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ORIGINAL ARTICLE

Investigation of the Impact of COVID-19 Pandemic Process on Sleep Habits of Children and Adolescents

COVID-19 Pandemi Sürecinin Çocuk ve Ergenlerin Uyku Alışkanlıklarına Etkisinin Araştırılması

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ABSTRACT

Background/Aims: The aim of this study is to investigate the effect of the COVID-19 pandemic process on sleep habits and problems in children.
Methods: The study included mothers of children and adolescents aged 0-18 who applied to the Afyon Health Sciences University Child Health and Diseases Clinic for outpatient healthcare services between May 15 and June
15, 2020. A structured questionnaire was administered to mothers who volunteered to participate in the study to evaluate their children's sleep habits before and after the pandemic and their opinions on the reasons for the change in their children's sleep habits.
Results: A total of 457 children, 237 girls (51.9%) and 220 boys (48.1%) participated in the study. The mean age of the participants was 10.03±4.4 years (Min:1 - Max:18). The average sleep time before the pandemic was 9.5 hours, and the average sleep time was 10 hours during the pandemic. A delay of 1 hour and 42 minutes was found between bedtime before the pandemic and bedtime during the pandemic (<0.001). A delay of 2 hours and 20 minutes was detected between the morning wake-up time before the pandemic and the morning wake-up time during the pandemic (<0.001). Compared to the pre-pandemic period, the presence of technological devices in the sleeping room increased significantly during the pandemic process, the problems of resisting lying down, having difficulty in lying down alone, falling asleep and teeth grinding problems were significantly increased, and the presence of pre-sleep preparation was significantly reduced (<0.001).
Conclusions: This study showed that during the COVID-19 pandemic, the sleep habits of children and adolescents changed significantly compared to the pre-pandemic period, and some sleep problems increased. It is important for clinicians to guide parents and children on healthy sleep habits when living conditions are changing and challenging, such as during a pandemic.

Keywords: Sleep, Pandemic, COVID-19, Child, Adolescent

ÖZ

Amaç: Bu çalışmanın amacı COVID-19 pandemi sürecinin çocuklardaki uyku alışkanlıkları ve sorunlarına etkisini araştırmaktır.
Gereç ve Yöntemler: Araştırma Afyon Sağlık Bilimleri Üniversitesi Çocuk Sağlığı ve Hastalıkları Kliniğine 15 mayıs ve 15 haziran 2020 tarihleri arasında, ayaktan sağlık hizmeti almak için başvuran, 0-18 yaş aralığında çocuk ve ergenlerin anneleri dahil edildi. Çalışmaya gönüllü olarak katılan annelere, çocuklarının pandemi öncesi ve sonrası uyku alışkanlıklarını ve çocuklarının uyku alışkanlıklarındaki değişimin nedenlerine ilişkin görüşlerini değerlendirmek amacıyla yapılandırılmış bir anket uygulandı.
Bulgular: Çalışmaya 237 kız (%51.9) 220 erkek (%48.1) toplam 457 çocuk katıldı. Katılımcıların yaş ortalaması 10.03±4.4 yıl (Min:1 - Max:18) idi. Pandemi öncesi uyku süresi ortalama 9,5 saat, pandemi süresince uyku süresi ortalama 10 saat saptandı. Pandemi öncesinde yatma saati ile Pandemi sürecinde yatma saati arasında 1 saat 42 dk gecikme bulundu (<0.001). Pandemi öncesinde sabah uyanma saati ile Pandemi sürecinde sabah uyanma saati arasında 2 saat 20 dk gecikme saptandı(<0.001). Pandemi öncesi döneme göre Pandemi sürecinde uyku odasında teknolojik alet varlığı belirgin artmış, yatağa yatmakta direnç gösterme, yalnız yatmakta zorlanma, uykuya dalmakta zorlanma ve uykuda diş gıcırdatma sorunları belirgin artmış, uyku öncesi hazırlık varlığı belirgin azalmış saptandı (<0.001).
Sonuç: Bu çalışma, COVID-19 pandemisi sırasında çocuk ve ergenlerin uyku alışkanlıklarının pandemi öncesine kıyasla belirgin değiştiğini ve bazı uyku sorunlarının arttığını gösterdi. Klinisyenlerin pandemi gibi yaşam koşullarının değiştiği ve zorlaştığı durumlarda ebeveynlere ve çocuklara sağlıklı uyku alışkanlıkları konusunda rehberlik etmesi önemlidir.

Anahtar Kelimeler: Uyku, Pandemi, COVID-19, Çocuk, Ergen

Introduction

Since December 2019, healthcare systems around the world have been struggling with an increasing number of cases linked to the Viral respiratory syndrome outbreak that emerged in China (1). The cause of this syndrome is a new strain from the Coronavirus family and is called '2019 novel coronavirus (2019-nCoV), SARS-CoV-2 or COVID-19 (2). In China, COVID-19 has affected children ages 3 months to 17 years old, the majority of whom have been in close contact with infected people or are members of a family where the infection is clustered (3). Although it is thought that children are less affected by the COVID-19 epidemic than adults, the first reports from China reported that the epidemic affected children and adolescents

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psychologically and caused behavioral problems. It has been reported that children are no different from adults in terms of the dramatic impact of the COVID-19 pandemic, and that they face negative experiences such as fear, uncertainty, physical and social isolation, and missing school. Fear of asking questions about the epidemic and the health status of their relatives, sleep problems such as nightmares, decreased appetite, physical disorders, agitation and inattention, overindulgence and separation problems are among the main psychological problems investigated in children in this process (4).

Beyond a situation where the main goal is to rest, sleep is now defined as a time of repair. Sleep takes approximately one-third of human life. It is known that the sleep-wake cycle varies with age, while a newborn baby sleeps 16-20 hours a day, this period decreases to 6.5 hours on average in an adult. As we get older, the rhythmicity of sleep deteriorates and night wakings and sleep disorders become more common (5). Studies reveal that nearly a quarter of children have sleep problems (6). It is stated that inappropriate sleep habits and the resulting insufficient sleep duration have become widespread in children and have become a public health problem. Decrease in good sleep time and the need to sleep during the day can affect children's physical and spiritual life, school success, and family relationships (7). According to a study, it was determined that during the pandemic, factors such as unrestricted sleep schedules, worsening sleep quality, more flexible sleep/wake routines, prolonged daytime naps, increased screen exposure, reduced daylight exposure, decreased physical activity, increased sedentary behaviors, reduced social interactions, and heightened stress and anxiety contributed to sleep disorders (8).

The aim of this study is to investigate the effect of the COVID-19 pandemic process on sleep habits and problems in Turkish children.

Materials And Methods

Study design

This cross-sectional descriptive study was carried out in a university hospital between 15 May and 15 June 2020. Healthy children aged 0-18 years and their mothers who applied to the outpatient clinic were included in the study. Children with a history of chronic physical or mental illness were excluded from the study.

Data collection

A structured questionnaire was applied to mothers who volunteered to participate in the research. With this questionnaire form, children's sociodemographic characteristics, sleep habits before and during the pandemic, sleep problems, parents' ability to set rules for these habits, children's compliance and the reasons for the difficulties they experienced were questioned. Mothers' opinions on the reasons for the change in their children's sleep habits during the pandemic were also examined.

Statistical analysis

SPSS 23 program was used to analyze the data. The data obtained were evaluated with descriptive statistics (arithmetic mean, median, standard deviation, percentage distributions). When comparing the average between groups, first the suitability for normal distribution was evaluated with the Kolmogorov Smirnov Test. It was determined that the variables did not comply with normal distribution. Mann Whitney U test was used in bivariate independent groups where parametric conditions were not met, and Wilcoxon test was used in bivariate dependent groups. Mcnemar ki-kare test was used in dependent groups in the analysis of categorical variables. In all tests, the statistical significance level $p<0.05$ was considered significant.

Ethics Committee Approval: This study was approved by the Afyonkarahisar Health Sciences University Ethics Committee.

Results

A total of 457 children, 237 girls (51.9%) and 220 boys (48.1%), participated in the study. The mean age of the participants was 10.03±4.4 years (Min: 1 - Max: 18). Sociodemographic characteristics of the children are given in Table 1.

Table 1. Sociodemographic characteristics of children

N=457		n(%)
Age	≤5 years 5-10 years 10-15 years ≥15 years	78 (17.1) 155 (33.9) 144 (31.5) 80 (17.5)
Gender	Female Male	237 (51.9) 220 (48.1)
Maternal age	<35 years ≥35 years	123 (26.9) 334 (73.1)
Paternal age	<35 years ≥35 years	53 (11.6) 404 (88.4)
Maternal Education	<high school ≥high school	134 (29.3) 323 (70.7)
Paternal Education	<high school ≥high school	121 (26.5) 336 (73.5)
Residence	Province District	396 (86.7) 61 (13.3)

Family type	Nuclear Extended	419 (91.7) 38 (8.3)
Number of children	1 2 ≥3	109 (23.8) 255 (55.9) 93 (20.3)
Maternal occupation during pandemic	Going to work Working at home due to flexible work *schedule* No	69 (15.1) 91 (19.9) 297 (65.0)
Paternal occupation during pandemic	Going to work Working at home due to flexible work *schedule* No	205 (44.9) 117 (25.6) 135 (29.5)
Maternal Caregiver during pandemic	Parents Relatives Nursemaid Alone	395 (86.4) 21 (4.6) 20 (4.4) 20 (4.4)
Sharing the sleeping room	Single With sibling With parents	262 (57.3) 152 (33.3) 43 (9.4)

The mean sleep duration before the pandemic (9.5 hours) was found to be significantly shorter than the average sleep duration during the pandemic period (10 hours) (p<0.001). When it was evaluated whether there was a difference in sleep duration according to gender, it was found that sleep duration was significantly longer in girls than in boys during the pandemic period (p<0.001), while there was no difference before the pandemic (p>0.05). Sleep durations were found to be significantly longer (<0.001) in those who shared the same room with their parents before the pandemic.

When the status of the mother and father being a healthcare professional was questioned in terms of sleep duration of their children, it was found that the sleep duration was statistically significantly shorter in those whose mothers were healthcare professionals during the pandemic compared to those who were not healthcare professionals (p<0.001), while no such difference was found if the father was a healthcare professional.

While the mean bedtime before the pandemic was 22:23 (earliest 20:00-latest 03:00), the mean bedtime during the pandemic was 20:05 (earliest 20:30-latest 07:00), and a delay of 1 hour and 42 minutes was found in bedtime (<0.001). Before the pandemic, the mean morning wake-up time was 07:50 (earliest 05:00-latest 13:00), while during the pandemic period the average wake-up time was 10:10 (earliest 06:00-latest 17:00), and a delay of 2 hours and 20 minutes was detected in the wake-up time (<0.001).

Tablo 2. Comparison of sleep habits of children and adolescents before and during the pandemic

Technological device presence in the sleeping room, n=457			**During pandemic**		***p***
			Yes	**No**	***0.002***
	Before pandemic	Yes	206 (97.6%)	5 (2.4%)	
		No	21 (8.5%)	225 (91.5%)	
Preparation before sleep, n=457			**During pandemic**		***p***
			Yes	**No**	***0.024***
	Before pandemic	Yes	335 (94.1%)	21 (5.9%)	
		No	8 (7.9)	93 (92.1%)	
Resistance to falling asleep, n=457			**During pandemic**		***p***
			Yes	**No**	***<0.001***
	Before pandemic	Yes	112 (87.5%)	16 (12.5%)	
		No	79 (24.0%)	250(76.0%)	
Trouble sleeping alone, n=457			**During pandemic**		***p***
			Yes	**No**	***0.003***
	Before pandemic	Yes	82 (95.3%)	4 (4.7%)	
		No	19 (5.1%)	352(94.9%)	
Trouble falling asleep, n=457			**During pandemic**		***p***
			Yes	**No**	***<0.001***
	Before pandemic	Yes	54 (75.0%)	18 (25.0%)	
		No	63 (16.4%)	322(83.6%)	
Grinding teeth in sleep, n=457			**During pandemic**		***p***
			Yes	**No**	***0.021***
	Before pandemic	Yes	23 (71.9%)	9 (28.1%)	
		No	1 (0.2)	424(99.8%)	

Comparison of the sleep habits of children and adolescents before the pandemic and during the pandemic is given in Table 2. Compared to before the pandemic, the presence and number of technological devices in the room where the child slept increased significantly during the pandemic (p=0.002). When children's bedtime routines were questioned, it was seen that the frequency of implementing bedtime routines decreased significantly during the pandemic compared to before the pandemic (p=0.024). When children's sleep problems were questioned, it was determined that problems such as resistance to going to bed at bedtime, difficulty sleeping alone, difficulty falling asleep and teeth grinding during sleep increased significantly during the pandemic compared to before the pandemic (p<0.001, p=0.003, p<0.001, p=0.021, respectively). No significant difference was observed in problems such as difficulty sleeping in the dark, going to someone else's bed at night, waking up frequently at night, delirium, sleepwalking, night terrors, nightmares, snoring, and bedwetting (p>0.05).

Mothers' opinions about changes in the sleep habits of children and adolescents and the problems experienced before and during the pandemic are given in Table 3.

Tablo 3. Mothers' views on the reasons for the change in sleep habits of children and adolescent during the pandemic

Reasons reported by mothers, n=457	**n(%)**
I don't care as we have similar problems	74 (16.1)
I am flexible as we are always at home during this period	227 (49.6)
I think the need for sleep is reduced as her physical activity decreases	135 (29.5)
I make a rule for my child to have a sleep routine	116 (25.3)
We are more tolerant due to the difficulty of the process	195 (42.6)
We cannot intervene because we work in the workplace	15 (3.2)
Same as before the pandemic	26 (5.6)

Discussion

On January 30, 2020, the World Health Organization declared the global outbreak of 2019 novel coronavirus (COVID-19) disease a major international public health emergency (9). The first case in Turkey was diagnosed on March 11, 2020, a little later than other European countries. As of this date, schools and nurseries were closed on March 12 as a result of the national pandemic measures taken by the scientific committee in Turkey. A curfew was imposed on those under the age of 20 on April 3 (10). During the curfew, some citizens in strict quarantine were reported to be at risk of less exposure to sunlight than usual, especially in homes with small windows and no outdoor space, while many are at risk of less exercise due to the cancellation of regular sports activities and limited opportunities to leave the house (11). Similarly the rate of children doing regular sports before the pandemic was found to have decreased during the pandemic period in our study.

There need to be a bedtime and sleep time table that gives a developmentally suitable quantity of sleep. Bedtime need to coincide with the kid`s natural sleep onset time. A regular nightly bedtime will assist reinforce the circadian clock and assist the kid go to sleep extra easily (12). In the present study, it was found that sleep duration was longer during the pandemic period, and there was a significant delay between the bedtime and wake-up times of children before the pandemic and during the pandemic. In a study conducted during the quarantine period, it was observed that children's bedtime and wake-up times shifted to later hours, and their sleep patterns and sleep quality deteriorated (13). In contrast, it was reported that total sleep time and sleep quality increased in adolescents during the restrictions during the pandemic period (14). Adolescents tend to sleep later than pre-adolescents due to the hormonal changes they experience. For this reason, it is known that in school settings where face-to-face education is provided, adolescents' total sleep hours on weekdays and weekends are different, and they sleep less than their normal sleep hours on weekdays (15). It has been observed that the elimination of going to school, especially in the morning, due to the pandemic enables adolescents to sleep longer, wake up later and wake up in a later circadian phase (16). In addition, they stayed away from the stressors in the school environment during online education (17).

Behavioral sleep problems in children (behavioral insomnia) include bedtime denial or resistance, late sleep onset, and nighttime awakenings requiring parental intervention. All of these problems are not uncommon in the pediatric population and often negatively impact the quality of life of children and caregivers. Although most children experience temporary insomnia occasionally, more persistent insomnia increases the risk of mood and behavior

problems, academic failure, and even worsening health-related conditions (18). In a study conducted during the pandemic period, it was observed that the most common sleep disorders were bedtime resistance, delay in falling asleep, and night awakenings (19). Similarly, in our study, we observed that the problems of resistance to bedtime, difficulty sleeping alone, difficulty falling asleep, and teeth grinding during sleep increased significantly during the pandemic compared to before the pandemic.

Establishing a regular bedtime ordinary is beneficial for all signs of behavioral insomnia (bedtime resistance, extended sleep onset, and night time wakings) (20). The routine have to ultimate approximately twenty to forty five mins and consist of 3 to 4 enjoyable activities, for instance bathing, putting on pajamas, and reading a story; must not contain televisions or other electronic devices (21). When we questioned the sleep routines of children in our study, it was seen that they abandoned their sleep routines significantly during the pandemic compared to before the pandemic, and the presence and number of technological devices in the room where the child slept increased significantly during the pandemic. It has been also reported that not using electronic devices with light-emitting screens, such as smartphones, laptops, and gaming systems, at least one hour before lights out can increase sleep duration and improve daytime functionality. It was strongly recommended that these devices be kept out of the bedroom, especially at night (22). A study conducted during the pandemic period showed that children's screen time and playing digital games increased significantly (23). In our study, it was thought that the increase in the presence of technological devices in the sleeping room may be a result of both the increase in children's screen exposure during the pandemic period and the continuation of online education at home.

Daytime sleepiness may be a symptom of a sleep disorder or another disease and is observed as a tendency to sleep during daytime hours. Excessive daytime sleepiness can significantly affect people's quality of life (19). In our study, we found that daytime sleepiness decreased significantly compared to before the pandemic. This may be due to children being more inactive at home and their need for sleep decreasing, and can be considered among the positive effects of the pandemic.

There are external factors that interfere with parents' or caregivers' ability to set clear limits both during the day and at bedtime. These factors may include emotional stress, mental illness, distraction from other responsibilities, or long working hours (24). Environmental factors, such as a child sharing a bedroom with a parent, siblings, or other family members living in the home (e.g., grandparents), can negatively impact sleep patterns by impairing parents' ability to set rules (24). In our study, when mothers' opinions were questioned about the change in sleep habits in children during the pandemic, it was revealed that mothers were more tolerant about sleep habits rules. Moreover, when the conditions of the rooms where the children participating in our study slept were evaluated, it was seen that 57.3% of them were sleeping alone, 33.3% were sharing the same room with their siblings, and 9.4% were sharing the same room with their parents.

Study Limitations

This study had some limitations. First, because this study was a descriptive cross-sectional study and the sample was small, the generalizability of the results is limited. Second, because this is a self-report survey study, it may contain biases such as exaggeration, concealment, and short-term memory biases. The third limitation is that standard scales were not used to evaluate sleep habits due to the wide age range of the participants.

Conclusion

This study showed that during the COVID-19 pandemic, children and adolescents' sleep habits have changed significantly compared to before the pandemic, and some sleep problems have increased.

Recognizing and reducing sleep problems is an important responsibility of healthcare professionals in terms of child health. It is important to guide parents and children in terms of healthy sleep habits. In this way, children can develop coping skills against possible risks to their sleep habits during humanitarian crises such as pandemics, where life habits change and become difficult.

Conflict of Interest

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

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References

1.Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565–74.

2.Fauci AS, Lane HC, Redfield RR. Covid-19—navigating the uncharted. N Engl J Med. 2020;382(13): 1268-1269.

3.Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, et al. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr. 2020;1–9.

4.Jiao WY, Wang LN, Liu J, Fang SF, Jiao FY, Pettoello-Mantovani M, et al. Behavioral and Emotional Disorders in Children during the COVID-19 Epidemic. J Pediatr. 2020; 221:264-266.

5.Farney RJ, Walker LE, Jensen RL, Walker JM. Ear oximetry to detect apnea and differentiate rapid eye movement (REM) and non-REM (NREM) sleep: screening for the sleep apnea syndrome. Chest. 1986;89(4):533–9.

6.Blunden S, Lushington K, Lorenzen B, Ooi T, Fung F, Kennedy D. Are sleep problems under-recognised in general practice? Arch Dis Child. 2004;89(8):708–12.

7.Gozal D, Kheirandish-Gozal L. Neurocognitive and behavioral morbidity in children with sleep disorders. Curr Opin Pulm Med. 2007;13(6):505–9.

8.Sharma M, Aggarwal S, Madaan P, Saini L, Bhutani M. Impact of COVID-19 pandemic on sleep in children and adolescents: a systematic review and meta-analysis. Sleep Med. 2021;84:259–67.

9.World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV) [Internet]. Available from: https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)

10.Öğütlü H. Turkey's response to COVID-19 in terms of mental health. Ir J Psychol Med. 2020;37(3):222–5.

11.Altena E, Baglioni C, Espie CA, Ellis J, Gavriloff D, Holzinger B, et al. Dealing with sleep problems during home confinement due to the COVID□19 outbreak: Practical recommendations from a task force of the European CBT□I Academy. J Sleep Res. 2020;29(4):e13052.

12.Owens JA. Behavioral sleep problems in children [Internet]. UpToDate. 2020. Available from: https://www.uptodate.com/contents/behavioral-sleep-problems-in-children?search=sleep children&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3

13.Cellini N, Di Giorgio E, Mioni G, Di Riso D. Sleep and psychological difficulties in Italian school-age children during COVID-19 lockdown. J Pediatr Psychol. 2021;46(2):153–67.

14.Çağlar S. COVID-19 pandemisinin okul çağı çocuklarının uyku alışkanlıkları üzerindeki etkileri: Literatür incelemesi. Zeugma Sağlık Araştırmaları Dergisi. 2021;3(2-3):88-93.

15.Crowley SJ, Acebo C, Carskadon MA. Sleep, circadian rhythms, and delayed phase in adolescence. Sleep Med. 2007;8(6):602–12.

16.Weingart R, Bryan C, Olson D, Gazmararian J, Rosati B, Hale L, et al. Adolescent sleep duration and timing during early COVID-19 school closures. Sleep Heal. 2021;7(5):543–7.

17.Gruber R, Saha S, Somerville G, Boursier J, Wise MS. The impact of COVID-19 related school shutdown on sleep in adolescents: a natural experiment. Sleep Med. 2020;76:33–5.

18.Combs D, Goodwin JL, Quan SF, Morgan WJ, Shetty S, Parthasarathy S. Insomnia, health-related quality of life and health outcomes in children: a seven year longitudinal cohort. Sci Rep. 2016;6(1):1–10.

19.Çimen İD, Çetin E, Fındık H, Çakın Memik N. Sleep Disorders and Associated Factors in Children Who Admitted to the Child and Adolescent Psychiatry Outpatient Clinics During the Pandemic. J Turkish Sleep Med [Internet]. 2023 Feb 14;10(1):26–35. Available from: http://cms.galenos.com.tr/Uploads/Article_58586/JTSM-10-26-En.pdf

20.Newton AT, Honaker SM, Reid GJ. Risk and protective factors and processes for behavioral sleep problems among preschool and early school-aged children: A systematic review. Sleep Med Rev. 2020;52:101303.

21.Foley LS, Maddison R, Jiang Y, Marsh S, Olds T, Ridley K. Presleep activities and time of sleep onset in children. Pediatrics. 2013;131(2):276–82.

22.Perrault AA, Bayer L, Peuvrier M, Afyouni A, Ghisletta P, Brockmann C, et al. Reducing the use of screen electronic devices in the evening is associated with improved sleep and daytime vigilance in adolescents. Sleep. 2019;42(9):zsz125.

23.Oflu A, Bükülmez A, Elmas E, Tahta EG, Çeleğen M. Comparison of screen time and digital gaming habits of Turkish children before and during the coronavirus disease 2019 pandemic. Turkish Arch Pediatr. 2021;56(1):22.

24.Lepore SJ, Kliewer W. Violence exposure, sleep disturbance, and poor academic performance in middle school. J Abnorm Child Psychol. 2013;41:1179–89.

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ORIGINAL ARTICLE

Prognostic and Predictive Factors for Uterine Sarcomas: A Single Center Experience

Uterus Sarkomlarında Prognostik ve Prediktif Faktörler: Tek Merkez Deneyimi

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ABSTRACT

Objective: To investigate the prognostic and predictive factors for uterine sarcomas, recognizing the challenge due to histological diversity and lack of definitive treatment.
Methods: We reviewed data from uterine sarcoma patients treated from July 2010 to August 2021. Cases were divided into endometrial stromal sarcoma (ESS), leiomyosarcoma (LMS), and others (rhabdomyosarcoma, adenosarcoma), examining clinicopathological features, age, survival rates, and recurrence risk factors.
Results: In 43 patients (average age, 59.1 years), the most common symptom was vaginal bleeding. The majority were postmenopausal, with a breakdown of 65.1% ESS, 18.6% LMS, and 16.3% other sarcomas. Most (65.1%) were stage 1. Surgery was primarily via laparotomy (95.3%), with 79.1% receiving adjuvant therapy. Recurrence was 18.6%. Significant differences in survival rates were found across groups, with LMS significantly affecting survival and recurrence risk linked to tumor size and surgical stage. Five-year overall survival was 72.1%, and disease-free survival was 67.4%.
Conclusion: ESS is the most common uterine sarcoma, but LMS presents the worst prognosis. Tumor size and surgical stage are key to recurrence risk, highlighting the need for further study on adjuvant treatments.

Keywords: Gynecological surgery, predictive, prognostic factors, survival, uterine sarcoma

ÖZ

Amaç: Histolojik çeşitlilik ve kesin tedavi eksikliğinden kaynaklanan zorluğun farkındalığı ile uterus sarkomlarının prognostik ve prediktif faktörlerini araştırmayı amaçlandı.
Yöntemler: Temmuz 2010'dan Ağustos 2021'e kadar tedavi edilen uterus sarkomu hastalarından elde edilen veriler incelendi. Vakalar, klinikopatolojik özellikler, yaş, hayatta kalma oranları, ve tekrarlama risk faktörlerine göre sınıflandırıldı.
Bulgular: 43 hastada (ortalama yaş 59,1) en sık görülen semptom vajinal kanamaydı. Çoğunluk menopoz sonrası dönemdeydi ve %65,1 ESS, %18,6 LMS ve %16,3 diğer sarkomlardan oluşuyordu. Çoğu (%65,1) evre 1 idi. Cerrahi esas olarak laparotomi (%95,3) yoluyla yapıldı ve %79,1'i adjuvan tedavi aldı. Nüks oranı %18,6 idi. Gruplar arasında hayatta kalma oranlarında önemli farklılıklar bulundu; LMS, tümör boyutuna ve cerrahi aşamaya bağlı olarak hayatta kalma ve nüks riskini önemli ölçüde etkiliyor. Beş yıllık genel sağkalım %72,1, hastalıksız sağkalım ise %67,4 olarak belirlendi.
Sonuç: ESS en sık görülen uterin sarkomdur ancak LMS en kötü prognoza sahiptir. Tümör boyutu ve cerrahi evre, nüks riskinin önemli göstergesidir ve adjuvan tedaviler konusunda daha fazla çalışma yapılması ihtiyacı vurgulanmaktadır.

Anahtar Kelimeler: Jinekolojik cerrahi, prediktif, prognostik faktörler, sağkalım, uterus sarkomu

Introduction

Uterine sarcomas are rare mesenchymal tumors characterized by a poor prognosis, representing 3-4% of all malignant uterine cancers (1). In 2002, the World Health Organization (WHO) classified uterine sarcoma into three categories: carcinosarcoma (CS), leiomyosarcoma (LMS), and endometrial stromal sarcoma (ESS) (2). However, in 2009, the diagnosis of carcinosarcoma was excluded from the uterine sarcoma classification, being redefined as type 2 endometrial cancer (3). As per the WHO's 2014 classification system, uterine sarcomas were divided into four subtypes: LMS, low-grade and high-grade endometrial stromal sarcoma, undifferentiated uterine sarcoma, and adenosarcoma (4). Among these,

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leiomyosarcoma, high-grade endometrial stromal sarcoma, undifferentiated sarcoma, and sarcomatous overgrowth adenosarcoma are associated with poor prognoses. In contrast, low-grade stromal sarcoma and adenosarcoma tend to have a more favorable prognosis (5).

The incidence of uterine sarcomas rises with age, ranging between 0.5 and 2.1 cases per 100,000 women (6, 7). They are most frequently diagnosed between the ages of 50 and 70, though the specific age of diagnosis can vary depending on the histological subtype (7, 8). Vaginal bleeding is a common symptom, yet there are no symptoms unique to sarcomas (9). In postmenopausal women who aren't on hormone replacement therapy, the presence of enlarging fibroids should prompt considerations of uterine sarcoma (10). These sarcomas are challenging to diagnose before surgery (11). Conventionally, the primary surgical treatment for uterine sarcomas is a total abdominal hysterectomy accompanied by bilateral salpingo-oophorectomy. The role of systemic lymph node dissection remains a topic of debate (12).

Histopathological diversity, an absence of definitive prognostic markers, rapid disease progression, high recurrence rates, and the potential for distant metastases define uterine sarcomas (13). One study found a recurrence rate of 30% for ESS and 60% for LMS, also noting that adjuvant chemotherapy neither reduced metastatic risk nor improved survival (11). While radiotherapy has been shown to enhance local control, it doesn't necessarily improve overall survival (14). Due to their propensity for early metastasis and recurrence, the overall 5-year survival rate for these sarcomas is often below 50%, signifying a grim prognosis (8, 15). Even now, the optimal treatment strategy for rare uterine sarcomas remains contentious. While surgery is the cornerstone of treatment, radiotherapy and chemotherapy serve as adjuvant treatments. In cases of metastatic or recurrent sarcomas, palliative treatments are employed (16). This study aims to investigate the prognostic and predictive factors for uterine sarcomas in a single center.

Materials and Methods

Ethical Consideration

The study received approval from the Selçuk University Ethics Committee on 04.10.2022, with the protocol number 2022/404.

Study Design

This retrospective study analyzed data from 43 patients diagnosed with uterine sarcoma who underwent surgery between July 2010 and August 2021. Based on prior classifications (3, 17), uterine sarcomas were categorized into three groups: endometrial stromal sarcoma (ESS), leiomyosarcoma (LMS), and other sarcomas (including adenosarcoma and rhabdomyosarcoma). Cases diagnosed with uterine carcinosarcoma (CS) were excluded due to their removal from the uterine sarcoma classification in 2009 (3). Patients were staged according to the 2017 uterine sarcoma staging guidelines (18).

Inclusion and Exclusion Criteria

Included were patients with a histologic diagnosis of ESS, LMS, or other sarcoma subtypes, and those who underwent surgery specifically for sarcoma. Exclusion criteria comprised a CS diagnosis, cases deemed inoperable, and those with prior chemotherapy and/or radiotherapy treatment.

Data Collection

The following parameters were collected and analyzed: age, menopausal status (premenopausal or postmenopausal), gravida, parity, presenting symptoms (such as vaginal bleeding, palpable mass, rapid growth, or incidental findings), preoperative hemoglobin (Hb) level, neutrophil-to-lymphocyte ratio (NLR), type of surgical procedure, pathological tumor size, presence of myometrial invasion, omentum metastasis, presence of positive abdominal fluid, surgical stage (early stage being stages 1 and 2, and advanced stage being stages 3 and 4), type of adjuvant treatment (chemotherapy (CT) or radiotherapy (RT)), recurrence status, disease-free survival (DFS), and overall survival (OS). OS was measured from the date of diagnosis to the date of death or the last follow-up, whereas DFS was the duration from diagnosis to the emergence of recurrence. Regression analysis was performed for the risk of recurrence.

Surgical Procedure

All surgical procedures were carried out by a single experienced surgeon. Lymph node dissections were methodically executed, ranging from the pelvic region to the renal vein level. This encompassed bilateral dissections from the obturator, internal iliac, external iliac, common iliac, aortic bifurcation, aortocaval space, vena cava, and paraaortic areas, which were identified as left and right paraaortic areas respectively.

Statistical Analysis

SPSS version 21 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA) was used for all statistical analyses. Data (mean, median, standard deviation, and percentage) were calculated using Descriptive Tests. Pearson Chi-Square and Fisher's Exact Test were used for categorical parameters. In comparisons between groups, the Independent T-test and One-Way ANOVA test were used for continuous data with normal distribution, and the Whitney U Test and Kruskal-Wallis H test were used for data without normal distribution. Bonferroni correction was made for multiple comparisons. Kaplan-Meier method was used for survival times. Factors affecting survival times were evaluated using Binary Logistic regression analysis. A P value less than 0.05 was considered statistically significant.

Results

Among the 43 patients evaluated, the mean age was 59.1±2.8 years. No significant age difference was observed among ESS, LMS, and, Other sarcomas. The majority, 28 (65.1%), were diagnosed with endometrial stromal sarcoma (ESS), 8 (18.6%) with leiomyosarcoma (LMS), and 7 (16.3%) fell into the category of other sarcomas. At the time of diagnosis, 34 (79.0%) patients were postmenopausal, while 9 (21%) were premenopausal. Vaginal bleeding was the most common presenting complaint at presentation, reported in 55.8% of the cases (Table 1).

Laparotomy was the primary surgical approach, employed in 95.3% of the cases, with the remaining undergoing laparoscopy or vaginal surgery. In terms of disease staging, 28 (65.1%) were at stage 1, 4 (9.3%) at stage 2, 8 (18.6%) at stage 3, and 3 (7.0%) at stage 4. Recurrence was identified in 8 cases, which constitutes 18.6% of the patients (Table 1).

A significant majority, 34 patients (79.1%), received adjuvant treatment post-surgery. Upon comparing the treatment modalities among patients who only underwent surgery (9 cases), received

Table 1: Comparison of the characteristics of uterine sarcoma cases

	ESS (n=28)	LMS (n=8)	Others (n=7)	Total (n=43)	(%)	p-value	
Age (years)		59.1±14.5	58.0±10.0	60.4±9.4	59.1±2.8		0.938
Menopausal status							0.513
	Premenopause	8	1	0	9	21.0	
	Postmenopause	20	7	7	34	79.0	
Gravida		3 (2-13)	3.5 (3-5)	2 (2-5)	3 (2-13)		0.351
Parity		3 (0-12)	3.5 (3-5)	2 (2-5)	3 (0-12)		0.438
Complaint							0.583
	Bleeding	18	4	4	26	60.5	
	Mass	2	2	2	6	14.0	
	Rapid growth	2	0	0	2	4.7	
	Incidental	6	2	1	9	20.9	
Preoperative Hb		11.3±1.6	12.0±1.3	11.2±2.1	11.4±1.6		0.793
Preoperative NLR		11.7±7.4	12.2±5.7	14.3±11.0	12.2±7.6		0.741
Surgery method							0.333
	Laparoscopy	1	0	0	1	2.3	
	Laparotomy	27	8	6	41	95.3	
	Vaginal	0	0	1	1	2.3	
Surgery type							0.029
	TAH	0	1	0	1	2.3	
	VAH	0	0	1	1	2.3	
	TAH+ BSO± Omentectomy	4	4	0	8	18.6	
	TAH+ BSO PPLND± Omentectomy	22	3	6	31	72.1	
	Debulkıng	2	0	0	2	4.7	
Omentectomy							0.840
	Malign	1	0	1	2	10.5	
	Benign	11	3	3	17	89.5	
Myometrial Invasion							0.540

	No	10	3	6	19	44.2	
	Yes	18	5	1	24	55.8	
Tumor diameter, mm		78.5±38.6	87.4±78.4	62.1±42.5	77.5±48.0		0.597
Tumor diameter cut-off (5 cm)							0.762
	≤5 cm	9	2	3	14	32.6	
	>5 cm	19	6	4	29	67.4	
Tumor diameter cut-off (10 cm)							0.917
	≤10 cm	22	6	5	33	76.7	
	>10 cm	6	2	2	10	23.3	
Peritoneal fluid							0.381
	Malign	1	0	1	2	4.7	
	Benign	27	8	6	41	95.3	
Lymphadenectomy							0.019
	No	4	5	3	12	27.9	
	Yes	24	3	4	31	72.1	
Lymph node positivity							0.821
	No	21	3	5	29	93.5	
	Yes	2	0	0	2	6.5	
Stages							0.912
	1	18	5	5	28	65.1	
	2	2	1	1	4	9.3	
	3	6	1	1	8	18.6	
	4	2	1	0	3	7.0	
Surgical stage							0.719
	Early	20	6	6	32	74.4	
	Advanced	8	2	1	11	25.6	
Adjuvant treatment							0.229
	CT	13	2	3	18	41.9	
	RT	3	0	0	3	7.0	
	CT+RT	5	5	3	13	30.2	
	Expectant	7	1	1	9	20.9	
Recurrence							0.199
	No	22	6	7	35	81.4	
	Yes	6	2	0	8	18.6	
Localization of recurrence							0.729
	Local	3	-	-	3	37.5	
	Locoregional	3	-	-	3	37.5	
	Distant	-	2	-	2	25	
Recurrence treatment							0.617
	Chemotherapy	1	1	0	2	25	
	Surgery and chemot-herapy	4	1	0	5	62.5	
	Surgery. Chemotherapy and Radiotherapy	1	0	0	1	12.5	
Ex status							0.002*
	No	21	2	7	30	69.8	
	Yes	7	6	0	13	30.2	
DFS (months) mean (min-max)		52.8 (1-153)	31.6 (3 -140)	103.1 (10-154)			0.001*
OS (months) mean (min-max)		56.3 (1-153)	32.3 (3-140)	104.3 (10-154)			0.002*

+p<0.017 was considered statistically significant.

Hb: Hemoglobulin, NLR: Neutrophil to lymphocyte ratio, TAH: Total abdominal hysterectomy, VAH: Vaginal hysterectomy, BSO: Bilateral salpingo-oophorectomy, PPLND: Pelvic para-aortic lymph node dissection, CT: Chemotherapy, RT: Radiotherapy, DFS: Disease-free survival, OS: Overall survival

radiotherapy (RT) post-surgery (3 cases), only received chemotherapy post-surgery (CT) (18 cases), and received both CT and RT post-surgery (13 cases), no statistically significant difference was found (p=0.199) (Table 1).

The total 5-year DFS and OS rates of the cases were calculated as 67.4% and 67.4%, respectively. A significant difference was evident between the groups in disease-free survival (DFS) and overall survival (OS) duration, with p-values of 0.001 and 0.002, respectively (Table 1, Figure 1, Figure 2). Regression analysis

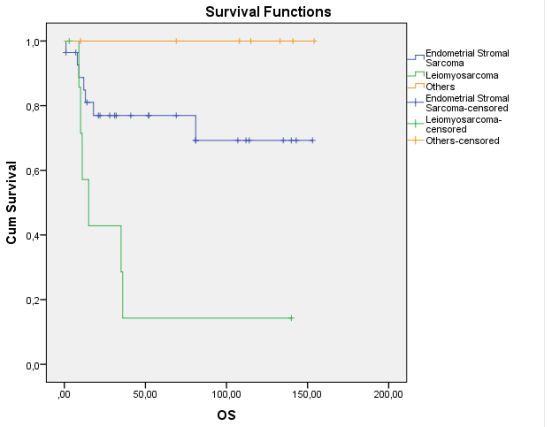

Figure 1. The effect of histologic types of uterine sarcoma cases on OS

indicated that the LMS histologic type was a significant risk factor influencing both DFS and OS (p=0.003 HR=6.155, 95% CI 1.871-20.250 and p=0.003 HR=6.075, 95% CI 1.846-19.996, respectively) (Table 2). Analyzing factors for recurrence, only tumor diameter showed statistical significance (p=0.04) (Table 3). Additionally, tumor diameter and surgical stage were significant factors for recurrence risk, with p-values of 0.033 and 0.022, respectively (Table 4). The overall 5-year OS was 72.1%, and DFS was 67.4%. ESS had a 5-year OS of 78.6% and a DFS of 71.4%, while LMS had both a 5-year OS and DFS of 25%.

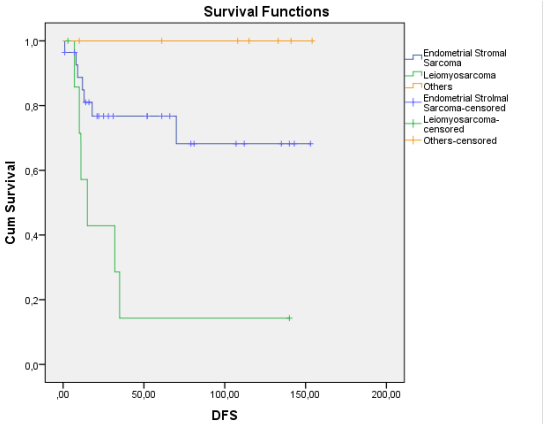

Figure 2. The effect of histologic types of uterine sarcoma cases on DFS

Discussion

Due to the histologic differences in uterine sarcomas, there isn't a widely accepted optimal treatment method. Traditionally, the management of these tumors entails a total abdominal hysterectomy coupled with a bilateral salpingo-oophorectomy. The predominant source of information on uterine sarcomas is based on extensive case series (5, 19, 20). In this study, we endeavor to share our clinical findings regarding the long-term outcomes of patients diagnosed with uterine sarcoma when a standardized management plan isn't available and to elucidate the factors that influence recurrence.

Table 2. Regression analysis of OS and DFS factors (-2 log Likelihood 78.944 p=0.045)

	OS				DFS			
Variables	*p*-value	HR	%95 CI		P value	HR	%95 CI	
NLR	0.950	1.003	0.916	1.098	0.998	1.000	0.913	1.095
Menopausal status	0.190	0.377	0.088	1.621	0.173	0.365	0.086	1.556
LMS vs others	0.003*	6.155	1.871	20.250	0.003*	6.075	1.846	19.996
Early vs advanced	0.609	0.686	0.161	2.913	0.651	0.716	0.169	3.038
Adjuvant treatment	0.236	3.158	0.472	21.140	0.278	2.821	0.432	18.400
Presence of recurrence	0.783	1.212	0.308	4.776	0.913	1.079	0.275	4.240

*p<0.05 was considered statistically significant. CI: Confidence interval, DFS: Disease-free survival, HR: Hazard ratio,

NLR: neutrophil to lymphocyte ratio, LMS: leiomyosarcoma, OS: Overall survival

Vaginal bleeding, a prevalent symptom associated with uterine sarcomas, has been reported in 25% to 92% of cases across various studies (1, 7, 16, 21, 22). In our cohort, this symptom was identified in 60.5% of patients. Typically, these malignancies are diagnosed at a more advanced age (8, 15, 16). The age of diagnosis also differs according to the histologic subtype, with studies suggesting an earlier onset for

Table 3: Comparison of uterine sarcoma cases in terms of recurrence

Variables		Recurrence Yes (n=8)	(%)	Recurrence No (n=35)	(%)	Total (n=43)	(%)	*p*-value
Age (years)		57.0±15.7		59.6±12.3				0.988
Menopausal status								0.541
	Premenopause	2	25.0	7	20.0	9	20.9	
	Postmenopause	6	75.0	28	80.0	34	79.1	
Parity		3 (2-7)		3 (0-12)				0.930
NLR		8.3±5.3		12.1±8.1				0.947
Omentectomy								0.795
	Malign	0	0	2	11.8	2	10.5	
	Benign	2	100.0	15	88.2	17	89.5	
Myometrial Invasion								0.493
	No	3	37.5	16	45.7	19	44.2	
	Yes	5	62.5	19	54.3	24	55.8	
Tumor diameter (mm)		88.1±41.0		70.4±39.3		108. 7±70.2		0.040
Tumor diameter cut-off (5 cm)								0.180
	≤5 cm	1	12.5	13	37.1	14	32.6	
	>5 cm	7	87.5	22	62.9	29	67.4	
Tumor diameter cut-off (10 cm)								0.610
	≤10 cm	6	75.0	27	77.1			
	>10 cm	2	25.0	8	22.9			
Peritoneal fluid								0.659
	Malign	-	-	2	5.7	2	4.7	
	Benign	8	100	33	94.3	41	95.3	
Lymph node positivity								0.645
	No	6	100	23	92.0	29	93.5	
	Yes	0	0	2	8.0	2	6.5	
Stages								0.137
	1	4	50.0	24	68.6	28	65.1	
	2	0	0	4	11.4	4	9.3	
	3	2	25.0	6	17.1	8	18.6	
	4	2	25.0	1	2.9	3	70	
Surgical stage								0.099
	Early	4	50.0	28	80.0	32	74.4	
	Advanced	4	50.0	7	20.0	11	25.6	
LMS *vs* others								0.467
	LMS	2	25.0	6	17.1	8	18.6	
	Others	6	75.0	29	82.9	35	81.4	
Ex status								0.458
	No	5	62.5	25	71.4	30	69.8	
	Yes	3	37.5	10	28.6	13	30.2	
Adjuvant treatment								0.207
	No	3	37.5	6	17.1	9	20.9	
	Yes	5	62.5	29	82.9	34	79.1	
DFS (months)		59.1±9.5 (84.1-127.0)		108.0±12.1 (84.3-131.6)				0.837
OS (months)		81.7±14.6 (53.2-110.8)		108.0±12.1 (84.3-131.6)				0.945

*p<0.05 was considered statistically significant.

NLR: Neutrophil-lymphocyte ratio, LMS: Leiomyosarcoma, DFS: Disease-free survival, OS: Overall survival

both ESS and LMS (7, 16, 22). Our findings are consistent with this, showing a mean diagnosis age of 59.1 years. A key distinction of our study from others is the exclusion of carcinosarcoma (CS) cases. Laparotomy remains the preferred surgical approach. Our results, with a significant 95.3% of patients undergoing laparotomy,

Table 4: Regression analysis of factors for recurrence (Sensitivity of the test, 88.4% and p=0.03 -2Log likelihood 25.810 Nagelkerke R Square=0.49)

Variables	*p*-value	HR	%95 CI	
Age (years)	0.324	0.932	0.810	1.072
NLR	0.334	0.923	0.784	1.086
Tumor diameter (mm)	0.033*	1.028	1.002	1.055
Menopausal status	0.427	4.591	0.107	196.507
LMS vs others	0.622	0.475	0.025	9.106
Early vs others	0.022*	61.565	1.804	2101.347
Adjuvant treatment	0.109	0.080	0.004	1.748

*p<0.05 was considered statistically significant. CI: Confidence interval,

NLR: Neutrophil to lymphocyte ratio, LMS: Leiomyosarcoma, HR: Hazard ratio

align with previous findings (16, 23). The rate of LMS detection in other studies varies between 40% and 83.6% (7, 8, 15, 22, 24). In our sample, 65.1% of the cases were diagnosed as ESS, followed by LMS at 18.6%, and other sarcomas at 16.3%. A significant feature of our patient group, diverging from some other studies, is the majority being diagnosed at an early stage (16, 21-23).

The hormone-sensitive nature of ESS mandates consideration for bilateral salpingo-oophorectomy, even during the premenopausal stage in stage 1 (7). In the meta-analysis by Rossini et al., it was suggested that ovarian tissue could be preserved in premenopausal patients even if there was a consensus on BSO in menopausal patients. However, there was insufficient evidence in the literature to recommend this procedure (25). In our patient pool, this procedure was also performed on premenopausal ESS patients, resulting in a total of 41 cases (90.7%) undergoing BSO.

The utility of lymph node dissection in uterine sarcomas remains contentious (12). In this study, lymphadenectomy was performed in 72.1%. Lymphadenectomy was performed most frequently in the ESS group and least frequently in the LMS group. While some studies highlight the advantages of postoperative radiotherapy, others suggest that adjuvant treatments don't considerably alter the disease progression (16, 26). In our study, 79.1% of the patients underwent some form of adjuvant treatment. Recurrence rates, as highlighted in previous research, fluctuate between 22% and 70% (8, 11, 21, 27, 28). Our study indicated a recurrence rate of 18%, with the majority being locoregional.

Regarding prognostic factors, the literature yields mixed results. Variables such as age, menopausal status, tumor stage, tumor size, and histological type have been pinpointed as crucial to overall survival in some studies (22, 23, 27-31). In contrast, our findings identify LMS histology as the only prognostic factor for survival. Tumor histologic type and size emerged as significant influencers of survival outcomes. The role of inflammatory cells surrounding cancer tissues in determining cancer progression and prognosis is pivotal (32). High preoperative NLR was shown to be an independent prognostic marker for predicting poor prognosis in soft tissue sarcoma (33, 34). Yet, our analysis showed that the preoperative neutrophil-lymphocyte ratio (NLR) didn't significantly correlate with survival.

There is still no standard approach to the management of uterine sarcomas today. Because uterine sarcomas are both a heterogeneous group and their diagnosis is histopathological. Therefore, factors that can be used or predicted in the preoperative diagnosis of uterine sarcoma are being investigated. However, the studies conducted are retrospective. There are still no prospective studies on this subject. In this study, lymphadenectomy and surgical procedure were significant factors for ESS, LMS, and other sarcoma groups, while only histological type was found to be a significant factor in regression analysis. When the cases were evaluated in terms of recurrence, only the tumor diameter at the time of diagnosis was found to be a significant factor. In other words, as the tumor diameter increases, the risk of recurrence also increases. In this study, no cut-off value was found for tumor diameter recurrence. Studies with more cases are needed to explain the relationship between tumor diameter and recurrence.

This study's constraints encompass its retrospective design, its single-center scope, and the limited number of cases. However, it offers valuable insights by presenting the clinical features and long-term outcomes of patients diagnosed with uterine sarcoma,

emphasizing factors affecting recurrence, and deliberately excluding carcinosarcoma diagnoses.

Conclusions

The predominant histologic subtype of uterine sarcoma is endometrial stromal sarcoma. Leiomyosarcoma is the subtype associated with the most adverse prognosis. Tumor size and surgical stage are the most critical determinants of recurrence rates in uterine sarcomas. Although early surgical intervention is effective in the management of sarcomas, additional research is urgently needed to determine the benefits of adjuvant therapies.

References

1.D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol 2010; 116: 131-139.

2.Bocker W. [WHO classification of breast tumors and tumors of the female genital organs: pathology and genetics]. Verh Dtsch Ges Pathol 2002; 86: 116-119.

3.FIGO Committee on Gynecologic Oncology. FIGO staging for uterine Sarcomas. Int. J. Gynecol. Obstet. 2009, 179, Corrigendum in Int. J. Gynecol. Obstet. 2009, 106, 277.

4.Benson C, Miah AB (2017) Uterine sarcoma—current perspectives. Int J Womens Health 9:597–606.

5.Shushkevich AT, P.H.; Littell, R.D.; Shah, N.A.; Chiang, S.; Thornton, K.; Hensley, M.L.; Slomovitz, B.M.; Holcomb, K.M.; Leitao, M.M.; et al. State of the science: Uterine sarcomas: From pathology to practice. Gynecol. Oncol. 2020, 159, 3–7.

6.Cantú de León DG, H.; Pérez Montiel, D.; Coronel, J.; Pérez-Plasencia, C.; Villavicencio-Valencia, V.; Soto-Reyes, E.; Herrera, L.A. Uterine sarcomas: Review of 26 years at The Instituto Nacional de Cancerologia of Mexico. Int. J. Surg. 2013, 11, 518–523.

7.Burghaus SH, S.; Gass, P.; Mehlhorn, G.; Schrauder, M.G.; Lux, M.P.; Renner, S.P.; Beckmann, M.W.; Hein, A.; Thiel, F.C. Outcome and prognosis in uterine sarcoma and malignant mixed Mullerian tumor. Arch. Gynecol. Obstet. 2016, 294, 343–351.

8.Kyriazoglou AL, M.; Ziogas, D.C.; Zagouri, F.; Koutsoukos, K.; Tsironis, G.; Tsiara, A.; Kaparelou, M.; Zakopoulou, R.; Thomakos, N.; et al. Management of uterine sarcomas and prognostic indicators: Real-world data from a single institution. BMC, Cancer 2018, 1247.

9.Wickerham DL FB, Wolmark N, Bryant J, Costantino J, Bernstein L, Runowicz CD. Association of tamoxifen and uterine sarcoma. J Clin Oncol 2002; 20: 2758-2760.

10.Chu CS LL, Rubin SC. Cancer of the uterine body. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology. 8th ed. DeVita VT, Lawrence TS, Rosenberg SA, editors. Philadelphia: WoltersKluwer/Lippincott Williams &Wilkins; 2008. pp 1543-1563.

11.Sagae S YK, Ishioka S, et al. Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido, Japan. Oncology 2004;67:33-39.

12.Gadducci A CS, Romanini A, Genazzani AR. The management of patients with uterine sarcoma: a debated clinical challenge. Crit Rev Oncol Hematol 2008;65:129-142.

13.Akahira J TH, Toyoshima M, Takano T, Nagase S, Yoshinaga K, Tase T, Wada Y, Ito K, Niikura H, Yamada H, Sato A, Sasano H, Yaegashi N. Prognoses and prognostic factors of carcinosarcoma, endometrial stromal sarcoma and uterine leiomyosarcoma: a comparison with uterine endometrial adenocarcinoma. Oncology 2006; 71: 333-340.

14.Chauveinc L DE, Plancher C, et al. Uterine sarcomas: the Curie Institute experience. Prognosis factors and adjuvant treatments. Gynecol Oncol 1999;72:232-237.

15.Eiriz IV, M.; Gomes, F.; Braga, S. Uterine Sarcomas: A Retrospective Analysis of a Cohort of 62 Patients. Cureus 2021, 13, e13349.

16.Ruiz-Minaya M M-VE, Vasquez-Jimenez W, Perez-Burrel L, Aracil-Moreno I, Agra-Pujol C, Bernal-Claverol M, Martínez-Bernal BL, Muñoz-Fernández M, Morote-Gonzalez M, Ortega MA, Lizarraga-Bonelli S, De Leon-Luis JA. Retrospective Analysis of Patients with Gynaecological Uterine Sarcomas in a Tertiary Hospital. J Pers Med. 2022 Feb 6;12(2):222.

17.Oliva E CM, Carinelli SG, et al. Mesenchymal Tumors of the Uterus. In: Kurman RJ, Carcangiu ML, Herrington CS, Young RH, eds. WHO Classification of Tumours of Female Reproductive Organs. 4th ed. Lyon, France: IARC Press, 2014. 135-147.

18.Amin MB ES, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.

19.Kostov S KY, Ivanova V, Dzhenkov D, Metodiev D, Watrowski R, Ivanova Y, Slavchev S, Mitev D, Yordanov A. New Aspects of Sarcomas of Uterine Corpus - A Brief Narrative Review. Clin Pract. 2021 Nov 22;11(4):878-900. doi: 10.3390/clinpract11040103.

20.Suchetha S VT, Rema P, Sivaranjith J, Kumar A, Krishna KMJ, James FV. Uterine Sarcoma: Retrospective Study From A Single Institute. J Obstet Gynaecol India. 2022 Aug;72(Suppl 1):306-312. doi: 10.1007/s13224-021-01612-9. .

21.Sait HKA, N.M.; El Sayed, M.E.; Alkhayyat, S.S.; Ghanem, A.T.; Abayazid, R.M.; Sait, K.H. Uterine sarcoma. Clinicopathological characteristics and outcome. Saudi Med. J. 2014, 35, 1215–1222.

22.Wang F DX, Chen H, Hu X, Wang Y. Clinical characteristics and prognosis analysis of uterine sarcoma: a single-institution retrospective study. BMC Cancer. 2022 Oct 7;22(1):1050. doi: 10.1186/s12885-022-10129-x.

23.Gao Y, Meng H, Zhang Y, Jiao T, Hui N. Retrospective analysis of 80 cases with uterine carcinosarcoma, leiomyosarcoma and endometrial stromal sarcoma in China, 1988-2007. Int J

Clin Exp Pathol. 2014 Mar 15;7(4):1616-24. .

24.Nano, O.; Nieto, M.J.; Saif, M.W.; Tarabichi, M. Retrospective Analysis of Patients with Gynecological Uterine Sarcomas: Leiomyosarcomas and other Histological Subtypes at a Single Institution from 1996 to 2015. Cancer Med. J. 2020, 3, 30–37.

25.Ronsini C FA, Giudice M, Reino A, La Verde M, Della Corte L, Bifulco G, Franciscis P, Cianci S, Capozzi VA. Is Adnexectomy Mandatory at the Time of Hysterectomy for Uterine Sarcomas? A Systematic Review and Meta-Analysis. Medicina (Kaunas). 2022 Aug 23;58(9):1140. doi: 10.3390/medicina58091140.

26.Reed NS MC, Malmströ m H, et al. Phase III randomized study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas stages I and II: A European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group Study (protocol 55874). Eur J Cancer 2008;44:808-818.

27.Nam JH. Surgical treatment of uterine sarcoma. Best Pract Res Clin Obstet Gynaecol 2011;25:751-760.

28.Barquet-Muñoz, S.A.; Isla-Ortiz, D.; Montalvo-Esquivel, G.; Cantú-de-León, D.; Salcedo-Hernández, R.A.; Cordoba-Gonzalez, V.; Herrera-Gómez, Á. Prognostic factors associated with uterine sarcomas: The experience of a single institution. J. Obstet. Gynaecol. 2019, 39, 231–236.

29.Li D YN, Du G, Wang S, Xiao Z, Chen J, Chen W. A Real-World Study on Diagnosis and Treatment of Uterine Sarcoma in Western China. Int J Biol Sci. 2020 Jan 1;16(3):388-395. doi: 10.7150/ijbs.39773.

30.Wang LL, S.; Zhang, Z.; Jia, J.; Shan, B. Prevalence and occult rates of uterine leiomyosarcoma. Medicine 2020, 9, e21766.

31.Nordal RN KK, Stenwig AE, Tropé CG. Leiomyosarcoma (LMS) and endometrial stromal sarcoma (ESS) of the uterus. A survey of patients treated in the Norwegian Radium Hospital 1976 - 1985. Int J Gynecol Cancer 1993;3:110-115.

32.Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002 Dec 19-26;420(6917):860-7. doi: 10.1038/nature01322. .

33.Szkandera J AG, Liegl-Atzwanger B, Pichler M, Stotz M, Samonigg H, Glehr M, Zacherl M, Stojakovic T, Gerger A, Leithner A. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. Br J Cancer. 2013 Apr 30;108(8):1677-83. doi: 10.1038/bjc.2013.135. .

34.Jeong MJ PJ, Hur SY, Kim CJ, Nam HS, Lee YS. Preoperative Neutrophil-to-Lymphocyte Ratio as a Prognostic Factor in Uterine Sarcoma. J Clin Med. 2020 Sep 8;9(9):2898. doi: 10.3390/jcm9092898.

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ORIGINAL ARTICLE

The Role of Blood Inflammatory Parameters in the Evaluation of Otitis Media with Effusion in Children with Obstructive Adenoid Hypertrophy: A Retrospective Study

Obstrüktif Adenoid Hipertrofili Çocuklarda Kan İnflamatuar Parametrelerinin Efüzyonlu Otitis Media Değerlendirilmesindeki Yeri: Retrospektif Bir Çalışma

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ABSTRACT

Aim: It has been reported that inflammatory parameters of neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), eosinophil-basophil ratio (EBR), systemic immune-inflammatory index (SII), and mean platelet volume (MPV) in the blood have prognostic and diagnostic values in diseases accompanied by inflammation. Serous/Mucoid differentiation of otitis media with effusion (OME) and the decision to apply a ventilation tube (VT) can be difficult. Our study aimed to examine the importance of blood inflammatory parameters in the evaluation of effusion character in OME with obstructive adenoid hypertrophy (OAH).
Methods: Preoperative blood tests of 215 pediatric patients operated on with the diagnosis of OAH in our clinic between January 1st and December 31st, 2022 were scanned. Patients with OME were grouped as Serous OME (Group 1, n=33) and Mucoid OME (Group 2, n=69). Children without accompanying OME were considered the control group (Group 3, n=113). NLR, PLR, EBR, SII, and MPV values of the groups were compared.
Results: NLR value was found to be significantly lower in Group 1 than in Group 3 (p=0.023). MPV values were found to be significantly lower in Group 2 compared to Group 3 (p=0.015). No significant difference was detected between the groups in terms of other parameters.
Conclusion: The low NLR may suggest that the effusion may be the serous character. In patients with low MPV, it should be taken into account that mucoid EOM increases.

Keywords: Adenoidectomy, lymphocyte, neutrophil, obstructive adenoid hypertrophy, otitis media with effusion, thrombocyte

ÖZ

Amaç: Enflamasyonun eşlik ettiği hastalıklarda kanda nötrofil lenfosit oranı (NLO), trombosit lenfosit oranı (TLO), eozinofil bazofil oranı (EBO), sistemik immun-inflamatuar indeks (SII) ve ortalama trombosit hacmi (MPV) enflamatuar parametrelerinin prognostik ve tanısal değeri olduğu bildirilmiştir. Efüzyonlu Otitis Media'da (EOM), efüzyonun seröz/müköz ayrımı ve Ventilasyon Tüpü (VT) uygulama kararı zor olabilir. Çalışmamızda, Obstrüktif Adenoid Hipertrofi (OAH) sebebi ile opere olan çocuklarda, kan inflamatuar parametrelerinin EOM varlığında efüzyon karakterini belirlemedeki yerini değerlendirmek amaçlanmıştır.
Yöntem: 1 Ocak-31 Aralık 2022 arasında kliniğimizde OAH tanısı ile opere edilen 215 çocuk hastanın preoperatif kan tetkikleri tarandı. EOM olan hastalar, Seröz EOM (Grup 1, n:33) ve Müköz EOM (Grup 2, n:69) olarak gruplandı. EOM eşlik etmeyen çocuklar kontrol grubu (Grup 3, n:113) olarak değerlendirildi. Grupların NLO, TLO, EBO, SII ve MPV değerleri karşılaştırıldı.
Bulgular: NLO değeri, Grup 1'de Grup 3'e göre anlamlı derecede düşük bulundu (p=0,023). MPV değeri, Grup 2'de Grup 3'e göre anlamlı derecede düşük bulundu (p=0,015). Diğer parametreler açısından gruplar arasında anlamlı fark saptanmadı.
Sonuç: OAH ve EOM olan çocuklarda NLO'nun düşük olması efüzyonun seröz karakterde olabileceğini düşündürebilir. MPV'nin düşük olduğu hastalarda müköz EOM'nın arttığı gözönünde bulundurulmalıdır.

Anahtar Kelimeler: Adenoidektomi, efüzyonlu otitis media, lenfosit, nötrofil, obstrüktif adenoid hipertrofi, trombosit

Introduction

Otitis media with effusion (OME) is the accumulation of fluid in the middle ear without acute signs of infection. It is important to diagnose it early because it may cause speech delay, a decrease in school performance, and behavioral problems in children older than 2 years of age due to hearing loss (1). Eustachian tube dysfunction, adenoid, and allergic diseases are often blamed for etiology (2). Studies conducted in recent years argue that inflammatory markers in the blood have prognostic and diagnostic value in diseases accompanied by inflammation (3,4). Results showing a relationship between effusion character and these parameters in OME have been reported (5-7). However, in previous studies, the etiological factor was not specified in OME patients. Obstructive adenoid hypertrophy (OAH) alone may cause differences in inflammatory parameters, independent of OME (8). Comparing the differences in inflammatory parameters

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in children with OME, regardless of the OAH factor, may be more informative. For this purpose, we have planned a study in which all groups will consist of children undergoing surgery for OAH with or without OME. The objective of this study is to assess the role of blood inflammatory parameters in predicting the type of effusion in OME.

Materials And Methods

In this retrospective study, preoperative blood tests and surgery notes of children operated on for OAH by 3 otorhinolaryngology physicians in our clinic between January 1st and December 31st, 2022 were scanned. The term OAH was used for adenoid hypertrophy causing 60% or more obstruction compared to the choanae during flexible nasopharynx examination. Patients not having a preoperative blood test and whose intraoperative effusion characteristics were not specified were excluded from the study.

In patients with OME undergoing ventilation tube (VT), the effusion character was recorded as serous or mucoid in the operating notes. Children without OME were considered as the control group (Group 3, n:113). Patients with OME were grouped as serous OME (Group 1, n=33) and mucous OME (Group 2, n=69). Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), eosinophil-basophil ratio (EBR), systemic immune-inflammatory index (SII), and mean platelet volume (MPV) inflammatory parameters obtained from the preoperative blood tests of the patients were compared statistically.

