz-Ochoa, et al. Commissural dentate granule cell projections and their rapid formation in the adult brain. PNAS Nexus. 2023;2:pgad088.
58. Buckmaster PS, Strowbridge BW, Kunkel DD, et al. Mossy cell axonal projections to the dentate gyrus molecular layer in the rat hippocampal slice. Hippocampus. 1992;2:349-362.
59. Buckmaster PS, Wenzel HJ, Kunkel DD, et al. Axon arbors and synaptic connections of hippocampal mossy cells in the rat in vivo. J Comp Neurol. 1996;366:271-292.
60. Soriano E, Frotscher M. Mossy cells of the rat fascia dentata are glutamate-immunoreactive. Hippocampus. 1994;4:65-69.
61. Scharfman HE. Electrophysiological evidence that dentate hilar mossy cells are excitatory and innervate both granule cells and interneurons. J Neurophysiol. 1995;74:179-194.
62. Mizuno M, Yamada K, Olariu A, et al. Involvement of brain-derived neurotrophic factor in spatial memory formation and maintenance in a radial arm maze test in rats. J Neurosci. 2000;20:7116-7121.
63. Linnarsson S, Björklund A, Ernfors P. Learning deficit in BDNF mutant mice. Eur J Neurosci. 1997;9:2581-2587.
64. Gorski JA, Balogh SA, Wehner JM, et al. Learning deficits in forebrain-restricted brain-derived neurotrophic factor mutant mice. Neuroscience. 2003;121:341-354.
65. Heldt SA, Stanek L, Chhatwal JP, et al. Hippocampus-specific deletion of BDNF in adult mice impairs spatial memory and extinction of aversive memories. Mol Psychiatry. 2007;12:656-670.
66. Deshmukh SS, Knierim JJ. Hippocampus. Wiley Interdiscip Rev Cogn Sci. 2012;3:231-251.
67. Eichenbaum H. The Hippocampus as a Cognitive Map ... of Social Space. Neuron. 2015;1:9-11.
68. Best PJ, White AM, Minai A. Spatial processing in the brain: the activity of hippocampal place cells. Annu Rev Neurosci. 2001;24:459-486.
69. Cirulli F, Berry A, Alleva E. Intracerebroventricular administration of brain-derived neurotrophic factor in adult rats affects analgesia and spontaneous behaviour but not memory retention in a Morris Water Maze task. Neurosci Lett. 2000;287:207-210.
70. Fischer W, Sirevaag A, Wiegand SJ, et al. Reversal of spatial memory impairments in aged rats by nerve growth factor and neurotrophins 3 and 4/5 but not by brain-derived neurotrophic factor. Proc Natl Acad Sci USA. 1994;91:8607-8611.
71. Yan Q, Matheson C, Sun J, et al. Distribution of intracerebral ventricularly administered neurotrophins in rat brain and its correlation with trk receptor expression. Experimental Neurology. 1994;127:23-36.
72. Cirulli F, Berry A, Chiarotti F, et al. Intrahippocampal administration of BDNF in adult rats affects short-term behavioral plasticity in the Morris water maze and performance in the elevated plus-maze. Hippocampus. 2004;14:802-807.
73. Daniel JM, Lee CD. Estrogen replacement in ovariectomized rats affects strategy selection in the Morris water maze. Neurobiol Learn Mem. 2004;82:142-149.

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2025.57983
J Ankara Univ Fac Med 2025;78(2):106-112

SURGICAL MEDICAL SCIENCES / CERRAHİ TIP BİLİMLERİ

Surgical Outcomes of Carpal Tunnel Syndrome in Rheumatologic Patients

Romatolojik Hastalarda Karpal Tünel Sendromu Cerrahisi Sonuçları

Yusuf Kıratlıoğlu, Uğur Bezirgan

Ankara University Faculty of Medicine, Department of Orthopedic and Traumatology, Division of Hand Surgery, Ankara, Türkiye

Abstract

Objectives: Carpal tunnel syndrome (CTS) is a common condition that often coexists with rheumatologic diseases, leading to significant functional impairment and reduced quality of life. This study aimed to evaluate the outcomes of open decompression surgery for CTS in individuals with rheumatologic diseases, focusing on symptom severity and functional status improvements.

Materials and Methods: A retrospective analysis was conducted on 27 patients diagnosed with CTS and concomitant rheumatologic diseases. These patients underwent open decompression surgery under local anesthesia between January 2021 and June 2023. Outcomes were assessed using the Boston symptom severity scale (BSSS) and the Boston functional status scale (BFSS) preoperatively and at follow-up appointments postoperatively.

Results: Postoperative evaluations revealed significant improvements in both BSSS and BFSS scores. Patients reported marked relief in symptom severity and improvements in their ability to perform daily activities. These improvements were consistent across the cohort, indicating the reliability of surgical intervention.

Conclusion: The findings suggest that open decompression surgery is an effective and reliable method for managing CTS symptoms in patients with rheumatologic diseases. This surgical approach not only alleviates symptom severity but also enhances functional capabilities, contributing to a better quality of life.

Keywords: Carpal tunnel syndrome, rheumatologic diseases, open decompression surgery, Boston carpal tunnel questionnaire

Öz

Amaç: Karpal tünel sendromu (KTS), sıklıkla romatolojik hastalıklarla birlikte görülen ve belirgin fonksiyonel bozukluklara ve yaşam kalitesinde düşüşe neden olan yaygın bir durumdur. Bu çalışmada, romatolojik hastalıklara sahip bireylerde KTS için açık dekompresyon cerrahisinin sonuçları, semptom şiddeti ve fonksiyonel durum iyileşmeleri açısından değerlendirildi.

Gereç ve Yöntem: Ocak 2021 ile Haziran 2023 arasında lokal anestezi altında açık dekompresyon cerrahisi uygulanan, KTS ve eşlik eden romatolojik hastalık tanısı konmuş 27 hasta retrospektif olarak analiz edildi. Sonuçlar, ameliyat öncesinde ve ameliyat sonrası kontrol muayenelerinde Boston semptom şiddet ölçeği (BSSÖ) ve Boston fonksiyonel durum ölçeği (BFDÖ) kullanılarak değerlendirildi.

Bulgular: Ameliyat sonrası değerlendirmelerde hem BSSÖ hem de BFDÖ skorlarında anlamlı iyileşmeler gözlendi. Hastalar, semptom şiddetinde belirgin azalma ve günlük aktivitelerini gerçekleştirme yeteneklerinde iyileşme bildirdi. Bu iyileşmeler tüm hasta grubunda tutarlı bir şekilde gözlemlendi ve cerrahi müdahalenin güvenilirliğini ortaya koydu.

Sonuç: Bulgular, açık dekompresyon cerrahisinin romatolojik hastalıklara sahip hastalarda KTS semptomlarının yönetiminde etkili ve güvenilir bir yöntem olduğunu göstermektedir. Bu cerrahi yaklaşım, yalnızca semptom şiddetini azaltmakla kalmayıp, fonksiyonel yetenekleri de geliştirerek daha iyi bir yaşam kalitesine katkıda bulunmaktadır.

Anahtar Kelimeler: Karpal tünel sendromu, romatolojik hastalıklar, açık dekompresyon cerrahisi, Boston karpal tünel anketi

Address for Correspondence/Yazışma Adresi: Yusuf Kıratlıoğlu,
Ankara University Faculty of Medicine, Department of Orthopedic and Traumatology, Division of Hand Surgery, Ankara, Türkiye
E-mail: yusufkiratlioglu@gmail.com **ORCID ID:** orcid.org/0000-0002-7806-9521

Received/Geliş Tarihi: 21.01.2025 **Accepted/Kabul Tarihi:** 05.03.2025 **Epub:** xxxxx **Publication Date/Yayınlanma Tarihi:** 27.06.2025

Cite this article as/Atıf: Kıratlıoğlu Y, Bezirgan U. Surgical outcomes of carpal tunnel syndrome in rheumatologic patients. J Ankara Univ Fac Med. 2025;78(2):106-112

Introduction

Carpal tunnel syndrome (CTS) is a common peripheral nervous system disorder and the most frequently observed entrapment neuropathy. It occurs in approximately 23% of rheumatoid arthritis (RA) patients and may present as the initial symptom of the disease (1). CTS is more prevalent in women than in men and is most commonly diagnosed between the ages of 45 and 60 (2). It is characterized by pain, numbness, and motor dysfunction, particularly in the wrist and hand, resulting from compression of the median nerve within the carpal tunnel.

The prevalence of CTS increases in individuals with rheumatologic diseases due to systemic inflammation and progressive tissue damage (3). Rheumatologic diseases associated with CTS include RA, psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), systemic sclerosis, and Sjögren's syndrome. The pathogenesis of these rheumatologic diseases is known to be associated with the presence of autoantibodies (4).

In RA patients, CTS symptoms may not be pronounced, as chronic pain, joint damage, and increased disability commonly observed in these individuals can mask the specific signs and symptoms of CTS (5-9). Moreover, patients often fail to clearly express CTS-specific symptoms as they may have adapted to the functional limitations imposed by their disease.

PsA, like RA, is an inflammatory erosive arthritis affecting peripheral joints. Studies have shown that the prevalence of CTS is higher in PsA patients compared to healthy controls, with electrodiagnostic examinations detecting CTS in 30.76% of PsA patients (10).

Behçet's disease is a multisystemic condition with an unknown pathogenesis (11). It is characterized by recurrent oral and genital ulcers, skin lesions, uveitis, joint, vascular, and neurological manifestations. Peripheral neuropathy, including CTS, is observed in 2.2% to 49% of Behçet's disease cases but does not show a significant correlation with disease activity based on electromyography (EMG) findings (12).

In ankylosing spondylitis, central nervous system involvement is more common than peripheral nerve involvement. However, electrophysiological studies have shown evidence of peripheral nerve involvement in 40.6% of ankylosing spondylitis patients (13,14).

Familial Mediterranean fever (FMF) is a hereditary disease characterized by systemic organ involvement due to amyloid fibril deposition. It is particularly prevalent in the Middle East and Eastern Mediterranean regions (15). Amyloid deposits, especially in the transverse carpal ligament, are a rare cause of CTS. Reports of CTS cases related to familial amyloidosis associated with FMF are limited (16). Bilateral CTS can often be an early clinical sign of amyloid deposition. Pathological examination for amyloid deposits should be considered during CTS surgeries, especially in these cases (17). In this study, CTS was observed in three FMF patients (11%), which may be attributed to the geographical prevalence of FMF. This finding emphasizes the importance of considering amyloid deposition during CTS surgery in such populations.

Given the increasing prevalence of CTS, understanding its underlying mechanisms and ensuring early diagnosis are critical for minimizing unnecessary pain and costs. Therefore, evaluating every RA patient for CTS is essential. However, there is limited information in the literature on the effectiveness and outcomes of surgical interventions in this patient group. This study aims to examine the impact of CTS surgery on symptom severity and functional status in patients with rheumatologic diseases.

Materials and Methods

This retrospective study included rheumatologic patients diagnosed with CTS who underwent open surgical treatment at the Hand Surgery Clinic of the Orthopedics and Traumatology Department in a University Hospital between January 2021 and June 2023.

Inclusion Criteria

Patients aged 18 years and older diagnosed with CTS based on clinical examination and confirmed by EMG.

Only patients with moderate and severe CTS, as determined by EMG findings, were included. Mild CTS cases were excluded due to the typically conservative management approach.

Patients with underlying rheumatologic diseases, including RA, SLE, and ankylosing spondylitis, were included to evaluate the impact of surgery on this specific population.

Exclusion Criteria

Patients with mild CTS or those without EMG confirmation of CTS.

Patients with prior carpal tunnel release surgery or other hand and wrist surgeries that could affect postoperative outcomes.

Cases with concomitant neurological disorders (e.g., cervical radiculopathy, peripheral neuropathy) that could confound symptom interpretation.

Incomplete medical records or lack of postoperative follow-up data.

Grouping and Classification

Based on EMG results, patients were categorized into moderate and severe CTS groups.

Subsequently, the patients were classified according to the Stanley classification 6 (Table 1), which considers clinical and anatomical findings to determine the severity and progression of CTS.

Ethical Considerations

Informed consent was obtained from all patients in accordance with the 1975 Declaration of Helsinki. The study protocol complied with the ethical guidelines of the institution where the study was conducted and was approved by the Ankara University Human Research Ethics Committee (approval number: i11-898-24, date: 13.01.2025).

Surgeries were performed under local anesthesia using the WALANT (wide awake local anesthesia no tourniquet) technique. A standard zigzag carpal tunnel incision was made, extending 2-3 cm proximally to the wrist crease between the palmaris longus and flexor carpi ulnaris tendons. Following skin incision, the palmar fascia, antebrachial fascia, and transverse carpal ligament were divided longitudinally. Careful median nerve neurolysis was performed, separating the nerve from the tenosynovium and flexor tendons (Figure 1). Tenosynovectomy of the flexor pollicis longus, flexor digitorum superficialis, and flexor digitorum profundus tendons was not performed. Bone protrusions from the volar surface of the carpal bones (especially the scaphoid) were not investigated for flexor tendon rupture risk. Patients were followed according to routine postoperative care protocols for idiopathic CTS surgery.

The Boston Carpal Tunnel Questionnaire (BCTQ), a patient-reported outcome measure, was utilized to evaluate symptom severity and functional status in patients with CTS. Assessments were conducted using the Boston symptom severity scale (BSSS) and the Boston functional status scale (BFSS) at multiple time points: preoperatively and postoperatively at 1, 3, and 6 months.

Rheumatology consultations were requested for all patients using antirheumatic drugs to ensure suspension of these medications preoperatively and resumption postoperatively.

In this study, statistical analyses were performed using Jamovi version 2.3.2. The normality of data distribution was evaluated using the Shapiro-Wilk test. Descriptive statistics for numerical data are reported as mean ± standard deviation and range (minimum-maximum values). Categorical data are presented as percentages. To compare more than two groups, Kruskal-Wallis was used for non-normally distributed data and one-way ANOVA test was used for normally distributed data. The Wilcoxon test and Student's t-test were used to compare repeated measures on the same subjects. Statistical significance was determined at a 95% confidence interval, with $p<0.005$ considered statistically significant.

Results

The study included 27 patients with a mean age of 58.62±8.48 years. The majority of patients were female (96.3%, n=26), and 78% were right-hand dominant. CTS affected the left side in 51.8% of cases and the right side in 48.2%. Among the patients, 14 had RA, 6 had ankylosing spondylitis, 3 had familial Mediterranean fever, 2 had Behçet's disease, and 2 had PsA.

Fourteen patients were diagnosed with moderate CTS, and thirteen with severe CTS. According to the Stanley classification, 10 patients were categorized in group A, 11 in group B, and 6 in group C. No patients were classified in groups D or E. The mean duration of symptoms was 28.51±19.91 months (Table 2).

Significant improvements were observed in both BSSS and BFSS scores following surgery. The mean BSSS score decreased from 3.23±0.61 preoperatively to 1.92±0.67 at 1 month postoperatively, 1.76±0.67 at 3 months, and 1.82±0.78 at 6 months. Similarly, the BFSS score decreased from 3.43±0.9 preoperatively to 2.56±1.04 at 1 month, 1.9±0.8 at 3 months, and 1.93±0.92 at 6 months (Table 3).

Analysis based on the Stanley classification revealed a significant difference in preoperative BSSS and BFSS scores among the groups. Post hoc analysis indicated that this difference primarily originated from group B. However, this difference was no longer observed in the 6-month postoperative evaluations (Table 4).

Table 1: Stanley classification

Types	Characteristics of the disease
A: Destructive type	Slow progression type without significant osteoarthritis
B: Reactive type	Slow progressive type with marked osteoarthritis
C: Ligamentous type	Progressive soft tissue disruption
D: Mutilans type	Progressive bony destruction
E: Juvenile type	Spontaneous intercarpal ankylosis
Stages	**Description**
I	Early erosions with reducible translation
II	Translation/subluxation with non-reducible radiocarpal osteoarthritis
III	Midcarpal joint loss
IV	Disorganized wrist with significant bone loss

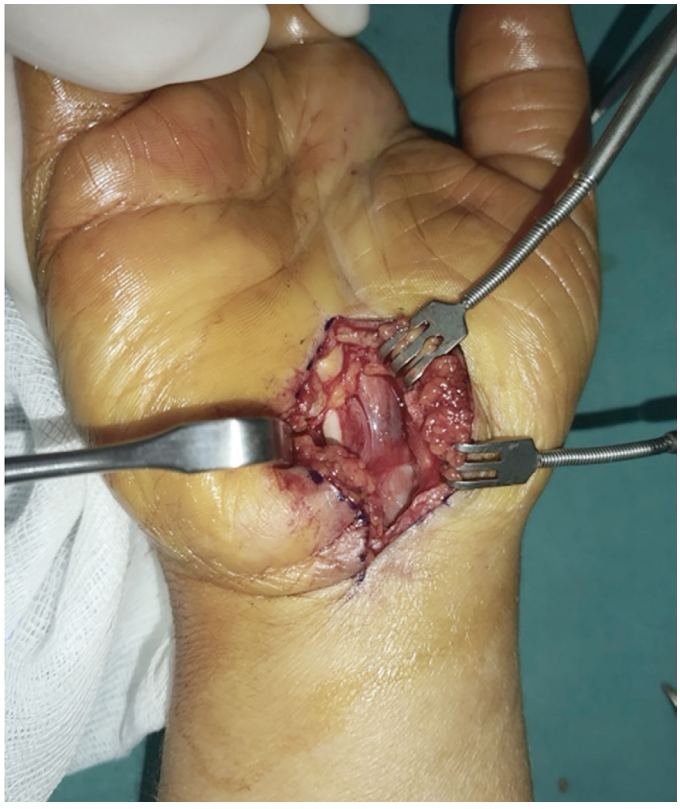

Figure 1: Extended open surgical approach in carpal tunnel syndrome surgery. Hourglass deformity and bluish discoloration of the nerve due to compression

Table 2: The demographic and clinical data	
Age (years, mean ± SD)	58.62±8.48 (44-77)
Gender (n, %)	
Female	26 (96.3%)
Male	1 (3.7%)
Side (n, %)	
Left	14 (51.8%)
Right	13 (48.2%)
Dominant hand (n, %)	
Left	6 (22%)
Right	21 (78%)
Disease (n, %)	
Rheumatoid arthritis	14 (51.8%)
Ankylosing spondylitis	6 (22.2%)
Familial mediterranean fever	3 (11.1%)
Behçet's disease	2 (7.4%)
Psoriatic arthritis	2 (7.4%)
Carpal tunnel syndrome severity (n, %)	
Moderate	14 (51.8%)
Severe	13 (48.2%)
Stanley classification (n, %)	
A	10 (37%)
B	11 (40.7%)
C	6 (22.2%)
D	0 (0%)
E	0 (0%)
Symptom duration (months, mean ± SD)	28.51±19.91 (6-72)
SD: Standard deviation	

Discussion

Summary of Key Findings

This study demonstrated that open CTS surgery in patients with rheumatologic diseases is effective in alleviating symptoms and improving functional outcomes. Significant improvements were observed in both symptom severity and quality of life following surgery. These findings support the use of open surgical intervention as a viable treatment option for moderate to severe CTS in this patient population.

However, the long-term impact of systemic inflammation and tissue damage associated with rheumatologic diseases on surgical outcomes remains uncertain and requires evaluation in larger patient cohorts. Despite significant functional gains, the heterogeneity of the patient group and the absence of postoperative EMG evaluations limit the generalizability of the results.

This article highlights critical points in the etiopathogenesis and diagnostic process of CTS in rheumatologic diseases. In RA, autoantibodies are responsible for persistent synovitis and widespread inflammation (7). CTS is the most common neurological finding in RA (8). Studies have reported that CTS develops more frequently in RA patients with flexor tendinopathy than in those without flexor tendinopathy (1). For diagnosis, ultrasound offers higher accuracy in CTS detection, particularly in patients with clinical symptoms and negative nerve conduction study results (9). In this study, the diagnoses of RA patients were clinically confirmed and supported by EMG findings.

Given the limitations of clinical tests, complementary EMG is recommended for suspected CTS in patients with rheumatologic diseases. In RA and PsA, EMG helps assess CTS severity and guides treatment decisions (8,18). EMG also helps identify the location and severity of nerve compression, monitor postoperative outcomes, and rule out conditions like cervical radiculopathy, brachial plexopathy, and peripheral neuropathy (19). CTS diagnosis, even in the presence of polyneuropathy, is not a contraindication for surgery (1). EMG-based classifications of CTS severity include severe CTS [Severe: Absence of sensory response and abnormal distal motor latency (DML)], moderate CTS (Moderate: Anormal finger-wrist conduction and abnormal DML), and mild CTS (Mild: Abnormal finger-wrist conduction with normal DML) (20). Regardless of CTS severity on EMG, all patients in this study showed significant postoperative functional improvement. However, the lack of postoperative EMG evaluation is a limitation.

Table 3: Boston carpal tunnel questionnaire results preoperatively and at 1, 3, and 6 months postoperative				
	Boston symptom severity scale (Mean ± SD)		Boston functional status scale (Mean ± SD)	
Preoperative	3.23±0.61		3.43±0.9	
Postoperative 1-month	1.92±0.67	p^1=0.000	2.56±1.04	p^1=0.004
Postoperative 3-month	1.76±0.67	p^2=0.066	1.90±0.80	p^2=0.011
Postoperative 6-month	1.82±0.78	p^3=0.593	1.93±0.92	p^3=0.839
p^1: Comparison between preoperative and postoperative 1 month, p^2: Comparison between postoperative 1 month and postoperative 3 months, p^3: Comparison between postoperative 3 months and postoperative 6 months SD: Standard deviation				

Table 4: Comparison of symptom duration, preoperative, and postoperative BSSS and BFSS at 6 months according to stanley staging				
	Stanley group A (Mean ± SD)	Stanley group B (Mean ± SD)	Stanley group C (Mean ± SD)	p-value
Symptom duration (months)	23.5±19.35	36.72±18.89	21.83±20.53	0.209
Preoperative BSSS	2.93±0.24	3.57±0.46	3.10±0.47	**0.044**
Preoperative BFSS	3.15±0.57	4.01±0.6	2.87±1.27	**0.014**
Postoperative 6-month BSSS	1.74±0.69	2.14±0.9	1.36±0.44	0.132
Postoperative 6-month BFSS	1.66±0.69	2.14±1.02	2±1.1	0.496
BSSS: Boston symptom severity scale, BFSS: Boston functional status scale, SD: Standard deviation				

Clinical Implications

Rheumatologic diseases involve complex autoimmune mechanisms that are not yet fully understood. Rheumatoid wrists exhibit synovial proliferation, joint erosions, and ligament laxity, leading to decreased carpal tunnel size and increased pressure. Consequently, median nerve and vascular compression result in disrupted axonal transport and ischemia. Additional potential causes of CTS in rheumatologic diseases include drug toxicity, vasculitis, and amyloidosis (21). Long-standing RA can result in synovial proliferation and tendon damage, causing histopathological changes. In RA, synovial hyperplasia and the formation of invasive synovial tissue, known as pannus, can reduce carpal tunnel space and lead to CTS compression (22). Prolonged compression results in ischemia, venous congestion, and local metabolic changes in the median nerve. Over time, inflammation in the joints leads to joint destruction, cartilage loss, and bone erosions, altering the carpal tunnel structure (23). Symptoms of CTS are reported to resolve rapidly after decompression surgery, highlighting the ischemic nature of the injury (1,3). This study aligns with previous research, showing improved postoperative BCTQ scores following standard open median nerve decompression surgery in all patients (24). Patients with joint arthrosis on Stanley classification exhibited worse BCTQ scores. However, the results demonstrated that standard open decompression of the median nerve is successful even in the presence of arthrosis in the wrist joints of rheumatologic patients.

In rheumatologic diseases, diagnosing flexor tenosynovitis can be challenging when joint stiffness restricts passive movement, making it difficult to distinguish between limited movement caused by joint stiffness and flexor tendon involvement. Flexor tenosynovitis causes swelling in the volar aspect of the distal forearm and wrist, which is typically less apparent than dorsal tenosynovitis. Flexor tendon function should be evaluated due to the risk of tendon rupture. In RA patients with minimal flexor tenosynovitis, carpal tunnel release can be performed using the same techniques as in idiopathic CTS cases (1). In this study, the degree of flexor tenosynovitis was not addressed, focusing solely on median nerve decompression.

This study's primary advantage was the absence of Stanley type D patients with progressive bone destruction. However, preoperative and intraoperative evaluation of flexor tendons is crucial in Stanley type C patients with soft tissue damage. Future studies comparing median nerve decompression with and without flexor tenosynovectomy in type C patients are needed.

Study Limitations

Several limitations of this study must be acknowledged:

Sample Size and Heterogeneity: The relatively small sample size and the heterogeneity of the patient population limit the generalizability of the findings. Future studies should include larger and more homogeneous cohorts to validate these results.

Absence of Postoperative EMG Evaluation: The lack of postoperative EMG assessments restricts the objective evaluation of surgical effectiveness. Incorporating EMG in future studies would provide a more comprehensive analysis of nerve recovery and functional outcomes.

Retrospective Design: As a retrospective study, potential biases related to data collection and patient recall could not be

completely eliminated. A prospective study design would allow for more controlled and systematic data collection.

Flexor Tenosynovitis Assessment: This study focused solely on median nerve decompression and did not evaluate the degree of flexor tenosynovitis, which could influence surgical outcomes. This should be considered in future research, especially in patients with RA.

Recommendations for Future Research

To build on the findings of this study, the following recommendations are made for future research:

Larger and Homogeneous Sample Groups: Future studies should focus on larger, more homogeneous patient populations, preferably with a single type of rheumatologic disease, to enhance the validity and generalizability of the results.

Prospective and Long-term Follow-up Studies: Long-term follow-up studies and prospective designs are recommended to better understand the durability of functional improvements and complication rates.

Incorporation of Postoperative EMG Assessments: Including EMG evaluations alongside clinical outcome measures would provide a more objective and comprehensive assessment of surgical effectiveness.

Evaluation of Flexor Tenosynovitis: Future studies should compare median nerve decompression with and without flexor tenosynovectomy, particularly in Stanley type C patients with soft tissue damage. This would provide valuable insights into the optimal surgical approach for this subgroup.

Multidisciplinary Approach and Personalized Treatment Plans: Given the systemic and complex nature of rheumatologic diseases, future research should explore personalized surgical and rehabilitation strategies involving a multidisciplinary team. This approach could optimize functional recovery and minimize postoperative complications.

Conclusion

Open CTS surgery is an effective method for alleviating symptoms and achieving functional improvement in individuals with rheumatologic diseases. These findings highlight the significance of CTS surgery within the context of rheumatologic conditions. Early surgical intervention may lead to better outcomes and improved patient quality of life.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ankara University Human Research Ethics Committee (approval number: i11-898-24, date: 13.01.2025).

Informed Consent: Informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.B., Concept: U.B., Design: U.B., Data Collection and/or Processing: U.B., Analysis and/or Interpretation: Y.K., Literature Search: Y.K., Writing: Y.K.

Conflict of Interest: According to the authors, there are no conflicts of interest related to this study.

Financial Disclosure: This study received no financial support.

References

1. Feldon P, Terrono AL. Carpal tunnel syndrome in rheumatoid arthritis. Techniques in Orthopaedics. 2006;21:42-47.
2. Osiak K, Elnazir P, Walocha JA, Pasternak A. Carpal tunnel syndrome: state-of-the-art review. Folia Morphol (Warsz). 2022;81:851-862.
3. Bîrsanu L, Vulpoi GA, Cuciureanu DI, Antal C, Popescu I, Turliuc D. Carpal tunnel syndrome related to rheumatic disease (Review). Exp Ther Med. 2024;28.
4. Didier K, Bolko L, Giusti D, et al. Autoantibodies associated with connective tissue diseases: What meaning for clinicians? Front Immunol. 2018;9.
5. Al Maini M, Adelowo F, Al Saleh J, et al. The global challenges and opportunities in the practice of rheumatology: White paper by the world forum on rheumatic and musculoskeletal diseases. Clin Rheumatol. 2015;34:819-829.
6. Vergara-Amador E, Rojas A. The rheumatoid wrist. Essential aspects in the treatment. Revista Colombiana de Reumatología (English Edition). 2016;23:24-33.
7. Joaquim AF, Appenzeller S. Neuropsychiatric manifestations in rheumatoid arthritis. Autoimmun Rev. 2015;14:1116-1122.
8. Kaya Subaşı P, Güler T, Yurdakul FG, Ataman Ş, Bodur H. Carpal tunnel syndrome in patients with rheumatoid arthritis and psoriatic arthritis: an electrophysiological and ultrasonographic study. Rheumatol Int. 2021;41:361-368.
9. Aktürk S, Büyükavcı R, Ersoy Y. Median nerve ultrasound in carpal tunnel syndrome with normal electrodiagnostic tests. Acta Neurol Belg. 2020;120:43-47.
10. Tezcan EA, Levendoglu F, Durmaz MS, et al. Carpal tunnel syndrome in patients with psoriatic arthritis: ultrasonography and magnetic resonance imaging findings. J Rheum Dis. 2023;30:36-44.
11. Birol A, Ulkatan S, Koçak M, Erkek E. Peripheral neuropathy in Behçet's disease. J Dermatol. 2004;31:455-459.
12. Lee J, Cho S, Kim DY, Zheng Z, Park H, Bang D. Carpal tunnel syndrome in Behçet's disease. Yonsei Med J. 2015;56:1015-1020.
13. Khedr EM, Rashad SM, Hamed SA, El-Zharaa F, Abdalla AKH. Neurological complications of ankylosing spondylitis: Neurophysiological assessment. Rheumatol Int. 2009;29:1031-1040.
14. Gündüz OH, Kiralp MZ, Özçakar L, Çakar E, Yildirim P, Akyuz G. Nerve conduction studies in patients with ankylosing spondylitis. J Natl Med Assoc. 2010;102:243-246.
15. Akpolat T, Yilmaz E, Akpolat I, Dilek M, Karagoz F, Balci B, Ozen S. Amyloidosis in Behçet's disease and familial Mediterranean fever. Rheumatology (Oxford). 2002;41:592-3.
16. Bademci G, Erdemoglu AK, Evliyaoglu C, Atasoy P, Keskil S. Bilateral carpal tunnel syndrome associated to familial Mediterranean fever. Clin Neurol Neurosurg. 2005;108:77-79.

17. Nestle FO, Burg G. Bilateral carpal tunnel syndrome as a clue for the diagnosis of systemic amyloidosis. In: Dermatology. 2001;202:353-355.
18. Mahmoud W, El-Naby MM, Awad AA. Carpal tunnel syndrome in rheumatoid arthritis patients: the role of combined ultrasonographic and electrophysiological assessment. Egyptian Rheumatology and Rehabilitation. 2022;49:62.
19. Gervasio A, Stelitano C, Bollani P, Giardini A, Vanzetti E, Ferrari M. Carpal tunnel sonography. J Ultrasound. 2020;23:337-347.
20. Padua L, Lo Monaco M, Padua R, Gregori B, Tonali P. Neurophysiological classification of carpal tunnel syndrome: Assessment of 600 symptomatic hands. Ital J Neurol Sci. 1997;18:145-150.
21. Sakthiswary R, Singh R. Has the median nerve involvement in rheumatoid arthritis been overemphasized? Rev Bras Reumatol. 2017;57:122-128.
22. Filippucci E, Gabba A, Di Geso L, Girolimetti R, Salaffi F, Grassi W. Hand tendon involvement in rheumatoid arthritis: An ultrasound study. Semin Arthritis Rheum. 2012;41:752-760.
23. López-Ferrer A, Laiz A, Puig L. Psoriatic arthritis. Med Clin (Barc). 2022;159:40-46.
24. Heybeli N, Kutluhan S, Demirci S, Kerman M, Mumcu EF. Assessment of outcome of carpal tunnel syndrome: a comparison of electrophysiological findings and a self-administered Boston questionnaire. J Hand Surg Br. 2002;27:259-264.

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2025.13281
J Ankara Univ Fac Med 2025;78(2):113-119

MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Avascular Necrosis and Risk Factors in Kidney Transplant Recipients: A Single-Center Experience

Böbrek Nakli Alıcılarında Avasküler Nekroz ve Risk Faktörleri: Tek Merkez Deneyimi

Ömer Faruk Akçay, Asil Demirezen, Veysel Baran Tomar, Ozant Helvacı, Galip Güz

Gazi University Faculty of Medicine, Department of Nephrology, Ankara, Türkiye

Abstract

Objectives: Renal osteodystrophy, osteoporosis, bone fractures, and avascular necrosis (AVN) are prevalent complications observed in the post-transplant period among kidney transplant recipients (KTRs). Despite notable advancements, AVN remains a significant and devastating complication following kidney transplantation (KT).

Materials and Methods: The study included all patients who underwent KT at our transplantation unit and had at least one year of routine follow-up (n=343). Cases of symptomatic AVN were diagnosed by X-radiation, radioisotope bone scan, or magnetic resonance imaging. We evaluated the baseline characteristics, laboratories, and immunosuppressive treatments of KTRs.

Results: The frequency of AVN in our KTRs was 7.9% during the follow-up period, with a median diagnosis time of 15.2 (10.2-34.9) months. In KTRs with AVN, the leading cause of end-stage renal disease was glomerulonephritis (GN) (52% vs. 20%, p<0.001), and more rejection episodes occurred at follow-up (33% vs. 15%, p=0.01). In univariate analysis, GN [odds ratio (OR): 4.325, 95% confidence interval (CI), 1.936-9.661], cumulative steroid dosage at the post-transplant first year (OR: 1.001, 95% CI, 1.000-1.002), and rejection episodes (OR: 2.792, 95% CI, 1.185-6.578) detected as possible risk factors for AVN. Upon multivariate analysis, GN was identified as an independent risk factor for the development of AVN (OR: 4.373, 95% CI, 1.935-9.880, p<0.001).

Conclusion: Our study found GN to be associated with an increased risk of AVN. A higher prevalence of AVN may attributed to long-term pre-transplant steroid therapy in this group. In KTRs with a history of GN, greater awareness should be paid to cumulative steroid dosages, and early discontinuation of steroids may be considered.

Keywords: Avascular necrosis, glomerulonephritis, mineral bone disease, renal transplantation, steroid therapy

Öz

Amaç: Renal osteodistrofi, osteoporoz, kemik kırıkları ve avasküler nekroz (AVN), böbrek nakli alıcılarında (BNA) transplantasyon sonrası dönemde yaygın komplikasyonlardır. Kaydedilen önemli ilerlemelere rağmen, AVN böbrek nakli (BN) sonrası hala ciddi ve yıkıcı bir komplikasyon olmaya devam etmektedir.

Gereç ve Yöntem: Çalışmaya, transplantasyon ünitemizde BN yapılan ve en az bir yıl düzenli takip edilen tüm hastalar (n=343) dahil edildi. Semptomatik AVN olguları röntgen, radyoizotop kemik taraması veya manyetik rezonans görüntüleme ile teşhis edildi. BNA'ların temel özellikleri, laboratuvar sonuçları ve immünsüpresif tedavileri değerlendirildi.

Bulgular: BNA'larda AVN sıklığı %7,9 olup, medyan teşhis süresi 15,2 (10,2-34,9) ay olarak belirlendi. AVN gelişen BNA'larda, son dönem böbrek hastalığının en yaygın nedeni glomerulonefrit (GN) idi (%52'ye karşı %20, p<0,001) ve takip sürecinde daha fazla rejeksiyon epizodu görüldü (%33'e karşı %15, p=0,01). Tek değişkenli analizde GN [olasılık oranı (OR): 4,325; %95 güven aralığı (GA), 1,936-9,661], nakil sonrası ilk yıldaki kümülatif steroid dozu (OR: 1,001; %95 GA, 1,000-1,002) ve rejeksiyon epizodları (OR: 2,792; %95 GA, 1,185-6,578) AVN için olası risk faktörleri olarak saptandı. Çok değişkenli analizde ise GN, AVN gelişimi için bağımsız bir risk faktörü olarak belirlendi (OR: 4,373; %95 GA, 1,935-9,880; p<0,001).

Address for Correspondence/Yazışma Adresi: Asst. Prof., Ömer Faruk Akçay,
Gazi University Faculty of Medicine, Department of Nephrology, Ankara, Türkiye
E-mail: omerfaruk_akcay@yahoo.com **ORCID ID:** orcid.org/0000-0001-6587-4938

Received/Geliş Tarihi: 28.01.2025 **Accepted/Kabul Tarihi:** 07.03.2025 **Epub:** 12.05.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025

Cite this article as/Atıf: Akçay ÖF, Demirezen A, Tomar VB, Helvacı O, Güz G. Avascular necrosis and risk factors in kidney transplant recipients: A single-center experience. J Ankara Univ Fac Med. 2025;78(2):113-119

Sonuç: Çalışmamız GN'nin AVN riskini artırdığını göstermiştir. Bu grupta AVN'nin daha yüksek prevalansı, uzun süreli nakil öncesi steroid tedavisine bağlanabilir. GN öyküsü olan BNA'larda kümülatif steroid dozlarına daha fazla dikkat edilmesi ve steroidlerin erken kesilmesi düşünülebilir.

Anahtar Kelimeler: Avasküler nekroz, glomerülonefrit, mineral kemik hastalığı, böbrek nakli, steroid tedavisi

Introduction

Kidney transplantation (KT) is considered the gold standard for managing kidney failure, offering recipients significant long-term advantages, such as enhanced survival rates and an improved quality of life (1). However, bone disease is commonly observed among kidney transplant recipients (KTRs), including conditions such as renal osteoporosis, bone fractures, and avascular necrosis (AVN). These bone diseases result from the ongoing effects of chronic kidney disease-mineral and bone disorder (CKD-MBD), as well as the influence of immunosuppressive therapies on bone health following transplantation (2). Although KT significantly improves patient outcomes, it does not entirely reverse the underlying CKD-MBD (3).

AVN is a debilitating bone condition that can arise in KTRs in the setting of CKD-MBD, frequently resulting in significant functional impairment. Prior to the development of modern immunosuppressive therapies, and mainly due to the effects of high-dose glucocorticoid treatments used in earlier years, AVN affected around 40% of KTRs (4). However, with recent advancements in both transplantation techniques and immunosuppressive strategies, the incidence of AVN has dropped to less than 5% (5,6). Despite these significant improvements, AVN remains a serious complication that continues to affect the quality of life of KTRs, emphasizing the importance of ongoing research and improved management approaches.

The underlying pathophysiological process of AVN is a compromised blood flow to the bone, which triggers necrosis and leads to progressive bone damage (7). Steroid-induced suppression of bone formation plays a significant role in bone loss, as glucocorticoids enhance osteoclast activity while exerting toxic effects on osteoblasts (8). The femoral head is most often the site of involvement, with other weight-bearing long bones also commonly affected. Some potential risk factors identified for AVN including diabetes, secondary hyperparathyroidism (HPT), and autoimmune diseases (9-11). Effective treatment focuses on preventing the collapse of these compromised bones, making it crucial to identify high-risk patients and detect AVN in its early stages.

To address this issue, we conducted a retrospective analysis to determine the prevalence of AVN, paying particular attention to the impact of patient demographics and post-transplant factors on its development. We aimed to identify the key risk factors for AVN and evaluate its clinical outcomes in KTRs under modern immunosuppressive therapy.

Materials and Methods

Study Population and Data Collection

The study included all patients who underwent KT in our transplantation unit and maintained regular follow-up. However, individuals under 18 years of age at the time of KT or with a follow-up duration of less than one-year post-transplantation were excluded. Clinical and demographic data were gathered, encompassing age, gender, smoking status, renin-angiotensin-aldosteron system (RAAS) inhibitors treatment, primary causes of end-stage renal disease (ESRD), and comorbid conditions like diabetes mellitus and hypertension. Additionally, we assessed transplantation-specific factors, such as type of donor (living or deceased), induction therapy, delayed graft function (requiring dialysis within the first week post-transplant), immunosuppressive treatment, the development of new-onset diabetes after transplantation, biopsy-confirmed rejection episodes, and cases of allograft failure. Laboratory evaluations encompassed estimated glomerular filtration rate, serum parathyroid hormone (PTH) levels, and proteinuria measurements. We utilized laboratory values obtained three months after KT as the baseline. This approach was taken to minimize the influence of early fluctuations in renal function and to ensure its stabilization. Persistent HPT was defined as PTH levels exceeding the upper reference threshold of our laboratory (>88 pg/mL) within the first year after transplantation.

Symptomatic AVN was identified using standard anterior-posterior pelvic X-radiation, radioisotope bone scans, or magnetic resonance imaging of the shoulder, knee, hip, or pelvis. In addition, various medical and surgical interventions for AVN have been documented, including steroid withdrawal, hyperbaric oxygen therapy, core decompression, and joint replacement. Gazi University Ethics Committee approved the study protocol (protocol number: E-77082166-604.01-1148721, date: 21.01.2025) under the Declaration of Helsinki and ethical standards for human research. Since this was a retrospective study and all procedures were part of standard clinical care, informed consent was not required.

Immunosuppression and Rejection Treatments

The choice of induction therapy (none, basiliximab, or antithymocyte globulin) was determined based on the immunological risk profile of the recipients. All patients received 500 mg of intravenous methylprednisolone (MPZ) on the day of surgery. The initial dose was reduced by half over the

subsequent days and then switched to a daily oral regimen of 20 mg prednisolone. The dosage was progressively decreased by 5 mg every two weeks until a maintenance level of 5-10 mg was achieved. In the absence of contraindications, a minimum daily dose of 5 mg prednisolone was continued during routine follow-up. The maintenance immunosuppressive regimen included prednisolone in combination with a calcineurin inhibitor (CNI), such as tacrolimus or cyclosporine, along with an antimetabolite, either mycophenolate mofetil or azathioprine. Mammalian target of rapamycin inhibitors was considered an alternative treatment option for patients who could not tolerate the side effects of CNI or antimetabolite treatment.

Suspected cases of acute rejection were evaluated through kidney biopsy and classified according to the Banff criteria (12). Treatment involved an initial course of intravenous steroids at doses ranging from 250 to 500 mg for 3 to 5 days, followed by oral steroids at a daily dose of 1 mg/kg. For patients on cyclosporine, tacrolimus was initiated. The cumulative oral and bolus corticosteroids administered during the first year post-transplantation were also calculated.

Statistical Analysis

Numerical data were summarized using descriptive statistics based on their distribution. Variables with a normal distribution were presented as means with standard deviations, while those without a normal distribution were expressed as medians with interquartile ranges. Nominal data were represented by counts (n) and percentages (%). The Mann-Whitney U test was used for group comparisons of variables that did not follow a normal distribution, while the independent samples t-test was applied to variables with a normal distribution. Nominal variables were compared using chi-square or Fisher's exact tests. Binary logistic regression analyses were conducted to identify independent risk factors linked to AVN. Variables with a p-value below 0.1 in the univariate analysis were included in the multivariate analysis. Statistical significance was defined as a p-value of less than 0.05. All statistical analyses were performed using SPSS software, version 20.0 (IBM Corp., Chicago, IL, USA).

Results

The study included 343 KTRs, with a mean follow-up duration of 125.3±68.9 months. Among the cohort, 37% (n=127) were female, and the average age at the time of transplantation was 34.8±14.4 years. During routine follow-up, 7.9% (n=27) of participants developed AVN, with a median diagnosis time of 15.2 (10.2-34.9) months after KT. In KTRs with AVN, the leading cause of ESRD was GN (52% vs. 20%, p<0.001). Preemptive transplantation, cadaveric transplantation, and induction therapies were similar between groups. RAAS inhibitor treatment rates are also similar between the two groups (%35 vs. %37, p=0.86). However, long-term follow-up revealed that patients with a history of AVN experienced significantly higher rates of rejection episodes compared to those without AVN (33% vs. 15%, p=0.01). The demographic and clinical characteristics were comparable across the study population, as detailed in Table 1.

AVN was diagnosed in 24 patients (89%), most commonly affecting the femoral head, 2 (7%) in the knee, and 1 (4%) in the humerus (Figure 1). After the diagnosis, corticosteroid therapy was discontinued in 52% of KTRs and reduced in 26%. Furthermore, 18 KTRs (67%) required surgical intervention at the affected sites due to AVN, while 2 (7%) underwent hyperbaric oxygen therapy. Treatment interventions against AVN are shown in Figure 2.

In univariate analysis, GN [odds ratio (OR):4.325, 95% confidence interval (CI), 1.936-9.661], cumulative steroid doses at post-transplant first year (OR: 1.001, 95% CI, 1.000-1.002) and rejection episodes (OR: 2.792, 95% CI, 1.185-6.578) detected as possible risk factors for AVN. Upon multivariate analysis, GN was identified as an independent risk factor for the development of AVN (OR: 4.373, 95% CI, 1.935-9.880; p<0.001) (Table 2).

Discussion

In this study, the prevalence of AVN among our KTRs was 7.9%. Patients with a history of AVN were found to have experienced more frequent rejection episodes; however, their long-term allograft survival rates were comparable. Moreover, our findings revealed that GN, the primary cause of ESRD, is an independent risk factor for the development of AVN. Our results may indicate the importance of close monitoring and tailored management strategies for high-risk KTRs, particularly those with GN as the underlying cause of ESRD.

Solid organ transplantation has become a cornerstone of modern medicine, advancing hope and enhancing the quality of life for individuals experiencing end-stage organ failure. The growing number of KTRs has brought to light new challenges, including post-transplant complications such as AVN. While the prevalence of AVN was reported as 24-40% in historical data, this rate is around 5% in current studies (4,13,14). Although its frequency is decreasing, our research emphasizes that AVN is still an important complication in KTRs. Also, the median diagnosis time of AVN in our cohort (15.2 months after KT) aligns with findings from prior studies, which have reported diagnosis timelines ranging from 12 to 24 months post-transplantation (7,15).

Besides, we found that AVN usually affected the femoral head, and 67% of KTRs with AVN required surgical interventions. One study reported that 83% of AVN cases required surgical treatment, and it is reminded that a substantial proportion of patients need surgery (6). The frequent need for surgical

Table 1: Demographic characteristics and outcomes of kidney transplant recipients with avascular necrosis				
	Total n=343	**No AVN n=316 (92.1%)**	**AVN n=27 (7.9%)**	**p-value**
Age at transplantation (years)	34.8±14.4	35±14.7	32.4±11.7	0.87
Sex (female)	127 (37%)	116 (37%)	11 (41%)	0.67
DM, n (%)	37 (11%)	35 (11%)	2 (7%)	0.75
HT, n (%)	241 (70%)	220 (70%)	21 (78%)	0.37
ADPKD, n (%)	22 (6%)	22 (7%)	0 (0%)	0.15
GN, n (%)	77 (22%)	63 (20%)	14 (52%)	**<0.001**
NODAT, n (%)	58 (17%)	55 (17%)	3 (11%)	0.59
Smoking, n (%)	84 (25%)	74 (23%)	10 (37%)	0.11
Preemptive transplantation, n (%)	94 (27%)	83 (26%)	11 (41%)	0.10
Previous transplantation	24 (7%)	24 (8%)	0 (0%)	0.23
Cadaveric transplantation, n (%)	81 (24%)	73 (23%)	8 (30%)	0.44
Induction, n (%) **ATG** **Basiliximab** **None**	 140 (41%) 98 (29%) 105 (30%)	 129 (41%) 93 (29%) 94 (30%)	 11 (41%) 5 (18%) 11 (41%)	0.36
Delayed graft function, n (%)	34 (10%)	32 (10%)	2 (7%)	1.00
Immunosuppressive treatment **CNI, n (%)** **Antimetabolite, n (%)** **mTORi, n (%)**	 303 (88%) 293 (85%) 65 (19%)	 280 (87%) 269 (85%) 61 (19%)	 23 (85%) 24 (89%) 4 (15%)	 0.59 0.78 0.79
RAAS inhibitors, n (%)	122 (36%)	112 (35%)	10 (37%)	0.86
PTX before transplantation, n (%)	22 (6%)	20 (6%)	2 (7%)	0.68
Persistent HPT, n (%)	158 (46%)	142 (45%)	16 (59%)	0.15
Bisphosphonate, n (%)	28 (8%)	25 (8%)	3 (11%)	0.47
Total steroid dose at first year (mg)	3437±282	3429±270	3535±395	0.06
eGFR at baseline (mL/min/1.73 m²)	74 (60-97)	74 (61-97)	65 (55-102)	0.70
Proteinuria at baseline (mg/24h)	247 (160-408)	249 (156-406)	231 (185-511)	0.64
Rejection episode, n (%)	57 (17%)	48 (15%)	9 (33%)	**0.01**
Allograft lost, n (%)	50 (15%)	44 (14%)	6 (22%)	0.24
Follow-up time (months)	125.3±68.9	123±67.6	144.6±80.8	0.20

ADPKD: Autosomal dominant polycystic kidney disease, ATG: Anti-thymocyte globülin, CNI: Calcineurin inhibitör, DM: Diabetes mellitus, eGFR: estimated glomerular filtration rates, GN: Glomerulonephritis, HPT: Hyperparathyroidism, HT: Hypertension, mTORi: Mammalian target of rapamycin inhibitors, NODAT: New-onset diabetes after transplantation, PTX: Parathyroidectomy, RAAS: Renin angiotensin aldosteron system.

Table 2: Univariate and multivariate analysis of risk factors for the development of avascular necrosis				
	Univariate, OR (%95 CI)	**p-value**	**Multivariate, OR (%95 CI)**	**p-value**
Sex (Female)	0.844 (0.379-1.879)	0.67		
Age at transplantation	0.987 (0.960-1.015)	0.36		
GN	4.325 (1.936-9.661)	<0.001	4.373 (1.935-9.880)	**<0.001**
DM	0.642 (0.146-2.829)	0.55		
Smoking	1.924 (0.844-4.382)	0.11		
Preemptive transplantation	1.930 (0.861-4.328)	0.11		
Total steroid dose at first year	1.001 (1.000-1.002)	0.07	1.000 (0.999-1.002)	0.61
Rejection episode	2.792 (1.185-6.578)	0.02	2.395 (0.794-7.224)	0.12
Persistent HPT	1.782 (0.802-3.963)	0.15		

DM: Diabetes mellitus; GN: Glomerulonephritis, HPT: Hyperparathyroidism, OR: Odds ratio, CI: Confidence interval

intervention in this vulnerable patient group is an important issue that needs to be underlined. A systematic review revealed that patients with solid organ transplants face significantly higher rates of acute kidney injury, cardiac complications, pneumonia, and surgical complications, such as transfusions and deep vein thrombosis following hip arthroplasty (16). Furthermore, these patients also exhibited notably higher rates of readmission and 90-day mortality.

Steroids are a key factor in the pathogenesis of AVN, with some studies indicating a strong association between both high cumulative doses and short-term high-dose exposures during rejection episodes and the occurrence of AVN (17). Although we examined total corticosteroid doses in the first year of KT, our study found no significant association with AVN. In line with our findings, some previous studies have not established a clear correlation between steroid dosage and AVN incidence (18,19). However, these results should be interpreted cautiously, considering the potential influence of confounding factors and variations in study methodologies. For instance, Khwaja et al. (20) implemented a maintenance protocol without long-term steroid use, involving a single intraoperative dose of MPZ (500 mg) and a short course of prednisone (1 mg/kg on the first postoperative day, tapered over four days and discontinued by day five). Within their cohort of 349 KTRs, they reported no cases of AVN (20).

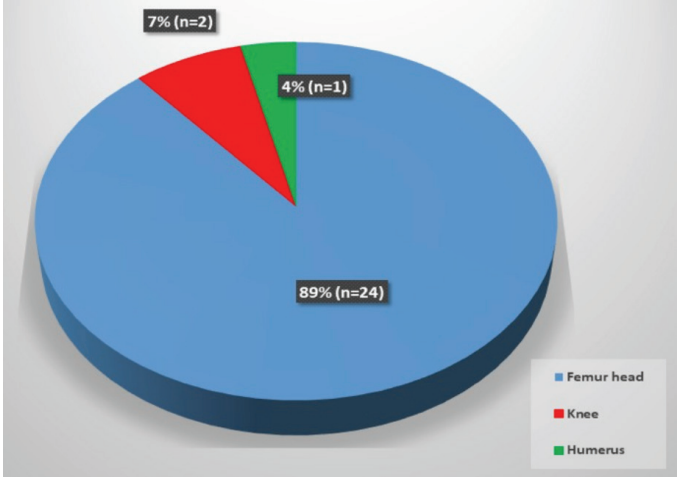

Figure 1: Site of avascular necrosis in kidney transplant recipients

Bone health in KTRs is a multifaceted issue influenced by pre-existing conditions such as renal osteodystrophy, secondary HPT, and adynamic bone disease (21). However, these bone lesions can also occur in patients with relatively preserved kidney function and are often unrelated to PTH levels. Our study suggests AVN may develop independently of traditional markers like serum PTH levels, parathyroidectomy before KT, or bisphosphonate medication. This findings highlight the complex interplay of factors contributing to post-transplant bone diseases, including pre-existing renal osteodystrophy and immunosuppressive therapy.

Previous studies have reported the critical role of the RAS in regulating bone marrow mesenchymal stem cells, which are vital for bone regeneration and remodeling, particularly in femoral head necrosis (22). RAS plays a key role in promoting angiogenesis by stimulating vascular endothelial growth factor (VEGF) production through angiotensin II, enhancing paracrine signaling, supporting cell survival, and facilitating bone repair (23). A reduction in angiogenesis, however, can impair nutrient and oxygen delivery to bone tissue, leading to demineralization, trabecular thinning, and, ultimately, structural collapse (24). Given that RAAS inhibitors are widely used to reduce proteinuria and prolong renal survival in KT recipients, these drugs may have an additive contribution to the development of AVN. Nevertheless, we did not observe any correlation between RAS inhibitor treatment and the onset of AVN in our study.

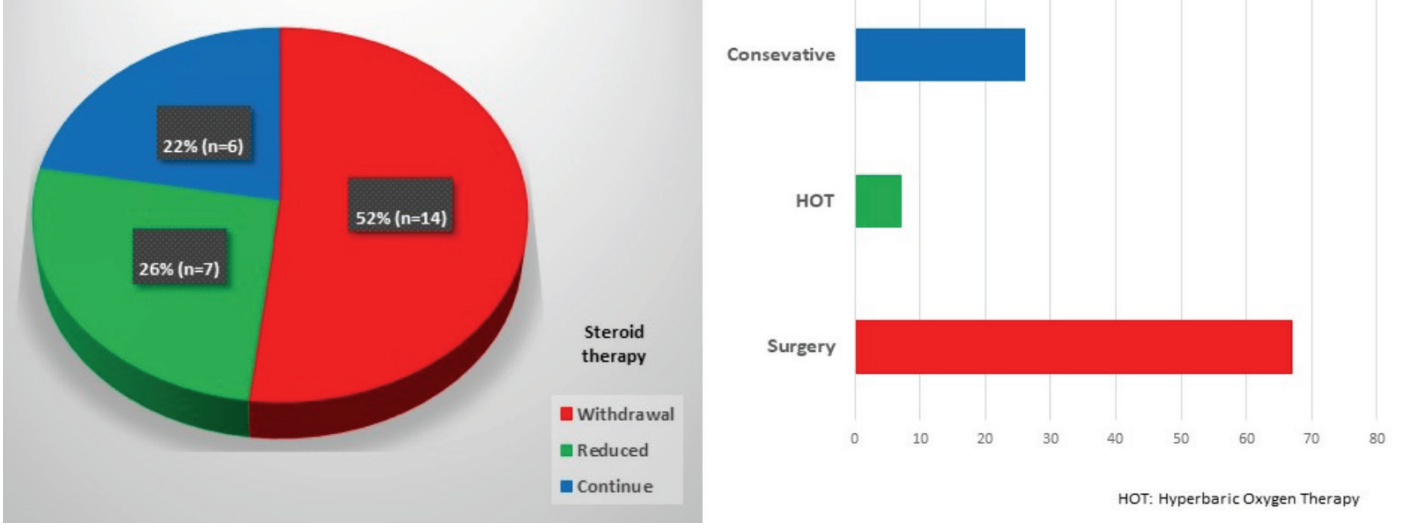

Figure 2 A-B: Treatment interventions for avascular necrosis in kidney transplant recipients

Interestingly, our findings revealed that KTRs with GN as the primary cause of ESRD demonstrated an independent risk factor for AVN. This observation may be linked to prolonged pre-transplant steroid use and higher total cumulative steroid doses in these patients. Similar to our result, Schachtner et al. (6) reported that AVN incidence post-transplantation was higher in KTRs with ANCA vasculitis as the underlying disease. In addition, Yu et al. (25) compared 23 lupus patients with a history of KT to 94 matched controls. The results revealed a notably higher AVN rate in the lupus group (17.4% vs. 2.1%, p=0.04). The researchers concluded that the extended use of corticosteroids before transplantation may play a role in the development of AVN. The higher prevalence of AVN observed in this subgroup emphasizes the importance of closely monitoring steroid doses and considering immunosuppressive therapy strategies more carefully to minimize the risk of AVN.

Study Limitations

The study's limitations primarily stem from its retrospective and single-center design, which can significantly affect the validity and generalizability of the findings. Since the data is drawn from a single institution, the cohort might lack the diversity necessary to properly represent the broader patient population. Moreover, some missing values concerning human leukocyte antigen typing and patient weight hindered a comprehensive assessment of potential connections between these factors and AVN. While the chance of pre-existing or asymptomatic AVN cases is rare, it is a possibility that should be considered in the context of this study. Lastly, several possible confounding factors might have influenced the observed association between GN and AVN, such as the duration of the primary disease, the intensity of previous steroid therapy, and immunosuppressive therapies for the primary disease.

Conclusion

AVN is a debilitating bone disease that often causes significant functional impairment and reduces the quality of life in KTRs. Our study identified an association between GN underlying disease and an elevated risk of developing AVN. This increased incidence of AVN in patients with a history of GN may be linked to the prolonged use of steroid therapy prior to transplantation. Given the potential complications related to AVN, healthcare providers need to maintain heightened attention regarding the cumulative doses of steroids administered to these patients. Furthermore, an early discontinuation of steroid therapy may be a viable strategy for these vulnerable patients to reduce the risk of AVN. Future prospective studies are needed to investigate the benefits of steroid-sparing immunosuppressive protocols and examine the impact of GN on AVN.

Ethics

Ethics Committee Approval: Gazi University Ethics Committee approved the study protocol (protocol number: E-77082166-604.01-1148721, date: 21.01.2025).

Informed Consent: Informed consent was not required.

Footnotes

Authorship Contributions

Concept: Ö.F.A., O.H., G.G., Design: Ö.F.A., O.H., G.G., Data Collection and/or Processing: Ö.F.A., A.D., V.B.T., Analysis and/or Interpretation: Ö.F.A., O.H., G.G., Literature Search: Ö.F.A., A.D., V.B.T., Writing: Ö.F.A.

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

Financial Disclosure: The authors did not receive any funding.

References

1. Abecassis M, Bartlett ST, Collins AJ, et al. Kidney transplantation as primary therapy for end-stage renal disease: a National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQITM) conference. Clin J Am Soc Nephrol. 2008;3:471-480.
2. Teh JW, Mac Gearailt C, Lappin DWP. Post-Transplant bone disease in kidney transplant recipients: diagnosis and management. Int J Mol Sci. 2024;25:1859
3. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). Kidney Int Suppl (2011). 2017;7:1-59. Erratum in: Kidney Int Suppl (2011). 2017;7:e1.
4. Nehme D, Rondeau E, Paillard F, et al. Aseptic necrosis of bone following renal transplantation: relation with hyperparathyroidism. Nephrol Dial Transplant. 1989;4:123-128.
5. Takao M, Sakai T, Nishii T, Yoshikawa H, Takahara S, Sugano N. Incidence and predictors of osteonecrosis among cyclosporin- or tacrolimus-treated renal allograft recipients. Rheumatol Int. 2011;31:165-70.
6. Schachtner T, Otto NM, Reinke P. Cyclosporine use and male gender are independent determinants of avascular necrosis after kidney transplantation: a cohort study. Nephrol Dial Transplant. 2018;33:2060-2066.
7. Felten R, Perrin P, Caillard S, Moulin B, Javier RM. Avascular osteonecrosis in kidney transplant recipients: Risk factors in a recent cohort study and evaluation of the role of secondary hyperparathyroidism. PLoS One. 2019;14:e0212931.
8. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. Ann Intern Med. 1990;112:352-364.
9. Ferrari P, Schroeder V, Anderson S, et al. Association of plasminogen activator inhibitor-1 genotype with avascular osteonecrosis in steroid-treated renal allograft recipients. Transplantation. 2002;74:1147-1152.
10. Lai SW, Lin CL, Liao KF. Real-world database examining the association between avascular necrosis of the femoral head and diabetes in Taiwan. Diabetes Care. 2019;42:39-43.
11. Tsai HL, Chang JW, Lu JH, Liu CS. Epidemiology and risk factors associated with avascular necrosis in patients with autoimmune diseases: a nationwide study. Korean J Intern Med. 2022;37:864-876.
12. Jeong HJ. Diagnosis of renal transplant rejection: Banff classification and beyond. Kidney Res Clin Pract. 2020;39:17-31.

13. Hedri H, Cherif M, Zouaghi K, et al. Avascular osteonecrosis after renal transplantation. Transplant Proc. 2007;39:1036-1038.
14. Metselaar HJ, van Steenberge EJ, Bijnen AB, Jeekel JJ, van Linge B, Weimar W. Incidence of osteonecrosis after renal transplantation. Acta Orthop Scand. 1985;56:413-415.
15. Paydas S, Balal M, Demir E, Sertdemir Y, Erken U. Avascular osteonecrosis and accompanying anemia, leucocytosis, and decreased bone mineral density in renal transplant recipients. Transplant Proc. 2011;43:863-866.
16. Kim CH, Lim EJ, Lee J. Clinical outcomes following primary hip replacement arthroplasties in patients with solid organ transplantation: a systematic review and meta-analysis. Hip Pelvis. 2022;34:127-139.
17. Weinstein RS. Glucocorticoid-induced osteonecrosis. Endocrine. 2012;41:183-190.
18. Higuchi Y, Tomosugi T, Futamura K, et al. Incidence and risk factors for osteonecrosis of the hip in renal transplant patients: a prospective single-centre study. Int Orthop. 2020;44:1927-1933.
19. Ekmekci Y, Keven K, Akar N, et al. Thrombophilia and avascular necrosis of femoral head in kidney allograft recipients. Nephrol Dial Transplant. 2006;21:3555-3558.
20. Khwaja K, Asolati M, Harmon J, et al. Outcome at 3 years with a prednisone-free maintenance regimen: a single-center experience with 349 kidney transplant recipients. Am J Transplant. 2004;4:980-987.
21. Khairallah P, Nickolas TL. Bone and mineral disease in kidney transplant recipients. Clin J Am Soc Nephrol. 2022;17:121-130.
22. Zhao J, He W, Zheng H, Zhang R, Yang H. Bone regeneration and angiogenesis by co-transplantation of angiotensin ii-pretreated mesenchymal stem cells and endothelial cells in early steroid-induced osteonecrosis of the femoral head. Cell Transplant. 2022;31:9636897221086965.
23. Shi RZ, Wang JC, Huang SH, Wang XJ, Li QP. Angiotensin II induces vascular endothelial growth factor synthesis in mesenchymal stem cells. Exp Cell Res. 2009;315:10-15.
24. Wang P, Shao W, Wang Y, Wang B, Lv X, Feng Y. Angiogenesis of avascular necrosis of the femoral head: a classic treatment strategy. Biomedicines. 2024;12:2577.
25. Yu TM, Chen YH, Lan JL, et al. Renal outcome and evolution of disease activity in Chinese lupus patients after renal transplantation. Lupus. 2008;17:687-694.

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2025.79058
J Ankara Univ Fac Med 2025;78(2):120-127

MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Menopausal Status at Diagnosis is a Prognostic Indicator in Patients who are Operated for Uterine Carcinosarcoma

Rezeksiyon Edilmiş Uterin Karsinosarkom Tanılı Hastalarda Prognostik Bir Gösterge Olarak Tanı Anındaki Menopozal Durum

Hatice Bölek[1], Merih Yalçıner[1], Serhat Sekmek[2], Furkan Ceylan[2], Orhun Akdoğan[3], Doğan Uncu[2], Ozan Yazıcı[3], Elif Berna Köksoy[1]

[1]Ankara University Faculty of Medicine, Department of Medical Oncology, Ankara, Türkiye
[2]Ankara Bilkent City Hospital, Clinic of Medical Oncology, Ankara, Türkiye
[3]Gazi University Faculty of Medicine, Department of Medical Oncology, Ankara, Türkiye

Abstract

Objectives: Uterine carcinosarcoma is a rare type of uterine cancer, and due to its rarity, there is limited evidence for prognostic factors and treatment. The objective of this study is to assess the influence of histologic, clinical, and demographic characteristics on overall survival (OS) and recurrence-free survival (RFS).

Materials and Methods: Patients who had diagnosis of uterine carcinosarcoma and followed by the medical oncology department of three hospitals from Türkiye between January 2013 and January 2023 were retrospectively evaluated. All patients had local disease and were surgically managed, and patients were excluded if they did not have primary surgical management.

Results: The study included 62 women who were primarily treated with surgery and had a median age of 64.5 (interquartile range=14) years. Recurrence was observed in 26 patients (41.9%), with a median RFS of 11.63 months [95% confidence interval (CI): 1.99-21.26]. A shorter RFS was observed in patients with myometrial invasion [hazard ratio (HR) 2.48, 95% CI 1.04-5.93, p=0.04], while postmenopausal diagnosis was a predictor for longer RFS (HR 0.02, 95% CI 0.004-0.14, p<0.001). The median OS was 43.17 months. Postmenopausal diagnosis was associated with prolonged OS (HR 0.003, 95% CI 0-0.45, p<0.001).

Conclusion: The results of our study show that being diagnosed before menopause is linked to a shorter RFS and OS in women with uterine carcinosarcoma who had surgery to treat local disease.

Keywords: Uterine carcinosarcoma, prognostic factor, menopausal status

Öz

Amaç: Uterin karsinosarkom, nadir görülen bir uterus kanser türüdür ve nadir olması nedeniyle prognostik faktörler ve tedavi konusunda sınırlı veri bulunmaktadır. Bu çalışmanın amacı, histolojik, klinik ve demografik özelliklerin genel sağkalım (OS) ve nükssüz sağkalım (RFS) üzerindeki etkisini değerlendirmektir.