Statistical analysis

Values in the table are given as mean ± standard deviation (SD). The Windows-based Statistical Package for Social Sciences, version 24.0 program (SPSS, IBM Inc., Armonk, NY, USA) was used for appropriate statistical analyses. In the two-group analysis, the student t-test was used to compare normally distributed variables, and Mann Whitney U test was used to compare non-normally distributed variables. P <0.05 was considered as the significance threshold. This study was approved by the ethics committee (Bursa City Training and Research Hospital, Clinical Research Ethical Committee, 2023-5/2, 05.04.2023) and was conducted under the 1961 Declaration of Helsinki Principles and its later amendments.

Results

Two hundred and fifteen children (103 girls and 112 boys) undergoing surgery due to OAH were included in the study. Among children with OME, 33 children with serous effusion were evaluated as Group 1, and 69 children with mucoid effusion were evaluated as Group 2. One hundred and thirteen children with no OME formed the control group (Group 3). The average age of groups was 5.7, 5.9, and 5.3 years, respectively (p=0.406), and the proportion of males was 54.5, 50.7, and 52.2%, respectively (p=0.936). The distribution of blood inflammatory parameters by groups is given in the table (Table 1).

Table 1. The distribution of blood inflammatory parameters by groups

Variables	Group 1 (n=33)	Group 2 (n=69)	Group 3 (n=113)
Age (years)	5.70±2.14	5.96±1.98	5.38±2.44
Neutrophil (10^3/uL)	3.96±2.02	4.43±2.14	4.20±1.76
Lymphocyte (10^3/uL)	4.48±1.86	3.95±1.30	3.71±1.28
Platelets (10^3/uL)	366.9±124.78	364.25±87.42	348.91±87.36
MPV (fL)	9.40±0.95	9.21±0.81	9.51±0.78
NLR	0.97±0.53	1.23±0.73	1.36±1.57
PLR	89.39±29.32	99.22±34.57	103.02±39.75

MPV: Mean platelet volume, n: Number of patients, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio,

In Group 1, the neutrophil count (3.96 103/uL) was low and the lymphocyte count (4.48 103/uL) was high compared to the other groups. NLR was found to be significantly lower in Group 1 compared to the control group (mean 0.97 and 1.36, respectively; p = 0.023). There was no significant difference in NLR between Group 2 and the control group (mean 1.23 and 1.36, respectively; p = 0.793).

The MPV value was found to be significantly lower in Group 2 compared to the control group (mean 9.21 and 9.51, respectively; p = 0.015). There was no significant difference between Group 1 and the control group in terms of MPV (mean 9.40 and 9.51, respectively; p = 0.345).

No significant difference was detected between the groups in terms of PLR, SII, and EBR values. A comparison of inflammatory parameters between groups (Mann-Whitney U test) is given in Table 2. Mucous OME was observed to increase in spring and winter compared to other months (p = 0.04). The distribution of the groups according to seasons is given in Table 3.

Table 2. Comparison of inflammatory parameters between groups by the Mann-Whitney U test

Group Number	NLR	PLR	SII	EBR	**MPV**
1-3	p: 0.023	p: 0.160	p: 0.083	p: 0.574	p: 0.345
1-2	p: 0.067	p: 0.369	p: 0.087	p: 0.895	p: 0.440
2-3	p: 0.793	p: 0.532	p: 0.789	p: 0.247	p: 0.015

EBR: Eosinophil-basophil ratio, MPV: Mean platelet volume, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, SII: Systemic immune index

Table 3. The distribution of the groups by seasons

Operation time	Group 1 (n=33)	Group 2 (n=69)	Group3 (n=113)	Total (n=215)
Spring	27.3%	31.9%	15%	22.3%
Summer	18.2%	20.3%	31%	25.6%
Autumn	24.2%	17.4%	31%	25.6%
Winter	30.3%	30.4%	23%	26.5%

n: Number of patients

Discussion

OME is a common condition observed in children aged 1 to 3 and by the age of 4, the cumulative incidence of OME reaches 80% (9). Experimental studies have shown that when a ventilation disorder develops in the middle ear, there is an increase in partial CO2 pressure, leading to vacuum and membrane retraction in the middle ear cavity. In cases where sufficient ventilation cannot be achieved, the middle ear cavity starts to accumulate serous fluid during the acute inflammation period due to the influence of the vacuum. It has been demonstrated that chronic inflammation leads to metaplasia in the middle ear mucosa, an increase in goblet cells, increased vascular permeability, and the occurrence of mucoid effusion through inflammatory mediators (9-12).

Adenoidectomy and VT insertion, in children with OAH and OME, can significantly reduce the recurrence rate of otitis and shorten the drainage time of middle ear effusion and provide better hearing outcomes (13). Rasheed et al. suggested that VT insertion in conjunction with adenoidectomy is statistically superior to adenoidectomy with myringotomy alone in the treatment of OME (13). However, some studies recommended only myringotomy with adenoidectomy as the first choice of surgical treatment to avoid complications of VT insertion (14). In a study conducted by Zhang et al. on 312 children with OME, they performed just myringotomy for serous fluid in the tympanic cavity and VT insertion for jelly fluid in the tympanic cavity. They found no statistically significant difference between the outcomes of the groups and concluded that the treatment of OME should not only be combined with the disease course but also with different hearing loss and the characteristics of effusion in the tympanic cavity (15).

Surgical intervention and VT insertion are generally recommended to eliminate mucous effusion (16). Knowing the effusion character in OME can help the surgeon in planning medical treatment, follow-up period, or early surgical intervention (6). However, assessing viscosity without paracentesis is difficult. It has been reported that hearing loss is detected more frequently in mucous OME, but the level of hearing loss may not be determined in age groups where hearing test evaluation is not possible (5). USG application through the external auditory canal was attempted to define the effusion character as thin or thick. However, it was reported that the waveforms could not be interpreted on the computer in 34% of the cases, and therefore reliable results could not be obtained (17). Currently, no predictor can be used to determine the viscosity of middle ear effusion.

It has been reported that there may be changes in neutrophils, lymphocytes, platelets, and MPV in the blood in inflammatory diseases, depending on the severity of inflammation. NLR may help evaluate the etiology and prognosis of these diseases (5, 18-20). Neutrophils are responsible for persistent inflammation, while lymphocytes play a role in the regulatory immune pathway. NLR provides information about both inflammatory and immune pathways (21). Platelets, when stimulated due to inflammation, release pro-inflammatory substances and their numbers increase. High NLR and PLR values have been associated with the severity of inflammation (21, 22). SII is a newly defined inflammatory index, calculated as "platelet count multiplied by neutrophil count divided by lymphocyte count," which has been suggested as a prognostic marker for malignancy and inflammatory conditions (23).

In previous studies, it has been reported that lymphocyte counts were lower and NLR and PLR values were significantly higher in serous OME compared to healthy children (5-7). In our study, we found that children with serous OME undergoing surgery for OAH had higher lymphocyte counts and significantly lower NLR values (<1) compared to children without otitis. No difference was observed in PLR values among

the three groups. These differing results suggest that inflammatory parameters may vary depending on the causative factor in OME. Previous studies have compared children with OME, where the causative factor was unspecified, to completely healthy children. In our study, all three groups consisted of children undergoing surgery with a diagnosis of OAH. Therefore, our findings may be more useful in differentiating between serous or mucous OME, which can occur simultaneously, especially in children with OAH. Generally, a high NLR is associated with poor prognosis and severe inflammation (23). The low NLR value in serous OME may be due to the lower severity of inflammation and the dominance of the regulatory pathway in inflammation. One study reported that a low MPV value in OME favored mucoid effusion (5). In our results, we found that MPV was significantly lower in children with mucous OME undergoing surgery for OAH compared to children with OAH where otitis was not detected. Another study reported that a high SII (>510) was associated with an inflammatory state and poor prognosis in patients with sensorineural hearing loss (23). No studies were found regarding the evaluation of SII in OME. In our patients, no significant difference was found in terms of SII among the three groups.

In our study,it was observed that mucous OME increased in the spring and winter months compared to other months. In a previous study by Tian et al, it was reported that the incidence of OME in the winter and spring months was higher than in the summer and autumn months, and this situation was found to be consistent with the seasonal change of meteorological environmental factors and was related to air quality, air pressure and temperature (24). They reported that the average daily OME patient number increased as air quality worsened, air pressure increased and temperature decreased (24). Nevertheless, we think that an increase in allergic and viral rhinitis during the spring and winter months may contribute to a higher prevalence of mucoid effusions in these seasons.

The limitations of our study are that it was a single-centered retrospective study and effusion character was evaluated subjectively. We think that multi-center and prospective clinical studies are necessary in this area.

Conclusion

In children with OAH and OME, NLR and MPV values may help clinicians distinguish between serous or mucous effusion based on clinical findings. A low NLR may suggest that the effusion is serous in pattern. The presence of a low MPV should raise the possibility of mucous effusion in patients.

Author Contribution

All authors contributed to the concept, design, data collection, literature review, and analysis of the study. The corresponding author was responsible for writing the article.

References

1. Upadhya I, Datar J. Treatment options in otitis media with effusion. Indian J Otolaryngol Head Neck Surg 2014;66:191-197

2. Park CW, Han JH, Jeong JH, et al. Detection rates of bacteria in chronic otitis media with effusion in children. J Korean Med Sci 2004;19:735-738

3. Ha R, Lim BW, Kim DH, Park JW, Cho CH, Lee JH. Predictive values of neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and other prognostic factors in pediatric idiopathic sudden sensorineural hearing loss. Int J Pediatric Otorhinolaryngol 2019;120:134-139

4. Doğan A, Apaydın E, Özcan KM, Dere H. New diagnostic indicators in chronic otitis media with effusion: neutrophil to lymphocyte ratio and thrombocyte lymphocyte ratio. ENT Updates 2016;6:12-15

5. Yükkaldıran A, Erdoğan O, Kaplama ME. NLR and PLR in otitis media with effusion in children: diagnostic role and audiological correlation. Int J Clin Pract 2021;75:e13805

6. Boztepe OF, Demir M, Gün T, Bilal N, Ensari NA, Doğru H. A novel predictive marker for the viscosity of otitis media with effusion. Int J Pediatr Otorhinolaryngol 2015;79:2355-2358

7. Elbistanlı MS, Koçak HE, Acıpayam H, Yiğider AP, Keskin M, Kayhan FT. The Predictive Value of NLR and PLR for the effusion viscosity in otitis media. J Craniofac Surg 2017;28:e244-e247

8. Marcano-Acuna ME, Carrasco-Llatas M, Tortajada-Girbes M, Dalmau-Galofre J, Codoner-Franch P. Impact of adenotonsillectomy on the evolution of inflammatyory markers. Clin Otolaryngol 2019;44(6):983-988

9. Hızalan İ. Ed. Önerci M, part ed. Güneri A. Book Ear Nose Throat Diseases Head Neck Surgery 2021:223-240

10. Kim TH, Chae SW, Kim HJ, et al. Effect of recombinant vascular endothelial growth factor on experimental otitis media with effusion. Acta Otolaryngol 2009;125:256-259

11. Vanneste P, Page C. Otitis media with effusion in children: Pathophysiology, diagnosis, and treatment. A review. J Otol 2019;14:33-39

12. Matkovic S, Vojvodic D, Baljosevic I. Cytokine levels in groups of patients with different duration of chronic secretory otitis. Eur Arch Otorhinolaryngol 2007;264:1283-1287

13. Rasheed AM, Abbas AM, Hilal SA, Homadi NJ. Adenoidectomy and Endoscopic Myringotomy with and without ventilation tube insertion for Treatment of Otitis Media with Effusion in 6-12-year-old children. Int Tinnitus J. 2023 Dec 4;27(1):27-33.

14. Tao J, Luo R, Chen Y, Hou C, Qin H. Myringotomy or tympanostomy tube insertion, comparison of surgical treatment of adenoid hypertrophy and otitis media with effusion in children. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi (J Clin Otorhinolaryngol Head Neck Surg). 2020;34(3):207-10.

15. Zhang Y, Fu Y. Different treatment methods and efficacy analysis of otitis media with effusion in children with different hearing loss. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi (J Clin Otorhinolaryngol Head Neck Surg). 2022;36(10):731-5.

16. Chung MH, Choi JY, Lee WS, et al. The compositional difference in middle ar effusion: Mucous Versus Serous. Laryngoscope 2002;112:152-155

17. Seth R, Discolo CM, Palcczewska GM, et al. Ultrasound characterization of Middle ear Effusion. Am J Otolaryngol 2013;34:44-50

18. Bucak A, Ulu S, Oruc S, et al. Neutrophil to Lymphocyte ratio as a novel-potential marker for predicting prognosis of Bell palsy. Laryngoscope 2014;124:1678-1681

19. Kum RO, Ozca M, Baklacı D, et al. Elevated neutrophil to lymphocyte ratio in squamous cell carcinoma of larynx compared to benign and precancerous laryngeal lesions. Asian Pac J Cancer Prev 2014;15:7351-7355

20. Boztepe OF, Gun T, Demir M, et al. A novel predictive marker for the recurrence of nasal polyposis following endoscopic sinus surgery. Eur Arch Otorhinolaryngol 2016;273:1439-1444

21. Guo Y, Liu J. The Roles Played by Blood Inflammatory Parameters in Sudden Sensorineural Hearing Loss. Ear Nose Throat J 2021 Oct 18;145561320960355

22. Kum RO, Özcan M, Baklacı D, Kum NY, Yılmaz YF, Unal A, et al. Investigation of NLR and MPV in sudden hearing loss. Braz J Otorhinolaryngol 2015;81:636-641

23. Ulu Ş, Kınar A, Bucak A, Özdemir M. SII of patients with idiopathic SSHL: comparison of NLR and PLR values. Ear Nose Throat J 2021;100:726-730

24. Tian H, Zhang H, Chen Y, Zhong C. A Study of the Influence of Meteorological and Environmental Factors on Otitis Media with Effusion in Lanzhou. Indian J Otolaryngol Head Neck Surg. 2024;76(6):5234-5247.

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ORIGINAL ARTICLE

Evaluation of Her2 Positivity in Gastric Cancer Using Two Different Methods: A Prospective Study

Mide Kanserinde Her2 Pozitifliğinin Farkli İki Yöntemle Değerlendirilmesi: Prospektif Bir Çalışma

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ABSTRACT

Aim: Gastric cancer, a common type of gastrointestinal (GI) system malignancy, has an incidence associated with various factors. These include ethnic background, dietary habits, socioeconomic status, lifestyle, geographic region, and the prevalence of Helicobacter pylori. As with all malignancies, the pathogenesis of gastric cancer involves various genetic factors, one of which is the human epidermal growth factor receptor-2 (EGFR-2) (Her2/neu or c-erbB2) gene. The objective of this study is to compare the amplification levels of the Her2/neu gene in gastric cancer samples obtained from our patients using Real-Time polymerase chain reaction (RT-PCR) with the overexpression of Her2 protein, assessed through immunohistochemistry (IHC) on the same tissue samples. Additionally, the study aims to investigate the relationship between Her2 positivity and prognostic factors such as age, stage, gender, tumor localization, and histological type.
Method: This study was conducted prospectively on newly diagnosed 50 gastric cancer patients. Her2 gene expression at the mRNA level was assessed using RT-PCR on both tumor and normal fresh gastric tissue samples from all 50 patients. Additionally, Her2 protein levels were evaluated through IHC on paraffin blocks from these same 50 patients, and the results were compared with each other.
Results: In the evaluation of IHC, Her2 overexpression was observed in five patients (10%), and Her2 amplification was detected in five patients (10%) using RT-PCR. However, it was notable that there was no correlation between these two methods, and the result was statistically insignificant ($p > 0.05$). Additionally, no statistically significant difference was observed between Her2 gene expression in tumor tissues and prognostic factors ($p > 0.05$).
Conclusion: Her2 protein overexpression and Her2 gene amplification may contribute to potential tumor development. As no correlation was found between these two methods, further studies are needed to evaluate false negativity, investigate patient survival in terms of its contribution to prognosis, and validate our hypothesis.

Keywords: Gastric cancer, Her2 (c-erbB2), immunohistochemistry, Real-Time polymerase chain reaction

ÖZ

Amaç: Gastrointestinal sistem malignitelerinin sık görülen bir tipi mide kanserinin insidansı çeşitli faktörlerle ilişkilendirilmiştir. Etnik köken, beslenme şekli, sosyoekonomik durum, yaşam tarzı, coğrafi bölge koşulları ve H. pylori prevalansı ile değişkenlik göstermektedir. Tüm malignitelerdeki gibi gastrik kanserin patogenezinde çeşitli genetik faktörler yer almaktadır ve human epidermal büyüme faktörü reseptörü 2 (Her2/neu ya da c-erb B2) geni de bunlardan biridir. Gastrik kanser hastalarımızdan alınan örneklerde Her2/neu geninin Real-Time polimeraz zincir reaksiyonu (RT-PCR) ile amplifikasyon düzeyini, yine aynı dokudan alınmış ve IHC ile çalışılan Her2 protein overekspresyonu ile karşılaştırmaktır. Pozitiflik saptandığı durumda yaş, evre, cinsiyet, tümoral lokalizasyon ve histolojik tip gibi prognostik faktörlerle ilişkisini araştırmaktır.
Yöntem: Bu çalışma, prospektif olarak yeni tanı alan 50 mide kanseri hastası üzerinde yapılmıştır. Elli hastanın hem tümöral ve hem de normal taze mide dokusundan RT-PCR yöntemiyle mRNA düzeyinde Her2 gen ekspresyonu bakılmıştır. Yine bu elli hastanın IHC değerlendirme için parafin bloklar üzerinden Her2 protein seviyesi çalışılmıştır ve bu sonuçlar birbirleriyle karşılaştırılmıştır.
Bulgular: IHC ile yapılan değerlendirmede beş hastamızda (% 10) Her2 overekspresyonu ve Real-Time PCR ile beş hastamızda (% 10) amplifikasyon saptandı. Ancak bu iki yöntem arasında korelasyon bulunmadığı dikkatimizi çekti ve istatistiksel olarak anlamsızdı ($p> 0.05$). Ayrıca tümör dokularındaki Her2gen ekspresyonları ile prognostik faktörler arasında istatistiksel olarak anlamlı bir fark gözlenmedi ($p> 0.05$).
Sonuç: HER2 protein overekspresyonu ve Her2 gen amplifikasyonu potansiyel tümör gelişimine katkıda bulunabilir. Bu iki yöntem arasında korelasyonun olmaması sonucunda; yanlış negatifliğin değerlendirilmesi ve prognoza katkısı açısından hasta sağkalımlarının araştırılması gerekmektedir, bu hipotezimizin doğrulanması için daha ileri çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Mide kanseri, Her2 (c-erb B2), immunohistokimya, Real-Time PCR

Introduction

Gastric cancer is a common malignancy of the gastrointestinal (GI) tract (1-3). It is one of the leading causes of cancer-related mortality worldwide (3,4). Its incidence varies depending on both environmental and genetic factors, such as ethnicity, geographic conditions, dietary habits, socioeconomic status, lifestyle, and the prevalence of Helicobacter pylori (1,3,4).

Among the genetic factors contributing to gastric cancer, the inactivation of adenomatous Polyposis coli (APC) and tumor protein 53 (tP53), the most frequently inactivated genes among tumor suppressor genes, as

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well as mutations, amplifications, or overexpressions in the proto-oncogenes rat sarcoma (RAS), cellular myelocytomatosis (C-myc), and human epidermal growth factor receptor-2 (EGFR-2) (Her2), a member of the EGFR family, have been identified (5,6).

The Her2 protein (also known as c-erbB2/neu) is a transmembrane tyrosine kinase receptor encoded by the Her2/neu gene located on the long arm of chromosome 17. It is primarily responsible for regulating various cellular events, including differentiation, proliferation, apoptosis, and cell survival. Her2 proteins contribute to tumor cell biology by enhancing cell proliferation through amplification and protein overexpression resulting from mutations in tumor tissues, disrupting apoptosis, and participating in processes such as adhesion and migration (1,2,7). These findings suggest that Her2 is an oncogene.

Studies have shown that the Her2 gene plays a role in many types of cancer. Her2 amplification and/or overexpression has been detected in approximately 34% of invasive breast cancer cases and other cancer types such as colon, esophageal, gastric, bladder, endometrial, and lung cancers, as well as head and neck tumors (2,8).

Several studies have demonstrated the importance of Her2 in the pathogenesis, prognosis, and novel treatments of gastric cancers. Additionally, several studies have investigated anti-Her2 agents in response to the need for new therapeutic approaches in aggressive gastric cancers (8-12).

In light of this information, the objective of this study is to immunohistochemically assess Her2 receptor levels in the tumor tissue of newly diagnosed gastric cancer patients who have not received any prior treatment, to detect Her2/neu gene expression at the mRNA level using the polymerase chain reaction (PCR) method in both normal and tumor gastric tissues, to compare these levels, and to examine their effects on prognosis. Given that Her2 overexpression and increased Her2 activity are poor prognostic factors, any increase in Her2 expression could be used as a prognostic biomarker in diagnosis and as a therapeutic target in treatment. In summary, we aim to contribute to the development of new gastric cancer treatment strategies using anti-Her2 agents, thereby increasing patients' life expectancy.

Material And Method

Study Design

The protocol for this prospective study was approved by the Gaziantep University Medical Ethics Committee before the commencement of the study (Approval No. 115, Approval Date: March 13th, 2012). The study sample consisted of 50 patients who visited the Gastroenterology Polyclinic at our hospital or were referred from an external center for endoscopy, underwent endoscopy at the Endoscopy Unit, were diagnosed with gastric adenocarcinoma in the pathology department, and volunteered for the study. Informed consent forms were obtained from each patient included in the study.

If a peptic ulcer or tumor formation was detected during the endoscopy procedures of the patients selected for this study, biopsies were taken from both normal and tumor gastric tissues for Her2/neu gene analysis, after obtaining the relevant consent from the patients, in addition to the biopsy taken for pathological evaluation.

Clinical Diagnosis and Data Collection

After obtaining the relevant informed consent from patients with suspected gastric cancer, biopsies were taken during the endoscopy procedures performed at the Endoscopy Unit. Patients' data, including age, gender, complaints at admission, and whether they had received treatment for known stomach diseases, were collected from their medical histories. Localization was determined by endoscopy. All patients underwent a physical examination. Patients' demographic characteristics and family histories were recorded. Pathological evaluation, along with imaging methods, including abdominal and thoracic CT scans, were performed to determine the cancer stages and to detect the histological type, differentiation, invasion, and lymph node involvement. The pathological evaluation of patients with early gastric cancer or resectable advanced gastric cancer, following surgical procedures, was conducted at the Pathology Laboratory of the Faculty of Medicine. Tissue samples from patients diagnosed with gastric cancer were tested for Her2 positivity by immunohistochemical (IHC) staining.

Her2/neu gene expression was investigated in both normal and tumor gastric tissue samples taken from patients whose gastric cancer was diagnosed based on pathological findings, using the Real-Time PCR (RT-PCR) method after RNA isolation in the Medical Genetics Laboratory.

Immunohistochemical Assessment

The diagnosis of gastric adenocarcinoma in the patients was made in the Department of Pathology by IHC analysis using antibodies developed against Her2. Formalin-fixed paraffin blocks were deparaffinized with xylene solutions after being heated at 60°C in an oven. IHC staining was performed via the immunoperoxidase method, followed by chromogenic staining. Subsequently, the preparations were examined under light microscopy using primary rabbit monoclonal HER2 antibody (1:100), and those showing diffuse field staining were evaluated. The percentage and intensity of the staining were scored as '-', indicating no staining; '1+', indicating light staining; '2+', indicating moderate staining; and '3+', indicating strong staining (Table 1).

Table 1. IHC Scoring System in Gastric Cancer

Membrane Staining Pattern	Assessment Results	Additional Evaluation
No staining reactivity	Negative	Not necessary
Light or indistinct membranous staining	Negative	Not necessary
Moderate basolateral or lateral membranous staining	Doubtful	ISH Correlation Recommended
Strong basolateral or lateral membranous staining	Positive	Not necessary

IHC: Immunohistochemistry, ISH: In situ hybridization

Samples scored as '-' were considered negative, and those scored as '3+' were considered positive. On the other hand, samples scored as '1+' and '2+' were re-evaluated with fluorescence in situ hybridization (FISH) (13).

RNA Isolation

The tubes containing tumor and normal tissue samples obtained by endoscopy were stored in a liquid nitrogen tank and then sent to the Medical Genetics Laboratory. The samples were removed from liquid nitrogen and divided into 25 mg pieces. RNAs were extracted using the QIAamp RNA Blood Mini Kit following the manufacturer's recommended method. After centrifugation, the supernatant was removed. The samples were placed on a filter tube and centrifuged. Next, 90 µl of DNase Incubation Buffer and 10 µl of DNase I solution were added to the filter tube and incubated at room temperature for 15 minutes. 500 µl of Wash Buffer I was added to the filter tube and centrifuged. Subsequently, 500 µl of Wash Buffer II was added to the filter tube and centrifuged. Then, 300 µl of Wash Buffer II was added and centrifuged. After centrifugation at 8,000xg for 1 minute, the RNAs were removed from the filter tube and stored at -85 °C.

cDNA Synthesis

Copy DNAs (cDNAs) were synthesized using the Ipsogen Reverse Transcription-Dx Kit. PCR conditions were adjusted, and the PCR mixture was prepared as specified in the kit. Necessary amounts of RNAs were obtained by measuring RNAs using a nanodrop. They were prepared for a total of 100 samples; 50 were tumor tissue samples, and the other 50 were normal tissue samples. PCR was performed using the AB Applied Biosystems Veriti 96-Well Thermal Cycler PCR device.

Real-time polymerase chain reaction (RT-PCR)

Detection of Her2 gene expression by RT-PCR: The Her2 gene region was studied using the Qiagen primer set.

RT-PCR Determination of ACTB expression: Actin Beta (ACTB) was used as the housekeeping gene, and the following mixture was prepared for a total of 100 samples to compare Her2 and ACTB.

Statistical Analysis

Statistical analyses of the collected data were conducted using SPSS 15.0 (Data Analysis Software System, Version 15.0, 2006). The Kolmogorov-Smirnov test was used to analyze the normal distribution characteristics of the continuous variables. In the comparison of two independent groups, the student's t-test was used for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. The relationship between categorical variables was analyzed using Pearson's chi-square test. The descriptive statistics obtained from the collected data were expressed as frequencies (n), percentages (%), and mean ± standard deviation values. Probability (p) values of < 0.05 were considered statistically significant. Pearson's correlation analysis was used to investigate the correlations between different parameters.

Results

The sample for this prospective study consisted of 50 patients who presented to the Department of Gastroenterology and were diagnosed with gastric cancer based on endoscopic procedures. Of these patients, 34 (68%) were male and 16 (32%) were female, yielding a male-to-female ratio of 2.1:1. The mean age of the sample was 60.22 ± 14.7 years, with a range from 29 to 88 years.

Among the 50 patients, 28 (56%) had previously sought medical attention for stomach-related complaints

and had a history of gastritis, peptic ulcer disease, or gastroesophageal reflux disease. Additionally, 19 (38%) patients, including 16 males and 3 females, were using proton pump inhibitors (PPIs) as part of their treatment regimen. Furthermore, 39 (78%) patients, including 4 with a history of GI bleeding, were taking acetylsalicylic acid (ASA) and/or nonsteroidal anti-inflammatory drugs (NSAIDs) (Table 2).

Table 2. Distribution of Patients' Socio-Demographic Characteristics by Gender

	Male (n=34)	Female (n=16)
Mean Age (years)	61.38±11.47	57.75±20.17
Patients with comorbidities	68%	32%
Patients with known stomach disease	20	8
Patients with a history of PPI use	16	3
Patients with a history of ASA or NSAID use	29	10
Patients with a history of GI bleeding	4	0
Patients with a history of familial cancer	19	9
Patients with a history of familial gastric cancer	0	3

A total of 28 patients (56%) had a familial history of cancer. Among them, three patients (6%) had a family history specifically of gastric cancer, and all of these individuals were female (Table 2).

Among the 50 patients, 28 (56%) had comorbidities, all of whom were on additional medications. Within this group, 4 patients (8%) had only hypertension, 5 (10%) had heart disease, 10 (20%) had diabetes, and 3 (6%) had cancer. Additionally, 39 patients (78%) were using ASA and/or NSAIDs, and 19 (38%) were using PPIs. The study identified 33 active smokers (66%), while 7 patients (14%) reported alcohol use. Notably, all patients who consumed alcohol were also active smokers, representing 14% of the sample. Among the 50 patients diagnosed with gastric adenocarcinoma, 17 (34%) had the signet ring cell type, 3 (6%) had a mixed type, and the remaining 30 (60%) were classified with other types of adenocarcinoma.

Based on the staging of gastric cancers among the patients, 3 patients (6%) were classified as stage 1, 7 (14%) as stage 2, 8 (16%) as stage 3, and 32 (64%) as stage 4. A total of 44 patients (88%) exhibited lymph node metastases, while 6 patients (12%) showed no lymph node involvement.

IHC assessments conducted after the pathological evaluation of gastric cancer diagnoses revealed that 41 patients had negative Her2 staining, 3 (6%) exhibited 1+ staining, 1 patient (2%) exhibited 2+ staining, and 5 (10%) exhibited 3+ Her2 staining. Patients with 1+ and 2+ Her2 staining underwent additional evaluation using silver in situ hybridization (SISH), which confirmed negative Her2 status. In contrast, patients with 3+ Her2 staining were deemed positive for Her2 without requiring further SISH testing. Overall, only 5 patients (10%) were found to have Her2 overexpression based on 3+ IHC staining.

Analysis of Her2 overexpression by gender revealed that 4 patients (80%) with Her2 positivity were male, while 1 patient (20%) was female. There was no significant difference in age between patients with Her2 positivity and those with Her2 negativity. Similarly, no statistically significant correlation was observed between tumor localization and Her2 positivity (p=0.375). None of the 17 patients with signet ring cell adenocarcinoma or the 3 patients with mixed-type adenocarcinoma exhibited Her2 positivity. Her2 negativity in patients with signet ring cell adenocarcinoma was considered borderline significant (p=0.056). Additionally, no significant correlation was identified between cancer stage, metastasis, and Her2 positivity (p=0.845) (Table 3).

Table 3. Distribution of Her2 Overexpression by Patient Subgroups

Her2 Overexpression (IHC)			p-value
	Patients with Her2-Negativity	Patients with Her2-Positivity	
Localization:			0.375
Upper zone	7 (15.6%)	1 (20%)	
Trunk	10 (22.3%)	2 (40%)	
Pyloric antrum	12 (26.7%)	1 (20%)	
Multiple zones	16 (35.5%)	1 (20%)	
Histological Type:			0.056
Signet ring	17 (37.8%)	0 (0%)	
Mixed	3 (6.7%)	0 (0%)	
Other	25 (55.6%)	5 (100%)	
Cancer Stages: I	3 (6.7%)	0 (0%)	0.845
II	6 (13.3%)	1 (20%)	
III	7 (15.6%)	1 (20%)	
IV	29 (64.4%)	3 (60%)	

IHC: Immunohistochemistry

To evaluate Her2 gene amplification in our patients, the housekeeping gene ACTB was used to calculate Her2 levels in tumoral and normal tissue samples. Patients with a ratio above 1.25 (n=5) were classified as having Her2 amplification, while those with a ratio below 0.75 (n=3) were classified as having decreased Her2 expression.

All 5 patients with Her2 gene amplification were male. Among three patients with decreased Her2 expression, two were female, and one was male. Regarding tumor localization, three patients (60%) with Her2 gene amplification had multi-zone involvement, one (20%) had involvement in the pyloric antrum and one (20%) in the gastric trunk. No significant relationship was found between tumor localization and gene amplification (p=0.459). Similarly, there was no significant association between histological type and gene amplification (p=0.290). Three of five patients (60%) with Her2 gene amplification were cases of stage IV cancer. However, no significant correlation was observed between cancer stage and gene amplification (p=0.382) (Table 4).

Table 4. Distribution of Her2 Gene Amplification by the Subgroups of Patients

	Her2 Gene Amplification (PCR) T/N tissue ratio			p-value
	Amplified	Normal	Decreased	
Localization:				
Upper zone	0 (0%)	8 (19.0%)	0 (0%)	
Trunk	1 (20%)	11 (26.2%)	0 (0%)	
Pyloric antrum	1 (20%)	10 (23.8%)	2 (66.7%)	0.459
Multiple zones	3 (60%)	13 (31.0%)	1 (33.3%)	
Histological Type:				
Signet ring	2 (40%)	14 (33.3%)	1 (33.3%)	
Mixed	1 (20%)	1 (2.4%)	1 (33.3%)	0.290
Other	2 (40%)	27 (64.3%)	1 (33.3%)	
Cancer Stages:				
I	0 (0%)	3 (7.1%)	0 (0%)	
II	1 (20%)	6 (14.3%)	0 (0%)	
III	1 (20%)	4 (9.5%)	3 (100%)	0.382
IV	3 (60%)	29 (69.0%)	0 (0%)	

PCR: Polymerase chain reaction

Furthermore, no significant correlation was identified between Her2 gene amplification and Her2 protein overexpression as determined by IHC (p=0.397) (Table 5).

Table 5. Comparison of Her2 Overexpression and Gene Amplification

	Her2 Gene Amplification (PCR) T/N tissue ratio			p-value
IHC assessment	**Amplified**	**Normal**	**Decreased**	
Negative	5 (100%)	37 (88.1%)	3 (100%)	
Positive	0 (0%)	5 (11.9%)	0 (0%)	0.397
Total	5 (100%)	42 (100%)	3 (100%)	

IHC: Immunohistochemistry, PCR: Polymerase chain reaction

Discussion

Surgery is the cornerstone of gastric cancer treatment and is supplemented with chemotherapy as neoadjuvant or adjuvant therapy. Given the relatively low overall survival rates associated with standard treatment regimens for gastric cancer, targeted therapies have gained significant attention. In this context, various studies have been conducted targeting the Her2 gene, known as an oncogene, which has become a focal point of research, and Her2-positivity was determined as a poor prognostic factor for breast cancer. Consequently, trastuzumab, an anti-Her2 agent, became one of the standard agents in the treatment of breast cancer (9, 14).

The methods used to assess Her2 gene amplification and protein overexpression were primarily developed based on studies investigating Her2 positivity in breast cancer. FISH and IHC are the two most commonly employed methods for primary assessment. Among these two options, IHC is the most widely used due to its affordability and speed. However, as a quality control-dependent method, IHC can produce subjective and relatively variable results. In contrast, FISH is more expensive but offers greater reliability. The reported correlation between FISH and IHC results ranges from 73% to 98% (9, 15-17). Consistent with the literature, this study utilized the IHC method to assess protein overexpression and the PCR method to evaluate gene amplification.

Her2 overexpression in gastric cancer was first studied by Sakai et al. in 1986 using the IHC method (18). Subsequent studies have reported Her2 positivity rates in gastric cancer ranging from 8.5% to 32%, depending on the methods used. It has been concluded that Her2 positivity is a poor prognostic factor in gastric cancer patients due to its association with lymph node involvement, an aggressive disease course, and shorter survival (2, 19-21). However, other studies argue that Her2 positivity is not linked to prognosis or lymph node involvement. They attribute findings of Her2 positivity as a poor prognostic factor to methodological differences, including variations in techniques used to assess Her2 overexpression, the choice of IHC antibody, sample size, histopathological subtypes, degree of differentiation, and stage of disease (22, 23).

The wide range of Her2 positivity rates (8.5% to 32%) reported in gastric cancer studies may be attributed to factors such as tumor histology, patient population, age group, disease stage, and, most importantly, the method used to determine Her2 overexpression. Even among studies employing the same method,

variations in methodological details, such as the specific antibody used for IHC, stand out as significant contributors to these differences (24, 25).

Notably, there are key distinctions in evaluating Her2 overexpression with the IHC method in gastric cancer compared to breast cancer. Firstly, membranous staining reactivity tends to be incomplete in gastric cancer. Secondly, tumoral heterogeneity is observed at a higher frequency in gastric cancer than in breast cancer (13, 26, 27).

In a meta-analysis by Wang et al. (28) investigating potential correlations between Her2 overexpression and various parameters, including age, gender, localization, stage, and histological type, Her2 overexpression was found to be positively associated with intestinal type, advanced stage, and disease spread. In contrast, in this study, the correlation between Her2 overexpression and histological type was only borderline significant (p = 0.056).

In another study examining Her2 positivity using IHC and SISH, 7 of 14 IHC 2+ patients were evaluated as SISH positive, while all 8 IHC 3+ patients were found to be SISH positive. This study concluded that as the depth of invasion increases, Her2 negativity also increases (p=0.03) (29). In our study, the depth of invasion was not evaluated.

Kimura et al. (22) reported no significant relationship between Her2 positivity and stage, lymph node involvement, or invasion in gastric cancer, concluding that Her2 positivity lacks prognostic value. However, the Her2 positivity rate was determined to be 24% using the IHC method.

In the study conducted by Baykara et al. (30), IHC evaluation was performed, and FISH analysis was applied specifically to the low IHC-positive group. A positivity rate of 15% was observed in this patient cohort. Furthermore, it was highlighted that Her2 positivity in early-stage cases is linked to a worse prognosis.

In another study, Her2 positivity in gastric cancer was reported at 8%. In this study, all 7 patients with IHC 2+ and one of the 12 patients with IHC 3+ were found to be FISH negative (31).

In a review by Chua et al. (32), it was stated that IHC is the most commonly used method for determining Her2 positivity, followed by ISH. The study reported an average Her2 positivity rate of 18%, based on data from several studies, and noted that Her2-positive patients tend to have shorter lifespans compared to Her2-negative patients. Her2 positivity was also identified as a poor prognostic factor. However, it was concluded that Her2 positivity is not correlated with parameters such as age, gender, localization, tumor size, invasion, or stage. In comparison, this study determined that five of the 50 patients exhibited Her2 positivity based on IHC findings. Further analysis of four patients with low Her2 staining using FISH revealed that these patients were, in fact, negative for Her2. In this study, Her2 positivity was not associated with age, gender, tumor localization, or stage (p>0.05). Based on the histopathological evaluation of tissue biopsies and the presence of a signet ring cell component, patients were categorized into three gastric adenocarcinoma groups: signet ring cell type, mixed type, and other types. The IHC assessment revealed no Her2-positive cases in the signet ring cell or mixed-type groups. The patients found to be Her2-positive all had other types of gastric adenocarcinoma. The difference in Her2 positivity between the "other types" group and the signet ring cell and mixed type groups was borderline significant (p = 0.056).

In the study by Gürbüz et al. (33), Her2 positivity was detected at a rate of 18.1% in IHC evaluation. Additionally, it was noted that the presence of a signet-ring cell component was negatively correlated with Her2 positivity.

In a study comparing Her2 positivity using IHC and FISH, samples from 10 patients included only gastric biopsies, 10 patients had only gastric resection specimens, and 20 patients had both biopsy and gastric resection specimens (a total of 40 patients). Her2 positivity was confirmed with both methods in nine patients (22.5%), and heterogeneity was observed in 5 patients. This heterogeneity was validated using both FISH and IHC in both biopsy and surgical resection specimens (34). As previously emphasized, heterogeneity is more common in gastric cancer compared to breast cancer.

In a study investigating the relationship between Her2 positivity and atypical gastric tumors, Giuffré et al. (35) determined that Her2 positivity, as evaluated by IHC, is associated with high-grade and advanced-stage gastric cancer. As a result, they concluded that Her2 overexpression is a poor prognostic factor linked to low survival rates and high mortality.

PCR analysis revealed gene amplification in 5 out of the 50 patients included in this study. No significant correlation was found between positive gene

amplification and factors such as age, localization, histological type, or stage ($p > 0.05$). Additionally, there was no significant correlation between the results obtained through PCR and IHC methods ($p > 0.05$). Notably, gene amplification was not detected in patients identified as having Her2 overexpression by the IHC method, and conversely, Her2 overexpression was not observed in patients with gene amplification determined by the PCR method.

Risio et al. (36) emphasized that the timing of IHC analysis significantly impacts the results. They reported that as the time between the preparation of paraffin blocks and the IHC analysis increases, the rate of Her2 negativity also rises. In this study, the IHC assessment of samples collected from 50 patients over two years was conducted collectively at the end of the study. Consequently, a higher Her2 positivity rate was observed in the samples from patients with more recent diagnoses.

In a study evaluating Her2 positivity exclusively in tumoral tissues using three different methods, Kim et al. (25) reported that Her2-positive cases were associated with moderate-to-well-differentiated tumors. They also found no relationship between Her2 positivity and factors such as age, stage, or gender. Patients assessed with FISH were further analyzed using PCR, revealing a 97.6% concordance between the two methods. Notably, four patients who were determined to have Her2-negative staining via the IHC method were found to exhibit gene amplification through PCR. Additionally, in one patient with 1+ Her2-positive staining by IHC, PCR detected high amplification, while FISH yielded a negative result.

In a study comparing the results of gene amplification assessment using the RT-PCR method with heterozygosity and IHC results, Königshoff et al. (37) stated that the RT-PCR method has limited use due to difficulties in sample stabilization. They noted that if stabilization is not achieved, RNA degradation will increase, leading to a decrease in the reliability of RT-PCR. Additionally, they mentioned that gene amplification is a tissue-limited phenomenon, highlighting the importance of heterogeneity. They emphasized a correlation between transcriptional or post-translational activation in patients with positive IHC staining and the absence of gene amplification detected by PCR. They attributed the finding that patients identified as having gene amplification by the PCR method exhibited negative IHC staining to the lack of the promoter region in the area where amplification was detected. Furthermore, they indicated that if amplification had occurred recently, the protein overexpression step might not have been initiated yet. In other words, they stressed that there is a certain time lag between amplification and overexpression. They also stated that the probability of obtaining negative results with the IHC method increases as time elapses before the paraffin blocks are analyzed.

Another important concern that should be noted in patients with positive IHC staining and no gene amplification is the content of the sample obtained by biopsy. As Dabbs et al. (38) stated, even if the tissue is directly taken from the tumoral area, it may contain a small or insufficient amount of invasive tumor tissue. Additionally, since the tissue biopsied from the tumoral region includes peripheral tissue elements such as adipose tissue, fibrous tissue, necrotic tissue, and connective tissue, as well as immune system components like reactive cells, lymphocytes, and macrophages, tumor mRNA can be diluted, resulting in a false-negative PCR result. Furthermore, the gastric intratumoral area has a heterogeneous structure. Thus, the likelihood of false-negative results increases if the biopsied portion coincides with a region exhibiting low or no gene amplification of Her2. Conversely, biopsy samples taken from patients with positive gene amplification may show IHC staining ranging from 1+ and 3+ due to this heterogeneity. These false-negative results contribute to a low correlation between IHC and PCR results in patients with positive gene amplification. Therefore, it is widely believed that at least two different methods, such as IHC and FISH, should be used before treatment to confirm the results obtained with PCR.

In two separate studies conducted by Lemoine (39) and Kameda (40), a low correlation was found between gene amplification and protein overexpression rates. They suggested that gene amplification is not the primary mechanism in patients who exhibit high overexpression despite negative amplification results. They noted that various genes can mediate overexpression, which may occur through increased transcriptional activation or alterations in post-transcriptional processes. Conversely, more recent studies have reported higher correlations between gene amplification and protein overexpression rates assessed by different methods.

O'Malley et al. (41) investigated the correlation between Her2 evaluation results obtained using three different IHC techniques and those obtained through

the PCR method. They found that the results from the three IHC techniques correlated with the PCR results in 82%, 89%, and 80% of the patients, respectively. Additionally, IHC staining results were negative in 8 patients who were identified as having positive gene amplification by the PCR method. This finding suggests that even the use of three different high-sensitivity antibody detection kits was insufficient to detect low protein levels. Conversely, the PCR results for 11 patients who exhibited positive IHC staining across all three antibody types were negative. The authors attributed the negative gene amplification results from the PCR method in these 11 patients' tumor tissue samples to the heterogeneity of the samples.

The HER2 positivity of gastric cancer was evaluated in the Trastuzumab for Gastric Cancer (ToGA) study conducted by Bang et al. (42). As a result, trastuzumab was incorporated into treatment protocols for gastric cancer patients as a first-line therapy. In the study, an 87% concordance rate was observed between the results obtained using the IHC and FISH methods. Targeting Her2 positivity as a therapeutic approach significantly improved survival time. One of the study's most important findings was that anti-Her2 agents are ineffective in patients with positive gene amplification unless there is overexpression of the Her2 protein.

In this study, Her2 positivity was detected in 10% of gastric carcinoma patients using the IHC method, and gene amplification was also identified in 10% of gastric carcinoma patients using the PCR method. These rates are consistent with those reported in the literature. However, despite reports in the literature indicating a 60% to 95% correlation between the results obtained by the two methods, no significant correlation was found between them in this study. The use of the ISH method may be more effective in addressing the inconsistency between these methods and reducing false-negative results. Considering that the rate of negative IHC results increases as the time between preparation and analysis of paraffin blocks lengthens, it is essential to analyze paraffin blocks immediately after preparation.

In this study, biopsies were taken from both tumoral and normal tissues, and pathological evaluation reports were available for the tumoral tissues. However, tissues deemed normal were assessed macroscopically rather than histopathologically. Therefore, it should be noted that tissues considered normal may contain tumor cells. This could affect the amplification rate in patients with normal or low amplification levels, potentially leading to false-negative results.

Given the significance of heterogeneity in gastric cancer, the biopsy specimen used for IHC analysis must be adequate. An insufficient biopsy specimen can obscure heterogeneity and increase the likelihood of false-negative results. Additionally, care must be taken to prevent the tissue intended for gene amplification studies from becoming diluted.

In conclusion, while targeted treatments such as trastuzumab are effective in gastric cancer patients with Her2 overexpression, we believe that evaluation methods for Her2 require further validation through clinical studies. Therefore, future researches, including analyses of other mutations and polymorphisms, are needed to uncover potential relationships.

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Ethics Committee Approval

Gaziantep University Medical Ethics Committee, Approval No: 115, Date: March 13th, 2012.

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Conflict of Interest

The authors have no conflicts to disclose concerning the authorship and/ or publication of this article.

Author contributions

AIHS, AS, and MA contributed to the study design. AIHS, IS, SO, and BC collected the data. AIHS, IS, and SO analyzed the data and ensured the accuracy of the data analysis. AIHS, IS, MA, and SO interpreted the data and drafted the manuscript. AIHS, IK, and MA critically revised the manuscript for important content. All authors read and approved the final manuscript.

References

1.Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies. Int J Mol Sci. 2020 Jun 4;21(11):4012.

2.Gravalos C, Jimeno A. Her2 in gastric cancer: a new prognostic factor and a novel therapeutic target. Ann Oncol. 2008;19(9): 1523-1529.

3.Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet. 2020 Aug 29;396(10251):635-648.

4.Yang WJ, Zhao HP, Yu Y, Wang JH, Guo L, Liu JY, et al. Updates on global epidemiology, risk, and prognostic

factors of gastric cancer. World J Gastroenterol. 2023 Apr 28;29(16):2452-2468.

5.Nemtsova MV, Kuznetsova EB, Bure IV. Chromosomal Instability in Gastric Cancer: Role in Tumor Development, Progression, and Therapy. Int J Mol Sci. 2023 Nov 30;24(23):16961.

6.Christodoulidis G, Koumarelas KE, Kouliou MN, Thodou E, Samara M. Gastric Cancer in the Era of Epigenetics. Int J Mol Sci. 2024 Mar 16;25(6):3381.

7.Friedlaender A, Subbiah V, Russo A, Banna GL, Malapelle U, Rolfo C et al. EGFR and HER2 exon 20 insertions in solid tumors: from biology to treatment. Nat Rev Clin Oncol. 2022 Jan;19(1):51-69.

8.Valenza C, Guidi L, Battaiotto E, Trapani D, Sartore Bianchi A, Siena S et al. Targeting HER2 heterogeneity in breast and gastrointestinal cancers. Trends Cancer. 2024 Feb;10(2):113-123.

9.Okines AF, Cunningham D. Transtuzumab in gastric cancer. Eur J Cancer 2010;46(11): 1949-1959.

10.Kang Y, Bang Y, Lordick F, Park SR, Sawaki A, Chung HC, et al. Incidence of gastric and gastro-esophageal cancer in the ToGA trial: correlation with HER2 positivity 2008 Gastrointestinal Cancers Symposium. 75 (Abstr 11).

11.Guan WL, He Y, Xu RH. Gastric cancer treatment: recent progress and future perspectives. J Hematol Oncol. 2023 May 27;16(1):57.

12.Yu J, Fang T, Yun C, Liu X, Cai X. Antibody-Drug Conjugates Targeting the Human Epidermal Growth Factor Receptor Family in Cancers. Front Mol Biosci. 2022 Feb 28;9:847835.

13.Hofmann M, Stoss O, Shi D, Büttner R, van de Vijver M, Kim W et al. Assessment of a HER2 scoring system for gastric cancer: results from a validation study. Histopathology. 2008 Jun;52(7):797-805.

14.Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011 Oct 6;365(14):1273-83.

15.Lillemoe TJ, Rendi M, Tsai ML, Knaack M, Yarosh R, Grimm E et al. HER2 Testing Characteristics Can Predict Residual Cancer Burden Following Neoadjuvant Chemotherapy in HER2-Positive Breast Cancer. Int J Breast Cancer. 2021 May 24;2021:6684629.

16.Krystel-Whittemore M, Xu J, Brogi E, Ventura K, Patil S, Ross DS et al. Pathologic complete response rate according to HER2 detection methods in HER2-positive breast cancer treated with neoadjuvant systemic therapy. Breast Cancer Res Treat. 2019 Aug;177(1):61-66.

17.Caselli E, Pelliccia C, Teti V, Bellezza G, Mandarano M, Ferri I et al. Looking for more reliable biomarkers in breast cancer: Comparison between routine methods and RT-qPCR. PLoS One. 2021 Sep 23;16(9):e0255580.

18.Sakai K, Mori S, Kawamoto T, Taniguchi S, Kobori O, Morioka Y etal. Expression of epidermal growth factor receptors on normal human gastric epithelia and gastric carcinomas. J Natl Cancer Inst. 1986 Nov;77(5):1047-52. PMID: 3464796.

19.Junior PN, Neto RA, Forones NM. Her2 expressıon as a prognostıc factor ın metastatıc gastrıc cancer. Arq Gastroenterol. 2016 Apr-Jun;53(2):62-7.

20.Yonemura Y, Ninomiya I, Yamaguchi A, Fushida S, Kimura H, Ohoyama S et al. Evaluation of immunoreactivity for erbB-2 protein as a marker of poor short-term prognosis in gastric cancer. Cancer Res. 1991 Feb 1;51(3):1034-8. PMID: 1670998

21.Kim KC, Koh YW, Chang HM, Kim TH, Yook JH, Kim BS, et al. Evaluation of HER2 protein expression in gastric carcinomas: comparative analysis of 1,414 cases of whole-tissue sections and 595 cases of tissue microarrays. Ann Surg Oncol. 2011 Oct;18(10):2833-40.

22.Feizy A, Karami A, Eghdamzamiri R, Moghimi, Taheri H, Mousavinaseb N. HER2 Expression Status and Prognostic, Diagnostic, and Demographic Properties of Patients with Gastric Cancer: a Single Center Cohort Study from Iran. Asian Pac J Cancer Prev. 2018 Jun 25;19(6):1721-1725.

23.Roviello G, Aprile G, D'Angelo A, Iannone LF, Roviello F, Polom K, Mini E, Catalano M. Human epidermal growth factor receptor 2 (HER2) in advanced gastric cancer: where do we stand? Gastric Cancer. 2021 Jul;24(4):765-779.

24.Jørgenson JT, Hersom M. HER2 as a prognostic marker in gastric cancer – A systematic analysis of data from the literature. J Cancer 2012;3: 137-144.

25.Kim MA, Jung EJ, Lee HS, Lee HE, Jeon YK, Yang HK et al. Evaluation of HER-2 gene status in gastric carcinoma using immunohistochemistry, fluorescence in situ hybridization, and real-time quantitative polymerase chain reaction. Hum Pathol. 2007 Sep;38(9):1386-93.

26.Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: An update. World J Gastroenterol. 2016 May 21;22(19):4619-25.

27.Rüschoff J, Nagelmeier I, Baretton G, Dietel M, Höfler H, Schildhaus HU et al. Her2-Diagnostik beim Magenkarzinom. Was ist anders im Vergleich zum Mammakarzinom? [Her2 testing in gastric cancer. What is different in comparison to breast cancer?]. Pathologe. 2010 May;31(3):208-17. German.

28.Wang HB, Liao XF, Zhang J. Clinicopathological factors associated with HER2-positive gastric cancer: A meta-analysis. Medicine (Baltimore). 2017 Nov;96(44):e8437.

29.Senel F. Clinicopathologic significance of human epidermal growth factor receptor 2 expression and gene amplification in gastric carcinoma. J Cancer Res Ther. 2022 Dec;18(Supplement):S299-S304

30.Baykara M, Benekli M, Ekinci O, Irkkan SC, Karaca H, Demirci U et al. Anatolian Society of Medical Oncology (ASMO). Clinical significance of HER2 overexpression in gastric

and gastroesophageal junction cancers. J Gastrointest Surg. 2015 Sep;19(9):1565-71.

31.Uprak TK, Attaallah W, Çelikel ÇA, Ayrancı G, Yeğen C. HER-2 incidence in gastric cancer, its association with prognosis and clinicopathological parameters. J of National Surg. 2015 Aug 18;31(4):207-13.

32.Chua TC, Merrett ND. Clinicopathologic factors associated with HER2-positive gastric cancer and its impact on survival outcomes - A systematic review: Int J. Cancer 2012;130: 2845-2856.

33.Gurbuz M, Doğan İ, Akkuş E, Karadag I, Karakaya S, Erol C et al. Clinicopathological Factors concerning HER2 Status in Metastatic Gastric Cancer: A Retrospective Observational Study Journal of oncological sciences 2022 8(1);14-19

34.Nergiz D, Alikanoğlu AS, Süren D, Gömceli İ, Öztürk B. Concordance of HER2 status tested by IHC and FISH in biopsy and surgical resection specimens and comparison with clinicopathological features in gastric carcinoma. Indian J Pathol Microbiol. 2022 Apr-Jun;65(2):321-327.

35.Giuffrè G, Ieni A, Barresi V, Caruso RA, Tuccari G. HER2 status in unusual histological variants of gastric adenocarcinomas. J Clin Pathol 2012;65: 237-241.

36.Risio M, De Rosa G, Sarotto I, Casorzo L, Capussotti L, Torchio B et al. HER2 testing in gastric cancer: molecular morphology and storage time-related changes in archival samples. Int J Oncol. 2003 Nov;23(5):1381-7. PMID: 14532980.

37.Königshoff M, Wilhelm J, Bohle RM, Pingoud A, Hahn M. HER-2/neu gene copy number quantified by real-time PCR: comparison of gene amplification, heterozygosity, and immunohistochemical status in breast cancer tissue. Clin Chem. 2003 Feb;49(2):219-29.

38.Dabbs DJ, Klein ME, Mohsin SK, Tubss RR, Shuai Y, Bhargava R. High false-negative rate of HER2 quantitative reverse transcription polymerase chain reaction of the Oncotype DX test: An independent quality assurance study. J Clin Oncol 2011;29(32): 4279-4285.

39.Lemoine NR, Jain S, Silvestre F, Lopes C, Hughes CM, McLelland E, et al. Amplification and overexpression of the EGF receptor and c-erbB-2 proto-oncogenes in human stomach cancer. Br J Cancer. 1991 Jul;64(1):79-83.

40.Kameda T, Yasui W, Yoshida K, Tsujino T, Nakayama H, Ito M et al. Expression of ERBB2 in human gastric carcinomas: the relationship between p185ERBB2 expression and the gene amplification. Cancer Res. 1990 Dec 15;50(24):8002-9. PMID: 1979253.

41.O'Malley FP, Parkes R, Latta E, Tjan S, Zadro T, Mueller R, et al. Comparison of HER2/neu status assessed by quantitative polymerase chain reaction and immunohistochemistry. Am J Clin Pathol. 2001 Apr;115(4):504-11.

42.Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al; ToGA Trial Investigators. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet. 2010 Aug 28;376(9742):687-97.

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ORIGINAL ARTICLE

The Effects of Complementary Alternative Methods in Labor on Fear of Birth, Birth Satisfaction, and Childbirth Perceptions

Doğumdaki Tamamlayıcı Alternatif Yöntemlerin Doğum Korkusuna, Doğum Memnuniyetine ve Doğum Algısına Etkisi

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ABSTRACT

Aim: This research was conducted to compare the fear of birth, birth satisfaction, and childbirth perceptions of postpartum women using complementary alternative methods (CAMs) in labor.
Methods: This descriptive, cross-sectional study was conducted with 391 volunteer pregnant women at a university hospital in Türkiye. Data were collected in two stages: during pregnancy and at the end of delivery. A personal information form was completed by face-to-face interview at 37-41 weeks of pregnancy. At the end of delivery, the puerperants were contacted by phone for questions about CAMs they used in their deliveries, Traumatic Childbirth Perception Scale (TCPS), Wijma Delivery Expectancy/Experience Questionnaire (W-DEQ) Version B and Birth Satisfaction Scale-Short (BSS-S) Form were applied.
Results: 69.8% of women used CAMs during delivery. In the regression model, younger maternal age (OR:0.933), being a high school (OR:2.343) and university graduate (OR:2.165), moderate-income level (OR:7.259), being primiparous (OR:0.489), participation in prenatal education classes (OR:0.320), and receiving 4 or more prenatal care (OR:2.476) were determined to be the predictors of the use of CAMs at birth. It was determined that the mean score of the W-DEQ Version B of those using CAMs was significantly lower than those not using CAMs (p=0.024) and the mean score of the BSS-R was significantly higher (p<0.001).
Conclusion: In the study, it was determined that postpartum women using CAMs experienced less fear of birth and had higher birth satisfaction.

Keywords: Birth satisfaction; complementary alternative methods; fear of birth; postpartum; traumatic childbirth perception

ÖZ

Amaç: Bu araştırma, doğumdaki tamamlayıcı alternatif yöntemlerin kullanım durumuna göre lohusaların doğum korkusu, doğum memnuniyeti ve doğum algılarının karşılaştırılması amacıyla yapılmıştır.
Gereç ve Yöntem: Tanımlayıcı, kesitsel nitelikte tasarlanan bu çalışma, Türkiye'de bir üniversite hastanesinde gönüllü 391 gebe ile yürütülmüştür. Veriler gebelikte ve doğum sonunda olmak üzere iki aşamada toplanmıştır. Verilerin toplanmasında gebeliğin 37-41. haftalarında kişisel bilgi formu yüz yüze görüşme yöntemi ile, doğum sonunda ise telefonla ulaşılan lohusalara, doğumlarında kullandıkları tamamlayıcı alternatif yönteme yönelik sorular, Travmatik Doğum Algısı Ölçeği (TDAÖ), Wijma Doğum Beklentisi/Deneyimi Ölçeği B Versiyonu ve Doğum memnuniyet ölçeği-Kısa formu (DMÖ-K) uygulanmıştır.
Bulgular: Çalışmada lohusaların %69.8'inin doğumda herhangi bir tamamlayıcı alternatif yöntem kullandığı belirlenmiştir. Regresyon modelinde daha genç anne yaşının (OR: 0.933), lise (OR: 2.343) ve üniversite (OR: 2.165) mezunu olmanın, orta düzeyde gelir durumunun (OR: 7.259), primipar olmanın (OR: 0.489), doğum öncesi eğitim sınıflarına katılmanın (OR: 0.320) ve doğum öncesi dönemde 4 ve üzeri bakım almanın (OR: 2.476) doğumda tamamlayıcı alternatif yöntem kullanımının yordayıcıları olduğu belirlenmiştir. Wijma Doğum Beklentisi/Deneyimi Ölçeği B Versiyonu ve DMÖ-K puan ortalamaları karşılaştırıldığında, tamamlayıcı alternatif yöntem kullananların Wijma Doğum Beklentisi/Deneyimi Ölçeği B Versiyonu puan ortalamasının, tamamlayıcı alternatif yöntem kullanmayanlardan anlamlı düzeyde daha düşük olduğu (p=0.024) ve DMÖ-K puan ortalamasının ise anlamlı düzeyde daha yüksek olduğu saptanmıştır (p<0.001).
Sonuç: Çalışmada tamamlayıcı alternatif yöntem kullanan lohusaların daha az doğum korkusu yaşadıkları ve doğum memnuniyetlerinin daha yüksek olduğu belirlenmiştir.

Anahtar Kelimeler: Doğum korkusu; doğum memnuniyeti; lohusa; tamamlayıcı alternatif yöntemler; travmatik doğum algısı

Introduction

Traditional medicine is defined as all knowledge, skills, and practices based on beliefs, theories, and experiences specific to different cultures in the prevention, treatment, diagnosis, health protection, and promotion of physical and mental illnesses (1). Supplements, mindfulness, massage, and essential oils are common examples of complementary medicine. Generally, these treatments do not require a doctor's order or prescription (2). The term alternative medicine refers to a complete system of medical care used in place of traditional medicine. Practices such as homeopathy, naturopathy, acupuncture, and herbalism are common examples of alternative medicine (2, 3). Herbal treatments, vitamins, meditation, massage, and yoga are among the most used complementary alternative methods (CAMs) (4, 5). More than three-quarters of the world's population rely on CAMs for health care services (6).

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Birth, a natural and physiological event, is a turning point in women's lives. The use of CAMs during pregnancy and birth has a widespread distribution between 1% and 87% (6-10). Labor pain is defined as one of the most intense pains a person can feel and leads to negative birth perceptions such as anxiety and fear, which negatively affect women's birth experiences. It is widely accepted that the greater the anxiety, the greater the pain (7, 11, 12). Inadequate management of pain may lead to medical complications and adverse obstetric and neonatal outcomes, as well as prolonged hospital stays (13, 14). Considering that the factors affecting labor pain are not only physiological and are affected by many factors, it is stated that CAMs are effective (15). Methods to be used in labor pain management should reduce pain and increase the woman's satisfaction with birth (16). Breathing techniques, massage, hypnotherapy, reflexology, herbal medicine, homeopathy, hypnosis, music, and acupuncture are some of the non-pharmacological pain management techniques (17). CAMs enable the pregnant woman to participate in the labor process actively, reduce birth interventions, and positively affect birth, maternal, and newborn outcomes. Although midwifery practices, especially during labor, have the most important role in reducing labor pain in pregnant women, the use of these methods also helps the pregnant woman create a positive childbirth perception during labor and increase her level of satisfaction by increasing the quality of midwifery practices and providing women-centered care (18, 19). In the Cochrane Systematic Review of pain management in labor, acupuncture, relaxation, massage, and hypnotherapy were found to assist in the management of labor (20). Based on these, the importance of using CAMs by healthcare professionals to support women giving birth emerges (18). Türkiye has a deep-rooted history in the use of traditional medicine, and its use has been increasing in recent years. However, previous studies in Türkiye generally cover the pregnancy period and focus on different purposes of the use of CAMs (21, 22). For this reason, in the present study, postpartum fear of birth, birth satisfaction, and childbirth perceptions were compared according to the pregnant women's use of CAMs.

Research questions:

(1) What are the rates of the use of CAMs by women?

(2) Are there any differences in obstetric and demographic characteristics according to women's use of CAMs?

(3) Are there any differences between birth interventions, birth satisfaction, fear of birth, and childbirth perceptions according to the use of CAMs by postpartum women?

(4) Are there any differences in birth satisfaction, fear of birth, and childbirth perceptions according to the CAMs used by postpartum women?