Gereç ve Yöntem: Ocak 2013 ile Ocak 2023 tarihleri arasında Türkiye'deki üç hastanenin tıbbi onkoloji bölümünde takip edilen uterin karsinosarkom tanısı almış hastalar retrospektif olarak değerlendirildi. Tüm hastalar tanı anında lokal hastalığa sahipti ve cerrahi olarak tedavi edildi; tanı anında metastatik olan veya primer cerrahi yapılmayan hastalar çalışmaya dahil edilmedi.

Bulgular: Çalışmaya, primer olarak cerrahi tedavi uygulanmış 62 kadın dahil edildi ve hastaların ortanca yaşı 64,5 (çeyrekler arası aralık=14) yıldı. Nüks, 26 hastada (%41,9) gözlendi ve ortanca RFS süresi 11,63 ay [%95 güven aralığı (GA): 1,99-21,26] olarak bulundu. Miyometrial invazyonu

Address for Correspondence/Yazışma Adresi: Hatice Bölek, MD
Ankara University Faculty of Medicine, Department of Medical Oncology, Ankara, Türkiye
E-mail: hati.kocc@gmail.com **ORCID ID:** orcid.org/0000-0001-8659-7327

Received/Geliş Tarihi: 28.09.2024 **Accepted/Kabul Tarihi:** 27.03.2025 **Epub:** 12.05.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025

Cite this article as/Atıf: Bölek H, Yalçıner M, Sekmek S, et al. Menopausal status at diagnosis is a prognostic indicator in patients who are operated for uterine carcinosarcoma. J Ankara Univ Fac Med. 2025;78(2):120-127

kısalmış RFS ile ilişkili bulunurken [risk oranı (HR) 2,48; %95 GA 1,04-5,93, p=0,04], tanı anında postmenopozal olmak daha uzun bir RFS ile ilişkili bulundu (HR 0,02; %95 GA 0,004-0,14, p<0,001). Ortanca OS süresi 43,17 aydı. Postmenopozal tanı, uzamış OS ile ilişki bulundu (HR 0,003; %95 GA 0-0,45, p<0,001).

Sonuç: Bu çalışma lokal hastalık için cerrahi ile tedavi edilen karsinosarkom tanılı hastalarda premenopozal dönemde tanı almanın daha kısa RFS ve OS ile ilişkili olduğunu göstermiştir.

Anahtar Kelimeler: Uterin karsinosarkom, prognostik faktör, menapoz durumu

Introduction

Uterine carcinosarcoma, also known as malignant mixed Müllerian tumor, is a rare form of gynecological malignancy, constituting less than 5% of all uterine neoplasms (1). Typically characterized by aggressive behavior, uterine carcinosarcoma is often associated with 15% of all uterine cancer deaths (2). Even in early-stage cases the rate of relapse exceeds 50% (3-5). The median overall survival (OS) rate is less than 2 years for patient with stage 3-4 disease, and the 5-year cancer specific survival rates are about 60%, 20% and 10% for women with stage 1/2, 3, and 4 disease, respectively (6-9).

Endometrial carcinosarcoma is an atypical neoplasm distinguished by its biphasic composition, comprising mesenchymal and epithelial elements (1). Tumor behavior of uterine carcinosarcoma is mainly driven by the carcinomatous component of the disease, whereas endometrial carcinosarcomas exhibit a metastatic pattern that utilizes the lymphatic and intraperitoneal pathways, similar to epithelial tumors and epithelial component is more commonly observed in metastasis (1,10,11). The staging system for carcinosarcoma aligns with that of endometrial carcinoma and based on the International Federation of Gynecology and Obstetrics (FIGO) guidelines. FIGO stage, tumor size, deep myometrial invasion (≥1/2), cervical involvement, parametrial involvement, lymphovascular invasion (LVI), lymph node involvement, presence of heterologous element affect survival (4,6,12-14).

Due to the rarity of the disease, there is limited evidence for the treatment. Currently, surgery is the mainstay of the treatment and followed by adjuvant chemotherapy and radiotherapy (RT). There is no clear consensus regarding the adjuvant treatment of the carcinosarcoma. Although adjuvant RT is associated with lower local recurrence rate, there is no OS gain with adjuvant RT (15,16). While adjuvant chemotherapy is generally recommended for resected stage I-IV uterine carcinosarcoma, there remains no clear consensus regarding its use in stage imperforate anus disease (17,18). Cochrane review of phase III trials revealed that paclitaxel and ifosfamide regimen and cisplatin, ifosfamide, and mesna regimens were associated with longer recurrence-free survival (RFS) and OS compared to ifosfamide alone or RT (19). Based on the findings from the Gynecologic Oncology Group (GOG)-232B and GOG-261 trials, which demonstrated non-inferiority, and a better toxicity profile compared to the ifosfamide/paclitaxel regimen, the carboplatin/paclitaxel regimen is recommended as the preferred first-line treatment (20,21).

This retrospective study aimed to identify factors influencing the prognosis in resected uterine carcinosarcoma. Its primary objective was to assess the impact of demographic, clinical, and histologic characteristics on RFS and OS.

Materials and Methods

This is as a retrospective observational study. Patients who had diagnosis of uterine carcinosarcoma and followed by the medical oncology department of three hospitals from Türkiye between January 2013 and January 2023 were included in the study. All patients had local disease and were surgically managed, and none received neoadjuvant chemotherapy. Patients were excluded if they did not have primary surgical management. Patients were included in survival analysis if they had any post-operative follow-up contact with medical oncology department. Clinicodemographic features, pathology results and the treatments if any, and recurrence and survival data of the patients were recorded retrospectively. Patients were staged according to the 2023 FIGO staging system for endometrial carcinoma. Staging groups were classified as early FIGO stage (I-II) and advanced FIGO stage (III-IV).

RFS was defined as the date from surgery to the date of first recurrence or in absence of recurrence, to the date of death. OS was calculated from the date of diagnosis to the date of death.

This study has been approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (approval no.: İ06-385-23, date: 16.06.2023).

Statistics Analysis

We conducted all statistical analyses using the IBM SPSS Statistics 24.0 Statistical Package Program. We described continuous variables as medians [interquartile range (IQR)] and categorical variables as percentages. The chi-square test was used to compare categorical variables, and the Mann-Whitney U test/Student's t-test was used to compare continuous variables. Kaplan-Meier method and log-rank tests were conducted for survival analysis. We performed multivariate analyses using

variables that had a p-value of less than 0.20 in the univariate analyses. To perform multivariable analyses and calculate hazard ratios (HRs) with 95% confidence intervals (CIs), we conducted Cox regression analyses. P-values of <0.05 were considered significant.

Results

From January 2013 to January 2023, 62 patients who primarily treated with surgery were included the analysis. Median age was 64.5 and majority of patients were postmenopausal (n=54, 87.1%). Fifty-two (83.9%) patients presented with abnormal uterine bleeding while 7 (11.3%) patients had abdominal pain. Most performed surgery type was total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), pelvic lymph node dissection and omentectomy. 91.5% of surgeries provided negative surgical margins. Median tumor size was 5.5 (IQR=5.2) cm. Almost half of the patients (48.4) had LVI and 53.2 % had deep myometrial invasion (≥1/2). Thirty-two (51.6%) patients had FIGO stage I-II disease. Other patients' characteristics were given in Table 1. Half of the patients received any type of adjuvant RT, and 34 (54.8%) patients treated with adjuvant chemotherapy other than concurrent chemoradiotherapy. Most commonly utilized chemotherapy regimen was carboplatin and paclitaxel combination (n=23) and followed by ifosfamide, mesna and doxorubicine combination (n=7).

Median follow-up time was 26.4 months. Recurrence occurred in 26 (41.9%) patients and of these 26 recurrences, 6 patients (23.1%) presented with local recurrence only and 20 patients (76.9%) presented with recurrence outside the pelvis (with or without local recurrence) (Table 2). Only 3 of the 7 patients who underwent surgery for the recurrence had negative surgical margins. At recurrence, 19 (73.1%) out of 26 patients

Table 1: Clinicodemographic and pathologic features of the patients

		Number (n=62)
Age (median-IQR)		64.5 (14)
Menopausal status	Postmenopausal (%)	54 (87.1)
	Premenopausal (%)	8 (12.9)
Symptom	Abnormal uterine bleeding (%)	52 (83.9)
	Pain (%)	7 (11.3)
	Other (%)	3 (4.8)
Pathologic malignity diagnosis before surgery	Carcinosarcoma	27 (43.6)
	Undifferentiated tumor or different malignancy	17 (27.4)
	No malign pathology	18 (29)
Type of surgery	TAH + USO (%)	2 (3.2)
	TAH + BSO (%)	13 (21)
	TAH + BSO + PLND (%)	11 (17.7)
	TAH + BSO + PLND + omentectomy (%)	35 (56.5)
	TAH + BSO + omentectomy (%)	1 (1.6)
Negative surgical margin (%)		54 (91.5)
Tumor size (cm, median, IQR)		5.5 (5.2)
Lymphovascular invasion	Yes	30 (48.4)
	No	30 (48.4)
	Not known	2 (3.2)
Myometrial invasion	<1/2 (%)	25 (40.3)
	≥1/2 (%)	33 (53.2)
	Not known (%)	4 (6.5)
Cervical involvement (%)		21 (33.9)
Adnexal involvement (%)		12 (19.3)
Lymph node involvement (%)		19 (30.6)
Hormone receptor status	ER and PR negative (%)	3 (9.7)
	Only PR positive (%)	1 (3.2)
	ER and PR positive (%)	5 (16.1)
	Not known (%)	22 (71)

Table 1: Continued		
		Number (n=62)
Grade	2 (%)	2 (3.2)
	3 (%)	15 (24.2)
	Not known (%)	45 (72.6)
FIGO stage	1-2 (%)	32 (51.6)
	3-4 (%)	30 (48.4)
Carcinoma type	Endometroid (%)	15 (24.2)
	Serous (%)	18 (29)
	Undifferentiated (%)	4 (6.5)
	Squamous differentiation (%)	5 (8.1)
	Not known (%)	20 (32.3)
Sarcoma type	Stromal sarcoma (%)	6 (9.7)
	Leiomyosarcoma (%)	11 (17.7)
	Undifferentiated stromal sarcoma (%)	11 (17.7)
	Rhabdomyosarcoma (%)	11 (17.7)
	Chondrosarcoma (%)	4 (6.5)
	Leiomyosarcoma + Rhabdomyosarcoma (%)	2 (4.3)
	Not known (%)	17 (27.4)
Adjuvant (chemo) radiotherapy (%)		31 (50)
Adjuvant chemotherapy (%)		34 (54.8)

BSO: Bilateral salpingo-oophorectomy, ER: Estrogen receptor, IQR: Interquartile range, PLND: Pelvic lymph node dissection, PR: Progesterone receptor, TAH: Total abdominal hysterectomy, USO: Unilateral salpingo-oophorectomy, FIGO: International Federation of Gynecology and Obstetrics guidelines

Table 2: Characteristics of recurrence		
		n=26
Initial FIGO stage	1-2 (%)	10 (38.5)
	3-4 (%)	16 (61.5)
Site of recurrence	Pelvis (%)	6 (23.1)
	Abdomen (%)	1 (3.8)
	Distant (%)	6 (23.1)
	Pelvis and abdomen (%)	5 (19.2)
	Pelvis and distant (%)	3 (11.5)
	Abdomen and distant (%)	5 (19.2)
Surgery for recurrence (%)		7 (26.9)
Chemotherapy (%)		19 (73.1)

FIGO: International Federation of Gynecology and Obstetrics guidelines

received chemotherapy, with the most commonly utilized regimens being carboplatin and paclitaxel (n=5), ifosfamide, mesna, and doxorubicin combination (n=5), and gemcitabine and docetaxel (n=3). Median RFS was 11.63 (95% CI 1.99-21.26) months (Figure 1A). In univariate analysis (Table 3), the presence of LVI (HR 2.11, 95% CI 1.01-4.31, p=0.04) and deep myometrial invasion (HR 3.14, 95% CI 1.34-7.34, p=0.008) were both associated with a shorter RFS (Tables 3, 4). Upon multivariate analysis, deep myometrial invasion was significantly associated with poorer RFS (HR 2.48, 95% CI 1.04-5.93, p=0.04) while postmenopausal diagnosis was a significant predictor for longer RFS (HR 0.02, 95% CI 0.004-0.14, p<0.001) (Figure 2A).

Median OS was 43.17 months (Figure 1B). Use of adjuvant chemotherapy was associated with poorer survival both in univariate and multivariate analysis (HR 2.76, 95% CI 1.09-6.96, p=0.03 and HR 5.74, 95% CI 1.87-17.36, p=0.002, respectively). In multivariate analysis, similar to RFS, postmenopausal diagnosis was associated with prolonged OS (HR 0.003, 95% CI 0-0.45, p<0.001) (Figure 2B, Table 2). Out of 32 patients who received adjuvant chemotherapy, 21 (65.6%) had FIGO stage III-IV disease. 61.1% of patients who received chemotherapy had serous carcinoma, whereas only 38.9% of patients in the no chemotherapy arm had serous carcinoma.

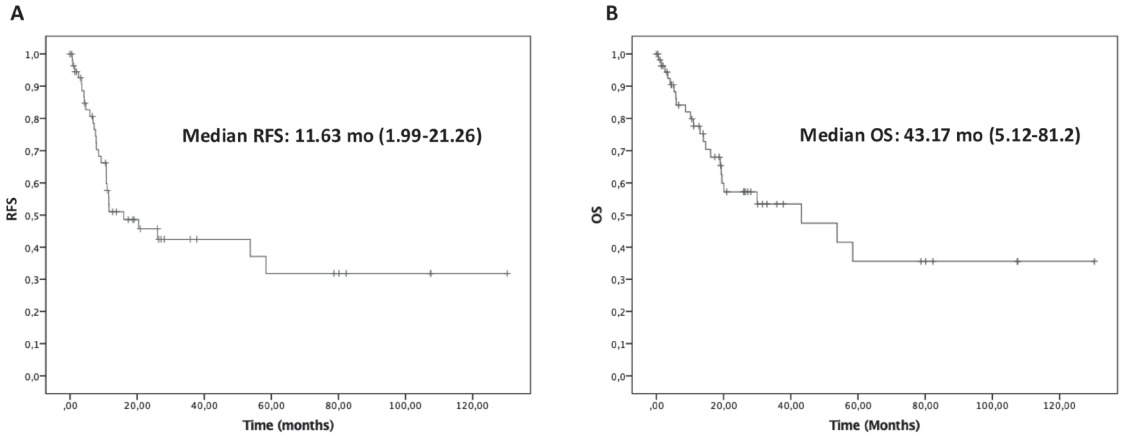

Figure 1: Recurrence free survival (A) and Overall survival (B)
OS: Overall survival, RFS: Recurrence-free survival

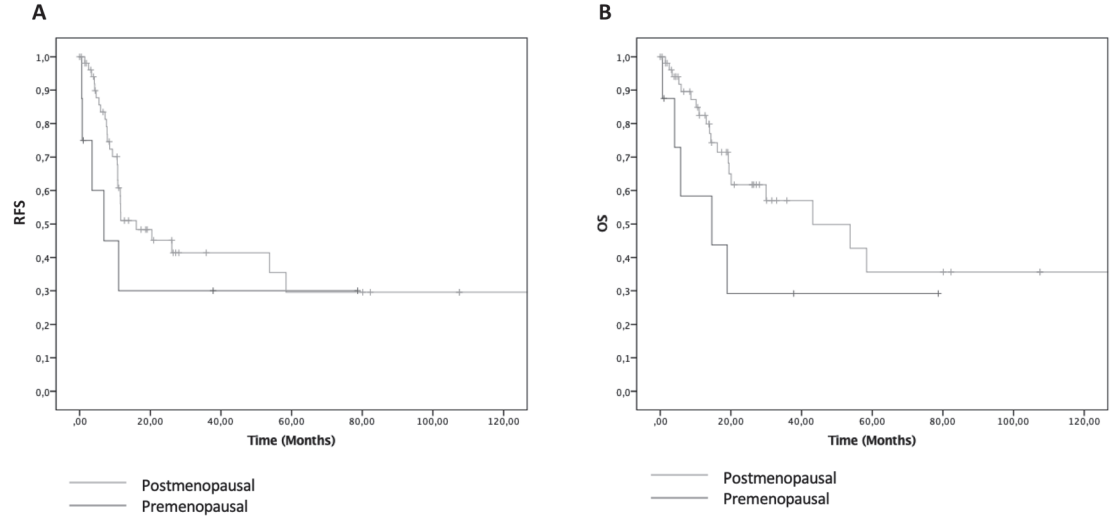

Figure 2: Recurrence free survival regarding menopausal status (A) and Overall survival regarding menopausal status (B)
OS: Overall survival, RFS: Recurrence-free survival

Table 3: Predictors of recurrence free survival

	Univariable analysis		Multivariable analysis, initial model		Multivariable analysis, final model	
Predictors	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age ≥65	0.80 (0.39-1.62)	0.54	0.60 (0.23-1.51)	0.27	-	
Menopausal status/ Postmenopausal	0.56 (0.21-1.47)	0.24	0.01 (0.002-0.13)	<0.001	0.02 (0.004-0.14)	**<0.001**
Lymphovascular invasion	2.11 (1.01-4.31)	0.04	1.94 (0.71-5.27)	0.19	-	
Deep myometrial invasion	3.14 (1.34-7.34)	0.008	2.70 (1.00-7.24)	0.04	2.48 (1.04-5.93)	**0.04**
Cervical invasion	1.82 (0.90-3.67)	0.09	0.64 (0.21-1.94)	0.43	-	
Adnexal invasion	1.41 (0.58-3.53)	0.42	0.60 (0.15-2.37)	0.46	-	
Lymph node positivity	1.93 (0.95-3.92)	0.06	1.00 (0.24-4.12)	0.99	-	
FIGO stage (I-II or III-IV)	1.57 (0.78-3.17)	0.20	0.97 (0.26-3.66)	0.97	-	
Adjuvant (chemo) radiotherapy (yes)	1.09 (0.53-2.22)	0.80	0.54 (0.22-1.32)	0.17	-	
Adjuvant chemotherapy (yes)	2.10 (0.97-4.52)	0.05	2.33 (0.90-6.00)	0.07	2.07 (0.88-4.82)	0.09

FIGO: International Federation of Gynecology and Obstetrics guidelines, CI: Confidence interval, HR: Hazard ratio

Table 4: Predictors of overall survival						
	Univariable analysis		Multivariable analysis, initial model		Multivariable analysis, final model	
Predictors	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Age ≥65	0.77 (0.33-1.77)	0.53	0.38 (0.11-1.31)	0.12	-	
Menopausal status/ Postmenopausal	0.47 (0.17-1.26)	0.13	0.002 (0-0.06)	<0.001	0.003 (0-0.45)	**<0.001**
Lymphovascular invasion	1.50 (0.65-3.48)	0.33	1.55 (0.51-4.74)	0.43	-	
Deep myometrial invasion	2.13 (0.83-5.46)	0.11	1.70 (0.51-5.60)	0.38	-	
Cervical invasion	1.61 (0.71-3.64)	0.24	0.47 (0.11-2.06)	0.32	-	
Adnexal invasion	0.89 (0.26-3.04)	0.85	0.14 (0.01-1.58)	0.11	0.16 (0.02-1.26)	0.08
Lymph node positivity	1.62 (0.70-3.72)	0.25	0.86 (0.13-5.55)	0.87	-	
FIGO stage (I-II or III-IV)	1.16 (0.52-2.60)	0.70	1.03 (0.19-5.55)	0.97	-	
Adjuvant (chemo) radiotherapy (yes)	0.89 (0.39-2.02)	0.78	0.24 (0.06-0.86)	0.03	0.42 (0.16-1.10)	0.07
Adjuvant chemotherapy (yes)	2.76 (1.09-6.96)	0.03	7.89 (1.91-23.5)	0.002	5.74 (1.87-17.36)	**0.002**

FIGO: International Federation of Gynecology and Obstetrics guidelines, CI: Confidence interval, HR: Hazard ratio

Discussion

Uterine carcinosarcoma is an uncommon condition, and the absence of a standardized therapeutic method hinders the conduction of studies on this cancer. We conducted a retrospective analysis of data from 62 patients who had local uterine carcinosarcoma and were treated with surgery. The study investigated the clinical features and pathological factors that impact RFS and OS. Carcinosarcomas are recognized as one of the most aggressive types of uterine tumors, characterized by a propensity for hematogenous spread, leading to poor OS outcomes. Peak incidence is observed in sixth and seventh decades (6). In our study, the median age at which patients were diagnosed was 64.5 years (IQR=14), with the majority (87.1%) being postmenopausal.

In our study, recurrence rate was 41.9% within 26.4 months of median follow-up time. Recurrence rate was reported within the range 27-82% in the literature (12,13,22-24). Differences between recurrence rates may be related to patients' characteristics, disease stage and the duration of the follow-up time. Median RFS was 11.63 (95% CI 1.99-21.26) months in our study. A Japanese study with similar patient characteristics regarding FIGO stage, deep myometrial invasion, and presence of LVI, but with a higher percentage (91%) of patients receiving adjuvant chemotherapy, reported a RFS of 16.4 months (25). But in that study, adjuvant chemotherapy did not show a significant impact on RFS (HR 1.93, 95% CI 0.55-6.74, p=0.30) (25). Relative these studies in the literature, underutilization of adjuvant therapy may be the cause of shorter RFS in our study. GOG-150 trial showed benefit of adjuvant chemotherapy over RT with 5 years recurrence rates of 58% vs. 52%, respectively (26). Although the supporting evidence is limited, adjuvant platinum-based chemotherapy has an impact on RFS, rather than RT, single-agent chemotherapy, or observation in patients with FIGO stage IB-IV carcinosarcoma. In our study, deep myometrial invasion was associated with shorter RFS while postmenopausal diagnosis was associated with prolonged RFS in multivariate analysis (HR 2.48, 95% CI 1.04-5.93, p=0.04 and HR 0.02, 95% CI 0.004-0.14, p<0.001, respectively). Previous studies showed that deep myometrial invasion alongside the larger tumor size, FIGO stage, presence of residual tumor, cervical invasion, adnexal involvement, nodal involvement, higher cancer antigen (CA)-125 levels, sarcoma dominance were associated with early recurrence in uterine carcinosarcoma (6,13,25,27,28).

Median OS was 43.17 months in our study and OS was longer in postmenopausal patients (HR 0.003, 95% CI 0-0.45, p<0.001). Although studies have shown varying results regarding the impact of age on recurrence and OS, the menopausal state has not been commonly evaluated in these studies (12,29). In a retrospective study, late onset of the menopause was associated with a lengthened OS (29). Estrogen receptors were expressed in 44% of patients with uterine carcinosarcoma, potentially indicating an association with better histological differentiation (30). Median OS for patients with hormone receptor positive carcinosarcoma was significantly longer than for patients with hormone receptor negative tumors (31). However, effect of patient's hormonal status on prognosis of carcinosarcoma is unknown. Additionally, almost all the patients in our study underwent BSO, so the OS advantage observed in postmenopausal women in our study can be attributed to the more aggressive tumor behavior rather than the effect of hormonal status in premenopausal women. Adjuvant chemotherapy was associated with poor survival in our study. While adjuvant chemotherapy

extends RFS, it does not have a beneficial effect on OS in also other studies (26,28,32). It may be due to the high proportion of serous carcinoma and FIGO stage III-IV disease in chemotherapy arm. Use of less effective regimens after adjuvan chemotherapy may be another cause.

Study Limitations

We acknowledge the various limitations of our study. Initially, the sample size in certain patient subgroups is very limited, hence restricting our capacity to carry out comprehensive subgroup analysis. Furthermore, because this study is retrospective, there is a lack of data regarding markers that may affect the prognosis, such as tumor grade, hormone receptor status, CA-125 levels. Lastly, the lack of standardized treatment protocols among patients can impact the results of the study. These constraints underscore the necessity of exercising prudence while interpreting and extrapolating the findings of the study. We need future research with larger, more comprehensive datasets and standardized protocols to address these limitations and provide more definitive conclusions.

Conclusion

In conclusion, due to the rarity of uterine carcinosarcoma, conducting prospective studies with large sample sizes is challenging. The information available in the literature on this cancer type is conflicting, and our understanding of prognostic factors and optimal adjuvant treatments remains limited, with several gray areas requiring clarification. Our study findings suggest that a premenopausal diagnosis is associated with shorter RFS and OS. A multidisciplinary approach is essential to improve survival outcomes and enhance the quality of life for patients with uterine carcinosarcoma.

Ethics

Ethics Committee Approval: This study has been approved by the Ankara University Faculty of Medicine Human Research Ethics Committee (approval no.: İ06-385-23, date: 16.06.2023).

Informed Consent: This is as a retrospective observational study.

Footnotes

Authorship Contributions

Concept: H.B., E.B.K., Design: H.B., E.B.K., Data Collection and/or Processing: H.B., M.Y., S.S., F.Y., O.A., D.U., O.Y., Analysis and/or Interpretation: H.B., M.Y., Literature Search: H.B., E.B.K., Writing: H.B., D.U., O.Y., E.B.K.

Conflict of Interest: There is no potential conflict of interest to declare.

Financial Disclosure: This study received no financial support.

References

1. Pezzicoli G, Moscaritolo F, Silvestris E, et al. Uterine carcinosarcoma: an overview. Critical Rev Oncol/Hematol. 2021;163:103369.
2. El-Nashar SA, Mariani A. Uterine carcinosarcoma. Clin Obstet Gynecol. 2011;54:292-304.
3. Leath CA 3rd Numnum TM, Kendrick JE 4th, et al. Patterns of failure for conservatively managed surgical stage I uterine carcinosarcoma: implications for adjuvant therapy. Int J Gynecol Cancer. 2009;19:888-891.
4. Sartori E, Bazzurini L, Gadducci A, et al. Carcinosarcoma of the uterus: a clinicopathological multicenter CTF study. Gynecologic Oncology. 1997;67:70-75.
5. Major FJ, Blessing JA, Silverberg SG, et al. Prognostic factors in early-stage uterine sarcoma: a Gynecologic Oncology Group Study. Cancer. 1993;71:1702-1709.
6. Matsuzaki S, Klar M, Matsuzaki S, Roman LD, Sood AK, Matsuo K. Uterine carcinosarcoma: contemporary clinical summary, molecular updates, and future research opportunity. Gynecol Oncol. 2021;160:586-601.
7. Raffone A, Travaglino A, Raimondo D, et al. Uterine carcinosarcoma vs endometrial serous and clear cell carcinoma: a systematic review and meta-analysis of survival. Int J Gynecol Obstet. 2022;158:520-527.
8. Toboni MD, Crane EK, Brown J, Shushkevich A, et al. Uterine carcinosarcomas: from pathology to practice. Gynecol Oncol. 2021;162:235-241.
9. Gonzalez Bosquet J, Terstriep SA, Cliby WA, et al. The impact of multi-modal therapy on survival for uterine carcinosarcomas. Gynecol Oncol. 2010;116:419-423.
10. Bogani G, Ray-Coquard I, Concin N, et al. Endometrial carcinosarcoma. Int J Gynecol Cancer. 2023;33:147-174.
11. Gotoh O, Sugiyama Y, Takazawa Y, et al. Clinically relevant molecular subtypes and genomic alteration-independent differentiation in gynecologic carcinosarcoma. Nature Communications. 2019;10:4965.
12. Kurnit KC, Previs RA, Soliman PT, et al. Prognostic factors impacting survival in early stage uterine carcinosarcoma. Gynecol Oncol. 2019;152:31-37.
13. Terblanche L, Botha MH. Uterine carcinosarcoma: a 10-year single institution experience. PloS One. 2022;17:0271526.
14. Zhu J, Wen H, Bi R, Wu X. Clinicopathological characteristics, treatment and outcomes in uterine carcinosarcoma and grade 3 endometrial cancer patients: a comparative study. J Gynecol Oncol. 2016;27:18.
15. Callister M, Ramondetta LM, Jhingran A, et al. Malignant mixed Müllerian tumors of the uterus: analysis of patterns of failure, prognostic factors, and treatment outcome. Int J Oncol Biol Phys. 2004;58:786-796.
16. Nemani D, Mitra N, Guo M, et al. Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: a SEER analysis. Gynecol Oncol. 2008;111:82-88.
17. NCCN Guidelines version 3.2025 Uterine Neoplasms [Internet]. [Retrieved on 2025] Available from: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf.
18. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;26:2-30.
19. Galaal K, van der Heijden E, Godfrey K, et al. Adjuvant radiotherapy and/or chemotherapy after surgery for uterine carcinosarcoma. Cochrane Database Syst Rev. 2013;2013:CD006812.
20. Powell MA, Filiaci VL, Hensley ML, et al. Randomized phase III trial of paclitaxel and carboplatin versus paclitaxel and ifosfamide in patients with carcinosarcoma of the uterus or ovary: an NRG oncology trial. J Clin Oncol. 2022;40:968-977.
21. Powell MA, Filiaci VL, Rose PG, et al. Phase II evaluation of paclitaxel and carboplatin in the treatment of carcinosarcoma of the uterus: a Gynecologic Oncology Group study. J Clin Oncol. 2010;28:2727-2731.
22. Wu TI, Chang TC, Hsueh S, et al. Prognostic factors and impact of adjuvant chemotherapy for uterine leiomyosarcoma. Gynecol Oncol. 2006;100:166-172.

23. Abeler VM, Røyne O, Thoresen S, et al. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. Histopathology. 2009;54:355-364.
24. Chantharasamee J, Wong K, Potivongsajarn P, et al. Retrospective analysis of adjuvant treatment for localized, operable uterine leiomyosarcoma. Cancer Med. 2022;11:2906-2912.
25. Harano K, Hirakawa A, Yunokawa M, et al. Prognostic factors in patients with uterine carcinosarcoma: a multi-institutional retrospective study from the Japanese Gynecologic Oncology Group. Int J Clin Oncol. 2016;21:168-76.
26. Wolfson AH, Brady MF, Rocereto T, et al. A gynecologic oncology group randomized phase III trial of whole abdominal irradiation (WAI) vs. cisplatin-ifosfamide and mesna (CIM) as post-surgical therapy in stage I–IV carcinosarcoma (CS) of the uterus. Gynecol oncol. 2007;107:177-185.
27. Abdulfatah E, Lordello L, Khurram M, et al. Predictive histologic factors in carcinosarcomas of the uterus: a multi-institutional study. Int J Gynecol Pathol. 2019;38:205-215.
28. Galaal K, Kew F, Tam K, et al. Evaluation of prognostic factors and treatment outcomes in uterine carcinosarcoma. Eur J Gynecol Reprod Biol. 2009;143:88-92.
29. Bodner-Adler B, Bodner K, Obermair A, et al. Prognostic parameters in carcinosarcomas of the uterus: a clinico-pathologic study. Anticancer Res. 2001;21:3069-3074.
30. Ioffe Y, Li A, Walsh C, et al. Hormone receptor expression in uterine sarcomas: prognostic and therapeutic roles. Gynecol Oncology. 2009;115:466-71.
31. Jones NL, Wu S, Xiu J, et al. Association of the presence of estrogen and progesterone receptors in uterine carcinosarcoma with improved survival and increased immunogenicity. J Clin Oncol. 2021;39(Suppl 15)5588.
32. Chiang C-Y, Huang H-J, Chang W-Y, et al. Adjuvant therapy and prognosis in uterine carcinosarcoma. J Formos Med Assoc. 2021;120:1977-1987.

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2025.92668
J Ankara Univ Fac Med 2025;78(2):128-136

SURGICAL MEDICAL SCIENCES / CERRAHİ TIP BİLİMLERİ

Comparative Assessment of Urological Emergency Cases Before and After the COVID-19 Outbreak

COVID-19 Pandemisi Öncesi ve Sonrası Ürolojik Acil Olguların Karşılaştırmalı Değerlendirmesi

Selçuk Sarıkaya[1], İbrahim Kılıççalan[2], Selim Can Peker[3], Selahattin Bedir[1]

[1]University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Urology, Ankara, Türkiye
[2]İstanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, Department of Emergency Medicine, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Gülhane Faculty of Medicine, Ankara, Türkiye

Abstract

Objectives: Coronavirus disease-2019 (COVID-19) pandemic originated from China and has affected all countries in the world as well as Türkiye. In our study, we aimed to evaluate the effects of COVID-19 pandemic on urological emergency admissions.

Materials and Methods: Urological emergency admissions between March 2019-February 2020 and March 2020-February 2021 periods were noted and evaluated in detail. The admissions were divided into two groups as non-traumatic and traumatic admissions for both periods. Traumatic and non-traumatic admissions were analyzed in detail and statistical analysis was performed in order to analyse the differences in terms of admission type and gender.

Results: Two thousand two hundred fifty-two cases were evaluated (1,096 before the pandemic, 1,156 after the pandemic). The renal traumas, ureteral traumas, bladder traumas, penile traumas, scrotal traumas, simultaneous penile and scrotal traumas and other trauma types were evaluated in detail. Non-traumatic urological emergencies were also investigated for the same time periods. Testicular torsions, acute scrotum, urinary tract infections, fournier gangrenes, hematuria, urolithiasis, glob vesicale, pregnants with urological complaints, priapism and other urological conditions were seen and evaluated in detail. Statistically significant difference has been observed between the periods.

Conclusion: Emergency admissions have been affected by the COVID-19 pandemic. The deferred complaints changed the emergency admission conditions. Most of the people delayed their routine outpatient clinic follow-ups or their first admissions due to the disease transmission concerns. These factors have resulted in changes and mostly caused late diagnosis and treatment.