Methods

Research Design and Sample

This research, designed in the form of a descriptive and cross-sectional study, was conducted at a university hospital in Türkiye between January 2023 and July 2023. The population of the research consisted of pregnant women applying to the obstetrics and gynecology outpatient clinics of the university hospital. In the power analysis used to determine the sample size with the 5% error level, 383 pregnant women were needed with a 95% confidence interval at the two-sided significance level and 80% power. Considering the data losses in the study, it was planned to recruit 20% more, and 460 volunteer pregnant women were included in the sample. Data were collected in two stages: during pregnancy and at the end of birth. 42 pregnant women gave birth by cesarean section and 27 pregnant women could not be reached at the end of delivery. Thus, the research was completed with a total of 391 postpartum mothers. The study included women over the age of 18, understanding Turkish, without any pregnancy-related risks to the fetus, having a singleton or live fetus, planning to have a vaginal birth, and at 37-41 weeks of gestation were included. Prenatal forms were collected by face-to-face interviews and telephone information was obtained. Pregnant women were called at the end of the birth, according to their estimated birth dates, and postpartum forms were filled out.

Data Collection Tools

The Personal Information Form, Traumatic Childbirth Perception Scale (TCPS), Wijma Delivery Expectancy/ Experience Questionnaire (W-DEQ) Version B, and Birth Satisfaction Scale-Revised (BSS-R) were used to collect the data. 37-41 weeks of pregnancy. After filling out the Personal Information Form by utilizing the face-to-face interview method during the 2nd week, the pregnant women were contacted by phone at the end of the delivery and were asked questions about CAMs they used during labor; additionally, the TCPS,

W-DEQ Version B, and BSS-R were applied.

Personal Information Form

The form created by the researchers included women's sociodemographic data (age, employment, educational level, family type, income level, etc.), obstetric characteristics (parity, participation in prenatal education classes, miscarriage status, number of taking prenatal care treatments, etc.), questions about their current delivery (painkiller use during delivery, amniotomy, fundal compression, episiotomy, laceration, etc.), and CAMs they used during labor (10, 19, 20, 22). The women in this study stated that they used one or more mind-body methods (breathing and relaxation exercises, music, art therapy, hypnosis, yoga, meditation, prayer, mental recovery, focusing, dreaming), biologically based treatment (foods, vitamins) ve manipulative and body-based methods (massage, hydrotherapy, acupressure, hot application, perineal heat application, cold application) as CAMs. The distribution of CAMs used by women during labor is given in Table 3.

Traumatic Childbirth Perception Scale (TCPS)

This scale evaluates the traumatic childbirth perceptions of women of reproductive age. The scale includes 13 questions. The mean score of the scale indicates the level of traumatic childbirth perception. The lowest score to be obtained from the scale is 0 and the highest score is 130. The mean score range of the scale is between 0-26, indicating very low perception, 27-52 indicating low perception, 53-78 indicating moderate perception, 79-104 indicating high perception, and 105-130 indicating very high traumatic childbirth perception. The Cronbach's alpha reliability coefficient of the scale was calculated as 0.89 (23). In this study was found to be 0.92.

Birth Satisfaction Scale-Revised (BSS-R)

To determine women's birth satisfaction levels, the form was developed by Martin CJH and Martin CR (2014), and its short form was created; the validity and reliability study of the scale in Turkish was conducted by Serhatlıoğlu et al. (2018). The scale consists of 10 items, the minimum score is 0 and the maximum score is 40, and the Cronbach's alpha reliability coefficient of the scale was calculated as 0.74 (24). For this study was calculated as 0.51.

Wijma Delivery Expectancy/Experience Questionnaire (W-DEQ) Version B

The Turkish adaptation of the questionnaire, which was first developed by K. Wijma et al. (1998), was made by Uçar and Beji in 2013. The questionnaire includes fear, trust, feelings of loneliness, happiness, etc. It consists of a total of 33 questions. Each item is in the form of a 6-point Likert type with scores between 1-6. 1 means "extremely" and 6 means "not at all". The minimum score on the questionnaire is 33, and the maximum score is 198. An increase in the score indicates an increase in fear of childbirth. The negatively charged items in the questionnaire (2, 3, 6, 7, 8, 11, 12, 15, 19, 20, 24, 25, 27, 31) are calculated by reversing them to ensure consistency in measurement. The Cronbach's alpha reliability coefficient of the questionnaire was found to be 0.88 (25). For this study was calculated as 0.90.

Data Collection

The data were collected by the researcher using the face-to-face interview method in the hospital. The sections of the Personal Information Form containing sociodemographic and obstetric characteristics were applied to the pregnant women at the first meeting. Pregnant women, whose phone numbers were taken at the first meeting, were contacted via phone on their estimated date of birth according to their last menstrual period, and the Personal Information Form's questions regarding birth characteristics, questions regarding the CAMs they used at birth, and the TCPS, W-DEQ Version B, and BSS-R were applied.

Data Analysis

Data analysis was performed using SPSS 25.0 software. Visualization was performed with R language software programming language. In Figures 1 and 2, the mean and standard errors of the scales according to the CAM method used are integrated. Column bars in the figure represent the mean and error bars represent the standard error. In the statistical analysis of the data, mean and standard deviation were used to evaluate numerical data, and frequency and percentage values were used to evaluate nominal data (demographic). The chi-square test was used to compare women's categorical independent variables. In evaluating continuous data, firstly, the Kolmogrow-Smirnov test was used to investigate whether the variables met the condition of normal distribution. Since the data showed normal distribution, an independent samples t-test was used for comparisons between two groups, and a one-way analysis of variance was used for comparisons of more than two groups. Post-hoc Tukey and Tamhane's

T2 tests were used in multiple comparisons to determine the differences between groups. Variables affecting the use of CAMs in women were evaluated with logistic regression analysis. While determining the variables to be included in the regression model, variables that had a significant relationship with CAM use status ($p<0.05$) were included in the model. Accordingly, age, educational level, income level, parity, participation in prenatal education classes, and the number of receiving care during the prenatal period were taken into the regression model. Statistical significance was determined as $p<0.05$.

Ethics

To conduct the research, ethical approval was obtained from the Non-Interventional Research Ethics Committee of Fırat University (Session Number: 382022/15-38, Session date: 15.12.2022) and necessary permissions were obtained from the university hospital where the research would be conducted (Approval Number E-19003918-100-274500). Before starting data collection, the purpose of the study was explained to the pregnant women voluntarily participating in the study. Each pregnant woman included in the study was informed about the research and verbal and written consent was obtained from the women accepting to participate in the research. The principle of volunteering was taken as a basis for determining the women who would participate in the research. The purpose of the study was explained to the women and informed consent was obtained. Data collected for the study were used only for this research.

Results

In the study, it was determined that 69.8% of postpartum women used CAMs during labor. Table 1 presents the comparison of women using and not using CAMs in labor according to their sociodemographic, obstetric, and birth-related characteristics. It was determined that the use of CAMs was higher among those aged 28 and under, graduating from high school/university, with a moderate-income level, primiparous, attending prenatal training classes, and in those receiving four or more prenatal care sessions, and the differences between the groups were statistically significant. In addition, it was determined that less fundal compression and episiotomy were applied in labor in those using CAMs and the differences between the groups were statistically significant ($p<0.05$; Table 1).

Table 1. The comparison of women using complementary alternative methods in delivery and those not using under sociodemographic, obstetric, and birth-related characteristics (n=391)

Characteristics	CAM users (n=273)		Non-CAM users (n=118)		Test	**p-value**
	n	%	n	%		
Age (years)						
≤ 28	172	63.0	54	45.8	X^2=10.040	0.002[a]
≥ 29	101	37.0	64	54.2		
Education level						
Primary school graduate	56	20.5	41	34.7	X^2=10.228	0.017[a]
Secondary school graduate	53	19.4	24	20.3		
High school graduate	96	35.2	30	25.4		
University graduate	68	24.9	23	19.5		
Social security						
Yes	253	92.7	103	87.3	X^2=2.309	0.129[b]
No	20	7.3	15	12.7		
Employment status						
Employed	44	16.1	16	13.6	X^2=0.241	0.623[b]
Unemployed	229	83.9	102	86.4		
Income status						
Less than income	2	0.7	6	5.1	X^2=5.766	0.011[c]
Equivalent to income	271	99.3	112	94.9		
More than income	-	-	-	-		
Family type						
Nuclear family	264	96.7	111	94.1	X^2=0.864	0.267[c]
Extended family	9	3.3	7	5.9		
Parity						
Primipara	100	36.6	26	22.0	X^2=8.037	0.005[a]
Multipara	173	63.4	92	78.0		
Previous history of abortion						
Yes	50	18.3	25	21.2	X^2=0.273	0.602[b]
No	223	81.7	93	78.8		
Participation in antenatal education classes						
Yes	27	9.9	4	3.4	X^2=3.920	0.048[b]
No	246	90.1	114	96.6		
Number of antenatal care						
≤ 3	13	4.8	13	11.0	X^2=4.234	0.040[b]
≥ 4	260	95.2	105	89.0		
Analgesic use in labor						
Yes	48	17.6	21	17.8	X^2=0.429	0.807[a]
No	176	64.5	79	66.9		
I don't know	49	17.9	18	15.3		
Amniotomy						
Yes	37	13.6	20	16.9	X^2=0.515	0.473[b]
No	236	86.4	98	83.1		
Fundal pressure						
Yes	64	23.4	41	34.7	X^2=5.358	0.021[a]
No	209	76.6	77	65.3		
Episiotomy						

Yes	197	72.2	97	82.2	X^2=4.454	0.035[a]
No	76	27.8	21	17.8		
Laceration						
Yes	81	29.7	39	33.1	X^2=0.443	0.506[a]
No	192	70.3	79	66.9		

[a]Chi-squared test, [b]Continuity Correction, [c]Fisher's Exact Test, CAM: Complementary alternative method

In univariate analysis, age, educational level, income level, parity, participation in prenatal education classes, and number of prenatal care sessions were determined as independent risk factors for women's use of CAMs in labor. As age increases, the use of CAMs decreases (p=0.001). When age increases by one unit, the rate of the use of CAMs decreases by 0.933 times. Those graduating from high school were 2.343 times more likely to use CAMs than primary school graduates (p=0.004), and those graduating from university or higher were 2.165 times (p=0.015) more likely to use CAMs than primary school graduates. Those whose income level was "income is equal to expenses" were 7.259 times more likely to use CAMs

Table 2. Factors associated with the use of CAMs among women in labor (n=391)

	CAM		Univariate		Multivariate (Enter)	
	Non-CAM users	**CAM users**	OR (%95 CI)	p	OR (%95 CI)	p
Age (years)		0.933	(0.896-0.972)	**0.001**	0.954 (0.908-1.003)	0.063
Education level						
Primary school			Reference			
Secondary school		1.617	(0.863-3.031)	0.134	1.504 (0.782-2.890)	0.221
High school		2.343	(1.319-4.163)	**0.004**	1.638 (0.873-3.072)	0.124
University		2.165	(1.163-4.028)	**0.015**	1.569 (0.794-3.099)	0.195
Income status						
Less than income			Reference			
Equivalent to income		7.259	(1.443-36.511)	**0.016**	5.938 (0.996-35.406)	0.051
Parity						
Primigravida			Reference			
Multigravida		0.489	(0.297-0.806)	**0.005**	0.766 (0.411-1.427)	0.401
Participation in antenatal training classes						
Yes			Reference			
No		0.320	(0.109-0.935)	**0.037**	0.336 (0.111-1.018)	0.054
Number of antenatal care						
≤ 3			Reference			
≥ 4		2.476	(1.111-5.519)	**0.027**	1.495 (0.610-3.663)	0.379
Constant					2.548	0.434

Cox & Snell R Square: 0.072; Nagelkerke R Square:0.102; Accuracy:0.714; CAM: Complementary alternative method, OR: Odds ratio, CI: Confidence interval

Table 3. Distribution of the use of CAMs by women in labor (n=273)

***Types of CAMs**	**Frequency (n)**	**Percentage (%)**
Mind-Body Methods	222	81.3
Breathing and relaxation exercises	81	29.7
Music	16	5.9
Art therapy	22	8.1
Hypnosis	17	6.2
Yoga	14	5.1
Meditation	14	5.1
Prayer	150	54.9
Mental recovery	13	4.8
Focusing	23	8.4
Dreaming	50	18.3

Biologically Based Treatment	27	9.9
Foods	14	5.1
Vitamins	13	4.8
Manipulative and Body-Based Methods	24	8.8
Massage	3	1.1
Hydrotherapy	7	2.6
Acupressure	1	0.4
Hot application	4	1.5
Perineal heat application	8	2.9
Cold application	1	0.4

* More than one response was given. CAM: Complementary alternative method

than those whose income level was "income is less than expenses" (p=0.016). In addition, primiparous women were 0.489 times more likely than multiparous (p=0.005), those attending prenatal education classes were 0.320 times more likely than those not attending (p=0.037), and those receiving four or more prenatal care sessions were 2.476 times (p=0.027) more likely than those receiving three or fewer care sessions. There is a possibility of using more CAMs. No significance was found in multivariate analysis. The correct classification rate obtained with the created model was found to be 71.4% (Table 2).

Table 3 presents the distribution of CAMs used by women in labor. It was determined that the majority of women used Mind-Body Methods (81.3%), while 9.9% of them used Biologically Based Treatment and 8.8% used Manipulative and Body-Based Methods.

Table 4; Figure 1). The mean scores of the BSS-R and its subscales (Quality of care provision (BSS-QC) and Stress experienced during labor (BSS-SL) of postpartum women using CAMs (Mean ± SD: 18.88±3.80; 7.58±1.82;

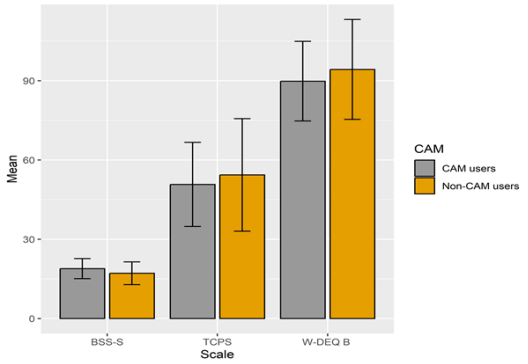

Figure 1. The mean scores of the W-DEQ B Version, TCPS, and BSS-S of women using and not using CAMs in labor (n=391). W-DEQ Version B: Wijma Delivery Expectancy/Experience Questionnaire B Version, BSS-S: Birth Satisfaction Scale-Short, TCPS: Traumatic Childbirth Perception Scale, CAM: Complementary alternative method

Table 4. Comparison of the mean scores of the W-DEQ Version B, TCPS, BSS-R, and its subscales of women using and not using CAMs in labor (n=391)

Measurements	**CAM users (n=273)**	**Non-CAM users (n=118)**	**Test***	**p**
	Ort ± SS	**Ort ± SS**		
W-DEQ Version B	89.83±15.08	94.29±18.90	t=-2.270	**p=0.024**
BSS-S	18.88±3.80	17.12±4.32	t=3.835	**p<0.001**
Quality of care	7.58±1.82	6.79±1.87	t=3.844	**p<0.001**
Women's characteristics	3.05±1.67	2.97±2.36	t=0.334	p=0.739
Stress experienced during childbirth	8.24±2.81	7.35±3.38	t=2.508	**p=0.013**
TCPS	50.75±15.91	54.35±21.28	t=-1.649	p=0.101

*Independent samples *t*-test. W-DEQ Version B: Wijma Delivery Expectancy/Experience Questionnaire B Version, BSS-S: Birth Satisfaction Scale-Short, TCPS: Traumatic Childbirth Perception Scale, CAM: Complementary alternative method

In the study, statistically significant differences were found between the mean scores of the W-DEQ Version B, BSS-R, and its subscales (Quality of care provision (BSS-QC) and Stress experienced during labor (BSS-SL) of the postpartum women (p<0.05; Table 4; Figure 1). It was determined that the mean score of the W-DEQ Version B total was significantly lower in postpartum women using CAMs (Mean ± SD: 89.83±15.08) than in those not using CAMs (Mean ± SD: 94.29±18.90) (p<0.05; 8.24±2.81, respectively) were significantly higher (p<0.05; Table 4; Figure 1) than those not using CAMs (Mean ± SD: 17.12±4.32; 6.79±1.87; 7.35±3.38, respectively).

Women's W-DEQ Version B, BSS-R, and TCPS mean scores vary according to groups. The mean score of the fear of birth in the manipulative and body-based methods group was statistically lower than in

the mind-body methods group (p=0.012; Table 5; Figure 2). Similarly, the mean score of the TCPS was statistically lower in the manipulative and body-based methods group than in the mind-body methods group (p=0.018; Table 5; Figure 2). The mean score of the BSS-R was found to be statistically higher in the mind-body methods group than in the biologically-based treatment methods group (p=0.024; Table 5; Figure 2).

Table 5. Comparison of the mean scores of the W-DEQ, TCPS, BSS-R, and its subscales under the use of CAMs (n=273)

Measurements	Mind-Body Methods (n=222)	Biologically-Based Treatment (n=27)	Manipulative and Body-Based Methods (n=24)	Test	p
W-DEQ Version B	90.7 ± 13.8^{b}	91.6 ± 21.3^{ab}	80.2 ± 15.6^{a}	F*=4.973	**0.012**$^{\#}$
BSS-S	19.2 ± 3.6^{b}	17.2 ± 3.8^{a}	18.2 ± 4.8^{ab}	F**=3.763	**0.024**$^{\&}$
Quality of care	7.6 ± 1.9	6.9 ± 1.8	7.8 ± 1.5	F**=2.314	0.101$^{\&}$
Women's characteristics	3.2 ± 1.6	2.7 ± 2.0	2.6 ± 2.0	F**=2.072	0.128$^{\&}$
Stress experienced during childbirth	8.4 ± 2.7	7.6 ± 2.8	7.8 ± 3.6	F**=1.176	0.310$^{\&}$
TCPS	51.4 ± 15.7^{b}	52.4 ± 18.0^{ab}	42.7 ± 13.5^{a}	F*=4.440	**0.018**$^{\#}$

*One Way ANOVA(Welch), **One Way ANOVA $^{a-b}$: There is no difference between groups with the same letter for each row ($^{\#}$: Tamhane's T2; $^{\&}$: Tukey). W-DEQ Version B: Wijma Delivery Expectancy/Experience Questionnaire B Version, BSS-S: Birth Satisfaction Scale-Short, TCPS: Traumatic Childbirth Perception Scale, CAM: Complementary alternative method

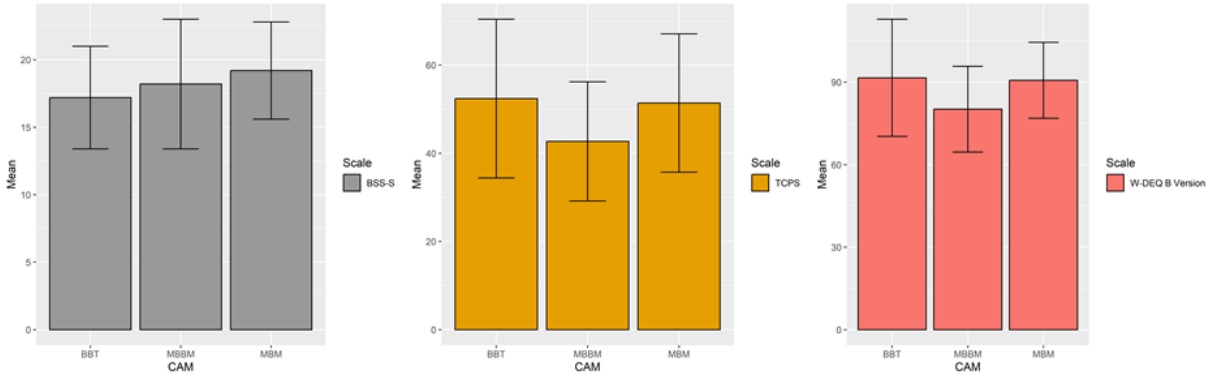

Figure 2. The mean scores of the W-DEQ Version B, TCPS, and BSS-S under the use of CAMs (n=273). BBT: Biologically Based Treatment,MBBM: Manipulative and Body-Based Methods, MBM: Mind-Body Methods, CAM: Complementary alternative method

more prenatal care sessions (p< 0.05; Table 1). In the established regression model, the same parameters (age, educational level, income level, parity, participation in prenatal education classes, and number of prenatal care sessions) were found to be important determinants of the use of CAMs (p<0.05; Table 2). In the study, it was determined that the use of CAMs increased as age decreased (p<0.05; Table 1, Table 2). Similar to the current study in the literature, a study conducted to investigate the prevalence and determinants of the use of CAMs in England found that those using CAMs were younger than those not using them (26). In the study, it was determined that the use of CAMs was higher in high school/university graduates than in primary school/secondary school graduates (p<0.05; Table 1, Table 2). Similar to the current study's finding, a study aiming to investigate the prevalence of the use of CAMs and related factors in Japan found that increasing the level of education enhanced the use of CAMs (3). It is thought that as the academic level increases, both the ability and capacity to critically evaluate information and collect information increases and this increases the use of CAMs. In the study, it was found that those with medium income use CAMs more than those with low income (p <0.05; Table 1, Table 2). Similarly, in a study conducted to determine the use of

Discussion

This study reveals that the rate of the use of CAMs by women during labor in Türkiye is high, and more than two-thirds of women (69.8%) used CAMs during labor. This finding is supported by the study conducted to determine the effects of complementary and alternative medicine use on labor pain management, which revealed that more than two-thirds of women used CAMs (17). However, variations in the rates of the use of CAMs may be attributable to differences in the definition of CAM, types of traditional CAMs included in the studies, location, and cultural differences.

When women using and not using CAMs were compared in the study, it was determined that the use of CAM was higher in those 28 years of age or younger, high school/university graduates, those with middle income, primiparous women, those attending prenatal training classes, and those receiving four or

CAMs by women with breast cancer or gynecological cancer, it was found that having a medium or high monthly income was one of the factors predicting the use of CAMs (27). In the present study, it was observed that primiparas used CAMs more at labor compared to multiparas ($p<0.05$; Table 1, Table 2). It is reported in the literature that women not giving birth tend to turn to positive health practices (28, 29). Similar to the finding of the present study, a study aiming to investigate the prevalence of the use of CAMs and related factors in Japan found that the use of CAMs was higher in primiparas (3). One of the limiting factors for women with multiple children is the cost and time required for the implementation of CAMs. Therefore, it is thought that multiparous women in the study do not have time to do research on CAMs and learn these methods. In the study, it was determined that the use of CAMs in labor was higher among women attending prenatal education classes and those receiving four or more prenatal care sessions ($p<0.05$; Table 1, Table 2). It was stated in the literature that women need information about the risks and benefits of nonpharmacological methods and that they need to communicate with healthcare professionals about the use of CAMs (30, 31). In the study conducted to determine the effects of teaching guides on pregnant women's knowledge and practices regarding complementary treatments, it was concluded that the training guides had positive effects on improving pregnant women's knowledge and practices regarding complementary treatments (32). In support of the current study's findings, in a study conducted to determine pregnant women's use of health services, it was found that women meeting healthcare professionals (physicians, midwives) more frequently also met with the practitioners of CAMs (33). In this regard, it is thought that attending prenatal education classes and receiving 4 or more prenatal care sessions contributes to obtaining more information about CAMs from healthcare professionals.

When birth interventions were evaluated in the study, it was determined that less fundal compression and episiotomy were applied in labor for those using CAMs ($p<0.05$; Table 1). It is known that the use of CAMs in labor reduces interventions (34). In parallel with the current study's findings, many studies using CAMs in labor have found that the use of CAMs reduces episiotomy and fundal compression attempts (35-39).

In the present study, it was found that women using CAMs had less fear of birth ($p<0.05$; Table 4; Figure 1). Similar results were obtained in the literature in studies investigating the birth fears of women using CAMs in labor (38, 40-42). In a study conducted to examine the effects of yoga and meditation applied during pregnancy and in labor on the birth process, it was found that women applying yoga and meditation had lower fear of birth (38). In the study conducted in labor to determine the effectiveness of the Emotional Freedom Technique and breathing awareness applications in reducing the fear of birth, it was found that the fear of birth was lower in women practicing these applications (40). In a study where aromatherapy was applied to reduce fear in labor, it was found that aromatherapy helped reduce fear (41). In a study in which supportive care through the Hypnobirthing Philosophy was applied to pregnant women, it was found that the application reduced the fear of birth (42). Therefore, it is considered that by using CAMs, women make the birth process a positive experience and can cope with the fear of birth.

The present study found that women using CAMs had higher birth satisfaction. It was also determined that their satisfaction with the stress experienced during labor and satisfaction with the quality of care were higher ($p<0.05$; Table 4; Figure 1). In the study conducted to determine the effects of hydrotherapy application in vaginal births on maternal-newborn outcomes and birth satisfaction, it was determined that the birth satisfaction of women receiving hydrotherapy was higher. (43) Similarly, in a study investigating the effects of breathing exercises applied in labor on pregnant women's satisfaction and the birth processes, it was determined that breathing exercises increased birth satisfaction (44). Within the framework of these results, it is thought that the present study's findings are similar to the literature and that the use of CAMs enables the women to be involved in the process, increases their self-confidence, supports the ability to control the birth processes, and therefore increases birth satisfaction.

The present study also examined the levels of fear of birth, birth satisfaction, and childbirth perceptions according to the CAMs used. It was found that the lowest levels of fear of birth and traumatic childbirth perceptions were in the manipulative and body-based methods group, and the highest satisfaction was in the mind-body methods group ($p<0.05$; Table 5; Figure 2). When the literature was examined, no study was found that evaluated the levels of fear of birth and traumatic childbirth perceptions among pregnant women using CAMs. In a study conducted to determine the effects of the use of complementary and alternative

treatments on the quality of life in pregnant women diagnosed with hyperemesis gravidarum, when the satisfaction levels were examined according to the CAMs, it was found that the highest satisfaction was in "Mind and Body Treatments" (45). This finding supports the current study's findings.

Limitations of the study

This study has several limitations. The limitations of the research are that it was conducted on limited dates, that the research was conducted only in a hospital in an eastern province in Türkiye, and that it was based on the statements of the participants. However, in the literature review, no study was found comparing the fear of birth, birth satisfaction, and childbirth perceptions of postpartum women according to the use of CAMs in labor. Therefore, it is thought that the study will contribute to the literature.

Conclusion And Recommendations

According to the results of the current study, it was determined that younger maternal age, having a moderate level of income, being primiparous, attending prenatal education classes, and receiving 4 or more prenatal care sessions increased the use of CAMs. Additionally, this study demonstrated the effectiveness of the use of CAMs in reducing birth interventions, fear of birth, and perception of traumatic childbirth perceptions, and increasing birth satisfaction. In this regard, it is recommended to prepare training programs on CAM to first raise awareness among healthcare professionals and then integrate it into midwifery practices. In addition, it is recommended to increase the number of studies to determine the effects of the use of CAMs in labor on the birth processes, fear of birth, childbirth perceptions, and birth satisfaction.

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Disclosure statement

The authors declare no conflict of interest.

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Authors' Contribution

All authors contributed to the conception, design of the study, data collection, data analysis, and assembly. The manuscript was written and approved by all authors.

Presentation Statement

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References

1.Zhang X, Organization WH. Traditional medicine strategy 2002 2005. Ginebra. 2002.

2.Health UDo, Services H. Complementary, alternative, or Integrative Health: What's in a name. National Center for Complementary and Integrative Health. 2021.

3.Watanabe A, Inoue S, Okatsu A, Eto H, Oguro M, Kataoka Y. Complementary and alternative medicine use by pregnant women in Japan: a pilot survey. BMC Complementary Medicine and Therapies. 2023;23.

4.James PB, Bah AJ, Tommy MS, Wardle J, Steel A. Herbal medicines use during pregnancy in Sierra Leone: An exploratory cross-sectional study. Women Birth. 2018;31(5):e302-e9.

5.Clarke TC, Barnes PM, Black LI, Stussman BJ, Nahin RL. Use of Yoga, Meditation, and Chiropractors Among U.S. Adults Aged 18 and Over. NCHS Data Brief. 2018(325):1-8.

6.Yusof J, Mahdy ZA, Noor RM. Use of complementary and alternative medicine in pregnancy and its impact on obstetric outcome. Complement Ther Clin Pract. 2016;25:155-63.

7.Martínez JM, Delgado M. Nivel de dolor y elección de analgesia en el parto determinada por la realización de educación maternal. Revista chilena de obstetricia y ginecología. 2013;78(4):293-7.

8.Adams J, Lui CW, Sibbritt D, Broom A, Wardle J, Homer C, et al. Women's use of complementary and alternative medicine during pregnancy: a critical review of the literature. Birth. 2009;36(3):237-45.

9.Steel A, Adams J, Sibbritt D, Broom A, Frawley J, Gallois C. Relationship between complementary and alternative medicine use and incidence of adverse birth outcomes: an examination of a nationally representative sample of 1835 Australian women. Midwifery. 2014;30(12):1157-65.

10.Hall HR, Jolly K. Women's use of complementary and alternative medicines during pregnancy: a cross-sectional study. Midwifery. 2014;30(5):499-505.

11.Smith CA, Collins CT, Cyna AM, Crowther CA. Complementary and alternative therapies for pain management in labor. Cochrane Database Syst Rev. 2003(2): Cd003521.

12.Topcu İ, Dissiz M. Manipulative and Body-based Complementary/Alternative Methods in Labor. Journal of Nursing Science. 2018;1(2):33-7.

13.De Molina-Fernández I, Rubio-Rico L, Roca-Biosca A, Jimenez-Herrera M, De la Flor-Lopez M, Sirgo A. Ansiedad y miedos de las gestantes ante el parto: la importancia de su detección. Rev Port de Enferm Saúde Mental. 2015;13:17-24.

14.Mazoni SR, de Carvalho EC, dos Santos CB. Clinical validation of the nursing diagnosis of labor pain. Rev Lat Am Enfermagem. 2013;21 Spec No:88-96.

15.Salud OMdl. Estrategia de la OMS sobre medicina tradicional 2014-2023. OMS Ginebra; 2013.

16.Yılar Erkek Z, Pasinlioğlu T. Complementary treatment methods used in labor pain. Anatolian Journal of Nursing and Health Sciences. 2016;19(1):71-7.

17.Steel A, Adams J, Sibbritt D, Broom A, Frawley J, Gallois C. The influence of complementary and alternative medicine use in pregnancy on labor pain management choices: results from a nationally representative sample of 1,835 women. J Altern Complement Med. 2014;20(2):87-97.

18.Öztürk R, Emi Nov A, Ertem G. Use of complementary and alternative medicine in pregnancy and labor pain: a cross-sectional study from Turkey. BMC Complement Med Ther. 2022;22(1):332.

19.Kacar N. Nonpharmacological Midwifery Practices in the Management of Labor Pain. Journal of Health Sciences and Research. 2020;2(2):113-30.

20.Jones L, Othman M, Dowswell T, Alfirevic Z, Gates S, Newburn M, et al. Pain management for women in labor: an overview of systematic reviews. Cochrane Database Syst Rev. 2012;2012(3): Cd009234.

21.Koc Z, Sağlam Z, Topatan S. Determination of the usage of complementary and alternative medicine among pregnant women in the Northern Region of Turkey. Collegian. 2017;24(6):533-9.

22.Yuvaci HU, Yazici E, Yazici AB, Cevrioglu S. How often do women use non-drug treatment methods for psychiatric symptoms during pregnancy and postpartum periods? Ment Illn. 2019;11(1):7988.

23.Yalnız H, Canan F, Ekti Genc R, Kuloglu MM, Gecici Ö. Development of a scale of traumatic childbirth perception. Turkish Medical Journal. 2016;8(3):81-8.

24.Göncü Serhatlıoğlu S, Karahan N, Hollins Martin CJ, Martin CR. Construct and content validity of the Turkish Birth Satisfaction Scale-Revised (T-BSS-R). J Reprod Infant Psychol. 2018;36(3):235-45.

25.Ucar E, Kizilkaya Beji N. The study on the reliability and validity of the Turkish form of scale B version of the wijma delivery expectancy/experience questionnaire [Master's Thesis]. Istanbul: Haliç University; 2013.

26.Hunt KJ, Coelho HF, Wider B, Perry R, Hung SK, Terry R, et al. Complementary and alternative medicine use in England: results from a national survey. Int J Clin Pract. 2010;64(11):1496-502.

27.Stöcker A, Mehnert-Theuerkauf A, Hinz A, Ernst J. Utilization of complementary and alternative medicine (CAM) by women with breast cancer or gynecological cancer. PLoS One. 2023;18(5):e0285718.

28.Cannella BL, Yarcheski A, Mahon NE. Meta-Analyses of Predictors of Health Practices in Pregnant Women. West J Nurs Res. 2018;40(3):425-46.

29.Güney E, Ünver H, Bal Z, Uçar T. Psychosocial factors and health practices in pregnancy: A cross-sectional study. Int J Nurs Pract. 2022;28(3):e13021.

30.Thomson G, Feeley C, Moran VH, Downe S, Oladapo OT. Women's experiences of pharmacological and non-pharmacological pain relief methods for labor and childbirth: a qualitative systematic review. Reprod Health. 2019;16(1):71.

31.Barnes LAJ, Barclay L, McCaffery K, Aslani P. Women's health literacy and the complex decision-making process to use complementary medicine products in pregnancy and lactation. Health Expect. 2019;22(5):1013-27.

32.Hassan Saied Khalil H, Salah Shalaby Salama N, Abdelhamed Deyab B, Abd Elazeem Abd Elsalam Fathla N, Ali Maher Nashaat N. Effect of Instructional Guidelines on Pregnant Women'Knowledge and Practice regarding Complementary Therapies. Egyptian Journal of Health Care. 2021;12(1):1419-34.

33.Steel A, Adams J, Sibbritt D, Broom A, Gallois C, Frawley J. Utilisation of complementary and alternative medicine (CAM) practitioners within maternity care provision: results from a nationally representative cohort study of 1,835 pregnant women. BMC Pregnancy Childbirth. 2012;12:146.

34.Yuksel H, Cayir Y, Kosan Z, Tastan K. Effectiveness of breathing exercises during the second stage of labor on labor pain and duration: a randomized controlled trial. J Integr Med. 2017;15(6):456-61.

35.Karacan E, Çevik S. The effect of breathing exercises and virtual reality applications performed during pregnancy and delivery action on birth pain, birth duration, and birth satisfaction level [Doctoral Thesis]. Gaziantep Gaziantep University; 2022.

36.Öncü Celik H, Okumus F. Effect of birth pain and the duration of birth of acupressure on labor practices [Master's Thesis]. Institute of Health Sciences: Istanbul Medipol University; 2016.

37.Bayri Bingol F, Demirgöz Bal M, Yİlmaz Esencan T, Karakoç A, Küçükoğlu S, Ciftci R, et al. Evaluation of the Effect of Physical Support on the Pregnancy on Birth Outcome. Journal of Academic Research in Nursing (JAREN). 2020;6(3):506-13.

38.Yilmaz Esencan T, Rathfisch G. Effects of Yoga and Meditation on the Birth Process. Altern Ther Health Med. 2023;29(1):6-14.

39.Lewis L, Hauck YL, Butt J, Hornbuckle J. Obstetric and neonatal outcomes for women intending to use immersion in water for labor and birth in Western Australia (2015-2016): A retrospective audit of clinical outcomes. Aust N Z J Obstet Gynaecol. 2018;58(5):539-47.

40.Irmak Vural P, Aslan E. Emotional freedom techniques and breathing awareness to reduce childbirth fear: A randomized controlled study. Complement Ther Clin Pract. 2019;35:224-31.

41.Burns E, Blamey C, Ersser SJ, Lloyd AJ, Barnetson L. The use of aromatherapy in intrapartum midwifery practice an observational study. Complement Ther Nurs Midwifery. 2000;6(1):33-4.

42.Uludağ E, Mete S. The effect of nursing care provided based on the philosophy of hypnobirthing on fear, pain, duration, satisfaction and cost of labor: a single-blind randomized controlled study. Health Care Women Int. 2021;42(4-6):678-90.

43.Erisen Y, Kaya N. The effect on the mother-newborn outcomes and birth satisfaction of hydrotherapy in vaginal deliveries [Master's Thesis]. Graduate Education Institute: Istanbul University-Cerrahpaşa; 2022.

44.Geceli M, Avcı N. The effect of breathing exercises applied in labor on pregnant satisfaction and birth process [Master's Thesis]. Graduate Education Institute: Biruni University; 2022.

45.Iskender Ö, Kaplan S. The association between quality of life and complementary and alternative medicine use in pregnant women with hyperemesis gravidarum. J Obstet Gynaecol Res. 2021;47(6):2005-13.

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ORIGINAL ARTICLE

Impact of Fear due to the COVID-19 Pandemic and Level of Compliance in Preventive Precautions on the Status of Home Health Care Services Utilization and Attitudes on Home Care

COVID-19 Pandemisi Nedeniyle Yaşanan Korku ve Önlemlere Uyum Düzeyinin Evde Sağlık Hizmetlerine Başvuru Durumu ve Evde Bakım Hizmetleri Tutumuna Etkisi

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ABSTRACT

Background/Aims: To determine the impact of the fear of the society due to the COVID-19 pandemic and the level of compliance in preventive precautions on the status of home health care services utilization and the attitudes of home care services.
Material and Methods: This study was cross-sectional and administered through a web-based survey. The present study focuses on the 5,467 participants' responses. "Fear of COVID-19 Scale" was used to determine the fear of COVID-19 and "Attitude Scale for Home Care" to determine the attitude towards home care services on individuals.
Results: Higher levels of COVID-19 fear have a positive effect on the attitude toward home care and significantly explained receiving more home health care services. Participants' compliance level with precautionary behavior practices or preventive measures related to COVID-19 had a direct effect on their attitude for home care. However, higher compliance level with precautionary behavior practices or preventive measures related to COVID-19 have a negative effect on the receiving home health care services.
Conclusions: Our results showed that it is possible to improve the attitude for home care by promoting compliance level with precautionary behavior practices or preventive measures.

Keywords: COVID-19, Fear, Home Care, Home Health Care, Pandemics

ÖZ

Amaç: Toplumun COVID-19 pandemisi nedeniyle yaşadığı korkunun ve belirlenen önlemlere uyum düzeyinin evde sağlık hizmetlerine başvuru durumlarına ve evde bakım hizmetleri tutumlarına etkisini değerlendirmektir.
Gereç ve Yöntem: Bu çalışma kesitsel bir çalışmadır ve web tabanlı bir anketle uygulanmıştır. Mevcut çalışma, 5467 katılımcının yanıtlarına odaklanmaktadır. COVID-19 korkusunu belirlemek için "COVID-19 Korku Ölçeği" ve bireylerin evde bakım hizmetlerine yönelik tutumlarını belirlemek için "Evde Bakım Hizmetleri Tutum Ölçeği" kullanılmıştır.
Bulgular: COVID-19 korkusunun yüksek düzeyleri, evde bakım hizmetlerine yönelik tutum üzerinde olumlu bir etkiye sahip olup, daha fazla evde sağlık hizmeti alınmasını önemli ölçüde açıklamaktadır. Katılımcıların COVID-19 ile ilgili önleyici davranış uygulamaları veya tedbirlere uyum düzeyleri, evde bakım hizmetlerine yönelik tutumları üzerinde doğrudan bir etkiye sahipti. Ancak, COVID-19 ile ilgili önleyici davranış uygulamaları veya önlemlere uyum düzeyinin yüksek olması, evde sağlık hizmeti alma üzerinde olumsuz bir etkiye sahiptir.
Sonuç: Bulgularımız, önleyici davranış uygulamaları veya önlemlere uyum düzeyini teşvik ederek evde bakım hizmetlerine yönelik tutumu iyileştirmenin mümkün olduğunu göstermiştir.

Anahtar Kelimeler: COVID-19, Korku, Evde Bakım, Evde Sağlık Bakımı, Pandemi

Introduction

Accessibility of primary health care services by the entire society and wide-spreading the scope and quality of services are extremely important, especially during the pandemic. However, it has been observed that the COVID-19 pandemic has seriously affected primary health services globally, especially in countries with limited resources, and the utilization of primary health services has been partially or completely disrupted (1, 2). The rapid spread of infection among healthcare professionals has hampered the capacity of healthcare systems to respond to COVID-19 patients (1). In this process, the focus of home health care services in providing services to chronic diseases, hospice, or disabled individuals has changed to include infectious diseases and the whole society with the COVID-19 pandemic. It has come to the fore as an alternative solution to effectively alleviate the pandemic burden in the early phase of the pandemic (3). However, home care providers have had to rapidly develop innovative solutions that provide situational (recruitment from different service sectors such as social media, hospitality, tourism, etc.), structural (e.g., facilitating outdoor concerts and performances in response to patients' need for activation), and systemic (e.g., infection monitoring software) flexibility using existing resources (4). New home health care models have been

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rapidly adopted, covering the preparation, training, and payment structure of multi-sectoral logistics support such as telehealth interventions that support with telephone, automatic scanning algorithms, safety or security systems in the implementation of administrative measures and sanctions, basic food support of municipalities, communication and support systems, supply of adequate medical equipment, supplies and personnel, etc. (3).

Although individual differences in compliance and non-compliance with pandemic measures vary according to several factors, including personal, social, cultural, mental, and economic variables, one of the strongest factors in persuading to comply with preventive rules is fear (5). In the acute period of the pandemic, it was observed that many individuals resorted to functional (migration from city to village or going to holiday areas, using traditional and complementary medicine practices, reporting those who do not comply with quarantine rules to the police, praying, etc.) and dysfunctional (caring about their own health but not caring about the health of others, suicide cases due to extreme fear or restrictions resulting from pandemic measures, etc.) psychosocial coping styles with feelings of fear, anxiety, and panic (6). Although anxiety and fear that people experience due to the increasing number of COVID-19-related cases and deaths, and quarantine practices globally and regionally, have decreased with the availability of the vaccine and the decrease in the number of deaths, people still do not feel completely safe due to vaccine hesitancy and non-compliance with preventive measures (1, 7). High case-fatality rates due to COVID-19 among home care patients in connection with old age and comorbid diseases have caused patients, their families, and caregivers tend to be more cautious (8). In a study with Massachusetts home health and home care agency managers, most agencies (98.7%) reported that they experienced a decrease in demand for home visits during the COVID-19 pandemic (9). Moreover, another study emphasizes that eliminating or reducing access to services during the pandemic greatly affected home care clients and their caregivers and left them vulnerable (10). However, according to the statements made by the Ministry of Health in Türkiye, there has been an upsurge of 500% in applications made to the Home Health Services Communication Center to receive home care services in the first days of the pandemic (11). This study aimed to evaluate the impact of fear experienced by society due to the COVID-19 pandemic and the level of compliance with preventive precautions on the status of home health care services utilization and attitudes to home care services.

Research questions

- What is the level of fear that society is experiencing due to the COVID-19 pandemic?

- What is the compliance level of the society with the precautionary behavior practices or preventive measures determined due to the COVID-19 pandemic?

- How is the status of receiving home health care services and attitudes toward home care of society due to the COVID-19 pandemic?

- What variables affect society's attitudes toward home care and their fear levels of COVID-19?

Materials and Methods

Study design and setting

This study was conducted in a cross-sectional design. We recruited adults aged 18 years and over between November 2020 - May 2021 through a cross-sectional web-based survey using Google Forms in Türkiye. The highest number of COVID-19 cases and deaths reported daily in Türkiye during the study were 63,082 and 394, and the lowest number of cases and deaths were 5,277 and 62, respectively (12).

Participants

For this study, participants were eligible if they were literate, aged 18 years or older, currently living in Türkiye, and agreed to participate. Sample size calculation was not made at the beginning of the study. A total of 5,598 responses were received using the snowball and chaining method. We excluded 131 participants for being aberrant responses (n = 16; 0.28%), outliers data (n = 48; 0.85%), and not meeting the eligibility criteria (n = 67; 1.19%). The final analysis included 5,467 participants. The posthoc power analysis, obtained for the sample size, was performed using the online calculator ClinCalc (available at https://clincalc.com/stats/samplesize.aspx, accessed on 02/09/2021). The posthoc power analysis was performed to assess the power of the study to detect significant differences concerning the primary outcome measure, attitude toward homecare, between compared the subgroups diagnosed or not diagnosed with COVID-19 and subgroups receiving home healthcare services or not receiving during the COVID-19 pandemic. The study's

power to discriminate differences in both subgroups was high (88.3% and 93.7%, respectively).

Procedure and data-collection

Within the scope of the study, the web-based survey link prepared on Google Forms with an information sheet and informed consent form open to everyone's access was shared from and put through some social networking sites such as Facebook, Instagram, and various WhatsApp groups. Individuals were invited to participate in the study by a link to the web-based survey. The web-based survey was fully anonymous and voluntary. Respondents were asked to consent to participate and were not provided incentives to complete the web-based survey. The study was conducted following the principles of the Declaration of Helsinki.

Covariates

Demographic data included age, gender, education level, family income (Income higher than the expense, Income lower than the expense, Income equal to expense), and the region they resided in Türkiye was collected. Health status data, which include any diagnosed chronic disease, the presence of any chronic prescription medication use, and the status of the being diagnosed with COVID-19 who was a participant or one of his/her family, were collected. Participants were asked to indicate if they applied for health or home care services for themselves or a relative during the pandemic. Participants' precautionary behavior practices were measured with 21 statements with only one negative. Of them, 14 statements contained preventive measures against COVID-19, which were prepared by the Ministry of Health (13). The other statements were related to personal hygiene practices, social-distancing measures, using personal protective equipment, etc. Also, the types of masks they used against COVID-19 were measured.

Outcome variables

The Fear of COVID-19 Scale developed by Ahorsu et al. (2020) was used to determine the fear of COVID-19 in evaluating the psychological effects of COVID-19 on individuals. The reliability and validity of the Turkish version of the scale were established by Satıcı et al. (2020). It is a unidimensional scale consisting of 7 items. It has a 5-point Likert-type answer option that changes from "(1) Strongly Disagree" to "(5) Strongly Agree". The lowest score that can be obtained from the scale is 7, and the highest score is 35. Higher scores obtained from the scale indicate more fear. Cronbach's Alpha value was .84 in the original study for the scale (14). Cronbach Alpha value for this study was .88.

The Attitude Scale for Home Care (ASHC) developed by Duru, Örsal and Karadağ (2015) was used to determine the attitude toward home care services individuals. The scale consists of 3 subdimensions, named as "Attitudes towards transpersonal caring relationships between home care team and patient", "Attitudes towards support experienced in home care", and "Attitudes towards comparing hospital health care and home care", and 29 items. It has a 5-point Likert-type answer option that changes from "(1) Strongly Disagree" to "(5) Strongly Agree". The lowest score that can be obtained from the scale is 29, and the highest score is 145. Higher scores obtained from the scale indicate positive attitudes towards home care services. Cronbach's Alpha value was .93 in the original study for the scale (15). Cronbach Alpha value for this study was .95.

Statistical analysis

The collected data from Google drive was converted to a Microsoft Excel file, and statistical analyses were performed using SPSS (version 25.0). Before starting the analysis, a complete data set was created by assigning the data set average for missing data. The percentage of missing data in the data set was <1‰ (n = 13). Outliers were checked using boxplot and z scores. Z scores greater than +3 or less than -3, that was, multivariate outliers (n = 48) were identified in the data set. Data containing outliers (n = 48) was deleted from the data set. Skewness and kurtosis coefficients of scale scores were checked as the assumption of normality, and it was found that skewness and kurtosis coefficients were between -1 and +1, and their absolute values were not greater than twice their standard errors. Descriptive statistics were used to describe the sample, including means and standard deviations (SD) for continuous variables and frequency distribution and percentages for categorical variables. Statistical analysis of the data was assessed by using a t-test, one-way analysis of variance (ANOVA) test, Pearson Correlation test, and Structural Equation Model (SEM). The statistical significance level was taken as $p < .05$.

Results

Participants

The present study focuses on the 5,467 participants'

responses. In the study group, 62.7% (n = 3,429) were female, and the mean age was 28.14 ± 10.77 (min.18.00, max. 89.00) years. The majority of participants had a higher education level (56.6%), had an income equal to expense (58.4%), and lived in the Central Anatolia region in Türkiye (39.2%). Most participants had no chronic diseases (89.6%) or any chronic prescription medication use (85%). In addition, 33.6% of the participants had been diagnosed with COVID-19 or had a family member previously diagnosed with COVID-19.

The level of fear that society was experiencing due to the COVID-19 pandemic

Participants' mean COVID-19 fear score was 19.18 ± 6.51 (median 19.00, min 7.00, max 35.00). The distribution of the mean of the participants' fear of COVID-19 by some sociodemographic characteristics and some precautionary behavior practices were presented in Table 1 and Table 2, respectively.

Table 1. The distribution of the mean of the participants' fears of COVID-19 and attitude for homecare scores by some related socio-demographic characteristics

Variables	n	The fear of COVID-19		The attitude for home care	
		Mean ± SD	t / F; p	Mean ± SD	t / F; p
Gender					
Female	3429	19.22±6.42	.572; .567	113.60±17.93	-.145; .885
Male	2038	19.12±6.67		113.677±17.95	
Age group					
18-25 (1)	3464	19.13±6.51		113.20±18.10	
26-30 (2)	595	19.29±6.50	.369; .692	113.67±17.73	3.312; **.037**
≥ 31 (3)	1408	19.28±6.53		114.66±17.59	
Pairwise comparison*				3 > 1	
Education level					
High-school or lower	2085	19.25±6.57	.602; .547	114.07±18.24	1.453; .146
Associate degree or higher	3382	19.14±6.47		113.35±17.74	
Family income					
Income lower than expense	1168	19.58±6.50		113.12±17.57	
Income equal to expense	3192	19.04±6.54	2.923; .054	113.61±18.02	1.070; .343
Income higher than expense	1107	19.18±6.43		114.22±18.07	
Chronic disease					
No	4899	19.15±6.51	-1.212; .225	113.53±17.97	-1.142; .253
Yes	568	19.50±6.53		114.44±17.60	
Regular use of medication					
No	4648	19.18±6.50	-.209; .834	113.72±17.89	.916; .360
Yes	819	19.23±6.60		113.10±18.18	
Being diagnosed with COVID-19 herself/himself or a family member					
No	3631	19.05±6.59	-2.207; **.027**	114.17±17.89	3.145; **.002**
Yes	1836	19.45±6.35		112.55±17.98	
Delaying the application to the hospital as much as possible due to any illness other than COVID-19 during the pandemic					
No	3101	19.27±6.45	1.114; .265	113.50±18.01	-.568; .570
Yes	2366	19.07±6.60		113.78±17.84	
Delaying the application to the family doctor as much as possible due to any illness other than COVID-19 during the pandemic					
No	4099	19.27±6.59	1.789; .074	113.34±18.13	-2.059; **.040**
Yes	1368	18.91±6.58		114.49±17.33	
Receiving home health care services for herself/himself or a relative during COVID-19 pandemic					
No	5016	19.07±6.49	-4.438; **.000**	113.91±17.69	3.479; **.001**
Yes	451	20.49±6.65		110.47±20.27	
Receiving home health care services before the COVID-19 pandemic					
No	5258	19.15±6.51	-1.924; .054	113.64±17.92	.348; .728
Yes	209	20.03±6.39		113.20±18.25	
Preferring to receive home health care services instead of applying to the hospital or family doctor during the COVID-19 pandemic					
No	4207	19.20±6.48	.340; .734	113.69±18.01	.407; .615
Yes	1260	19.13±6.62		113.40±17.70	
Thinking that home health care services should be widespread					
No	2509	19.11±6.45	-.766; .444	113.59±18.13	-.113; .910
Yes	2958	19.25±6.56		113.65±17.78	
Total	5467	19.18±6.51		113.62±17.94	

*Scheffe test

The level of compliance of society with the precautionary behavior practices or preventive measures due to the COVID-19 pandemic

While 0.3% (n=18) of the participants stated that they complied with all precautionary behavior practices or preventive measures (n=21), 0.03% (n=2) of them reported that they complied with none of them. Of the participants, 3.1% (n=171) reported that they did not comply with any precautionary behavior practices or preventive measures related to masks, 3.4% (n=187) distance, and 0.3% (n=14) hygiene. Of the participants, 7.8% (n=411) who stated that they comply with any preventive measures related to

Table 2. The distribution of the mean of the participants' fears of COVID-19 and attitude for homecare scores by some precautionary behavior practices or preventive measures

Variables	n	The fear of COVID-19		The attitude for home care	
		Mean ± SD	t / F; p	Mean ± SD	t / F; p
Individual-level compliance with social distancing rules (minimum distance of 1,5 metres / 3 feet)					
No	631	18.27±6.53	-3.744; **.000**	107.95±17.44	-8.502; **.000**
Yes	4836	19.30±6.50		114.36±17.87	
Wearing a mask when going out or in crowded environments					
No	439	18.30±7.06	-2.761; **.006**	106.11±21.18	-7.853; **.000**
Yes	5028	19.26±6.46		114.28±17.47	
Using the mask to fully cover the mouth and nose					
No	445	17.60±7.03	-4.994; **.000**	105.81±20.66	-8.419; **.000**
Yes	5022	19.32±6.44		114.32±17.51	
Using a face shield					
No	5004	19.09±6.41	-2.951; **.003**	113.43±17.85	-2.645; **.008**
Yes	463	20.15±7.41		115.78±18.69	
Cleaning hands frequently with hand sanitizer or products containing at least 70% alcohol					
No	1534	17.64±6.61	-10.883; **.000**	110.72±18.66	-7.298; **.000**
Yes	3933	19.79±6.37		114.76±17.52	
Using gloves when going out or touching something while shopping					
No	4326	18.81±6.35	-8.010; **.000**	113.32±17.81	-2.416; **.016**
Yes	1141	20.62±6.90		114.77±18.38	
Reusing the mask by washing or disinfecting					
No	4688	18.97±6.46	-5.846; **.000**	113.37±17.85	-2.567; **.010**
Yes	779	20.44±6.68		115.15±18.36	
Washing hands frequently by rubbing with soap and water for at least 20 seconds.					
No	1154	17.92±6.79	-7.172; **.000**	108.49±19.05	-10.488; **.000**
Yes	4313	19.52±6.39		115.00±17.37	
Keeping at least 3-4 steps distance from people who have symptoms of a cold					
No	2055	18.28±6.55	-8.019; **.000**	109.63±18.31	-12.792; **.000**
Yes	3412	19.73±6.43		116.03±17.27	
To ventilate the environment frequently					
No	1348	18.20±6.68	-6.275; **.000**	108.35±19.02	-12.001; **.000**
Yes	4119	19.50±6.42		115.35±17.22	
Washing clothes at 60-90 degrees with normal detergent					
No	2606	18.40±6.33	-8.572; **.000**	110.56±18.23	-12.229; **.000**
Yes	2861	19.90±6.59		116.42±17.20	
Going to a health facility by wearing a mask for complaints in such as fever, cough, and shortness of breath					
No	2072	18.41±6.61	-6.819; **.000**	109.45±18.53	-13.399; **.000**
Yes	3395	19.65±6.40		116.17±17.07	
Covering the mouth and nose with a disposable wipe when coughing or sneezing, or using the inside of the elbow if there is no wipe					
No	1725	18.32±6.64	-6.579; **.000**	109.04±19.22	-12.432; **.000**
Yes	3742	19.58±6.41		115.74±16.90	
Canceling or postponing international travel					
No	4710	19.08±6.44	-3.492; **.001**	113.39±17.75	-2.317; **.021**
Yes	757	19.99±6.89		115.10±19.02	
Cleaning frequently used surfaces such as door handles, armatures, sinks with water and detergent every day					
No	3647	18.41±6.25	-12.314; **.000**	111.92±17.79	-10.070; **.000**
Yes	1820	20.74±6.74		117.05±17.75	

Variables	n	The fear of COVID-19		The attitude for home care	
		Mean ± SD	t / F; p	Mean ± SD	t / F; p
Avoiding close contact, such as handshaking and hugging					
No	1398	18.00±6.76	-7.675; **.000**	109.12±19.45	-10.344; **.000**
Yes	4069	19.59±6.37		115.17±17.12	
If there are cold symptoms, not to contact with the elderly and chronic patients, not to go out without wearing a mask					
No	2075	18.37±6.58	-7.188; **.000**	109.41±18.89	-13.806; **.000**
Yes	3392	19.68±6.42		116.20±16.82	
Avoiding to touch eyes, mouth and nose with hands					
No	2182	18.19±6.47	-9.279; **.000**	109.67±18.25	-13.358; **.000**
Yes	3285	19.84±6.46		116.25±17.23	
Spending the first 14 days at home after returning from an international travel					
No	5172	19.13±6.47	-2.512; **.012**	113.59±17.80	-.483; **.630**
Yes	295	20.18±7.07		114.17±20.24	
Not sharing any personal belongings (daily items such as towels)					
No	2543	18.77±6.50	-4.428; **.000**	111.31±18.49	-8.929; **.000**
Yes	2924	19.55±6.50		115.64±17.19	
Consuming plenty of fluids, eating a balanced diet and paying attention to sleeping patterns					
No	2383	19.24±6.41	.613; .540	110.71±18.41	-10.590; **.000**
Yes	3084	19.14±6.59		115.88±17.23	
Total	5467	19.18±6.51		113.62±17.94	

the mask reported that they received home health care services during the COVID-19 pandemic, 7.8% (n=410) related to distance, and 8.3% (n=450) related to hygiene. Overall, the findings indicated that 92% of the participants used medical or surgical masks, 8.9% used nano masks, 8.8% used N95, 4.6% used the mask they made at home on their own, 4.1% used FFP1, 3.2% used FFP2, 3% used FFP3, 0.7% used N99, and 0.4% used N100. The distribution of participants' precautionary behavior practices or preventive measures were presented in Table 2.

The status of receiving home health care services and attitudes toward home care the society due to the COVID-19 pandemic

While 3.8% of the participants received home health care before the COVID-19 pandemic, 8.2% applied for home health care services for themselves or a relative during the COVID-19 pandemic (Table 1). Most participants (54.1%) reported that home healthcare services should be widespread. The mean of attitudes on home care score of participants was 113.62 ± 17.94 (median 114.00, min 56.00, max 145.00).

The variables that affect the attitudes toward home care the society and their fear levels of COVID-19

Participants being diagnosed with COVID-19 themselves or a family member had higher levels of COVID-19 fear ($p < .05$; Table 1) and less positive attitudes towards home care ($p < .001$; Table 1) than others. Participants receiving home health care services for themselves or a relative during the COVID-19 pandemic had a higher level of COVID-19 fear than those who had not received any ($p < .000$; Table 1).

Except for consuming plenty of fluids, eating a balanced diet, and paying attention to sleeping patterns, the participants who adhered to all precautionary behavior practices or preventive measures related to COVID-19 had more fear of COVID-19 (for each, $p < .05$; Table 2). Moreover, except for the variable of spending the first 14 days at home after returning from an international trip, the participants who adhered to all precautionary behavior practices or preventive measures related to COVID-19 had more positive attitudes towards home care services (for each, $p < .05$; Table 2). Although it is an undesirable behavior, it is also noteworthy that participants who reused their masks by washing or disinfecting had more fear of COVID-19 and positive attitudes towards home care services (for each, $p < .05$; Table 2).

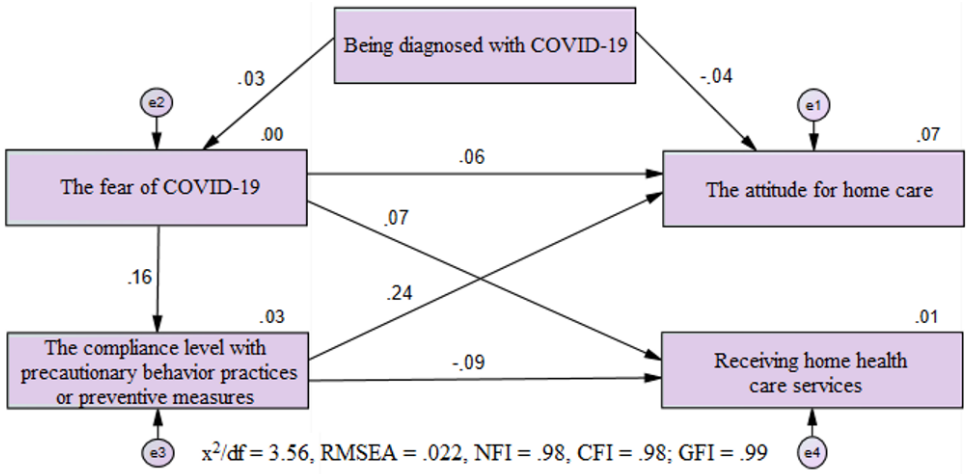
As the participants' COVID-19 fear levels increased, their positive attitudes towards home care services increased, receiving home health care services increased, and their compliance levels with precautionary behavior practices or preventive measures also increased (for each, $p < .001$; Table 3). As the participants' compliance levels with precautionary behavior practices or preventive measures increased, their receiving home health care services decreased, and their positive attitudes towards home care services increased (for each, $p < .001$; Table 3).

Table 3. A table of correlations

Variables	1	2	3	4	5
[1] The fear of COVID-19	1	-	-	-	-
[2] The attitude for home care	.098**	1	-	-	-
[3] Receiving home health care services	.060**	-.053**	1	-	-
[4] The compliance level with precautionary behavior practices or preventive measures	.163**	.250**	-.078**	1	-
[5] Age	.015	.020	-.004	.025	1

** p < .001

(β = .075, p < .001). Participants' compliance level with precautionary behavior practices or preventive measures related to COVID-19 had a direct effect on their attitude toward home care (β = .240, p < .001). However, higher compliance levels with precautionary behavior practices or preventive measures related to COVID-19 negatively affect the receiving home health care services (β = -.090, p < .001).



Structural Equation Model			Standardized β	SE	t	p
Being diagnosed with COVID-19	--->	The fear of COVID-19	.029	.187	2.180	.029
The fear of COVID-19	--->	The compliance level with precautionary behavior practices or preventive measures	.163	.009	12.249	< .001
The compliance level with precautionary behavior practices or preventive measures	--->	Receiving home health care services	-.090	.001	-6.633	< .001
The fear of COVID-19	--->	Receiving home health care services	.075	.001	5.480	< .001
The fear of COVID-19	--->	The attitude for home care	.060	.36	4.563	< .001
The compliance level with precautionary behavior practices or preventive measures	--->	The attitude for home care	.240	.055	18.151	< .001
Being diagnosed with COVID-19	--->	The attitude for home care	-.043	.496	-3.267	.001

Figure 1. The results of structural equation model

The SEM model developed in this study showed the associations between the fear of COVID-19, being diagnosed with COVID-19, compliance with precautionary behavior practices or preventive measures, receiving home health care services, and attitude toward home care variables (Figure 1). The fitting indices obtained by the structural equation model were appropriate and overall acceptable (x2/df = 3.56, RMSEA = .022, NFI = .98, CFI = .98, GFI = .99), and all paths were statistically significant in the research model (for each, p < .05; Figure 1 and Table 4). Higher levels of COVID-19 fear positively affect the attitude toward home care (β = .060, p < .001). Moreover, higher levels of COVID-19 fear significantly explained receiving more home healthcare services

Table 4. The fitting indices obtained by structural equation model

Compliance indices	Excellent fit	Good fit	Non-fit	Obtained value	Fit
x^2/df	0-2	2-5	> 5	3.56	Good compliance
RMSEA	0-.05	.05-.10	> .10	.022	Excellent compliance
NFI	.90-1	.80-.90	< .80	.98	Excellent compliance
CFI	.90-1	.80-.90	< .80	.98	Excellent compliance
GFI				.99	Accept

x^2 : Minimum Fit Function Chi-Square ; df :Degrees of Freedom, RMSEA : Root Mean Square Error of Approximation ; NFI: Normed Fit Index ; CFI: Comparative Fit Index; GFI : Goodness of Fit Index

Discussion

It is known that the perception of a high risk of infection in hospitals and the reluctance of healthcare professionals to provide healthcare services due to fear of contamination has led to the fact that the public is reluctant to visit health facilities and receive health care unless necessary, and the pandemic has caused changes in health-seeking behavior (1, 2). In our study, the proportion of participants who stated that they postponed their appointments as much as possible for any illness other than COVID-19 during the pandemic was 43.3%, and the proportion of those who postponed their family doctor appointments was 25%. After taking public health precautions such as wearing a face mask against COVID-19, social distancing, and hand hygiene, the number of people admitted to the hospital due to community-related infectious diseases has greatly decreased (16). In our study, it was observed that compliance with the recommended public health safety measures, such as wearing a face mask (96.9%), social distancing (96.6%), and hand hygiene (99.7%), was high. Moreover, during the pandemic management in Türkiye, those with chronic diseases could obtain their medicines from pharmacies if a consultation was not required. The extension of the duration of drug reports by the Social Security Institution may have played a role in the postponement of appointments, as a positive development that facilitated the short-term lives of patients with chronic and rare diseases.

In our study, fear of COVID-19 positively affected the attitude toward home care, and higher levels of fear of COVID-19 significantly explained receiving more home health care services. However, in a study conducted with Massachusetts Home Health and Home Care agency managers, it was reported that clients cancelled visits due to concern that home care providers would expose them to the COVID-19, and family members assumed direct care tasks that were previously provided by home care providers (9). In Türkiye, there has been a 5-fold increase in the demand for home care services compared to pre-pandemic (11). Of course, this may be because home care services in Türkiye are not yet widespread and participants with a high fear of COVID-19 perceived home care services as safer than hospital admissions due to the risk of infection transmission. Interest in-home care is not influenced by disease cases, except when more detailed medical treatment for cases is needed in hospitals (17). In our study, 3.8% of the participants received home health care before the pre-pandemic, while 8.2% applied to receive home health care for themselves or a relative during the COVID-19 pandemic. Most of the participants (54.1%) reported that they thought home health care should be widespread. The fact that hospital visits are limited due to infection control measures and the rapid restructuring of home health and social services in Türkiye together with COVID-19 may have had an impact on this situation.

Leaving aside the irreversible losses or damages caused by the pandemic to humanity, it is seen that it has several unforeseen positive impacts, such as the willingness and compliance of the society to accept and act on public health messages and increasing self-care and health awareness (16). In our study, it was determined that participants who comply with all precautionary behavior practices or preventive measures related to COVID-19, except for consuming plenty of fluids, paying attention to a balanced diet, and paying attention to sleep patterns, experienced more fear of COVID-19. However, unlike our study, it is stated that individuals who perceive a higher risk of disease may be affected by the psychological effects of anxiety and panic, which is effective in weakening individuals' intentions to act in self-precautionary behavior (18). Even if the COVID-19 disease's risk was perceived as highly severe, it was noted that a high level of anxiety was ineffective in creating behavioral change (19). Similarly, Yıldırım et al. (2021) reported that those with a high fear of COVID-19 were more likely to engage in preventive behaviors (20). Therefore, it can be thought that participants who believed they were vulnerable, perceived a high risk of infection, and had a greater fear of COVID-19, paid more attention to preventive measures. In our study, participants' level of compliance with precautionary behavior practices or preventive measures related to COVID-19 had a positive effect on their attitudes toward home care, while it negatively affected receiving home health care services. These findings may be due to the fact that the belief that home care contributes to COVID-19 measures positively affects attitudes towards home care, while those with high levels of compliance with the measures do not need home care.

The anger of those in quarantine caused by their isolation can turn into violence In our study, participants diagnosed with COVID-19 themselves or a family member had higher levels of COVID-19 fear than others and less positive attitudes towards home

care. Page et al. (2020) reported a greater need for support at-home care during quarantine (21). Attitudes towards home care of participants who themselves or a family member suffered from COVID-19 may have been affected by the following circumstances such as feeling lonely during the isolation process, feeling unsafe at home, thinking that their care needs were too much, and having an unsuitable home environment for care. Much more research is needed on this issue.

Limitations

One of the limitations of this study was that it was self-reported and lacked external observation.

Another limitation was that due to the personal data protection law, the contact information of people receiving home care services had not been shared with researchers. For the research invitation, the fact that these people could not be reached directly may have negatively impacted the representation of the segment receiving home care services in the sample.

Implications for practice and policy

These findings provide implications for public health nurses, home care service staff, other providers, policymakers, and researchers. The community's interest in home care services has increased with the pandemic. More than half of the participants thought home care services should be widespread. Public health nurses can play a key role in launching and regulating the necessary lobbying activities and campaigning by public authorities, local organizations and professional associations for the widespread and support of home care services, which play a complementary and/or supporting role in health and social services during the pandemic. More research is needed to increase the positive attitudes of people with low compliance with preventive measures and low fear of COVID-19 towards home care services. Concerning reaching home care service recipients so that advocacy activities can be carried out based on evidence, it is necessary to assist researchers in conducting more community-based research.

Conclusion

The study's findings showed that participants' mean COVID-19 fear score was 19.18 ± 6.51 and that participants had a moderate level of COVID-19 fear. Compliance with the recommended public health safety measures was high such as wearing a face mask (96.9%), social distancing (96.6%), and hand hygiene (99.7%). While 3.8% of the participants received home health care before the COVID-19 pandemic, 8.2% applied for home health care services for themselves or a relative during the COVID-19 pandemic. Our results showed that it is possible to improve the attitude toward home care by promoting compliance levels with precautionary behavior practices or preventive measures.

Ethical Aspects of the Research

First, permission to use the scales was obtained from the authors who developed the scales used in this study. For the study, the approval of the Ministry of Health Scientific Research Platform dated 25/06/2020, the institutional approval of the Eskisehir Public Health Directorate dated 02/02/2021, and the ethical approval of the Eskisehir Osmangazi University Non-Interventional Clinical Research Ethics Committee dated 14/07/2020 (No:39) were obtained.

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

The authors declared that this study received no financial support.

Authors' Contribution

All authors listed meet the authorship criteria according to the guidelines of the International Committee of Medical Journal Editors (ICMJE). P.D., Ö.Ö. and D.B. developed the design of the study, P.D. and D.B. involved in the collection and management of the data. P.D. analyzed the statistical data. P.D. interpreted the results. P.D. drafted the manuscript, and P.D., Ö.Ö. and D.B. critically revised the manuscript for important intellectual content. All authors approved their manuscript of final submitted version.

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References

1.Singh DR, Sunuwar DR, Shah SK, Karki K, Sah LK, Adhikari B, et al. Impact of COVID-19 on health services utilization in Province-2 of Nepal: a qualitative study among community members and stakeholders. BMC Health Serv. Res. 2021;21(1):1-14.

2.Ayele W, Biruk E, Kifle A, Habtamu T, Taye G, Wondarad Y. Patterns of essential health services utilization and routine health information management during COVID-19 pandemic at primary health service delivery point Addis Ababa,

Ethiopia. Ethiop J Health Dev. 2021;35(1):90-97.

3.Örsal Ö, Duru P. Diagnosis, monitoring, treatment and care of COVİD-19 cases at home. In Aksayan S, editor. COVID-19 pandemic and public health nursing. 1st ed. Ankara: Turkey Clinics; 2020. p. 42-49.

4.Lyng HB, Ree E, Wibe T, Wiig S. Healthcare leaders' use of innovative solutions to ensure resilience in healthcare during the COVID-19 pandemic: a qualitative study in Norwegian nursing homes and home care services. BMC Health Serv. Res. 2021;21(1):1-11.

5. Demirtaş-Madran HA. Accepting restrictions and compliance with recommended preventive behaviors for COVID-19: A discussion based on the key approaches and current research on fear appeals. Front. Psychol. 2021;12: 558437.

6.Malak B, Aydın A. Türkiye'de COVID-19'a yönelik ilk psikososyal tepkiler: Bir içerik analizi (Acute psychosocial responses to COVID-19 in Turkey: A content analysis). Turk. J. Fam. Med. Prim. Care. 2021:15(3):581-593.

7.Willis DE, Andersen JA, Bryant□Moore K, Selig JP, Long CR, Felix HC, et al. COVID□19 vaccine hesitancy: Race/ethnicity, trust, and fear. Clin. Transl. Sci. 2021:14(6);2200-2207.

8.Alqahtani AM, Alshahrani FM, Esmail KMM, Rezk SR. Outcome of COVID-19 among homecare patients and its relation to chronic diseases. World Fam. Med. / Middle East J. Fam. Med. 2021:19(4);111-117.

9.Sama SR, Quinn MM, Galligan CJ, Karlsson ND, Gore RJ, Kriebel D, et al. Impacts of the COVID-19 pandemic on home health and home care agency managers, clients, and aides: a cross-sectional survey, March to June, 2020. Home Health Care Manag. Pract. 2021:33(2);125-129.

10.Weeks LE, Nesto S, Hiebert B, Warner G, Luciano W, Ledoux K, et al. Health service experiences and preferences of frail home care clients and their family and friend caregivers during the COVID-19 pandemic. BMC Res Notes. 2021:14(1);1-5.

11.Kronos. (2020, 06.04.2020). Evde sağlık için talepler 10 günde yüzde 500 artı https://kronos34.news/tr/evde-saglik-icin-talepler-10-gunde-yuzde-500-artti/

12.Republic of Turkey Ministry of Health. (2021). COVID-19 information platform. Retrieved 25.09.2021 from https://COVID19.saglik.gov.tr/TR-66935/genel-koronavirus-tablosu.html

13.Republic of Turkey Ministry of Health. (2020). Novel coronavirus disease. (COVID-19). Retrieved 02/09/2021 from https://COVID19bilgi.saglik.gov.tr/tr/

14.Satici B, Gocet-Tekin E, Deniz ME, Satici SA. Adaptation of the fear of COVID-19 scale: Its association with psychological distress and life satisfaction in Turkey. Int J Ment Health Addict. 2021:19; 1980-1988.

15.Duru P, Örsal Ö, Karadağ E. Development of an attitude scale for home care. Res. Theory Nurs. Pract. 2015:29(4);306-324.

16.Hoo HE, Loh HC, Ch'ng ASH, Hoo FK, Looi I. Positive impacts of the COVID-19 pandemic and public health measures on healthcare. Prog. Microbes Mol. Biol. 2021:4(1);1-17.

17.Nugroho C, Suryono BW. The analysis of homecare interest in pandemic COVID-19 period based on disease case in Indonesia. European Journal of Medical and Health Sciences. 2020:2(5);1-3.

18.Wang RN, Zhang YC, Wu RK, Li B, Li CW, Yu BT, et al. A study of self-precaution against the background of the COVID-19 pandemic from the perspective of risk perception attitude theory and social support. BMC Public Health. 2021:21(1);1-12.

19.Can F, Ergül-Topçu A, Topçu, G. Health beliefs in association with behaviors in compliance with COVID-19 public health guidelines: A cross-sectional study. Soc Work Public Hlth 2021;1-14.

20.Yıldırım M, Geçer E, Akgül Ö. The impacts of vulnerability, perceived risk, and fear on preventive behaviours against COVID-19. Psychol Health Med. 2021:26(1);35-43.

21.Page N, Naik V, Singh P, Fernandes P, Nirabhawane V, Chaudhari S. Homecare and the COVID-19 pandemic–Experience at an urban specialist cancer palliative center. Indian J Palliat Care. 2020:26(Suppl 1);63-69.

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ORIGINAL ARTICLE

Exploring Therapeutic Potentials of Natural Agents Against Breast Cancer Using Molecular Modeling

Moleküler Modelleme Kullanılarak Meme Kanserine Karşı Doğal Ajanların Terapötik Potansiyellerinin Araştırılması

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ABSTRACT

Background/Aims: This study examines the crystal receptor structure of the BRCA1 gene and its relationships with natural agents like curcumin, resveratrol, and quercetin, aiming to discover alternative natural agents to 5-Fluorouracil (5FU) and their therapeutic potential.
Method: The study focuses on the crystal structure of the BRCA1 gene, mutated into wild-type and mutant-type 3FA2, and evaluates binding affinities and structural stabilities with natural ligands like curcumin, quercetin, resveratrol, and 5FU chemical ligands.
Results: As a result of molecular dockings performed using mutant-type and wild-type 3FA2 receptors and natural agent and chemical drug ligands, the binding affinities of natural agents were found to be -6.6 kcal/mol and below, while the affinity score of the chemical drug ligand was -5.6 kcal/mol. RMSD, RMSF, Rg and RDF analyses performed as a result of molecular dynamics simulation show that receptor-ligand complex structures formed especially with natural agents have a very good stability. Among these structures, it was found that curcumin, which has the lowest binding score and stable values, has a strong binding affinity with receptors, a stable structure, and pharmacokinetic properties that carry the potential to be a good drug candidate compared to other ligands.
Conclusion: Curcumin, quercetin, and resveratrol indicate that natural agents may be alternative therapeutic drug candidates to the chemical drug 5FU in the treatment of breast cancer caused by BRCA1 gene mutation. Especially, curcumin has a good binding interaction score with receptors associated with BRCA1 genes, forms a stable structure, and has the expected pharmacokinetic profile, which promises hope for the discovery of new therapeutic natural agents for breast cancer treatment.

Keywords: Breast cancer, BRCA1, molecular docking, molecular dynamics simulation

ÖZ

Arka Plan/Amaçlar: Bu çalışma, BRCA1 geninin kristal reseptör yapısını ve kurkumin, resveratrol ve kuersetin gibi doğal ajanlarla ilişkilerini inceleyerek, 5-Florourasil (5FU)'e alternatif doğal ajanları ve bunların terapötik potansiyellerini keşfetmeyi amaçlamaktadır.
Yöntem: Çalışma, vahşi tip ve mutant tip 3FA2'ye mutasyona uğramış BRCA1 geninin kristal yapısına odaklanmakta ve kurkumin, kuersetin, resveratrol ve 5FU kimyasal ligandları gibi doğal ligandlarla bağlanma afinitelerini ve yapısal kararlılıklarını değerlendirmektedir.
Bulgular: Mutant-type ve wild-type 3FA2 reseptörleri ve doğal ajan ile kimyasal ilaç ligandları kullanılarak yapılan moleküler yerleştirmelerin sonucunda doğal ajanların bağlanma afiniteleri -6.6 kcal/mol ve altında değerlerde bulunurken kimyasal ilaç ligandının afinite skoru -5.6 kcal/mol değerindedir. Moleküler dinamik simülasyon sonucunda yapılan RMSD, RMSF, Rg ve RDF analizleri özellikle doğal ajanlar ile oluşturulan reseptör-ligand kompleks yapılarının oldukça iyi bir stabiliteye sahip olduğu sonucunu göstermektedir. Bu yapılardan en düşük bağlanma skoru ve stabil değerlere sahip kurkuminin diğer ligandlara kıyasla reseptörler ile güçlü bir bağlanma afinite, kararlı bir yapı ve iyi bir ilaç adayı olma potansiyelini taşıyan farmakokinetik özelliklere sahip olduğu bulgularına ulaşılmıştır.
Sonuç: BRCA1 gen mutasyonu kaynaklı meme kanseri tedavisinde kurkumin, kuersetin, resveratrol doğal ajanların kimyasal ilaç 5FU'ya alternatif terapötik ilaç adayları olabileceğini göstermektedir. Özellikle kurkuminin BRCA1 genleri ile ilişkili reseptörlerle iyi bir bağlanma etkileşim skoruna sahip olması, kararlı bir yapı oluşturması ve beklenen farmakokinetik profilinin olması meme kanseri tedavisine yönelik yeni terapötik doğal ajanların keşfedilmesi için umut vaadetmektedir.

Anahtar Kelimeler: BRCA1, meme kanseri, moleküler yerleştirme, moleküler dinamik simülasyon

Introduction

The most well-known type of cancer, whose incidence is increasing day by day worldwide, is breast cancer. It is characterized by normal cells in the breast area becoming abnormal and multiplying uncontrollably, leading to the formation of malignant tumor cells (1, 2). Given that this type of cancer has led to a rise in the mortality rate among women in recent years, it has become an even more serious disease for which alternative treatment methods must be sought (1). One of the major factors contributing to the onset of breast cancer is mutations in genes (3, 4). The most well-known gene associated with breast cancer is BRCA1 (Breast Cancer Gene 1). The BRCA1 gene is a tumor suppressor gene that regulates cell division and the repair of DNA damage (5). This tumor suppressor gene encodes a protein that plays a role in repairing damaged DNA mechanisms, thereby preventing abnormal cell division and the formation of breast

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cancer by restoring the damaged DNA mechanism (6, 7). As a result of the mutation of the BRCA1 gene, the DNA repair mechanism does not function properly, leading to negative events such as DNA damage, unrepaired DNA, and abnormal cell growth and division (5, 6). The occurrence of these conditions caused by mutations in the BRCA1 gene increases the risk of developing breast cancer and accelerates the progression of existing cancer (8). For all these reasons, the BRCA1 gene, a tumor suppressor gene, is crucial for maintaining genomic stability, and mutations in this gene pose significant challenges in the treatment of breast cancer. (9). For this reason, it is crucial to explore alternative treatment methods, especially for breast cancer caused by BRCA1 gene mutations (10, 11).

When literature studies are examined, methods such as radiotherapy, chemotherapy, and immunotherapy are utilized in the treatment of various types of cancer, particularly breast cancer (12). Radiotherapy slows down the growth of cancerous cells and destroys them with the assistance of high-energy rays. The high-energy rays utilized in this method fragment the DNA material within cancer cells (5). In this way, it leads to the death of cancerous cells. Radiotherapy, also known as radiation therapy, aims to eliminate potentially cancerous cells left behind after lumpectomy and mastectomy in BRCA1-related breast cancer type (12, 13). In chemotherapy, drugs targeting cancer cells are utilized to eliminate damaged cells. This method is employed to reduce tumor size before surgical procedures or to eradicate cells deemed potentially cancerous post-surgery. Immunotherapy is a significant method capable of enhancing DNA repair mechanisms and anti-tumor immune responses (14, 15). These methods are the most common treatment options utilized in addressing various types of cancer such as breast cancer. However, while these treatments combat cancer, they also induce numerous side effects on the human body (16, 17). For example, following radiotherapy, patients may experience fatigue, hair loss, difficulty breathing and swallowing; increased risk of infection and anemia may occur after chemotherapy; susceptibility to autoimmune diseases after immunotherapy can lead to irregularities in the functions of vital organs such as the liver (18). For these reasons, it is important to discover alternative solutions in the treatment of breast cancer caused by BRCA1 gene mutations that do not have side effects on human health (19).

It is crucial to utilize therapeutic natural agents in the treatment of breast cancer that have minimal side effects on human health. Naturally sourced agents such as plant extracts and algae pigments exhibit anticancer properties by combating cancerous cells (20). Thus, it is of great importance for human health to discover new treatment methods using alternative therapeutic drug agents instead of treatment practices that involve chemical drugs and their associated side effects (17). The natural agents curcumin, resveratrol, and quercetin obtained from extracts of turmeric, red grapes, and various fruits and vegetables used in this study possess numerous bioactive properties (20, 21). Curcumin exhibits antioxidant properties by combating free radicals and oxidative stress in the body. Additionally, it possesses anti-inflammatory properties for conditions such as inflammation in the body, and it has anti-cancer properties by fighting cancer cells (21). Resveratrol battles free radicals similar to curcumin. It safeguards the DNA mechanism from oxidative damage through its antioxidant properties. Additionally, it combats cancerous cells by inhibiting the proliferation of breast cancer cells (22, 23). Another natural agent, quercetin, is a flavonoid. It possesses bioactive properties such as antioxidant and anti-inflammatory effects. This natural agent prevents the growth of cancerous cells by stimulating apoptotic processes (24). In this way, it addresses situations such as metastasis, causing tumor cells to spread to other parts of the body (25).

In the literature studies of Thai et al., it was emphasized that BRCA1 somatic gene mutations are associated with breast cancer (26). In addition, many literature studies have revealed that the valine amino acid at position 695 in the BRCA1 gene is mutated and somatically transformed into a leucine amino acid, and its relationship with breast cancer (26, 27). The utilization of molecular modeling approaches with different perspectives, such as molecular docking and molecular dynamics simulation, in studies found in the literature, will shed light on the discovery of treatment methods for vital diseases such as breast cancer (28, 29). Taking the studies of Thai et al. as a reference, within the scope of this study, the valine amino acid at position 695 of the A chain bound by the ligand was mutated by converting it to leucine in the crystal structure receptor with double chain 3FA2 PDB ID, A and B, obtained from the Protein Data Bank (PDB) (26). It was aimed to discover a new treatment method by performing molecular docking and molecular dynamics simulations of the obtained

mutant-type 3FA2 and wild-type 3FA2 receptors with the chemical drug 5-Fluorouracil (5FU), as well as such natural agents as curcumin, resveratrol, and quercetin ligands, which are among the most widely used drugs in the treatment of breast cancer in the market. One of the main aims of this study on breast cancer caused by BRCA1 gene mutation is to understand the interaction of ligands selected as therapeutic natural agents in breast cancer treatment with wild-type and mutant-type receptors associated with the BRCA1 gene, and to compare the biological structure of the mutant-type complex with the wild-type structure, giving meaning to their functions.

Within the scope of this study, the relationship between the wild-type and mutant-type 3FA2 crystal receptor structures, obtained by normal and point mutation of the BRCA1 gene associated with breast cancer, and chemical drug and natural agent ligands was examined through molecular docking. The mutation mechanism was analyzed by examining the molecular docking results in both wild-type and mutant-type receptor structures. A molecular dynamics simulation was conducted based on the docking results obtained. As a result of the simulation, graphics including RMSD (Root Mean Square Deviation), RMSF (Root Mean Square Fluctuation), Rg (Gyration Radius), and RDF (Radial Distribution Function) were obtained. Due to the data obtained, the therapeutic potential of the natural agents curcumin, resveratrol, and quercetin, as well as the chemical agent 5FU, on the wild-type and mutant-type receptors associated with the BRCA1 gene, was analyzed. The pharmacokinetic and pharmacodynamic properties of the ligands belonging to the most stable and favored conformations obtained as a result of docking and MD simulations were compared with ADMET analysis, revealing that these ligands possess therapeutic bioactive components. In summary, this literature study aimed to demonstrate that natural agents such as curcumin, resveratrol, and quercetin serve as new drug agents of natural origin, showcasing their therapeutic potential in breast cancer caused by gene mutations to be as effective as chemical drugs. This research contributes to the exploration of alternative treatment methods for breast cancer caused by BRCA1 gene mutation.

Computational Setup

Provision and Mutation of The Receptor

Criteria such as resolution, organism, and PDB validation table values of many receptor structures related to the BRCA1 gene were analyzed for use in this study. The Crystal Structure of the BRCA1 Associated Ring Domain (BARD1) Tandem BRCT Domains structure with PDB ID 3FA2, which has two repeated chains, A/B, and a resolution of 2.20 Å, was chosen as the most suitable structure. The 3FA2 receptor Figure 1 was obtained in 3D format from the Protein Data Bank (https://www.rcsb.org/) (30).

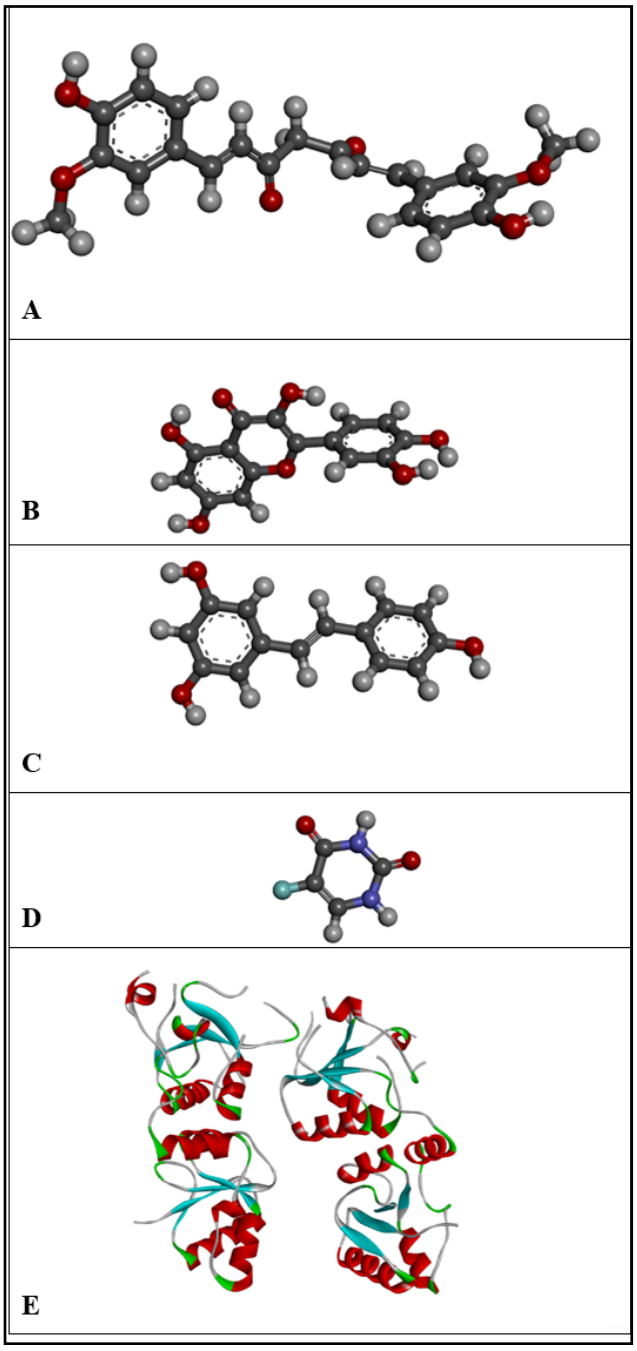

Figure 1. The structures of the ligand molecules shown in 3D models. The ligands are the chemical drug substance curcumin (A), quercetin (B), resveratrol (C), and 5FU (D). Dark gray, light gray, red, blue, and cyan colors for ligands are carbon (C), oxygen (H), oxygen (O), nitrogen (N), and fluorine (F), respectively. Red and blue ribbons for the 6M14

structure are A and B chains, respectively. The receptor is the solution Crystal Structure of the BRCA1 Associated Ring Domain (BARD1) Tandem BRCT Domains (PDB code: 3FA2) (E). The 3FA2 structure comprises two chains, designated as A and B, respectively.

The 3FA2 crystal receptor structure was opened using the PyMOL program. Later, based on the location of the breast cancer mutation associated with the BRCA1 gene in their study, Thai et al. transformed the VAL amino acid at position 695 in the A chain into the LEU amino acid, and somatic mutation was carried out (26, 27). Since the ligand-binding region of the 3FA2 receptor is on the A chain, it was decided that the mutation would only occur in the A region of this structure, which has A and B chains. At the end of all these stages, in this study, both mutant-type and wild-type 3FA2 receptors were obtained to understand the interactions between mutated and unmutated receptors, natural agents, and chemical drugs (27, 31).

Preparation of Receptors for The Docking Step

3FA2 receptors, both wild-type and mutant-type, were opened separately using USCF Chimera 1.17.3. Template ligands, such as GOL and PO4, along with water molecules, were deleted from the receptor structures. The structures underwent the dock prep process and were saved in '.mol2' format. Both receptor structures, wild-type, and mutant-type 3FA2, were then prepared for the molecular docking step (30, 32).

Preparation of Ligands for The Docking Step

Within the scope of this study, one drug and three natural agents, 5FU, curcumin, resveratrol, and quercetin, were selected as ligands. These ligand structures were obtained in 3D format from PubChem (https://pubchem.ncbi.nlm.nih.gov/). Each ligand structure was opened via USCF Chimera 1.17.3. Hydrogens were added to minimize the ligands, and the charge assignment process was applied. Then, the charges of the ligands were neutralized and recorded in '.mol2' format. The ligands are now ready for the docking phase.

Determination of The Active Regions of The Receptors

The position of the binding site amino acids, created with the template ligands of the crystal structure with PDB ID 3FA2, was examined in the PDB. It was determined that the binding site of the 3FA2 receptor is around amino acids at positions 650 to 750. In line with this information, the AutoGridFR 1.2 program, a bioinformatics tool, was used to determine the coordinates of the active site (33). The 3FA2 receptor and ligands, converted to the '.pdbqt' format via the AutoDock Vina program, were transferred to the AutoGridFR 1.2 program. Binding site amino acids at positions 650 to 750, referenced from the PDB, were selected. A target file with a '.trg' extension was created. The codes required to create a grid box were written in the Git CMD interface (27, 33). These steps were also repeated for the mutant-type 3FA2. According to the coordinates obtained, grid box parameters were determined for the docking stages with wild-type and mutant-type receptors and various ligands. In wild-type and mutant-type 3FA2 structures, the grid box parameters are 11.451, 18.284, and -35.160 for the center and 70, 70, and 70 for size, respectively, according to the XYZ coordinates.

Molecular Docking Analysis

A previously prepared receptor and a ligand in '.mol2' format were opened one above the other in the USCF Chimera 1.17.3 program. Using the Surface/Binding Analysis and AutoDock Vina options in the program, the previously determined grid box parameters were set for the appropriate receptor and ligand. Then, docking was performed (34, 35). In this step, eight docking processes were performed by applying wild-type and mutant-type 3FA2 receptors and 5FU, curcumin, resveratrol, and quercetin ligands. As a result of the docking processes for all receptor-ligand pairs, eight different lowest binding energy scores were obtained.

Molecular Dynamics Simulation

A 25 ns molecular dynamics simulation was performed via the GROMACS program to understand the stability, energy interactions, and hydrogen bond analysis of the receptor-ligand complex structures obtained from the eight lowest binding energy scores for each receptor and ligand (34). As a result of the simulation, RMSD (Root Mean Square Deviation), RMSF (Root Mean Square Fluctuation), gyration radius, and RDF (Radial Distribution Function) graphs were drawn to understand the interaction between receptors and ligands. The obtained results were analyzed and interpreted (4, 10).

Results

Molecular Docking and Interaction Analysis

A separate docking process is carried out with the

natural agents, including curcumin, quercetin, and resveratrol, which are predicted to have therapeutic potential in the treatment of breast cancer associated with mutant-type and wild-type 3FA2 receptors and the BRCA1 gene, as well as with the chemical drug 5FU, which is widely used in the market. The result of these receptor-ligand complexes is the binding affinity data shown in Table 1.

Table 1. Energy-based docking results for each model.

Receptor	Name of Ligand	Binding affinity (kcal/mol)
Mutant-type 3FA2	Curcumin	-7.8
	Quercetin	-7.9
	Resveratrol	-6.6
	5FU	-5.8
Wild-type 3FA2	Curcumin	-7.6
	Quercetin	-8.1
	Resveratrol	-6.8
	5FU	-5.6

Binding affinities obtained with curcumin, quercetin, resveratrol, and 5FU for the mutant-type 3FA2 receptor, which was created by somatic mutation by converting the VAL amino acid at position 695 in the A chain to the LEU amino acid of the crystal structure with PDB ID 3FA2 associated with the BRCA1 gene, are -7.8, -7.9, -6.6, and -5.8 kcal/mol. The results obtained from the docking phase of the wild-type 3FA2 receptor and the ligands are -7.6, -8.1, -6.8, and -5.6 kcal/mol.

The interactions of complexes formed between mutant-type 3FA2 and wild-type 3FA2 receptors, along with other ligands, are depicted in Figure 2 and Figure 3, respectively. The Discovery Studio 2021 Client program was employed to visualize the interactions within the receptor and ligand complex. In A1 of Figure 3, the bond interactions between the 3FA2 receptor and the curcumin ligand resulting from docking are observed. Curcumin interacts with the receptor through the Van der Waals amino acid Serine (SER) at position 761. Additionally, amino acids Serine (SER), Lysine (LYS), and serine (SER) numbered 616, 688, and 760, respectively, are also visible. Additionally, alkyl and pi-alkyl interactions are evident in amino acids 680, 684, and 764, namely Lysine (LYS), Isoleucine (ILE), and Tryptophan (TRP). Amide-pi stacked interactions are also evident in the receptor-ligand complex map obtained after A2 docking in Figure 3. When examining the receptor-ligand map of the wild-type 3FA2 and quercetin receptor in A2 after docking, conventional hydrogen bonds are observed at amino acid residues Arginine (ARG) and Tyrosine (TYR) at positions 705, 745, and 678, respectively. Additionally, unfavorable donor-donor interactions are observed between amino acid number 765 of asparagine (ASP) and amino acid number 688 of Lysine (LYS). Upon examination of the wild-type 3FA2 and resveratrol complex map in A3, a pi-donor hydrogen bond is found in the SER amino acid at position 616, van der Waals interaction in the SER amino acid at position 761, and a conventional hydrogen bond in the 686th Histidine (HIS) amino acid, 688th LYS. Additionally, there is pi-cation interaction, amide-pi stacking at SER at position 760, and pi-alkyl interactions at the ILE amino acid at position 764. In the A4 image in Figure 2, in the complex formed with the 5FU ligand and mutant-type 3FA2, conventional hydrogen bonds are present in the HIS and GLU amino acids at positions 686 and 740. Carbon hydrogen bonds and pi-donor hydrogen bonds are present in the HIS amino acid at position 685 and the SER amino acids at positions 760 and 761. When examining the interaction of the 5FU ligand and wild-type 3FA2 complex with amino acids in the A4 image in Figure 3, there are conventional hydrogen bonds and unfavorable hydrogen bond interactions in the HIS amino acid at position 686. While there is only a conventional hydrogen bond in the GLU amino acid at position 740, there are pi-donor hydrogen bonds in the SER amino acids at positions 760 and 761. Upon inspecting the curcumin complex map in B1 of Figure 3 after MDS, it is observed that amino acids PRO, ALA, Glutamic acid (GLU), and Methionine (MET) are located at positions 610, 613, 655, and 768, respectively. When examining the receptor-ligand maps of the mutant-type 3FA2 and various ligands after docking and MDS in images A1 and B1 in Figure 2, it is observed that the amino acids TRP at position 680, LYS at position 688, SER at position 761, ASP at position 765, and MET at position 768 remain consistent. When images A2 and B2 in Figure 3 are examined, it is observed that the amino acids ARG, ASP, and LEU, numbered 705, 763, and 773, respectively, remain unchanged in the quercetin complex map. Additionally, In the B4 image in Figure 2, in the complex formed with the 5FU ligand and mutant-type 3FA2, the amino acids GLY at position 681 and SER at position 761 contain carbon-hydrogen bonds, THR at position 682 and GLU at position 740 contain conventional hydrogen bonds, ASP at position 741 contains unfavorable donor-donor interactions, and HIS at position 685 contains

pi-pi stacked interactions. In the B4 image in Figure 3, when examining the interaction of the 5FU ligand and wild-type 3FA2 complex with amino acids, LYS at position 684, GLU at position 740, and SER at position 760 contain conventional hydrogen bonds, and HIS at position 685 contains unfavorable donor-donor and pi-pi stacking interactions.

Root Mean Square Fluctuation (RMSF)

RMSF values for receptor-ligand complexes, comprising four distinct ligands - namely, curcumin, quercetin, resveratrol, and 5FU - utilizing the mutant-type 3FA2 receptor depicted in Figure 4A, are presented. Throughout the 25 ns simulation, the mean RMSF values of the complex structures involving the mutant-

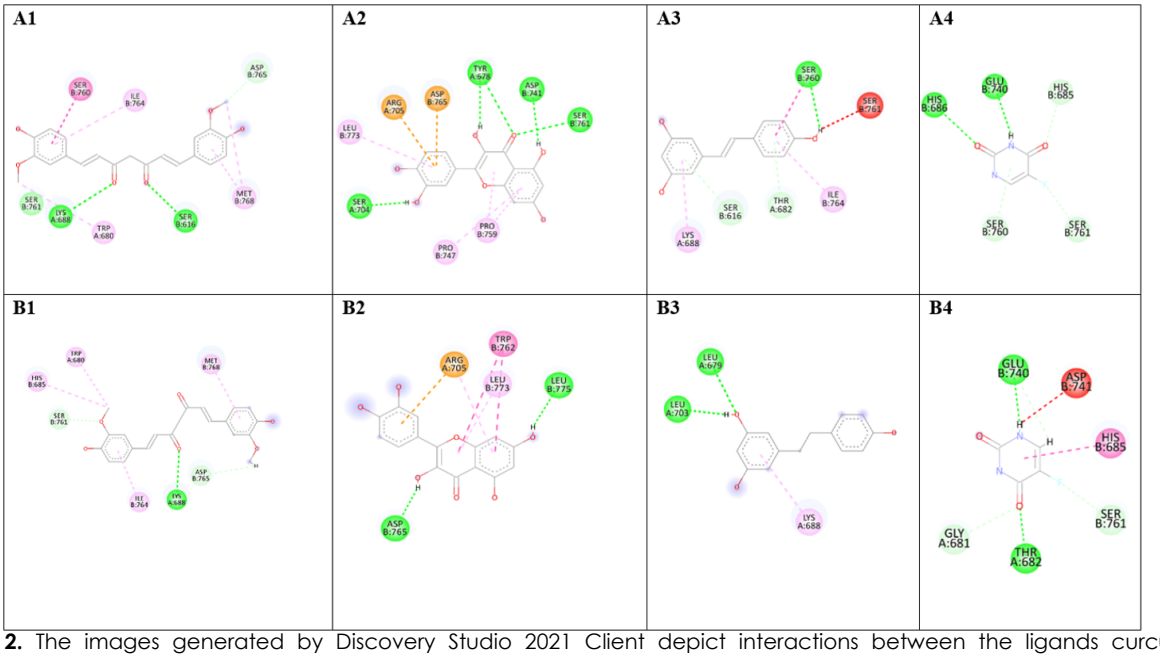

Figure 2. The images generated by Discovery Studio 2021 Client depict interactions between the ligands curcumin, quercetin, resveratrol, 5FU, and the mutant-type 3FA2 receptor, respectively. The top row modes represent the lowest binding conformations calculated in binding studies **(A1, A2, A3, A4)**, while the bottom row frames represent final snapshots from MD simulations **(B1, B2, B3, B4)**, respectively.

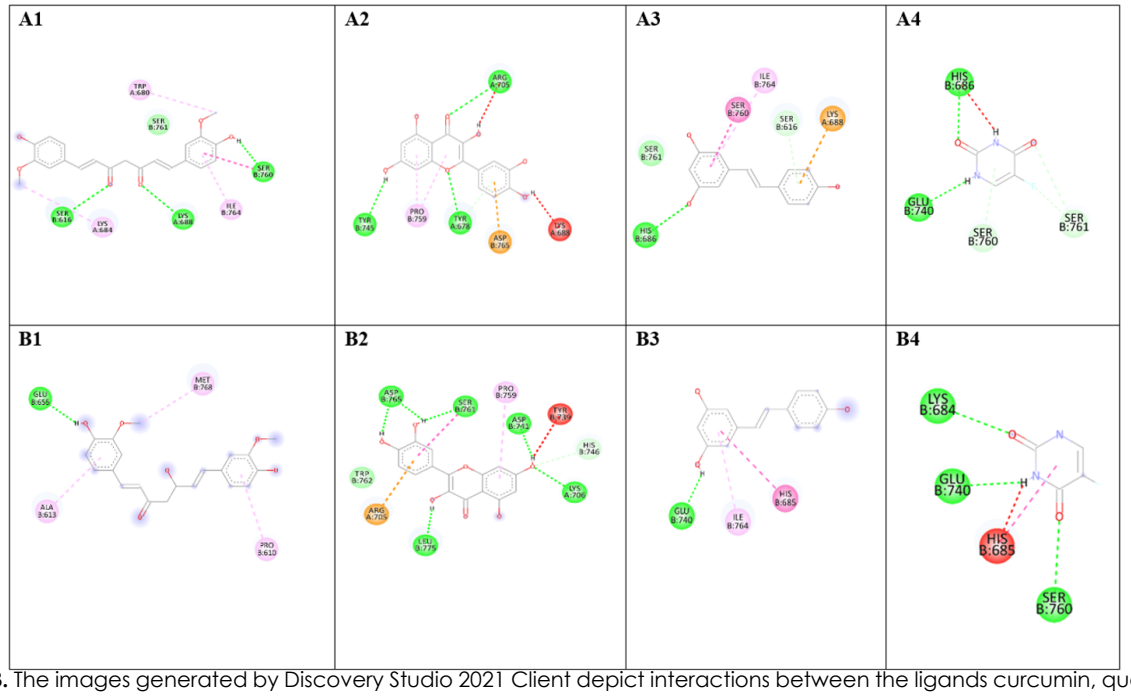

Figure 3. The images generated by Discovery Studio 2021 Client depict interactions between the ligands curcumin, quercetin, resveratrol, 5FU, and the wild-type 3FA2 receptor, respectively. The top row modes represent the lowest binding conformations calculated in binding studies **(A1, A2, A3, A4)**, while the bottom row frames represent final snapshots from MD simulations **(B1, B2, B3, B4)**, respectively.

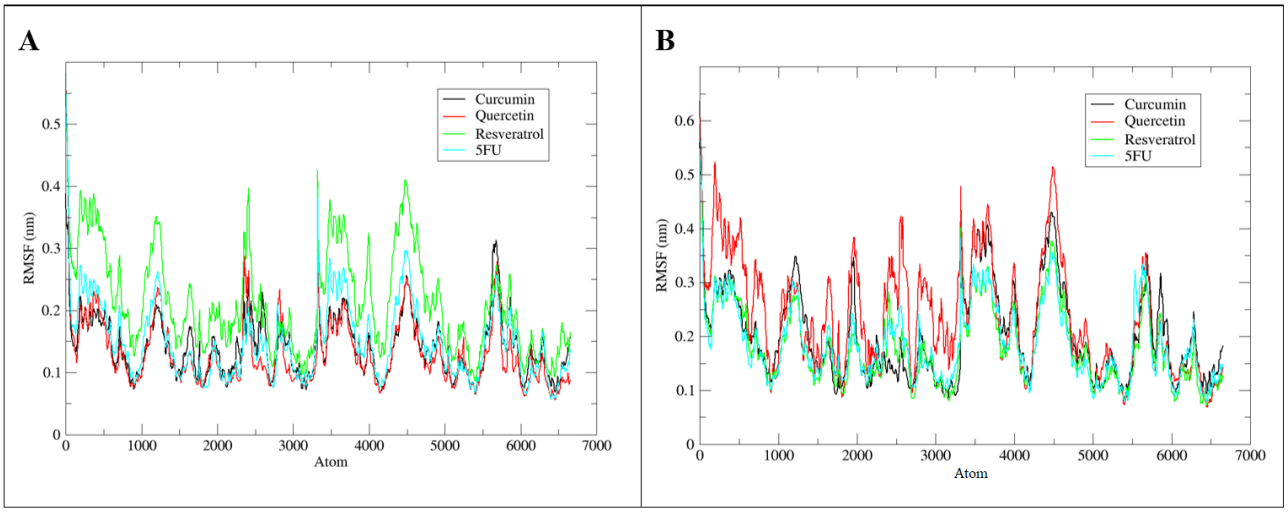

Figure 4. RMSF graph depicting the fluctuations of the mutant-type 3FA2 receptor **(A)** and wild-type 3FA2 receptor **(B)** in complex with ligands, respectively.

type 3FA2 receptor paired with curcumin, quercetin, resveratrol, and 5FU ligands are 0.20, 0.15, 0.30, and 0.25 nm, respectively. Upon detailed examination of the RMSF graph of the mutant-type 3FA2 and curcumin complex, peaks are observed at atoms 2347, 3472, and 4521. Similarly, in the RMSF graph of the complex formed with quercetin, peaks are identified at atoms 2353, 3337, 4508, and 5692. In the RMSF graph of the mutant-type 3FA2 and resveratrol complexes, peak values are observed at atoms 1182, 2424, 3305, and 4476. Additionally, in the RMSF graph of the complex formed with 5FU, peak values occur at atoms 1203, 3333, 4490, and 5567. Figure 4B depicts the RMSF graphs of the receptor-ligand complexes formed with the wild-type 3FA2 receptor and four different ligands: curcumin, quercetin, resveratrol, and 5FU. The average RMSF values of the complex structures formed with curcumin, quercetin, resveratrol, and 5FU ligands of the wild-type 3FA2 receptor are 0.20, 0.30, 0.25, and 0.28 nm, respectively. Upon examination of the RMSF graph of the wild-type 3FA2 and curcumin complex, peaks are observed at atoms 1206, 1937, 3656, and 4464. In the RMSF graph of the complex formed with quercetin, peaks are identified at atoms 3310 and 4471. Furthermore, in the RMSF graph of wild-type 3FA2 and resveratrol complexes, it is noted that the values peak at atomic positions similar to quercetin.

Radial Distribution Function (RDF)

The RDF graphs of the complexes formed by curcumin,

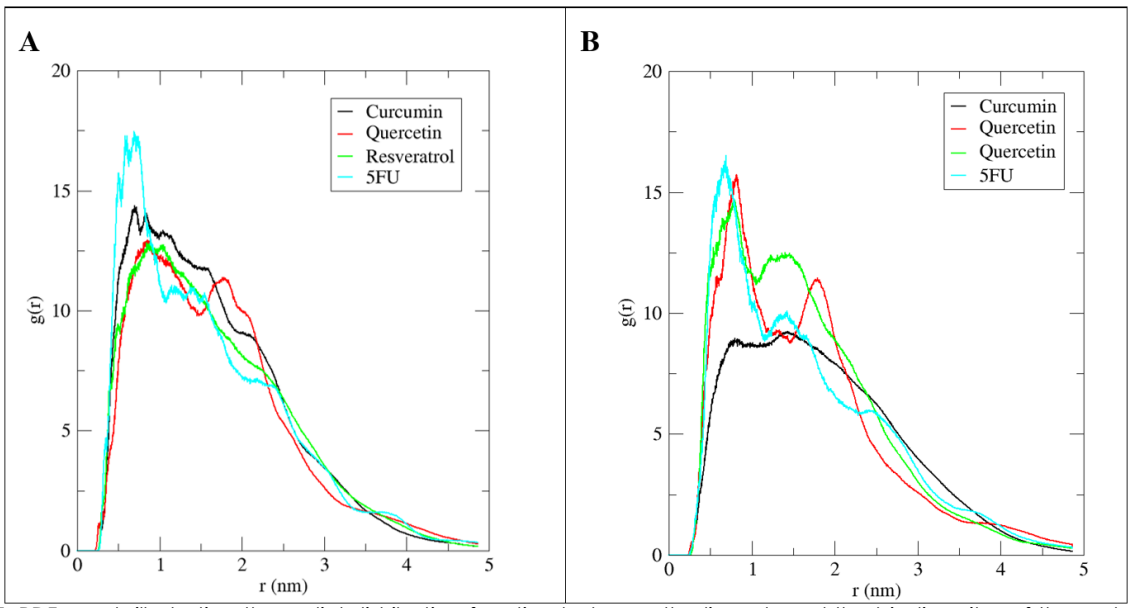

Figure 5. RDF graph illustrating the radial distribution function between the ligands and the binding sites of the mutant-type 3FA2 receptor **(A)** and wild-type 3FA2 receptor **(B)**, respectively.

quercetin, resveratrol, and 5FU ligands with the mutant-type and wild-type 3FA2 receptors during the 25-nanosecond molecular dynamics simulation are shown in Figure 5. Upon inspection of the values for the complex formed with curcumin in Figure 5A, a peak is observed at 0.81 nm with a value of 13.23. The peak value for the quercetin complex is 12.91 at 0.84 nm. Although a distinct peak is not observed in the resveratrol complex, its highest value is 17.75 at 0.86 nm. 5FU is at a distance of 17.48 with a value of 0.73 nm. The graphical results show that curcumin and quercetin ligands are densely present in the receptor structure at a distance of 1 nm and establish strong interactions. When examining the RDF graphs depicted in Figure 5B, it is observed that the complex formed with the natural agent curcumin and the wild-type 3FA2 receptor lacks a distinct peak point. However, the highest value is 9.23 at a distance of 1.40 nm. In contrast, distinct peak points are observed in the RDF values for the complexes formed with quercetin and resveratrol. These values are 15.46 at 0.81 nm and 14.64 at 0.77 nm, respectively. There is a distinct peak in the chemical ligand 5FU complex. If it is necessary to specify the peak value of the RDF value, it is 16.34 at 0.67 nm.

Root Mean Square Deviation (RMSD)

The results of the RMSD analyses conducted to examine the stability of the protein and ligand complexes are shown in Figure 6. When examining the RMSD values of different ligand complexes with the mutant-type 3FA2 receptor in Figure 6A, it is evident that the graphs of the curcumin and quercetin complexes exhibit remarkable stability. The values for these two complexes range from 0.2 to 0.3 nm. The resveratrol complex was observed to stabilize at approximately 0.2 nm after 6.80 ns. The graph of the 5FU complex progresses quite stable throughout the simulation. The average RMSD values of this complex are around 0.3 nm. In the RMSD graphs of the wild-type 3FA2 receptor and various ligand complexes in Figure 6B, the curcumin complex exhibits overall stability. Upon closer inspection, it adopts a more stable form around 1.43 nm after 13 ns. Similar results were obtained for the graphs of the quercetin and resveratrol complexes. The RMSD values of both complexes are around 0.5 nm, indicating a highly stable graph representation. The graph of the receptor-ligand complex formed with 5FU, a chemical ligand, is quite stable. In general, stability was reached around 0.4 nm after 3 ns of simulation.

Radius of Gyration (Rg)

Rg analyses were conducted to understand the compactness of the complexes formed by the mutant-type and wild-type 3FA2 receptors with curcumin, quercetin, resveratrol, and 5FU ligands. The Rg analysis data for all structures are shown in Figure 7. When examining the Rg graphs of the mutant-type 3FA2 receptor and other ligand complexes in Figure 7A, it is observed that the values of the curcumin complex remained stable at around 2.5 nm throughout the 25 ns simulation period, corresponding to 25000 ps. The quercetin complex exhibited stability around 2.3 nm between 5 and 16 ns, although some fluctuations are present in the graph. The Rg values obtained for the resveratrol complex fluctuated between 2 and 2.5 nm. 5FU showed values around 2.48 nm. When the

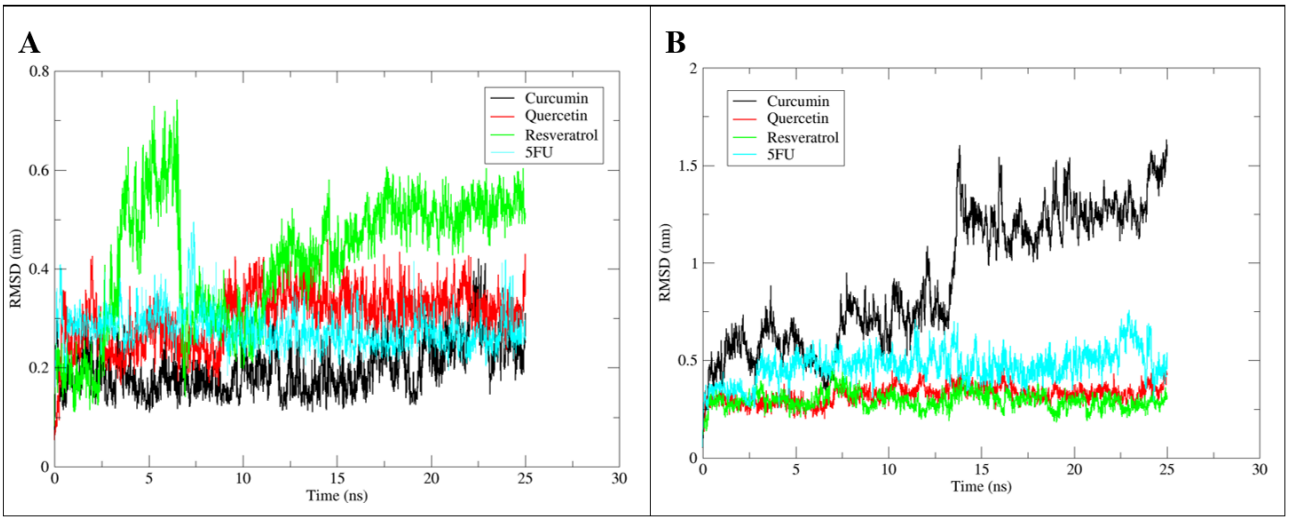

Figure 6. RMSD graph showing the structural deviations of the mutant-type 3FA2 receptor **(A)** and wild-type 3FA2 receptor **(B)** during the simulation in the presence of ligands, respectively.

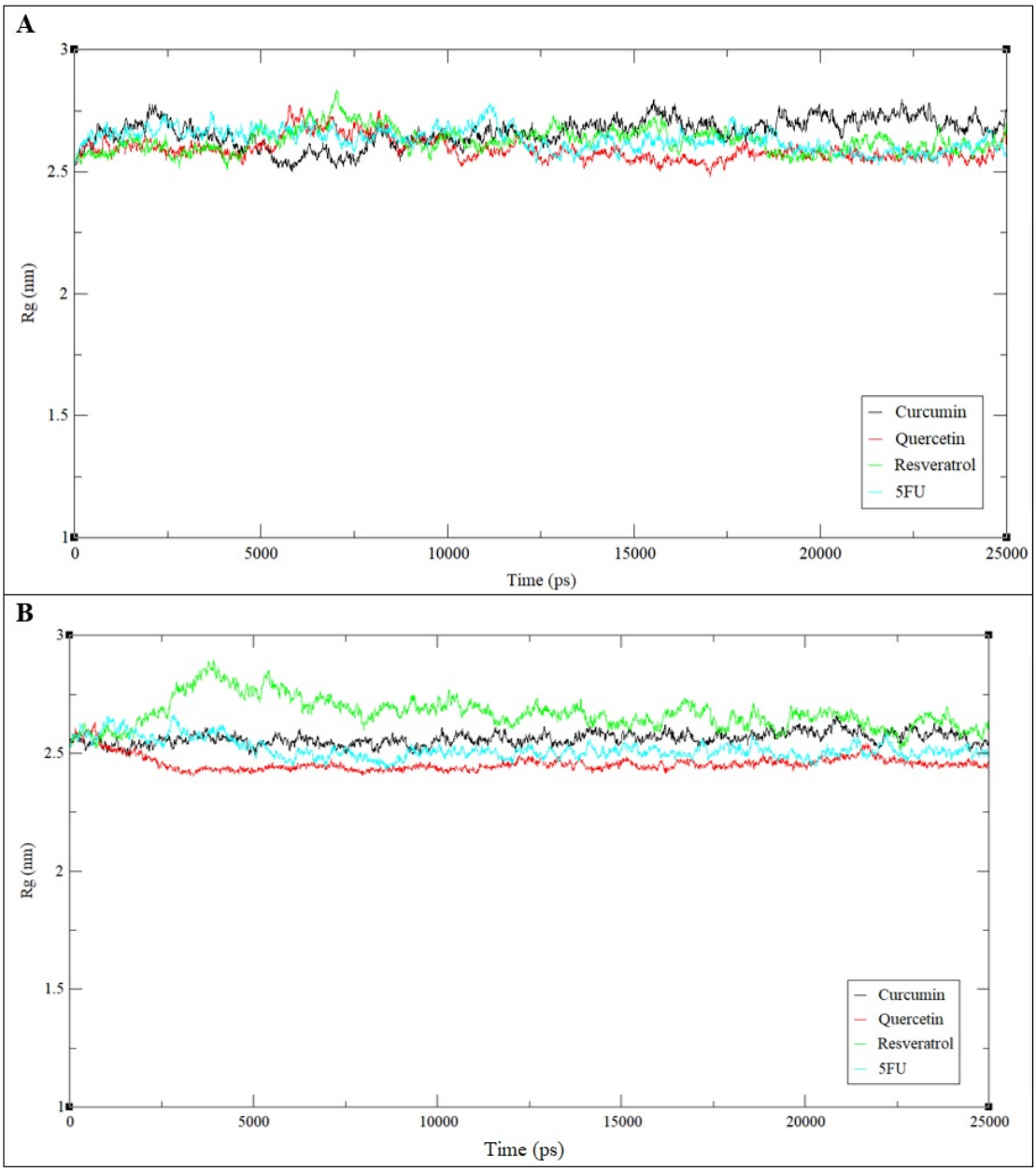

Figure 7. Rg graph representing the compactness of the mutant-type 3FA2 receptor **(A)** and wild-type 3FA2 receptor **(B)** in complex with ligands throughout the simulation, respectively.

Rg graphs of the wild-type 3FA2 and different ligand complexes in Figure 7B are examined, it is observed that the Rg values of the complex formed with curcumin ranged between 2.4 and 2.6 nm throughout the simulation. The quercetin complex fluctuated between 1.75 and generally 2 nm, the resveratrol complex ranged generally between 2.18 and 2.4 nm, and finally, the 5FU complex hovered around 2.5 nm. The value of the complex formed with curcumin is higher than the other ligands, but the difference is only 0.1 nm. The quercetin complex stabilized around 2.3 nm after 7.5 ns. In the resveratrol complex, a smoother graph is observed around 1 ns at approximately 2.5 nm, yet increasing fluctuations persist throughout the simulation period. The average Rg values of the 5FU ligand complex throughout the simulation are between 2.4 and 2.6 nm, but there is a constant fluctuation.

ADMET Properties Prediction of Ligand Molecules

When examining the data in Table 2, the results of ADMET analysis of the complexes formed by the mutant-type 3FA2 receptor with different natural agent ligands after docking and MDS are observed. In the docking results section, curcumin exhibits a Consensus Log Po/w value of 3.03, indicating its high lipophilic properties. While the Log Kp (skin permeation) value was -6.28 cm/s in the data obtained after docking, it

decreased to -2.28 cm/s post-MDS. When examining Table 3 for the ADMET analyses of wild-type 3FA2 and natural ligands after docking and MDS, similar results to Table 2 are observed. In Table 3, while the Consensus Log P/o (Log Po/w) value of the quercetin ligand after docking was 1.23, it decreased to 0.51 after MDS. The ADMET analysis results generally demonstrate favorable outcomes for each natural agent for both the mutant-type and wild-type 3FA2 receptors. Based on these analyses, curcumin emerges as the ligand with the most favorable properties. Subsequent data for both docking and MDS of ADMET assays obtained with mutant-type and wild-type 3FA2 receptors of the 5FU ligand in Table 2 and Table 3 are identical. This ligand is generally good as a drug.

Discussion

Within the scope of this study, natural and chemical ligands of mutant-type and wild-type 3FA2 receptors associated with the BRCA1 gene were analyzed using molecular modeling techniques such as molecular docking and molecular dynamics simulations. As a result of these analyses, the binding affinities and structural stability of the receptor-ligand complex structures were evaluated. According to the findings, it is an expected result that 5FU, which is widely used in the treatment of breast cancer, has a high affinity with the receptors. The fact that the docking results obtained with natural agents are higher than -6 kcal/mol, and especially the result of the quercetin ligand being even better than the 5FU ligand, shows that natural agents provide a

Table 2. ADMET properties prediction results for ligands from mutant-type.

Results	Ligand	Consensus Log Po/w	Log Kp (skin) permeation, cm/s)	GI Absorption	BBB Permeant	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Bioavailability Score
Docking	Curcumin	3.03	-6.28	High	No	No	No	No	Yes	No	Yes	0.55
	Quercetin	1.23	-7.05	High	No	No	Yes	No	No	Yes	Yes	0.55
	Resveratrol	2.48	-5.47	High	Yes	No	Yes	No	Yes	No	Yes	0.55
	5FU	0.13	-7.73	High	No	No	No	No	No	No	No	0.55
MD	Curcumin	3.03	-2.28	High	No	No	No	No	Yes	No	Yes	0.55
	Quercetin	1.23	-7.05	High	No	No	Yes	No	No	Yes	Yes	0.55
	Resveratrol	2.49	-5.52	High	Yes	No	Yes	No	No	Yes	Yes	0.55
	5FU	0.13	-7.73	High	No	No	No	No	No	No	No	0.55

Table 3. Wild-type 3FA2 receptors and natural agents ligands ADMET properties prediction results.

Results	Ligand	Consensus Log Po/w	Log Kp (skin) permeation, cm/s)	GI Absorption	BBB Permeant	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Bioavailability Score
Docking	Curcumin	3.03	-6.28	High	No	No	No	No	Yes	No	Yes	0.55
	Quercetin	1.23	-7.05	High	No	No	Yes	No	No	Yes	Yes	0.55
	Resveratrol	2.48	-5.47	High	Yes	No	Yes	No	Yes	No	Yes	0.55
	5FU	0.13	-7.73	High	No	No	No	No	No	No	No	0.55
MD	Curcumin	3.05	-6.58	High	No	No	No	No	No	Yes	Yes	0.55
	Quercetin	0.51	-7.48	High	No	No	No	No	No	No	No	0.55
	Resveratrol	2.49	-5.52	High	Yes	No	Yes	No	No	Yes	Yes	0.55
	5FU	0.13	-7.73	High	No	No	No	No	No	No	No	0.55

strong binding with the receptor. This proves that the natural agents curcumin, quercetin, and resveratrol provide much better interactions with the crystal receptor structures of the BRCA1 gene associated with breast cancer (23, 35). In our study, the binding energy results presented in Table 1 indicate that the scores for wild-type and mutant-type BRCA1 receptors are relatively similar. While this finding suggests that the control and experimental group ligands exhibit a broad interaction spectrum, it also raises the possibility of a lack of selectivity between the two receptor types. Reduced selectivity, in particular, could potentially result in off-target effects and lead to drug-related side effects. Nevertheless, this study specifically focuses on evaluating the individual effects of each ligand on BRCA1-related wild-type and mutant-type receptors. It is crucial to highlight that no combinatorial effects of the ligands were investigated within the scope of this study.

Amino acids and interactions formed between mutant type 3FA2 and wild type 3FA2 receptors and other ligands are visualized both after docking and MDS to determine the stability of the complex structures and are shown in Figures 2 and 3. Van der Waals interactions between receptors and ligands, conventional hydrogen bonds, alkyl, and pi-alkyl interactions, amide-pi stacked, unfavorable donor-donor, pi-anion, pi-alkyl, pi-donor interactions, hydrogen bond, and pi-cation interactions can be seen. Conventional hydrogen bonds are observed on these amino acids, facilitating hydrogen bond formation between the curcumin ligand and the hydrogen bond donor (35). Amide-pi interaction type is characterized by the electrostatic attraction forces between the amide hydrogen or carbonyl oxygen of the amide group and the pi-electron cloud in the aromatic ring 34. These interactions occur between aromatic amino acid residues in the active site of the receptor and amide groups in the ligand (35, 36). The resulting interactions and bond types influence the biological activities of the receptor and ligand by enhancing their binding affinity to each other (37). Pi-anion interactions indicate the attractive force between a negatively charged anion group and an aromatic system. Their effect on the receptor and ligand is to assist in identifying specific binding sites (38). Thanks to these interactions, the ligand binds to the receptor more compactly. Unfavorable Donor-Donor Interactions occur when the distance between two hydrogen bond donors is short, but no energy is sought here (39). This type of interaction can affect the binding energy and stability state of the ligand (39, 40). Pi-donor hydrogen bond and pi-cation interaction types increase the binding affinity by strengthening the stability between the protein and the ligand.