Keywords: COVID-19, pandemic, outbreak, urological emergency, emergency

Öz

Amaç: Çin kaynaklı koronavirüs hastalığı-2019 (COVID-19) pandemisi, Türkiye'nin yanı sıra tüm dünya ülkelerini etkisi altına aldı. Çalışmamızda COVID-19 salgınının ürolojik acil başvurulara etkilerini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Mart 2019-Şubat 2020 ve Mart 2020-Şubat 2021 dönemleri arasındaki ürolojik acil başvuruları kayıt edilerek detaylı olarak değerlendirildi. Başvurular her iki dönem için de travmatik ve travmatik olmayan başvurular olarak iki gruba ayrıldı. Travmatik ve travmatik olmayan başvurular ayrıntılı olarak incelendi ve istatistiksel analiz yapıldı. İstatistiksel analiz, başvuru nedenlerine ve cinsiyete göre farklılıkları ortaya koymak için yapıldı.

Bulgular: İki bin iki yüz elli olgu değerlendirildi (pandemiden önce 1096, pandemiden sonra 1156). Böbrek travmaları, üreter travmaları, mesane travmaları, penis travmaları, skrotal travmalar, eş zamanlı penil ve skrotal travmalar ve diğer travma türleri detaylı olarak değerlendirildi. Aynı

Address for Correspondence/Yazışma Adresi: Selçuk Sarıkaya
University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Urology, Ankara, Türkiye
E-mail: drselcuksarikaya@hotmail.com **ORCID ID:** orcid.org/0000-0001-6426-1398

Received/Geliş Tarihi: 20.03.2024 **Accepted/Kabul Tarihi:** 01.04.2025 **Epub:** 12.05.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025

Cite this article as/Atıf: Sarıkaya S, Kılıççalan İ, Peker SC, Bedir S. Comparative assessment of urological emergency cases before and after the COVID-19 outbreak. J Ankara Univ Fac Med. 2025;78(2):128-136

zaman dilimlerinde travmatik olmayan ürolojik aciller de araştırıldı. Testis torsiyonları, akut skrotum, idrar yolu enfeksiyonları, fournier gangren, hematüri, ürolitiazis, glob vesikale, ürolojik şikayeti olan gebeler, priapizm ve diğer ürolojik patolojiler detaylı olarak değerlendirildi. Dönemler arasında istatistiksel olarak anlamlı farklılıklar gözlenmiştir.

Sonuç: Acil servis başvuruları COVID-19 salgınından etkilendi ve ertelenen şikayetler acil başvurularını değiştirdi. Çoğu kişi hastalık bulaşma endişesi nedeniyle rutin poliklinik takiplerini ya da ilk başvurularını erteledi. Ertelenen başvurular çoğunlukla geç tanı ve tedaviye neden olmuştur.

Anahtar Kelimeler: COVID-19, pandemi, salgın, ürolojik acil, acil

Introduction

Coronavirus disease-2019 (COVID-19) epidemic, which has been accepted as pandemic since March 2020 in the world, has brought many problems (1). While these problems increase the workload for hospitals and doctors, it has also affected the communication between patients and healthcare professionals. However, the reduction of hospital capacities due to the COVID-19 epidemic has limited the treatment of other pathological conditions, especially the emergent pathologies. In addition, it is thought that the diagnosis and treatment of urological emergencies, which have an important place in urology practice, have been affected as well as the other emergent conditions. Urological emergencies to the emergency department have been evaluated in our study by dividing them into two groups as non-traumatic and traumatic. Traumatic urological emergencies were classified as kidney trauma, ureter trauma, bladder trauma, penile trauma and scrotal trauma. Non-traumatic urological emergencies were classified as testicular torsion, acute scrotum, urinary tract infections, Fournier's gangrene, hematuria, urolithiasis, glob vesicale (acute urinary retention), hydronephrosis, pregnants urological complaints, priapism (2). In our study, it was aimed to examine the possible differences between the emergency admissions to our hospital in terms of urological emergency conditions between the pre-pandemic period and the pandemic period. In our study, it was aimed to determine the possible changes in the frequency of urological emergencies depending on the pandemic period, possible changes in the frequency order of urological emergencies, the underlying causes of urological emergencies, if any, and detailed analysis for these conditions. In this context, the frequency of urological emergencies and the distribution of admissions were examined by including the urological emergency applications made to the Gülhane Training and Research Hospital, Department of Urology between March 2019-February 2020 and March 2020-February 2021.

Materials and Methods

In our study, the data of patients who admitted to the emergency department during the pre-pandemic period (March 2019-February 2020) and the pandemic period (March 2020-February 2021) were compared. The study protocol was first registered in the data of the Turkish Republic Ministry of Health Scientific Research Committee and then approved by the Committee on the Scientific Research Ethics of the University of Health Sciences Türkiye, Gülhane Faculty of Medicine (date: 03.06.2021, number: 2021/11). The design of the study was retrospective record review. Urological emergencies were evaluated with statistical analysis in terms of emergency types, period and gender. Emergency patients that were consulted to urology deperatment with adequate records have been included in the study. Non-emergent patients and the patients with missing data were excluded from the study.

In the study, urological emergencies were basically divided into two main groups as traumatic and non-traumatic urological emergencies. Traumatic urological emergencies were grouped as renal traumas, ureteral trauma, bladder trauma, penile trauma and scrotal trauma. Non-traumatic urological emergencies were classified as testicular torsion, acute scrotum, urinary tract infections, Fournier's gangrene, hematuria, urolithiasis, glob vesicale (acute urinary retention), hydronephrosis, pregnants urological complaints and priapism.

Statistical Analysis

Statistical Package for the Social Sciences version 22.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis of the data obtained within the scope of the study. Pre-pandemic and pandemic period records were examined retrospectively in detail as traumatic and non-traumatic. Admissions before and during the pandemic period, traumatic emergencies, non-traumatic emergencies and the data of patients in terms of gender were evaluated separately. The normality status of the variables were evaluated with using Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson chi-square test was used for statistical comparison of the variables. Within the scope of all statistical analyzes, the value of $p<0.05$ was accepted as statistically significant. In addition, the values for each emergency types and the ratios were also examined and presented.

Results

The number of urological emergency admissions and the details were evaluated in our study. The admissions were analysed in terms of admission types and gender. While evaluating the

urological emergency admissions, it was observed that; 1,096 of the cases were in the pre-pandemic period and 1,156 of them were in the pandemic period. A statistically significant difference was observed between these groups (p<0.05). The number of cases were evaluated in detail (Figure 1, and Tables 1, 2).

Non-traumatic and traumatic male patient patients for pre-pandemic and pandemic periods were compared and no statistically significant differences were observed (p=0.243, p=0.227). Non-traumatic and traumatic female patient patients for pre-pandemic and pandemic periods were compared and no statistically significant differences were observed (p=0.213, p=0.261).

Two thousand two hundred fifty-two patients that evaluated as urological emergencies and were consulted to urology department. One thousand and ninety-six cases were admitted in pre-pandemic and 1,156 admitted during pandemic periods (p<0.05). There was a statistically significant increase for the pandemic period.

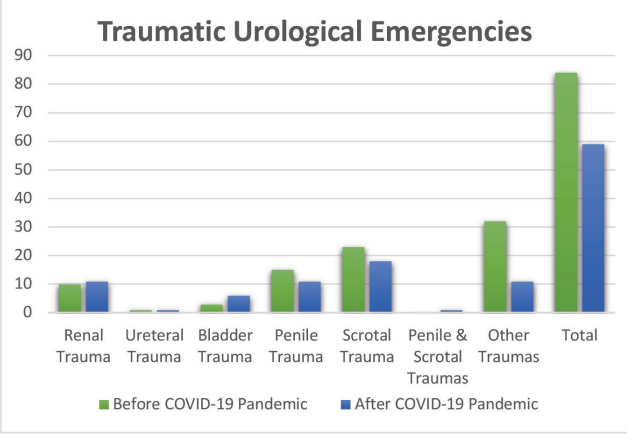

Figure 1: Traumatic urological emergencies
COVID-19: Coronavirus disease-2019

Pre-pandemic traumatic urological emergency admissions were 84 (73 male, 11 female), pandemic traumatic urological emergency admissions were 59 (53 male, 6 female). However the difference was not statistically significant (p=0.236). Traumatic urological emergencies decreased during the pandemic period. In addition, traumatic urological emergency admissions were significantly higher in males than females for both periods (pre-pandemic 6.63 times and pandemic 8.83 times). The differences were not statistically significant. There was no statistical significant difference for traumatic male and female patient admissions in terms of periods (p=0.243, p=0.261) (Tables 3, 4).

- **Renal Trauma:** For pre-pandemic period, 7 cases were male, 3 were female (M/F=2.33) (11.9% of all traumas). For pandemic period, 10 cases male and 1 female (M/F=10) (18.6% of all traumas) (Figures 2, 3).
- **Ureteral Trauma:** One case for each periods were observed. And both were female (pre-pandemic 1.1% and pandemic 1.69% of all traumas) (Figures 2, 3).
- **Bladder Trauma:** Pre-pandemic 1 male and 2 female patients were observed (M/F=0.5). Pandemic 5 male and 1 female patients were observed (M/F=5) (pre-pandemic 3.5% and pandemic 10.1% of all traumas) (Figures 2, 3).
- **Penile Trauma:** Fifteen pre-pandemic, 11 pandemic cases were observed (pre-pandemic 17.8% and pandemic 18.6% of all traumas) (Figures 2, 3).
- **Scrotal Trauma:** Thirty-two pre-pandemic, 18 pandemic cases were observed (pre-pandemic 27.3% and pandemic 30.5% of all traumas) (Figures 2, 3).

Pre-pandemic non-traumatic cases were 1,012 (641 male, 371 famele), Pandemic non-traumatic cases were 1,097 (754 male, 347 famele). The number of cases were increased in the pandemic period but not statistically significant (p=0.089). In addition, non-traumatic urological emergency admissions were observed to be significantly higher in males than females for both periods (pre-pandemic 1.72 times, pandemic 2.17 times).

Table 1: Distribution of traumatic urological emergencies by gender, before and after the pandemic

Urological emergency admissions	Before COVID-19 pandemic			COVID-19 pandemic		
	Male	Female	Total	Male	Female	Total
Traumatic						
Renal trauma	7	3	10	10	1	11
Ureteral trauma	0	1	1	0	1	1
Bladder trauma	1	2	3	5	1	6
Penile trauma	15	0	15	11	0	11
Scrotal trauma	23	0	23	18	0	18
Penile and scrotal traumas	0	0	0	1	0	1
Other traumas	27	5	32	8	3	11
Total	73	11	84	53	6	59

COVID-19: Coronavirus disease-2019

No statistically significant non-traumatic male and female admission differences for pre-pandemic and pandemic periods p=0.229, p=0.243. Non-traumatic urological emergencies were more common in males and no statistically significant difference observed for non-traumatic male patient admissions during the pre-pandemic and pandemic periods (p=0.231). Also no statistically significant outcomes were observed for females (p=0.243).

Table 2: Distribution of non-traumatic urological emergencies by gender, before and after the pandemic

Urological emergency admissions	Before COVID-19 pandemic			COVID-19 pandemic		
	Male	Female	Total	Male	Female	Total
Non-traumatic						
Testicular torsion	5	0	5	10	0	10
Acute scrotum	167	0	167	160	0	160
Urinary tract ınfection	35	39	74	62	46	108
Fournier gangrene	3	2	5	2	1	3
Hematuria	116	55	171	120	45	165
Urolithiasis	176	125	301	243	134	377
Glob vesicale	45	8	53	61	12	73
Hydronephrosis	17	12	29	32	16	48
Pregnants urological complaints	0	96	96	0	62	62
Hematuria and urolithiasis	9	9	18	10	3	13
Urolithiasis and hydronephrosis	2	8	10	1	1	2
Acute scrotum and hematuria	2	0	2	1	0	1
Urinary tract infection and hematuria	3	3	6	1	5	6
Urinary tract infection and urolithiasis	1	4	5	6	5	11
Urinary tract infection and glob vesicale	0	1	1	0	0	0
Hematuria and hydronephrosis	5	0	5	0	1	1
Acute scrotum and glob vesicale	1	0	1	0	0	0
Urolithiasis and glob vesicale	1	0	1	0	0	0
Urinary tract infection and hydronephrosis	1	1	2	2	3	5
Hematuria and glob vesicale	2	2	4	0	0	0
Urinary tract infection, hematuria and hydronephrosis	0	1	1	3	0	3
Priapism	8	0	8	6	0	6
Other urological conditions	42	5	47	34	9	43
Total	641	371	1012	754	343	1097

COVID-19: Coronavirus disease-2019

Table 3: Statistical analysis in terms of period, gender and admission type

Period		Before pandemic			
	Gender and type	Non-traumatic female	Non-traumatic male	Traumatic female	Traumatic male
Before pandemic	Non-traumatic female	-	p=0.229	p=0.213	-
	Non-traumatic male	p=0.229	-	-	p=0.243
	Traumatic female	p=0.213	-	-	p=0.213
	Traumatic male	-	p=0.243	p=0.213	-
Period		After pandemic			
	Gender & type	Non-traumatic female	Non-traumatic male	Traumatic female	Traumatic male
After pandemic	Non-traumatic female	-	p=0.243	p=0.261	-
	Non-traumatic male	p=0.243	-	-	p=0.227
	Traumatic female	p=0.261	-	-	p=0.261
	Traumatic male	-	p=0.227	p=0.261	-

Table 4: Statistical comparison of the total number of patients			
Trauma type	**Traumatic admissions**		
Period/Gender	**Male patients**	**Female patients**	**Total**
Before the pandemic vs during the pandemic	p=0.243	p=0.261	p=0.236
Trauma type	**Non-traumatic admissions**		
Period/Gender	**Male patients**	**Female patients**	**Total**
Before the pandemic vs during the pandemic	p=0.231	p=0.243	p=0.089

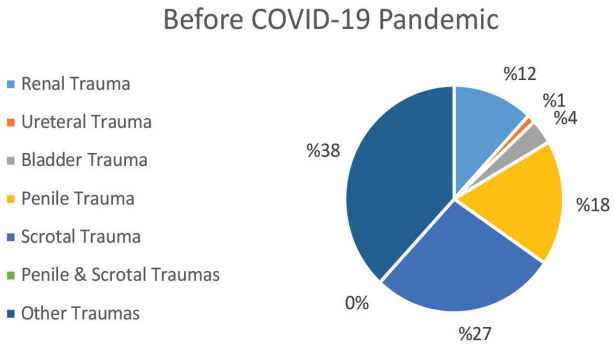

Figure 2: Distribution of traumatic urological emergencies before the COVID-19 pandemic
COVID-19: Coronavirus disease-2019

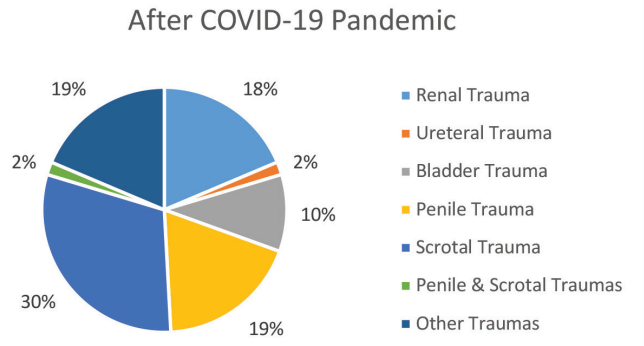

Figure 3: Distribution of traumatic urological emergencies after the COVID-19 pandemic
COVID-19: Coronavirus disease-2019

• **Testicular Torsion:** Five pre-pandemic, 10 pandemic cases were observed (pre-pandemic 0.49% and pandemic 0.91% of all non-traumatics). Admissions increased 1.85 times in the pandemic period.

• **Acute Scrotum:** One hundred and sixty-seven pre-pandemic, 160 pandemic cases were observed (pre-pandemic 16.5% and pandemic 14.5% of all non-traumatics). Admissions were similar for both periods.

• **Urinary Tract Infections (Pyelonephritis, Urethritis, Urosepsis):** For pre-pandemic period, 35 cases were male, 39 were female (M/F=0.89) (7.3% of all non-traumatics). For pandemic period, 62 cases male and 46 female (M/F=1.3) (9.84% of non-traumatics).

• **Fournier's Gangrene:** For pre-pandemic period, 3 cases were male, 2 were female (M/F=1.5). For pandemic period, 2 cases male and 1 female (M/F=2).

• **Hematuria:** For pre-pandemic period, 116 cases were male, 55 were female (M/F=2.1) (16.8% of all non-traumatics) For pandemic period, 120 cases male and 45 female (M/F=2.6) (15.04% of all non-traumatics).

• **Urolithiasis:** For pre-pandemic period, 176 cases were male, 125 were female (M/F=1.4) (29.7% of all non-traumatics). For pandemic period, 243 cases male and 134 female (M/F=1.8) (34.3% of all non-traumatics).

• **Glob Vesicale (Acute Urinary Retention):** For pre-pandemic period, 45 cases were male, 8 were female (M/F=5.6) (5.2% of all non-traumatics). For pandemic period, 61 cases male and 12 female (M/F=5.08) (6.6% of all non-traumatics).

• **Hydronephrosis:** For pre-pandemic period, 17 cases were male, 12 were female (M/F=1.4) (2.8% of all non-traumatics). For pandemic period, 32 cases male and 16 female (M/F=2) (4.3% of all non-traumatics).

• **Pregnants Urological Complaints:** Ninety-six pre-pandemic, 62 pandemic cases were observed (pre-pandemic 9.4% and pandemic 5.6% of all non-traumatics). Admissions during pandemic period decreased by 1.67 times compared to pre-pandemic period.

• **Priapism:** Eight pre-pandemic, 6 pandemic cases were observed (pre-pandemic 0.7% and pandemic 0.5% of all non-traumatics).

Discussion

COVID-19 pandemic period has changed hospital admissions. When the results were evaluated in detail, it was clearly observed that urologic emergency admissions have increased with statistically significance during the pandemic period. When the results were investigated in terms of gender, traumatic urological emergency admissions were significantly higher in males than females for both periods. There were also differences in terms of gender and admission type between periods but most of the results were not statistically significant.

In a retrospective study of Bašković et al. (3), 15-month periods before and after pandemic were compared, emergent

pediatric surgical consultations that were evaluated as urological emergencies were examined. The cases were grouped as abdominal pain, acute scrotum, upper extremity injuries and lower extremity injuries. The surgeries were grouped as total surgery cases (emergency + elective), appendectomy, scrotal exploration, surgical fracture repair. A significant decrease in examinations was observed for pandemic period and no significant difference was observed for the number of operations (3). In a study, by Motterle et al. (4), cases in a 36-day period after the onset of the COVID-19 pandemic, in a single center, who applied to emergency department and were evaluated as urological emergencies. Comparison was made with urological emergencies in the same period of the previous year and significant decrease was observed for pandemic period (4). In the study of Grasso et al. (5), the cases that applied to the emergency service during the first 3-months after the onset of COVID-19 pandemic at four centers were evaluated. Urological emergencies were compared with 2018 and 2019. Significant decrease was detected for pandemic period (5). In our study, statistically significant increase was observed. This condition would be observed due to the geographical differences and the limited number of patients that have been examined in the urology outpatient clinics during the pandemic period.

However an increase was observed for emergency cases during the pandemic period, there was a decrease for traumatic cases. This is an interesting result as there are limited number of studies investigating these admission types. This would be due to the limitation for working hours and being outside home during that period. Traumatic and non-traumatic admissions were evaluated in detail with analysis results in our study.

Renal trauma is divided as penetrating and blunt traumas. Blunt traumas are the most common (90-95%) (6,7). It constitutes 1-5% of all traumas (7). It is observed three times more frequently in men (7). In our study, there is a decrease in the number of traumatic urological emergencies in the pandemic period and the increased rate of renal traumas among traumatic cases in our center.

Ureteral trauma is rare and usually occurs iatrogenic (8). Penetrating trauma is the most common etiology after iatrogenic injuries (8). Its incidence has been reported as 3 in 10,000 (9). These data reveal the low rates of ureteral trauma among traumatic emergencies.

Bladder injuries are rare injuries with high mortality and morbidity (10-22%), which are divided into two main groups as extraperitoneal and intraperitoneal (10). Extraperitoneal injuries often occur with pelvic fractures (11). Intraperitoneal traumas occur due to exposure of the bladder to high-energy traumas (11). Bladder traumas usually present with pelvic pain and macroscopic hematuria (12). Treatment depends on its type. While conservative approach (with catheter drainage) is mainly considered for extraperitoneal injuries, surgical treatment is usually performed for intraperitoneal injuries (10).

Penile traumas are rare traumas that can occur due to penetrating and non-penetrating traumas. Diagnosis mainly depends on history and physical examination. Non-penetrating injuries can cause fibrosis and erectile dysfunction by causing hematomas within the cavernous tissues (13). Therefore, emergent treatment is important.

Scrotal trauma is a rare trauma that mostly occurs due to blunt trauma. Scrotal traumas are observed due to traumatic urological emergencies. Coexistence of penile and scrotal traumas can also be observed. There was no coexistent penile and scrotal trauma in our center during the pre-pandemic period and there was only 1 case during the pandemic period.

Testicular torsion is the clinical condition that occurs when one or both testicles rotate around the spermatic cord and blood flow cannot be provided. It is observed at a rate of 1/4,000 in young men under the age of 25 (14). Testicular torsion shows a bimodal distribution in terms of age. It makes its first peak in the newborn period, while the second peak is in the puberty period. Extravaginal torsion is usually observed during the neonatal period and intravaginal torsion is usually observed in the puberty period. Testicular torsion accounts for 10-15% of acute scrotal diseases in children (15). The orchiectomy rate in these patient groups is 42% (15). It is important to exclude testicular torsion in patients presenting with acute scrotum, since it is seen with increased frequency and high rate of orchiectomy. The diagnosis of testicular torsion is usually made clinically. Patients often present with common acute unilateral scrotal pain, nausea and vomiting. When testicular torsion is detected, manual detorsion must be performed during the acute period. If the testis cannot be detorted, surgical detorsion must be applied. Delay in treatment can lead to the decrease in fertility potential (15). It may also require orchiectomy (15). Contrary to our study, in the study by Norton et al. (16) among the pediatric group, a decrease in testicular torsion cases was detected in the first 3-month period after the onset of the pandemic compared to the same period of the previous year. In the study by Littman et al. (17), no significant difference was observed for pre-pandemic and pandemic periods. In our study, unlike the related studies, admissions increased 1.85 times during the pandemic period.

Acute scrotum is a group of diseases that can occur for various reasons. It often presents with acute onset of scrotal swelling, pain, and redness. Clinical, physical examination and radiological imaging are used in the diagnosis. Doppler ultrasonography plays an important role in diagnosis (18). Differential diagnosis is made by monitoring the central arterial circulation and venous drainage of the testicles with Doppler ultrasound. Testicular torsion accounts for approximately

25% of acute scrotum cases and needs to be quickly exclusion (18). In a study of Bašković et al. (3), decrease in the number of acute scrotum cases for pandemic period was observed but not statistically significant. This result supports the data we obtained in our study.

Urinary tract infections are among the most common infections in the community and hospitals. Urinary tract infections are more common in women (19). In the study of Kuitunen et al. (20) in Finnish children, it was reported that the incidence of cystitis and pyelonephritis decreased in children aged 1-6 years after the COVID-19 pandemic. However, in a study conducted in the USA, it was determined that there was a decrease in the number of urinary tract infection cases during the period of social restriction (21). In our study, the number of cases increased in and this result is similar to a study in a tertiary hospital in Italy (22).

Fournier's gangrene is a rare, surgically treated, fulminant, necrotizing soft tissue infection that usually involves the anoperineal region and external genitalia (between genitals and rectum) (23). Fournier's gangrene has high mortality rate and often affects men (24). Risk factors can be listed as diabetes, alcoholism, malignancy, immune system suppression (25). Clinically, there are findings such as edema, fever and crepitus in the relevant region. Various radiological imaging methods are used for diagnosis. However the diagnosis is usually made clinically, radiodiagnostic imaging is also used to support the diagnosis (23). In the treatment, hemodynamic stabilization is provided, broad-spectrum antibiotics are preferred and surgical debridement is applied (24). Early surgical debridement is the primary component of treatment (24,26). If surgical treatment is delayed, the prognosis is negatively affected (26). In our study, the number of cases decreased during the pandemic period.

Hematuria is the presence of erythrocyte cells in the urine. It is examined in two main groups as macroscopic and microscopic hematuria. In a patient presenting with hematuria, first of all, it should be evaluated whether the patient is hemodynamically stable. In the evaluation of hemodynamic stability; physical examination findings, hemoglobin/hematocrit values, clinical findings of the patient are used (27). The causes of hematuria that cause hemodynamic instability are intraperitoneal bladder rupture, ureteroarterial fistula, hemorrhagic cystitis, traumas (27). In our study, the number of patients are similar for both periods.

Urolithiasis is a common disease with an increasing incidence globally (28). Urinary system stone formation and the chemical composition of the stone depend on age and gender (29). The incidence of urinary stones increases with age. However, besides age, obesity, dietary habits, lifestyle habits, diseases are risk factors for urinary stone formation. Urinary system stones can be classified according to their chemical components: calcium stones (80%), uric acid stones (9%), struvite stones (10%), cystine stones (1%) (30). Calcium stones are the most common among urinary system stones. Urinary system stones, with the exception of infection stones, are more common in men than in women (28). History taking, physical examination and radiology are the main tools for diagnosis. Radiologically, the gold standard diagnostic method is non-contrast computerised tomography (31). In our study, an increase was observed during the pandemic period.

Glob vesicale (acute urinary retention) is a common non-traumatic urological emergency that often affects men (32). Patients often presents withs suprapubic or lower abdominal pain and difficulty in spontaneous voiding (33). Obstructive causes are divided into intrinsic and extrinsic causes. Benign prostatic hyperplasia (BPH) is common among the intrinsic obstructive causes (32,34). In addition to BPH, intrinsic causes include lower urinary tract malignancies, hematoglob and bladder stones (33). Extrinsic causes; abdominal or pelvic tumors, phimosis and paraphimosis would be seen among men, pelvic organ prolapses would be seen among women. The main treatment for glob vesicale is to decompress the bladder and eliminate the underlying cause (33,35). The number of patients increased during pandemic period in our study.

Hydronephrosis is bilateral or unilateral dilatation of the renal pelvis and calyces (36). If ureteral dilatation is also present, it is called hydroureteronephrosis. The most common cause of unilateral hydronephrosis is obstruction of the ureteric calculi or idiopathic ureteropelvic junction obstruction (36). Bilateral hydronephrosis often occurs in men secondary to BPH. In a study conducted in 1994, hydronephrosis was observed in 7% of patients with BPH. Renal failure was observed in 33% of these patients with hydronephrosis (37). Hydronephrosis may present as a manifestation of ipsilateral renal pain, acute kidney injury, nausea, vomiting, hematuria and sepsis (38). The number of patients increased during pandemic period in our study.

Physiological hydronephrosis is observed in 50-90% of pregnant women in the last trimester (39,40). However, surgical treatments in pregnancy also have risks. Symptomatic urolithiasis is the most common indication for surgical treatment in pregnancy (41).

Priapism is a condition in which a penile erection lasts longer than 4 hours without sexual stimulation (42-44). Priapism; it is divided into three main types as ischemic, non-ischemic and stuttering (recurrent or intermittent). Ischemic type priapism is the most common (43). Ischemic-type priapism is considered a urological emergency (44). The number of patients decreased during pandemic period in our study.

COVID-19 pandemic was thought to have major effects on health center admissions and emergency admissions but as it was observed in our study, there were not major differences.

Only the increase in urological emergency admission during the pandemic period was statistically significant. There were limitations in both outpatient clinic admission numbers and the number of surgical operations during the pandemic period. The delays in surgical operations and health center admissions would cause more severe health problems.

Study Limitations

The limitations of our study is that our study was conducted in a single center with a limited number of cases. In addition there were lack of detailed analyzes of the patients according to age, complaints, comorbid diseases and treatment methods. Also the classification of urological emergencies, making a holistic comparison by gender and distribution analyses, comparison of large patient groups and comparison of longer time intervals would reveal more valuable outcomes. Multi-center studies can be carried out in the future and the evaluation of time intervals with a wider range are important in terms of obtaining more reliable data.

Conclusion

Our study revealed that emergency cases, contrary to expectations, increased during the pandemic period ($p<0.05$). Also a decrease was observed for traumatic cases and an increase for non-traumatic cases during the pandemic period. Urological emergencies are observed more frequently in men before and after the pandemic.

Ethics

Ethics Committee Approval: The ethical approval was obtained from the Committee on the Scientific Research Ethics of the University of Health Sciences Türkiye, Gülhane Faculty of Medicine (date: 03.06.2021, number: 2021/11).

Informed Consent: This was a retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.S., S.B., Concept: S.S., S.B., Design: S.S., S.B., Data Collection and/or Processing: İ.K., S.C.P., Analysis and/or Interpretation: İ.K., S.C.P., Literature Search: S.S., İ.K., S.C.P., Writing: S.S.

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

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

References

1. Pollard CA, Morran MP, Nestor-Kalinoski AL. The COVID-19 pandemic: a global health crisis. Physiol Genomics. 2020;52:549-557.
2. Ludvigson AE, Beaule LT. Urologic emergencies. Surg Clin North Am. 2016;96:407-424.
3. Bašković M, Čizmić A, Bastić M, Župančić B. The impact of the COVID-19 pandemic on the most common diagnoses in pediatric surgery: abdominal pain, acute scrotum, upper and lower extremity ınjuries tertiary center experience. Turk Arch Pediatr. 2021;57:38-45.
4. Motterle G, Morlacco A, Iafrate M, et al. The impact of COVID-19 pandemic on urological emergencies: a single-center experience. World J Urol. 2021;39:1985-1989.
5. Grasso AAC, Massa G, Castelnuovo M. the ımpact of COVID-19 pandemic on urological emergencies: a multicenter experience on over 3,000 patients. Urol Int. 2021;105:17-20.
6. Erlich T, Kitrey ND. Renal trauma: the current best practice. Ther Adv Urol 2018;10:295-303.
7. Chouhan JD, Winer AG, Johnson C, Weiss JP, Hyacinthe LM. Contemporary evaluation and management of renal trauma. Can J Urol. 2016;23:8191-8197.
8. Engelsgjerd JS, LaGrange CA. Ureteral injury. StatPearls, Treasure Island (FL): StatPearls Publishing; 2022.
9. Siram SM, Gerald SZ, Greene WR, et al. Ureteral trauma: patterns and mechanisms of injury of an uncommon condition. Am J Surg. 2010;199:566-570.
10. Mahat Y, Leong JY, Chung PH. A contemporary review of adult bladder trauma. J Inj Violence Res. 2019;11:101-106.
11. Kang L, Geube A. Bladder trauma. StatPearls, Treasure Island (FL): StatPearls Publishing; 2022.
12. Simon LV, Sajjad H, Lopez RA, Burns B. Bladder rupture. StatPearls, Treasure Island (FL): StatPearls Publishing; 2022.
13. Cozzi D, Verrone GB, Agostini S, et al. Acute penile trauma: imaging features in the emergency setting. Radiol Med. 2019;124:1270-1280.
14. Keays M, Rosenberg H. Testicular torsion. CMAJ. 2019;191:E792.
15. Sharp VJ, Kieran K, Arlen AM. Testicular torsion: diagnosis, evaluation, and management. Am Fam Physician. 2013;88:835-840.
16. Norton SM, Considine S, Dowling C, D'Arcy F. Where are the paediatric patients with testicular torsion during the COVID-19 pandemic? Ir J Med Sci. 2022;191:2423-2426.
17. Littman AR, Janssen KM, Tong L, et al. Did COVID-19 affect time to presentation in the setting of pediatric testicular torsion? Pediatr Emerg Care. 2021;37:123-125.
18. Günther P, Rübben I. The acute scrotum in childhood and adolescence. Dtsch Arztebl Int. 2012;109:449-457;quiz 458.
19. Foxman B. The epidemiology of urinary tract infection. Nat Rev Urol. 2010;7:653-660.
20. Kuitunen I, Artama M, Haapanen M, Renko M. Urinary tract infections decreased in Finnish children during the COVID-19 pandemic. Eur J Pediatr. 2022;181:1979-1984.
21. Hatoun J, Correa ET, Donahue SMA, Vernacchio L. Social distancing for COVID-19 and diagnoses of other ınfectious diseases in children. Pediatrics. 2020;146:e2020006460.
22. Liguoro I, Pilotto C, Vergine M, Pusiol A, Vidal E, Cogo P. The impact of COVID-19 on a tertiary care pediatric emergency department. Eur J Pediatr. 2021;180:1497-1504.
23. Bağcioğlu M, Kayiş A. Fournier gangreni. Türkiye Klinikleri J Urology-Special Topics. 2017;10:321-328.
24. Thwaini A, Khan A, Malik A, et al. Fournier's gangrene and its emergency management. Postgrad Med J. 2006;82:516-519.
25. Gülşen T, Sücüllü İ, Balta AZ, Demir M, Kurt Y. Fournier's gangrene. Turk J Colorectal Dis. 2019;29:206-210.
26. Paty R, Smith AD. Gangrene and Fournier's gangrene. Urol Clin North Am. 1992;19:149-162.
27. Avellino GJ, Bose S, Wang DS. Diagnosis and management of hematuria. Surg Clin North Am. 2016;96:503-515.