Examining the receptor-ligand complex maps after the molecular docking and molecular dynamics simulation phase is very important in terms of understanding the interactions between structures, the changing behavior of the interactions over time, and the changing behavior depending on the changing environment. Upon inspecting the curcumin complex map in B1 of Figure 3 after MDS, it is observed that amino acids PRO, ALA, Glutamic acid (GLU), and Methionine (MET) are located at positions 610, 613, 655, and 768, respectively. These amino acids and their positions differ from those observed in A1. This variation may be attributed to factors such as receptor and ligand flexibility, solvent effects, and ion interactions. While the docking stage occurs in a simplified solvent or vacuum environment within the in-silico setting, molecular dynamics simulations are typically conducted using solvent models and ions that closely mimic experimental conditions (41). Such environmental distinctions possess the capability to alter the behavior and interactions of the receptor and ligand within the binding region. Despite the presence of different amino acid residues in the wild-type 3FA2 and quercetin complex map in B2, it encompasses the amino acid residues obtained following the docking stage. Nevertheless, certain types of bond interactions between amino acids have undergone alterations. This phenomenon can be attributed to various factors, including binding stability and conformational modifications (37). The consistent identification of the same amino acids obtained during docking through molecular dynamics simulation indicates stable binding between the ligand and the receptor (36). The shift in bond types is indicative of robust interactions. When examining the ligand complex maps of resveratrol in A3 and B3, the sole common amino acid observed is ILE. Generally, all other amino acids exhibit variations. This observation suggests that the binding site of the wild-type 3FA2 receptor displays flexibility, while the ligand undergoes conformational changes. Moreover, they strive to achieve stable binding by minimizing energy when the receptor and ligand interact. The rationale behind this alteration post-docking and MDS is to attain an appropriate docking position that adheres to the specified criteria. The consistent presence of the

ILE amino acid in the receptor-ligand map following both steps signifies its pivotal role in stability during receptor-ligand binding. Overall, upon scrutinizing the receptor-ligand bond maps of the wild-type 3FA2 receptor and various ligands after docking and MDS, it becomes evident that quercetin, with similar amino acid residues and offering the highest stability, stands out. When examining the receptor-ligand maps of the mutant-type 3FA2 and various ligands after docking and MDS in images A1 and B1 in Figure 2, it is observed that the amino acids TRP at position 680, LYS at position 688, SER at position 761, ASP at position 765, and MET at position 768 remain consistent. These findings suggest that the amino acid composition of the mutant-type 3FA2 receptor and the curcumin ligand remains unchanged, indicating stability in the binding interactions and positioning of the complex (41). The fact that the curcumin ligand interacts with the same amino acids in both stages reveals that the conformations of the complex structure are highly minimized (40). The formation of the same receptor-ligand map after docking and MDS shows that the binding affinity is quite good (41). When images A2 and B2 in Figure 3 are examined, it is observed that the amino acids ARG, ASP, and LEU, numbered 705, 763, and 773, respectively, remain unchanged in the quercetin complex map. Additionally, TRP at position 762 and LEU amino acids at position 775 are newly identified following MDS. The persistence of quercetin's interaction with the same amino acids post both docking and MDS suggests the stability of the ligand within the binding site. The emergence of new amino acids after MDS may be attributed to conformational changes in the receptor and ligand-induced by factors such as solvent and ion presence during MDS (38, 41). Furthermore, this phenomenon may be due to the optimization of bonding configurations to minimize energy. When examining the interaction map between the receptor-ligand in A3 and B3, it is observed that only the LYS amino acid number 688 remains consistent with resveratrol after both docking and MDS. With the mutant-type 3FA2 receptor, the resveratrol ligand appears to exhibit significantly lower stability and binding affinity compared to the curcumin and quercetin ligands. In the B4 image in Figure 2, in the complex formed with the 5FU ligand and mutant-type 3FA2, the amino acids GLY at position 681 and SER at position 761 contain carbon-hydrogen bonds, THR at position 682 and GLU at position 740 contain conventional hydrogen bonds, ASP at position 741 contains unfavorable donor-donor interactions, and HIS at position 685 contains pi-pi stacked interactions. In the B4 image in Figure 3, when examining the interaction of the 5FU ligand and wild-type 3FA2 complex with amino acids, LYS at position 684, GLU at position 740, and SER at position 760 contain conventional hydrogen bonds, and HIS at position 685 contains unfavorable donor-donor and pi-pi stacking interactions.

As a result of the molecular dynamics simulation, RMSF, RDF, RMSD, and Rg analyses were performed. These analyses are conducted to evaluate the stability of receptor-ligand complex structures formed by natural and chemical agents (42). Root Mean Square Fluctuation (RMSF) measures the average deviations in the positions of atoms over time (43). RMSF values serve as analytical tools to evaluate the stability, flexibility, and dynamic behavior of receptor and ligand structures and to understand the conformational changes occurring in the active site of the receptor (42, 43). When the RMSF values of mutant-type and wild-type receptors and ligand complexes in Figure 4 are compared, it is seen that the complexes formed with natural agent ligands are close to the complex formed with chemical drug ligands when the RMSF is examined. This is because natural agents exhibit greater stability with the mutant-type 3FA2 receptor associated with breast cancer and form stronger binding interactions than chemical drugs (12, 42). As a result of RMSF analyses, it is concluded that the structure showing the highest stability among natural agent ligands and mutant-type 3FA2 receptor complexes is the complex formed by the quercetin ligand. This is due to the strong structure and bioactive properties of quercetin (44). From the results of RMSF analyses of wild-type 3FA2 receptors and ligands, it has been revealed that curcumin shows drug potential that can perform various tasks such as regulating the DNA mechanism of the breast cancer-related BRCA1 gene. This shows that curcumin exhibits a strong interaction with the BRCA1 gene receptor associated with breast cancer and has the potential to strengthen the repair mechanism of this gene (45). The fact that both mutant-type and wild-type 3FA2 receptors give the best results with curcumin shows that it has the potential to be an alternative therapeutic agent, especially to the chemical ligand 5FU, in the treatment of breast cancer.

RDF analysis is a mathematical function used to discover the particle pair density of entities such as atoms and molecules located at certain distances

(46). In the field of molecular dynamics simulation, RDF plots are used to analyze distance distributions between proteins and ligands. These RDF plots allow for the investigation of the locations of strong interaction regions between the protein and ligand and the study of the formation mechanisms of complex structures and conformational changes (47). When the RDF graph in Figure 5A is examined, it is seen that the peak values of curcumin and quercetin are more prominent than resveratrol. The sharp peaks in the RDF graphs formed by these two ligands and the mutant-type 3FA2 receptor are interpreted as the ligands providing strong stability and structural order with the receptor structure (42, 46). The absence of distinct peaks in the graph of the resveratrol complex indicates that, according to the RDF definition, atom pairs at a certain distance are distributed over a wide area and the stability of the receptor-ligand complexes decreases (46). As a result of examining the RDF values of the complexes obtained with the mutant-type 3FA2 receptor, it can be said that the curcumin complex is the most suitable. The presence of a single peak in this structure suggests a strong binding affinity between curcumin and the mutant-type 3FA2 receptor. The decrease in RDF values of curcumin beyond a 1 nm distance indicates that there is a specific binding site between the receptor and the ligand. The fact that there is a distinct peak in the RDF graph of the mutant-type 3FA2 complex formed with RDF indicates that it has a specific binding point. In general, good results were obtained in the complexes obtained with the wild-type 3FA2 receptor in Figure 5B. Particularly distinct peaks are observed for quercetin and resveratrol ligands. High RDF values indicate that the interactions between the receptor and the ligand are strong (42, 47). The absence of peaks and lower RDF values in the graphs of curcumin complexes indicate conformational changes in the receptor-ligand binding regions (47). The fact that curcumin does not give the expected RDF results in the wild-type 3FA2 receptor but gives good results in the mutant-type 3FA2 receptor of the BRCA1 gene associated with breast cancer suggests that the natural agent curcumin has the potential to play a therapeutically effective role in BRCA1-induced breast cancer (46, 47). When the values of wild-type 3FA2 and ligands are examined, it appears that the natural agents curcumin, quercetin, and resveratrol have the potential to regulate and repair the BRCA1 gene mechanism (46). However, all three natural agents give similar and good results in mutant-type 3FA2 complexes, such as the complexes formed with the chemical ligand 5FU, indicating that they are natural therapeutic agents that can be used in cancer treatment.

In mathematical terms, RMSD is the deviation of the mean squares of the positions of atoms over a given time (48). In this study, RMSD plots are used to analyze the stability and structural changes of protein and ligand complexes. The graphs of curcumin and quercetin complexes formed with the mutant-type 3FA2 receptor in Figure 6A show remarkable stability, indicating an extremely compact, stable, and favorable interaction (46). The fact that the values of the resveratrol complex are slightly higher and irregular compared to other natural agent complexes is due to the structure of resveratrol (44). The fact that the RMSD values of the mutant-type 3FA2 receptor and the 5FU chemical ligand are so stable indicates that they have a strong binding affinity. In the RMSD analysis of the complexes formed with wild-type 3FA2 in Figure 6B, it was seen that quercetin, resveratrol, and 5FU formed a more stable graph compared to the other complexes. It shows that the wild-type 3FA2 receptor binds tightly and consistently to the binding site of quercetin and resveratrol ligands (48). The reason why the graph of the receptor-ligand complex formed with the chemical ligand 5FU progresses quite stably is that the chemical structure of the 5FU ligand is quite small and simple, it has a good binding affinity with the receptor, and stable RMSD values are emphasized (29, 46). In our RMSD graphs, it is observed that particularly for wild-type and mutant-type receptors, curcumin and resveratrol ligands show noticeable fluctuations at the beginning of the simulation (44). However, those mentioned ligands are natural agents containing various functional groups and aromatic rings (25). Therefore, they can undergo conformational changes by exhibiting flexibility during binding to the receptor, which can be reflected in the RMSD graphs (48). The fact that each ligand-receptor complex eventually reaches a stable form and that the RMSD values, including fluctuations, remain below 1 nm aligns with values accepted in other literature studies (29). This demonstrates that the protein-ligand complex and the simulation system are stable. Numerous studies by Singh and colleagues suggest that such fluctuations are caused by the dynamic conformational changes of the ligands and the flexibility of the receptor's binding pocket(44). Consequently, the RMSD results obtained in this study fall within the 0 to 1 nm range accepted in the literature and are consistent with

studies indicating that the overall system stability is not adversely affected, as expected.

The term Rg is defined mathematically as the square root of the weighted average of the squares of the distances of their masses, taking the center of mass of the molecules as a reference (49). Within the scope of molecular dynamics simulation, Rg is used to measure the compactness of the protein and ligand complex and to analyze the behavior of the complex over time (50). The reason why there are some fluctuations in the graphs of the complexes obtained with the mutant-type 3FA2 receptor in Figure 7A is that the ligands undergo some conformational changes during binding with the receptor (49). According to the results obtained, it is seen that although the binding stability of resveratrol with the receptor is moderate, it exhibits a strong binding affinity with curcumin. The quercetin ligand also showed positive results within the scope of Rg graphs, revealing that it formed a compact structure with the receptor and the values stabilizing around 2.3 nm after 7.5 ns. Low Rg values and ensuring certain stability are critical features for potential drug candidates in the treatment of BRCA1 gene-related breast cancer (51). When the Rg graphs of the wild-type 3FA2 receptor and different ligand complexes in Figure 7B are examined, the fluctuations in the curcumin complex are much lower than the others, resulting in a more stable and smooth graph. Therefore, it is concluded that the complex formed with curcumin maintains a stable conformation throughout the simulation (50). The quercetin complex with the wild-type 3FA2 receptor appears to stabilize after a certain point. This reveals that there are conformational changes due to increased fluctuations compared to the curcumin results. The observation of greater fluctuation in the 5FU complex and other ligand complexes is due to conformational changes (49, 51). The average Rg values of the 5FU complex were observed to have small fluctuations throughout the simulation, indicating that a stable complex was formed. In conclusion, when the Rg values and graphs are examined, the stability of the graphical fluctuations of the curcumin complex indicates that the complex formed with the wild-type 3FA2 receptor is stable and its binding is compact. This complex has a potentially high affinity. As a result, in wild and mutant-type receptor species, curcumin ligand Rg showed low fluctuations and a stable structure in graphical values and showed the best compactness compared to other complexes (44). Although resveratrol and quercetin ligands showed good results in terms of Rg value, the fluctuations they showed indicated that both ligands underwent conformational changes. The control group ligand 5FU showed a good stability profile with the receptors, but it did not fully reach the binding properties as good as natural agents (48).

Consisting of five basic concepts: absorption, distribution, metabolism, excretion, and toxicity, ADMET analyzes the pharmacokinetic and pharmacodynamic properties of natural or chemical substances during the drug discovery process (52). While the binding behavior of the ligand to the receptor is examined as a result of docking and MDS, the properties of the ligand in biological systems are examined through ADMET analysis (53). Evaluations from these analyses help to understand the clinical applicability of natural or chemical ligands with discovered therapeutic potential (54). The analyses obtained with SwissADME yield terms such as Consensus Log Po/w value, Log Kp (skin permeability), GI absorption, BBB passage, P-gp substrate, and CYP enzyme inhibitors (53). Considering these concepts, the consensus Log Po/w value represents the lipophilicity level of the ligands (55). A high lipophilicity value of the ligands indicates that they can easily cross the cell membrane. The Log Kp (skin permeability) value indicates the ability of ligands to pass through the skin, and GI absorption indicates the absorption potential in the gastrointestinal tract (52, 55). BBB passage indicates the ability to cross the blood-brain barrier, and P-gp substrate indicates whether the ligand is a substrate for p-glycoprotein (56). CYP enzyme inhibitors show the potential to inhibit P450 (CYP) enzymes (55). ADMET analysis results of ligands after docking and MDS are compared. The reason for this comparative analysis is to measure the stability of data such as the Consensus Log Po/w obtained after the ADMET analysis of the ligands and to determine the stability of the ligands accordingly (54, 56). When the results were examined in general, it was seen that the Log Kp (skin permeability) value obtained after docking in the curcumin ligand decreased after MDS. This can be explained by the fact that during MDS, it is affected by the presence of solvents and ions in the environment, leading to the formation of new interactions (e.g., van der Waals) (54, 57). However, the decrease in this value during MDS indicates an increase in the skin permeability of the ligand. Repeating the ADMET analysis with an in silico experiment is important to ensure the reliability of both the ligand and the resulting data (57, 58).

In both scenarios, the curcumin ligand shows high absorption in the gastrointestinal tract. However, data obtained after docking and MDS lack BBB passage, P-gp substrate, and CYP2C19 and CYP2D6 inhibitors. The lack of BBB passage prevents the curcumin ligand from passing into the central nervous system (53). In this case, if this ligand has any neurotoxic effects, it helps reduce them. However, the lack of BBB permeability of the curcumin ligand intended for breast cancer treatment reveals its inability to reach metastases spread to the central nervous system. The absence of a P-gp substrate indicates the potential to increase the intracellular concentration of the curcumin ligand. Thus, curcumin may exhibit more effective biological activity within the cell. Many drugs are metabolized in the presence of CYP2C19 and CYP2D6 enzymes. The fact that the curcumin ligand does not inhibit these enzymes reduces the risk of side effects that may occur with other drugs. Additionally, the fact that curcumin does not inhibit these enzymes is very important for liver health. When the presence of CYP2C9 and CYP3A4 inhibitors is examined, curcumin shows the potential to remain in the body for a longer time due to this feature. However, these enzymes are also capable of metabolizing many drugs. Therefore, it is important to monitor for possible side effects of curcumin and other medications. The bioavailability score of the curcumin ligand is 0.55, like other ligands, and shows moderate bioavailability and therapeutic properties. This ligand is effectively absorbed into the body orally and is viewed as a potential therapeutic natural agent that specifically targets the breast cancer-associated BRCA1 gene structure (54). When ADMET analyses of other natural ligands were examined, similar data were observed with curcumin. The Log Kp (skin permeability) value of the resveratrol ligand obtained after docking decreased by 5 cm/s after MDS. Although this decrease is relatively small, it indicates that the skin permeability of the resveratrol ligand decreased after simulation (55). In Table 3, the decrease in the Consensus Log P/o (Log Po/w) value of the quercetin ligand after docking and MDS shows that there is a decrease in the lipophilicity of the quercetin ligand, its hydrophobic interactions decrease, and its hydrophilic properties increase. For other ligands, no significant changes were observed in the data obtained after docking and MDS. ADMET analysis results generally show positive results for both mutant-type and wild-type 3FA2 receptors for each natural agent. Based on these analyses, curcumin stands out as the ligand with the most favorable properties. Subsequent data of docking and post-MDS ADMET assays of the 5FU ligand with mutant-type and wild-type 3FA2 receptors in Tables 2 and 3 are identical. This ligand is generally considered a good medicine. However, low lipophilicity means that it may be inadequate in exceptional cases such as central nervous system metastasis of breast cancer. Therefore, these chemical drug ratios indicate that natural agents have better drug potential (57, 58).

Based on molecular docking and molecular dynamics simulation approaches, this study shows that the natural agents including curcumin, quercetin, and resveratrol may be alternative therapeutic drug candidates to the chemical drug 5FU in the treatment of breast cancer due to the BRCA1 gene mutation. In particular, the fact that curcumin has a good binding interaction score with receptors associated with BRCA1 genes forms a stable structure, and has the expected pharmacokinetic profile is promising for the discovery of new therapeutic natural agents for breast cancer treatment.

Conclusion

Breast cancer arises when normal cells in the breast region undergo abnormal changes, proliferating uncontrollably and forming malignant tumor cells. Gene mutations within the BRCA1 gene, associated with breast cancer, represent significant contributing factors to the advancement of this disease. Various chemical drugs, such as 5FU, are available to prevent harm to this gene and rectify mutations. Nevertheless, chemical drugs often entail numerous side effects that adversely affect the organs of the body, further exacerbating the toll of cancer treatment. Therefore, the discovery of new drug agents of natural origin with minimal side effects presents promising strategies for treating breast cancer associated with BRCA1 gene mutations. In this study, the receptor linked to the BRCA1 gene was identified and point-mutated. Natural agents including curcumin, quercetin, and resveratrol, targeted for discovering anticancer bioactive properties, along with the widely used drug 5FU in the market, were selected for comparison of results. Through separate molecular docking and dynamic simulations with wild-type and mutant-type 3FA2 receptors and other ligands, it was revealed that natural agents offer interactions akin to the chemical drug 5FU. These natural agents demonstrated strong stability with receptors and exhibited favorable pharmacokinetic properties as assessed by ADMET assays. It was observed that curcumin exhibited the

most favorable pharmacokinetic properties among the natural agents, meeting the feasibility criteria for a therapeutic natural drug in the treatment of breast cancer associated with BRCA1 gene mutation. This study underscores the significance of plant-derived natural agents as potential treatments for critical cancer diseases like breast cancer. By shedding light on other literature studies aimed at discovering and developing the bioactive and therapeutic properties of these natural agents, such as their anticancer effects, in the in silico environment, this research offers hope for survival to numerous cancer patients and humanity at large.

Authors' contributions

Conception: DK; Design: NS, DK; Supervision: DK; Data Collection and/or Processing: NS, DK; Analysis-Interpretation: NS, DK; Literature Review: NS; Writing: NS, DK; Critical Review: NS, DK.

References

1.Bozorgi A, Khazaei S, Khademi A, Khazaei M. Natural and herbal compounds targeting breast cancer, a review based on cancer stem cells. Iran J Basic Med Sci. 2020;23(8):970-83.

2.Shiozaki EN, Gu L, Yan N, Shi Y. Structure of the BRCT repeats of BRCA1 bound to a BACH1 phosphopeptide: implications for signaling. Mol Cell. 2004;14(3):405-12.

3.Esteva FJ, Sahin AA, Cristofanilli M, Arun B, Hortobagyi GN. Molecular prognostic factors for breast cancer metastasis and survival. Semin Radiat Oncol. 2002;12(4):319-28.

4.Taghizadeh MS, Niazi A, Moghadam A, Afsharifar A. Experimental, molecular docking and molecular dynamic studies of natural products targeting overexpressed receptors in breast cancer. PLoS One. 2022;17(5):e0267961.

5.Lukasiewicz S, Czeczelewski M, Forma A, Baj J, Sitarz R, Stanislawek A. Breast Cancer-Epidemiology, Risk Factors, Classification, Prognostic Markers, and Current Treatment Strategies-An Updated Review. Cancers (Basel). 2021;13(17).

6.Thirumal Kumar D, Udhaya Kumar S, Jain N, Sowmya B, Balsekar K, Siva R, et al. Computational structural assessment of BReast CAncer type 1 susceptibility protein (BRCA1) and BRCA1-Associated Ring Domain protein 1 (BARD1) mutations on the protein-protein interface. Adv Protein Chem Struct Biol. 2022;130:375-97.

7.Fu X, Tan W, Song Q, Pei H, Li J. BRCA1, and Breast Cancer: Molecular Mechanisms and Therapeutic Strategies. Front Cell Dev Biol. 2022;10:813457.

8.Abu-Helalah M, Azab B, Mubaidin R, Ali D, Jafar H, Alshraideh H, et al. BRCA1 and BRCA2 genes mutations among high-risk breast cancer patients in Jordan. Sci Rep. 2020;10(1):17573.

9.Burguin A, Diorio C, Durocher F. Breast Cancer Treatments: Updates and New Challenges. J Pers Med. 2021;11(8).

10.Sarma H, Kiewhuo K, Jamir E, Sastry GN. In silico investigation on the mutational analysis of BRCA1-BARD1 RING domains and its effect on nucleosome recognition and ubiquitination. Biophys Chem. 2023;300:107070.

11.Bonofiglio D, Giordano C, De Amicis F, Lanzino M, Ando S. Natural Products as Promising Antitumoral Agents in Breast Cancer: Mechanisms of Action and Molecular Targets. Mini Rev Med Chem. 2016;16(8):596-604.

12.Smolarz B, Nowak AZ, Romanowicz H. Breast Cancer-Epidemiology, Classification, Pathogenesis and Treatment (Review of Literature). Cancers (Basel). 2022;14(10).

13.Kopke MM, Aktas B, Ditsch N. Recommendations for the diagnosis and treatment of patients with early breast cancer: update 2023. Curr Opin Obstet Gynecol. 2023;35(1):67-72.

14.Alduais Y, Zhang H, Fan F, Chen J, Chen B. Non-small cell lung cancer (NSCLC): A review of risk factors, diagnosis, and treatment. Medicine (Baltimore). 2023;102(8):e32899.

15.Debien V, De Caluwe A, Wang X, Piccart-Gebhart M, Tuohy VK, Romano E, et al. Immunotherapy in breast cancer: an overview of current strategies and perspectives. NPJ Breast Cancer. 2023;9(1):7.

16.Franzoi MA, Agostinetto E, Perachino M, Del Mastro L, de Azambuja E, Vaz-Luis I, et al. Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer. Lancet Oncol. 2021;22(7):e303-e13.

17.Pawar A, Diwan A, Mahobia V. Complementary and Alternative Medicine Use and Its Impact on the Delayed Presentation and Advanced Stage of Breast Cancer in Newly Diagnosed Indian Women. Indian J Med Paediatr Oncol. 2024;45:495–501.

18.van den Boogaard WMC, Komninos DSJ, Vermeij WP. Chemotherapy Side-Effects: Not All DNA Damage Is Equal. Cancers (Basel). 2022;14(3).

19.Iddrisu M, Aziato L, Dedey F. Psychological and physical effects of breast cancer diagnosis and treatment on young Ghanaian women: a qualitative study. BMC Psychiatry. 2020;20(1):353.

20.Kiewhuo K, Jamir E, Priyadarsinee L, Nagamani S, Sastry GN. Screening of phytochemicals for potential breast cancer targets BRCA1 and BARD1: A network pharmacology approach. Indian J Biochem Bio. 2023;60:393-405.

21.Sarkar E, Khan A, Ahmad R, Misra A, Dua K, Mahdi AA, et al. Synergistic Anticancer Efficacy of Curcumin and Doxorubicin Combination Treatment Inducing S-phase Cell Cycle Arrest in Triple-Negative Breast Cancer Cells: An In Vitro Study. Cureus. 2023;16(12):e75047.

22.Sinha S, Paul S, Acharya SS, Das C, Dash SR, Bhal S, et al. The combination of Resveratrol and PARP inhibitor Olaparib efficiently deregulates the homologous recombination repair

pathway in breast cancer cells through inhibition of TIP60-mediated chromatin relaxation. Med Oncol. 2024;41(2):49.

23.Tran LTT, Dang NYT, Nguyen Le NT, Nguyen HT, Ho DV, Do TT, et al. In Silico and in Vitro Evaluation of Alkaloids from Goniothalamus elegans Ast. for Breast Cancer Treatment. Nat Prod Commun. 2022;17(3).

24.Selvakumar P, Badgeley A, Murphy P, Anwar H, Sharma U, Lawrence K, et al. Flavonoids and Other Polyphenols Act as Epigenetic Modifiers in Breast Cancer. Nutrients. 2020;12(3).

25.Ghobadi N, Asoodeh A. Co-administration of curcumin with other phytochemicals improves anticancer activity by regulating multiple molecular targets. Phytother Res. 2023;37(4):1688-702.

26.Thai TH, Du F, Tsan JT, Jin Y, Phung A, Spillman MA, et al. Mutations in the BRCA1-associated RING domain (BARD1) gene in primary breast, ovarian, and uterine cancers. Hum Mol Genet. 1998;7(2):195-202.

27.Chen T, Yeh HW, Chen PP, Huang WT, Wu CY, Liao TC, et al. BARD1 is an ATPase-activating protein for OLA1. Biochim Biophys Acta Gen Subj. 2022;1866(5):130099.

28.Kruswick A, Lam FC, Kong YW, Smerdon SJ, Yaffe MB. BRCT domains as chromatin readers: Structure, function, and clinical implications. Chrom Read Hea Dis. 2024;35:31-56.

29.Hossain R, Ray P, Sarkar C, Islam MS, Khan RA, Khalipha ABR, et al. Natural Compounds or Their Derivatives against Breast Cancer: A Computational Study. Biomed Res Int. 2022;2022:5886269.

30.Choudhary S, Kesavan AK, Juneja V, Thakur S. Molecular modeling, simulation and docking of Rv1250 protein from Mycobacterium tuberculosis. Front Bioinform. 2023;3:1125479.

31.Dehury B, Raina V, Misra N, Suar M. Effect of mutation on structure, function, and dynamics of receptor binding domain of human SARS-CoV-2 with host cell receptor ACE2: a molecular dynamics simulations study. J Biomol Struct Dyn. 2021;39(18):7231-45.

32.Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, et al. UCSF Chimera--a visualization system for exploratory research and analysis. J Comput Chem. 2004;25(13):1605-12.

33.Zhang Y, Forli S, Omelchenko A, Sanner MF. AutoGridFR: Improvements on AutoDock Affinity Maps and Associated Software Tools. J Comput Chem. 2019;40(32):2882-6.

34.Abraham MJ, Murtola T, Schulz R, Páll S, Smith JC, Hess B, et al. GROMACS: High-performance molecular simulations through multi-level parallelism from laptops to supercomputers. SoftwareX. 2015;1-2:19-25.

35.Chatterjee P, Karn R, Emerson IA, Banerjee S. Docking and Molecular Dynamics Simulation Revealed the Potential Inhibitory Activity of Amygdalin in Triple-Negative Breast Cancer Therapeutics Targeting the BRCT Domain of BARD1 Receptor. Mol Biotechnol. 2024;66(4):718-36.

36.Adasme MF, Linnemann KL, Bolz SN, Kaiser F, Salentin S, Haupt VJ, et al. PLIP 2021: expanding the scope of the protein-ligand interaction profiler to DNA and RNA. Nucleic Acids Res. 2021;49(W1):W530-W4.

37.Bondock S, Albarqi T, Abdou MM, Mohamed NM. Computational insights into novel benzenesulfonamide-1,3,4-thiadiazole hybrids as a possible VEGFR-2 inhibitor: design, synthesis and anticancer evaluation with molecular dynamics studies. New J Chem. 2023;47(44):20602-18.

38.Lin FY, MacKerell AD, Jr. Improved Modeling of Cation-pi and Anion-Ring Interactions Using the Drude Polarizable Empirical Force Field for Proteins. J Comput Chem. 2020;41(5):439-48.

39.Roy A, Anand A, Garg S, Khan MS, Bhasin S, Asghar MN, et al. Structure-Based In Silico Investigation of Agonists for Proteins Involved in Breast Cancer. Evid Based Complement Alternat Med. 2022;2022:7278731.

40.Bilal MS, Ejaz SA, Zargar S, Akhtar N, Wani TA, Riaz N, et al. Computational Investigation of 1, 3, 4 Oxadiazole Derivatives as Lead Inhibitors of VEGFR 2 in Comparison with EGFR: Density Functional Theory, Molecular Docking and Molecular Dynamics Simulation Studies. Biomolecules. 2022;12(11).

41.Ahmad I, Singh AK, Mohd S, Katari SK, Nalamolu RM, Ahmad A, et al. In Silico Insights into the Arsenic Binding Mechanism Deploying Application of Computational Biology-Based Toolsets. ACS Omega. 2024;9(7):7529-44.

42.Skariyachan S, Gopal D, Chakrabarti S, Kempanna P, Uttarkar A, Muddebihalkar AG, et al. Structural and molecular basis of the interaction mechanism of selected drugs towards multiple targets of SARS-CoV-2 by molecular docking and dynamic simulation studies- deciphering the scope of repurposed drugs. Comput Biol Med. 2020;126:104054.

43.Gu S, Shen C, Yu J, Zhao H, Liu H, Liu L, et al. Can molecular dynamics simulations improve predictions of protein-ligand binding affinity with machine learning? Brief Bioinform. 2023;24(2).

44.Munjal NS, Shukla R, Singh TR. Physicochemical characterization of paclitaxel prodrugs with cytochrome 3A4 to correlate solubility and bioavailability implementing molecular docking and simulation studies. J Biomol Struct Dyn. 2022;40(13):5983-95.

45.Muhammad S, Saba A, Khera RA, Al-Sehemi AG, Algarni H, Iqbal J, et al. Virtual screening of potential inhibitor against breast cancer-causing estrogen receptor alpha (ERa): molecular docking and dynamic simulations. Mol Simul. 2022;48(13):1163-74.

46.Hufner-Wulsdorf T, Klebe G. Role of Water Molecules in Protein-Ligand Dissociation and Selectivity Discrimination: Analysis of the Mechanisms and Kinetics of Biomolecular Solvation Using Molecular Dynamics. J Chem Inf Model. 2020;60(3):1818-32.

47.Lamichhane TR, Ghimire MP. Evaluation of SARS-CoV-2

main protease and inhibitor interactions using dihedral angle distributions and radial distribution function. Heliyon. 2021;7(10):e08220.

48.Deshpande SH, Muhsinah AB, Bagewadi ZK, Ankad GM, Mahnashi MH, Yaraguppi DA, et al. In Silico Study on the Interactions, Molecular Docking, Dynamics and Simulation of Potential Compounds from Withania somnifera (L.) Dunal Root against Cancer by Targeting KAT6A. Molecules. 2023;28(3).

49.Rampogu S, Lee G, Park JS, Lee KW, Kim MO. Molecular Docking and Molecular Dynamics Simulations Discover Curcumin Analogue as a Plausible Dual Inhibitor for SARS-CoV-2. Int J Mol Sci. 2022;23(3).

50.Ghahremanian S, Rashidi MM, Raeisi K, Toghraie D. Molecular dynamics simulation approach for discovering potential inhibitors against SARS-CoV-2: A structural review. J Mol Liq. 2022;354:118901.

51.Bhattacharyya J, Bellucci JJ, Weitzhandler I, McDaniel JR, Spasojevic I, Li X, et al. A paclitaxel-loaded recombinant polypeptide nanoparticle outperforms Abraxane in multiple murine cancer models. Nat Commun. 2015;6:7939.

52.El Fadili M, Er-Rajy M, Kara M, Assouguem A, Belhassan A, Alotaibi A, et al. QSAR, ADMET In Silico Pharmacokinetics, Molecular Docking and Molecular Dynamics Studies of Novel Bicyclo (Aryl Methyl) Benzamides as Potent GlyT1 Inhibitors for the Treatment of Schizophrenia. Pharmaceuticals (Basel). 2022;15(6).

53.En-Nahli F, Hajji H, Ouabane M, Aziz Ajana M, Sekatte C, Lakhlifi T, et al. ADMET profiling and molecular docking of pyrazole and pyrazolines derivatives as antimicrobial agents. Arab J Chem. 2023;16(11).

54.Srivastava V, Yadav A, Sarkar P. Molecular docking and ADMET study of bioactive compounds of Glycyrrhiza glabra against main protease of SARS-CoV2. Mater Today Proc. 2022;49:2999-3007.

55.Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep. 2017;7:42717.

56.Uslu H, Koparir P, Sarac K, Karatepe A. ADME predictions and molecular docking study of some compounds and drugs as potential inhibitors of COVID-19 main protease: A virtual study as comparison of computational results. Med Sci Int Med J. 2021;10(1):18-30.

57.Shah V, Bhaliya J, Patel GM. In silico docking and ADME study of diketene curcumin derivatives (DKC) as an aromatase inhibitor or antagonist to the estrogen-alpha positive receptor (Eralpha(+)): potent application of breast cancer. Struct Chem. 2022;33(2):571-600.

58.Yalcin S. Molecular Docking, Drug Likeness, and ADMET Analyses of Passiflora Compounds as P-Glycoprotein (P-gp) Inhibitor for the Treatment of Cancer. Curr Pharmacol Rep. 2020;6(6):429-40.

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ORIGINAL ARTICLE

Predictors of Prenatal Breastfeeding Self-Efficacy of Women With and Without Gestational Diabetes: Results of a hospital based case-control study in Türkiye

Gestasyonel Diyabeti Olan ve Olmayan Kadınlarda Prenatal Emzirme Öz Yeterliliğinin Belirleyicileri: Türkiye'de hastane temelli bir vaka-kontrol çalışmasının sonuçları

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ABSTRACT

Background: Prenatal breastfeeding self-efficacy is an important parameter affecting the breastfeeding success and intention of women. Prenatal breastfeeding self-efficacy should be evaluated in all women with and without GDM.
Aim: The aim of the study was to examine the prenatal breastfeeding self-efficacy of women with and without Gestational Diabetes (GDM) and to determine the factors that predict prenatal breastfeeding self-efficacy.
Method: The research is a hospital-based case-control study was conducted. The study was carried out with 96 women with GDM who were compared with 98 without GDM, who were admitted to the endocrinology policlinic of a university hospital, in western Türkiye. The data were collected using the "Individual Identification Form" and the "Prenatal Breastfeeding Self-Efficacy Scale (PBSES)". For statistical analysis, t test and Chi-square test were used. Regression analyses were used to identify predictors of prenatal breastfeeding self-efficacy.
Results: PBSES of cases was 79.64±15.12 and controls was 72.01±15.62. PBSES scores of cases were significantly higher than controls ($p<0.05$). Working, family type, and information about breastfeeding were associated with breastfeeding self-efficacy in women with GDM ($p<0.05$, $R2=0.341$); educational level, working, family type, income level, trimester, information about breastfeeding, and duration of previous breastfeeding were associated with breastfeeding self-efficacy in women without GDM ($p<0.05$, $R2=0.612$). GDM increased prenatal breastfeeding self-efficacy scores by 7.6 units ($B=7.636$, $R2=0.059$).
Conclusions: The study revealed that prenatal breastfeeding self-efficacy was higher in women with GDM, it was high in both groups. Prenatal breastfeeding self-efficacy (PBSE) was affected by some sociodemographic, obstetric, and breastfeeding-related characteristics. Health professionals should determine the breastfeeding self-efficacy of pregnant women, know the factors affecting them, and consider them when providing education and counseling. Prenatal education and support programs should be developed to increase the breastfeeding self-efficacy of women with and without GDM.

Keywords: breastfeeding, self-efficacy, diabetes, gestational, pregnant

ÖZ

Giriş: Doğum öncesi emzirme öz yeterliliği, kadınların emzirme başarısını ve niyetini etkileyen önemli bir parametredir. Doğum öncesi emzirme öz yeterliliği GDM'si olan ve olmayan tüm kadınlarda değerlendirilmelidir.
Amaç: Çalışmanın amacı Gestasyonel Diyabeti (GDM) olan ve olmayan kadınların doğum öncesi emzirme öz yeterliliklerini incelemek ve doğum öncesi emzirme öz yeterliliğini yordayan faktörleri belirlemektir.
Yöntem: Araştırma hastane tabanlı bir vaka-kontrol çalışmasıdır. Çalışma, Türkiye'nin batısındaki bir üniversite hastanesinin endokrinoloji polikliniğine başvuran GDM'li 96 kadın ile GDM'si olmayan 98 kadının karşılaştırılmasıyla gerçekleştirilmiştir. Veriler "Birey Tanımlama Formu" ve "Prenatal Emzirme Öz Yeterlilik Ölçeği (PEÖTÖ)" kullanılarak toplanmıştır. İstatistiksel analiz için t testi ve Ki-kare testi kullanılmıştır. Regresyon analizleri doğum öncesi emzirme öz yeterliliğinin belirleyicilerini tanımlamak için kullanılmıştır.
Bulgular: Olguların PEÖTÖ'i 79.64±15.12 ve kontrollerin 72.01±15.62'dir. Olguların PEÖTÖ puanları kontrollere göre anlamlı olarak daha yüksektir ($p<0.05$). GDM'li kadınlarda çalışma, aile tipi ve emzirme hakkında bilgi sahibi olma emzirme öz yeterliliği ile ilişkiliyken ($p<0.05$, $R2=0.341$); GDM'si olmayan kadınlarda eğitim düzeyi, çalışma, aile tipi, gelir düzeyi, trimester, emzirme hakkında bilgi sahibi olma ve daha önce emzirme süresi emzirme öz yeterliliği ile ilişkiliydi ($p<0.05$, $R2=0.612$). GDM, prenatal emzirme öz yeterlilik puanlarını 7,6 birim artırmıştır ($B=7,636$, $R2=0,059$).
Sonuçlar: Çalışma, doğum öncesi emzirme öz yeterliliğinin GDM'li kadınlarda daha yüksek olduğunu, her iki grupta da yüksek olduğunu ortaya koymuştur. Prenatal emzirme öz yeterliliği (PEÖY) bazı sosyodemografik, obstetrik ve emzirme ile ilgili özelliklerden etkilenmiştir. Sağlık profesyonelleri gebelerin emzirme öz yeterliliklerini belirlemeli, etkileyen faktörleri bilmeli ve eğitim ve danışmanlık verirken bunları göz önünde bulundurmalıdır. GDM'si olan ve olmayan kadınların emzirme öz yeterliliğini artırmak için doğum öncesi eğitim ve destek programları geliştirilmelidir.

Anahtar Kelimeler: emzirme, öz yeterlilik, diyabet, gestasyonel, gebe

Introduction

Prenatal breastfeeding self-efficacy (PBSE) encompasses a pregnant woman's confidence, intention, proficiency, and understanding regarding her ability to successfully breastfeed her infant postpartum.

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It also refers to her belief in her ability to successfully initiate, maintain, and intend breastfeeding. It is a key factor that can influence a woman's decision to breastfeed and her confidence in her breastfeeding capabilities (1,2). PBSE was influenced by women's access to accurate and comprehensive information about breastfeeding during pregnancy, social support systems (partners, family, friends, and health professionals), previous breastfeeding experiences, and barriers to breastfeeding (concerns about milk production and milk adequacy, etc.) (3-6). PBSE should be questioned in all pregnant women because it affects breastfeeding intention and success and even breastfeeding duration. It was reported that women with low PBSE had problems with initiating breastfeeding and stopped breastfeeding early (3,7,8).

Gestational diabetes mellitus (GDM) affects approximately 7-15% of pregnancies worldwide and breastfeeding contributes significantly to the management of GDM (8). Gestational diabetes mellitus (GDM) is a type of diabetes that manifests during pregnancy when the body is unable to produce sufficient insulin to accommodate the heightened physiological demands, resulting in elevated blood glucose levels. Breastfeeding in women with GDM has been reported to have potential benefits in terms of blood glucose control (6,7). Breastfeeding helped to utilize glucose for milk production, which contributed to better management of blood glucose in the mother (3-5). Therefore, increasing PBSE in women with GDM increased motivation to breastfeed and potentially helped blood glucose control. Providing information to women with GDM about the benefits of breastfeeding in blood glucose management and concerns or barriers to breastfeeding self-efficacy also increased women's success in breastfeeding after delivery (7, 9-11).

For mothers with GDM, breastfeeding offers additional benefits such as improved glucose regulation and reduced long-term diabetes risk. However, these individuals often face unique barriers that can affect their confidence and ability to initiate and maintain breastfeeding. Understanding the concept of breastfeeding self-efficacy, which refers to a mother's confidence in her ability to successfully breastfeed, is critical for designing interventions tailored to this population. Identifying PBSE in women with GDM has provided an opportunity to assess and support the breastfeeding beliefs, intentions, desires, and skills of these women diagnosed with GDM during pregnancy (12-14). Our study revealed the points that healthcare professionals should pay attention to.

It was necessary to ensure that women with GDM had access to breastfeeding counselors or breastfeeding support groups and to offer support. This support, which should start during pregnancy and continue in the postnatal period, can further increase breastfeeding self-efficacy and promote successful breastfeeding (7,9). Considering all these, prenatal breastfeeding self-efficacy played a key role in the breastfeeding process (an important influence on breastfeeding decision and ability) in women with GDM (7,9,13-15). In women with GDM, addressing breastfeeding self-efficacy was becoming even more critical because of its potential role in blood glucose control and overall maternal and infant health (16-18). Identifying and addressing the factors affecting breastfeeding self-efficacy and perceived barriers to breastfeeding in all pregnant women increased self-efficacy (18-20). Our study aimed to help health professionals to develop strategies to overcome these barriers for pregnant women. Health professionals should provide accurate information, address concerns, and offer guidance during antenatal visits. Recognizing that each woman's experience is unique, health professionals should tailor their support and education to the individual needs and circumstances of women with and without GDM and provide psychosocial support. Health professionals should prioritize assessing and addressing self-efficacy during antenatal care to improve breastfeeding outcomes and promote the numerous health benefits of breastfeeding for both mother and child (14,17, 21,22). Our study contributes to the breastfeeding self-efficacy of women with GDM in many ways. It also sheds light on how the presence of gestational diabetes can affect a woman's self-confidence and readiness to breastfeed her newborn. It also contributes to a better understanding of how gestational diabetes can affect PBSE and informs strategies to support women with and without gestational diabetes in their breastfeeding process. Our study also revealed factors associated with PBSE. It contributed to the development of evidence-based strategies to support breastfeeding self-efficacy in this population to improve maternal and newborn health outcomes. In this context, the aim of the study was to examine the PBSE of women with and without Gestational Diabetes (GDM) and to determine the factors that predict PBSE.

Materials and Methods

Study Design

A hospital-based case-control study was conducted in the endocrinology policlinic of a university hospital in Izmir, in western Türkiye, to assess prenatal breastfeeding self-efficacy for women with and without GDM, between April 2023 and August 2023.

Participants

The study cases included 96 women with GDM who were admitted to the endocrinology policlinic of a university hospital in western Türkiye. To achieve the desired sample size, researchers visited the clinic twice weekly (on Tuesdays and Thursdays) during the study period. Out of 152 women who attended the clinic, all were invited to participate in the study. However, 34 women with GDM were excluded from the sample as they did not meet the inclusion criteria (11 of them had Type 1 diabetes, 8 had another chronic disease, 2 had any pregnancy complication, 2 problems restricting breastfeeding, 8 were illiterate, 2 can not speak Turkish, and 1 had neurological or psychiatric disorders), 14 women refused the study and 8 women did not complete the questionnaires. The study involved 96 women diagnosed with GDM.

The study controls included 98 women without gestational diabetes mellitus (GDM) residing in the same geographical region, who were admitted to the endocrinology policlinic of the same hospital during the same interval. All pregnant women are referred to the endocrinology policlinic. All pregnant women undergo oral glucose tolerance test and the results are evaluated for GDM. Women with a negative oral glucose tolerance test were included in the control group. To recruit the control group, researchers visited the clinic twice weekly (on Mondays and Wednesdays) during the study period. Of the 165 women without GDM who attended the clinic for routine check-ups, all were invited to participate in the control sample. However, throughout the study duration, 40 women were excluded from the control sample due to their failure to meet the predefined inclusion criteria (10 had another chronic disease, 16 women with GDM, 2 had any pregnancy complication, 5 had problems restricting breastfeeding, 4 were illiterate, 2 can not speak Turkish, and 1 had neurological or psychiatric disorders), 17 women declined participation in the study, and an additional 10 women did not complete the questionnaires. The controls comprised 98 women who did not have GDM.

The sample size analysis indicated a sufficient statistical power of 84% at the moderate to large effect size level, assuming a medium-large effect size of 0.65, with a significance level (alpha) of 0.05, and with 31 women allocated to each group. Finally, the analysis included 96 cases and 98 controls. The introductory, obstetric, and breastfeeding characteristics of both groups were found to be similar ($p > 0.05$). All participants provided informed consent, and the procedures adhered to the ethical standards outlined in the Helsinki Declaration. The study was conducted and reported in accordance with the STROBE statement.

Data Collection Tools

The data of the study were collected using the "Individual Identification Form" (16 questions) and the "Prenatal Breastfeeding Self-Efficacy Scale (PBSES)" (20 items). All forms were gathered through face-to-face interviews and completed by the pregnant women themselves. The completion of forms required approximately 15 minutes.

Individual Identification Form

The Individual Introduction Form was prepared by the researchers based on previous international and national studies (3,11,13,21,22). The form comprised two sections. The first section comprised 10 questions pertaining to the introductory and obstetric characteristics of pregnant women, such as age, education level, Body Mass Index (BMI), number of pregnancies, among others. The second section comprised 6 questions related to the breastfeeding characteristics of pregnant women, including breastfeeding experience, satisfaction from breastfeeding, and similar aspects.

Prenatal Breastfeeding Self-Efficacy Scale (PBSES)

The scale utilized in this study was developed by Wells et al. (2006) to assess breastfeeding self-efficacy perceptions among pregnant women. It comprises 20 items, with responses ranging from 1 "Not at all sure" to 5 "Completely sure" on a five-point Likert scale. Scores range from 20 to 100, with higher scores indicating greater perceived self-efficacy. The scale encompasses four subgroups, including skills and demands required for breastfeeding (8 items), gathering information about breastfeeding (5 items), feelings of embarrassment during breastfeeding (4 items), and social pressure when breastfeeding (3 items). The Cronbach's alpha value for the original scale was reported as 0.89 (2). Aydın and Pasinlioğlu

(2018) conducted a study to validate the scale in Turkish, yielding a Cronbach's alpha value of 0.85. In this current study, the Turkish version of the scale demonstrated a Cronbach's alpha value of 0.79, consistent with previous research (1,4,23).

Data collection

Following ethical approval from the university and the study hospital, the principal investigator liaised with the nursing departments of the hospital to secure support for the study. Approval was obtained from the nurses overseeing the endocrinology policlinic. Pregnant women attending the endocrinology policlinic, both with and without GDM, were approached for participation. Prior to administering the forms, researchers provided detailed explanations regarding the study's objectives, potential benefits, expected duration of participation, and obtained verbal and written consent from the participants. Informed consent was obtained from all participants. Upon signing the consent forms, participants completed an individual identification form and the Turkish version of the PBSES. Form completion required approximately 15 minutes, during which researchers remained available to address any inquiries. All forms were collected through face-to-face interviews conducted in a designated room within the hospital, ensuring participant privacy.

Data analysis

Data analysis was performed using the statistical package program SPSS 25.0 (IBM SPSS Statistics, Armonk, NY, USA). Comparative analyses of the introductory, obstetric, and breastfeeding characteristics between women with and without GDM were performed using Chi-square ($\chi 2$) and t-tests for categorical and continuous variables, respectively. Normality of distribution was assessed using the Kolmogorov–Smirnov test. Breastfeeding self-efficacy was assessed using the Turkish version of the PBSES, as developed by Aydın and Pasinlioğlu (2018). The PBSES scores of women with and without GDM were compared using t-tests. Linear regression analysis was conducted to ascertain the predictive impact of GDM on prenatal breastfeeding self-efficacy. Logistic regression analysis was utilized to identify predictors of prenatal breastfeeding self-efficacy in both groups (with and without GDM). The coefficient of determination (R2) was employed to calculate effect sizes in the regression models. Results were interpreted at a 95% confidence interval, with statistical significance set at $p<0.05$.

Results

Population characteristics

Among the participants who consented to the study, 96 women with GDM and 98 women without GDM completed the questionnaires. Following propensity score matching, no significant differences were observed in the introductory, obstetric, and breastfeeding characteristics between women with and without GDM. These characteristics included age, education level, employment status, income, number of pregnancies, number of living children, satisfaction from breastfeeding, duration of previous breastfeeding, and information about breastfeeding ($p>0.05$) (Table 1).

PBSES scores of women with and without GDM

The comparison of the PBSES sub-dimension and total scores of women with and without GDM was detailed in Table 2. The PBSES score of women with GDM was 79.64±15.12 and women without GDM was 72.01±15.62. PBSES sub-dimension and total scores of women with GDM were significantly higher than women without GDM ($p<0.05$) (Table 2).

Linear regression analysis of the effect of GDM on prenatal breastfeeding self-efficacy

In the study, it was determined that women with GDM affected prenatal breastfeeding self-efficacy 7.6 times more positively than women without GDM (B=7.636, p=0.001). It was determined that women with GDM were responsible for 06% of the variance in their prenatal breastfeeding self-efficacy ($p<0.05$, R2=0.059) (Table 3).

Logistic regression analysis of the factors associated with PBSES in women with and without GDM

Finally, a logistic regression analysis was used to detect any variation independently related to PBSE (dependent variables) in women with GDM. The results of multiple linear regression analysis showed that in women with GDM, PBSE was negatively associated with not working (B=-8.321, p=0.008), having a large family (B=-13.408, p=0.001) and positively associated with receiving information about breastfeeding (B=18.195, p=0.000) and explained 34% of the variance in prenatal breastfeeding self-efficacy ($p<0.05$, R2=0.341) (Table 3).

The results of multiple linear regression analysis showed that in women without GDM, PBSE was negatively associated with not working (B=-13.162, p=0.002),

Table 1. Comparison of the introductory, obstetric, and breastfeeding characteristics of women with and without GDM (n=194)

Characteristics	GDM (n=96)		Non-GDM (n=98)		Test*/p
	Mean±SD		Mean±SD		
Age	33.65±4.97		32.42±5.06		-1.704/0.090
Gestational week	28.17±3.11		27.76±3.36		-0.884/0.378
Number of pregnancy	1.80±0.93		1.69±0.72		-0.902/0.370
Number of living child	1.76±0.87		1.63±0.67		-1.134/0.260
Duration of previous breastfeeding (month)	14.20±5.71		12.09±6.58		-1.709/0.091
Desired duration of breastfeeding (month)	18.91±5.59		18.05±5.94		-2.253/0.065
	n	%	n	%	Test**/p
Education					
Under high school	24	25.0	34	34.7	2.174
High school and above	72	75.0	64	65.3	0.140
Partner' Education					
Under high school	22	22.9	27	27.6	0.552
High school and above	74	77.1	71	72.4	0.458
Work					
Working	68	70.8	57	58.2	3.397
Not working	28	29.2	41	41.8	0.065
Income					
Low	20	20.8	27	27.6	3.029
Middle	70	72.9	69	70.4	0.220
High	6	6.3	2	2.0	
Family type					
Nuclear	82	85.4	83	84.7	0.020
Extended	14	14.6	15	15.3	0.888
BMI					
Normal (19.8-26)	13	13.5	19	19.4	1.500
High (26.1-29)	20	20.8	22	22.4	0.472
Obese (29.1 and above)	63	65.6	57	58.2	
Breastfeeding experience					
Yes	49	51.0	51	52.0	0.019
No	47	49.0	47	48.0	0.889
Satisfaction from breastfeeding					
Yes	33	67.3	35	68.6	0.527
No	10	20.4	8	15.7	0.768
Don't know	6	12.2	8	15.7	
Information about breastfeeding					
Yes	86	89.6	94	95.9	2.907
No	10	10.4	4	4.1	0.088
Receiving information					
Health professionals	78	90.7	58	61.7	1.761
Social media	2	2.1	4	4.2	0.221
Friends	6	7.2	32	34.0	

SD: Standard deviation. *t: Independent two sample 't' test. **X^2: Chi-square test, p<0.05. BMI: Body Mass Index. GDM: Gestational Diabetes Mellitus

Table 2. Comparison of PBSES sub-dimension and total scores of women with and without GDM (n=194)

Scale	GDM (n=96)	Non-GDM (n=98)	
	Mean±SD	Mean±SD	Test*/p
PBSES	79.64±15.12	72.01±15.62	-3.457/0.001
PBSES sub-dimension			
Skills and demands required for breastfeeding	33.29±5.91	31.35±5.81	-2.299/0.023
Gathering information about how to breastfeed	18.79±4.73	16.67±4.68	-3.134/0.002
Breastfeeding around other people and feelings of embarrassment during breastfeeding	14.67±4.17	12.39±4.18	-3.799/0.000
Social pressure when breastfeeding	12.88±2.19	11.58±2.83	-3.576/0.000

PBSES: Prenatal Breast-Feeding Self-Efficacy Scale. SD: Standard deviation. *t: Independent two sample 't' test, p<0.05.

had extended family (B=-9.011, p=0.006), having a low income level (B=-7.241, p=0.022), being in the 3rd trimester (B=-10.597, p=0.006) and positively associated with the educational level of high school and above (B=9.377, p=0.007), receiving information about breastfeeding (B=15.436, p=0.033), and duration of previous breastfeeding (B=1.403, p=0.000) and explained 61% of the variance in prenatal breastfeeding self-efficacy (p<0.05, R2=0.612) (Table 3).

Discussion

The study was conducted to examine the PBSE of women with and without GDM and to determine the factors that predict PBSE. In this study, the PBSES score of the women with GDM (79.64±15.12) was significantly higher than women without GDM (72.01±15.62). In our study, it was found that women with GDM had a better

Table 3. Linear regression analysis to examine the effect of GDM on prenatal breastfeeding self-efficacy (n=194)

Independent Variables	B	Standard Error	β	t	CI 95%		R	R^2	Adjusted R^2	Durbin-Watson	p
Constant	72.010	1.554	-	46.340	68.945	75.075	0.242	0.059	0.054	2.125	0.000
Group (Women with GDM)	7.636	2.209	0.242	3.457	3.279	11.993					0.001
Predictors of PBSES among women with GDM (n=96)											
Constant	67.729	4.132		16.392	59.522	75.935	0.584	0.341	0.320	2.115	0.000
Work status (Not working)	-8.321	3.068	-0.251	-2.712	-14.415	-2.228					0.008
Family type (Extended)	-13.408	3.978	-0.314	-3.371	-21.309	-5.508					0.001
Information about breastfeeding (Yes)	18.195	4.257	0.369	4.274	9.740	26.651					0.000
Predictors of PBSES among women without GDM (n=98)											
Constant	50.490	8.063	-	6,262	34,194	66,787	0.782	0.612	0.534	2.938	0.000
Education (High school and above)	9.377	3.274	0.366	2,864	2,759	15,995					0.007
Work status (Not working)	-13.162	3.938	-0.444	-3,342	-21,121	-5,203					0.002
Family type (Extended)	-9.011	3.089	0.336	2,917	-15,253	-2,768					0.006
Income (Low)	-7.241	3.039	-0.293	-2,383	-13,383	-1,099					0.022
Gestational week (3rd trimester)	-10.597	3.670	-0.378	-2,887	-18,015	-3,179					0.006
Longer Previous Breastfeeding Duration (month)	1.403	0.232	0.702	6,050	,934	1,872					0.000
Information about breastfeeding (Yes)	15.436	6.975	0.247	2,213	1,338	29,534					0.033

B: Unstandardized Coefficient. β:Standardized Coefficient. CI: Confidence Interval. PBSES: Prenatal Breast-Feeding Self-Efficacy Scale. R^2: Coefficient of determination, $p<0.05$.
Women with GDM: Backward selected. Excluded Variables: Age, education, partner's education, income, gestational week, number of pregnancies, number of living children, breastfeeding experience. desired duration of breastfeeding.
Women without GDM: Backward selected. Excluded Variables: Age, education, partner's education, income, gestational week, number of pregnancies, number of living children, breastfeeding experience. desired duration of breastfeeding.

perception of breastfeeding self-efficacy. In addition, GDM positively affected the PBSES scores of pregnant women by 7.6 units. This may be because women with GDM blame themselves for the disease and think that diabetes will harm their babies. In previous studies, it was reported that pregnant women with GDM blamed themselves for the disease, were anxious and tense, and did not have enough information about the disease and its effects on the baby (15,16). Therefore, pregnant women with GDM may have more positive thoughts and attitudes about the breastfeeding process, which may have positively affected prenatal breastfeeding self-efficacy.

In the study, the PBSES scores of women with and without GDM in our study (79.64±15.12; 72.01±15.62) were higher than those of Alyousefi et al. (64.07±16.3) (13), Ince et al. (57.16±6.92) (4) and Konukoğlu and Pasinlioğlu (68.08±14.48) (23). This may be because most of the women with and without GDM in our study had breastfeeding experience, were satisfied with breastfeeding, and received information about breastfeeding. Breastfeeding self-efficacy is affected by factors such as women's individual experiences with breastfeeding, whether they want to breastfeed, and how they apply what they see around them (24, 25). In addition, the fact that women with GDM who applied to the endocrinology policlinic were informed about GDM by diabetes nurses may have increased their awareness of the breastfeeding process and breastfeeding self-efficacy. Therefore, we think that PBSES scores were higher for the women with GDM compared to women without GDM.

In the present study was determined that not working was a predictor of PBSE in women with and without GDM. Not working negatively affected PBSE. Working women have higher socioeconomic status and social support than non-working women. Lower socioeconomic status was also associated with lack of access to care and worse health outcomes (26-28). Therefore, women with low socioeconomic status may have reduced accessibility to health services related to the health problem in pregnancy, these women may be exposed to more health problems and may have difficulty in controlling the health problems.

Working is one of the important factors that increase women's social support and these women were able to reach solutions to problems more quickly (9,29). In this context, unemployed pregnant women may not have received adequate social support during pregnancy and may have more difficulty in coping with the problems and accessing health care (9,26). All these reasons may increase the health problems that unemployed women will experience during pregnancy, reduce their support, prevent their access to health care, and cause them to put breastfeeding on the back burner. Therefore, PBSE of unemployed women may have been negatively affected.

It was determined in our study that living in an extended family was a predictor of PBSE in women with and without GDM. Breastfeeding self-efficacy included the headings of desire, skill, knowledge, embarrassment, and social pressure related to breastfeeding (1,2). In many cultures, women living in extended families are responsible for the care of other family members and have more roles and responsibilities within the household (30), and therefore women may not have enough time to breastfeed their babies. However, most of the women living in extended families lived in rural areas and had difficulties accessing health care (31) therefore these women may also find it difficult to access information about breastfeeding. In addition, women living in large families had problems such as not spending enough time with their babies during breastfeeding and not having a private area where they could breastfeed (6). For this reason, women may feel ashamed of the other people they live with, may have negative perceptions about breastfeeding think that they will not have privacy, and may feel pressure to breastfeed (32) and PBSE may be negatively affected. Living in a nuclear family had a positive effect on breastfeeding motivation and breastfeeding readiness of pregnant women (33).

Receiving information about breastfeeding was an important predictor of prenatal breastfeeding self-efficacy. Receiving information about breastfeeding increased PBSES scores by 18.2 units in women with GDM and by 15.4 units in women without GDM, which was in agreement with previous studies (15, 21, 22). We would also like to draw attention to the fact that in this study, most of the information about breastfeeding was received from health professionals in women with and without GDM. This result in our study was very important in terms of revealing that health professionals were at an important step regarding breastfeeding processes and the self-efficacy of women during pregnancy. National (21, 22) and international (3,8,11,13) studies have revealed the positive effect of breastfeeding education given to women during pregnancy on women's breastfeeding self-efficacy both during pregnancy and the postpartum period. It was reported that breastfeeding education by health professionals and nurses had a positive effect on breastfeeding self-efficacy in the postnatal period (7,14).

In our study, we found a positive relationship between the educational level of high school and above and PBSE in women without GDM, which was in agreement with other studies conducted by Alyousefi et al. (13) and Corby et al. (3). Educational level is an important parameter affecting the awareness of pregnant women about breastfeeding. Pregnant women with higher educational levels were more willing to receive information about breastfeeding and to breastfeed. Because these women were more aware of the benefits of breastfeeding for both mother and baby (4,21,22).

We found a negative relationship between low income level and PBSE in women without GDM. We may associate this result with the lower PBSE of unemployed pregnant women. This was because not working reduced the income level of the person and could negatively affect access to health and social support (9,26-28). Women with low income levels who had problems accessing health care and whose social support was negatively affected also had less access to adequate and accurate information about breastfeeding (7,14), and may have false beliefs about the breastfeeding process and their breastfeeding success could be affected. Therefore, PBSE of low-income pregnant women may have been negatively affected.

In our study, being in the 3rd trimester decreased the PBSE of pregnant women by 10.6 units. It was reported that women's fear of childbirth, anxiety about their babies and themselves, and physical symptoms increased as they approached the end of their pregnancies. It was stated that the interest of pregnant women in the last trimester was focused on the birth process and having a healthy baby (19,20,34). Therefore, in our study, we think that the ambivalent emotional states experienced by pregnant women in the 3rd trimester in this period diverted their attention and negatively affected their PBSE.

The length of previous breastfeeding duration of

pregnant women positively affected PBSE, which was in agreement with other studies conducted by Corby et al. (3) and Salarvand et al. (5). Breastfeeding is an important period that strengthens the mother-baby bond and has numerous benefits for both mother and baby. At the beginning of the breastfeeding process, there may be some problems. However, as breastfeeding continued, the mother's sense of achievement and desire to breastfeed increased and the mother-infant bond was strengthened. Therefore, the length of the breastfeeding process supported positive breastfeeding experiences. Because breastfeeding is a learned behavior (17, 18). Accordingly, the length of the breastfeeding period strengthened the relationship between mother and infant, increased satisfaction, and encouraged repeat breastfeeding. Therefore, we suggest that the length of previous breastfeeding has a positive effect on PBSE.

Limitations and strengths of the study

The strength of our study was that it was the first study to determine PBSE and the factors affecting it in Turkish pregnant women with and without GDM. However, our study had some limitations. The first limitation was that the study was conducted in a single hospital. Another limitation was that the study was conducted only with pregnant women attending the endocrinology policlinic.

Practical implications

Breastfeeding is a very important issue for women during pregnancy and the postnatal period. Education and counseling on breastfeeding by health professionals (especially nurses) and breastfeeding counselors should start during pregnancy and continue in the postnatal period. In this way, women's breastfeeding duration, success, desire, and thus their breastfeeding self-efficacy may increase. In this context, the factors affecting PBSE in all women with and without GDM should be known and taken into consideration when providing education and counseling. In addition, awareness of all health professionals and breastfeeding counselors about PBSE should be increased. In future studies, it was recommended to give structured training on breastfeeding to women with and without GDM starting during pregnancy and continuing in the postnatal period and to conduct experimental or qualitative studies in which women's breastfeeding experiences and changes in self-efficacy are determined.

Conclusions

In conclusion, this study determined the level of PBSE of women with and without GDM and the factors predicting prenatal breastfeeding self-efficacy. In our study, PBSE was high in women with and without GDM, but it was higher in women with GDM. The factors predicting PBSE in women with GDM were employment status, family type, and receiving information about breastfeeding, while the factors predicting PBSE in women without GDM were educational status, employment status, family type, income status, trimester, length of previous breastfeeding and receiving information about breastfeeding. Women need to be assessed comprehensively in terms of breastfeeding self-efficacy both during pregnancy and in the postpartum period.

Ethical Statement & Informed Consent

Ethical approval was obtained from Izmir Katip Celebi University Non-Interventional Clinical Research Ethics Committee (Date: 23.02.2023; IRB: 0058) and permission from the hospital where the study was conducted (Date: 05.04.2023). Permission was obtained from the researchers who conducted the Turkish validity and reliability of the scale used in the study. The purpose, nature, confidentiality, anony - mity and right of women to refuse to participate in the study were explained to the participants. Written and verbal consent was obtained from women with and without GDM who voluntarily agreed to participate in the study and met the inclusion criteria. Informed consent was obtained from all women included in the study. The research was conducted in accor- dance with the Principles of the Declaration of Helsinki.

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References

1.Aydın A, Pasinlioglu T. Reliability and validity of a Turkish version of the prenatal Breastfeeding Self-

Efficacy Scale. Midwifery. 2018;64:11-6. doi:10.1016/j.midw.2018.05.007.

2.Wells KJ, Thompson NJ, Kloeblen-Tarver AS. Development and psychometric testing of the prenatal breast-feeding self-efficacy scale. American Journal of Health Behavior. 2006;30(2):177-87. doi:10.5993/AJHB.30.2.7.

3.Corby K, Kane D, Dayus D. Investigating predictors of prenatal breastfeeding self-efficacy. Canadian Journal of Nursing Research. 2021;53(1):56-63.

4.İnce T, Aktaş G, Aktepe N, Aydın A. Evaluation of the factors affecting mothers' breastfeeding self-efficacy and breastfeeding success. Journal of Dr. Behcet Uz Children's Hospital. 2017;7(3):183-90.

5.Salarvand S, Ghazvineh S, Mousivand F, Ahmadi Gharaei H, Bitaraf S. Health literacy and its related factors as predictors for the breastfeeding self-efficacy in a western province in Iran. BMC Public Health. 2023;23(1):593.

6.Wu W, Zhang J, Silva Zolezzi I, Fries LR, Zhao A. Factors influencing breastfeeding practices in China: A meta□ aggregation of qualitative studies. Maternal & Child Nutrition. 2021;17(4):e13251.

7.Brockway M, Benzies K, Hayden KA. Interventions to improve breastfeeding self-efficacy and resultant breastfeeding rates: a systematic review and meta-analysis. Journal of Human Lactation. 2017;33(3):486-499.

8.Park S, Kim B, Paudel J, Park HO. Effects of Breastfeeding Knowledge and Health Beliefs Regarding Gestational Diabetes Mellitus on the Breastfeeding Intention of Pregnant Women. Research Square. 2023. https://doi.org/10.21203/rs.3.rs-3343250/v1

9.Battulga B, Benjamin MR, Chen H, Bat-Enkh E. The impact of social support and pregnancy on subjective well-being: A systematic review. Frontiers in Psychology. 2021;12:710858.

10.Chambers A, Emmott EH, Myers S, Page AE. Emotional and informational social support from health visitors and breastfeeding outcomes in the UK. International Breastfeeding Journal. 2023;18(1):14.

11.Nguyen PTH, Pham NM, Chu KT, Van Duong D, Van Do D. Gestational diabetes and breastfeeding outcomes: a systematic review. Asia Pacific Journal of Public Health. 2019;31(3):183-198.

12.Han RR, Xiang, ZX, Zhang SH, Gao LL. Predictors of anxiety among pregnant women with gestational diabetes mellitus and their partners: The mediating role of marital satisfaction. International Journal of Nursing Practice. 2024;30(1):e13155.

13.Alyousefi N, Alemam A, Altwaijri D, Alarifi S, Alessa H. Predictors of Prenatal Breastfeeding Self-Efficacy in Expectant Mothers with Gestational Diabetes Mellitus. International Journal of Environmental Research and Public Health. 2022;19(7):4115.

14.Piro SS, Ahmed HM. Impacts of antenatal nursing interventions on mothers' breastfeeding self-efficacy: an experimental study. BMC Pregnancy and Childbirth. 2020;20:1-12.

15.Draffin C, Alderdice FA, McCance DR, Maresh M, Harper R, McSorley O, Holmes VA. Exploring the needs, concerns and knowledge of women diagnosed with gestational diabetes: A qualitative study. Midwifery. 2016;40:141-147.

16.Hirst JE, Tran TS, Do MAT, Rowena F, Morris JM, Jeffery HE. Women with gestational diabetes in Vietnam: a qualitative study to determine attitudes and health behaviours. BMC pregnancy and childbirth. 2012;12:1-10.

17.Peñacoba C, Catala P. Associations between breastfeeding and mother–infant relationships: a systematic review. Breastfeeding Medicine. 2016;14(9):616-629.

18.Shariat M, Abedinia N. The Effect of Psychological Intervention on MotherInfant Bonding and Breastfeeding. Iranian Journal of Neonatology. 2017;8(1). doi: 10.22038/ijn.2017.16673.1191

19.Abdolalipour S, Charandabi SMA, Mashayekh-Amiri S, Mirghafourvand M. The effectiveness of mindfulness-based interventions on self-efficacy and fear of childbirth in pregnant women: A systematic review and meta-analyses. Journal of Affective Disorders, 2023;333:257-270. https://doi.org/10.1016/j.jad.2023.04.020.

20.Jokić-Begić N, Žigić L, Nakić Radoš S. Anxiety and anxiety sensitivity as predictors of fear of childbirth: different patterns for nulliparous and parous women. Journal of Psychosomatic Obstetrics & Gynecology. 2014;35(1):22-28.

21.Duman FN, Gölbaşı, Z. Investigation of the Effect of Breastfeeding Education on Mothers' Breastfeeding Self-Efficacy Levels in Turkey. Turkish Journal of Family Medicine and Primary Care. 2022;16(1):140-150.

22.Şenol DK, Pekyiğit AÇ. Effects of Breastfeeding Education Given in Childbirth Preparation Classes for Primipara Women on Their Perceived Prenatal Breastfeeding Self-Efficacy. Bozok Medical Journal. 2021;11(2):15-21.

23.Konukoğlu T, Pasinlioğlu T. Breastfeedıng self-effıcacy ın pregnant women and evaluation of affectıng factors. J Midwifery and Health Sci. 2021;4(1):12-22.

24.Blyth R, Creedy D, Dennis CL. Effect of maternal confidence on breastfeeding duration: an application of breastfeeding self-efficacy theory. Birth. 2002;29:278-84. doi:10.1046/j.1523-536X.2002.00202.x

25.Dennis CL, Faux S. Development and psychometric testing of the Breastfeeding Self□Efficacy Scale. Research in Nursing & Health. 1999;22(5):399-409. doi:10.1002/(SICI)1098-240X(199910)22:5<399::AID-NUR6>3.0.CO;2-4

26.Angerer S, Waibel C, Stummer H. Discrimination in health care: a field experiment on the impact of patients' socioeconomic status on access to care. American Journal of Health Economics. 2019;5(4):407-427.

27.Gulliford MC, Sedgwick JEC, Pearce AJ. Cigarette smoking, health status, socio-economic status and access to health care in diabetes mellitus: a cross-sectional survey. BMC health services research. 2003;3:1-9.

28.McMaughan DJ, Oloruntoba O, Smith ML. Socioeconomic status and access to healthcare: interrelated drivers for healthy aging. Frontiers in public health. 2020;8:512143.

29.Maharlouei N. The importance of social support during pregnancy. Women's Health Bulletin. 2016;3(1):1-1.

30.Georgas J, Mylonas K, Bafiti T, Poortinga YH, Christakopoulou S, Kagitcibasi C, et al. Functional relationships in the nuclear and extended family: A 16□culture study. International Journal of Psychology. 2001;36(5):289-300.

31.Attah PA. Impact of the Extended Family System and Access to Health Care Services in Kogi State, Nigeria. KIU Journal of Social Sciences. 2023;9(1):143-149.

32.Mphego Z, Madiba S, Ntuli B. The influence of the family on adherence to exclusive breastfeeding: experiences of women living in extended family households in poorly resourced communities of Mpumalanga Province, South Africa: child nutrition and feeding practices. African Journal for Physical Health Education, Recreation and Dance. 2014;20(sup-1):279-290.

33.Mulyani S. Pregnant women with extended family on knowledge, motivation, and readiness in exclusive breastfeeding. International Journal of Emerging Trends in Social Sciences. 2017;1(2):104-107.

34.Koyuncu SB, Bülbül M. The impact of yoga on fear of childbirth and childbirth self-efficacy among third trimester pregnants. Complementary Therapies in Clinical Practice. 2021;44:101438.

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ORIGINAL ARTICLE

Breastfeeding Myths and Influencing Factors in Married Women

Evli Kadınlarda Emzirme Mitleri ve Etkileyen Faktörler

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ABSTRACT

Background/Aims: Breastfeeding myths in married women are thoughts and beliefs without any scientific basis that prevent full breastfeeding, especially in the first six months of life. The aim of this study was determine breastfeeding myths and influencing factors in married women.
Methods: This was a cross-sectional descriptive study conducted between May 1 and July 1, 2024, at Yozgat Bozok University Research and Application Hospital Polyclinics. The study included 576 married women over 18 who applied to the polyclinics for any reason, were literate, and volunteered to participate. Data were collected using a "Descriptive Information Form" and the "Breastfeeding Myths Scale (BMS)." Permission was obtained from the Yozgat Bozok University Social and Human Sciences Ethics Committee (Date: 20.03.2024; Decision No: 12/21).
Results: The mean age of the participants was 39.30±14.10 years. Of the women, 30.9% were between the ages of 25-34, 24.8% were high school graduates, 67.4% were non-working, and 70.8% were from nuclear families. Additionally, 38.4% had three or more children, 27.4% had vaginal deliveries, 74% had breastfeeding experience, and 45.7% received support while breastfeeding. The mean BMS score was 81.64±21.62. Socio-demographic and obstetric variables such as age, educational status, current employment status, income status, number of pregnancies, number of living children, number of live births, number of vaginal deliveries, and breastfeeding experience significantly affected breastfeeding myths ($p<0.05$). There was no statistically significant correlation between BMS scores and family type, place of residence, number of cesarean deliveries, or receiving support while breastfeeding ($p>0.05$).
Conclusion: The study found that married women have breastfeeding myths, although their level of belief in these myths is low. Sociodemographic and obstetric variables such as age, educational status, number of live births, number of vaginal deliveries, and breastfeeding experience significantly affect breastfeeding myths. It is recommended to raise awareness among married women about breastfeeding myths and their potential harms.

Keywords: breast milk; breastfeeding; myths; breastfeeding myths; woman

ÖZ

Amaç: Evli kadınlarda emzirme mitleri, özellikle yaşamın ilk altı ayında tam emzirmeyi engelleyen ve hiçbir bilimsel dayanağı olmayan düşünce ve inançlardır. Bu çalışmanın amacı evli kadınlarda emzirme mitleri ve etkileyen faktörlerin belirlenmesidir.
Gereç ve Yöntem: Araştırma kesitsel tipte tanımlayıcı bir çalışmadır. Araştırma, 1 Mayıs- 1 Temmuz 2024 tarihleri arasında Yozgat Bozok Üniversitesi Araştırma ve Uygulama Hastanesi Polikliniklerinde, polikliniklere herhangi bir sebepten başvuran 18 yaş ve üstü, okuryazar olan ve çalışmaya katılmaya gönüllü olan 576 evli kadın ile yürütülmüştür. Verilerin toplanmasında "Tanıtıcı bilgi formu" ve "Emzirme mitleri ölçeği (EMÖ)" kullanılmıştır. Araştırmada Yozgat Bozok Üniversitesi Sosyal ve Beşeri Bilimler Etik Kurulu'ndan izin alınmıştır (Tarih: 20.03.2024; Karar No: 12/21).
Bulgular: Çalışmaya katılan kadınların yaş ortalaması 39,30±14,10 yıldır. Araştırmaya katılan kadınların %30,9'unun 25-34 yaş aralığında, %24,8'inin lise mezunu, %67,4'ünün çalışmadığı, %70,8'inin çekirdek aile tipinde olduğu belirlenmiştir. Kadınların %38,4'ünün üç ve üzeri sayıda çocuğu olduğu, %%27,4'ünün vajinal doğum yaptığı, %74'ünün emzirme deneyimi yaşadığı, %45,7'sinin emzirirken destek aldığı belirlenmiştir. Kadınların EMÖ puan ortalaması, 81,64±21,62'dir. Yaş, eğitim durumu, güncel çalışma durumu, gelir durumu, gebelik sayısı, yaşayan çocuk sayısı, canlı doğum sayısı, vajinal doğum sayısı, emzirme deneyimi yaşama durumu gibi sosyoedemografik ve obstetrik değişkenlerin emzirme mitlerini anlamlı derecede etkilediği belirlenmiştir ($p<0,05$). Kadınların EMÖ puanları ile aile tipi, yaşanılan yer, sezaryen doğum sayısı, emzirirken destek alma durumları arasında istatistiksel olarak anlamlı bir ilişki bulunmamıştır ($p>0,05$).
Sonuç: Araştırmada evli kadınların emzirme mitlerine sahip olduğu ve emzirme mitlerine sahip olma düzeylerinin düşük olduğu; yaş, eğitim durum, canlı doğum sayısı, vajinal doğum sayısı, emzirme deneyimi yaşama durumu gibi sosyodemografik ve obstetrik değişkenlerin emzirme mitleri üzerinde önemli derecede etkili olduğu belirlenmiştir. Bu kapsamda, evli kadınların emzirme mitlerine ve mitlerin olası zararlarına yönelik bilinçlendirilmesi önerilmektedir.

Anahtar Kelimeler: anne sütü; emzirme; mitler; emzirme mitleri; kadın

Introduction

Breastfeeding is one of the most effective ways to protect child's health (1). The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) emphasize that breast milk is the optimal nutrition for infants, and breastfeeding is crucial in protecting against many common childhood illnesses. Furthermore, initiating breastfeeding within the first hour after birth, exclusively breastfeeding for the first six months, and continuing breastfeeding alongside appropriate complementary foods for at least two years after that are recommended (1, 2). Despite recommendations from both organizations, globally only 46% of newborns start breastfeeding within the first hour, 48% of infants aged 0-5 months are exclusively

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breastfed, and 59% of children aged 12-23 months continue breastfeeding with complementary foods (2, 3). Reasons for not achieving breastfeeding initiation as recommended include maternal employment, health issues for both mother and baby during breastfeeding, individual factors, maternal perceptions of inadequate milk supply, and sociocultural factors (4, 5). Maternal perceptions of inadequate milk supply and sociocultural factors are directly linked to societal myths (5). Myths are incorrect, distorted, or incomplete beliefs without any scientific basis (5, 6). Beliefs such as "colostrum should be expressed and discarded before feeding the baby," "water should be given to the baby after every breastfeeding session," and "a mother's milk in the first few days after birth is insufficient to satisfy the baby" are societal myths that hinder many women from breastfeeding as recommended (6).

It is crucial to identify breastfeeding myths and influencing factors among married women aged 18 and above to ensure effective breastfeeding initiation after birth. No direct studies have been found in the literature regarding our research topic. Existing literature focuses on studies using data collection forms developed by researchers to investigate breastfeeding behaviors, breastfeeding practices, and traditional behaviors related to breastfeeding during pregnancy (7, 8) and the postpartum period (5, 9, 10) among women. This study aims to identify breastfeeding myths and influencing factors among married women aged 18 and above. It is expected that this research will increase awareness about the topic, shed light on protective practices, educational and counseling services related to breastfeeding myths, and contribute to the literature.

Research questions

To what extent do married women have breastfeeding myths?

Do sociodemographic characteristics of married women affect their level of having breastfeeding myths?

Do obstetric characteristics of married women affect their level of having breastfeeding myths?

Material and Methods

The study is a cross-sectional descriptive study conducted between May and July 2024 in Yozgat Bozok University Research and Practice Hospital Outpatient Clinics with married women who applied to outpatient clinics for any reason.

The population of the study consisted of all married women aged 18 years and older who applied to the outpatient clinics of Yozgat Bozok University Research and Practice Hospital for any reason and who agreed to participate in the study. The minimum sample size targeted for this study was calculated as 400 with the help of the Minitap 16 Statistical Package Program (standard deviation: 1.0, difference: 0.15, alpha: 0.05, power of test: 0.85). However, in order to better represent the population, it continued until it came to a halt and the study was completed with 576 women. Interviews with women were conducted in outpatient clinics. After being informed about the subject and purpose of the study, consent was obtained from those who agreed to participate in the study. The data collection form was then filled in by the women themselves under observation. This process took approximately 10-15 minutes.

The inclusion criteria were being 18 years of age or older, being literate, and volunteering to participate in the study. Illiterate women, women under the age of 18, single women, women with perception disorders that prevent communication, women with psychiatric disorders, and married women who refused to participate in the study were not included in the study.

The data for this study were collected using the "Introductory Information Form" and the "Breastfeeding Myths Scale (BMS)". The "Introductory Information Form" was developed by the researchers based on a review of relevant literature. It comprised a total of 17 questions, including sociodemographic details (age, age at marriage, family type, educational status, current employment status, place of permanent residence, income status) (7 questions) and obstetric characteristics (number of pregnancies, number of live births, number of living children, mode of delivery, breastfeeding experience, support received during previous breastfeeding periods, information received about breast milk and breastfeeding before) (10 questions) (5, 9, 10).

The Cronbach's alpha value of the BMS scale, developed by Yilmaz Sezer et al. (6), was determined to be 0.91. The scale consists of 30 items within one dimension, all of which are reverse coded. The minimum possible score on the scale is 30, and the maximum score is 150. Higher scores indicate a greater belief in breastfeeding myths, whereas lower scores indicate fewer beliefs in such myths. Furthermore, the scale's cutoff score was set at 119.50. Therefore, individuals scoring below 119.50 are considered to

have low levels of belief in breastfeeding myths, while those scoring above 119.50 are considered to have high levels of belief in breastfeeding myths (6).

The research data were analyzed using Statistical Package for the Social Sciences (SPSS) version 23.0. The normal distribution of continuous variables was assessed using skewness and kurtosis tests, confirming normality. Continuous variables were presented as mean and standard deviation, while categorical variables were presented as number and percentage.

The Independent Samples T-Test was employed to compare two independent groups, and the one-way ANOVA test was used to compare more than two groups. Additionally, the Games-Howell test was applied to compare two quantitative datasets. A statistical significance level of $p < 0.05$ was adopted.

Results

The mean age of women participating in the study was 39.30±14.10 years. Among the participants, 30.9% were aged 25-34, 24.8% were high school graduates, 67.4% were non-working, 62.8% income equals their expenses, 70.8% belonged to nuclear families, and 59.4% lived in urban districts (Table 1).

Table 1. Distribution of women according to socio-demographic characteristics (n= 576)

Socio-demographic Characteristics		n	%
Age (Mean ± SD)	39.30±14.10		
Age groups	18-24 years	77	13.3
	25-34 years	178	30.9
	35-44 years	148	25.8
	+45 years	173	30.0
Education status	Literate	98	17.1
	Primary School	120	20.8
	Middle School	78	13.5
	High School	143	24.8
	Bachelor's degree and higher	137	23.8
Current employment status	Working	188	32.6
	Non-working	388	67.4
İncome status	Income is less than expenses	129	22.4
	Income equals expenses	362	62.8
	Income exceeds expenses	85	14.8
Family type	Nuclear family	408	70.8
	Extended family	168	29.2
Place of residence	Provincial center / City	144	25.0
	District	342	59.4
	Village	90	15.6

Regarding obstetric characteristics, 38.4% of women had 3 or more children, 34.5% had experienced 3 or more live births, 33.9% had 3 or more living children, 27.4% had vaginal deliveries, 16.8% had cesarean deliveries, 74% had previous breastfeeding experience, 45.7% received support during breastfeeding, and 66.8% received support from healthcare professionals (Table 2).

Table 2. Distribution of obstetric characteristics among women (n= 576)

Obstetric Characteristics		n	%
Number of pregnancies	0	74	12.8
	1	133	23.1
	2	148	25.7
	3 and above	221	38.4
Number of live births	0	100	17.4
	1	137	23.8
	2	140	24.3
	3 and above	199	34.5
Number of living children	0	96	16.7
	1	135	23.4
	2	150	26.0
	3 and above	195	33.9
Vaginal delivery	0	103	17.9
	1	112	19.6
	2	101	17.5
	3 and above	158	27.4
Cesarean section	0	302	52.4
	1	97	16.8
	2	58	10.1
	3 and above	19	3.4
Experience of breastfeeding	Deceased	150	26.0
	Living	426	74.0
Support received for breastfeeding	Received	263	45.7
	Did not receive	213	37.0
Source of support while breastfeeding*	Mother. mother-in-law	218 225	64.7 66.8
	Health worker	59	17.5
	Internet-TV	32	9.5
	Other		

*More than one election was held.

The mean score on the BMS scale for women in the study was 81.64 ± 21.62. Specific mean scores on the BMS scale were as follows: 91.60 ± 25.31 for women aged 45 years and over, 91.61 ± 26.32 for women with primary school education, 86.29 ± 22.83 non-working women, 85.32 ± 25.00 for women with ıncome is less than expenses, 88.61 ± 23.12 for women living in extended families, 82.10 ± 23.81 for women residing in districts, 87.23 ± 23.00 for women with 3 or more children, 86.97 ± 23.58 for those with 3 or more living children, 88.71 ± 25.11 for those with 3 or more vaginal deliveries, 84.31 ± 22.87 for those with 3 or more cesarean deliveries, 82.99 ± 22.46 for women with breastfeeding experience, and 84.45 ± 23.64 for those who received no support during breastfeeding (Table 3).

Discussion

The current study aimed to investigate breastfeeding myths and their influencing factors among married women. Women aged 45 years and above had a higher mean BMS score compared to other age groups. It is thought that this may be due to the fact that the education levels of women aged 45 and over in the study are lower than other groups and that traditional practices for breastfeeding become more

Table 3. BMS score differences according to socio-demographic and obstetric characteristics of women (n= 576)

Variables		BMS		Test değeri	p
		X□	SS		
Age groups	18-24 years (1) 25-34 years (2) 35-44 years (3) +45 years (4)	75.31 77.4719 78.31 91.60	17.60 18.12 18.79 25.31	F=19.535	**p=0.00** 1,2,3-4
Education status	Literate (1) Primary School (2) Middle School (3) High School (4) Bachelor's degree and above (5)	86.37 91.61 83.39 76.73 73.71	20.22 26.32 18.75 17.75 19.16	F=19.535	**p=0.00** 1-4,5; 2-4,5; 3-5
Current employment status	Working (1) Non-working (2)	77.04 86.29	19.68 22.83	F=7.325	**p=0.01**
İncome status	Income is less than expenses (1) Income equals expenses (2) Income exceeds expenses (3)	85.32 81.24 77.72	25.00 20.41 21.13	F=3.351	**p=0.036** 1-3
Family type	Nuclear family Extended family	79.15 88.61	20.49 23.12	t=2.408	p=0.121
Place of residence	Provincial center / City District Village	80.2 82.1 82.1	18.71 23.81 16.73	F=0.401	p=0.670
Number of pregnancy	0 (1) 1 (2) 2 (3) 3 and above (4)	75.93 78.65 78.83 87.23	19.09 19.24 20.39 23.40	F=8.650	**p=0.000** 1,2,3 -4
Number of live births	0 (1) 1 (2) 2 (3) 3 and above (4)	76.68 78.60 80.22 87.22	19.06 18.87 21.52 23.54	F=7.519	**p=0.000** 1,2,3 -4
Number of living children	0 (1) 1 (2) 2 (3) 3 and above (4)	77.61 79.34 79.72 86.97	18.73 19.19 20.69 23.58	F=5.362	**p=0.001** 1,2,3 -4
Number of vaginal births	0 (1) 1 (2) 2 (3) 3 and above (4)	80.07 77.84 82.19 88.71	20.34 17.22 21.65 25.11	F=5.845	**p=0.001** 1,2 -4
Number of cesarean sections	0 (1) 1 (2) 2 (3) 3 and above (4)	83.12 80.23 83.82 84.31	21.96 23.24 20.00 22.87	F=0.526	p=0.665
Experience of breastfeeding	Deceased Living	79.78 82.99	17.74 22.46	t=8.642	**p=0.003**
Receiving support while breastfeeding	Received Did not receive	81.22 84.45	20.52 23.64	t=3.604	p=0.058

BMS: Breastfeeding Myths Scale; F: ANOVA test; t: t test

common as age increases.

In our study, women with primary school education had higher mean BMS scores compared to women with other educational levels. Gölbaşı et al. (5) found that participation in breastfeeding myths was significantly higher among women with secondary school education or below compared to those with high school education or higher. Turan et al. (9) reported that women with primary school education tended to believe and follow traditional breastfeeding practices more than those with high school education. Conversely, Manjapallikkunnel et al. (11) noted that mothers with higher educational qualifications demonstrated better knowledge about breastfeeding. Additionally, Sabo et al. (12) found that women with tertiary education were more likely to practice exclusive breastfeeding for the first six months. On the other hand, In a study conducted with breastfeeding mothers in Kenya (13), it was found that women, including those with primary school education, demonstrated high levels of knowledge and adherence to breastfeeding practices, emphasizing the importance of complementary feeding.

In our study, it was assumed that women with primary

education had inadequate knowledge about breastfeeding and therefore misconceptions acquired from the family or the environment were reinforced or perpetuated. The mean BMS score of non-working women was higher than that of working women. Sabo et al. (12) reported that women who worked and received community support had higher levels of exclusive breastfeeding in the first six months. Şimşek et al. (14) reported that the majority of mothers did not work and that employment status did not influence breastfeeding behaviour. In our study, retired women are in the non-working group. The high age of non-working women suggested that they may have grown up in families with low levels of education. Therefore, it was thought that they may have held false beliefs and their knowledge about breastfeeding may have been inadequate.

In our study, the mean BMS score was higher among those with income is less than expenses and among those living in extended families. Shafaei et al. (15) reported that there was no difference in breastfeeding self-efficacy between those with high, medium and low-income status. It was thought that women with low-income status were non-working, often had low levels of education and therefore low levels of breastfeeding knowledge. It is thought that increased domestic workload and an uncomfortable, crowded environment, which are among the difficulties of living in a large family, reduce breastfeeding experience and increase breastfeeding myths due to misconceptions held by elders.

In our study, the average BMS score of women living in the districts was higher than that of women living in other settlements. It was thought that false beliefs increased in districts, which are smaller settlements compared to provincial centers due to fewer educational opportunities.

In our study, the mean BMS score of those with three or more pregnancies and the mean BMS score of those with three or more living children were found to be higher than the other number of pregnancies. Turan et al. (9) reported that those with three or more living children were more likely to believe in and practice traditional approaches to breastfeeding. A study of breastfeeding mothers in Kenya reported that breastfeeding knowledge and practices were high among women with primary education and one living child (13). According to data from the Turkish Statistical Institute (TÜİK) (16), fertility rates have been declining in our country, and it is assumed that women with three or more children have low levels of education and do not work; therefore, their breastfeeding knowledge is assumed to be low.

In our study, the mean BMS score was higher in women who had three or more normal vaginal deliveries and the mean BMS score was higher in women who had three or more caesarean sections. Women who gave birth vaginally were found to have lower breastfeeding knowledge. Koç et al. (17) reported that 28.9% of mothers who gave birth by caesarean section and 61.0% of those who gave birth normally started breastfeeding in the first two hours after delivery. Ünal and Şenol (18) reported that vaginal or caesarean delivery did not affect the breastfeeding success of pregnant women. Eroğlu et al. (19) found that vaginal delivery increased the breastfeeding rate. In our study, the low breastfeeding rate may be due to the difficulties caused by caesarean delivery, and this situation may affect the breastfeeding experience and perpetuate false beliefs. Given the possibility that vaginal births are more common among those who give birth frequently, and that the education level of those who give birth frequently is low, as mentioned above, it is likely that their breastfeeding knowledge is low.

In our study, the mean BMS score of women who had breastfeeding experience was higher than the mean score of women who did not receive breastfeeding support. Sabo et al. (12) reported that women who received support from their communities had higher levels of exclusive breastfeeding in the first six months. Eroğlu et al. (19) found that spousal support increased breastfeeding rates. Postpartum mothers need support to adapt to new roles and to reduce their workload. In this case, it was thought that meeting the need for support would facilitate the mother's breastfeeding process and help her to do more research and learn from the health worker by finding time for herself. The mean BMS score of the women in the study was 81.64±21.62. The increase in the women's mean score showed that they believed more in breastfeeding myths. In our study, women's belief in breastfeeding myths was found to be low.

Limitations

As the study was conducted in Yozgat province, the results are only for the women included in the study and cannot be generalised to all women.

Conclusion and Recommendations

It was found that married women had breastfeeding myths and their level of breastfeeding myths was low; the variables of age, educational status, current employment status, income status, number of pregnancies, number of live births, number of living children, number of vaginal deliveries and breastfeeding experience had a significant effect on breastfeeding myths. Therefore, it is recommended that breastfeeding myths be included in maternal and child health education and that women and families be made aware of the potential harm of myths.

Acknowledgment

We thank all the women who participated in the study.

Ethical aspects of the research

Approval was received from Yozgat Bozok University Social and Human Sciences Ethics Committee to conduct the research (Date: 20.03.2024; Decision No: 12/21). Institutional approval from Yozgat Bozok University Research and Application Hospital was also obtained from the Chief Physician (Date: 29.04.2024; Number: 1692). Additionally, informed consent was obtained from all women participating in the study, and all principles of the Declaration of Helsinki were followed in the research.

References

1. World Health Organization (WHO). Breastfeeding. https://www.who.int/health-topics/breastfeeding#tab=tab_1 (Accessed 26 April 2024).

2. United Nations International Children's Emergency Fund (UNICEF). Breastfeeding. https://data.unicef.org/topic/nutrition/breastfeeding/#:~:text=From%20birth%20to%206%20months,no%20matter%20where%20they%20live (Accessed 16 April 2024).

3. UNICEF global databases, 2023, based on MICS, DHS and other nationally representative sources.

4. Balogun OO, Dagvadorj A, Anigo KM, Ota E, Sasaki, S. Factors influencing breastfeeding exclusivity during the first 6 months of life in developing countries: a quantitative and qualitative systematic review. Matern Child Nutr 2015; 11:433-451. doi: 10.1111/mcn.12180

5. Gölbaşı Z, Eroğlu K, Kaya D. Doğum yapan kadınların anne sütü ve emzirme mitlerine inanma durumlarının belirlenmesi. KOU Sag Bil Derg 2018; 4(2):32-43. doi: 10.30934/kusbed.402892

6. Yilmaz Sezer N, Aker MN, Gönenç İM, Topuz, Ş. Development of the breastfeeding myths scale. Breastfeed Med 2024; 19(1):40-46. doi: 10.1089/bfm.2023.020

7. Sámano R, Lara-Cervantes C, Martínez-Rojano H, Chico-Barba G, Sánchez-Jiménez B, Lokier O, et al. Dietary knowledge and myths vary by age and years of schooling in pregnant mexico city residents. Nutrients 2020; 12(2):362. doi: 10.3390/nu12020362

8. Abdalla M, Zein MM, Sherif A, Essam B, Mahmoud H. Nutrition and diet myths, knowledge and practice during pregnancy and lactation among a sample of Egyptian pregnant women: a cross-sectional study. BMC Pregnancy Childbirth 2024; 24(1):1-9. doi: 10.1186/s12884-024-06331-3

9. Turan A, Kutlu L. Bebeklerin ilk emzirilmesinde geleneksel yaklaşımların etkisinin değerlendirilmesi. Haliç Üniv Sağ Bil Der 2020; 3(1):53-64.

10. Güner Ö, Koruk F. Şanlıurfa'da 0-6 aylık bebeklerin sadece anne sütü alma durumları ve etkileyen faktörler. Harran Univ Tıp Fak Derg 2019; 16(1):111-116.

11. Manjapallikkunnel SR, Nair ANK, Sujatha C. Knowledge, attitude and practices among mothers of ınfants regarding breastfeeding. J Family Reprod Health 2023; 17(3):136-141. doi: 10.18502/jfrh.v17i3.13536

12. Sabo A, Abba J, Sunusi Usman U, Musa Saulawa I, Alzoubi MM, Al-Mugheed K, et al. Knowledge, attitude, and practice of exclusive breastfeeding among mothers of childbearing age. Front Public Health 2023; 11:1277813. doi: 10.3389/fpubh.2023.1277813.

13. Uusimäki K, Schneider L, Lubeka C, Kimiwye J, Mutanen M. Mothers' knowledge and practices on breastfeeding and complementary feeding in an urban slum area and rural area in Kenya: A cross-sectional interview study. J Child Health Care 2023; 27(4):612-627. doi: 10.1177/13674935221083451.

14. Şimşek A, Balkan E, Çalışkan E, Genç R. Annelerin emzirme öyküleri ve emzirme davranışlarının incelenmesi: Bir Türkiye örneği. J Midwifery and Health Sci 2021; 4(3):222-231.

15. Shafaei FS, Mirghafourvand M, Havizari S. The effect of prenatal counseling on breastfeeding self-efficacy and frequency of breastfeeding problems in mothers with previous unsuccessful breastfeeding: a randomized controlled clinical trial. BMC Womens Health 2020; 5;20(1):94. doi: 10.1186/s12905-020-00947-1.

16. Türkiye İstatistik Kurumu (TÜİK). 2022. Adrese Dayalı Nüfus Kayıt Sistemi Sonuçları.

17. Koç Ö, Özkan H, Sidar N, Can D. Annelerin emzirme koçluğu hakkındaki bilgi, görüş ve tutumlarının değerlendirilmesi. J Contemp Med 2017; 7(2):175-183.

18. Ünal E, Şenol DK. Primipar annelerde doğum şeklinin doğum sonu konfor ve emzirme başarısına etkisi. Ordu University J Nurs Stud 2022; 5(2):158-165.

19. Eroğlu N, Akbaş DB, Göçmen H, Darıcı H, Arman Ö, Boyar R. İnegöl'de yaşayan kadınların anne sütü farkındalığını ve emzirmeyi etkileyen faktörler. TJTFP 2023; 14(4):223-233.

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ORIGINAL ARTICLE

Preventable Cause of Vision Loss: Demographic and Clinical Findings of Penetrating Eye Injuries

Önlenebilir Bir Görme Kaybı Nedeni: Delici Göz Yaralanması Olgularının Demografik ve Klinik Bulguları

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ABSTRACT

Background/Aims: To raise awareness about the preventability of penetrating eye injuries and contribute to the implementation of appropriate protective measures by identifying the causes and risk factors of such injuries.
Methods: The files of patients admitted to the Department of Ophthalmology due to penetrating eye injuries and undergoing repair for penetrating eye injuries between 2019 and 2023 were retrospectively reviewed. Patients' age, gender, the location where the trauma occurred, the incident causing the injury, the presence of a foreign body in the eye after the injury, and the need for repeated surgeries were examined, and the follow-up periods of the patients were recorded.
Results: A total of 107 patient files were included in the study. Of 107 patients, 82.24% (n=88) were male, and 17.76% (n=19) were female. The average age of the patients was 33.5 years, with a minimum age of one year and a maximum age of 86. The median age was 30.5 years. Among the patients, 29.91% (n=32) were under the age of 18. The most common trauma location was outdoor/garden/street at 41.12% (n=44), followed by the workplace at 25.23% (n=27) and home at 23.36% (n=25). Among the causes of trauma, metal objects were the leading cause at 23.36% (n=25), followed by natural objects like wood, stone, and tree branches at 14.95% (n=16), and cutting/piercing tools at 11.21% (n=12). The most frequent injuries were corneal injuries (n=43) (40.19%). Thirty-seven patients required additional surgery, with the most common second surgery being cataract surgery (n=22) (20.56%). A foreign body inside the eye was detected in 24 patients.
Conclusions: Penetrating eye injuries are a significant cause of preventable vision loss. Public education, raising awareness, early intervention methods, and encouraging the use of protective equipment are critically important in preventing these injuries.

Keywords: Eye health, penetrating eye injuries, preventable vision loss, protective eyewear

ÖZ

Amaç: Delici göz yaralanmalarının önlenebilirliği konusundaki farkındalığı artırmak ve bu tür yaralanmaların nedenlerini ve risk faktörlerini belirleyerek, uygun koruyucu tedbirlerin alınmasına katkıda bulunmaktır.
Gereç-Yöntem: 2019-2023 yılları arasında Selçuk Üniversitesi Tıp Fakültesi Hastanesi Göz Hastalıkları Kliniğine delici göz yaralanması nedeniyle başvurarak delici göz yaralanması tamiri yapılan hastaların dosyaları retrospektif olarak tarandı. Hastaların yaşı, cinsiyeti, travmanın gerçekleştiği yer ve yaralanmaya neden olan olay, göz içinde yaralanma sonrası yabancı cisim varlığı ve tekrarlayan ameliyat ihtiyaçları olup olmadığı incelenerek hastaların takip süreleri kaydedildi.
Bulgular: Toplamda 107 hasta dosyası çalışmaya dahil edildi. Hastaların %82,24'ü (n=88) erkek, %17,76'sı (n=19) kadındı. Hastaların ortalama yaşı 33,5 yıl olup, minimum yaş 1 ve maksimum yaş 86 idi; medyan yaş ise 30,5 yıl olarak kaydedildi. Hastaların %29,91'i (n=32) 18 yaşın altındaydı. En sık travma yeri dış ortam/bahçe/sokak %41,12 (n=44) olup bunu sırası ile iş yeri %25,23 (n=27) ve ev %23,36 (n=25) takip ediyordu. Travma nedenleri arasında metal nesneler %23,36 (n=25), odun, taş ve ağaç dalı gibi doğal nesneler %14,95 (n=16), kesici/delici aletler %11,21(n=12) ilk sırada geliyor idi. En sık yaralanmalar kornea (n=43, %40,19) yaralanmaları idi. 37 hastada ek ameliyata ihtiyaç duyulmuştu ve en sık yapılan ikinci ameliyat katarakt (n=22, %20,56) ameliyatı idi. 24 hastada göz içinde yabancı cisim tespit edilmişti.
Sonuç: Penetran göz yaralanmaları, önlenebilir görme kayıplarının önemli nedenlerindendir. Toplum eğitimi, farkındalığın artırılması, erken müdahale yöntemleri ve koruyucu ekipman kullanımının teşvik edilmesi, bu yaralanmaların önlenmesinde kritik öneme sahiptir.

Anahtar kelimeler: Göz sağlığı, penetran göz yaralanmaları, önlenebilir görme kaybı, koruyucu gözlük

Introduction

Eye injuries, particularly penetrating eye injuries, are significant causes of vision impairment and loss, which adversely affect quality of life and increase workforce loss (1). As a leading cause of preventable unilateral blindness, these injuries represent a major public health issue worldwide (2). Penetrating eye injuries are especially prevalent among children, industrial workers, and victims of traffic accidents. Despite advancements in diagnosis and treatment, these injuries continue to pose serious social and economic challenges (3). The impact of these injuries extends beyond physical health, significantly affecting psychological and emotional well-being. The long-term treatment processes and the need for recurrent surgeries following an injury severely

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compromise patients' quality of life. Additionally, the economic burden of these injuries is substantial. Treatment costs, loss of productivity, and patients' rehabilitation processes impose significant strains on both individuals and healthcare systems.

Materials and Methods

Ethics

This study received approval from the Local Ethics Committee of Selcuk University Faculty of Medicine (12.03.2024 2024/155).

Participants

Records of patients who presented to the Department of Ophthalmology with penetrating eye injuries and underwent repair between 2019 and 2023 were retrospectively reviewed. Data collected included the patient's age, gender, location and cause of injury, presence of intraocular foreign bodies, need for additional surgeries, and follow-up durations.

Statistical analysis

Data analysis was performed using SPSS (version 22.0 IBM Corp. Armonk, NY, USA), with basic descriptive statistics reported as frequencies, percentages, mean ± standard deviation, and median (interquartile range). The chi-square test was used to compare categorical parameters.

Results

The patients were 82.24% male (n=88) and 17.76% female (n=19). The average age of the patients was 33.5 years, with a minimum age of 1 and a maximum age of 86; the median age was 30.5 years (Figure 1). Among the patients, 29.91% (n=32) were under the age of 18. The left eye (n=63) was more frequently affected than the right eye (n=44). The annual distribution of the total 107 patients was as follows: 23 in 2019, 15 in 2020, 18 in 2021, 21 in 2022, and 30 in 2023. Although there were fewer admissions in 2020, the pandemic year, the difference in admission numbers between 2020 and other years was not statistically significant (p=0.256).

The most common trauma location was the outdoor environment/garden/street (41.12%, n=44), followed by the workplace (25.23%, n=27) and home (23.36%, n=25) (Figure 2). Among the causes of trauma, metal objects (23.36%, n=25), natural objects like wood, stone, and tree branches (14.95%, n=16), and sharp/piercing tools (11.21%, n=12) were the most common (Figure 3). For patients under 18 years of age, the most common trauma location was the outdoor environment/garden/street (n=14, 43.75%). In this age group, the leading cause of trauma was natural objects (n=7, 21.875%). For patients aged 18 and over, the most common trauma location was the outdoor environment/garden/street, and the leading cause of trauma was metal objects (n=25, 28.38%). In this age group, 39.19% (n=29) of the patients experienced trauma in the outdoor environment/garden/street, and 32.43% (n=24) experienced trauma in the workplace.

During the strict lockdown period in our country from March 2020 to June 2021, a detailed examination of trauma cases revealed diverse locations and causes of ocular injuries. Most traumas occurred outdoors (12 cases), followed by incidents at home (8 cases), and at workplaces (3 cases), with 2 cases from unspecified locations. The causes included natural objects such as stones and branches (6 cases), sharp or penetrating objects like knives and nails (5 cases), and other objects such as hose ends and bottle caps (3 cases). Additionally, falls and impacts, including traffic accidents, accounted for 4 cases, while there was 1 case involving a firearm, 2 cases caused by metal objects, 2 by glass objects, and 1 case of

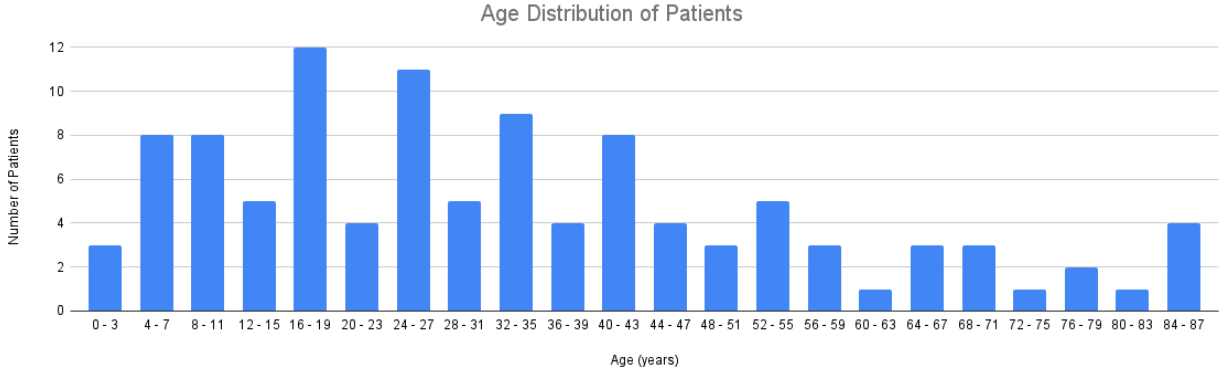

Figure 1. Distribution of patient ages. The average age of the patients was 33.5 years, with a minimum age of 1 and a maximum age of 86. The median age was 30.5 years.

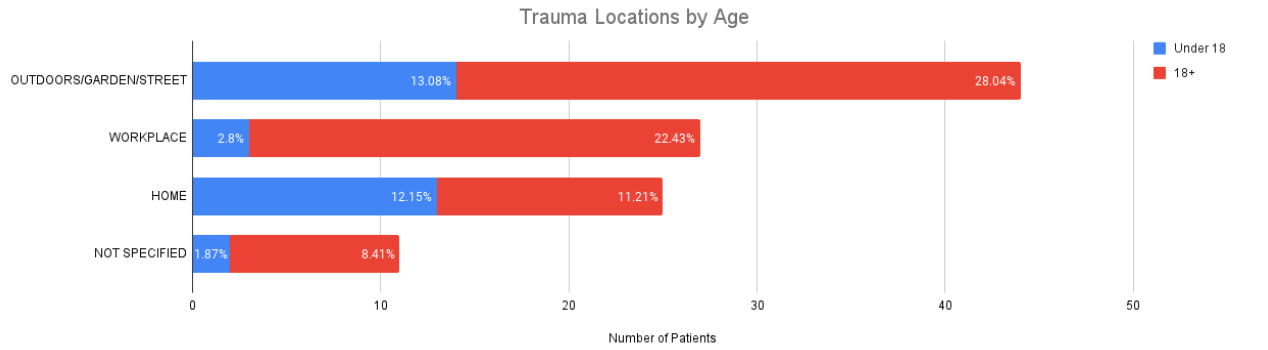

Figure 2. Trauma locations among patients. The most common trauma location was the outdoor environment/garden/street (41.12%, n=44), followed by the workplace (25.23%, n=27) and home (23.36%, n=25).

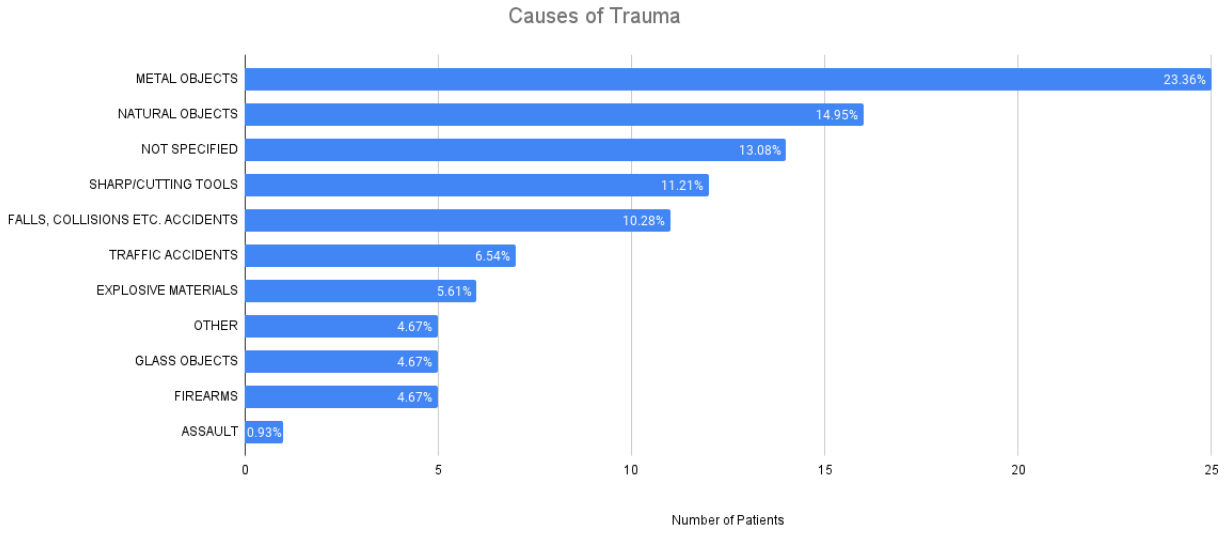

Figure 3. Causes of trauma among patients. The most common causes of trauma were metal objects (23.36%, n=25), natural objects like wood, stone, and tree branches (14.95%, n=16), and sharp/piercing tools (11.21%, n=12).

assault. The initial best corrected visual acuity (BCVA) of the patients was 1.6 logMAR, while the final BCVA improved to 1.0 logMAR. Of the 107 patients, 30 (28%) had a final visual acuity below the legal blindness threshold of 20/200.

Based on the available records, ocular trauma scores (OTS) could be definitively calculated for 9 patients. Among these, the OTS correlated with the final visual acuity in 7 patients. For the two remaining patients with an OTS score of 2, the final visual acuity was found to be 1.0 logMAR in one case and 0.4 logMAR in the other.

The most common injuries were corneal injuries (n=43, 40.19%) (Image 1). Thirty-seven patients required additional surgery, with cataract surgery being the most common second surgery (n=22, 20.56%). Foreign bodies were detected inside the eye in 24 patients. The average follow-up period for the patients was 178 days.

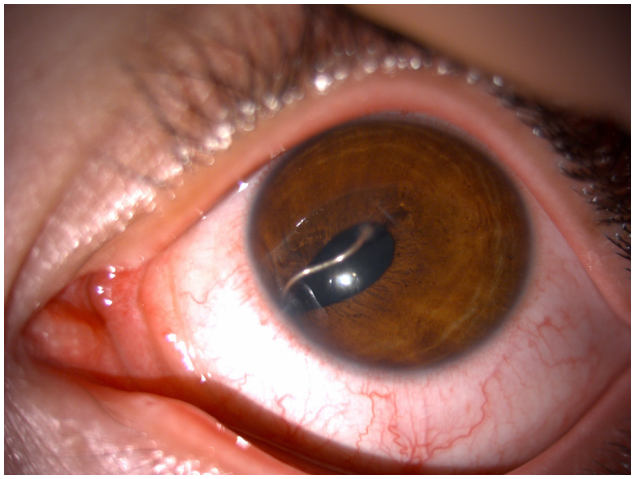

Image 1. Anterior segment photograph of a patient with corneal injury and a metallic foreign body in the anterior chamber. The image demonstrates the extent

of the corneal injury as well as the position of the foreign object, highlighting the severity of the trauma.

Discussion

Vision loss due to eye injuries accounts for 8-10% of all visual impairments and 5% of severe vision losses (4). Although eye injuries are not fatal, they can cause permanent visual impairment and are a significant cause of hospital admissions, especially in developing countries (5). It is estimated that annually, 55 million eye injuries occur, leading to more than one day of activity restriction, 750,000 cases require hospitalization, and 200,000 cases are due to penetrating eye injuries (6).

In a multicenter study including patients over 65 years old followed for ocular trauma, the most common occupations among injured males were farming (38.5%) and trade (26.9%), while 15.4% were retired. Among females, 59.3% were merchants, and 25.9% were housewives (7). Penetrating eye injuries were more common in males and the working-age population in our study.

In children, potentially preventable ocular trauma continues to be a significant cause of visual morbidity. Estimates using global population data show that 160,000 to 280,000 children under 15 years of age experience ocular trauma severe enough to require hospitalization each year (8). Although fewer articles focus on ocular trauma in children, injuries in this age group are more often preventable (9) and also more severe (10). In our study, 29.91% of the patients were under 18 years old.

A study examining ocular trauma patients during the pandemic found that the mechanisms of ocular trauma, injury locations, and demographic characteristics changed significantly during the pandemic, and eye injuries decreased in children during the total lockdown period in 2020 due to the absence of street, school, and sports activities (11). In our study, despite the decrease in admission numbers during the pandemic period, this decrease was not statistically significant compared to other years. The detailed analysis of trauma cases during the strict lockdown period from March 2020 to June 2021 provides valuable insights into the patterns of ocular injuries in our population. Notably, the majority of traumas occurred outdoors, likely reflecting increased engagement in activities such as gardening or other outdoor tasks during lockdowns when other forms of recreation were restricted. The significant number of incidents at home also underscores the role of domestic environments in injury occurrence during this period, possibly due to prolonged home confinement and engagement in household tasks. The presence of falls, traffic accidents, and other unintentional injuries further highlights the unpredictable nature of trauma, even during periods of limited mobility. Interestingly, there were also cases involving metal and glass objects, reflecting the potential risks associated with everyday household and workplace items. Understanding these trauma patterns is critical for developing targeted prevention strategies and safety guidelines, especially in times of restricted movement such as during a pandemic.

Identifying risk factors for eye trauma and taking necessary precautions is crucial due to the preventable nature of vision loss. In this study, 28% (n=30) of the patients had a final visual acuity below the legal blindness threshold of 20/200. The best treatment for occupational open-eye injuries is prevention. Most of these injuries can be prevented by the proper use of protective eyewear or other protective equipment. Numerous studies have demonstrated that the use of protective eyewear in the workplace prevents eye injuries (12, 13). Additionally, even the requirement for workers to use eye protection reduces the risk of eye injury (12).

A study analyzing the USEIR data reported that the majority of injured eyes achieved functional visual acuity levels with appropriate surgical and medical intervention. Prescription glasses and even non-prescription sunglasses provide measurable protection, resulting in fewer severe eye injuries among those wearing glasses (14). Another implied factor is that worker fatigue is a significant cause of occupational eye injuries. A previous study showed that the timing of injuries peaked twice during the workday, with most injuries occurring either before lunch or towards the end of the day (13).

To address the study limitations, several factors must be considered. First, the retrospective nature of the data collection may have introduced selection bias, as only cases that were treated and recorded in the hospital system were analyzed, potentially overlooking milder cases of ocular trauma that did not seek medical attention. Additionally, the study was conducted at a single center, which limits the generalizability of the findings to other populations or regions. Another limitation is the incomplete data regarding ocular trauma scores (OTS), as not all patients had OTS values available, which may affect the accuracy of the

correlation analysis between OTS and visual outcomes. Interestingly, two patients with low OTS scores still had relatively good visual outcomes, which could be attributed to early intervention and appropriate treatment, or the nature of their injuries being less severe than initially anticipated. This highlights the fact that while OTS is a valuable prognostic tool, individual patient factors and timely management play critical roles in recovery. Furthermore, the information on trauma causes and locations was sometimes incomplete, with some cases lacking precise details. The pandemic itself also created a unique context in which behavioral patterns, healthcare accessibility, and reporting mechanisms were affected, making it challenging to generalize these findings to non-pandemic periods. Lastly, we were unable to control for other variables such as pre-existing eye conditions or socio-economic factors that could have influenced trauma susceptibility.

Penetrating eye injuries are a significant cause of preventable vision loss. Social education, increasing awareness, adopting early intervention methods, and promoting the use of protective equipment are necessary for preventing eye injuries, especially at home and in the workplace. Future studies could allow for more personalized prevention strategies by examining injury patterns in different demographic groups in more detail.

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Declaration of Conflicting Interests

The authors declare that there is no conflict of interest.

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Author Contributions

Conception, E.T.K.; design, E.T.K., N.E.A., H.S.K., E.K., H.Y., H.U., C.D., M.B.A., E.A., A.O., A.E.U., F.B., E.E.; supervision, E.T.K.; resource, E.T.K.; materials, E.T.K., N.E.A., H.S.K., E.K., H.Y., H.U., C.D., M.B.A., E.A., A.O., A.E.U., F.B., E.E.; data collection and/or processing, E.T.K., N.E.A., H.S.K., E.K., H.Y., H.U., C.D., M.B.A., E.A., A.O., A.E.U., F.B., E.E.; analysis and/or interpretation E.T.K., N.E.A., H.S.K., E.K., H.Y., H.U., C.D., M.B.A., E.A., A.O., A.E.U., F.B., E.E.; literature review, E.T.K., N.E.A., H.S.K., E.K., H.Y., H.U., C.D., M.B.A., E.A., A.O., A.E.U., F.B., E.E.; writer, E.T.K.; critical review, E.T.K.

References

1.Sönmez A, Mesci C, Arı Yaylalı S, Horoz H, Erbil HH. Perforan göz yaralanmalarının epidemiyolojik değerlendirmesi. Göztepe Tıp Dergisi. 2007;21(3):92-94.

2.Thylefors B. Epidemiological patterns of ocular trauma. Aust N Z J Ophthalmol. 1992;20(2):95-98.

3.Sternberg P, Aaberg TM. The persistent challenge of ocular trauma. Am J Ophthalmol. 1989;107(4):421-424.

4.Kuhn F, Mester V, Witherspoon CD, Morris R, Maisiak R. Epidemiology and socioeconomic impact of ocular trauma. In: Alfaro DV III, Liggett PE, eds. Vitreoretinal surgery of the injured eye. Philadelphia: Lippincott-Raven; 1999. p. 17-24.

5.Wong TY, Tielsh JM. Epidemiology of ocular trauma. In: Tasman W, Jaeger EA, eds. Duane's clinical ophthalmology. Philadelphia: Lippincott Williams and Wilkins; 1999. p. 1-13.

6.Glynn RJ, Seddon JM, Berlin BM. The incidence of eye injuries in New England adults. Arch Ophthalmol. 1988;106(6):785-789.

7.Onakpoya OH, Adeoye A, Adeoti CO, Ajite K. Epidemiology of ocular trauma among the elderly in a developing country. Ophthalmic Epidemiol. 2010;17(5):315-320.

8.Abbott J, Shah P. The epidemiology and etiology of pediatric ocular trauma. Surv Ophthalmol. 2013;58(5):476-485.

9.Coody D, Banks JM, Yetman RJ, Musgrove K. Eye trauma in children: epidemiology, management, and prevention. J Pediatr Health Care. 1997;11(4):182-188.

10.Macewen CJ. Eye injuries: a prospective survey of 5671 cases. Br J Ophthalmol. 1989;73(11):888-894.

11.Akova Budak B, Kıvanç SA. Türkiye'nin En Çok Endüstrileşmiş Bölgesinde Pandemi Döneminde Oküler Travma Sebebi ile Acile Başvuran Hastaların Özellikleri. Uludağ Tıp Derg. 2021;47(1):43-8.

12.Yu TSI, Liu H, Hui K. A case-control study of eye injuries in the workplace in Hong Kong. Ophthalmology. 2004;111(1):70-74.

13.Chen S-Y, Fong P-C, Lin S-F, Chang C-H, Chan C-C. A case-crossover study on transient risk factors of work-related eye injuries. Occup Environ Med. 2009;66(8):517-522.

14.Kuhn F, Mester V, Berta A, Morris R. Epidemiology of serious ocular trauma. The United States Eye Injury Registry (USEIR) and the Hungarian Eye Injury Registry (HEIR). Ophthalmology. 1998;95(5):332-343.

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ORIGINAL ARTICLE

Evaluation of Ischiofemoral and Quadratus Femoris Spaces, Quadratus Femoris Muscle Signal in Ischiofemoral Impingement Syndrome by Magnetic Resonance Imaging

Manyetik Rezonans Görüntüleme ile İskiofemoral Sıkışma Sendromunda İskiofemoral ve Quadratus Femoris Boşlukları, Quadratus Femoris Kas Sinyalinin Değerlendirilmesi

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ABSTRACT

Aim: Ischiofemoral impingement (IFI) syndrome is the presence of pressure and edema findings in the quadratus femoris muscle due to the narrowing of the space between the ischial tuberosity and lesser trochanter. We aimed to recognize the deformation or edema of the quadratus femoris muscle in IFI syndrome, measure the ischiofemoral space (IFS), and width of quadratus femoris space (QFS), and compare between the case and control groups.
Material and Methods: In this retrospective study, hip MRIs of 100 patients, 50 with IFI syndrome and 50 in the control group were evaluated. IFS, QFS, and quadratus femoris muscles were evaluated in the hip MRIs of patients. Edema and fatty atrophy in the quadratus femoris muscle were categorized into four grades. Differences in IFS, QFS, quadratus femoris muscle edema, and fatty infiltrations between both groups were evaluated.
Results: Mean IFS and QFS in the case group were significantly smaller than in the controls. There was a statistically significant difference between both groups (p <0.001). Also, female IFS and QFS widths were smaller than male IFS and QFS widths; there was a statistically significant difference between both groups (p <0.001). There was a strong positive (r=0.933) and significant (p <0.001) correlation between IFS and QFS. There was a statistically significant difference in the ischiofemoral and quadratus femoris distances between the control group with no edema and fatty atrophy in the quadratus femoris muscle and the case group with varying degrees of edema and fatty atrophy (p <0.001).
Conclusions: Narrowing of the ischiofemoral and quadratus femoris distances causes impingement in the quadratus femoris muscle and is a cause of posterior hip pain. The examination of MRI can provide reliable information to evaluate the ischiofemoral impingement syndrome.

Keywords: Ischiofemoral impingement, ischiofemoral space, quadratus femoris muscle, quadratus femoris spaces

ÖZ

Amaç: İskiofemoral sıkışma (İFS) sendromu, iskiyal tüberozite ile küçük trokanter arasındaki boşluğun daralması nedeniyle quadratus femoris kasında basınç ve ödem bulgularının varlığıdır. Amacımız, İFS sendromunda quadratus femoris kasının deformasyonunu veya ödemini tanımak, iskiofemoral mesafe (İFM), quadratus femoris mesafesinin (QFM) genişliğini ölçmek ve kontrol grubuyla karşılaştırmaktır.
Gereç ve Yöntemler: Bu retrospektif çalışmada, 50'si İFS sendromlu ve 50'si kontrol grubunda olmak üzere 100 hastanın kalça MRG'leri değerlendirildi. Hastaların kalça MRG'lerinde İFM, QFM ve quadratus femoris kasları değerlendirildi. Quadratus femoris kasındaki ödem ve yağlı atrofi dört derece olarak kategorize edildi. İki grup arasındaki İFM, QFM, quadratus femoris kas ödemi ve yağlı infiltrasyonlardaki farklılıklar değerlendirildi.
Bulgular: Vaka grubunda ortalama İFM ve QFM, kontrol grubundan anlamlı derecede daha küçüktü. İki grup arasında istatistiksel olarak anlamlı bir fark vardı (p <0,001). Ayrıca, kadın İFM ve QFM genişlikleri erkek İFM ve QFM genişliklerinden daha küçüktü; 2 grup arasında istatistiksel olarak anlamlı bir fark vardı (p <0.001). İFM ve QFM arasında güçlü bir pozitif (r=0.933) ve anlamlı (p <0.001) korelasyon vardı. Quadratus femoris kasında ödem ve yağlı atrofi olmayan kontrol grubu ile değişen derecelerde ödem ve yağlı atrofi olan vaka grubu arasında iskiofemoral mesafe ve quadratus femoris mesafelerinde istatistiksel olarak anlamlı bir fark vardı (p <0.001).
Sonuçlar: Sonuç olarak, İFM ve QFM daralması, quadratus femoris kasında sıkışmaya neden olur ve posterior kalça ağrısının bir nedenidir. MRI incelemesi, İFS sendromu değerlendirilmesi için güvenilir bilgiler sağlayabilir.

Anahtar Kelimeler: İschiofemoral boşluk, iskiofemoral sıkışma, quadratus femoris boşluğu, quadratus femoris kası

Introduction

Ischiofemoral impingement (IFI) syndrome is an independent cause of posterior hip pain and has an increasing incidence. IFI syndrome was first identified in 1977 in three individuals complaining of hip pain after hip surgery (1). Resection of the lesser trochanter relieved the IFI symptoms in these three cases (1). IFI is the term used to describe the narrowing of the quadratus femoris space (QFS), which is the shortest distance between the hamstring tendons and the medial cortex of the lesser trochanter of the femur, or the ischiofemoral space (IFS), which is the shortest distance between the lateral cortex of the ischial tuberosity

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and the medial cortex of the lesser trochanter of the femur. This results in edema and a chronic injury of the quadratus femoris muscle (QFM) (2, 3). It is frequently seen in middle-aged women and less common in men. In 25–40% of the cases, both hips are affected (4). Patients may exhibit hip or groin discomfort, as well as hip snapping, locking, or crepitus. Pain may sometimes radiate to the posterior thighs and knees (5, 6). Magnetic resonance imaging (MRI) revealed IFS shortening and compression in a patient with hip discomfort with no prior medical history of trauma or surgery (7). Although it may seem rare, IFS is more common than expected (2). Therefore, it is necessary to better understand the relevant anatomical features of IFI syndrome and to carefully examine this region on MRI so as not to miss the diagnosis and for appropriate treatment. To identify the signal changes of the QFM in patients with IFI syndrome, we measured and compared the IFS and QFS distances on MRI between normal subjects and patients with IFI syndrome.

Materials And Methods

Approval was obtained from the local clinical research ethics committee (File number: 2024/529).

Patients' Selection

In this retrospective study, hip MRIs of a total of 36 male and 64 female patients over 18 years of age between April 2023 and September 2024 were evaluated. Exclusion criteria were listed as patients with non-diagnostic MRI images, patients with a history of trauma or surgery, rheumatological diseases, and metal implants. A total of four patients were excluded from the study due to the following reasons: one was non-diagnostic due to artifact, one had material causing postoperative metallic artifact, and two patients had metastatic lesions in the pelvic bones.

MRI Protocol

MRI of the hip was performed in the supine position without sedation or intravenous contrast administration by using 3T MRI (Skyra, Siemens Healthcare, Erlangen, Germany) and 1.5 T (Aera, Siemens Healthcare, Erlangen, Germany) MRI scanners. The routine hip MRI protocol in our institute is coronal PDWI-FS (TR 4600 milliseconds, TE 40 milliseconds), NEX 2–4 times, FOV 200 mm × 250 mm, layer thickness 4 mm, matrix 320 × 200; coronal TSE-T1WI (TR 900 milliseconds, TE 10 milliseconds), NEX 2–4 times, FOV 200 mm × 250 mm, layer thickness 4 mm, matrix 320 × 200; axial PDWI-FS (TR 4600 milliseconds, TE 40 milliseconds), NEX 2–4 times, FOV 200 mm × 200 mm, layer thickness 4 mm, matrix 320 × 220; sagittal PDWI-FS (TR 3200 milliseconds, TE 30 milliseconds), NEX 2–4 times, FOV 200 mm × 200 mm, layer thickness 4 mm, matrix 320 × 220. Every image was sent in DICOM format to a picture archiving and communication system (PACS) for subsequent measurement.