28. Knoll T. Epidemiology, pathogenesis, and pathophysiology of urolithiasis. European Urology Supplements. 2010;9:802-806.
29. Daudon M, Doré J-C, Jungers P, Lacour B. Changes in stone composition according to age and gender of patients: a multivariate epidemiological approach. Urol Res. 2004;32:241-247.
30. Thakore P, Liang TH. Urolithiasis. StatPearls, Treasure Island (FL): StatPearls Publishing; 2022.
31. Moran CP, Courtney AE. Managing acute and chronic renal stone disease. Practitioner. 2016;260:17-20, 2-3.
32. Serlin DC, Heidelbaugh JJ, Stoffel JT. Urinary retention in adults: evaluation and initial management. Am Fam Physician. 2018;98:496-503.
33. Billet M, Windsor TA. Urinary retention. Emerg Med Clin North Am. 2019;37:649-660.
34. Gelber J, Singh A. Management of acute urinary retention in the emergency department. Emerg Med Pract. 2021;23:1-28.
35. Mavrotas J, Gandhi A, Kalogianni V, Patel V, Batura D. Acute urinary retention. Br J Hosp Med (Lond). 2022;83:1-8.
36. Patel K, Batura D. An overview of hydronephrosis in adults. Br J Hosp Med (Lond). 2020;81:1-8.
37. McConnell JD, Barry MJ, Bruskewitz RC. Benign prostatic hyperplasia: diagnosis and treatment. Agency for Health Care Policy and Research Clin Pract Guidel Quick Ref Guide Clin. 1994:1-17.
38. Krajewski W, Wojciechowska J, Dembowski J, Zdrojowy R, Szydełko T. Hydronephrosis in the course of ureteropelvic junction obstruction: An underestimated problem? Current opinions on the pathogenesis, diagnosis and treatment. Adv Clin Exp Med. 2017;26:857-864.
39. Pedro RN, Das K, Buchholz N. Urolithiasis in pregnancy. Int J Surg. 2016;36:688-692.
40. Grosjean J, Cannie M, de Meyer J-M. [Physiological hydronephrosis in pregnancy: Occurrence and possible causes. An MRI study]. Prog Urol. 2017;27:603-608.
41. Giusti G, Proietti S, Peschechera R, et al. Sky is no limit for ureteroscopy: extending the indications and special circumstances. World J Urol. 2015;33:257-273.
42. Carnicelli D, Akakpo W. Priapism: Diagnosis and management. Prog Urol. 2018;28:772-776.
43. Ericson C, Baird B, Broderick GA. Management of priapism: 2021 update. Urol Clin North Am. 2021;48:565-576.
44. Salonia A, Eardley I, Giuliano F, et al. European association of urology guidelines on priapism. Eur Urol. 2014;65:480-489.

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2025.82957
J Ankara Univ Fac Med 2025;78(2):137-143

BASIC MEDICAL SCIENCES / TEMEL TIP BİLİMLERİ

Identification of Mitochondrial-Related Genes as Potential Biomarkers for Docetaxel-Resistant Prostate Cancer

Docetaxel'e Dirençli Prostat Kanseri için Potansiyel Biyobelirteçler Olarak Mitokondriyal İlişkili Genlerin Tanımlanması

Yalda Hekmatshoar

Altınbaş University Faculty of Medicine, Department of Medical Biology, İstanbul, Türkiye

Abstract

Objectives: Prostate cancer (PC) is the most common cancer among men worldwide and a significant cause of cancer-related deaths. Docetaxel (DX), a taxane-based chemotherapeutic agent, was the first treatment to exhibit substantial efficacy in the management of PC. This study aims to demonstrate the mitochondrial genes that are affected by DX in PC using bioinformatics analysis.

Materials and Methods: For bioinformatics analysis, mRNA microarray data from DX-sensitive PC cell lines (DU145) and DX-resistant cell lines (DU145-DR), corresponding to the study GSE36135, were retrieved from the *Gene Expression Omnibus* (GEO) database. Differentially expressed genes (DEGs) were analyzed and identified using the Transcriptome Analysis Console 4.0 (TAC). Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway analyses were performed to pinpoint significant genes and biological pathways associated with DX therapy. Additionally, protein-protein interaction network analysis was conducted to identify critical proteins and interactions within these pathways.

Results: TAC applied criteria of an adjusted p-value <0.05, (*false discovery rate*-FDR<0.05) and |log2FC| >1.0 to identify DEGs. The analysis revealed the upregulation of 515 genes and the downregulation of 608 genes in DX-treated cells compared to controls. Enrichment analysis of DEGs indicated their involvement in pathways such as metabolic pathways, pathways of neurodegeneration involving multiple diseases, biosynthesis of cofactors, chemical carcinogenesis mediated by reactive oxygen species, valine, leucine, and isoleucine degradation, carbon metabolism, and oxidative phosphorylation. Among these, *ALDH4A1, ALDH6A1, ALDH2, PCCB, GLS, GATM, GLS2, IDH2, SUCLG2, ECI2, GLDC, IVD, ALDH7A1, ACACA, ALDH5A1, NDUFS7, PCK2, ARG2, FDXR,* and *CPT1A* were identified as the most significant candidate genes.

Conclusion: This comprehensive bioinformatics analysis sheds light on the molecular mechanisms underlying DX's action and highlights potential targets for combination therapies, offering promising strategies to enhance treatment efficacy in PC.

Keywords: Prostate cancer, docetaxel, bioinformatics, gene expression omnibus, gene expression

Öz

Amaç: Prostat kanseri (PK) dünya çapında erkekler arasında en yaygın kanserdir ve kansere bağlı ölümlerin önemli bir nedenidir. Taksan bazlı bir kemoterapötik ajan olan docetaxel (DX), PK tedavisinde önemli etkinlik gösteren ilk tedavi olmuştur. Bu çalışma, biyoinformatik analiz kullanarak PK'de DX'ten etkilenen mitokondriyal genleri göstermeyi amaçlamaktadır.

Gereç ve Yöntem: Biyoinformatik analiz için, GSE36135 çalışmasına karşılık gelen DX'e duyarlı PK hücre hatlarından (DU145) ve DX'e dirençli hücre hatlarından (DU145-DR) mRNA mikroarray verileri Gene Expression Omnibus-GEO veri tabanından alınmıştır. Diferansiyel olarak ifade edilen genler (DEG'ler) Transkriptom Analiz Konsolu 4.0 (TAC) kullanılarak analiz edilmiş ve tanımlanmıştır. Dosetaksel tedavisi ile ilişkili önemli genleri ve biyolojik yolları belirlemek için Gen Ontolojisi ve Kyoto Genler ve Genomlar Ansiklopedisi yol analizleri yapılmıştır. Ayrıca, bu yolaklardaki kritik proteinleri ve etkileşimleri belirlemek için protein-protein etkileşimi ağ analizi yapılmıştır.

Address for Correspondence/Yazışma Adresi: Yalda Hekmatshoar
Altınbaş University Faculty of Medicine, Department of Medical Biology, İstanbul, Türkiye
E-mail: yalda.hekmatshoar@altinbas.edu.tr **ORCID ID:** orcid.org/0000-0003-4683-074X

Received/Geliş Tarihi: 22.01.2025 **Accepted/Kabul Tarihi:** 09.04.2025 **Epub:** 12.05.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025

Cite this article as/Atıf: Hekmatshoar Y. Identification of mitochondrial-related genes as potential biomarkers for docetaxel-resistant prostate cancer. J Ankara Univ Fac Med. 2025;78(2):137-143

Bulgular: TAC, DEG'leri tanımlamak için düzeltilmiş p-değeri <0,05 (p<0,05) (*yanlış bulgu oranı*-FDR <0,05) ve |log2FC| >1,0 kriterlerini uygulamıştır. Analiz, DX ile tedavi edilen hücrelerde kontrollere kıyasla 515 genin yukarı regülasyonunu ve 608 genin aşağı regülasyonunu ortaya koymuştur. DEG'lerin zenginleştirme analizi, metabolik yollar, çoklu hastalıkları içeren nörodejenerasyon yolları, kofaktörlerin biyosentezi, reaktif oksijen türlerinin aracılık ettiği kimyasal karsinogenez, valin, lösin ve izolösin bozunması, karbon metabolizması ve oksidatif fosforilasyon gibi yolaklara dahil olduklarını göstermiştir. Bunlar arasında *ALDH4A1, ALDH6A1, ALDH2, PCCB, GLS, GATM, GLS2, IDH2, SUCLG2, ECI2, GLDC, IVD, ALDH7A1, ACACA, ALDH5A1, NDUFS7, PCK2, ARG2, FDXR* ve *CPT1A* en önemli aday genler olarak belirlenmiştir.

Sonuç: Bu kapsamlı biyoinformatik analiz, DX'in etkisinin altında yatan moleküler mekanizmalara ışık tutmakta ve kombinasyon tedavileri için potansiyel hedefleri vurgulayarak PK'de tedavi etkinliğini artırmak için umut verici stratejiler sunmaktadır.

Anahtar Kelimeler: Prostat kanseri, docetaxel, biyoinformatik, gen ekspresyonu omnibus, gen ekspresyonu

Introduction

Prostate cancer (PC) is the second most common cancer among men globally and the significant cause of cancer-related deaths in men (1,2). Androgen receptor (AR), a transcriptional factor essential for the development and spread of PC (3,4). The AR regulates numerous genes that are essential to the identity and behavior of PC cells (5). Depending on patient appropriateness, localized PC is generally treated with radiation or surgery. High-risk cases with locally progressed or high-grade tumors can induce distal metastases, the main cause of death connected to PC (4).

With the development of several treatments that increase overall survival, the treatment landscape for metastatic PC has undergone significant changes in recent years (6). Advancements in precision medicine have enabled the identification of distinct PC subtypes and genetic alterations that can predict the efficacy of specific treatments (1,7). These treatments include AR signaling inhibitors such as abiraterone acetate, enzalutamide, apalutamide, and darolutamide (8) as well as radioligand therapies like radium-223 and 177Lu-PSMA-617 (9,10). Patients with advanced PC initially respond remarkably well to androgen deprivation therapy. However, the treatment eventually selects for cancer cells that adapt to androgen deprivation, resulting in the development of castration-resistant PC (CRPC) (2,11). Patients with metastatic CRPC (mCRPC) face a reduced life expectancy, with a median overall survival of less than 2 years (2).

Over the past decade, treatment options for CRPC have significantly improved (10).

While AR inhibitors have greatly improved outcomes for metastatic PC, long-term use always results in treatment resistance as cancer cells adjust to androgen deprivation. As a consequence of this resistance, CRPC develops, necessitating the use of other treatment approaches such as chemotherapy with docetaxel (DX). DX chemotherapy elicits a good level of response as first-line treatment and provides a significant survival advantage in CRPC patients (12). DX, a taxane-based chemotherapeutic agent, was the first treatment to exhibit substantial efficacy in the management of this mCRPC (13). It promotes the phosphorylation of Bcl-2 *in vitro*, leading to its functional inactivation and subsequent induction of apoptosis (14,15).

Unfortunately, the therapeutic response to DX is inevitably time-limited, as patients eventually experience disease progression due to acquired drug resistance (13). Although the mechanisms underlying the development of DX resistance in PC are not fully understood, previous studies have identified several contributing factors and pathways involved in resistance. These mechanisms include increased intracellular drug efflux mediated by adenosine triphosphate-binding cassette transporters, expression of β-tubulin isoforms/mutations, alterations in cell death pathways, including apoptosis and autophagy, mutations in β-tubulin, and dysregulated AR signaling (13).

In this study, it was focused on gene expression profiles in parental DX-sensitive PC cell lines (DU145) and selected DX-resistant cells (DU145-DR) cells. In the recent studies, bioinformatics analysis has become a popular tool for the analysis and identification of novel and potential biomarkers as therapeutic targets for various diseases. Therefore, we utilized bioinformatics tools to analyze target genes and the interaction networks among them, providing deeper insights into the mechanisms underlying DX resistance.

Materials and Methods

Analysis of Differentially Expressed Genes

GSE36135 was generated using microarray-based gene expression analysis, and 2 replicate data for DU145-DR resistant and DU145-DS susceptible cells were used. The statistical power of the dataset was assessed for its adequacy to detect gene expression differences between groups. Transcriptome Analysis Console 4.0 uses methods such as robust multi-array average (RMA) normalization, ANOVA-based statistical analyses, and false discovery rate (FDR) corrections to analyze data from Affymetrix microarray platforms. RMA or signal space transformation normalization is applied. Quality control analyses are performed. The difference in expression of genes between two groups (e.g., resistant vs. susceptible) is calculated.

Differential gene expression is determined by ANOVA or Student's t-test. FDR correction is applied to increase the reliability of p-value thresholds (e.g., FDR<0.05).

In our study, RMA normalization was applied during the data analysis process, differential gene expression analysis was performed, and statistical correction was made so that FDR<0.05.

Gene expression datasets (GSE36135), freely accessible, were acquired from Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/). In each dataset, differentially expressed genes (DEGs) were selected based on p<0.05, FDR<0.05, and a log-fold change>1. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using DAVID software.

Identification of Mitochondria-associated DEGs

Mitochondria-associated DEGs (MitoDEGs) were screened and identified by comparing DU145 control and DU145-DR cells. A total of 1136 mitochondria-associated genes were obtained from the MitoCarta 3.0 database (http://www.broadinstitute.org/mitocarta). MitoDEGs were identified by cross-referencing the DEGs of interest from each dataset with the mitochondria-associated genes. The results were visualized using Venn diagrams generated with the MolBioTools platform (https://molbiotools.com/listcompare).

Analysis of Protein-protein Interactions

Protein-protein interaction (PPI) networks were constructed based on the MitoDEGs using the STRING database (https://string-db.org/). Hub-MitoDEGs were identified using Cytoscape software (version 3.8.1) through the CytoHubba (https://apps.cytoscape.org/apps/cytohubba) and MCODE (https://apps.cytoscape.org/apps/mcode) plugins.

For the protein interaction subnetworks identified via the MCODE plugin, the following parameter settings were used: Degree cut-off: 2, Maximum depth: 100, K-Core: 2, and Node score cut-off: 0.2. Subsequently, the CytoHubba plugin was employed to select hub genes within the PPI network with a Matthews correlation coefficient ≥60. The results were combined, and the top ten hub-MitoDEGs were selected for further analysis.

Results

Analysis of DEGs

Comparisons were performed as DU145-DR vs. DU145; 608 genes with decreased expression and 515 genes with increased expression were identified.

Subsequently, these genes were cross-referenced with the list of 1136 mitochondria-associated genes, and the number of overlapping genes was identified as 59 and visualized accordingly (Figure 1).

Functional Enrichment Analysis of DEGs

To identify the biological properties of the DEGs, GO enrichment analysis was performed on 438 downregulated and 469 upregulated DEGs using DAVID online tools. Biological processes with at least 20 clustered genes and a p-value <0.05, FDR<0.05 were considered significant. The analysis revealed that key enriched biological processes were primarily associated with chromatin remodeling, signal transduction, cell division, ATP activity, and protein kinase activity.

In the KEGG pathway analysis, the DEGs were found to be enriched in metabolic pathways, pathways of neurodegeneration-multiple diseases, biosynthesis of cofactors, chemical carcinogenesis-reactive oxygen species (ROS), valine, leucine and isoleucine degradation, carbon metabolism and oxidative phosphorylation (OXPHOS). Detailed results of the GO and KEGG pathway analyses are presented in Tables 1 and 2.

Construction of the PPI Network and Identification of Hub Genes

To investigate the interactions among DEGs and identify hub genes associated with DX resistance in PC, we utilized the STRING database to construct PPI networks. Subsequent analyses were performed using the CytoHubba plugin in Cytoscape software. Twenty hub genes were ranked based on their MCC scores, reflecting the number of gene interactions within the PPI network. *ALDH4A1*, *ALDH6A1*, *ALDH2*, *PCCB*, *GLS*, *GATM*, *GLS2*, *IDH2*, *SUCLG2*, *ECI2*, *GLDC*, *IVD*, *ALDH7A1*, *ACACA*, *ALDH5A1*, *NDUFS7*, *PCK2*, *ARG2*, *FDXR*, and *CPT1A* are among the hub genes which are upregulated and downregulated in DU145-DR compared to DU145 cells (Figure 2) (16).

Discussion

PC is the most common cancer among men worldwide and a leading cause of cancer-related deaths globally. DX has shown substantial efficacy in the management of PC, but its therapeutic response is limited, as patients inevitably develop resistance and disease progression (1,2,13). While the mechanisms underlying DX resistance in PC are not fully understood, several contributing factors and pathways have been identified (13). Still, there are studies which focus on the mechanisms involved in DX-resistance in PC.

Our bioinformatics analysis identified A*LDH4A1*, *ALDH6A1*, *ALDH2*, *PCCB*, *GLS*, *GATM*, *GLS2*, *IDH2*, *SUCLG2*, *ECI2*, *GLDC*, *IVD*, *ALDH7A1*, *ACACA*, *ALDH5A1*, *NDUFS7*, *PCK2*, *ARG2*, *FDXR*, and *CPT1A* as the most significant mitochondrial-related genes potentially implicated in DX resistance progression in PC. Moreover, our KEGG pathway analysis also reported the high

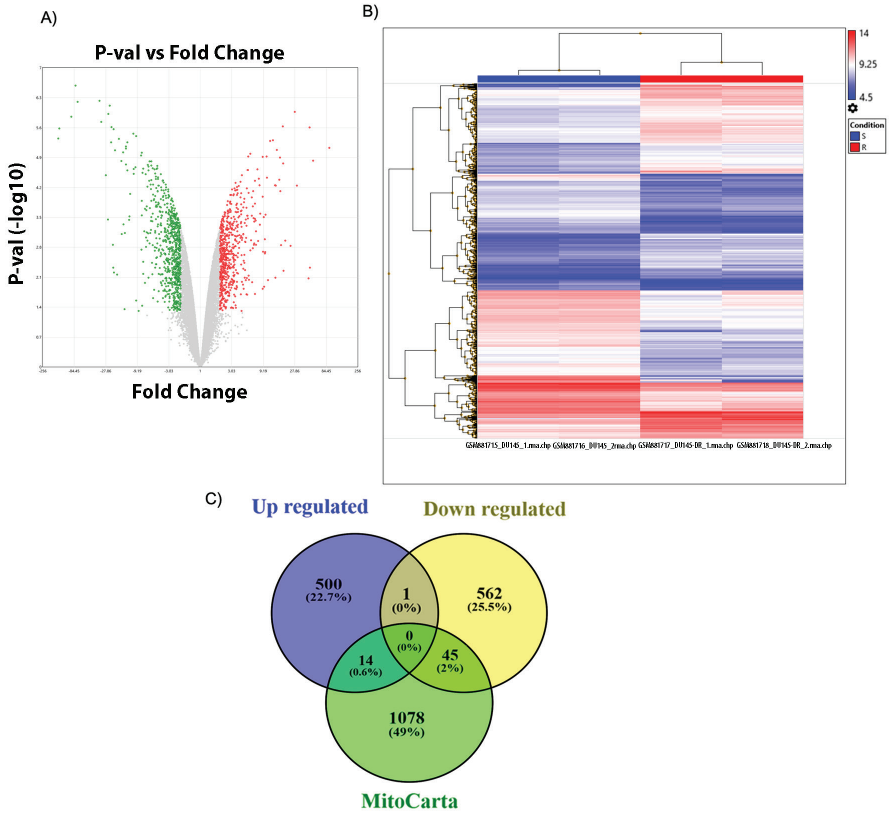

Figure 1: A) The number of DEGs identified in each comparison was recorded, and their distribution was visualized using volcano plots, (Green dots represent genes with decreased expression, while red dots indicate genes with increased expression); B) GSM881715_DU145_1, GSM881716_DU145_2 are Docetaxel-sensitive samples, and GSM881717_DU145-DR.1 and GSM881717_DU145-DR.2 are Docetaxel-resistant samples. The vertical axis is the DEG cluster, the horizontal axis is the sample cluster, the orange color represents up-regulated genes, and the blue color represents down-regulated genes; C) The intersecting upregulated and downregulated genes among groups obtained from Venn diagram
DEGs: Differentially expressed genes

Table 1: GO enrichment analysis of upregulated and downregulated genes (p<0.05) (FDR<0.05)

Category	Term	Count	Genes
GOTERM_BP_DIRECT	GO:0009060~aerobic respiration	4	*OXA1L, NDUFA6, UQCRB, UQCRC1*
	GO:0045333~cellular respiration	3	*UQCRB, COX4I1, UQCRC1*
	GO:1902600~proton transmembrane transport	4	*NDUFA6, COX4I1, UQCRC1, SLC25A4*
GOTERM_CC_DIRECT	GO:0005759~mitochondrial matrix	21	*ARG2, ACSM3, GLDC, IDH2, MRPS10, LIAS, COASY, DHTKD1, GLS, GSTZ1, ALDH4A1, OXA1L, ALDH6A1, NFS1, ALDH5A1, ALDH2, IVD, ETHE1, PCCB, LONP1, BCL2L1*
	GO:0005743~mitochondrial inner membrane	11	*OXA1L, NDUFA6, UQCRB, COX4I1, UQCRC1, MRPS10, SLC25A20, DNAJC15, SLC25A4, COQ6, BCL2L1*

GO: Gene Ontology, FDR: False discovery rate

number of genes enriched in the metabolic pathway, OXPHOS, carbon metabolism, and other sub-pathways of the metabolic pathway.

Recent studies reported that progression and resistance to treatment of PC are significantly affected by metabolic changes (17). Advanced-stage PC has been strongly linked to metabolic syndrome, a clinical condition defined by glucose intolerance, dyslipidemia, hypertension, and obesity (18). Both metabolic syndrome and diabetes are commonly associated with more aggressive PC characteristics and poorer patient outcomes (17). Metabolic profiling in PC holds dual clinical potential: serving as a diagnostic tool for identifying aggressive PC and enabling the selection of predictive biomarkers for therapies that target metabolic pathways to inhibit cancer progression (17). The study carried out by Ippolito et al. (19) reported that DX-resistant PC3 cells (PC3-DR) exhibit enhanced invasiveness,

Table 2: Results of KEGG pathway enrichment analysis of common genes by David (p<0.05) (FDR<0.05)		
Category	**Term**	**Count**
KEGG_PATHWAY	hsa01100: Metabolic pathways	27
KEGG_PATHWAY	hsa05022: Pathways of neurodegeneration - multiple diseases	6
KEGG_PATHWAY	hsa01240: Biosynthesis of cofactors	5
KEGG_PATHWAY	hsa05208: Chemical carcinogenesis - reactive oxygen species	5
KEGG_PATHWAY	hsa00280: Valine, leucine and isoleucine degradation	4
KEGG_PATHWAY	hsa01200: Carbon metabolism	4
KEGG_PATHWAY	hsa00190: Oxidative phosphorylation	4
KEGG: Kyoto Encyclopedia of Genes and Genomes, FDR: False discovery rate		

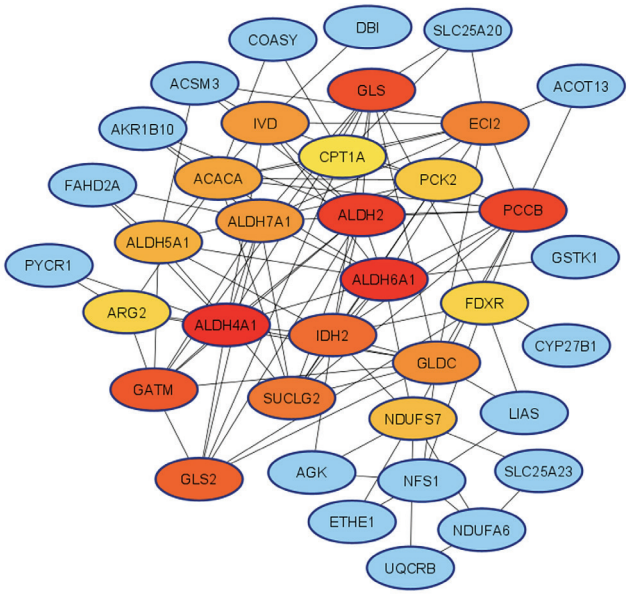

Figure 2: Top 20 hub genes screened by degree according to cytoHubba plug-in DU145-DR vs DU145 cells. The top 20 hub genes ranked by the MCC algorithm and their neighbors in the blue nodes. The red nodes represent genes with a high MCC score, while yellow nodes represent genes with a low MCC score

undergo epithelial-to-mesenchymal transition, and show reduced intracellular ROS and cell growth. Metabolic analysis indicates a shift toward a more efficient respiratory phenotype, utilizing glucose, glutamine (Gln), and lactate via mitochondrial OXPHOS (19).

Among these genes, *ALDH2* is the best-known isoform for converting acetaldehyde in alcohol metabolism (20). *ALDH2* has also been associated with the progression of various cancers. Decreased *ALDH2* expression has been observed in metastatic samples compared to primary PC and healthy prostate tissues (21). In studies investigating the biological mechanisms underlying lethal PC, *ALDH2* and *ALDH1A3* were found to be downregulated in lethal tumors (22). Feng et al. (23) identified *ALDH2* as a potential biomarker for predicting biochemical recurrence in PC patients and linked its expression to poor prognosis. Interestingly, *ALDH1A3, ALDH1B1*, and *ALDH2* mRNA expressions were reported to be increased in malignant PC samples compared to benign prostatic hyperplasia (24). Another significant mitochondrial-related gene, *IDH2*, plays a vital role in citrate metabolism (25). Silencing *IDH2* in PC cells has been shown to impair oxidative bioenergetics and increase ROS production (26). IDH1 and *IDH2* mutations are seen in 1-3% of patients with PC (25). In PC, two IDH1 mutations (R132C and R132H) are common and are not associated with the stage or grade of PC (27,28). Inhibition of IDH1 reduced the proliferation of PC cells *in vitro* and *in vivo*, and it has been reported that IDH1 can be used as a target for the treatment of PC (29).

The role of *glutaminase (GLS)* in PC has also been extensively studied. *GLS*, which facilitates Gln degradation, is overexpressed in PC samples compared to benign prostatic hyperplasia and correlates with advanced pathological stages (30). *GLS*-dependent proliferation has been observed in PC3 PC cells, where its suppression reduces cell growth, intracellular ATP levels, and invasiveness (30). High levels of oxidative stress have been detected in C4-2B PC cells, which release large extracellular vesicles that may promote bone metastases (31). *GLS* inhibition in these cells decreases exosome release, highlighting the importance of Gln metabolism in metastatic PC (31).

Furthermore, suppression of *GLS* in DU145 and PC-3 cells induces apoptosis and cell cycle arrest by increasing Bax and decreasing cyclinD1 and Bcl-2 levels. This suppression also downregulates the Wnt/β-catenin pathway, a critical pathway in cancer progression, making *GLS* a potential therapeutic target (32).

The role of *GLS* in PC is complex. Androgen depletion therapy suppresses the kidney-specific *GLS1* isoform while inducing the androgen-independent enzyme glutaminase C (GAC), which promotes cancer cell survival (33). Suppression of GAC has shown better therapeutic efficacy in testosterone-independent PC than in hormone-sensitive forms (33). Additionally, *GLS* overexpression has been linked to increased energy demands in radiotherapy-resistant PC and PC stem cells. Combining *GLS1* inhibition with radiotherapy and targeting Gln metabolism may improve treatment efficacy. However, as cancer cells can activate autophagy to survive Gln deficiency, the inclusion of autophagy inhibitors has also been suggested (34).

Although the exact processes underlying DX resistance are still unknown, a mesenchymal phenotype is linked to DX resistance (35). Since OXPHOS, which is largely driven by Gln, produces the majority of ATP, mesenchymal phenotypes have been associated with metabolic rewiring (35). In DX-resistant PC cells, Gln depletion and *GLS* suppression disrupt critical survival pathways, including OXPHOS and ATP production (35). In a study using cancer-associated fibroblasts together with PC cells by mimicking the tumor microenvironment, it was determined that fibroblasts metabolically reprogram cancer cells and *GLS* may be an important therapeutic target (36). In summary, mitochondrial-related genes such as *ALDH2*, *IDH2*, and *GLS* play crucial roles in PC progression and resistance mechanisms, particularly against DX.

In our study, although many genes have been shown to have different gene expression in prostate DX resistance, there are genes including *PCCB, GATM, IVD, ALDH5A1*, and *NDUS7*, which their roles in PC have not yet been studied.

In this study, the role of mitochondria-related genes identified by bioinformatic analyses in DX resistance was revealed. However, these findings need to be experimentally validated in the laboratory. Potential validation approaches include qPCR, Western blot, and functional assays.

In particular, qPCR can be used to measure the expression levels of selected genes in different cell lines and test the accuracy of bioinformatic analyses. By examining the changes in the protein levels of these genes with Western blotting, it can be evaluated how the differences at the transcript level are reflected at the protein level.

In addition, using functional assays (e.g., cell viability assays, invasion, and apoptosis assays), the effects of the identified genes on DX resistance can be directly observed. Specifically, the changes in the drug resistance profiles of cells when these genes are silenced or overexpressed should be analyzed.

Conclusion

The findings of this study highlight the potential of targeting specific genes through silencing or upregulating their expression as a promising approach for PC therapy. In future studies, the implementation of the experimental validation steps will contribute to the identification of new therapeutic targets, increasing the validity of bioinformatics findings in a clinical context. It is also important to integrate these genes with clinical data to determine their prognostic or predictive value in patients.

Ethics

Ethics Committee Approval: Not applicable. This paper does not involve human or animal subjects.

Informed Consent: Not applicable. This paper does not involve human or animal subjects.

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

References

1. van Dessel LF, van Riet J, Smits M, et al. The genomic landscape of metastatic castration-resistant prostate cancers reveals multiple distinct genotypes with potential clinical impact. Nat Commun. 2019;10:5251.
2. Le TK, Duong QH, Baylot V, et al. Castration-resistant prostate cancer: from uncovered resistance mechanisms to current treatments. Cancers (Basel). 2023;15:5047.
3. Bolek H, Yazgan SC, Yekeduz E, et al. Androgen receptor pathway inhibitors and drug-drug interactions in prostate cancer. ESMO Open. 2024;9:103736.
4. Huang J, Lin B, Li B. Anti-androgen receptor therapies in prostate cancer: a brief update and perspective. Front Oncol. 2022;12:865350.
5. Yuan X, Cai C, Chen S, et al. Androgen receptor functions in castration-resistant prostate cancer and mechanisms of resistance to new agents targeting the androgen axis. Oncogene. 2014;33(22):2815-25.
6. Tzang CC, Wu HW, Lou CA, et al. Efficacy and safety of PARP inhibitors in prostate cancer: an umbrella review of systematic reviews and meta-analyses. Crit Rev Oncol Hematol. 2025:104609.
7. Abida W, Armenia J, Gopalan A, et al. Prospective genomic profiling of prostate cancer across disease states reveals germline and somatic alterations that may affect clinical decision making. JCO Precis Oncol. 2017;2017.
8. Mitsiades N, Kaochar S. Androgen receptor signaling inhibitors: post-chemotherapy, pre-chemotherapy and now in castration-sensitive prostate cancer. Endocr Relat Cancer. 2021;28:T19-T38.
9. Sathekge MM, Lawal IO, Bal C, et al. Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): a multicentre, retrospective study. Lancet Oncol. 2024;25:175-183.
10. Iannantuono GM, Chandran E, Floudas CS, et al. Efficacy and safety of PARP inhibitors in metastatic castration-resistant prostate cancer: A systematic review and meta-analysis of clinical trials. Cancer Treat Rev. 2023;120:102623.
11. Takayama KI, Suzuki T, Fujimura T, et al. Dysregulation of spliceosome gene expression in advanced prostate cancer by RNA-binding protein PSF. Proc Natl Acad Sci U S A. 2017;114:10461-10466.
12. Sekino Y, Teishima J. Molecular mechanisms of docetaxel resistance in prostate cancer. Cancer Drug Resist. 2020;3:676-685.
13. Lima TS, Iglesias-Gato D, Souza LDO, et al. Molecular profiling of docetaxel-resistant prostate cancer cells identifies multiple mechanisms of therapeutic resistance. Cancers (Basel). 2021;13.
14. Haldar S, Chintapalli J, Croce CM. Taxol induces bcl-2 phosphorylation and death of prostate cancer cells. Cancer Res. 1996;56:1253-1255.
15. Domingo-Domenech J, Vidal SJ, Rodriguez-Bravo V, et al. Suppression of acquired docetaxel resistance in prostate cancer through depletion of notch- and hedgehog-dependent tumor-initiating cells. Cancer Cell. 2012;22:373-388.
16. Karadag Gurel A, Gurel S. To detect potential pathways and target genes in infantile Pompe patients using computational analysis. Bioimpacts. 2022;12:89-105.
17. Giunchi F, Fiorentino M, Loda M. The metabolic landscape of prostate cancer. Eur Urol Oncol. 2019;2:28-36.
18. Grundmark B, Garmo H, Loda M, et al. The metabolic syndrome and the risk of prostate cancer under competing risks of death from other causes. Cancer Epidemiol Biomarkers Prev. 2010;19:2088-2096.
19. Ippolito L, Marini A, Cavallini L, et al. Metabolic shift toward oxidative phosphorylation in docetaxel resistant prostate cancer cells. Oncotarget. 2016;7:61890-61904.