MRI Evaluation

The images were analyzed by two radiologists in the same session by consensus. Measurements were made with the MRI device software. IFS, QFS, and QFM were evaluated in the hip MRIs of the patients.

Image analyses and Measurements

IFS, QFS, and QFM edema were evaluated in axial fat-suppressed PD images.

IFS: Minimum distance from the lateral cortex of the ischial tubercle to the medial cortex of the lesser trochanter of the femur.

QFS: The shortest distance between the most lateral border of the hamstring tendon and the medial part of the lesser trochanter.

Four grades of QFM edema were identified:

Grade 0 (normal), the normal signal of QFM.

Grade 1 (mild), edema in QFM is limited to the ischiofemoral distance.

Grade 2 (moderate), edema in QFM extends beyond the ischiofemoral distance but is still limited to QFM.

Grade 3 (severe), edema in QFM has affected the adjacent soft tissues.

Fatty infiltration in QFM was examined in coronal T1W sequences by dividing into four grades as follows:

Grade 0, normal muscle signal

Grade 1 (mild), the small linear fat signal intensity between muscle fibers,

Grade 2 (moderate), fat signal intensity covering <50% of the muscle,

Grade 3 (severe), fat signal intensity covering >50% of the muscle,

Those with edema in QFM on fat-suppressed PD MRI sequence (grades 1, 2, and 3) were evaluated as the IFI syndrome. The same measurements were made on the hip joint MRI with a normal QFM signal (grade 0) and accepted as the control group. The differences between the IFS, QFS, and QFM signals, and fat

infiltrations were evaluated between the two groups.

Statistical analysis

The Statistical Package for Social Sciences software was used for all procedures (SPSS, Version 22.0, IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov, Shapiro-Wilk test, histogram, and Q-Q plots were used to determine the normality distribution of scale variables. For continuous numerical variables, descriptive statistics are presented as mean±standard deviation. Categorical variables are represented by the number of cases and percent. The Chi-square test was used to compare categorical variables, and the ANOVA test was used to compare continuous numerical variables. The Pearson correlation test was used to analyze the correlation between numeric measurements. Unless otherwise specified, the results were deemed statistically significant at $p < 0.05$.

Results

There were 100 hip MRIs in our study, 50 in the case group and 50 in the control group. The case group included 40 females and 10 males, aged 27 to 76 years, with a mean age of 55±13. The control group included 24 females and 26 males, aged 20 to 68 years, with a mean age of 46±14.

While the mean widths of IFS and QFS in the case group were 9.06±2.18 mm and 5.46±2.33 mm, respectively, they were 23.13±4.41 mm and 16.71±4.46 mm in the control group, respectively. The mean IFS and QFS in the case group were significantly smaller than in the control group (table 1). There was a statistically significant difference between the two groups ($p < 0.001$). Also, female IFS and QFS widths (13.90±6.96 mm, 9.06±5.45 mm) were smaller than male IFS and QFS widths (19.98±7.96 mm, 14.67±7.17 mm); there was a statistically significant difference between the two groups ($p < 0.001$) (Table 1). There was a strong positive ($r=0.933$) and significant ($p < 0.001$) correlation between IFS and QFS.

Table 1. General MRI features between case and control groups, and males and females

	Age (years)	IFS (mm)	QFS (mm)	p
Case Group (n=50)	55±13	9.06±2.18	5.46±2.33	**<0.001**
Control Group (n=50)	46±14	23.13±4.41	16.71±4.46	
Female (n=64)	52.11±12.65	13.90±6.96	9.06±5.45	**<0.001**
Male (n=36)	46.58±15.82	19.98±7.96	14.67±7.17	

IFS: Ischiofemoral space, QFS: Quadratus femoris space.

There was no edema in the QFM in the control group (grade 0). In the case group, 14 patients had grade 1, 10 patients had grade 2, and 26 patients had grade 3 edema. As the degree of edema increased, IFS and QFS decreased. In the case group, mean IFS was 10.68±1.58, 9.40±1.40 and 8.05±2.17 mm; mean QFS was 6.69±2.03, 5.97±1.63 and 4.60±2.41 mm in grades 1, 2 and 3, respectively. Mean IFS and QFS scores in grades 1, 2, and 3 were statistically significantly lower than those in grade 0 ($p < 0.001$) (Table 2). There was no statistically significant difference between the IFS and QFS edema groups in the case group.

Table 2. Comparison of ischiofemoral and quadratus femoris spaces by the edema of quadratus femoris muscle (n=100)

		n	Mean	F	p	Signal
IFS	(1) Grade 0	50	23.12±4.40	143.25	**<0.001**	1-2, 1-3, 1-4
	(2) Grade 1	14	10.68±1.58			
	(3) Grade 2	10	9.40±1.40			
	(4) Grade 3	26	8.05±2.17			
	Total	100	16.10±7.86			
QFS	(1) Grade 0	50	16.70±4.46	85.60	**<0.001**	1-2, 1-3, 1-4
	(2) Grade 1	14	6.69±2.03			
	(3) Grade 2	10	5.97±1.63			
	(4) Grade 3	26	4.60±2.41			
	Total	100	11.08±6.67			

ANOVA: Data are presented as mean±standard deviation, IFS: Ischiofemoral space, QFS: Quadratus femoris space

In all patients in the control group and 17 patients in the case group, there was no fatty atrophy in QFM (grade 0) in a total of 67 patients. In the case group, 30 patients had fatty streaks (grade 1) and three patients had less than 50% fatty atrophy (grade 2). There was no fatty atrophy greater than 50% in any group. In QFM, in the group without fatty atrophy, IFS was 19.72±7.06 mm, and QFS was 14.07±6.04 mm. In grade 1 and 2 atrophy, the IFS scores were 8.88±2.31 mm and 7.24±1.38 mm, respectively, and the QFS scores were 4.95±2.31 mm and 5.50±2.80 mm, respectively. There was a statistically significant difference between IFS and QFS distances in QFM between grade 0 and grade 1, grade 0 and grade 2 atrophy groups ($p < 0.001$); however, there was no statistically significant difference in IFS and QFS among grades 1 and 2 (Table 3).

Table 3. Comparison of ischiofemoral and quadratus femoris spaces by the fatty atrophy of quadratus femoris muscle (n=100)

		n	Mean	F	p	Signal
IFS	(1) Grade 0	67	19.72±7.06	37.56	**<0.001**	**1-2, 1-3**
	(2) Grade 1	30	8.88±2.31			
	(3) Grade 2	3	7.24±1.38			
	Total	100	16.09±7.87			
QFS	(1) Grade 0	67	14.07±6.04	34.13	**<0.001[a]** **<0.05[a]**	**1-2[a], 1-3[b]**
	(2) Grade 1	30	4.95±2.31			
	(3) Grade 2	3	5.50±2.80			
	Total	100	11.08±6.67			

ANOVA: Data are presented as mean±standard deviation, IFS: Ischiofemoral space; QFS: Quadratus femoris space

Discussion

Hip pain can be caused by a variety of conditions, including lumbar disc herniation, femoral acetabular impingement syndrome, musculi piriformis syndrome, osteoarthritis, iliopsoas bursitis, urinary tract infections, and avascular necrosis of the femoral head. IFI, which has been increasingly seen and investigated recently, is one of the pathologies causing hip pain. IFI, which occurs due to compression and edema of the QFM due to narrowing of the IFS or QFS, leads to hip and groin pain due to irritation of the adjacent sciatic nerve (2). People with severe symptoms had trouble standing up after sitting down or were unable to even squat (8). It is yet unknown what the best course of action is for treating this illness. Conservative therapy methods including rest, activity restriction, nonsteroidal anti-inflammatory medications, and rehabilitation methods may be helpful for people with this impingement syndrome as well as others. Pain may be reduced by administering local anesthetics and steroids to QFM (6). As opposed to the studies investigating the diagnosis of IFI syndrome, any clear physical examination criteria have yet to be determined. Therefore, the diagnosis of IFI syndrome is based on the MRI findings of the patients, as well as the clinic. Especially, MRI is an important method for the diagnosis of IFI syndrome due to its excellent tissue resolution (9).

In our study, we found that the widths of IFS and QFS in the MRI-diagnosed IFI syndrome, and the normal population were statistically significantly lower.

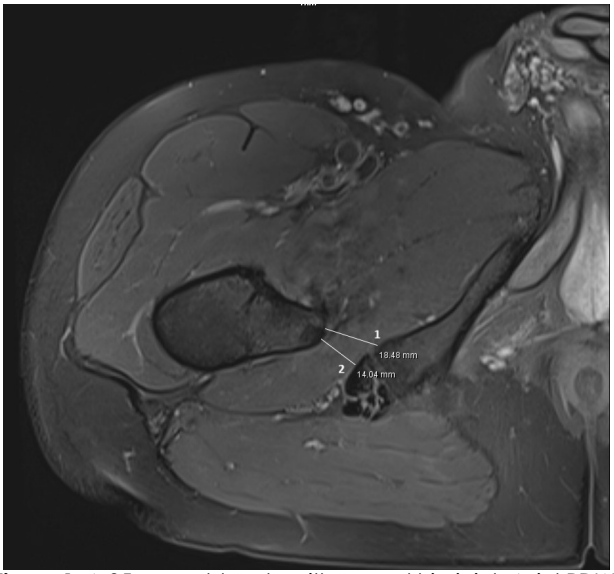
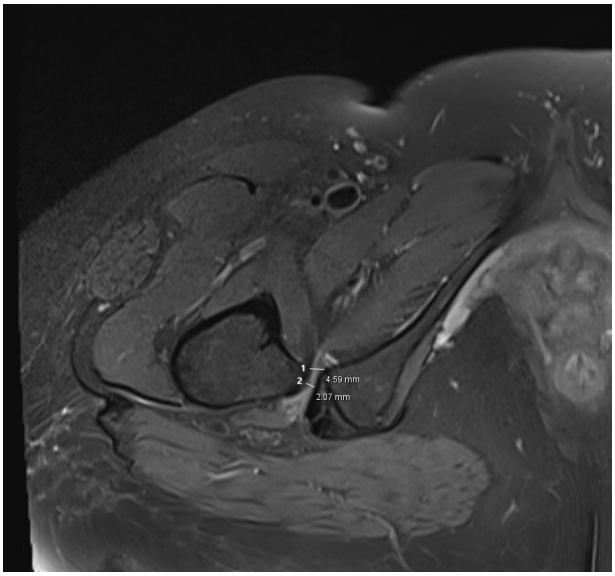


Figure 1. A 35-year-old male with normal hip joint: Axial PDWI fat-sat image; 1. IFS, and 2. QFS; normal quadratus femoris muscle



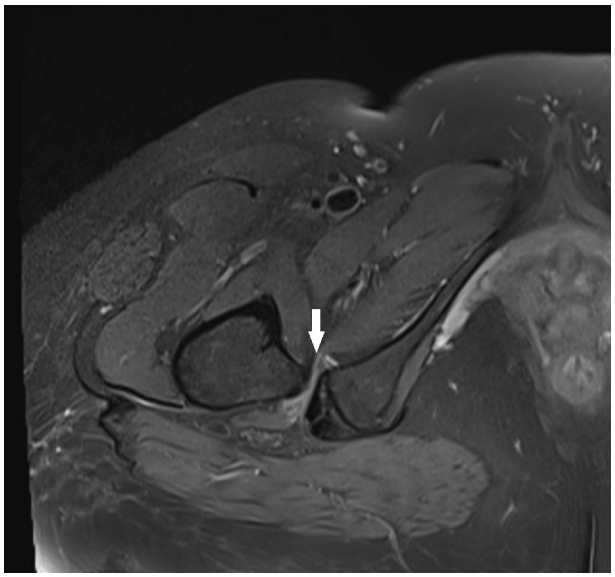


Figure 2a and 2b. A 52-year-old female with IFI: (a) Axial PDWI image, 1. IFS, and 2. QFS, (b) Axial PDWI-FS image; evident deformation and edema seen in quadratus femoris muscles and surrounding tissue (grade 3 edema) (white arrow).

Although the measurements in this study were similar to the QFS measurements in the study by Xing et al., we found the IFS measurements to be smaller (2). The physiological structure of the population and variations in sample size across regions could be the cause of this discrepancy. In the study where Tosun et al. compared the case group with pain and edema with the control group, the researchers reported that there was no change in MRI in terms of QFM. The difference in IFS and QFS values between symptomatic patients and the control group was statistically significant ($p < 0.001$) (4).

Our study shows that the widths of IFS and QFS are significantly smaller in females than in males. Hujazi et al. investigated normal IFS and its variations and found that IFS was significantly lower in women than in men (10). The reason for this situation can be explained by the difference in pelvic anatomy between men and women. Another possible explanation for why IFI syndrome is more prevalent in women is the greater prominence of the lesser trochanter in the female pelvis (9). The physiological structure of the female pelvis has a longer transverse diameter and shorter anterior and posterior diameters than men (2). Because of this, women are at a higher risk of developing IFI (4). Women constituted approximately 80% of IFI patients in our study. In a study in which Özdemir et al. prospectively evaluated IFS using 418 hip MRIs, the mean IFS and QFS values were 25.6±7.5 mm and 15.6±5.4 mm, respectively. The mean values for IFS and QFS were higher in men than in women, as in our study ($p < 0.01$) (11). Even though there were many patients in this study, the authors only assessed asymptomatic volunteers, and the majority of the men in the sample had an average age of 35.9 years. Nonetheless, the IFI syndrome is known to mostly impact women in their 50s (4).

In our study, IFS and QFS were significantly lower in the case group than in the control group. Our results are similar to the studies conducted by Singer et al. and Backer et al. (12, 13). Results from a case-control study by Barros et al. also revealed that the IFS and QFS scores of the IFI group were noticeably lower than those of the control group (14). The normal range of motion of QFM is restricted by a decrease in the distance between the ischial tuberosity and the femur lesser trochanter. IFI is caused by edema and chronic damage to QFM brought on by repetitive friction (2). There are several possible causes for the reduction in distance between the lesser trochanter of the femur and the ischial tuberosity, including congenital, acquired, and postural abnormalities (6). The IFS and QFS values were found to positively correlate in this study, which is essentially in line with the findings of earlier research (4, 13). This correlation suggests that IFS and QFS will narrow simultaneously, leading to chronic compression, deformation, and edema of the QFM, which may ultimately cause hip pain.

In light of our results, as IFS and QFS decrease, the amount of edema in the QFM increases. We consider that the degree of edema in QFM is correlated with the progression of the disease because a larger reduction in IFS and QFS exposes the muscle to more recurrent friction and impact. In IFI patients, the edema signal of QFM is usually located in the muscle belly and is accompanied by a decrease in IFS in these patients. A traumatic sprain or tear of QFM usually occurs at the myotendinous junction of the muscle without the IFS narrowing and usually has a history of trauma or sudden-onset disease (15). Differentiating this condition from IFI is important in terms of the treatment approach of patients.

In one study, mild-to-severe fatty replacement of QFM was detected in 94% of the patient group (4). Muscle atrophy and fatty muscle replacement can result from injuries, burns, corticosteroid treatments, immobilization, sciatic neuropathy, and spinal cord injuries (16). However, the precise cause of QFM fatty substitution is unknown. The sciatic nerve, which is next to the muscle, is probably irritated by abnormalities in QFM resulting in edema and fatty atrophy. This can cause discomfort traveling down the posterior thigh (17). In our study, a statistically significant difference was found between the IFS and QFS distances between grades 0 and 1, grades 0 and 2 atrophy groups in QFM.

There are several limitations to our study. The first is the retrospective nature of the study. The body weight and height of the patients were not measured, which could have an impact on the size of the areas inspected. The existence of IFI during activities may not be immediately related to the static evaluation of the areas under examination since IFI, like other impingements, is a dynamic situation. Additionally, the measurement of ischial intertuberal distance was not evaluated. Future studies with larger populations evaluating these conditions on MRI will be useful.

In conclusion, the etiology of hip pain is diverse and difficult to diagnose. Additionally, in some patients,

there are cases where the cause of pain cannot be identified. Radiologists should consider and report IFI primarily in patients with persistent posterior hip pain if their MRI shows the constriction of IFS and QFS together with the QFM distortion and edema.

Author Contribution

Conception: SE, AEA. Design: SE, AEA. Supervision: SE, AEA. Resource: SE, AEA. Materials: SE, AEA. Data Collection and/or Processing: SE, AEA. Analysis and/or Interpretation: SE, AEA. Literature Review: SE, AEA. Writer: SE. Critical Review: SE, AEA.

References

1.Johnson KA. Impingement of the lesser trochanter on the ischial ramus after total hip arthroplasty. Report of three cases. J Bone Joint Surg Am. 1977;59(2):268-9.

2.Xing Q, Feng X, Wan L, Cao H, Bai X, Wang S. MRI measurement assessment on ischiofemoral impingement syndrome. Hip Int. 2023;33(1):119-25.

3.Tan GJ, Chotai N, Tandon A. Clinics in diagnostic imaging (197). Left ischiofemoral impingement syndrome. Singapore Med J. 2019;60(7):329-33.

4.Tosun O, Algin O, Yalcin N, Cay N, Ocakoglu G, Karaoglanoglu M. Ischiofemoral impingement: evaluation with new MRI parameters and assessment of their reliability. Skeletal Radiol. 2012;41(5):575-87.

5.Tosun Ö, Çay N, Bozkurt M, Arslan H. Ischiofemoral impingement in an 11-year-old girl. Diagn Interv Radiol. 2012;18(6):571-3.

6.Ali AM, Whitwell D, Ostlere SJ. Case report: imaging and surgical treatment of a snapping hip due to ischiofemoral impingement. Skeletal Radiol. 2011;40(5):653-6.

7.Patti JW, Ouellette H, Bredella MA, Torriani M. Impingement of lesser trochanter on ischium as a potential cause for hip pain. Skeletal Radiol. 2008;37(10):939-41.

8.Lee S, Kim I, Lee SM, Lee J. Ischiofemoral impingement syndrome. Ann Rehabil Med. 2013;37(1):143-6.

9.Torriani M, Souto SC, Thomas BJ, Ouellette H, Bredella MA. Ischiofemoral impingement syndrome: an entity with hip pain and abnormalities of the quadratus femoris muscle. AJR Am J Roentgenol. 2009;193(1):186-90.

10.Hujazi I, Jones T, Johal S, Bearcroft P, Muniz-Terra G, Khanduja V. The normal ischiofemoral distance and its variations. J Hip Preserv Surg. 2016;3(3):197-202.

11.Maraş Özdemir Z, Aydıngöz Ü, Görmeli CA, Sağır Kahraman A. Ischiofemoral Space on MRI in an Asymptomatic Population: Normative Width Measurements and Soft Tissue Signal Variations. Eur Radiol. 2015;25(8):2246-53.

12.Backer MW, Lee KS, Blankenbaker DG, Kijowski R, Keene JS. Correlation of ultrasound-guided corticosteroid injection of the quadratus femoris with MRI findings of ischiofemoral impingement. AJR Am J Roentgenol. 2014;203(3):589-93.

13.Singer AD, Subhawong TK, Jose J, Tresley J, Clifford PD. Ischiofemoral impingement syndrome: a meta-analysis. Skeletal Radiol. 2015;44(6):831-7.

14.Barros AAG, Dos Santos FBG, Vassalo CC, Costa LP, Couto SGP, Soares A. Evaluation of the ischiofemoral space: a case-control study. Radiol Bras. 2019;52(4):237-41.

15.Palczewski P, Sułkowska K, Świątkowski J, Kocoń H, Gołębiowski M. Ischiofemoral Impingement Syndrome: A Case Report and a Review of Literature. Pol J Radiol. 2015;80:496-8.

16.Kamath S, Venkatanarasimha N, Walsh MA, Hughes PM. MRI appearance of muscle denervation. Skeletal Radiol. 2008;37(5):397-404.

17.O'Brien SD, Bui-Mansfield LT. MRI of quadratus femoris muscle tear: another cause of hip pain. AJR Am J Roentgenol. 2007;189(5):1185-9.

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ORIGINAL ARTICLE

Providing Satisfactory Improvement in Patients with Persistent Coxadydinia via Ganglion Impar Block

Ganglion İmpar Bloğu İle Dirençli Koksadinisi Olan Hastalarda Tatmin Edici İyileşme Sağlanması

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ABSTRACT

Aim: Coccydynia is a painful condition of the end of the spine, the most common etiological cause of which is direct-indirect trauma. In acute cases, healing is usually achieved by conservative treatment, while in more persistent cases, interventional treatment methods come to the fore. The injections, which usually consist of combinations of local anesthetics and corticosteroids, can be administered directly into the posterior coccygeal area as well as into the pre-coccygeal area under fluoroscopic control. The preferred pre-coccygeal block is the impar ganglion block. There are many different technical variations of this block technique. The current study aims to present the 1-year results of patients undergoing trans-coccygeal injection of ganglion impar bupivacaine plus methylprednisolone for resistant post-traumatic coxadynia.
Methods: Patients with posttraumatic coxadynia treated with impar ganglion block between October 2019 and April 2021 were retrospectively evaluated. Patients over 18 years of age at the time of injection, whose symptoms persisted for more than 6 months, and not responding to conservative treatment were included in the study. The visual analog scale (VAS) score SF -36 and Pittsburg Sleep Quality Index (PSQI) measurements recorded during the outpatient examination of patients before the procedure were evaluated. VAS, SF-36, and PSQI evaluations were repeated in all patients by calling them for the final control in the 6th month after the injection.
Results: When comparing our patients' assessments before the intervention and controls at month six, there was a significant decrease in VAS score, a significant improvement in SF -36 subcategories, and a significant increase in Pittsburgh Sleep Quality Index scores. ($p < 0.001$)
Conclusion: Ganglion impar injection is a treatment method that can help relieve pain, improve sleep quality, and improve daily life functions in cases that do not respond to medical treatment and lifestyle modification.

Keywords: Bupivacaine, ganglion impar blockade, methylprednisolone, Pittsburgh Sleep Quality Index, post-traumatic coxadynia, visual analog scale

ÖZ

Amaç: Koksidini, en sık etiyolojik nedeni direkt-indirekt travma olan, omurganın uç kısmının ağrılı bir durumudur. Akut vakalarda genellikle konservatif tedavi ile iyileşme sağlanırken, daha inatçı vakalarda girişimsel tedavi yöntemleri ön plana çıkmaktadır. Genellikle lokal anestezik ve kortikosteroid kombinasyonlarından oluşan enjeksiyonlar, floroskopi kontrolünde, doğrudan posterior koksigeal bölgeye uygulanabileceği gibi, prekoksigeal bölgeye de uygulanabilmektedir. Tercih edilen prekoksigeal blok impar ganglion bloğudur. Bu blok tekniğinin birçok farklı teknik varyasyonu vardır. Bu çalışma, dirençli travma sonrası koksadinia nedeniyle transkoksigeal ganglion impar bupivikain artı metilprednizolon enjeksiyonu uygulanan hastaların 1 yıllık sonuçlarını sunmayı amaçlamaktadır.
Gereç ve Yöntemler: Ekim 2019 ile Nisan 2021 tarihleri arasında impar ganglion bloğu ile tedavi edilen travma sonrası koksadinisi olan hastalar geriye dönük olarak değerlendirildi. Enjeksiyon sırasında 18 yaş üzerinde olan, semptomları 6 aydan uzun süredir devam eden ve konservatif tedaviye yanıt vermeyen hastalar çalışmaya dahil edildi. Hastaların işlem öncesi ayaktan muayenesi sırasında kaydedilen VAS, SF-36 ve Pittsburg Uyku Kalitesi İndeksi ölçümleri değerlendirildi. Tüm hastalara enjeksiyon sonrası 6. ayda son kontrole çağrılarak VAS, SF-36 ve Pittsburg Uyku Kalitesi İndeksi değerlendirmeleri tekrarlandı.
Bulgular: Hastalarımızın girişim öncesi ve altıncı aydaki kontrol değerlendirmeleri karşılaştırıldığında, VAS skorunda anlamlı düşüş, SF-36 alt kategorilerinde anlamlı iyileşme ve Pitssburgh Uyku Kalitesi İndeksi skorlarında anlamlı artış görüldü. ($p < 0,001$)
Sonuçlar: Ganglion impar enjeksiyonu, tıbbi tedaviye ve yaşam tarzı değişikliğine yanıt alınamayan durumlarda ağrının giderilmesine, uyku kalitesinin iyileştirilmesine, günlük yaşam fonksiyonlarının iyileştirilmesine yardımcı olabilecek bir tedavi yöntemidir.

Anahtar Kelimeler: Bupivikain, ganglion impar blokajı, metilprednizolon, Pittsburgh Uyku Kalitesi İndeksi, posttravmatik koksidini, VAS skoru

Introduction

The coccyx contributes to rectal control by providing an attachment point for the muscles that support the pelvic floor and, together with ischial tuberosity, forms tripodal support in the sitting position. Anatomical studies have shown that there are many variations, with partial or complete fusion observed at different levels (1). The coccyx is associated with the sacral nerve roots and the terminal ganglion of the sympathetic ring (2). The ganglion impar (Walther's ganglion) forms the termination of the paravertebral sympathetic chain. Although it is normally located at the level of the sacrococcygeal joint, in cadaver studies, it has been found that its height can vary by an average of 1.9 cm

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(3).

The term coccydynia refers to a painful condition in the last part of the spine. Although this term was first used by Simpson in 1859, the history of intervention for pain in the coccyx dates back to the ancient Greek physician Paul of Aegina (4). Coccydynia may occur with direct trauma, at birth, or through an unknown etiology. High body mass index and female sex have been reported as risk factors for coccydynia (5). The most common etiologic causes are direct or indirect trauma. The mechanism of trauma is often a backward fall (6). It has also been reported that prolonged sitting in hard and uncomfortable areas can cause coccydynia with a cumulative effect (7).

The predominant symptom of patients is pain over the coccyx, which worsens when sitting. The pain may be aggravated by defecation and sexual intercourse. On physical examination, there is usually pain on direct palpation of the coccyx. Radiologic evaluation is primarily done by direct radiography. Postacchini and Massobrio described six different configurations of the coccyx (2,8) (Figure 1). Instability of the coccyx has been reported to be more common in traumatic coccydynia cases than in non-traumatic cases (5).

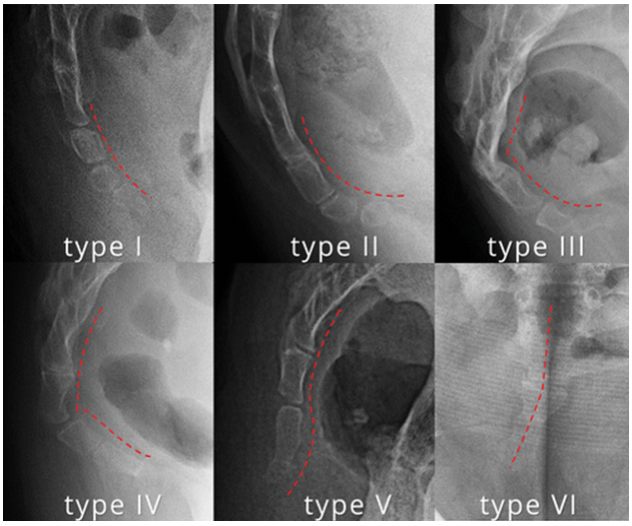

Figure 1. Classification of coccygeal angulation by Postacchini and Massobrio. Type 1 has a slight curvature, type 2 has an anteriorly increasing curvature, type 3 has a sharp angle, type 4 has a subluxation, type 5 has a retrusion of the coccyx and a bony spur, and type 6 has a scoliotic deformity.

Since, in most cases, there is a high rate of regression, conservative treatments are often preferred among the treatment options during the first stage (9). Many different studies have reported a very high success rate with conservative treatment (10).

Seat rings, coccyx triangle pillows, hot or cold baths, manual therapy, relaxation exercises for the levator ani, postural training, transcutaneous electrical stimulation, and topical or oral non-steroidal anti-inflammatory drugs (NSAIDs) are the preferred methods of conservative treatment. In patients not benefiting from any of these treatments, injection, and radiofrequency thermocoagulation treatments are the mainstay (11). Many different techniques have been described for the localization, content, and supporting imaging techniques of the injection in the treatment of coccydynia (11,12).

Injections, usually consisting of combinations of local anesthetics and corticosteroids, can be administered directly into the coccyx and can also be combined with rectal manipulation (13). Ganglion impar block is an acceptable treatment modality among injection treatments, with proven efficacy. This technique, first described by Plancarte for the treatment of cancer cases with pelvic metastases, has evolved and has been performed in several variants (14). Today, ganglion impar block is used in the treatment of many different types of pain and perianal hyperhidrosis (15), except for oncological pain and coccydynia (16). Anatomical studies have shown that the ganglion impar may be located at the sacrococcygeal joint, at the level of the coccyx, or the coccygeal type (3). The drugs used during the injection are essentially local anesthetics, corticosteroids, or neurolytic agents (14). Although the technique can be performed under fluoroscopy, USG (17) and CT-guided (18) blocks have also recently been described. In many of the techniques described, the trajectory of the needle may also differ: through the anococcygeal ligament (14), sacrococcygeal joint (19), intercoccygeal joint (20), bone segment (21), and paracoccygeal (20). The shape and structure of the needle to be used for injection may also vary. Curved needles, self-beveling needles, and a guided needle sent through a large-diameter guide needle can be used (14).

In addition to the proponents of exclusively conservative treatments with injections and manipulative techniques (22), some authors have reported good results with the option of coccygectomy in cases that do not respond to conservative treatments (23). Although more than a thousand years have passed since the definition of this disease, we are still far from a universally accepted treatment protocol for cases of resistant coccydynia.

Our study aimed to show the results of resistant coccydynia cases in which we performed a ganglion

impar blockade under fluoroscopy with the treatment algorithm that we used in our clinic, with a 1-year follow-up.

Materials And Methods

A pre-study power analysis based on previous data determined a sample size of at least 18 patients to reach the desired power of > 0.8. Pre- and postoperative VAS score was the primary outcome for two means T-test power analysis (12,24).

Patients were evaluated retrospectively after approval was obtained from the Gaziosmanpaşa University Clinical Research Ethics Committee (Decision No: 24-KAEK-109). The study was conducted under the principles of the Declaration of Helsinki.

Patients with posttraumatic coccydynia treated with impar ganglion block between October 2019 and April 2021 were retrospectively evaluated. Cases were included in the study if they were over 18 years of age at the time of injection, had a symptom duration of more than 6 months, and had failed at least two different treatments in the previous 6 months (drug pain management, manual therapy, use of a sitting ring, and superficial injection). Before the ganglion impar block, all patients received seat rings and oral and local treatment with non-steroidal anti-inflammatory drugs for 6 months. All patients received 750 mg of naproxen once daily for the first month after the block. Patients not adhering to the pre-and post-blockade treatment protocol and patients with known systemic inflammatory diseases, previous pelvic metastases, and a history of coccygectomy, pilonidal sinus surgery, colorectal surgery, rectal prolapse surgery, and rectal incontinence surgery were excluded from the study. (Figure 2)

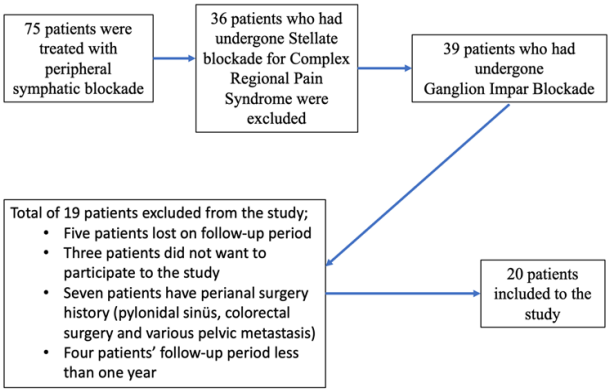

Figure 2. Flow chart presenting how the patients participated in our study under the inclusion and exclusion criteria.

All patients participating in the study were asked to complete an assessment form containing the Visual Analogue Scale (VAS), the Short Form Survey 36 (SF-36), and the Pittsburg Sleep Quality Index (PSQI) before the block procedure. The same assessment forms were repeated for all patients attending the first-year follow-up.

Radiological Technique: Before the procedure, all patients were placed on the operating table in the prone position, and the injection level was determined by a lateral view of the coccyx with a Philips BV Pulsera (Koninklijke Philips Electronics N.V., 5602 BG Eindhoven, the Netherlands) C-arm fluoroscopy device. After obtaining a lateral radiograph containing the sacrococcygeal joint and at least two coccygeal segments, the injection was started.

Injection Technique: Before the procedure, the patients underwent noninvasive cardiac monitoring and oxygen saturation monitoring with a saturation probe. While the patient was in the prone position, the injection level was first determined in the ap plane on the fluoroscopic table. Then, the fluoroscopy was positioned to take a lateral view, and the injection level was accurately determined in the lateral plane (Figure 3). After determining the injection level, subcutaneous infiltration anesthesia was performed with 2 ml of 0.25% bupivacaine using a 27 G x 2'' injector (Setocoject, Set Medikal, Istanbul, Turkey). Then, an 18G Quincke needle (Egemen International, 5514, İzmir, Turkey) was inserted into the lowest intercoccygeal space, visualized in lateral projection by fluoroscopy, with the stylet needle inside. In the case of possible intercoccygeal fusion, the needle was advanced under fluoroscopy control with circular movements together with the stylet. The solution prepared by diluting 1 ml of 74% ioversol solution (Optiray 350, Mallinckrodt Canada ULC, Pointe-Claire, Quebec, Canada) with 4 ml of saline was introduced into the area under fluoroscopy. Therapeutic injection was performed after the region was deemed suitable (Figure 4). Next, 10 ml of injection content, prepared by mixing 1 ml 40 mg methylprednisolone acetate (Depo-Medrol 40 mg/ml vial) 9 ml 0.5% bupivacaine hydrochloride (Buvicaine, Polifarma İlaç Sanayi Tekirdag, Turkey), was applied to the area. For final confirmation of the suitability of the injection site, it was recorded whether the contrast trace was obliterated. Heart rate and saturation were monitored during and for the first 5 minutes after injection. Cases without side effects (cardiac arrhythmias, low saturation, tinnitus,

metallic taste in the mouth, and dizziness) were referred for the service. The patients monitored for side effects in the service with blood pressure, fever, satiety, and heart rate monitoring at 15-minute intervals were mobilized and discharged after one hour of follow-up. No additional treatment protocol was applied to the patients in the postoperative period, and they were informed that they should not receive analgesic medical treatment.

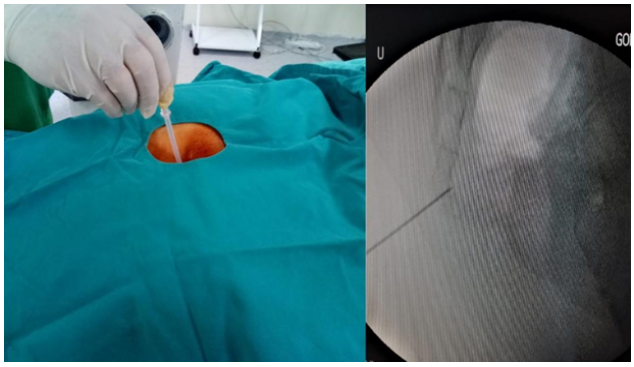

Figure 3. Advancing to the injection site with the lateral coccyx fluoroscopy before the procedure.

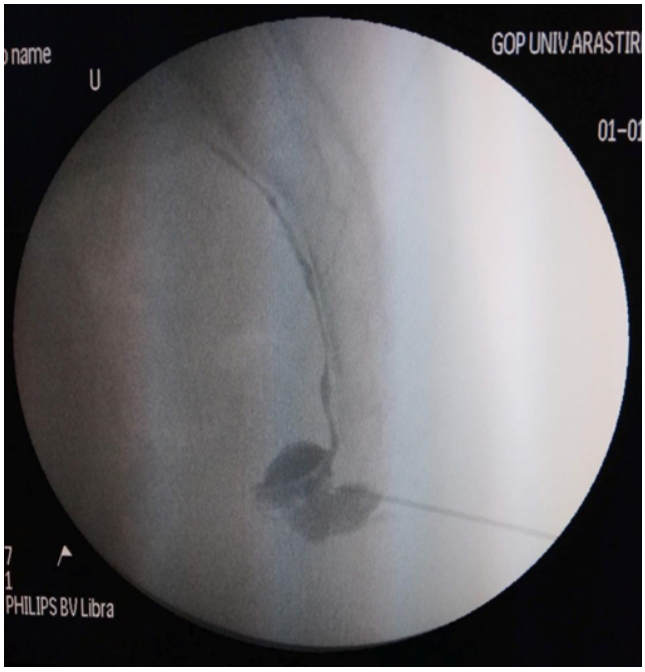

Figure 4. The contrast material image formed on the lateral radiograph after the injection of diluted radiographic contrast material was obtained to confirm that it was in the correct location.

Statistical analysis

Descriptive analyses were performed to obtain information on the general characteristics of the study groups. Data on continuous variables are reported in terms of mean ± standard deviation; data on categorical variables are reported as n (%). The Paired Sample-t test was used to compare the means of the measurements before and after the study. Pearson's correlation coefficient was used for the relationship between the quantitative variables. P-values below 0.05 were considered statistically significant. Prepackaged statistical software was used for the calculations (IBM SPSS Statistics 20, SPSS Inc., IBM Co., Somers, NY).

Results

Twenty patients meeting the study criteria and followed up for one year were included in the study. The mean age of the patients enrolled in the study was 41.05 ± 11.27 years (20–70). There were 17 female (85%) and three male (15%) patients. The mean symptom duration of the patients was 22.25 ± 17.06 (6–60) months. It was observed that pain started after falling in 18 patients (90%) and after heavy lifting in two patients (10%) (Table 1).

Table 1. Demographic characteristics of patients

Age (years)	41.05±11.27
Gender (Female/Male)	17/3
Follow-up period (months)	12,42
Symptom period (months)	22.25±17.06

When the scores of our patients were compared before the intervention and at the controls at the one year, there was a significant decrease in the VAS score ($p < 0.001$). The evaluation of the SF-36 score revealed a statistically significant increase in the subcategories of physical function, physical role limitation, emotional role limitation, energy/fatigue, emotional well-being, social function, pain, general health, and health change ($p < 0.001$). When patients' sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI), it was found that there was a significant increase in sleep quality scores after the injection ($p < 0.001$) (Table 2).

Table 2. Differences in clinical and functional scores before and after the interventions

	Pre-injection	Post-injection	p
VAS	9.35±0.99	3.1±2.05	<0.001
SF-36	45.25±11.86	75.5±10.87	<0.001
Physical function	45.25±11.86	75.5±10.87	<0.001
Physical restriction	25±18.14	62.5±19.02	<0.001
Emotional restriction	29.99±21.36	66.68±24.19	<0.001
Energy/fatigue	37.25±12.3	56±13.14	<0.001
Emotional wellness	43.6±10.61	60.6±12.33	<0.001
Social function	45.63±16.36	51.87±13	0.144

Pain	17.88±12.28	62.88±13.84	<0.001
Overall health change	33.75±9.01	55.75±13.6	<0.001
Health change	43.75±11.11	66.25±16.77	<0.001
Pitsburg sleep quality index	12.3±2.11	5.25±2.43	<0.001

The Paired Sample-t test was used to compare the means of the measurements before and after the study. A p-value was considered statistically significant if they were less than 0.05. VAS: Visual analog scale

No hematomas, superficial or deep infections, or persistent pain were observed at the injection sites of the patients participating in the study.

Discussion

The results of our study show that the ganglion impar block performed in our patients with refractory coxadonia led to a successful improvement in pain, sleep quality, and activities of daily living at the end of the one-year follow-up.

Although coccydynia can occur due to more than one etiological cause and has been defined for more than 100 years, its treatment can be difficult and complex due to unique diagnostic criteria and more than one cause (25). The ganglion impar in the sacrococcygeal region has nociceptive fibers, and successful results can be achieved with the blockade of this ganglion in cases where conservative treatment is unresponsive (26). Impar ganglion blockade has been shown in our results to be an effective method for pain relief and functional recovery. The summary of similar studies is shown in Table 3.

The age, sex, and etiological factors of the patients examined in our study were consistent with previous studies in the literature. Fogel et al. reported that women were affected about five times more often than men (27). Other studies on this topic have reported that admissions due to coccydynia are more common in the fifth decade of life and that they occur most frequently after falls on the coccyx (26,27).

In a study by Maigne et al., a stable coccyx, short duration of symptoms, and onset after trauma were reported as good prognostic factors in patients treated for coccydynia (28). In a study conducted by Mitra et al. on a series of 14 patients, it was found to result in significant improvement in VAS grade in acute and chronic cases after fluoroscopically guided steroid injection (12). Sencan et al. found a significant improvement in VAS and functional scores in patients with a mean symptom duration of 25.9 months in the first three months (29). Since about 90% of our patients had fallen before their symptoms appeared, we believe that they benefited from ganglion-impar blockade at the optimal level.

In a study by Şencan et al., the efficacy of the use of steroids in ganglion impar blockades was compared with the use of only local anesthetics (30). They found that the rate of pain relief after surgery did not change with the two methods; however, the reduction in pain level was significantly better in the third-month control in the steroid supplement group. Glucocorticoids act by preventing the secretion of many cytokines that can cause pain, thanks to their receptors, antidepressant properties, and anti-inflammatory action in centers where pain pathways predominate, such as the hippocampus and the amygdala (31). In addition, corticosteroids have been shown to have direct neural antinociceptive effects in experimental studies (31). In their study, Gunduz et

Tablo 3. The studies on transcoccygeal ganglion impar blockade.

Author	Mitra et al. 2007 (n=12)	Gunduz et al. 2015 (n=24)	Sencan et al. 2018 (n=29)	Sencan et al. 2019 (n=30)	Buttaci et al. 2005 (n=32)	Gonnade et al. 2017 (n=26)	Our study
Number of Patients	14	22	28	34	6	31	20
Age (years)	43.4	41	43.7	38.1	N/A	42.9	41
Gender (M/F)	7/7	2/20	5/23	6/28	N/A	13/18	3/17
Follow-up time (months)	N/A	6	6	3	N/A	6	12.42
Symptom Period (months)	N/A	N/A	25.9	16	N/A	N/A	22.2±17
Block Technique	TC	TC	TC	TC	N/A	TC	TC
Drugs	L+TA	B+MP	B+MP	B+MP	B	B+MP	B+MP
Scores	VAS >50% impro-vement	VAS 9□2.5	VAS 7.8□3.8 LANSS 15.1□6.82	NRS 7.8□4.9	VAS >50% improvement	NRS 7.9□3.2 ODI 48.9□26.1	VAS 9.3□3.1 SF-36 45.2□75.5

TC: Transcoccygeal, L: Lidocaine, TA: Triamcinolone acetate, B: Bupivacaine, MP: Methylprednisolone, NRS: Numeric rating scale, ODI: Oswestry disability index, LANSS: Leeds assessment of neuropathic symptoms and signs scale, VAS: Visual analog scale

al. showed that the analgesic effect lasted six months or longer in patients receiving a combined injection of local anesthetics and corticosteroids (24). On the other hand, studies examining the results of blockades with only one local anesthetic have reported that the analgesic effect disappears within a few weeks, and repeated injections are required (32). We believe that the significant improvement in our patients' outcomes at one-year follow-up in ganglionic impar blockade, which we performed by combining local anesthetics with long-acting corticosteroids, compared with the initial phase, is due to the neuromodulatory effect of corticosteroids, as found in previous studies.

Pain is the main problem for patients when sitting and sleeping while suffering from coccydynia. In our study, we investigated the sleep quality of patients and their changes in daily life after receiving bupivacaine plus methylprednisolone injection. A study by Sencan et al. reported that the sitting time of patients receiving bupivacaine plus methylprednisolone injection increased significantly after the procedure, but this was not sufficiently reflected in the SF-12 scores (29). With the results we obtained, a significant and durable improvement in both the SF-36 and PSQI scores at the one-year follow-up was observed. Our study is the first to investigate the relationship between ganglion impar block and sleep quality.

The ganglion impar is the last link of the sympathetic chain located in front of the coccyx and, unlike other sympathetic ganglia, is a single ganglion in the middle. It is involved in sensory and sympathetic innervation of the pelvic organs and perineal region (33). Ganglion impar block was first described by Plancart in 1990 and is performed with a retrograde needle through the anococcygeal ligament (14). Due to the risk of complications, such as infection and rectal perforation, that may accompany it, the method defined by Wemm and Saberski was developed and started to be applied via a guide needle originating from the sacrococcygeal junction (19). The success of ganglion impar blockade depends on the correct determination of the anatomical location of the ganglion and the appropriate placement of the needle (3,34). In studies performed on cadavers by Oh et al., it was shown that the ganglion impar is usually located 8.6 mm distal to the sacrococcygeal junction and 25 mm proximal to the coccygeal type (3). When the contrast medium is sent through the guide needle under fluoroscopy, the placement of the needle and the area where the drug is to be distributed is confirmed by the formation of a comma in front of the coccyx. Because there are no standard treatment methods in the treatment of coccydynia, the profit-and-loss ratios of the treatments to be used should be well thought out and decided. Although rare, rectal rupture, neuritis, and cauda equina syndrome may occur after ganglion-impar blocks (35). No complications were observed in our patients.

The lack of a control group, the limited follow-up period of 12 months, and the lack of interim controls were the limitations of our study. Our strengths were that our study was performed in a single center by a single surgeon and that it was supported by more than one functional scoring. In other studies in the literature, patients were assessed using the VAS and SF-12 only.

Conclusion

Ganglion impar blockade is a method that leads to successful pain relief and improvement of daily functions in cases where drug treatment and lifestyle changes are not possible.

Authors' Contributions

MG and MBE conceived of the presented idea. MG and MBE developed the theory and performed the computations. US verified the analytical methods. MG and US collected data. MG wrote the manuscript with the support of MBE. MG supervised the project.

References

1.Maigne JY, Guedj S, Straus C. Idiopathic coccygodynia lateral roentgenograms in the sitting position and coccygeal discography. Spine J. 1994;19(8):930-4.

2.Howard PD, Dolan AN, Falco AN, Holland BM, Wilkinson CF, Zink AM. A comparison of conservative interventions and their effectiveness for coccydynia: a systematic review. Man Ther. 2013;21(4):213-9.

3.Oh CS, Chung IH, Ji HJ, Yoon DM. Clinical implications of topographic anatomy on the ganglion impar. Anesthesiology. 2004;101(1):249-50.

4.Adams F. The seven books of Paulus Aegineta. C. 1. Sydenham Society; 1844.

5.Maigne JY, Doursounian L, Chatellier G. Causes and mechanisms of common coccydynia: role of body mass index and coccygeal trauma. Spine J. 2000;25(23):3072-9.

6.Schapiro S. Low back and rectal pain from an orthopedic and proctologic viewpoint with a review of 180 cases. Am J Surg. 1950;79(1):117-28.

7.Pennekamp PH, Kraft CN, Stütz A, Wallny T, Schmitt O, Diedrich O. Coccygectomy for coccygodynia: does pathogenesis matter? J Trauma Acute Care Surg. 2005;59(6):1414-9.

8.Postacchini F, Massobrio M. Idiopathic coccygodynia. Analysis of fifty-one operative cases and a radiographic study of the normal coccyx. JBJS. 1983;65(8):1116-24.

9.Maroy B. Spontaneous and evoked coccygeal pain in depression. Diseases of the colon & rectum. 1988;31:210-5.

10.Trollegaard A, Aarby N, Hellberg S. Coccygectomy: an effective treatment option for chronic coccydynia: retrospective results in 41 consecutive patients. J Bone Joint Surg Br. 2010;92(2):242-5.

11.Kırcelli A, Demirçay E, Özel Ö, Çöven I, Işık S, Civelek E, vd. Radiofrequency Thermocoagulation of the Ganglion Impar for Coccydynia Management: Long-Term Effects. Pain Pract. 2019;19(1):9-15.

12.Mitra R, Cheung L, Perry P. Efficacy of fluoroscopically guided steroid injections in the management of coccydynia. Pain Physician. 2007;10(6):775.

13.Seker A, Sarikaya IA, Korkmaz O, Yalcin S, Malkoc M, Bulbul AM. Management of persistent coccydynia with transrectal manipulation: results of a combined procedure. Eur Spine J. 2018;27:1166-71.

14.Plancarte R. Presacral blockade of the ganglion of Walther (ganglion impar). Anesthesiology. 1990;73:751.

15.Kim ST, Ryu SJ. Treatment of Hyperhidrosis Occurring during Hemodialysis: Ganglion Impar Block: A case report. Korean J Anesthesiol. 2005;48(5):553-6.

16.Scott-Warren JT, Hill V, Rajasekaran A. Ganglion impar blockade: a review. Curr Pain Headache Rep. 2013;17:1-6.

17.Gupta D, Jain R, Mishra S, Kumar S, Thulkar S, Bhatnagar S. Ultrasonography Reinvents the Originally Described Technique for Ganglion Impar Neurolysis in Perianal Cancer Pain: Retracted. Anesth Analg. 2008;107(4):1390-2.

18.Datir A, Connell D. CT-guided injection for ganglion impar blockade: a radiological approach to the management of coccydynia. Clin Radiol. 2010;65(1):21-5.

19.Wemm Jr K, Saberski L. Modified approach to block the ganglion impar (ganglion of Watther). Reg Anesth Pain Med. 1995;20(6):544-5.

20.Foye PM, Buttaci CJ, Stitik TP, Yonclas PP. Successful injection for coccyx pain. Am J Phys Med Rehabil. 2006;85(9):783-4.

21.Reig E, Abejón D, Del Pozo C, Insausti J, Contreras R. Thermocoagulation of the ganglion impar or ganglion of Walther: description of a modified approach. Preliminary results in chronic, nononcological pain. Pain Pract. 2005;5(2):103-10.

22.Kersey P. Non-operative management of coccygodynia. The Lancet. 1980;315(8163):318.

23.Grosso NP, van Dam BE. Total coccygectomy for the relief of coccygodynia: a retrospective review. Clin Spine Surg. 1995;8(4):328-30.

24.Gunduz OH, Sencan S, Kenis-Coskun O. Pain relief due to transsacrococcygeal ganglion impar block in chronic coccygodynia: a pilot study. Pain Med. 2015;16(7):1278-81.

25.Lirette LS, Chaiban G, Tolba R, Eissa H. Coccydynia: an overview of the anatomy, etiology, and treatment of coccyx pain. Ochsner J. 2014;14(1):84-7.

26.Gonnade N, Mehta N, Khera PS, Kumar D, Rajagopal R, Sharma PK. Ganglion impar block in patients with chronic coccydynia. Indian J Radiol Imaging. 2017;27(03):324-8.

27.Fogel GR, Cunningham III PY, Esses SI. Coccygodynia: evaluation and management. J Am Acad Orthop Surg. 2004;12(1):49-54.

28.Maigne JY, Chatellier G, Le Faou M, Archambeau M. The treatment of chronic coccydynia with intrarectal manipulation: a randomized controlled study. Spine J. 2006;

29.Sencan S, Kenis-Coskun O, Demir FGU, Cuce I, Ercalık T, Gunduz OH. Ganglion Impar block improves neuropathic pain in coccygodynia: A preliminary report. Neurol Neurochır Pol. 2018;52(5):612-7.

30.Sencan S, Edipoglu IS, Demir FGU, Yolcu G, Gunduz OH. Are steroids required in the treatment of ganglion impar blockade in chronic coccydynia? A prospective double-blinded clinical trial. Korean J Pain. 2019;32(4):301-6.

31.Schilling LS, Markman JD. Corticosteroids for pain of spinal origin: epidural and intraarticular administration. Rheum Dis Clin. 2016;42(1):137-55.

32.Buttaci CJ, Foye PM, Stitik TP. Coccydynia successfully treated with ganglion impar blocks: a case series. Am J Phys Med. 2005;84(3):218.

33.SAĞIR Ö, Özaslan S, Köroğlu A. Koksiks dislokasyonlu hastada impar ganglion bloğu uygulaması. Ağrı. 2011;23(3):129-33.

34.Loev MA, Varklet VL, Wilsey BL, Ferrante MF. Cryoablation: a novel approach to neurolysis of the ganglion impar. Anesthesiology. 1998;88(5):1391-3.

35.Gupta N, Garg R, Saini S, Bharti SJ, Kumar V. An unusual complication after ganglion impar block for chronic cancer pain management. AANA J. 2017;85(6):424-6.

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ORIGINAL ARTICLE

Investigation of Cytomegalovirus Seroprevalence in Adults in Erzurum and Its Surroundings

Erzurum ve Çevresinde Yetişkin Bireylerde Sitomegalovirüs Seroprevalansının Araştırılması

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ABSTRACT

Objective: Cytomegalovirus (CMV), a double-stranded DNA virus in the family Herpesviridae, like other known herpes viruses, remains latent throughout a person's life following the initial infection in CMV and causes recurrent infections. The study aimed to reveal the current status of CMV seroprevalence in adults in Erzurum and to investigate the trends in CMV infection by comparing the obtained seroprevalence data with the previously reported data.
Materials and Methods: In our study, the results of people whose anti-CMV IgG and anti-CMV IgM serology were investigated by family physicians in Erzurum between 2020-2023 were retrospectively analyzed. Blood samples of individuals were studied in Erzurum Public Health Serology Laboratory using the ELISA method and the Architect kit. To make comparisons between individuals, the working group was divided into six different age groups: 18-24, 25-29, 30,34, 35-39, 40-49 and ≥50.
Results: Our study consisted of 9,252 people between 18 and 103 who were investigated for anti-CMV IgG serology and 13,276 people between 18 and 97 for anti-CMV IgG. Anti-CMV IgG seropositivity was 98.5%, and anti-CMV IgM seropositivity was 2.1% in our study group. Anti-CMV IgG and IgM positivity were 98.7% and 2.1%, respectively, in women and 97.7% and 2.2% in men.
Conclusion: In our study, anti-CMV IgG seropositivity was found to be 98.7%, anti-CMV IgM seropositivity was found to be 2.1%, and CMV IgG seropositivity rates were found to be higher in our province compared to similar studies conducted in our country. The CMV IgM seropositivity rate is consistent with the data from Turkey. To reduce CMV infection in our region's community, public awareness of the route of transmission of CMV infection and ways to prevent disease should be increased.

Keywords: Cytomegalovirus, anti-CMV IgG, anti-CMV IgM, prevalence, Erzurum

ÖZ

Giriş: Herpesviridae ailesinde çift sarmallı bir DNA virüsü olan sitomegalovirüs (CMV) bilinen diğer herpes virüsleri gibi CMV'de ilk enfeksiyonu takiben kişinin hayatı boyunca latent kalır ve tekrar eden enfeksiyonlara neden olur. Çalışmanın amacı, Erzurum'da yetişkin bireylerde CMV seroprevalansının güncel durumunu ortaya koymak ve elde edilen seroprevalans verilerin daha önce bildirilen verilerle karşılaştırarak CMV enfeksiyonundaki eğilimleri araştırmaktır.
Materyal method: Çalışmamızda 2020-2023 yılları arasında Erzurum'da aile hekimlerince anti-CMV IgG ve anti-CMV IgM serolojisi araştırılan kişilere ait sonuçlar retrospektif olarak incelendi. Kişilere ait kan örnekleri Erzurum Halk Sağlığı Seroloji Laboratuvarında ELISA yöntemiyle Architect kiti kullanılarak çalışılmıştı. Bireyler arasında kıyaslama yapabilmek için çalışma grubu; 18-24, 25-29, 30,34, 35-39, 40-49 ve ≥50 olmak üzere 6 farklı yaş grubuna bölündü.
Bulgular: Araştırmamızın evreni anti-CMV IgG serolojisi araştırılan 18 ve 103 yaş arasında 9.252 kişiden, anti-CMV IgM ise 18 ve 97 yaşları arasında 13.276 kişiden oluşmakta idi. Çalışma grubumuzda anti-CMV IgG seropozitifliği %98.5, anti-CMV IgM seropozitifliği ise %2.1 oranında bulundu. Anti-CMV IgG ve IgM pozitifliği kadınlarda sırasıyla %98.7, %2.1; erkeklerde ise %97.7, %2.2 oranında bulundu.
Sonuç: Araştırmamızda anti-CMV IgG seropozitifliği %98.7, anti-CMV IgM seropozitifliği %2.1 oranında bulunmuş olup, ülkemizde yapılan benzer çalışmalarla kıyaslandığında CMV IgG seropozitiflik oranları ilimizde daha yüksek bulunmuştur. CMV IgM seropozitiflik oranı ise Türkiye verileriyle uyumludur. Bölgemizdeki toplumda CMV enfeksiyonunu azaltmak için, CMV enfeksiyonunun bulaşma yolu ve enfeksiyondan korunma yolları hakkında halkın farkındalığı artırılmalıdır.

Anahtar Kelimeler: Sitomegalovirüs, anti-CMV IgG, anti-CMV IgM, prevalans, Erzurum

Introduction

Cytomegalovirus (CMV), a double-stranded DNA virus in the herpesviridae family, is also known as human herpes virus-5 (HHV-5). Like other known herpes viruses, CMV remains latent throughout the person's life following the first infection and causes recurrent infections (1). CMV can be transmitted by contact with infectious body fluids, including blood, urine, saliva, tears, cervical secretions, seminal fluid, breast milk, and stem cell and organ transplantation (2). Infants and toddlers exposed to CMV infection are an important source of infection because they can spread the virus through urine or saliva months or even years after infection (3, 4).

Primary CMV infection may be asymptomatic in immunocompetent individuals or cause a mild disease, mostly self-limiting with fatigue, fever, myalgia, and headache (5, 6). In immunosuppressed individuals (patients with AIDS and other immune system disorders, organ transplant recipients, patients hospitalized in

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intensive care units, and older adults), the infection may lead to more severe clinical pictures. However, the highest disease burden is caused by congenital CMV infection (7, 8). Congenital CMV infection is the leading cause of neurological damage in children worldwide and has also been reported to be associated with hearing loss, growth retardation, permanent disabilities, and microcephaly (9, 10).

Different regions of the world can be divided into two areas with high seroprevalence (more than 70%) and low seroprevalence (50%-70%) (6, 9). CMV seroprevalence is generally higher in older age groups, women, individuals with low socio-economic standards, and in developing countries. It has been reported that the prevalence of CMV in women in the reproductive period varies between 45% and 100% (11). Currently, treatment options for CMV infections are limited, and no vaccine is currently in use. Therefore, efforts to develop vaccines to prevent CMV infection remain a high public health priority (2).

A limited number of studies have focused on CMV seroprevalence in adults in Turkey. This study aimed to reveal the current status of CMV seroprevalence in individuals over 18 years of age in Erzurum and investigate the trends in CMV infection in our province by comparing the seroprevalence data obtained with previously reported data.

Material and Methods

With this study, the results of people examined by family physicians in Erzurum city center for four years between 01.01.2020 and 31.12.2023 and whose anti-CMV IgG and anti-CMV IgM serology were evaluated retrospectively. Blood samples of individuals were studied in Erzurum Public Health Serology Laboratory using the ELISA method in the Architect I2000 model device (Abbott Laboratories, USA) using the Architect kit. The data were obtained from the laboratory automation system with the Scientific Research Permits dated 03.05.2024 obtained from the Erzurum Health Directorate. In our study, the laboratory analysis results were evaluated as Anti-CMV IgM <0.85 index negative, anti-CMV IgM >0.99 index result positive, 0.85 index <anti-CMV IgM <1.0 index results intermediate; anti-CMV IgG ≤5.99 AU/ml negative, anti-CMV IgG>5.99 AU/ml results positive. To make comparisons between individuals, the working group was divided into six different age groups: 18-24, 25-29, 30,34, 35-39, 40-49, and ≥50.

The necessary ethics committee approval for this research was obtained from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee, whose decision was dated 29.03.2024 and numbered 45.

Statistical Analysis

In the statistical evaluation of the data collected in our research, the SPSS 22.0 program was used. The chi-square test was used in the analysis of categorical data. The statistical significance limit was accepted as $p<0.05$.

Results

Our study population consisted of 9,252 individuals between the ages of 18 and 103 years who were investigated for anti-CMV IgG serology and 13,276 individuals between 18 and 97 years for anti-CMV IgM. The mean age of the group investigated for anti-CMV IgG serology was 32.4±10.09 years. The mean age of the anti-CMV IgM group was 32.6±9.27 years. In our study group, anti-CMV IgG seropositivity was found to be 98.5%, and anti-CMV IgM seropositivity was found to be 2.1%. Anti-CMV IgG and IgM positivity rates were 98.7% and 2.1% in women and 97.7% and 2.2% in men, respectively. Anti-CMV IgG positivity rate was higher in women than men, and the difference was statistically significant ($p<0.05$). Although the rate of anti-CMV IgM seropositivity was higher in males, this was not statistically significant ($p>0.05$). The highest CMV IgG seropositivity rate was found in the 40-49 age group, 99.8%; anti-CMV IgM positivity rate was 2.9% in the 18-24 age group. In our study, anti-CMV IgM results of 113 people were found to be intermediate. The data obtained in the study are presented in detail in Table 1 and Table 2.

Table 1. Distribution of anti-CMV IgG serology results by gender and age groups

		Anti-CMV IgG		
Variables		**Positive N (%)**	**Negative N (%)**	**Total N (%)**
Gender	Male	1918 (97.7)	46 (2.3)	1964 (100)
	Woman	2601 (98.7)	94 (1.3)	7288 (100)
	Total	4519 (98.5)	140 (1.5)	9252 (100)
P value	<0,05			
Age groups	18-24	1526 (97.6)	38 (2.4)	1564 (100)
	25-29	2601 (98,7)	34 (1.3)	2635 (100)
	30-34	2292 (98.2)	41 (1.8)	2333 (100)
	35-39	1220 (98.3)	21 (1.7)	1241 (100)
	40-49	879 (99.8)	2 (0.2)	881 (100)
	≥50	594 (99.3)	4 (0.7)	598 (100)
	Total	9112 (98.5)	140(1.5)	9252 (100)
P value		<0,05		

N: Number of patients, %: Percent

Table 2. Distribution of anti-CMV IgM serology results by gender and age groups

		Anti-CMV IgM			
Variables		Positive N (%)	Intermediate value N (%)	Negative N (%)	Total N (%)
Gender	Men	52 (2.2)	21 (0.9)	2291 (96.9)	2364 (100)
	Wo-man	228 (2.1)	92 (0.8)	10592 (97.1)	10912 (100)
	Total	280 (2.1)	113 (0.9)	12883 (97.0)	13276 (100)
P value	>0,05				
Age groups	18-24	51 (2.9)	20 (1.1)	1694 (96.0)	1765 (100)
	25-29	80 (2.2)	28 (0.8)	3589 (97.1)	3697 (100)
	30-34	75 (2.0)	30 (0.8)	3591 (97.2)	3696 (100)
	35-39	36 (1.8)	17 (0.8)	1995 (97.4)	2048 (100)
	40-49	28 (2.1)	12 (0.9)	1311 (97.0)	1351 (100)
	≥50	10 (1.4)	6 (0.8)	703 (97.8)	719 (100)
	Total	280 (2.1)	113 (0.9)	12883 (97.0)	13276 (100)
P value	>0,05				

N: Number of patients, %: Percent

Figure 1 shows a histogram graph of the change in anti-CMV IgG and anti-CMV IgM seropositivity rates in age groups and the total population.

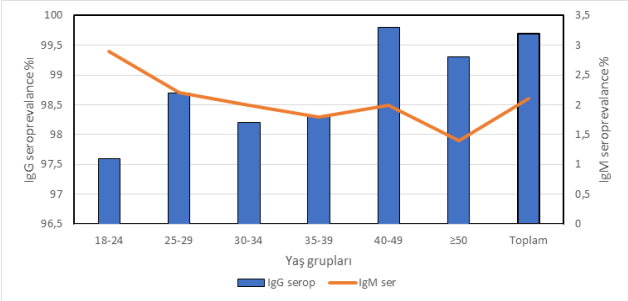

Figure 1. Variation of anti-CMV IgG and IgM seroprevalence by age groups

Discussion

The prevalence of CMV infection in different geographies varies depending on living conditions, social habits, and age. In a study conducted in the USA, the prevalence of CMV was reported to be 59% in the general population and 96.4% in Brazil (12, 13). In the European region, seropositivity was reported at a rate of 83% in Sweden, 77% in Portugal, 77% in the population in Croatia, and 56.5% in Germany (6, 14–16). CMV IgG seropositivity was reported to be 94.1% among Koreans on the Asian continent, 95.7% in Iraq, 91.8% in Iran, and 97.4% among blood donors in India. CMV IgG seropositivity was also reported to be 95.7% among blood donors in Saudi Arabia (17-21).