20. Püschel J, Dubrovska A, Gorodetska I. The multifaceted role of aldehyde dehydrogenases in prostate cancer stem cells. Cancers. 2021;13:4703.
21. Kim JW, Kim ST, Turner AR, et al. Identification of new differentially methylated genes that have potential functional consequences in prostate cancer. PLoS One. 2012;7:e48455.
22. Kelly RS, Sinnott JA, Rider JR, et al. The role of tumor metabolism as a driver of prostate cancer progression and lethal disease: results from a nested case-control study. Cancer Metab. 2016;4:22.
23. Feng D, Zhu W, You J, et al. Mitochondrial aldehyde dehydrogenase 2 represents a potential biomarker of biochemical recurrence in prostate cancer patients. Molecules. 2022;27.
24. Quattrini L, Sadiq M, Petrarolo G, et al. Aldehyde dehydrogenases and prostate cancer: Shedding light on isoform distribution to reveal druggable target. Biomedicines. 2020;8:569.
25. Gonthier K, Poluri RTK, Weidmann C, et al. Reprogramming of isocitrate dehydrogenases expression and activity by the androgen receptor in prostate cancer. Mol Cancer Res. 2019;17:1699-1709.
26. Wang Y, Agarwal E, Bertolini I, et al. IDH2 reprograms mitochondrial dynamics in cancer through a HIF-1α–regulated pseudohypoxic state. The FASEB Journal. 2019;33:13398.
27. Kang MR, Kim MS, Oh JE, et al. Mutational analysis of IDH1 codon 132 in glioblastomas and other common cancers. Int J Cancer. 2009;125:353-355.
28. Ghiam A, Cairns R, Thoms J, et al. IDH mutation status in prostate cancer. Oncogene. 2012;31:3826.
29. Gonthier K, Weidmann C, Berthiaume L, et al. Isocitrate dehydrogenase 1 sustains a hybrid cytoplasmic-mitochondrial tricarboxylic acid cycle that can be targeted for therapeutic purposes in prostate cancer. Mol Oncol. 2023;17:2109-2125.
30. Pan T, Gao L, Wu G, et al. Elevated expression of glutaminase confers glucose utilization via glutaminolysis in prostate cancer. Biochem Biophys Res Commun. 2015;456:452-458.
31. Dorai T, Shah A, Summers F, et al. NRH:quinone oxidoreductase 2 (NQO2) and glutaminase (GLS) both play a role in large extracellular vesicles (LEV) formation in preclinical LNCaP-C4-2B prostate cancer model of progressive metastasis. Prostate. 2018;78:1181-1195.
32. Zhang J, Mao S, Guo Y, et al. Inhibition of GLS suppresses proliferation and promotes apoptosis in prostate cancer. Biosci Rep. 2019;39.
33. Xu L, Yin Y, Li Y, et al. A glutaminase isoform switch drives therapeutic resistance and disease progression of prostate cancer. Proc Natl Acad Sci U S A. 2021;118.
34. Mukha A, Kahya U, Linge A, et al. GLS-driven glutamine catabolism contributes to prostate cancer radiosensitivity by regulating the redox state, stemness and ATG5-mediated autophagy. Theranostics. 2021;11:7844-7868.
35. Beier AK, Ebersbach C, Siciliano T, et al. Targeting the glutamine metabolism to suppress cell proliferation in mesenchymal docetaxel-resistant prostate cancer. Oncogene. 2024;43:2038-2050.
36. Honscheid PV, Baretton GB, Puhr M, et al. Prostate cancer's silent partners: fibroblasts and their influence on glutamine metabolism manipulation. Int J Mol Sci. 2024;25.

RESEARCH ARTICLE / ARAŞTIRMA MAKALESİ

DOI: 10.4274/atfm.galenos.2025.80775
J Ankara Univ Fac Med 2025;78(2):144-153

MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Assessment of Psychosocial Risks and Mental Health Status in a Faculty of Dentistry

Bir Diş Hekimliği Fakültesinde Psikososyal Riskler ve Ruh Sağlığı Durumunun Değerlendirilmesi

Betül Akkaya[1], Mine Esin Ocaktan[2]

[1]Defne District Health Directorate, Hatay, Türkiye
[2]Ankara University Faculty of Medicine, Department of Public Health, Ankara, Türkiye

Abstract

Objectives: It was aimed to evaluate the psychosocial risks, mental health status of the employees and related factors in a faculty of dentistry.

Materials and Methods: In this cross-sectional study, no sample was selected. It is planned to include all employees at the faculty of dentistry between November 2021 and January 2022. The data collection form included questions on socio-demographic characteristics, working life characteristics and Coronavirus disease-2019, the Turkish Copenhagen Psychosocial Questionnaire (COPSOQ-TR) and the General Health Questionnaire-12. Data were collected using a survey method under observation in the participant's workplace. Chi-square test and logistic regression analysis were applied in statistical analysis. Ethical approval was obtained for the study.

Results: Three hundred three (80% participation rate) employees were included in the study. The percentage of participants with high psychosocial risk scores is highest in the dimensions of lack of job satisfaction, insecurity over working conditions and work pace. The majority (52%) had poor mental health. Those with high risk scores in most dimensions of COPSOQ-TR have significantly poorer mental health status. In regression analysis, the variables of occupational group, access to adequate and appropriate personal protective equipment, lack of predictability, and burnout predicted poor mental health status.

Conclusion: It was found that the most important psychosocial risks are lack of job satisfaction, insecurity over working conditions and work pace. It has been demonstrated that the mental health status of the majority is poor and psychosocial risks are related to the mental health status of the participants.

Keywords: Occupational health, psychosocial factors, risk assessment, dentistry, mental health

Öz

Amaç: Diş hekimliği fakültesinde psikososyal riskleri, çalışanların ruh sağlığı durumunu ve ilgili faktörleri değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Kesitsel tipte olan çalışmada örneklem seçilmemiştir. Kasım 2021-Ocak 2022 tarihleri arasında diş hekimliği fakültesindeki tüm çalışanları kapsaması planlanmıştır. Veri toplama formunda sosyodemografik özellikler, çalışma yaşamı özellikleri ve Koronavirüs hastalığı-2019'a ilişkin sorular, Kopenhag Psikososyal Risk Değerlendirmesi Ölçeği (KOPSOR-TR) ve Genel Sağlık Anketi-12 yer almıştır. Veriler katılımcının işyerinde gözlem altında anket yöntemi kullanılarak toplanmıştır. İstatistiksel analizde ki-kare testi ve lojistik regresyon analizi uygulanmıştır. Çalışma için etik onay alınmıştır.

Bulgular: Çalışmaya 303 (%80 katılım oranı) çalışan dahil edilmiştir. Yüksek psikososyal risk puanına sahip katılımcıların yüzdesi en fazla iş doyumu eksikliği, çalışma koşulları güvencesizliği ve çalışma hızı boyutlarındadır. Çoğunluğun (%52) ruh sağlığı durumu kötüdür. KOPSOR-TR'nin çoğu

Address for Correspondence/Yazışma Adresi: Betül Akkaya, Defne District Health Directorate, Hatay, Türkiye
E-mail: betulakkayak@gmail.com **ORCID ID:** orcid.org/0000-0001-8902-0080
Received/Geliş Tarihi: 23.10.2024 **Accepted/Kabul Tarihi:** 02.05.2025 **Epub:** 13.06.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025

Cite this article as/Atıf: Akkaya B, Ocaktan ME. Assessment of psychosocial risks and mental health status in a faculty of dentistry. J Ankara Univ Fac Med. 2025;78(2):144-153

***This article has been sent as an abstract submission at the 8th International and 26th National Congress of Public Health.**

boyutunda risk puanı yüksek olanların ruh sağlığı durumu anlamlı ölçüde kötüdür. Regresyon analizinde, meslek grubu, yeterli ve uygun kişisel koruyucu donanıma ulaşabilme durumu, öngörülebilirlik eksikliği ve tükenmişlik ruh sağlığı durumunun kötü olması durumunu öngörmüştür.

Sonuç: En önemli psikososyal risklerin iş doyumu eksikliği, çalışma koşulları güvencesizliği ve çalışma hızı olduğu bulunmuştur. Çoğunluğun ruh sağlığı durumu kötüdür ve psikososyal risklerin katılımcıların ruh sağlığı durumuyla ilişkili olduğu gösterilmiştir.

Anahtar Kelimeler: İş sağlığı, psikososyal faktörler, risk değerlendirmesi, diş hekimliği, ruh sağlığı

Introduction

Psychosocial hazards are defined as factors that arise from inappropriate job design, organization and management and can lead to physical and mental illnesses in employees or managerial problems such as lack of productivity and absenteeism (1). Psychosocial risk is the probability that a psychosocial hazard will cause harm (2). However, the concepts of psychosocial hazard and risk, which are intertwined in many sources, are used interchangeably in the literature (3). The concepts of psychosocial risk and work-related stress, one of these risks, are often treated synonymously in the literature (3,4).

A quarter of employees in Europe report experiencing work-related stress. The most common psychosocial hazards are related to the employee's task type and work intensity (5). Different professions tend to involve different types of hazards (3). Work-related psychosocial hazards can have negative effects on the personal and professional relationships, physical and mental health of dental professionals (6). In their study in Taiwan, Lee et al. (7) reported that work stress and professional burnout were common among dental professionals. Severe acute respiratory syndrome-Coronavirus-2, spread rapidly all over the world and caused the coronavirus disease-2019 (COVID-19) pandemic. Although the global public health emergency was declared over in May 2023, the pandemic continues (8). In this process, healthcare workers have been exposed to additional psychological difficulties such as fear of infecting their families, being discriminated against by society as potential virus carriers, interruption of education and research activities, personal protective equipment (PPE) shortage and working under heavy workload and time pressure despite inadequate PPE (9,10). With the COVID-19 pandemic, psychosocial risks in the dental work environment have become even more important. During this period, dental professional practices were interrupted, new practices were introduced in dental procedures, and some dental treatments were postponed (9,11).

Psychosocial risks, like other important health and safety issues, can be managed effectively by applying an appropriate risk management approach (12). Risk assessment, the core element of the risk management process (13), is a systematic step-by-step approach (2).

Lee et al. (7) reported that job stress and burnout are common among dental professionals in their study in Taiwan. Various studies have found high levels of burnout in dentists (14-16). With the COVID-19 pandemic, psychosocial risk factors in the dentistry work environment have gained even more importance. During this period, dentistry professional practices were interrupted, new practices were implemented in dental procedures due to the high risk of cross-infection, and some dental treatments were postponed (11,17). COVID-19 has been a major concern among dental health workers because they work in close contact with the oral cavity and frequently perform aerosol-generating procedures (18). It has been observed that the number of studies examining psychosocial risks in the field of dentistry is limited, especially during the COVID-19 pandemic. Also in the literature review, there are a limited number of studies examining workplace psychosocial risks and employees' mental health status together. For these reasons, this study aims to evaluate psychosocial risks, mental health status and related factors at the faculty of dentistry; it was also aimed to determine the relationship between psychosocial risks and the mental health status of employees.

Materials and Methods

The cross-sectional study was conducted Ankara University Faculty of Dentistry. The universe consists of all employees working between November 2021 and January 2022. The sample was not selected. It was planned to include all people making up the universe within the scope of the research. Informed consent of the employees was obtained. Ethical approval was obtained from Ankara University Rectorate Ethics Committee (approval no.: 18/198, date: 22.11.2021), and necessary permissions were obtained from the faculty of dentistry and the Ministry of Health. Additionally, scale usage permissions were obtained. This article was extracted from the medical speciality thesis titled "Evaluation of Psychosocial Risks and General Health of Employees in a Faculty of Dentistry" prepared in Ankara, Türkiye in 2023.

Dependant variables are the scores employees received by the Türkiye Copenhagen psychosocial questionnaire (COPSOQ-TR) dimensions and the general health questionnaire-12 (GHQ-12). Independent variables are the socio-demographic, health and working life characteristics of the employees, the status of being assigned to the unit related to COVID-19, the ability to access sufficient and appropriate PPE, the possibility of flexible/remote working during the COVID-19 pandemic, the status of having COVID-19 and the most stressful work-related situations

experienced by employees during the COVID-19 pandemic. In comparisons made with GHQ-12 scores, the scores received by employees from the COPSOQ-TR dimensions were treated as independent variables.

Data were collected by survey method under observation. The data collection form consists of COPSOQ-TR and GHQ-12, as well as questions regarding socio-demographic, health and working life characteristics and COVID-19.

COPSOQ is a scale developed by Kristensen and Borg to collect valid and reliable information about basic psychosocial risk factors (19). The Türkiye validity and reliability study of the COPSOQ-3 scale (3rd edition) was conducted by Şahan et al. (20) in 2018. It was made by and named COPSOQ-TR. COPSOQ-TR consists of 25 dimensions and 87 items (1). The dimensions included in COPSOQ-TR are examined by dividing into five themes. These themes are: the demands theme, impact and development theme, interpersonal relations and leadership theme, other parameters theme and results theme (20). The Cronbach's alpha values of the lack of freedom at work and lack of predictability dimensions are 0.54 and 0.66, respectively. Cronbach's alpha values of the other 23 COPSOQ-TR dimensions are above 0.70 (20). In the analysis conducted in our research, the Cronbach's alpha value of all 25 dimensions is 0.70 and above. The scoring of each dimension was calculated on its own. Lack of job satisfaction was scored on a 4-point Likert scale, and all other dimensions were scored on a 5-point Likert scale. Scores at or above the median value, which is the cut-off point, indicate that the psychosocial risk in the relevant dimension is high, while scores below the median value indicate that the psychosocial risk in the relevant dimension is low (1,21).

GHQ-12 was developed by Goldberg to measure acute mental health problems common in society. Türkiye validity and reliability study was conducted by Kilic (22). While the Cronbach's alpha value in reliability calculations for GHQ-12 is 0.78 (22), it is 0.87 in the analysis conducted in our research. Likert type scoring method was used in our research (22). According to this scoring method, the highest score that can be obtained from the scale is 36, and a higher score indicates poorer mental health (23). The median value of the GHQ-12 total score is the cut-off point. Those with this value and above are categorised as having poor mental health, while those below that value are categorised as having good mental health (21).

Statistical Analysis

Data analysis was done using SPSS® statistics 25 programme. The suitability of numerical variables for normal distribution was evaluated using histograms, probability graphs and the Kolmogorov-Smirnov test. The first stage of an effective psychosocial risk assessment is job analysis (1). For this purpose, three categories are defined for the tasks performed by employees. Chi-square test was applied to compare categorical variables. Bonferroni correction was made from post-hoc tests. Variables predicting poor mental health status were evaluated using Backward Logistic Regression analysis. Multicollinearity between the numerical and ordinal variables in the model was evaluated with the Spearman correlation test. Variables with a significant relationship ($p<0.05$) in univariate analyses and in the literature, and variables with a $p<0.25$ although there was no significant relationship, were included in the model. Modelling was done with 29 variables in total. Since the Hosmer-Lemeshow test p-value=0.75, the final model was considered to have a good fit to the data. Statistical significance level was taken as $p<0.05$ (24,25).

Results

In this study, 305 (80%) people out of 380 people who made up the population were reached. One person was excluded from the research due to insufficient data and another person was excluded from the study due to the fact that she had only been working at the faculty for one day. Ultimately, 303 (80% participation rate) people were included in the research.

Table 1 presents the socio-demographic and working life characteristics of the participants. The average age of the participants is 38.36 (±11.18). The youngest participant is 23 years old, the oldest is 65 years old, 54% are women, 62% are married, 55% have children, 80% are higher education graduates and 18% have at least one of the following chronic physical illness, mental illness or disability.

Table 1: Socio-demographic and working life characteristics of the participants

Socio-demographic and working life characteristics	n (%)
Age (years) (n=302)	
20-29	105 (35)
30-39	61 (20)
40-49	81 (27)
≥50	55 (18)
Gender (n=303)	
Female	164 (54)
Male	139 (46)
Education level (n=303)	
Primary/Secondary education	62 (20)
Tertiary education	241 (80)
Marital status (n=301)	
Single	96 (32)
Married	188 (62)
Divorced/separated/widow	17 (6)

Table 1: Continued	
Socio-demographic and working life characteristics	**n (%)**
Parental status (n=303)	
Children	166 (55)
No children	137 (45)
Occupational group (n=303)	
Dentist[a]	165 (54)
Nurse	21 (7)
Health technician	16 (5)
Non-healthcare professional	101 (33)
Task (n=288)	
Academic unit academic task	168 (58)
Academic unit administrative task	66 (23)
Administrative unit administrative task	54 (19)
Weekly working hours (n=299)	
≤40	237 (79)
>40	62 (21)
Total working time (years) (n=299)	
0-5	104 (35)
6-15	62 (21)
16-25	73 (24)
≥26	60 (20)
[a]One medical doctor participated in the study and was included in the analyses in the dentist group	

In the faculty, 23% of employees stated that they were assigned to a unit related to COVID-19, 66% stated that they had access to sufficient and appropriate PPE during the pandemic, 76% stated that they had the opportunity to work flexibly/remotely during this period and 19% stated that they had COVID-19. One person stated that he had never been vaccinated and 91% of employees have received at least three doses of the COVID-19 vaccine and 99% have received at least two doses. In the study, 80% of the participants stated that the concern of infecting the family with the virus, 55% stated that the fear of contracting COVID-19, 48% stated that uncertainty in working conditions, and 33% stated that the reduced social interaction due to measures requiring physical distancing was one of the most stressful work-related situations during the COVID-19 pandemic.

Table 2 shows the distribution of risk scores of employees according to COPSOQ-TR dimensions. The dimensions with the highest median psychosocial risk score are cognitive demands, work pace and burnout, respectively (median value=75.00, 66.67, 62.50 respectively). When the scores received by employees from the COPSOQ-TR scale are categorised, the highest percentage of participants in the high-risk group is in the dimensions of lack of job satisfaction (57%), insecurity over working conditions (55%) and work pace (54%).

COPSOQ-TR dimension scores were compared according to the participants' occupational group and task. The occupational group was found to be associated with the participants' risk

Table 2: Distribution of participants' risk scores according to COPSOQ-TR dimensions			
COPSOQ-TR dimension (n)	**n (%)**	**COPSOQ-TR dimension (n)**	**n (%)**
Work pace (303)		**Role-conflicts (301)**	
Low score	138 (46)	Low score	197 (65)
High score	165 (54)	High score	104 (35)
Quantitative demands (302)		**Lack of quality of leadership (300)**	
Low score	144 (48)	Low score	153 (51)
High score	158 (52)	High score	147 (49)
Cognitive demands (303)		**Lack of social support from colleagues (301)**	
Low score	178 (59)	Low score	148 (49)
High score	125 (41)	High score	153 (51)
Emotional demands (302)		**Lack of social support from supervisors (300)**	
Low score	164 (54)	Low score	185 (62)
High score	138 (46)	High score	115 (38)
Demands for hiding emotions (303)		**Lack of sense of community (300)**	
Low score	169 (56)	Low score	163 (54)
High score	134 (44)	High score	137 (46)
Lack of influence at work (303)		**Insecurity over employment (301)**	
Low score	171 (56)	Low score	166 (55)
High score	132 (44)	High score	135 (45)

Table 2: Continued			
COPSOQ-TR dimension (n)	**n (%)**	**COPSOQ-TR dimension (n)**	**n (%)**
Lack of possibilities for development (298)		**Insecurity over working conditions (298)**	
Low score	163 (55)	Low score	134 (45)
High score	135 (45)	High score	164 (55)
Lack of freedom at work (298)		**Work life conflict (299)**	
Low score	174 (58)	Low score	179 (60)
High score	124 (42)	High score	120 (40)
Meaninglessness of work (298)		**Lack of trust (298)**	
Low score	189 (63)	Low score	188 (63)
High score	109 (37)	High score	110 (37)
Lack of commitment to the workplace (297)		**Lack of organisational justice and respect (297)**	
Low score	140 (47)	Low score	153 (52)
High score	157 (53)	High score	144 (48)
Lack of predictability (298)		**Lack of job satisfaction (298)**	
Low score	184 (62)	Low score	129 (43)
High score	114 (38)	High score	169 (57)
Lack of recognition (298)		**Burnout (298)**	
Low score	177 (59)	Low score	173 (58)
High score	121 (41)	High score	125 (42)
Lack of role-clarity (301)			
Low score	182 (60)		
High score	119 (40)		

COPSOQ-TR: Türkiye Copenhagen psychosocial questionnaire

levels of quantitative demands, emotional demands, work-life conflict, lack of influence at work, lack of possibilities for development, lack of predictability, role conflicts, lack of social support from colleagues and lack of social support from superiors ($p<0.05$). Quantitative demands, emotional demands, work-life conflict, lack of influence at work, lack of possibilities for development, lack of predictability, role conflicts, lack of social support from colleagues, lack of social support from superiors and burnout risk levels were found to be associated with the employee's task ($p<0.05$).

Comparison of participants' mental health status according to their characteristics related to working life and the COVID-19 pandemic is presented in Table 3. The median of the scores the participants received from the GHQ-12 scale is 12. When evaluated by categorising the GHQ-12 score, 52% of the participants (n=151) had a poor mental health condition. There is no statistically significant difference between the mental health status of the participants according to socio-demographic characteristics ($p>0.05$). The mental health status of those without a chronic disease or disability is significantly worse than that of people with the relevant condition ($p<0.05$).

Comparison of the participants' mental health status according to their COPSOQ-TR dimension scores is presented in Table 4. The mental health status of those with a high risk of quantitative demands, cognitive demands, emotional demands, work-life conflict, lack of influence at work, lack of freedom at work, meaninglessness of work, lack of commitment to the workplace, lack of predictability, lack of role-clarity, role conflicts, lack of quality of leadership, lack of social support from superiors, lack of organizational justice and respect, insecurity over employment, insecurity over working conditions, lack of job satisfaction and burnout is significantly worse than those with a low risk ($p<0.05$).

Table 5 presents the logistic regression analysis last step results regarding the effects of some characteristics of the participants and COPSOQ-TR dimensions on mental health status. It was found that the variables of occupational group, access to adequate and appropriate PPE, lack of predictability and burnout significantly affected the poor mental health status ($p<0.05$).

Discussion

It has been found that the most important psychosocial risks in the faculty are lack of job satisfaction, insecurity over working conditions, work pace, and the majority have poor mental health status. The strengths of our research are that it evaluates many problems at the same time and, as far as is known, it is the first

study in the field of dentistry where psychosocial risks, mental health status and factors related to the COVID-19 pandemic are examined together in all professional groups. Additionally, the risk assessment made a contribution to routine occupational health services. Since the number of studies conducted with COPSOQ for all employees in the field of dentistry is limited, it was thought that the discussion was incomplete in this respect.

Due to the nature of the COPSOQ-TR scale, the workplace must be evaluated within itself (1). Lack of job satisfaction, insecurity over working conditions and work pace, which are the dimensions with the highest percentage of participants in the high-risk group, are the most important psychosocial risks in the faculty. This may be due to reasons such as difficult working conditions, high risk of COVID-19 transmission, frequent changes in instructions, prolongation of practices due to new procedures, necessity to work with PPE, assignments outside their field, unintentional changes in working hours. In some studies conducted on healthcare workers, the most important psychosocial risks at work are often different from our study (26-28).

Psychosocial risks of dentists and academic staff in academic units are high in the dimensions that appear significant in the theme of demands. Previous studies have also reported that dentists have high risk levels in terms of demands (29-31). This may be due to the high amount of work dentists have to do in a limited time, the fact that they are faced with patient demands, the high probability of doing many tasks, including management, and the fact that dentists are mostly assigned during the pandemic.

Table 3: Comparison of participants' mental health status according to their characteristics related to working life and the COVID-19 pandemic

Characteristics	Mental health status			Characteristics	Mental health status		
	Good	Poor	p-value		Good	Poor	p-value
	n (%)	n (%)			n (%)	n (%)	
Occupational group				**Having COVID-19**			
Dentist	68 (43)	91 (57)	**0.037**	Yes	28 (51)	27 (49)	0.664
Nurse	13 (65)	7 (35)		No	112 (48)	123 (52)	
Health technician	5 (31)	11 (69)		**Fear of getting COVID-19[a]**			
Non-healthcare professional	54 (56)	42 (44)		Yes	71 (45)	87 (55)	0.238
Task				No	69 (52)	64 (48)	
Academic unit academic task	70 (43)	92 (57)	**0.027**	**Concern about infecting the family with the virus[a]**			
Academic unit administrative task	32 (50)	32 (50)		Yes	107 (46)	124 (54)	0.231
Administrative unit administrative task	33 (65)	18 (35)		No	33 (55)	27 (45)	
Total working time (years)				**Obligation to work with PPE[a]**			
0-5	39 (39)	60 (61)	0.205	Yes	36 (40)	54 (60)	0.064
6-15	32 (53)	29 (47)		No	104 (52)	97(48)	
16-25	33 (48)	36 (52)		**Interruption of education-research activities[a]**			
≥26	32 (55)	26 (45)		Yes	41 (46)	48 (54)	0.643
Weekly working hours				No	99 (49)	103 (51)	
≤40	108 (48)	117 (52)	0.864	**Uncertainty in working conditions[a]**			
>40	29 (47)	33 (53)		Yes	57 (41)	82 (59)	**0.020**
Status of being assigned to the unit related to COVID-19				No	83 (55)	69 (45)	
Yes	31 (46)	36 (54)	0.731	**New practices in dental procedures[a]**			
No	109 (49)	115 (51)		Yes	19 (50)	19 (50)	0.803
Availability of access to sufficient and appropriate PPE				No	12 (48)	132 (52)	
Yes	110 (57)	84 (43)	**0.000**	**Reduced social interaction due to measures[a]**			
No	30 (31)	66 (69)		Yes	51 (55)	42 (45)	0.115
Flexible/remote working opportunity during the pandemic				No	89 (45)	109 (55)	
Yes	106 (48)	114 (52)	0.880				
No	33 (47)	37 (53)					

a: *p<0.05, **p<0.01, ***p<0.01; Row percentages are used in the table
A during the COVID-19 pandemic, participants who reported the work-related caused the most stress were compared with those who did not
NS: Not significant; COVID-19: Coronavirus disease-2019, PPE: Personal protective equipment

It is noteworthy that the risk of lack of influence at work and lack of possibilities for development differs according to occupational groups, both in our research and in the relevant literature, and that the risk is lowest in the dentist/physician group (26,29,32). This may be due to the fact that dentists/physicians are generally in a supervisory position and education and research activities are mainly carried out among dentists. The risk of lack of influence at work and lack of possibilities for development for those working academically in academic units is significantly lower than other groups. The significant difference in the same dimensions of the theme of demands and impact and development according to occupational group and task is probably due to the fact that 98% of those working in academic units are dentists.

In the dimensions that are significant in the theme of interpersonal relations and leadership, mostly those who are not healthcare professionals and those who work in administrative positions have high psychosocial risks. Findings are diverse, especially in previous studies where evaluations were made according to occupations (29,31-33). The high risk of lack of predictability for those who are not healthcare professionals and those who work in administrative positions suggests that they may have been left in the background in terms of notification of decisions and information, due to reasons such as the fact that most of the managers are dentists and the education network is mainly among dentists. The risk of lack of social support from colleagues and superiors is also high in these groups. Those working in administrative units are more likely to work at a desk

Table 4: Comparison of participants' mental health status according to COPSOQ-TR dimension scores

COPSOQ-TR dimension		Mental health status			COPSOQ-TR dimension		Mental health status		
		Good	Poor	p-value			Good	Poor	p-value
		n (%)	n (%)				n (%)	n (%)	
Work pace	Low	65 (49)	67 (51)	0.725	**Role conflicts**	Low	99 (53)	88 (47)	**0.038**
	High	75 (47)	84 (53)			High	41 (40)	61 (60)	
Quantitative demands	Low	81 (58)	58 (42)	**0.001**	**Lack of quality of leadership**	Low	81 (55)	66 (45)	**0.018**
	High	59 (39)	92 (61)			High	58 (41)	83 (59)	
Cognitive demands	Low	92 (53)	80 (47)	**0.027**	**Lack of social support from colleagues**	Low	73 (52)	68 (48)	0.269
	High	48 (40)	71 (60)			High	67 (45)	81 (55)	
Emotional demands	Low	95 (59)	65 (41)	**0.000**	**Lack of social support from supervisors**	Low	95 (53)	83 (47)	**0.027**
	High	45 (35)	85 (65)			High	44 (40)	66 (60)	
Demands for hiding emotions	Low	83 (52)	78 (48)	0.191	**Lack of sense of community**	Low	79 (51)	76 (49)	0.322
	High	57 (44)	73 (56)			High	60 (45)	73 (55)	
Lack of influence at work	Low	88 (54)	76 (46)	**0.031**	**Insecurity over employment**	Low	89 (55)	72 (45)	**0.006**
	high	52 (41)	75 (59)			high	50 (39)	78 (61)	
Lack of possibilities for development	low	80 (51)	76 (49)	0.292	**Insecurity over working conditions**	low	76 (58)	56 (42)	**0.002**
	high	59 (45)	72 (55)			high	61 (39)	94 (61)	
Lack of freedom at work	Low	92 (55)	75 (45)	**0.008**	**Work-life conflict**	Low	102 (59)	71 (41)	**0.000**
	High	47 (39)	73 (61)			High	37 (32)	78 (68)	
Meaninglessness of work	Low	104 (57)	80 (43)	**0.000**	**Lack of trust**	Low	96 (52)	87 (48)	0.051
	High	35 (34)	68 (66)			High	43 (41)	63 (59)	
Lack of commitment to the workplace	Low	84 (62)	52 (38)	**0.000**	**Lack of organisational justice and respect**	Low	82 (55)	67 (45)	**0.012**
	High	55 (37)	95 (63)			High	56 (40)	83 (60)	
Lack of predictability	Low	101 (57)	77 (43)	**0.000**	**Lack of job satisfaction**	Low	79 (63)	47 (37)	**0.000**
	High	38 (35)	71 (65)			High	59 (36)	103 (64)	
Lack of recognition	Low	90 (53)	81 (47)	0.084	**Burnout**	Low	111 (66)	57 (34)	**0.000**
	High	49 (42)	67 (58)			High	27 (23)	93 (77)	
Lack of role-clarity	Low	96 (55)	78 (45)	**0.005**					
	High	44 (38)	71 (62)						

*p<0.05, **p<0.01, ***p<0.00; Row percentages are used in the table
NS: Not significant, COPSOQ-TR: Türkiye Copenhagen psychosocial questionnaire

Table 5: Last step results of logistic regression analysis on the effect of some characteristics of participants and COPSOQ-TR dimensions on mental health status			
Characteristics	**OR**	**95% CI**	**p-value**
Occupational group			**0,005**
Nurse (ref: dentist)	0.28	0.07-1.08	0,064
Health technician (ref: dentist)	3.14	0.77-12.81	0,111
Non-healthcare professional (ref: dentist)	0.37	0.17-0.83	**0,015**
Availability of access to sufficient and appropriate PPE No (ref: yes)	2.05	1.02-4.12	**0,044**
Fear of getting COVID-19 No (ref: yes)	0.55	0.29-1.03	0,063
Reduced social interaction due to measures requiring physical distancing No (ref: yes)	1.92	0.99-3.73	0,053
Quantitative demands High risk (ref: low risk)	1.81	0.92-3.55	0,087
Lack of commitment to the workplace High risk (ref: low risk)	1.88	0.95-3.70	0,068
Lack of predictability High risk (ref: low risk)	3.16	1.41-7.08	**0,005**
Role conflicts High risk (ref: low risk)	0.53	0.25-1.09	0,082
Lack of job satisfaction High risk (ref: low risk)	1.84	0.92-3.65	0,083
Burnout High risk (ref: low risk)	7.15	3.60-14.19	**0,000**

*p<0.05, **p<0.01, ***p<0.001
COPSOQ-TR: Türkiye Copenhagen psychosocial questionnaire, COVID-19: Coronavirus disease-2019, PPE: Personal protective equipment, Ref: Reference, CI: Confidence interval, NS: Not significant, OR: Odds ratio, NS: Not significant

and have the opportunity to work flexibly/remotely, and they are thought to have less contact with their colleagues. The risk of role conflicts for dentists and academic staff in academic units is higher than other professions and task groups. This finding may be due to their low seniority as the majority of the relevant groups are research assistants, their specialist training in addition to clinical work, and the responsibilities imposed by the pandemic.

While the risk of burnout in the results theme was found to be significantly higher in academic staff in academic units, findings in previous studies are diverse (34-36). This may be due to the fact that this group is more likely to be a healthcare member than the comparison groups.

The mental health status of participants with high psychosocial risk is significantly poor in most dimensions of the themes of demands, interpersonal relations and leadership, and in all dimensions of the themes of impact and development, other parameters and results. Our findings are consistent with previous studies conducted in healthcare workers (34,37-40).

Being a dentist, lack of access to adequate and appropriate PPE, lack of predictability and high risk of burnout increase the likelihood of poor mental health. In a study conducted among nurses, the likelihood of poor mental health was increased by a high risk of burnout, similar to our study, and by a high risk of cognitive demands, lack of social support from colleagues, and insecurity over working conditions (37). Although the findings in previous studies are diverse, it is noteworthy that, unlike our study, the mental health status of healthcare workers other than physicians/dentists is worse (30,41-43). In one study, the mental health status of healthcare workers who reported not being provided with adequate PPE was worse, consistent with our research (34).

Study Limitations

Since our study is cross-sectional, the cause-effect relationships between the variables are not strong.

Our results represent the employees of the dentistry faculty where the research was conducted and cannot be generalized to the society.

Although the employees were informed that personal information would be kept confidential, no connection would be established between personal information and individuals through the data, and that they would not encounter any negative situations, many participants did not want to specify the units they worked in detail; therefore, detailed unit analysis could not be conducted.

Conclusion

As a result, in order to manage psychosocial risks that may have significant consequences in terms of both worker health and safety and work efficiency, infrastructure should be prepared in workplaces with the participation of all parties, within the framework of a positive occupational health and safety culture, and practices should be continuous. The resilience of the workforce should be improved, uncertainties should be avoided, and effective teamwork should be carried out. It is thought that the number of studies examining psychosocial risks and mental health in dental assistant health personnel is insufficient, and studies should be planned to include all professional groups working in this field.

Ethics

Ethics Committee Approval: The ethical approval was obtained from Ankara University Rectorate Ethics Committee (approval no.: 18/198, date: 22.11.2021).

Informed Consent: Informed consent of the employees was obtained.

Footnotes

Authorship Contributions

Concept: B.A., M.E.O., Design: B.A., M.E.O., Data Collection and/or Processing: B.A., Analysis and/or Interpretation: B.A., M.E.O., Literature Search: B.A., Writing: B.A.

Conflict of Interest: There is no potential conflict of interest to declare.

Financial Disclosure: This study received no financial support.

References

1. Sahan C, Demiral Y. In: Copenhagen psychosocial risk assessment guideline. Sahan C, Demiral Y, editors. Psychosocial Risk Assessment at Work. 1st ed. İzmir: Occupational Hygienists Association (İHİDER); 2020. p.3-31.
2. Metzler YA, von Groeling-Müller G, Bellingrath S. Better safe than sorry: methods for risk assessment of psychosocial hazards. Saf Sci. 2019;114:122-139.
3. Vatansever C. A new dimension in risk assessment: psychosocial hazards and risks. Work Soc. 2014;40:117-138.
4. Leka S, Jain A. World Health Organization Health impact of psychosocial hazards at work: an overview.WHO; 2010: 4-89.
5. Eurofound and EU-OSHA. Psychosocial risks in Europe: prevalence and strategies for prevention. Publications Office of the European Union. Luxembourg. 2014:6.
6. Rada RE, Johnson-Leong C. Stress, burnout, anxiety and depression among dentists. J Am Dent Assoc. 2004;135:788-794.
7. Lee C-Y, Wu J-H, Du J-K. Work stress and occupational burnout among dental staff in a medical center. J Dent Sci. 2019;14:295-301.
8. WHO. Coronavirus disease (COVID-19) pandemic [Internet]. [Retrieved on 2024]. Available from: https://www.who.int/europe/emergencies/situations/covid-19
9. Mekhemar M, Attia S, Dörfer C, et al. Dental nurses' mental health in Germany: a nationwide survey during the COVID-19 pandemic. Int J Environ Res Public Health. 2021;18:8108.
10. Vergara-Buenaventura A, Chavez-Tuñon M, Castro-Ruiz C. The mental health consequences of Coronavirus Disease 2019 pandemic in dentistry. Disaster Med Public Health Prep. 2020;14:e31-34.
11. Derruau S, Bouchet J, Nassif A, et al. COVID-19 and dentistry in 72 questions: an overview of the literature. J Clin Med. 2021;10:779.
12. Cox T, Griffiths A, Stavroula L. Work organization and work-related stress. In: Gardiner K, Harrington JM, editors. Occupational Hygiene. 3rd ed. Wiley Online Library; 2005. p. 421-432.
13. World Health Organization. PRIMA-EF : guidance on the European framework for psychosocial risk management : a resource for employer and worker representatives. 2008. https://iris.who.int/handle/10665/43966
14. Osborne D, Croucher R. Levels of burnout in general dental practitioners in the south-east of England. Br Dent J. 1994;177:372-377.
15. Slabšinskienė E, Gorelik A, Kavaliauskienė A, et al. Burnout and ıts relationship with demographic and job-related variables among dentists in lithuania: a cross-sectional study. Int J Environ Res Public Health. 2021;18:3968.
16. Jin M-U, Jeong S-H, Kim E-K, et al. Burnout and its related factors in Korean dentists. Int Dent J. 2015;65:22-31.
17. Mekhemar M, Attia S, Dörfer C, et al. The psychological impact of the COVID-19 pandemic on dentists in Germany. J Clin Med. 2021;10:1008.
18. Sarialioglu Gungor A, Donmez N, Uslu YS. Knowledge, stress levels, and clinical practice modifications of Turkish dentists due to COVID-19: a survey study. Braz Oral Res. 2021;35:1-12.
19. COPSOQ Network. COPSOQ ınternational network [Internet]. [Retrieved on January 23, 2023]. Available from: https://www.copsoq-network.org/
20. Sahan C, Baydur H, Demiral Y. A novel version of Copenhagen psychosocial questionnaire-3: Turkish validation study. Arch Environ Occup Health. 2019;74:297-309.
21. Sahan C. Adaptation of the Copenhagen psychosocial risk assessment scale into Turkish (Public Health Master's Thesis). İzmir, Türkiye. Dokuz Eylul University Institute of Health Sciences. 2016.
22. Kilic C. General health questionnaire: reliability and validity study. Turkish J Psychiatry. 1996;7:3-9.
23. Liang Y, Wang L, Yin X. The factor structure of the 12-item general health questionnaire (GHQ-12) in young Chinese civil servants. Health Qual Life Outcomes. 2016;14:136.
24. Hayran M, Hayran M. Basic statistics for health research second edition. Omega Research Education Consultancy Limited Company; 2018; p.8-363.
25. Field A. Discovering statistics using IBM SPSS statistics. SAGE Publications Ltd; 4th edition. 2013;293-814.
26. Sato TD, de Faria BS, Albuquerque BB, et al. Poor health conditions among brazilian healthcare workers: the study design and baseline characteristics of the HEROES cohort. Healthcare (Basel). 2022;10:1-12.
27. Gouveia PA, Lopes D, Henriques AR, et al. Psychosocial risks among the healthcare workforce working in COVID services: findings from a cross-sectional study on psychosocial risks. Eur Psychiatry. 2022;65:253-254.
28. Bozdag F, Kurt AO, Bugdayci BN, et al. Evaluation of psychosocial risks of employees of a university hospital. In: 3 International 21 National Public Health Congress; 26-30 November, 2019; Antalya, Türkiye. Ankara; HASUDER. p.454-460.
29. Berthelsen H, Westerlund H, Hakanen JJ, et al. It is not just about occupation, but also about where you work. Community Dent Oral Epidemiol. 2017;45:372-379.
30. Gorter RC, Freeman R. Burnout and engagement in relation with job demands and resources among dental staff in Northern Ireland. Community Dent Oral Epidemiol. 2011;39:87-95.

31. Karatuna I, Owen M, Westerlund H, et al. The role of staff-assessed care quality in the relationship between job demands and stress in human service work: the example of dentistry. Int J Environ Res Public Health. 2022;19:12795.
32. Wagner A, Rieger MA, Manser T, et al. Healthcare professionals' perspectives on working conditions, leadership, and safety climate: a cross-sectional study. BMC Health Serv Res. 2019;19:53.
33. Koch P, Zilezinski M, Schulte K, et al. How perceived quality of care and job satisfaction are associated with ıntention to leave the profession in young nurses and physicians. Int J Environ Res Public Health. 2020;17:2714.
34. Turkili S, Aslan E, Tot S. Examination of difficulties, anxiety, depression and burnout syndrome among healthcare professionals in Türkiye due to the coronavirus outbreak. Mersin Univ J Heal Sci. 2022;15:74-87.
35. Chang HE, Cho S-H. The ınfluence of social support on the relationship between emotional demands and health of hospital nurses: a cross-sectional study. Healthcare (Basel). 2021;9:115.
36. Ozaydın O, Vural A, Balcı N, et al. Job satisfaction of healthcare workers during the COVID-19 epidemic. Gumushane Univ J Heal Sci. 2022;11:54-62.
37. Birdane G. Examining the psychosocial risks of nursing staff in a university hospital using the Copenhagen psychosocial risk assessment questionnaire and its relationship with mental well-being. (PhD Thesis). Ankara, Türkiye. Hacettepe University Institute of Health. 2022.
38. Freimann T, Merisalu E. Work-related psychosocial risk factors and mental health problems amongst nurses at a university hospital in Estonia: a cross-sectional study. Scand J Public Health. 2015;43:447-452.
39. Malinauskienė V, Leišytė P, Malinauskas R. Psychosocial job characteristics, social support, and sense of coherence as determinants of mental health among nurses. Medicina (Kaunas). 2009;45:910-917.
40. Puriene A, Aleksejuniene J, Petrauskiene J, et al. Self-perceived mental health and job satisfaction among lithuanian dentists. Ind Health. 2008;46:247-252.
41. Tunc S, Kose S. The frequency and determining factors of psychiatric symptoms in healthcare professionals. Psychiatry Behav Sci. 2019;9:94-101.
42. Bettinsoli ML, Di Riso D, Napier JL, et al. Mental health conditions of ıtalian healthcare professionals during the COVID-19 disease outbreak. Appl Psychol Heal Well-Being. 2020;12:1054-1573.
43. Eldridge LA, Estrich CG, Gurenlian JR, et al. US dental health care workers' mental health during the COVID-19 pandemic. J Am Dent Assoc. 2022;153:740-749.

CASE REPORT / OLGU SUNUMU

DOI: 10.4274/atfm.galenos.2025.46704
J Ankara Univ Fac Med 2025;78(2):154-156

SURGICAL MEDICAL SCIENCES / CERRAHİ TIP BİLİMLERİ

Incidental Detection of Congenital Cystic Adenomatoid Malformation After Thoracoscopic Repair of Diaphragmatic Hernia

Torakoskopik Diyafram Hernisi Onarımı Sonrası Rastlantısal Konjenital Kistik Adenomatoid Malformasyonun Saptanması

Denizcan İnal[1], Kutay Bahadır[2], Pari Khalilova[1], Ergun Ergün[1], Ufuk Ateş[1]

[1]Ankara University Faculty of Medicine, Department of Pediatric Surgery, Ankara, Türkiye
[2]Akdeniz University Faculty of Medicine, Department of Pediatric Surgery, Antalya, Türkiye

Abstract

Congenital pulmonary airway malformation (CPAM) is a rare benign lung lesion, and CPAM combined with congenital diaphragmatic hernia (CDH) is extremely rare. The patient being described was a neonatal boy with a left-sided CDH diagnosed after birth. Thoracoscopic repair was performed on the first postnatal day. On chest X-ray, a suspicious lesion in terms of recurrence was observed after the postoperative follow-up period. Type 2 CPAM was diagnosed based on computed tomography. The child is doing well on postoperative period and the lesion stays stable without any intervention. Congenital lung lesions with CDH are difficult to diagnose before the CDH repair. Although very rare, congenital lung lesions concurrent with CDH should be considered when managing these patients.

Keywords: Cystic adenomatoid malformation of lung, congenital, pulmonary surgical procedures, newborns, surgery, thoracoscopic

Öz

Konjenital pulmoner hava yolu malformasyonu (CPAM) nadir görülen benign bir akciğer lezyonudur ve konjenital diyafragma hernisi (KDH) ile birlikte CPAM oldukça nadirdir. Doğum sonrası sol taraflı konjenital diyafragma hernisi KDH tanısı alan yenidoğan erkek bir olgu sunulmuştur. Doğum sonrası birinci günde torakoskopik onarım yapıldı. Ameliyat sonrası takiplerinde çekilen akciğer grafisinde nüks açısından şüpheli lezyon görüldü. Tip 2 CPAM tanısı bilgisayarlı tomografi ile konuldu. Ameliyat sonrası dönemde çocuğun genel durumu iyi olup, lezyon herhangi bir müdahaleye gerek kalmadan stabil takip ediliyor. KDH ile birliktelik gösteren konjenital akciğer lezyonlarının KDH onarımından önce teşhis edilmesi zordur. Bu hastaların tedavisinde KDH ile birlikte nadir görülen konjenital akciğer lezyonları da göz önünde bulundurulmalıdır.

Anahtar Kelimeler: Akciğerin kistik adenomatoid malformasyonu, konjenital, akciğer cerrahisi işlemleri, yenidoğanlar, ameliyat, torakoskopik

Introduction

There are several theories explaining the development of pulmonary hypoplasia. Most accepted theory is that pulmonary hypoplasia occurs due to the mass effect of abdominal contents present in the thorax during lung development (1).

Structural defects with respiratory abnormalities which include congenital lung lesions such as congenital pulmonary airway malformation (CPAM) and bronchopulmonary sequestration (BPS) are rarely seen concurrent with congenital diaphragmatic hernia (CDH) (2). The presentation of an additional airway malformation rises concerns of morbidity with varying degrees of respiratory distress. There are also

Address for Correspondence/Yazışma Adresi: Assoc. Prof. Ergun Ergün
Ankara University Faculty of Medicine, Department of Pediatric Surgery, Ankara, Türkiye
E-mail: drergunergun@gmail.com **ORCID ID:** orcid.org/0000-0001-8806-4022
Received/Geliş Tarihi: 13.01.2024 **Accepted/Kabul Tarihi:** 06.01.2025 **Epub:** 02.05.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025
Cite this article as/Atıf: İnal D, Bahadır K, Khalilova P, et al. Incidental detection of congenital cystic adenomatoid malformation after thoracoscopic repair of diaphragmatic hernia. J Ankara Univ Fac Med. 2025;78(2):154-156

studies demonstrating no difference in the outcome of CDH patients with concurrent congenital lung lesions (3). However, there is no specific data about the prognosis of CDH and CPAM.

The aim of this study is to present a child who has CDH with concurrent CPAM.

Case Presentation

Informed consent was obtained from the parents. A male newborn was born through cesarean section at the 39th week to a 27-year-old mother who was prenatally followed by an obstetrics and gynecology specialist. He had an apgar score of 6/8 at birth and developed respiratory distress in delivery room. The newborn was admitted to neonatal intensive care unit and nasal intermittent positive pressure ventilation was initiated. Arterial blood gas was evaluated to show normal results (power of hydrogen pH:: 7.34, pressure of carbon dioxide pCO_2: 39.8, lactate: 1.2). A chest X-ray was taken due to respiratory distress (Figure 1). Even though CDH was not prenatally diagnosed, signs of CDH were presented on the X-ray and the patient was rapidly intubated. Thorax ultrasound (US) imaging showed that the intestines and the colon was partially located in the left hemithorax. Echocardiography of the newborn revealed patent ductus arteriosus and pulmonary hypertension. Abdominal and urinary US of the newborn revealed no other anomalies. On the first postnatal day, thoracoscopic diaphragmatic hernia repair was performed. After the operation the newborn was stayed on mechanical ventilation and extubated on 3rd day of operation. The baby did not require any oxygen or respiratory support afterwards. In the first postoperative day, chest X-ray revealed a suspicious lesion (there is a multiloculated cystic lesion which was thought to be recurrent diaphragmatic hernia) in terms of recurrence was observed while the patient was clinically asymptomatic without any need for oxygen support (Figure 2). Distal colon imaging was performed which showed no recurrence. Thorax computed tomography (CT) was performed, and a suspicious cystic lesion was seen to be compatible with type 2 CPAM (Figure 3). The patient was referred to pediatric pulmonologist for follow-up.

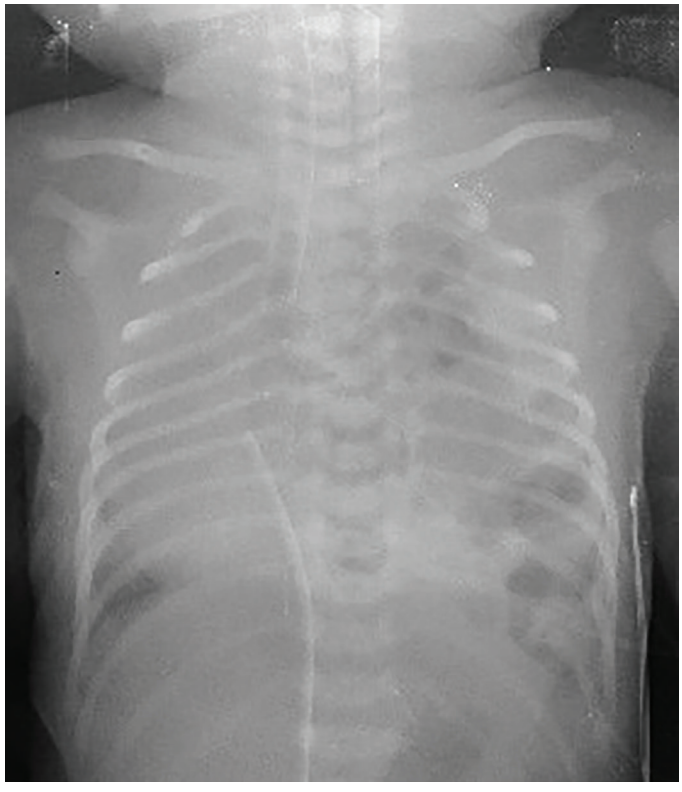

Figure 1: Chest X-ray which demonstrates congenital diaphragmatic hernia on the left side. Right hemithorax looks radiopaque possibly due to mediastinal shift

Discussion

We report a rare case of CPAM concurrent with CDH which is diagnosed after thoracoscopic CDH repair. Postoperative chest X-ray showed a lesion suspicious of bowel on the left hemithorax, which supported recurrence of CDH. CT was performed to reveal there was no recurrence but type 2 CPAM in the left lower lobe of the newborn was presented.

CDH is a life threating pathology in newborns and a cause of death due to pulmonary hypoplasia and pulmonary hypertension (4). On the other hand, CPAM has lower mortality but it is a potential cause of infection and malignancy (5). CDH is a major congenital anomaly caused by failure of closure of the pleuroperitoneal cavity by the fusion of septum transversum and pleuroperitoneal folds (2). In cases of pulmonary sequestration concurrence, it is hypothesized that the formation of sequestration during the embryonic period

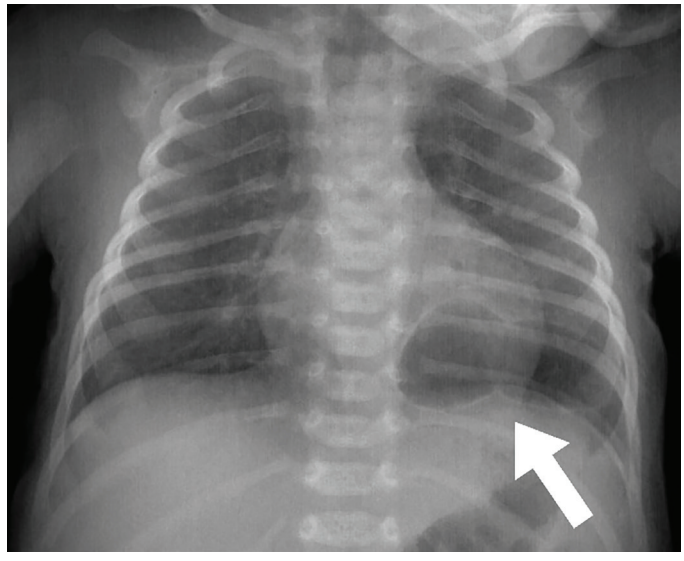

Figure 2: Chest X-ray shows suspicious lesion (there is a multiloculated cystic lesion which was thought to be recurrent diaphragmatic hernia) in the left lower zone

may interfere mechanically with the fusion of the lungs and the diaphragm (3).

In the literature, congenital lung lesions associated with CDH are rarely described and the exact incidence of these lesions concurrent with CDH is uncertain (2). Case series showed that the incidence of BPS with CDH are between 15 and 30% (4). Savic et al. (6) showed that the incidence of CDH with BPS were 3% and 27%. On the other hand, Soni et al. (4) showed that incidence of both CPAM and BPS with CDH was 7.2%. However, CPAM concurrent with CDH are reported very rarely.

CPAM is characterized by hamartomatous lesions of the lungs classified by the size of the cysts (7). Stocker's classification groups CPAM into three groups according to cyst size. Type 1 is the most common and has macrocystis larger than 2 cm. Type 2 which is associated with other congenital anomalies, has multiple cysts smaller than 2 cm. Type 3 has cysts smaller than 0.5 cm and includes solid components (7). In this case, type 2 CPAM was reported on CT following the operation for CDH. When CPAM appears as a single, localized, solid or cyst like lesion, it may be difficult to differentiate it from bronchogenic cysts, bronchial atresia and pulmonary sequestration (8).

The incidence rate of 5-65% for recurrence after CDH repair is reported in literature (9). The postoperative chest X-ray was suspicious of recurrence thus, a CT was performed to confirm diagnosis. CT showed two pulmonary cysts less than 2 cm in the left lower lobe, which was concordant with the lesion on the chest X-ray (Figure 3).

Surgery is a preferred method of treatment for symptomatic CPAM, but postnatal management of asymptomatic lesions are controversial (10). In the literature, some authors argue that early and elective thoracoscopic surgery prevent infective complications (11). By contrast, some authors argue that surgery is chosen based on patient according to the onset of symptoms (10).

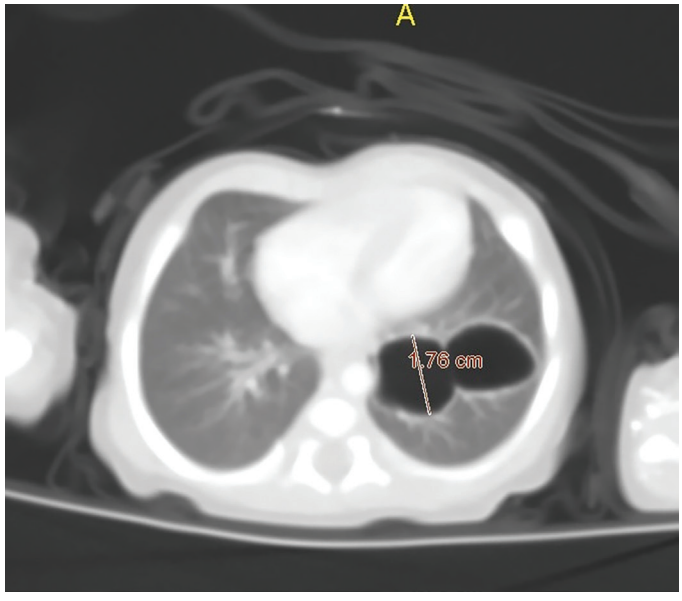

Figure 3: Axial CT scan of chest demonstrates a left lower lobe lesion with two cysts

CT: computed tomography

Congenital lung lesions with CDH are difficult to diagnose before the CDH repair. However, observations on the development of the lungs can be made by surgeons during the CDH repair. Although very rare, congenital lung lesions concurrent with CDH should be considered when managing these patients.

Ethics

Informed Consent: Informed consent was obtained from the parents.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.İ., P.K., E.E., U.A., Concept: D.İ., K.B., P.K., E.E., Design: D.İ., K.B., E.E., Data Collection or Processing: D.İ., E.E., U.A., Literature Search: D.İ., K.B., E.E., U.A., Writing: D.İ., K.B., P.K., E.E.

Conflict of Interest: The authors declare no conflict of interest.

Financial Disclosure: No financial assistance was received to support this study.

References

1. Dingeldein M. Congenital diaphragmatic hernia: management & outcomes. Adv Pediatr. 2018;65:241-247.
2. Kosiński P, Wielgoś M. Congenital diaphragmatic hernia: pathogenesis, prenatal diagnosis and management-literature review. Ginekol Pol. 2017;88:24-30.
3. Grethel EJ, Farrell J, Ball RH, et al. Does congenital diaphragmatic hernia associated with bronchopulmonary sequestration portend a better prognosis? Fetal Diagn Ther. 2008;23:250-253.
4. Soni S, Moldenhauer JS, Rintoul N, et al. Perinatal outcomes in fetuses prenatally diagnosed with congenital diaphragmatic hernia and concomitant lung lesions: A 10-year review. Fetal Diagn Ther. 2020;47:630-635.
5. Wagner R, Li H, Ayoub L, et al. Epithelial cell-adhesion protein cadherin 26 is dysregulated in congenital diaphragmatic hernia and congenital pulmonary airway malformation. Pediatr Surg Int. 2021;37:49-57.
6. Savic B, Birtel FJ, Tholen W, et al. Lung sequestration: report of seven cases and review of 540 published cases. Thorax. 1979;34:96-101.
7. Sintim-Damoa A, Cohen HL. Fetal imaging of congenital lung lesions with postnatal correlation. Pediatr Radiol. 2022;52:1921-1934.
8. Aljarad B, Alkhayer I, Alturk A, et al. A rare case of congenital pulmonary airway malformation in a 14-year-old male presenting with spontaneous pneumothorax. Ann Med Surg (Lond). 2021;68:102692.
9. Macchini F, Raffaeli G, Amodeo I, et al. Recurrence of congenital diaphragmatic hernia: risk factors, management, and future perspectives. Front Pediatr. 2022;10:823180.
10. Leblanc C, Baron M, Desselas E, et al. Congenital pulmonary airway malformations: state-of-the-art review for pediatrician's use. Eur J Pediatr. 2017;176:1559-1571.
11. Parikh DH, Rasiah SV. Congenital lung lesions: postnatal management and outcome. Semin Pediatr Surg. 2015;24:160-167.

CASE REPORT / OLGU SUNUMU

DOI: 10.4274/atfm.galenos.2025.85579
J Ankara Univ Fac Med 2025;78(2):157-160

MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

SARS-CoV-2 and *Mycobacterium Fortuitum* Coinfection: A Case Report

SARS-CoV-2 ve *Mycobacterium Fortuitum* Koenfeksiyonu: Olgu Sunumu

Tazegül Gül[1], Hatice Maraş[2], Özgür Demir[1], Ezgi Gülten[1], Güle Çınar[1], İrem Akdemir[1], Elif Mukime Sarıcaoğlu[1], Ebru Us[3], Mehmet Serhat Birengel[1]

[1]*Ankara University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Türkiye*
[2]*Ankara University Faculty of Medicine, Ankara, Türkiye*
[3]*Ankara University Faculty of Medicine, Department of Medical Microbiology, Ankara, Türkiye*

Abstract

Coronavirus disease-2019 (COVID-19) pandemic caused millions of people to become infected and had resulted several deaths. After initial resolution, in cases of clinical deterioration, it is essential to consider the possibility of coinfections. Non-tuberculous mycobacteria infections are rare and often overlooked. In this report, we present a severe acute respiratory syndrome-Coronavirus-2 and *Mycobacterium fortuitum* coinfected patient. Our intention is to bring attention to the possibility of such coinfection without a known history of any lung diseases or immunosuppression other than COVID-19 and thus, broadening the clinical thinking process of physicians.

Keywords: SARS-CoV-2, non-tuberculous mycobacteria, COVID-19

Öz

Koronavirüs hastalığı-2019 (COVID-19) pandemisi milyonlarca insanın enfekte olmasına ve çok sayıda ölüme neden olmuştur. Başlangıçtaki iyileşme döneminin ardından klinik kötüleşme olması halinde koenfeksiyon olasılığını düşünmek gerekmektedir. Tüberküloz dışı mikobakteri enfeksiyonları nadir olup sıklıkla gözden kaçırılmaktadır. Bu yazıda şiddetli akut solunum sendromu-Koronavirüs-2 ve *Mycobacterium fortuitum* koenfeksiyonu olan bir hasta sunmaktayız. Amacımız, eşlik eden akciğer hastalığı ve COVID-19 dışında immünosüpresyon öyküsü bulunmadığında da bu koenfeksiyonun gelişebileceğine dikkat çekmek ve hekimlerin klinik yaklaşımına katkı sağlamaktır.

Anahtar Kelimeler: SARS-CoV-2, tüberküloz dışı mikobakteri, COVID-19

Introduction

There are nearly 200 species of non-tuberculous mycobacteria (NTM), most of which live in soil and water in rural and urban areas (1). Almost half have been associated with opportunistic infections in animals and humans, causing sporadic outbreaks (1). NTM is acquired through exposure to water, aerosols, soil and dust via inhalation, ingestion, cracks due to skin injuries, surgical procedures, or catheterization (1). Almost all patients with NTM pulmonary disease have chronic or recurring cough. Other symptoms include sputum, fatigue, malaise, dyspnea, fever, hemoptysis, chest pain, and weight loss (1). Both 2020 "Treatment of Non-tuberculous Mycobacterial Pulmonary Disease" clinical practice guideline and expert panel group for management recommendations in NTM pulmonary diseases recommend using clinical (pulmonary symptoms, and

Address for Correspondence/Yazışma Adresi: Ezgi Gülten, Ankara University Faculty of Medicine, Department of Infectious Diseases and Clinical Microbiology, Ankara, Türkiye
E-mail: ezgioztop@gmail.com **ORCID ID:** orcid.org/0000-0003-0248-7716
Received/Geliş Tarihi: 12.02.2025 **Accepted/Kabul Tarihi:** 19.04.2025 **Epub:** 30.05.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025

Cite this article as/Atıf: Gül T, Maraş H, Demir Ö, et al. SARS-CoV-2 and *mycobacterium fortuitum* coinfection: a case report. J Ankara Univ Fac Med. 2025;78(2):157-160

***This case report was presented as an oral presentation during the Turkish Society of Clinical Microbiology and Infectious Diseases COVID-19 Symposium (10-12 September, 2021, İstanbul).**

exclusion of other diagnoses), radiographical (nodular or cavitary opacities on chest radiograph, or an high resolution computed tomography (CT) scan that shows multifocal bronchiectasis with multiple small nodules), and microbiological (positive cultures from at least two separate expectorated sputum samples, or one positive culture from bronchial lavage or biopsy) criteria for diagnosis (2,3).

A recent review assessing the prevalence of bacterial coinfection in Coronavirus disease-2019 (COVID-19) patients showed that the coinfection rate was between 2.5-5.1% (4). Although there are only a few studies dedicated to NTM coinfections, one case report stated a *Mycobacterium abscessus* and severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) coinfection in a patient with underlying multiple myeloma (5).

In this report, we present a SARS-CoV-2 and *Mycobacterium fortuitum* coinfected patient without a known history of any lung diseases or immunosuppression other than COVID-19.

Case Presentation

A 44-year-old male patient with hypertension presented with fever, cough, and shortness of breath. The patient's SARS-CoV-2 reverse transcriptase polymerase chain reaction (PCR) test was positive and he was on fifth day of treatment with favipiravir and acetylsalicylic acid. The physical examination showed body temperature of 36.3 °C, heart rate of 92/min, arterial blood pressure of 120/70 mmHg, oxygen saturation of 95% in room air by pulse oximeter and bilateral diffuse rales. The initial laboratory findings were as follows: leukocytes $5150x10^6$/L, neutrophil $4070x10^6$/L, lymphocyte $720x10^6$/L, platelet $153x10^9$/L, lactate dehydrogenase 344 U/L, D-dimer 1375 ng/mL, fibrinogen 3.27 g/L, ferritin 1585 ng/mL, C-reactive protein 71mg/L, procalcitonin 0.218 ng/mL. CT pulmonary angiogram showed diffuse multilobed, multifocal, predominantly peripherally located, ground glass consolidations with approximately 25-50% of lung parenchyma being affected (Figure 1).

The patient was admitted to COVID-19 ward and the treatment was rearranged as favipiravir 2x600 mg tb, enoxaparin 2x0.4 cc sc and acetylsalicylic acid 1x100 mg tb. During his 2nd day at the ward, methylprednisolone 1x80 mg IV was started upon the need for 2 Lt/min nasal oxygen support. Due to onset of fever (38.3 °C), increase of cough, new sputum complaints and significant rise in D-dimer levels (9767 ng/mL), CT pulmonary angiogram was repeated on 6th day of follow-up. The result revealed significant progression with approximately 50-75% of the lung parenchyma being affected (Figure 2). Accompanying laboratory results are summarized in Table 1. Antimicrobial therapy was initiated: meropenem 3x1 gr IV and tygecycline 2x50 mg IV following 1x100 mg IV loading dose. No growth in blood and urine culture was detected. Serum cytomegalovirus PCR, Galactomannan and *Aspergillus* spp. PCR, and sputum *Pneumocystis jirovecii* PCR were negative, as well. Evaluation of the gram-stained sputum smear under ×100 magnification revealed <10 epithelial cells and >25

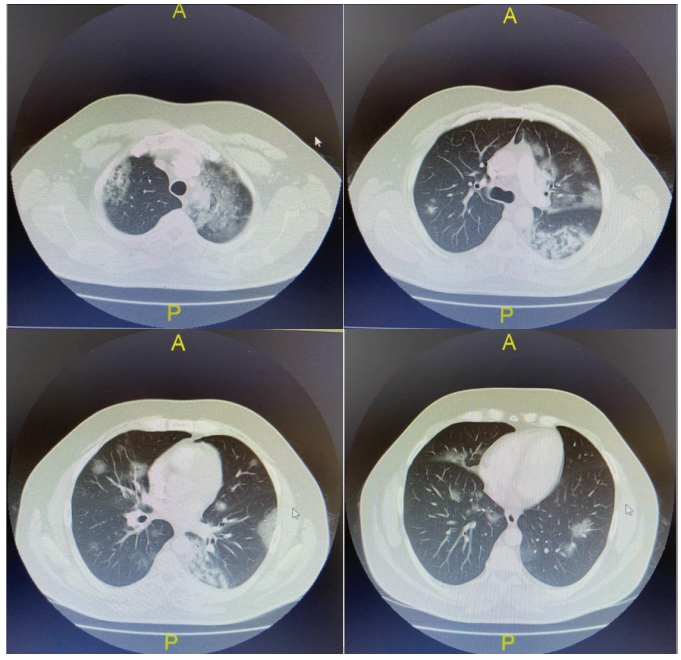

Figure 1: Initial computed tomography pulmonary angiogram: diffuse multilobed, multifocal, predominantly peripherally located, ground glass consolidations with approximately 25-50% of lung parenchyma being affected

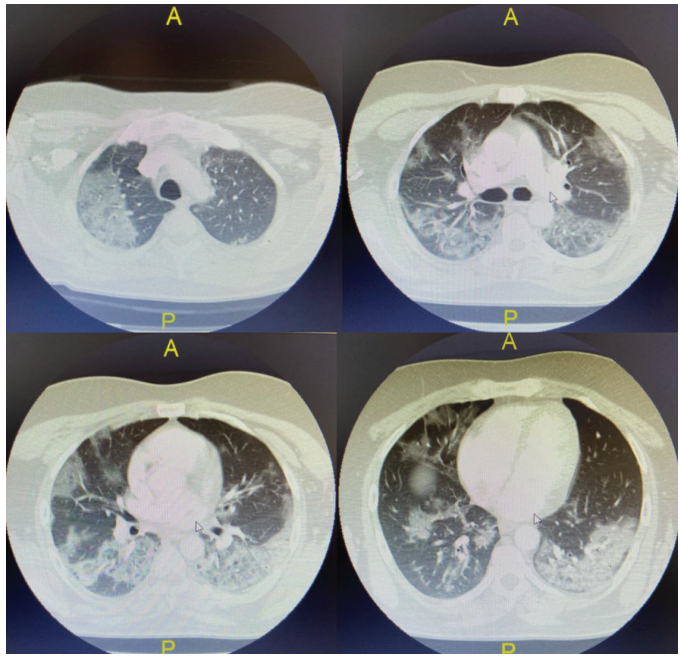

Figure 2: Repeated computed tomography pulmonary angiogram on 6th day of follow-up: Significant progression with approximately 50-75% of the lung parenchyma being affected

Table 1: Patient's laboratory results during follow-up

	Admission day	6th day of follow-up	Discharge day	End of *Mycobacterium fortuitum* treatment
Leukocytes (nx10^6/L)	5150	11150	13070	5820
Neutrophil (nx10^6/L)	4070	8190	6390	2630
Lymphocyte (nx10^6/L)	720	1230	2820	2190
Platelet (nx10^9/L)	153	238	293	293
Lactate dehydrogenase (U/L)	344	528	350	201
D-dimer (ng/mL)	1375	9767	196	Not available
Fibrinogen (g/L)	3.27	3.87	2.79	Not available
Ferritin (ng/mL)	1585	1453	625	Not available
C-reactive protein (mg/L)	71	91.2	5.1	2.5
Procalcitonin (ng/mL)	0.22	1.20	0.10	0.08

polymorphonuclear leukocytes per field, but no microorganisms were detected. Routine sputum culture showed no microbial growth after 24 hours of incubation at 35 °C on blood agar, eosin methylene blue agar, and chocolate agar. While sputum Erlich Ziehl Neelsen stain was negative, NTM were grown in mycobacteria culture medium on the 7th day of incubation. On the 16th day of in-hospital follow-up, the patient was discharged with the treatment plan as clarithromycin, rifampicin, and ethambutol and frequent follow-up appointments. The bacteria was found to be *Mycobacterium fortuitum* which was resistant to clarithromycin, ciprofloxacin and doxycycline and sensitive to moxifloxacin, amikacin and linezolid. Clarithromycin was displaced by moxifloxacin in treatment regimen. Upon clinical improvement, triple regimen was administered for six months till two consequtive sputum samples were negative for NTM.

Discussion

Mycobacterium fortuitum has been previously identified as the causative microorganism of skin and soft tissue infections, including post-surgery or post-traumatic nosocomial infections via comtaminated medical devices in immunocompetent patients (6,7). Although *Mycobacterium fortuitum* was associated with serious and life-threatening infections in immunocomprised patients before, there are also a few case reports defining pulmonary involvement in otherwise healthy patients, as well (8-10). While there are several reports indicating a rise in NTM infections in recent years, to the best ouf our knowledge there are no reports describing a pulmonary NTM involvement in a COVID-19 patient without any underlying pulmonary diseases (11).

Mycobacterium fortuitum is a common microorganism of environment and surfaces. Therefore, as mentioned in previous sections, it requires at least two positive cultures to conclude a patient with a diagnosis of pulmonary *Mycobacterium fortuitum* infection. In the presented case, although treatment was initiated before the growth of *Mycobacterium fortuitum* in the second sputum sample, the improvement in clinical symptoms following therapy and the growth of *Mycobacterium fortuitum* following sputum cultures strongly suggest the definitive diagnosis.

The identification of NTM at the species level is clinically important because treatment and response rates vary depending on different subtypes (12). Anti-microbial susceptibility testing breakpoints to guide the management of rapidly growing mycobacteria infections have been recently established and updated in "CLSI M24S-ED2: 2023 Performance Standards for Susceptibility Testing of Mycobacteria, *Nocardia* spp., and Other Aerobic Actinomycetes, 2nd edition" (13). In light of the current literature, it is suggested to treat NTM infections with more than one antimicrobial for a prolonged duration (14). Therefore, growing NTM in our patient's sputum sample was sent to Republic of Türkiye, Ministry of Health, General Directorate of Public Health National Tuberculosis Reference Laboratory, and the patient was treated for more than six months with three agents.

The presence of SARS-CoV-2 infection in our case may have caused a defect in the respiratory tract epithelial tissue. We assume that SARS-CoV-2 infection and corticosteroid therapy may also be a facilitating factor for NTM infection in our patient because of generating possible immunosuppression. This assumption needs to be studied further.

Conclusion

In conclusion, with NTM being on the rise and the severity of coinfections in COVID-19, this case report was presented to shed light on this topic and to bring awareness to the possible coinfection of *Mycobacterium fortuitum* and SARS-CoV-2.

Ethics

Informed Consent: Consent was obtained from the patient and his relative.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.G., Ö.D., E.G., G.Ç., İ.A., E.M.S., M.S.B., Concept: H.M., E.G., G.Ç., İ.A., E.M.S., M.S.B., Design: Ö.D., E.G., G.Ç., İ.A., E.M.S., M.S.B., Data Collection and/or Processing: T.G., H.M., Ö.D., E.G., Analysis and/or Interpretation: E.G., H.M., Ö.D., E.G., M.S.B., Literature Search: T.G., H.M., Ö.D., E.G., G.Ç., İ.A., E.M.S., Writing: T.G., H.M., Ö.D., E.G., G.Ç., İ.A., E.M.S., M.S.B.

Conflict of Interest: There is no potential conflict of interest to declare.

Financial Disclosure: This study received no financial support.

References

1. Griffith DE, Aksamit T, Brown-Elliott BA, et al. ATS mycobacterial diseases subcommittee; American Thoracic Society; Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175:367-416.
2. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J. 2020;56:2000535.
3. Lange C, Böttger EC, Cambau E, et al. Expert panel group for management recommendations in non-tuberculous mycobacterial pulmonary diseases. Consensus management recommendations for less common non-tuberculous mycobacterial pulmonary diseases. Lancet Infect Dis. 2022;22:e178-e190.
4. Wu HY, Chang PH, Chen KY, et al. GREAT working group. Coronavirus disease 2019 (COVID-19) associated bacterial coinfection: incidence, diagnosis and treatment. J Microbiol Immunol Infect. 2022;55:985-992.
5. Rodriguez JA, Bonnano C, Khatiwada P, et al. COVID-19 coinfection with Mycobacterium abscessus in a patient with multiple myyeloma. Case Rep Infect Dis. 2021;2021:8840536.
6. Tsai YC, Huang WC, Mao YC, et al. Mycobacterium fortuitum infection from needlefish impalement during diving: a diagnostic challenge. Travel Med Infect Dis. 2021;41:102056.
7. Singh Bhalla G, Grover N, Singh G, et al. Prevalence of non tuberculous mycobacterial infection in surgical site infections and their antibiotic susceptibility profile. Med J Armed Forces India. 2021;77:343-348.
8. Yeap KC, Sivagurunathan PD, Raman P, et al. Non-tuberculous mycobacterial ocular infection masquerading as choroidal tumour - a diagnostic conundrum. GMS Ophthalmol Cases. 2019;9:Doc25.
9. Cong J, Wang C, Ma L, et al. Septicemia and pneumonia due to Mycobacterium fortuitum infection in a patient with extronodal NK/T-cell lymphoma, nasal type: a case report. Medicine (Baltimore). 2017;96:e6800.
10. d'Incau S, Vargas MI, Calmy A, et al. Mycobaterium fortuitum disseminated infection in an immunocompetent patient without predisposing factors. BMJ Case Rep. 2020;13:e235842.
11. Dahl VN, Mølhave M, Fløe A, et al. Global trends of pulmonary infections with non-tuberculous Mycobacteria: a systematic review. Int J Infect Dis. 2022;125:120-131.
12. Kodana M, Tarumoto N, Kawamura T, et al. Utility of the MALDI-TOF MS method to identify non-tuberculous mycobacteria. J Infect Chemother. 2016;22:32-35.
13. CLSI. Performance standards for susceptibility testing of mycobacteria, *Nocardia* spp., and other aerobic actinomycetes. 2nd Edition. CLSI supplement M24S. Clinical and Laboratory Standards Institute; 2023.
14. Siddique N, Roy M, Ahmad S. Mycobacterium fortuitum abscess following breast nipple piercing. IDCases. 202021:e00847.

CASE REPORT / OLGU SUNUMU

DOI: 10.4274/atfm.galenos.2025.70893
J Ankara Univ Fac Med 2025;78(2):161-163

SURGICAL MEDICAL SCIENCES / CERRAHİ TIP BİLİMLERİ

Unusual Presentation of Type 3 Posterior Urethral Valve: A Case Report

Tip 3 PUV'nin Alışılmadık Bir Prezentasyonu: Bir Olgu Raporu

Hüseyin Emre Atasever, Gökhan Berktuğ Bahadır, Gülenay Korkmaz, İbrahim Yıldırım, Özlem Ekici, Oğuz Mehmet Çevik, Ervin Mambet, Suzi Demirbağ, İlhami Sürer

University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Department of Pediatric Surgery, Ankara, Türkiye

Abstract

Type 3 posterior urethral valves (PUV) are rare in pediatric urology departments and appear as a diaphragm with a central pinpoint opening in the urethra. A 14-year-old male patient presented with post-void hematuria and dribbling during micturition. Ultrasonography revealed no hydroureteronephrosis; however, the bladder wall appeared thickened and trabeculated. In the posterior urethra, an annular ring with a central opening permitting only guidewire passage was observed, characteristic of type 3 PUV. Ablation of the lesion was performed using a holmium: yttrium-aluminum-garnet laser. 14-french urinary catheter was placed, and the patient was discharged the next day without complaint. Even when there is urinary impairment, individuals may dismiss it as normal. This problem should be properly examined and investigated, particularly from the perspective of PUV type 3.

Keywords: Posterior urethral valve, haematuria, cystoscopy, dysuria

Öz

Tip 3 posterior üretral valv (PUV) çocuklarda kısmen nadir durumdur ve merkezinde iğne ucu kadar açıklığa sahip diyafram benzeri yapının gözlenmesi ile tanınır. On dört yaşında erkek hasta, hematüri ve idrarını kesik kesik akması şikayetiyle başvurdu. Ultrasonografi sonucunda hidroüreteronefroz saptanmadı, ancak mesane duvarının kalın ve trabeküle olduğu gözlendi. Daha sonra üretrosistoskopi planlandı, posterior üretrada halka şeklindeki diyafram benzeri lezyon intraoperatif tanındı. Tip 3 PUV'ye özgü olarak üretra noktasal bir açıklığa sahipti. Yalnızca kılavuz tel geçişine izin vermekteydi. Lezyonun ablasyonu için holmium: yttrium-aluminum-garnet lazer kullanıldı. Diyafram şekilli valv giderildi. Ardından, üretrosistoskopide her iki üreterin lateral pozisyonlandığı belirlendi. Hastaya üriner kateter yerleştirildi ve ertesi gün şikayetleri olmadan taburcu edildi. Bir hafta sonra kontrole çağırılan hastanın üriner kateterin çıkarılması ile eski şikayetlerinin gerilediği gözlendi. İdrar problemleri, bireyler tarafından özellikle adölesan çağlarda her zaman erken dönemde dile getirilmeyebilir. Üriner şikayetler detaylı irdelenmeli ve değerlendirilmelidir.

Anahtar Kelimeler: Posterior üretral valv, hematüri, sistoskopi, dizüri

Introduction

Posterior urethral valves (PUV) are one of the most common causes of lower urinary obstruction in the pediatric population. Young's classification divides this condition into three groups and type 3 valves are the rarest group among them. We aimed to discuss an unusual and late-onset PUV type 3 case in an adolescent patient.

Case Report

A 14-year-old male patient presented with post-void haematuria and indicated that his micturition always flows in a dripping pattern, and he thought that was normal. A blood test and urinalysis were performed. The patient's laboratory tests were unremarkable, with normal creatinine levels; however, 14 red blood cells were identified in the urinalysis. Ultrasonography

Address for Correspondence/Yazışma Adresi: Hüseyin Emre Atasever
University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Department of Pediatric Surgery, Ankara, Türkiye
E-mail: emreatasever@gmail.com **ORCID ID:** orcid.org/0000-0002-3415-7079

Received/Geliş Tarihi: 06.04.2024 **Accepted/Kabul Tarihi:** 25.04.2025 **Epub:** 26.05.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025

Cite this article as/Atıf: Atasever HE, Bahadır GB, Korkmaz G, et al. Unusual presentation of type 3 posterior urethral valve: a case report. J Ankara Univ Fac Med. 2025;78(2):161-163

was performed, and it was stated that the sizes of both kidneys were normal and there was no hydroureteronephrosis, but the bladder wall was thick and trabeculated. It was decided to perform cystourethroscopy without prior retrograde urethrography or voiding cystourethrography. A lesion compatible with PUV type 3 was seen in the posterior urethra (Figure 1), an annular ring with a hole in the centre that allows only guide passage. There was no history of prior surgical intervention or traumatic events to account for this condition. The lesion was ablated with a holmium: yttrium-aluminum-garnet (YAG) laser (Figure 2).

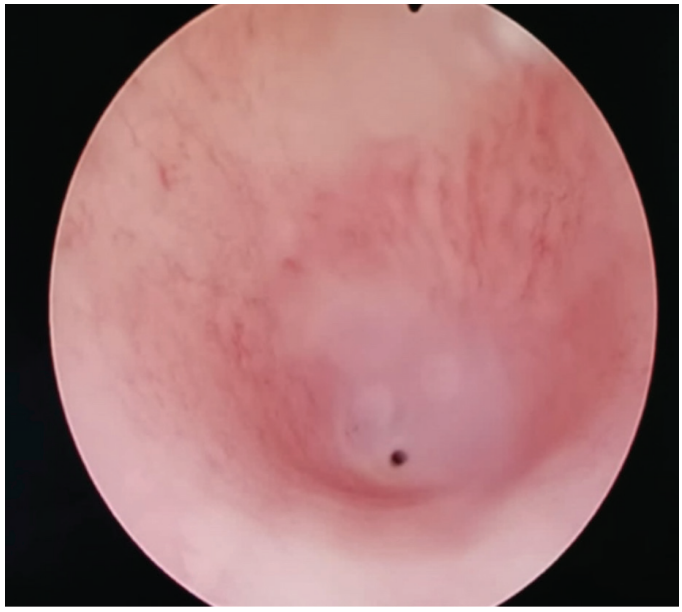

Figure 1: Figure showing the valve encountered in the posterior urethra during cystoscopy

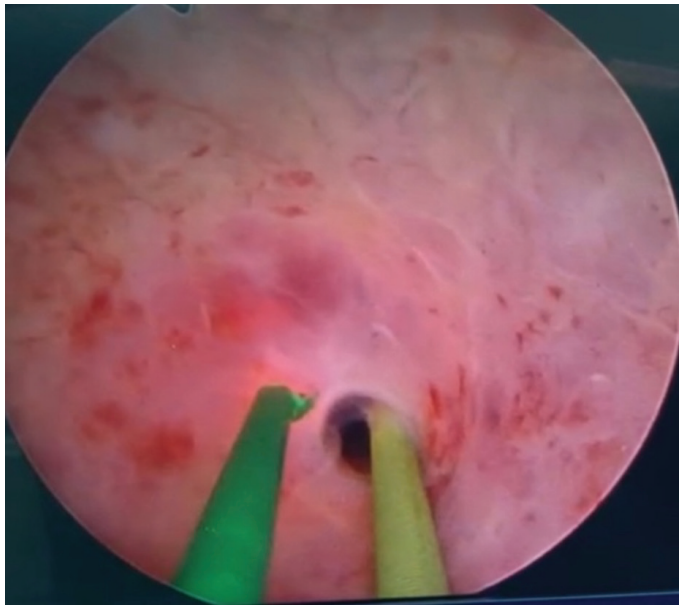

Figure 2: This figure shows the valve through which a catheter is sent and holmium-YAG laser is about to be applied
YAG: Yttrium-aluminum-garnet

Subsequently, the bladder was visualised, and it was determined that both ureters were positioned laterally according to physiological position. However, there were no signs of vesicoureteral reflux (VUR). After the procedure, a 14-french urinary catheter was inserted, and the patient was discharged one day later without any complaints. The patient was called to remove the urinary catheter three weeks later, and when he was checked in, it was observed that his micturition complaints were resolved. The patient is still being followed up, and there have been no complaints after the procedure at this point. The patient is planned to have a follow-up cystourethroscopy.

Discussion

Type 1 valves are the most common and extend distally from the verumontanum. Because type 2 valves extend proximally from the verumontanum to the bladder neck, they usually do not cause lower urinary obstruction. Type 3 valves, on the other hand, are less common and resemble diaphragms with a central pinpoint opening into the urethra. Type 3 valves have been proposed to be the urogenital membrane's embryonic persistence (1).

Uroflowmetry was not performed for our patient, this is planned for follow-up period. The diagnosis of PUV is now largely established prenatally by findings like oligohydramnios or hydroureteronephrosis as a result of recent technological and medical breakthroughs in the past few decades (2,3). Even in early ablated PUV situations in the newborn period, a variety of symptoms can occur in the subsequent stages of life, including VUR, hydroureteronephrosis, voiding dysfunction, sexual dysfunction, and valve-bladder syndrome (1-4). For a case presenting with such late-onset symptoms, we utilized a holmium-YAG laser. And after performing cystourethroscopy, we placed a catheter and discharged the patient with the catheter in place for three weeks. The reason for the three-week interval was our belief that it would heal with recurrent stricture. Additionally, since we did not suspect VUR, voiding cystourethrography was not performed. PUV should be considered in patients with voiding problems in adolescents. Examination should be carried out that purposive. It is important to remember that although PUV cases are commonly detected before birth, but might occur late and atypically. Dripping voiding and haematuria, especially in PUV type 3 cases, might be the initial presenting symptom. Even though there might be dysfunctional voiding, sometimes patients call it as normal. This situation should be carefully examined and investigated.

Ethics

Informed Consent: Informed consent was obtained from the patient and both parents before the preparation of this case report. Utmost effort was made to protect the data.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.A., G.K., Concept: G.B.B., O.M.Ç., Design: G.G.B., İ.S., Data Collection and/ or Processing: E.A., İ.Y., Ö.E., O.M.Ç., Analysis and/or Interpretation: G.K., Literature Search: G.B.B., E.M., S.D., Writing: E.A.

Conflict of Interest: All authors have disclosed no conflicts of interest.

Financial Disclosure: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Pellegrino C, Capitanucci ML, Forlini V, et al. Posterior urethral valves: Role of prenatal diagnosis and long-term management of bladder function; a single center point of view and review of literature. Front Pediatr. 2023;10:1057092.
2. Rosenfeld B, Greenfield SP, Springate JE, et al. Type III posterior urethral valves: presentation and management. J Pediatr Surg. 1994;29:81-85.
3. Manyevitch R, Wu WJ, Davis R, et al. Adolescent presentation of posterior urethral valves. Urology. 2020;136:e1-e2.
4. Nasir AA, Ameh EA, Abdur-Rahman LO, et al. Posterior urethral valve. World J Pediatr. 2011;73:205-216.

CASE REPORT / OLGU SUNUMU

DOI: 10.4274/atfm.galenos.2025.03779
J Ankara Univ Fac Med 2025;78(2):164-166

SURGICAL MEDICAL SCIENCES / CERRAHİ TIP BİLİMLERİ

Anesthesia Management in a Rare Case: Wolf-Hirschhorn Syndrome

Nadir Bir Olguda Anestezi Yönetimi: Wolf-Hirschhorn Sendromu

Özgün Ömer Asiller, Ezgi Yıldırım, Barış Sakul, Menekşe Özçelik

Ankara University Faculty of Medicine, Department of Anesthesiology and Reanimation, Ankara, Türkiye

Abstract

Wolf-Hirschhorn syndrome is a rare disease and may cause difficulties in airway management. In addition, intraoperative complications may occur. We will share with you our anesthesia management experience in a patient who is scheduled to undergo repair due to a cleft lip.

Keywords: Wolf-Hirschhorn syndrome, pediatric anesthesia, rare diseases

Öz

Wolf-Hirschhorn sendromu nadir görülen bir hastalıktır ve hava yolu yönetiminde zorluklara neden olabilir. Ayrıca, intraoperatif komplikasyonlar meydana gelebilir. Dudak yarığı nedeniyle onarım planlanan bir hastada anestezi yönetimi deneyimimizi sizinle paylaşacağız.

Anahtar Kelimeler: Wolf-Hirschhorn sendromu, pediatrik anestezi, nadir hastalıklar

Introduction

Wolf-Hirschhorn syndrome (WHS) (-) is characterized by 4p deletion and is characterized by pre- and postnatal growth retardation, cognitive dysfunction, epilepsy, and typical craniofacial components such as nasal hypertelorism, microcephaly, high forehead with prominent glabella, ocular hypertelorism, epicanthus, high arched eyebrows, short philtrum, downturned "fish like", micrognathia and underdeveloped ears. Prominent forehead, hypertelorism, and broad nasal bridge continuing toward the forehead caused the term "Greek warrior helmet appearance". This syndrome was first described by Hirschhorn and Cooper (1) in 1961. A second case was described by Wolf et al. (2). There is a 2:1 female:male ratio, with a frequency of 1:50,000-1:20,000 births. Various factors play a role in growth delay, including oral facial clefts, difficulty in sucking, poorly coordinated swallowing resulting in aspiration, and gastroesophageal (3,4). WHS is associated with a high mortality rate of approximately 30% in the first 2 years of life, and the most common causes of death are lower respiratory tract infections and congenital heart disease/heart failure (5). In this article, we will present a case of WHS who was operated for cleft palate.

Case Presentation

A cleft palate operation was planned for our patient who weighed 13 kg and 93 cm when she was 4 years and 39 weeks old. We obtained consent form from her family. Our patient with intrauterine growth retardation was followed up in the neonatal intensive care unit for 2.5 months without being intubated after she was born via cesarean section at 34 weeks and weighed 1300 gr. There was no consanguinity in her family history. Our patient was diagnosed with WHS when she was 5 months old. When she was diagnosed, ventricular septal defects (VSD), atrial septal

Address for Correspondence/Yazışma Adresi: Özgün Ömer Asiller
Ankara University Faculty of Medicine, Department of Anesthesiology and Reanimation, Ankara, Türkiye
E-mail: omerasiller@gmail.com **ORCID ID:** orcid.org/0000-0002-9573-4730

Received/Geliş Tarihi: 27.09.2024 **Accepted/Kabul Tarihi:** 01.06.2025 **Epub:** 16.06.2025 **Publication Date/Yayınlanma Tarihi:** 27.06.2025

Cite this article as/Atıf: Asiller ÖÖ, Yıldırım E, Sakul B, Özçelik M. Anesthesia management in a rare case: Wolf-Hirschhorn syndrome. J Ankara Univ Fac Med. 2025;78(2):164-166

defects (ASD), hypotonia, and epilepsy were present. The patient complained of frequent vomiting and had a history of intensive care hospitalization once due to aspiration pneumonia. The drugs she used were levetiracetam and growth hormone. There was only cleft lip surgery as in the previous operation. Hypertolerism and coarseness of breath sounds were the physical examination findings (Figures 1 and 2). In the last cardiology examination, ASD and VSD were closed. In the preoperative blood examination, potassium was 5.2 mmol/L, calcium: 11.3 mg/dL, phosphorus: 4.6 mg/dL, and the remaining electrolytes were normal. The vitamin D level was 31.17 ng/mL. In the thyroid function test, T4 and TSH were normal and only T3 was 7.8 pmol/L (upper limit 6.8). There were no abnormalities in hemoglobin, platelet, and bleeding parameters.

Solid food intake was stopped 8 h before the surgery, and liquid food intake was stopped with levetiracetam 4 h before the surgery. When she came to the operating room, the American Society of Anesthesiologists recommended monitoring was performed. Due to severe preoperative anxiety and inability to remain still, it was not possible to insert an intravenous line before induction. Therefore, inhalational induction with sevoflurane was preferred in order to avoid further distress and facilitate IV access in a controlled manner. The patient was induced with 1-8% sevoflurane. A nasogastric tube was inserted immediately after induction. One 24G and one 22G IV catheter were opened. The patient was started with 0.9% isotonic and 1/3 dextrose as fluid, and hourly blood glucose monitoring was planned. The patient was administered 5 mg ketamine, 5 mg fentanyl, and 5 mg lidocaine, followed by 60 mg propofol. Nasal intubation was performed using a 3.5-cuffed tube with a videolaryngoscope. The temperature probe was placed on the left axilla. Anesthesia was maintained with sevoflurane with MAC of 0.7. The patient whose hourly maintenance fluid was 130 mL became hypotensive at the minute 160 of the operation. Fluid boluses of 10 mL per kilo were administered three times. After fluid responsiveness, adrenaline infusion of 0.02 mcg/kg/min was initiated. Sevoflurane was turned off at minute 196. The patient was extubated at the minute 216. The patient was admitted to the postoperative care unit for 40 min. She was discharged on the day 3 after the operation.

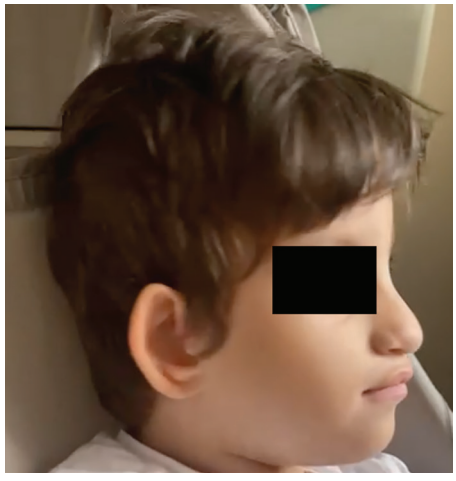

Figure 1: Physical examination from side

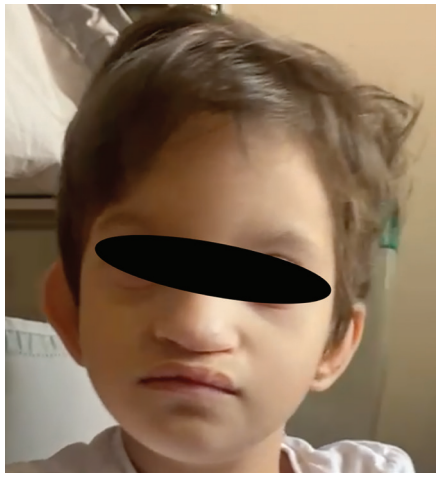

Figure 2: Physical examination from front

Discussion

Airway evaluation is important during preoperative evaluation. Due to the developmental delay of the patient, a smaller endotracheal tube may be required than that used in the normal age group in addition to difficult airway preparation (5,6). At this stage, the tracheal diameter at the c6 level is important (7). Heart defects reported in 50% of children with WHS are generally uncomplicated and are characterized by atrial and VSD, pulmonary stenosis, and patent ductus arteriosus associated with aortic regurgitation (3). Preoperative electrocardiogram and echocardiography should be performed in variants containing congenital heart disease (7).

On the day of surgery, patients should be administered antiepileptics (8). At this stage, the plasma concentration of many drugs will decrease because of drugs that increase liver enzyme activity, such as carbamazepine, phenobarbital, and phenytoin; if valproate is used, the metabolism of most drugs will be slowed down because of the inhibition of microsomal hepatic enzymes (9). If the patient is taking valproate for seizures, bleeding parameters and platelet function should be evaluated (10).

Antibody deficiencies have been reported in 69% of children with WHS (3). If the patient also has Ig-A deficiency, the patient may have an allergic or anaphylactic reaction to transfusions (11).

Although there is no obstacle in induction with inhalation, there is a risk of aspiration because gastroesophageal reflux may occur in this patient group (12).

If a patient with WHS develops fever during and after anesthesia, anesthetists should also consider malignant hyperthermia and other causes. Various unusual conditions during anesthesia may resemble malignant hyperthermia. These include iatrogenic overheating, infection, transfusion reaction, central nervous system dysfunction, allergic reactions, pheochromocytoma, thyrotoxicosis, drug-induced hyperthermia (tricyclic antidepressants, monoamine oxidase inhibitors, anticholinergics, amphetamines, etc.), machine valve malfunction, and rebreathing. The presence of a high temperature in the patient immediately after surgery may be associated with conditions such as sepsis or drug reaction, and this requires appropriate investigation. During this process, the risk of febrile convulsions due to hyperthermia should be avoided. Therefore, the patient should be provided with normothermia (6).

Malignant hyperthermia related to this syndrome has been observed in two cases till date (13,14), and one of them developed postoperatively (14). Generalized hypotonia, a feature of WHS, is usually associated with muscle hypotrophy of the lower legs (3). Doses of neuromuscular blocking agents should be titrated when the patient presents with generalized hypotonia (8). In addition to these, no relationship was found between malignant hyperthermia and WHS (ryanodine receptors are not genetically affected) (12-16).

Ethics

Informed Consent: Informed consent was obtained both orally and in writing from the patient's legal representative.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.Ö.A., E.Y., B.S., Concept: M.Ö., Data Collection and/or Processing: B.S., Analysis and/or Interpretation: Ö.Ö.A., E.Y., Literature Search: E.Y., Writing: Ö.Ö.A., M.Ö.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Financial Disclosure: The authors received no financial support for the research and/or authorship of this article.

References

1. Hirschhorn K, Cooper HL. Chromosomal aberrations in human disease. A review of the status of cytogenetics in medicine. Am J Med. 1961;31:442-470.
2. Wolf U, Reinwein H, Porsch R, Schröter R, Baitsch H. [Deficiency on the short arms of a chromosome No. 4]. Humangenetik. 1965;1:397-413.
3. Battaglia A, Carey JC, South ST. Wolf-Hirschhorn syndrome: A review and update. Am J Med Genet C Semin Med Genet. 2015;169:216-223.
4. Battaglia A, Filippi T, Carey JC. Update on the clinical features and natural history of Wolf–Hirschhorn (4p-) syndrome: Experience with 87 patients and recommendations for routine health supervision. Am J Med Genet C Semin Med Genet. 2008;148C:246-251.
5. Gamble JF, Kurian DJ, Udani AG, Greene NH. Airway management in a patient with Wolf-Hirschhorn syndrome. Case Rep Pediatr. 2016;2016:7070125.
6. Choi JH, Kim JH, Park YC, Kim WY, Lee Y-S. Anesthetic experience using total intra-venous anesthesia for a patient with Wolf-Hirschhorn syndrome-A case report. Korean J Anesthesiol. 2011;60:119-123.
7. Tsukamoto M, Yamanaka H, Yokoyama T. Anesthetic considerations for a pediatric patient with Wolf-Hirschhorn syndrome: a case report. J Dent Anesth Pain Med. 2017;17:231.
8. Kim HJ, You JA, Park S, Kim EJ, Park SJ, Kim HY. Anesthetic considerations for an adult with Wolf-Hirschhorn syndrome - A case report. Anesth Pain Med (Seoul). 2020;15:120-123.
9. Bloor M, Nandi R, Thomas M. Antiepileptic drugs and anesthesia. Paediatr Anaesth. 2017;27:248-250.
10. Abdallah C. Considerations in perioperative assessment of valproic acid coagulopathy. J Anaesthesiol Clin Pharmacol. 2014;30:7.
11. Sandler SG, Mallory D, Malamut D, Eckrich R. IgA anaphylactic transfusion reactions. Transfus Med Rev. 1995;9:1-8.
12. Bosenberg A. Anaesthesia and Wolf-Hirschhorn syndrome. SAJAA. 2014;13:31-34.
13. Ginsburg R, Purcell-Jones G. Malignant hyperthermia in the Wolf-Hirschhorn syndrome. Anaesthesia. 1988;43:386-388.
14. Chen JC, Jen RK, Hsu YW, et al. [4P- syndrome (Wolf-Hirschhorn syndrome) complicated with delay onset of malignant hyperthermia: a case report]. Acta Anaesthesiol Sin. 1994;32:275-278.
15. Hulin J, Veyckemans F. [Anaesthetic management of the Wolf-Hirschhorn syndrome: a report of two cases]. Ann Fr Anesth Reanim. 2012;31:89-90.
16. Humston C, Bernard R, Khan S, Tobias JD. Perioperative care of an infant with wolf-hirschhorn syndrome: is there a risk of malignant hyperthermia. J Med Cases. 2016;7:126-129.