World Health Organisation (WHO) has estimated CMV seroprevalence for different population groups regionally and globally. According to this estimate, the global average prevalence was 83% (95% UI: 78-88). The region with the highest estimated average prevalence was the Eastern Mediterranean at 90% (95% UI 85-94), while the lowest estimate was made for the European region with 66% (95% UI 56-74). In the European region, the lowest seroprevalence estimate was estimated at 39% (95% UI 18-62) for Ireland, while the highest seroprevalence estimate was reported as 96% (95% UI 93-98) for Turkey (22).

In the study conducted in the Antalya region of Turkey, anti-CMV seropositivity in the general population was reported as 97.8% in the 15-49 age group (23). In a study conducted on a massive population of men and women between the ages of 0-84 in Istanbul, seropositivity was reported as 94% (24). In many other studies conducted in different regions of Turkey, it has been reported that the prevalence of CMV in pregnant women varies between 92.6-98.2% (25, 26).

On CMV, seroprevalence has focused chiefly on pregnant women both in the world and in Turkey. This study is one of the few studies in Turkey to investigate CMV seroprevalence in the adult population, including men and women. In our study, total CMV seroprevalence was 98.5% in both sexes. Our result was slightly higher than the seropositivity rates in previous studies conducted on pregnant women. Our result is higher than the average prevalence estimated by WHO for Turkey.

The difference in seroprevalence between countries and regions can be explained by differences in baseline exposures related to CMV transmission. These include the frequency and duration of breastfeeding, childcare arrangements, crowding, and sexual behaviors (10). Some studies have reported a relationship between CMV seroprevalence and education level, household income, social status, race, and ethnicity (2, 27-29).

An analytical model has shown that hygiene education effectively prevents poor outcomes from CMV infection. It also estimated that hygiene promotion was associated with a 50% risk reduction for fetal infections in CMV seronegative people (30).

Many studies have examined whether there is a relationship between CMV seroprevalence and gender. In one study conducted in Germany, the prevalence of CMV was reported to be 59.8% in women and 50.8% in men (6). Many other studies conducted in Germany and the UK have reported a higher incidence of CMV in women (10, 31).

In our study, CMV IgG seropositivity was 98.7% among 7288 women and 97.7% among 1964 men. The difference was statistically significant. As observed in our study, CMV seroprevalence is higher in women than in men. Although it is not fully understood how gender differences affect this outcome, it is believed that the fact that women mainly do childcare contributes to this result. (2, 32, 33). To date, no vaccine has been developed to prevent CMV infection. However, several vaccine studies have been reported to be in clinical development (10, 34). CMV IgG seroprevalence in our study ranged from 97.6% to 99.8% between age groups, and there was a significant difference in seroprevalence between age groups. The highest seroprevalence was 99.8% in the 40-49 age group, followed by 99.3% in the 50 and over age group, and the lowest seropositivity was 97.6% in the 18-24 age group. A generally higher prevalence of CMV IgG was observed in age groups as the mean age increased. This may be because as people age, their interactions with and exposure to CMV risk factors increase. Two studies conducted in Japan in 2016 and Germany in 2012 reported that CMV seropositivity has decreased recently (35, 36). However, as observed in our research, there is no regression in seropositivity rates compared with the data in previous studies in our country. Since no CMV seroprevalence studies in our province included male and female adults, we could not comment on whether there is an increase or decrease in CMV seropositivity rates.

In a study conducted in Brazil, anti-CMV IgM seropositivity was reported to be 2.3% (13). In another study conducted in Kirkuk City, Iraq, the rate of IgM seropositivity in the population was reported to be 6.3% (18). In a study conducted in Iran, CMV IgM seropositivity was reported to be 0.2% (19). In some studies conducted in Turkey, anti-CMV IgM positivity rates were observed to be 0.2-3.2% (24, 37, 38). In our research, anti-CMV IgM positivity was found to be 2.1% (228/10912) in females and 2.2% (52/2364) in males in the general population. In our study group, the highest IgM seropositivity was observed in the 18-24 age group. In contrast to IgG seropositivity, IgM seropositivity was lower as the mean age increased in the age groups. The difference was not statistically significant. The results were similar to the data reported for CMV IgM seropositivity in Turkey.

Staras et al. (12) reported that increasing age was not a risk for CMV IgM seropositivity, whereas they confirmed that age was a risk for CMV IgG seropositivity. In addition, it has been reported that some CMV IgM positive results may be associated with false positive results known to occur due to cross-reactions (39).

Conclusion

Our study constitutes the seroprevalence data of a vast population representing the adult population living in Erzurum. In our research, anti-CMV IgG and anti-CMV IgM seropositivity rates were 98.7% and 2.1%, respectively. Compared with similar studies in Turkey, CMV IgG seropositivity rates were higher in our province. Our results were slightly higher than the CMV seroprevalence rate estimated by WHO for Turkey. The CMV IgM seropositivity rate was compatible with Turkey's data. To reduce CMV infection in our region's community, efforts should be made to increase public awareness about the transmission route of CMV infection and ways to prevent it.

Contribution to Authorship

MU, AY, and GB conceived and designed the study, analyzed the data and drafted the manuscript. They also participated in writing the final version of the manuscript.

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References

1.Gorun F, Motoi S, Malita D, Navolan DB, Nemescu D, Olariu TR, et al. Cytomegalovirus seroprevalence in pregnant women in the western region of Romania: A large-scale study. Exp Ther Med 2020;20:2439-2443.

2.Fowler K, Mucha J, Neumann M, Lewandowski W, Kaczanowska M, Grys M, et al. A systematic literature review of the global seroprevalence of cytomegalovirus: possible implications for treatment,

screening, and vaccine development. BMC Public Health 2022;22:1659.

3.Cannon MJ, Stowell JD, Clark R, Dollard PR, Johnson D, Mask K, et al. Repeated measures study of weekly and daily cytomegalovirus shedding patterns in saliva and urine of healthy cytomegalovirus-seropositive children. BMC Infect Dis 2014;14:1-10.

4.Revello MG, Campanini G, Piralla A, Furione M, Percivalle E, Zavattoni M, et al. Molecular epidemiology of primary human cytomegalovirus infection in pregnant women and their families. J Med Virol 2008;80:1415-1425.

5.Nolan N, Halai U-A, Regunath H, Smith L, Rojas-Moreno C, Salzer W. Primary cytomegalovirus infection in immunocompetent adults in the United States–A case series. IDCases 2017;10:123-126.

6.Hoehl S, Berger A, Ciesek S, Rabenau HF. Thirty years of CMV seroprevalence—a longitudinal analysis in a German university hospital. Eur J Clin Microbiol Infect Dis 2020;39:1095-1102.

7.Griffiths PD. The burden of disease associated with human cytomegalovirus and prospects for elimination by universal immunization. Lancet Infect Dis 2012;12:790-798.

8.Lancini D, Faddy HM, Flower R, Hogan C. Cytomegalovirus disease in immunocompetent adults. Med J Aust 2014;201:578-580.

9.Manicklal S, Emery VC, Lazzarotto T, Boppana SB, Gupta RK. The "silent" global burden of congenital cytomegalovirus. Clin Microbiol Rev 2013;26:86-102.

10.Lachmann R, Loenenbach A, Waterboer T, Brenner N, Pawlita M, Michel A, et al. Cytomegalovirus (CMV) seroprevalence in the adult population of Germany. PloS one 2018;13:e0200267.

11.Cannon MJ, Schmid DS, Hyde TB. Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection. Rev Med Virol 2010;20:202-213.

12.Staras SA, Dollard SC, Radford KW, Flanders WD, Pass RF, Cannon MJ. Seroprevalence of cytomegalovirus infection in the United States, 1988–1994. Clin Infect Dis 2006;43:1143-1151.

13.Souza MA, Passos AM, Treitinger A, Spada C. Seroprevalence of cytomegalovirus antibodies in blood donors in southern Brazil. Rev Soc Bras Med Trop 2010;43:359-361.

14.Lopo S, Vinagre E, Palminha P, Paixão MT, Nogueira P, Freitas MG. Seroprevalence to cytomegalovirus in the Portuguese population, 2002-2003. Euro Survei 2011;16:19896.

15.Vilibic-Cavlek T, Kolaric B, Beader N, Vrtar I, Tabain I, Mlinaric-Galinovic G. Seroepidemiology of cytomegalovirus infections in Croatia. Wien Klin Wochenschr 2017;129:129-135.

16.Olsson J, Kok E, Adolfsson R, Lövheim H, Elgh F. Herpes virus seroepidemiology in the adult Swedish population. Immu Ageing 2017;14:1-6.

17.Choi SR, Kim K-R, Kim DS, Kang J-M, Kim SJ, Kim JM, et al. Changes in cytomegalovirus seroprevalence in Korea for 21 years: a single center study. Pediatric Infection & Vaccine. 2018;25:123-131.

18.Aljumaili ZKM, Alsamarai AM, Najem WS. Cytomegalovirus seroprevalence in women with bad obstetric history in Kirkuk, Iraq. J Infect Public Health 2014;7:277-288.

19.Rahimzadeh G, Safar MJ, Rezai S, Rezai MS, Movahedi FS. Seroepidemiology of HBV, HCV, HIV, HTLV, and CMV in pregnant women referring to Sari Birth Cohort. Adv Biomed Res 2022;11:97.

20.Das A, Munian D, Maity C, Pandey S, Paul S, Bhattacharya P. Prevalence of cytomegalovirus infections in blood donors and the newborn versus utility of leukocyte-reduced blood transfusion in the premature newborn: an observation from Eastern India. Journal of Clinical Neonatology 2023;12:65-71.

21.Mahallawi W, Khabour OF, Al-Saedi A, Almuzaini Z, Ibrahim N. Human Cytomegalovirus Seroprevalence Among Blood Donors in the Madinah Region, Saudi Arabia. Cureus 2022;14:e21860.

22.Zuhair M, Smit GSA, Wallis G, Jabbar F, Smith C, Devleesschauwer B, et al. Estimation of the worldwide seroprevalence of cytomegalovirus: a systematic review and meta□analysis. Rev Med Virol 2019;29:e2034.

23.Ataman S, Colak D, Guenseren F, Senol Y, Colak T, Aktekin MR, et al. Investigation of cytomegalovirus seroepidemiology in Antalya with a population-based cross-sectional study and review of related data in Turkey. Mikrobiyol Bul 2007;414:545-555.

24.Demir E, Dinç HÖ, Özbey D, Akkuş S, Ergin S, Kocazeybek BS. Retrospective Evaluation of Toxoplasma gondii, Rubella and Cytomegalovirus Seropositivity and Avidity Test Results in patients

admitted to İU-C Cerrahpaşa Medical Faculty Hospital Between 2013-2018. Turk Mikrobiyol Cemiy Derg 2020;50:35-43.

25.Akpınar O, Akpınar H. Gebe Investigation Of The Rubella And Cytomegalovirus Seroprevalences By Elisa Method In Pregnant Women. Balıkesir Sağlık Bilimleri Dergisi 2017;6:11-15.

26.Bakacak M, Bostancı MS, Köstü B, Ercan Ö, Serin S, Avcı F, et al. Seroprevalance of Toxoplasma gondii, rubella and cytomegalovirus among pregnant women. Dicle Med J 2014;41:326-331.

27.Petersen MR, Patel EU, Abraham AG, Quinn TC, Tobian AA. Changes in cytomegalovirus seroprevalence among US children aged 1–5 years: the national health and nutrition examination surveys. Clin Infect Dis 2021;72:e408-e411.

28.Tiguman GMB, Poll LB, Alves CEdC, Pontes GS, Silva MT, Galvao TF. Seroprevalence of cytomegalovirus and its coinfection with Epstein-Barr virus in adult residents from Manaus: a population-based study. Rev Soc Brasil Med Trop 2020;53:e20190363.

29.Antona D, Lepoutre A, Fonteneau L, Baudon C, Halftermeyer-Zhou F, Le Strat Y, et al. Seroprevalence of cytomegalovirus infection in France in 2010. Epidemiol Infect 2017;145:1471-1478.

30.Billette de Villemeur A, Tattevin P, Salmi L-R. Hygiene promotion might be better than serological screening to deal with Cytomegalovirus infection during pregnancy: a methodological appraisal and decision analysis. BMC Infect Dis 2020;20:1-15.

31.Winter JR, Taylor GS, Thomas OG, Jackson C, Lewis JE, Stagg HR. Factors associated with cytomegalovirus serostatus in young people in England: a cross-sectional study. BMC Infect Dis 2020;20:1-9.

32.van Zuylen WJ, Zheng QY, Hamilton ST, Egilmezer EE, Craig ME, Gralton J, et al. Prevalence of cytomegalovirus carriage among childcare staff. J Paediatr Child Health 2017;53:724.

33.Wujcicka W, Gaj Z, Wilczyński J, Sobala W, Śpiewak E, Nowakowska D. Impact of socioeconomic risk factors on the seroprevalence of cytomegalovirus infections in a cohort of pregnant Polish women between 2010 and 2011. Eur J Clin Microbiol Infect Dis 2014;33:1951-1958.

34.Bernstein DI. Congenital cytomegalovirus: a "now" problem no really, now. Clin and Vaccine Immunol 2017;24: e00491-16.

35.Enders G, Daiminger A, Lindemann L, Knotek F, Bäder U, Exler S, et al. Cytomegalovirus (CMV) seroprevalence in pregnant women, bone marrow donors and adolescents in Germany, 1996–2010. Med Microbiol Immunol 2012;201:303-309.

36.Takemoto K, Nishimura N, Kozawa K, Hibino H, Kawaguchi M, Takeuchi S, et al. Time-series analysis comparing the prevalence of antibodies against nine viral species found in umbilical cord blood in Japan. Jpn J Infect Dis 2016;69:314-318.

37.Madendağ Y, Eraslan Şahin M, Çöl Madendağ İ, Şahin E, G. A. Investigation of toxoplasma, cytomegalovirus and rubella seroprevalence in pregnant women admitted to our hospital. Perinatoloji Dergisi 2018;26:7-10.

38.Çubuk F, Hasbek M, Kafa AHT, Çelik C. Evaluation of Serological Indicators for Toxoplasma, Rubella Virus and Cytomegalovirus Infections in Pregnant Women Applied to Our Hospital. Türk Mikrobiyoloji Cemiy Derg 2020;50:211-217.

39.Lazzarotto T, Guerra B, Gabrielli L, Lanari M, Landini MP. Update on the prevention, diagnosis and management of cytomegalovirus infection during pregnancy. Clini Microbiol Infect 2011;17:1285-1293.

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ORIGINAL ARTICLE

The Influence of Predominant Polarity and Chronotype on Lithium Response in Bipolar Disorder

Bipolar Bozuklukta Lityum Tepkisi Üzerindeki Predominant Polarite ve Kronotipin Etkisi

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ABSTRACT

Aim: This study investigates the prevalence and clinical correlates of predominant polarity (PP), depressive predominant polarity (DPP), and manic predominant polarity (MPP) in patients with bipolar disorder type 1 (BD-1), as well as their association with chronotype and lithium response.
Method: The present study with a cross-sectional design was conducted on 80 BD-1 patients in remission between 18-65 years of age. Data collection involved sociodemographic questionnaires and assessments using the Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HDRS), Biological Rhythms Interview of Assessment in Neuropsychiatry, (BRIAN) Morningness-Eveningness Questionnaire (MEQ), and the Alda Scale. DPP and MPP were defined as a lifetime ratio of ≥2:1 of either hypomanic/manic episodes or depressive episodes, respectively.
Results: Participants (mean age 35.32 ± 11.39 years; 61.25% female) showed two dominant polarities: DPP (46.25%) and MPP (53.75%). No significant differences were found in treatment, illness duration, or episode number (p>0.05). However, the MPP group had significantly earlier onset age (p=0.009) and higher scores on the BRIAN, MEQ, and Alda scales (all p<0.001). Manic episodes correlated positively with BRIAN and strongly with MEQ (rs1=-0.355, rs2=-0.373). The Alda scale showed strong positive correlations with BRIAN and MEQ, and strong negative correlations with depressive episodes (rs1=-0.355, rs2=-0.373, rs3=-0.274).
Conclusion: The present study demonstrates that PP and chronotype significantly influence lithium response in individuals with BD-I. The MPP group was found to have an earlier onset of the disorder and exhibit more pronounced evening characteristics. Additionally, the MPP group showed a stronger response to lithium.

Keywords: Bipolar disorder, chronotype, depression, lithium, mania, predominant polarity,

ÖZ

Amaç: Bu çalışmada, bipolar bozukluk (BD) tip 1 (BD-1) hastalarında baskın polarite (PP) - depresif baskın polarite (DPP) ve manik baskın polarite (MPP) - yaygınlığı ve klinik korelasyonları ile bunların kronotip ve lityum yanıtıyla ilişkisi araştırılmıştır.
Yöntem: 18-65 yaş aralığında, remisyondaki 80 BD-1 hastasında kesitsel bir çalışma yürütülmüştür. Veri toplama, sosyodemografik anketler ve Young Mani Derecelendirme Ölçeği (YMRS), Hamilton Depresyon Derecelendirme Ölçeği (HDRS), Nöropsikiyatride Değerlendirmenin Biyolojik Ritim Görüşmesi, (BRIAN) Sabah-Akşam Anketi (MEQ) ve Alda Ölçeği kullanılarak yapılan değerlendirmeleri içermektedir. DPP ve MPP, sırasıyla hipomanik/manik epizotların veya depresif epizotların yaşam boyu oranı ≥2:1 olarak tanımlanmıştır.
Bulgular: Katılımcılar (ortalama yaş 35,32 ± 11,39 yıl; %61,25 kadın) iki baskın kutupluluk gösterdi: DPP (%46,25) ve MPP (%53,75). Tedavi, hastalık süresi veya bölüm sayısında anlamlı bir fark bulunmadı (p>0,05). Ancak, MPP grubunun başlangıç yaşı önemli ölçüde daha erkendi (p=0,009) ve BRIAN, MEQ ve Alda ölçeklerinde daha yüksek puanlar vardı (hepsi p<0,001). Manik bölümler BRIAN ile pozitif ve MEQ ile güçlü bir şekilde ilişkiliydi (rs1=-0,355, rs2=-0,373). Alda ölçeği BRIAN ve MEQ ile güçlü pozitif korelasyonlar ve depresif bölümlerle güçlü negatif korelasyonlar gösterdi (rs1=-0,355, rs2=-0,373, rs3=-0,274).
Sonuç: Bu çalışma, PP ve kronotipin BD-I'li bireylerde lityum yanıtını önemli ölçüde etkilediğini göstermektedir. MPP grubunun bozukluğun daha erken başladığı ve daha belirgin akşam özellikleri sergilediği bulunmuştur. Ek olarak, MPP grubunun lityuma daha güçlü bir yanıt gösterdiği görülmüştür.

Anahtar Kelimeler: Baskın polarite, bipolar bozukluk, depresyon, kronotip, lityum, mani

Introduction

Bipolar disorder (BD) is a chronic and debilitating mental illness affecting approximately 2% of the global general population worldwide with large inter-individual variability (1). Typically emerging during adolescence or early adulthood, BD is characterized by recurrent episodes of depression, mania, or hypomania, in addition to subthreshold symptoms occurring between these mood episodes (2). Notably, around 50% of patients experience a predominance of depressive episodes, while the other half tend to have more manic episodes (3). Despite common epidemiological assumptions suggesting that individuals with BD spend a greater duration in depression compared to mania, the clinical trajectories of BD can be quite heterogeneous (4).

To better understand this heterogeneity, researchers have advocated for a more nuanced classification of BD accounting for predominant polarity (PP), a concept

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introduced by Jules Angst in a study of 95 individuals with BD (5). This classification distinguishes between two main types: depressive (DPP), for patients primarily experiencing major depressive episodes, and manic (MPP), for those with a predominance of (hypo)manic episodes (6).

Research has established strong correlations between PP and various clinical variables. MPP is typically associated with male gender, BP type 1 (BD-1), psychotic features, early age of onset, and manic onset, while DPP correlates with depressive onset, a higher frequency of mood episodes, and a history of suicide attempts (7, 8). Additionally, a study exploring the influence of affective temperament found links between cyclothymic and hyperthymic temperaments and MPP, indicating that temperament may shape the clinical presentation across different PP groups (9).

Identifying an individual's PP may enhance personalized management strategies for BD. Evidence suggests that patients with MPP or DPP may demonstrate varied responses to both acute and long-term treatments, as well as differential effectiveness of psychopharmacological agents during stabilization phases (8, 10). Previous reviews have posited that MPP and DPP could affect nearly half of all individuals with BD, potentially correlating with distinct individual characteristics (11). However, despite the growing interest in this area, systematic analyses comparing rates and individual characteristics of MPP versus DPP remain absent.

Chronotype, defined as an individual's circadian preference, reflects the physiological organization of the circadian system (12). Several cross-sectional studies suggest that individuals with BD are more likely to identify as evening types compared to control populations, indicating this may be an underexamined factor associated with a more adverse course of illness(13). However, to date, no studies have investigated the relationship between PP and chronotype.

This study aims to address this gap by identifying the prevalence and clinical correlates—specifically focusing on lithium response—of different mood predominance types in BD, as well as assessing their association with chronotype.

Methods

This cross-sectional study included 80 patients (initially 89, but nine were excluded due to missing data of PP) with BB-1 in remission, aged 18–65, and regularly followed up in the outpatient clinic of the XXX clinic in the Department of Psychiatry at XXX University.

The patients included in the study had already been diagnosed with BD under the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and were symptomatically in remission. At the time of the study, to exclude the presence of manic and depressive episodes Young Mania Rating Scale (YMRS) (14) and Hamilton Depression Rating Scale-17 (HAM-D) (15) were administered to all patients. Individuals with dementia, mild cognitive impairment, intellectual disabilities, shift work employment, and comorbid diagnoses of alcohol and substance abuse were excluded.

Initially, the demographic and clinical variables of the patients were recorded. This study used Colom's definition of PP to categorize patients (16). Based on this, MPP and DPP are defined as a lifetime ratio ≥2:1 of either hypomanic/manic episodes or depressive episodes, respectively. This restrictive definition splits patients into three categories (MPP, DPP, and undetermined PP). As no participants were classified as having undetermined PP, analyses were conducted only on participants with MPP or DPP.

The chronotypes of both groups were evaluated according to the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (17) and the Morningness-Eveningness Questionnaire (MEQ) (18). The patients' response to lithium treatment was determined according to the Lithium Treatment Response Scale (the Alda scale) (19). Briefly, the scale measures the degree of improvement in the course of treatment (Criterion A) weighted against clinical factors considered relevant for determining whether or not the observed improvement is due to the treatment (Criteria B1–B5). The total score is calculated by subtracting the total B score from the A score. The degree of response for each patient is quantified with a score from 0 to 10 (total score). Patients with a total score equal to 7≥ are considered lithium responders, while patients with a total score e lower than 7 are considered non-responders.

This study was granted ethical approval by the Local Ethics Committee of XXX (Decision Number: 2024/685). It was conducted under the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. Before participating in the study, written informed consent was obtained from all

participants after the nature of the procedures had been fully explained, and the local ethics committee approved the study.

Statistical Analysis

The data from the study were entered using the Statistical Package for the Social Sciences (SPSS) version 22. The Kolmogorov-Smirnov test was performed to determine whether the parameters followed a normal distribution. The Chi-square test was used to compare categorical variables, while the independent samples t-test was used to compare numerical variables between groups. Pearson correlation analysis was employed to assess the correlation between numerical variables. Statistical significance was defined as $p < 0.05$.

Results

The study was completed with 80 BB-1 patients. The mean age of the patients was 35.32 ± 11.39 years, with 61.25% being female (n=49). The PPs were 46.25% (n=37) DPP and 53.75% (n=43) MPP. No statistically significant difference was detected between the DPP and MPP groups in terms of gender, marital status, use of alcohol and smoking status, and other demographic parameters (p>0.05).

Also, no significant differences were found between DPP and MPP groups regarding types of pharmacotherapies, total duration of illness, or total episode count (p>0.05); however, the age of onset was 21.5 ± 6.6 years in the MPD group and significantly earlier in this group (p=0.009) Table 2 shows the demographic and clinical characteristics of groups.

Table 1. Comparison of demographic and clinical features under predominant polarity

Mean±SD/n (%)	DPP (n=37)	MPP (n=43)	χ2/t	p
Age (y)§	38.5±11.3	32.6±10.9	2.139	0.03
Gender/Female‡	23 (62)	26 (60)	0.034	0.85
Marital Status/Married‡	22 (59)	21 (48)	4.63	0.98
Education/University‡	11 (29)	15 (34)	1.20	0.75
Employment Status/Employed‡	16 (43)	21 (44)	0.03	0.95
Smoker/Yes‡	7 (18)	10 (23)	0.02	0.53
Alcohol use/Yes‡	1 (3)	2 (4)	0.03	0.95
Presence of Comorbid Medical Condition/Yes‡	7 (19)	5 (12)	0.98	0.25
Age of Onset (y)§	27.4±7.1	20.5±6.6	2.70	**0.04**
Duration of BPD(y)§	12.6±8.5	10.5±8.3	0.98	0.32
Number of Total Episodes§	6.2±4.7	4.9±5.2	1.13	0.26
Mania / Hypomania	2.2±1.9	3.6±3.1	-2.35	**0.02**
Depression	4.0±3.6	1.4±1.3	3.42	**0.01**
Number of Hospitalization§	6.2±3.7	5.1±3.2	1.23	0.31
Types OF Treatment‡	37 (100)	43 (100)	7.02	0.71
Lithium Monotherapy	12 (32)	6 (14)		
Lithium+AP	15 (40)	25 (58)		
Lithium+VLP+AP	3 (8)	6 (14)		
Others	7 (20)	6 (14)		
Psychotic Features/Yes‡	17 (46)	25 (58)	1.47	0.22
Family History for Psychiatric Disorders‡d	20 (54)	25 (58)	0.01	0.54

§= t-test; ‡= χ2 Test; SD=Standard deviation, P values in boldface indicate statistical significance, MPP: Manic predominant polarity, DPP: Depressive predominant polarity, AP: Antipsychotic, VLP: Valproic acid

When comparing two groups based on chronotype scale scores and Alda scale scores, the MPP group showed significantly higher scores on the BRIAN, MEQ, and Alda scales (t=-7.183, p=0.00; t=-3.968, p=0.00; t=-6.971, p=0.00, respectively) (Table 3).

Table 2. Comparison of psychometric properties under predominant polarity

Mean±SD/n (%)	DPP (n=37)	MPP (n=43)	χ2 / t	p
BRIAN	5.46±1.19	7.63±1.24	-7.18	**0.00**
MEQ	52.01±6.17	58.13±6.07	-3.968	**0.00**
ALDA	4.70±1.17	6.97±1.42	-6.971	**0.00**

§= t-test; ‡= χ2 Test; SD=Standard Deviation, P values in boldface indicate statistical significance, MPP: Manic Predominant Polarity, DPP: Depressive Predominant Polarity, BRIAN: Biological Rhythms Interview of Assessment in Neuropsychiatry, MEQ: Morningness-Eveningness Questionnaire, ALDA: Alda Lithium Response Scale

A weak positive correlation was found between manic episodes and BRIAN, while a strong positive correlation was observed with MEQ (respectively rs1=-0.355, rs2=-0.373). Additionally, strong positive correlations were noted between the Alda Scale and both BRIAN and MEQ, alongside strong negative correlations with the total number of depressive episodes (respectively rs1=-0.355, rs2=-0.373, rs4=-0.274) (Table 4)

Table 3. Pearson's product-moments correlation coefficients

	1	2	3	4	5	6	7
1. TDD	1.00						
2. NTE	**0.730****	1.00					
3. NM	**0.642****	**0.766****	1.00				
4. ND	**0.572****	**0.868****	**0.351****	1.00			
5. BRAIN	0.008	0.27	0.312*	-0.207	1.00		
6. MEQ	**0.323****	0,147	**0.357****	-0.500	**0.344****	1.00	
8. ALDA	-0.064	-0.159	0.178	**-0.352****	**0.324****	**0,429****	1.00

Note. * p <.05, ** p <.01, *** p <.001. TDD: Total Duration of Disease, NTE: Number of Total Episodes, NM: Number of mania/hypomania episodes, ND: Number of depression episodes, BRIAN: Biological rhythms interview of assessment in

neuropsychiatry, MEQ: Morningness-Eveningness Questionnaire, ALDA: Alda Lithium Response ScaleDiscussion

This study is the first to investigate the relationship between PP, chronotype, and lithium response in BD patients, thereby contributing to the existing literature by exploring the intricate associations among these variables. This cross-sectional study demonstrated a relatively balanced distribution between the DPP and MPP groups (46.25% vs. 53.75%), consistent with existing literature indicating considerable individual variability in the presentation of mood episodes. The absence of statistically significant differences between the groups concerning demographic factors such as marital status, education, and employment suggests that these variables do not effectively differentiate between DPP and MPP. A review of the literature reveals inconsistent data regarding the relationship between PP and demographic variables (20). Similarly, there were no statistically significant differences between groups for several clinical variables, including type of pharmacotherapy, total duration of illness, and total episode count. Although the literature presents conflicting evidence on this topic, some findings indicate a higher episode count in the MPP group and differences in the types of treatments utilized between the two groups. However, the small sample size may have contributed to these findings (21).

A notable difference emerged in the age of onset, which was significantly earlier in the MPP group (p=0.009). This finding aligns with prior research indicating an association between earlier onset and MPP, thereby reinforcing the consistency of our results with existing theories (7, 22). A meta-analysis conducted in 2024, which included 13 studies comprising 2,494 individuals with BD, provided strong evidence that individuals with MPP have an earlier onset of the disorder compared to those with DPP (10).

The most striking finding relates to the chronotype assessment. The MPP group exhibited significantly higher scores on both the BRIAN and MEQ scales, suggesting a greater inclination toward eveningness. This observation implies a potential connection between circadian rhythm preferences and PP in BD. Furthermore, the observed stronger correlation between the number of manic episodes and the eveningness scores supports the notion of a mechanistic relationship between circadian disruption and the expression of manic symptoms. Eveningness is associated with manic symptoms in BD (23) though null findings are more common (24). Additionally, based on social rhythm theory, it has been proposed that evening individuals experience greater disruptions in social rhythms and more sleep disturbances, correlating with increased manic episodes (25, 26).

The significant difference in lithium response, as indicated by the Alda scale, between the two groups is also critical. The MPP group exhibited substantially higher Alda scores, which suggests a potentially improved response to lithium treatment. Notably, the negative correlation between the Alda scale and the total number of depressive episodes, along with the positive correlation between the Alda scale and the total number of manic episodes, indicates that a higher frequency of manic episodes and a lower frequency of depressive episodes may be linked to a stronger lithium response. This finding, while not entirely surprising due to lithium's greater efficacy in managing manic episodes compared to depressive symptoms (27), warrants further investigation. Also, Scott et al. (2020) conducted a study involving 900 individuals diagnosed with BD-1, in which they identified MPP as a strong indicator of lithium response (28). Clinically, this finding is significant as it implies that PP could serve as a valuable predictor of treatment response, potentially informing personalized treatment strategies. Moreover, the strong positive correlations between the Alda scale and both BRIAN and MEQ scores further support the hypothesis that chronotype influences the effectiveness of lithium. Previous studies suggested a possible association between lithium response and chronotype in patients with BD (29), however, the predominance of cross-sectional studies limited causal inferences (23, 30, 31). Therefore, experimental studies are needed to establish causality in this field. Considering all these findings and evidence, it can be inferred that lithium has a stronger effect on individuals with MPP and evening chronotype. Further research with larger sample sizes is crucial to confirm this hypothesis.

While the study offers valuable insights, several limitations must be acknowledged. The cross-sectional design restricts the ability to establish causal relationships. The relatively small sample size, limited to BD-I patients in remission from a single clinic in Turkey, may affect the generalizability of the findings. Additionally, relying on self-report measures for chronotype assessment using BRIAN and MEQ may introduce potential biases. Furthermore, the study did not evaluate the possible effects of other pharmacotherapies on circadian rhythms.

Future research should focus on the following points:

1) Longitudinal studies to determine the temporal relationships between PP, chronotype, and lithium response.

2) Larger, more diverse samples (including BD-II and varied populations) to enhance generalizability.

3) Exploration of biological markers (e.g., genetic variations influencing circadian rhythms or lithium metabolism) to elucidate underlying mechanisms.

4) Mechanistic studies to investigate why MPP is associated with a better lithium response and earlier onset, potentially involving genetic and neurobiological examinations of circadian rhythms and mood regulation.

Conclusion

This cross-sectional study has demonstrated that PP and chronotype significantly influence lithium response in individuals with BD-I. It was found that individuals in the MPP group experience an earlier onset of the disorder and exhibit more pronounced characteristics of the evening chronotype. Additionally, the MPP group showed a stronger response to lithium, providing significant insights for personalizing treatment responses. These findings suggest that lithium has a greater effect on individuals with MPP and evening chronotype while emphasizing the need for validation in larger sample sizes and longitudinal studies. Overall, the results indicate that PP and chronotype are important factors in predicting treatment response, highlighting the necessity for further research in future studies.

References

1.McIntyre RS, Berk M, Brietzke E, Goldstein BI, López-Jaramillo C, Kessing LV, et al. Bipolar disorders. The Lancet. 2020;396(10265):1841-56.

2.Grande I, Goikolea J, De Dios C, González-Pinto A, Montes J, Saiz-Ruiz J, et al. Occupational disability in bipolar disorder: analysis of predictors of being on severe disablement benefit (PREBIS study data). Acta Psychiatrica Scandinavica. 2013;127(5):403-11.

3.Calabrese JR, Hirschfeld RM, Frye MA, Reed ML. Impact of depressive symptoms compared with manic symptoms in bipolar disorder: results of a US community-based sample. Journal of Clinical Psychiatry. 2004;65(11):1499-504.

4.Kupka RW, Altshuler LL, Nolen WA, Suppes T, Luckenbaugh DA, Leverich GS, et al. Three times more days depressed than manic or hypomanic in both bipolar I and bipolar II disorder 1. Bipolar disorders. 2007;9(5):531-5.

5.Angst J. The course of affective disorders. Psychopathology. 1986;19(Suppl 2):47-52.

6.Colom F, Vieta E, Suppes T. Predominant polarity in bipolar disorders: refining or redefining diagnosis? : Wiley Online Library; 2015. p. 324-6.

7.Atay E, Ermiş Ç, Gökbayrak Atay İN, Aydemir Ö, Özmen E. The role of predominant polarity on cognitive dysfunctions in patients with bipolar disorder. International Journal of Bipolar Disorders. 2024;12(1):41.

8.Sentissi O, Popovic D, Moeglin C, Stukalin YB, Mosheva M, Vieta E, et al. Predominant polarity in bipolar disorder patients: the COPE bipolar sample. Journal of Affective Disorders. 2019;250:43-50.

9.Azorin J, Adida M, Belzeaux R. Predominant polarity in bipolar disorders: Further evidence for the role of affective temperaments. Journal of Affective Disorders. 2015;182:57-63.

10.Bartoli F, Bassetti C, Gazzola M, Gianfelice L, Cavaleri D, Crocamo C, Carrà G. Prevalence and correlates of manic/hypomanic and depressive predominant polarity in bipolar disorder: systematic review and meta-analysis. BJPsych Open. 2024;10(3):e100.

11.Popovic D, Reinares M, Goikolea JM, Bonnin CM, Gonzalez-Pinto A, Vieta E. Polarity index of pharmacological agents used for maintenance treatment of bipolar disorder. European Neuropsychopharmacology. 2012;22(5):339-46.

12.Bailey SL, Heitkemper MM. Circadian rhythmicity of cortisol and body temperature: morningness-eveningness effects. Chronobiology international. 2001;18(2):249-61.

13.Boudebesse C, Lajnef M, Geoffroy P, Bellivier F, Nieto I, Gard S, et al. Chronotypes of bipolar patients in remission: validation of the French version of the circadian type inventory in the FACE-BD sample. Chronobiology international. 2013;30(8):1042-9.

14.Karadağ F, Oral ET, Aran Yalçın F, Erten E. Young mani derecelendirme ölçeğinin Türkiye'de geçerlik ve güvenilirliği. Türk Psikiyatri Dergisi. 2001;13(2):107-14.

15.Akdemir A, Türkçapar M, Örsel S, Demirergi N, Dag I, Özbay M. Reliability and validity of the Turkish version of the Hamilton Depression Rating Scale. Comprehensive psychiatry. 2001;42(2):161-5.

16.Colom F, Vieta E, Daban C, Pacchiarotti I, Sanchez-Moreno J. Clinical and therapeutic implications of predominant polarity in bipolar disorder. Journal of Affective Disorders. 2006;93(1-3):13-7.

17.Aydemir O, Akkaya C, Altinbas K, Kora K, Suculluoglu Dikici D, Akdeniz F, et al. Reliability and validity of Turkish version of biological rhythms interview of assessment in neuropsychiatry. ANADOLU PSIKIYATRI DERGISI-ANATOLIAN JOURNAL OF PSYCHIATRY. 2012;13(4).

18.Agargun MY, Cilli AS, Boysan M, Selvi Y. Turkish version of the morningness-eveningness questionnaire (MEQ). Sleep

and Hypnosis. 2007;9(1):16.

19.Grof P, Duffy A, Cavazzoni P, Grof E, Garnham J, MacDougall M, et al. Is response to prophylactic lithium a familial trait? Journal of Clinical Psychiatry. 2002;63(10):942-7.

20.Nivoli AM, Pacchiarotti I, Rosa AR, Popovic D, Murru A, Valenti M, et al. Gender differences in a cohort study of 604 bipolar patients: the role of predominant polarity. Journal of Affective Disorders. 2011;133(3):443-9.

21.Carvalho AF, McIntyre RS, Dimelis D, Gonda X, Berk M, Nunes-Neto PR, et al. Predominant polarity as a course specifier for bipolar disorder: a systematic review. Journal of Affective Disorders. 2014;163:56-64.

22.Fico G, Anmella G, Sague-Villavella M, Gomez-Ramiro M, Hidalgo-Mazzei D, Vieta E, Murru A. Undetermined predominant polarity in a cohort of bipolar disorder patients: prevalent, severe, and overlooked. Journal of Affective Disorders. 2022;303:223-9.

23.McCarthy MJ, Wei H, Nievergelt CM, Stautland A, Maihofer AX, Welsh DK, et al. Chronotype and cellular circadian rhythms predict the clinical response to lithium maintenance treatment in patients with bipolar disorder. Neuropsychopharmacology. 2019;44(3):620-8.

24.Kanagarajan K, Gou K, Antinora C, Buyukkurt A, Crescenzi O, Beaulieu S, et al. Morningness-Eveningness questionnaire in bipolar disorder. Psychiatry research. 2018;262:102-7.

25.Takaesu Y. Circadian rhythm in bipolar disorder: a review of the literature. Psychiatry and clinical neurosciences. 2018;72(9):673-82.

26.Taillard J, Sagaspe P, Philip P, Bioulac S. Sleep timing, chronotype and social jetlag: impact on cognitive abilities and psychiatric disorders. Biochemical pharmacology. 2021;191:114438.

27.Hsu C-W, Tsai S-Y, Tseng P-T, Liang C-S, Vieta E, Carvalho AF, et al. Differences in the prophylactic effect of serum lithium levels on depression and mania in bipolar disorder: a dose-response meta-analysis. European Neuropsychopharmacology. 2022;58:20-9.

28.Scott J, Bellivier F, Manchia M, Schulze T, Alda M, Etain B, et al. Can network analysis shed light on predictors of lithium response in bipolar I disorder? Acta Psychiatrica Scandinavica. 2020;141(6):522-33.

29.Rohr KE, McCarthy MJ. The impact of lithium on circadian rhythms and implications for bipolar disorder pharmacotherapy. Neuroscience letters. 2022;786:136772.

30.Hui T, Kandola A, Shen L, Lewis G, Osborn D, Geddes J, Hayes J. A systematic review and meta-analysis of clinical predictors of lithium response in bipolar disorder. Acta Psychiatrica Scandinavica. 2019;140(2):94-115.

31.Tekdemir R, Selvi Y, Altınbaş K, Koçak N. Decreased miR-15b-5p/miR-155-5p levels and increased miR-134-5p/miR-652-3p levels among BD patients under lithium treatment. Journal of Affective Disorders. 2022;317:6-14.

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ORIGINAL ARTICLE

Comparison of Anxiety and Depression Levels of Children with and without Healthcare Professionals Parents During the COVID-19 Pandemic

COVID-19 Pandemisi Döneminde Ebeveyni/Ebeveynleri Sağlık Personeli Olan ve Olmayan Çocukların Anksiyete ve Depresyon Düzeylerinin Karşılaştırılması

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ABSTRACT

Aim: Little is known about the effects of the pandemic on children and children whose parents are healthcare professionals. This study was conducted to compare the anxiety and depression levels of children aged 8-17 years with and without parents who are healthcare professionals during the COVID-19 pandemic period.
Material and Methods: This descriptive study was completed with 224 children. The research was conducted in Eskisehir, Turkiye, between 14 May and 14 June 2020, using the online survey method. The data were collected with the "Descriptive Information Form" and the "Depression Scale in Children-Renewed Form". p<0.05 was considered statistically significant in the study.
Results: The average age of the children (n=224) is 13.63±2.99. Children received information about COVID-19 from television/internet (86.6%), parents (74.1%) and teachers (44.6%). There was no relationship between children's information acquisition characteristics and anxiety and depression scores (p>0.05). The rate of parents working in the field of health is 51.3%. The anxiety and depression scores of children whose parent(s) were healthcare professional were statistically higher than those whose parents were not (p=0.030, p=0.040, respectively). It was determined that children whose parent(s) were healthcare professional were more worried about their parents going to work during the pandemic period and were afraid of contracting COVID-19 disease (p=0.005; p=0.029).
Conclusion: This study is important in terms of showing the effects of COVID-19 on children of healthcare workers and non-health professionals parents during the pandemic. It becomes clear that effective measures must be taken to protect the mental health of healthcare workers and their children, who are considered to be among the vulnerable groups during the epidemic period. For this reason, it may be beneficial to support children more effectively psychologically during pandemic periods and improve the working conditions of parents.

Keywords: Anxiety, COVID-19, Depression, Health Personnel, Child

ÖZ

Amaç: COVID-19 pandemisi özellikle sağlık çalışanlarının ruh sağlığını olumsuz yönde etkilemiştir. Pandemilerin yetişkinler üzerindeki etkisini gösteren çok sayıda araştırma bulunmaktadır. Ancak pandeminin çocuklar ve ebeveyni sağlık çalışanı olan çocuklar üzerine etkileri hakkında çok az şey bilinmektedir. Bu çalışma COVID-19 pandemisi döneminde ebeveyni/ebeveynleri sağlık personeli olan çocuklar ile, ebeveynleri sağlık personeli olmayan 8-17 yaş arası çocukların anksiyete ve depresyon düzeylerinin karşılaştırılması amacıyla yapıldı.
Gereç ve Yöntemler: Tanımlayıcı tipte olan bu araştırma, 224 çocuk ile tamamlandı. Araştırma Türkiye'nin Eskişehir ilinde 14 Mayıs- 14 Haziran 2020 tarihleri arasında online anket yöntemi ile yapıldı. Veriler "Tanıtıcı Bilgi Formu" ve "Çocuklarda Anksiyete ve Depresyon Ölçeği-Yenilenmiş Formu" ile toplandı. Çalışmada p<0.05 istatistiksel olarak anlamlı kabul edilmiştir.
Bulgular: Çocukların yaş ortalaması 13,63±2,99 (min:8 – max:17)'dur. Çocukların %86,6 (n=194)'sı televizyon/internetten, %74,1 (n=166)'i anne/babasından ve %44,6 (n=100)'sı öğretmenlerinden COVID-19 hastalığı hakkında bilgi aldığı belirlenmiştir. Çocukların bilgi edinme özellikleri ile anksiyete ve depresyon puanları arasında bir ilişki saptanmamıştır (p>0,05). Sağlık alanında görev yapan ebeveyn sayısı %51,3 (n=115)'tür. Ebeveyni/ebeveynleri sağlık personeli olan çocukların anksiyete ve depresyon puanları, ebeveyni sağlık personeli olmayanlara göre istatistiksel olarak fazla olduğu saptanmıştır (sırasıyla p=0,030, p=0,040). Ebeveyni/ebeveynleri sağlık personeli olan çocukların, pandemi döneminde anne/babasının işe gidip gelmesinden daha fazla endişe duyduğu ve COVID-19 hastalığına yakalanmasından korktuğu belirlenmiştir (p=0,005; p=0,029).
Sonuç: Araştırmamız salgın döneminde COVID-19'un sağlık personeli ve sağlık personeli olmayan ebeveynlerin çocukları üzerindeki etkileri göstermesi açısından önemlidir. Salgın döneminde savunmasız gruplar arasında yer aldıkları düşünülen sağlık çalışanı ve çocuklarının ruh sağlığını korumaya yönelik etkili önlemler (pandemi hakkında yapılandırılmış eğitim, psikolojik destek gibi) alınması gerektiği ortaya çıkmaktadır. Bu nedenle çocukların pandemi dönemlerinde ruhsal açıdan daha etkin şekilde desteklenmesi ve ebeveynlerin çalışma koşullarının iyileştirilmesi yararlı olabilir.

Anahtar Kelimeler: Anksiyete, COVID-19, Depresyon, Sağlık Personeli, Çocuk

Introduction

The COVID-19 (SARS-CoV-2) pandemic first started in Wuhan, China in December 2019 (1). After this date, the number of cases increased rapidly worldwide. In Turkiye, the first case was seen in March 2020 (2). According to the World Health Organization (WHO) report on the number of people infected with COVID-19 in the world, while the total number was 80 million in December 2020, it is seen that this number increased rapidly to 775 million in April 2024 (3). This situation has led countries to take strict rules such as social distancing and restrictive movement policies (such as closing schools, social activity centres, switching to remote

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working in many institutions, mandatory isolation) to prevent the transmission of the disease (4). This study was conducted in Turkiye during the peak of the COVID-19 pandemic and the implementation of strict rules.

At the beginning of the COVID-19 disease, higher morbidity and mortality was observed in older adults, suggesting that having an advanced age was in a risk group in this disease (5). However, as studies were conducted in this field, it was determined that there were other risk groups. These risk groups include healthcare professional, smokers, older adults, people with chronic diseases (such as heart disease, hypertension, respiratory disease, diabetes, cancer), travellers, pregnant women (6) and children (7,8). Symptoms in children are usually asymptomatic or mild to moderate. Children are mostly infected by family members (9,10). The most risky children in terms of domestic contact are the children of healthcare workers. During the pandemic period, the difficulties in working hours and working conditions of healthcare workers have increased even more in order to combat the disease. As a result, studies have shown that healthcare workers are more likely to develop this disease (11-13), sleep problems (14), anxiety, depression (15), disruption in the dynamics of family life and fear of infecting family members (16,17) compared to other professional groups. It can be said that the policies implemented by countries to reduce transmission during the pandemic process affect some groups more negatively (11-17).

Another important group affected by the policies implemented during the pandemic period is children. In this process, children have been subjected to compulsory restrictions in areas of socialization and physical activity, such as interrupting face-to-face education and social activities, and as a result, children have faced many negative situations. Exposure to unexplained and unpredictable situations such as the pandemic, lack of regular caregivers, decrease in parental support are perceived as a threat by children. As a result, children may experience negative physical and psychological symptoms (18,19).

This study was conducted to compare the anxiety and depression levels of children aged 8-17 years with and without parents who are healthcare professionals during the COVID-19 pandemic period.

Materials And Methods

Research type, location, and time

This study is of descriptive type. The research was conducted in Eskisehir province of Turkiye between May 14 and June 14, 2020.

Sampling and recruitment

The study was completed with 224 children, who could be reached online, who met the inclusion criteria and agreed to participate in the study. Data were gathered through snowball sampling. The survey was distributed from May 2020 to June 2020. Participants were sent a link to the survey and completed it remotely via an online survey platform (WhatsApp). In the instructions created for the research, necessary explanations were made (such as residing in Eskisehir, parent and child must fill out the survey together) and detailed information about how to fill out the measurement tools. Informed consent was obtained from all parents and children before survey completion.

The inclusion criteria were that the child was between the ages of 8-17, the child and the parent agreed to participate in the study, and all questions in the questionnaire were filled in completely.

Data collection tools

Data were collected with the 'Introductory Information Form' and 'Revised Child Anxiety and Depression Scales'.

Introductory Information Form

This form includes questions about the socio-demographic characteristics of the child and parents and information about the child's COVID-19 disease (9,20,21).

Revised Children's Anxiety and Depression Scale (RCADS)

It was developed by Chorpita et al. (2000). The Cronbach Alpha coefficient of the scale was found to be 0.95 and 0.90 (20). The scale was adapted into Turkish by Gormezet al. (2017) and the Cronbach Alpha coefficient was found to be 0.95. The scale consists of 47 questions aiming to screen anxiety disorders and depression in children and adolescents and is a 4-point Likert scale (0=never, 1=sometimes, 2=frequently, 3=always). The scale has 6 sub-dimensions. These are generalised anxiety disorder, separation anxiety disorder, panic disorder, obsessive-compulsive disorder, social phobia and major depressive disorder. For the total anxiety score; generalised anxiety disorder, separation anxiety disorder, panic disorder, obsessive-compulsive disorder and social phobia sub-dimension

items are summed. For the total internalising disorder score, major depressive disorder sub-dimension items are added to the total anxiety score. Higher scores indicate an increased level of anxiety and depressive symptoms (21). The Cronbach Alpha coefficient of this study was found to be 0.95.

Statistical analysis

Data were expressed as n, percentage, mean, standard deviation, minimum and maximum values. The suitability of the data for normal distribution was analysed by Kolmogorov-Smirnov and Shapiro-Wilk tests, descriptive statistics (skewness and kurtosis coefficients) and graphs (normal distribution curve and histogram). The range of skewness and kurtosis coefficient values for normal distribution was accepted as ±2.00 (22). Mann-Whitney U and Kruskal-Wallis H tests were applied to data sets consisting of independent variables and not normally distributed. Spearmen and Pearson Correlation tests were applied to non-normally distributed data sets to determine the relationship between variables and their directions. Analyses were performed using IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) programme. In the study, $p<0.05$ was considered statistically significant.

Results

The study was completed with 224 children. The mean age of the children was 13.63±2.99 (min:8 - max:17). 90.2% (n=202) of the children had a nuclear family structure, 65.6% (n=147) of the children's family income was equal to their expenses and 21.9% (n=49) of the children's family income was higher than their expenses. 24,1% (n=54) of the children are only children and 64,3% (n=144) have one or two siblings. 14.3% (n=32) of the children had chronic diseases (n=12 - 5.4% metabolic disease, n=5 - 2.2% heart disease and n=15 - n=6.7% respiratory system disease) and 1.8% (n=4) had psychological diseases (n=2 - 0.9% anxiety disorder, n=2 - 0.9% bipolar disorder and obsessive-compulsive disorder). 86.6% (n=194) of the children stated that they received information about COVID-19 disease from television/internet, 74.1% (n=166) from their parents and 44.6% (n=100) from their teachers. There was no relationship between these characteristics of the children and their anxiety and depression scores (RCADS) (p>0.05). The total number of parents working in the health field was 115 (51.3%) (n=81 - 70.4% nurses/midwives/health officers, n=20 -

Table 1. Comparison of children's characteristics and scores on the RCADS

Variables (n=224)	n (%)	Total Anxiety Score		Statistical Analysis	Total Internalising Disorder Score		Statistical Analysis
		Median	Min-Max		Median	Min-Max	
Age (X±SS; 13,63±2,99)							
Under 10 years of age	50 (22.3)	23.50	5.00-89.00	K=6.158 p=0.046	29.00	8.00-107.00	K=7.680 p=0.021
11-14 years	67 (29.9)	20.00	0.00-91.00		25.00	0.00-114.00	
Over 15 years	107 (47.8)	27.00	6.00-75.00		35.00	9.00-99.00	
Gender							
Female	137 (61.2)	25.00	3.00-91.00	U=-0.895 p=0.371	32.00	4.00-114.00	U=-1.443 p=0.149
Male	87 (38.8)	21.00	0.00-79.00		26.00	0.00-97.00	
Place of residence							
Village/District	48 (21.4)	27.00	3.00-89.00	U=-1.111 p=0.267	31.50	4.00-107.00	U=-0.980 p=0.327
Province	176 (78.6)	23.00	0.00-91.00		30.00	0.00-114.00	
Survival of Parents							
Yes	204 (91.1)	24.00	0.00-91.00	U=-1.454 p=0.146	30.00	0.00-114.00	U=-1.345 p=0.179
No	20 (8.9)	22.00	6.00-56.00		27.50	7.00-66.00	
Status of Diagnosed Chronic Diseases							
Yes	32 (14.3)	28.00	7.00-75.00	U=-1.527 p=0.127	36.50	11.00-99.00	U=-1.537 p=0.124
No	192 (85.7)	22.50	0.00-91.00		29.00	0.00-114.00	
Status of Diagnosed Psychological Disorders							
Yes	4 (1.8)	21.50	11.00-23.00	U=-0.732 p=0.464	29.00	16.00-32.00	U=-0.518 p=0.605
No	220 (98.2)	23.50	0.00-91.00		30.00	0.00-114.00	
Parent(s) being a Healthcare Professional							
Yes	98 (43.8)	28.00	5.00-91.00	U=5131.5 p=0.030	38.00	5.00-114.00	U=5226.5 p=0.040
No	126 (56.3)	20.00	0.00-60.00		26.00	0.00-83.00	

U= Mann-Whitney U test, K= Kruskal-Wallis test
RCADS= Revised Child Anxiety and Depression Scales

17.4% doctors, n=10 - 8.7% pharmacists/psychologists/ social workers/audiometrists/medical secretaries and n=4 - 3.5% health technicians). In Table 1, information about the comparison of the characteristics of the children and the scores of the RCADS is given.

Of children, 96.4% (n=216) know that COVID-19 is transmitted in close contact with people, 97.8% (n=219) know what COVID-19 is, 98.7% (n=221) know that it is important to wear a face mask to protect against COVID-19, and 99.6% (n=223) know that it is important to wash hands to protect against COVID-19. In addition, 75.9% (n=170) of the children knew that it is important to sleep regularly to prevent COVID-19, 92.0% (n=206) knew that it is important to eat a healthy diet to prevent COVID-19, 95.5% (n=214) knew that it is important to keep a distance of at least one meter between people to prevent COVID-19 transmission, and 98.7% (n=221) knew that it is important to avoid touching hands to face and mouth when going out of the house to prevent COVID-19 transmission. There was no relationship between these statements of the children and their anxiety and depression scores (RCADS) ($p>0.05$). Table 2 shows the comparison of the anxiety and fear of COVID-19 disease with whether the parents of the children were health professional or not.

Table 2. Comparison of worry and fear of COVID-19 disease in terms of whether the parents of the children are healthcare professionals or not

Variables (n=224)	Total n (%)	Health Professional Parents	Non-health Professional Parents	Statistical Analysis
During the COVID-19 disease period, the child worried about their mothers and/or fathers going/coming to and from work				
Yes	147 (65.6)	74 (76.3)	73 (%57.5)	χ^2=12.282 p=0.005
No	77 (34.4)	23(23.7)	54 (42.5)	
The child's fear their mother and/or father will contract COVID-19 while going to and coming from work				
Yes	183 (81.7)	86 (88.7)	97 (76.4)	χ^2=5.548 p=0.029
No	41 (18.3)	11 (11.3)	30 (23.6)	
The child's fear their mother and/or father will infect their with COVID-19 while going to and coming from work				
Yes	152 (67.9)	72 (74.2)	80 (63.0)	χ^2=3.183 p=0.101
No	72 (32.1)	25 (25.8)	47 (37.0)	
χ^2=Chi-square				

Discussion

This study aimed to compare the anxiety and depression levels of children whose parents are healthcare professionals and those whose parents are not during the COVID-19 pandemic. We found that children of healthcare professionals showed higher anxiety and depression scores compared to other children. In particular, children of healthcare professionals were more concerned about their parents going to work and contracting COVID-19. However, children's anxiety and depression was not impacted by their sources of COVID-19 information and the majority of children understood COVID-19 prevention knowledge. Previous studies (16,23-25) have shown that healthcare professionals who have children and work on the front lines during the pandemic period experience more anxiety. Similarly, in this study, it was found that children whose parents were healthcare professionals had higher anxiety, depression and concern scores. The higher anxiety and depression scores among children of healthcare professionals may be attributed to their heightened awareness of the risks faced by their parents. For example, exposure to stressful information, fear of their parents contracting the virus, unpredictable parental work hours, and prolonged separation may exacerbate children's mental health concerns (26). Furthermore, previous research indicates that children are sensitive to the stress levels and mental health of their parents (27), especially during pandemics when family functioning and routines are disrupted. Akdag et al. (2023) found that "physicians and nurses had significantly higher emotional exhaustion scores than others" (26). Finally, research from past pandemics (e.g., H1N1, SARS) also showed increased mental health issues among healthcare professionals, children of frontline workers, and psychosocial disruptions (28). In the light of these findings, it can be said that healthcare professionals and their children face more mental problems during the pandemic period.

The absence of a significant relationship between COVID-19 information sources, anxiety, and depression indicates that merely having information does not necessarily equate to reduced anxiety or depression. The quality and manner of information delivery may play a more critical role for children, who

have different learning needs and preferences. In our study, the majority of children received their COVID-19 information from media (television and internet), which are not always adapted for children. These adult-centric forms of communication may therefore have been difficult to understand for children (29). Additionally, children are highly influenced by their social contexts (30,31). Thus, decontextualized COVID-19 information derived from media may be less influential than the ways that their caregivers, friends, and social circles react to the information.

Strengths and limitations

The study was conducted in a single city (Eskisehir, Turkiye) and may not be representative of other regions or countries. Furthermore, the use of online surveys might have limited participation to those with internet access. In addition, this study used snowball sampling. This method is a non-probability sampling method, not all participants in the universe have an equal chance of being selected. Another limitation is that although the instructions for completing the questionnaire stated that the respondent had to reside in Eskişiehir province, it is possible that a respondent from a different province may have completed the questionnaire. Yet, by specifically targeting children whose parents are healthcare professionals, the study provides valuable insights into a vulnerable subgroup that is often at higher risk due to the stressful nature of their parents' jobs. The study also includes a substantial sample size of 224 children, yielding preliminary findings which set the stage for future investigations into this population and insights related to the social impacts of global pandemics.

Conclusion

This study underscores the significant mental health impact of the COVID-19 pandemic on children of healthcare professionals showed higher anxiety and depression scores compared to other children. These findings contribute to the understanding of stress experienced by family members of frontline workers, highlighting the need for targeted mental health support for children. Implementing support systems in schools and communities could mitigate these mental health issues as social support has been shown to foster resilience. Protecting the mental health of healthcare professionals and their families is crucial for the overall resilience of the healthcare systems and families during pandemics. Enhanced psychological support and improved working conditions for healthcare professionals can alleviate some of the burdens on their children, as well as community-based resources to support resilience.

Future studies should include diverse geographic locations to enhance generalizability and follow children over time to provide deeper insights. Finally, in-depth qualitative studies that explore the personal experiences and coping mechanisms of these children can help to inform specific interventions, policies, and practice.

Ethical approval

Ethics committee approval (date 28.05.2020 and number 25403353-050.99-E.50146) from the Eskisehir Osmangazi University and institutional permission from the of the Ministry of Health (2020-05-09T15_17_23) were obtained before the research was conducted. Only parents and their children whose informed consent was obtained after the information were included in the study.

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Declaration of competing interest

None.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The datasets generated during and analysed during the current research are available from the corresponding author on reasonable request.

References

1.T, Durantel D, Pasmant E, Lau G, Schinazi RF. COVID-19: Discovery, diagnostics and drug Asselah development. J Hepatol 2021;74(1):168-84.

2.T.C. Ministry of Health. Turkey's 1-year process of fighting against Covid-19. 2024 April 29. Available at: https://www.saglik.gov.tr/TR,80604/bakan-koca-turkiyenin-kovid-19la-1-yillik-mucadele-surecini-degerlendirdi.html. Accessed April 08, 2024.

3.The World Health Organization (WHO). COVID-19 dashboard. Number of COVID-19 cases reported to WHO (cumulative total). Available at: https://data.who.int/dashboards/covid19/cases. Accessed April 29, 2024.

4.Pokhrel S, Chhetri R. A literature review on impact of COVID-19 pandemic on teaching and learning. Higher Education for the Future 2021;8(1):133-41.

5.Gardner W, States D, Bagley N. The coronavirus and the risks to the elderly in long-term care. J Aging Soc Policy 2020;32(4-5):310-5.

6.Naveed M, Naeem M, Rahman M, et al. Review of potential risk groups for coronavirus disease 2019 (COVID-19). New Microbes New Infect 2021;41:100849.

7.Borrelli M, Corcione A, Castellano F, Fiori Nastro F, Santamaria F. Coronavirus disease 2019 in children. Front Pediatr 2021;9: 668484.

8.Zachariah P. COVID-19 in Children. Infect Dis Clin 2021;36(1):1-14.

9.Zhen-Dong Y, Gao-Jun Z, Run-Ming J, et al. Clinical and transmission dynamics characteristics of 406 children with coronavirus disease 2019 in China: a review. J Infect 2020;81(2):e11-5.

10.Zhu Y, Bloxham CJ, Hulme KD, et al. A meta-analysis on the role of children in severe acute respiratory syndrome coronavirus 2 in household transmission clusters. CID 2021;72(12):e1146-53.

11.Sabetian G, Moghadami M, Hashemizadeh Fard Haghighi L, et al. COVID-19 infection among healthcare workers: a cross-sectional study in southwest Iran. Virol J 2021;18:1-8.

12.Guedes AR, Oliveira MS, Tavares BM, et al. Reinfection rate in a cohort of healthcare workers over 2 years of the COVID-19 pandemic. Sci Rep 2023;13(1):712.

13.Pray IW, Grajewski B, Morris C, et al. Measuring work-related risk of coronavirus disease 2019 (covıd-19): comparison of COVID-19 Incidence by Occupation and Industry-Wisconsin, September 2020 to May 2021. CID 2023;76(3):e163-e171.

14.Sayik D, Acikgoz A, Mutlu F. Sleep quality of medical staff during the coronavirus pandemic: A meta-analysis. J Turk Sleep Med 2021;8(1):1-6.

15.Chen Y, Wang J, Geng Y, et al. Meta-analysis of the prevalence of anxiety and depression among frontline healthcare workers during the COVID-19 pandemic. Front Public Health 2022;10:984630.

16.Sayik D, Acikgoz A, Kaya S. Anxiety and sleep quality levels of emergency medical personnel and factors affecting them during the Coronavirus Disease-2019 Pandemic. J Turk Sleep Med 2022;9(1):27-36.

17.Wendlandt B, Kime M, Carson S. The impact of family visitor restrictions on healthcare workers in the ICU during the COVID-19 pandemic. Intensive Crit Care Nurs 2022;68:103123.

18.Nobari H, Fashi M, Eskandari A, Villafaina S, Murillo-Garcia Á, Pérez-Gómez J. Effect of COVID-19 on health-related quality of life in adolescents and children: a systematic review. Int J Environ Res Public Health 2021;18(9):4563.

19.Pizarro-Ruiz JP, Ordóñez-Camblor N. Effects of Covid-19 confinement on the mental health of children and adolescents in Spain. Sci Rep 2021;11(1):11713.

20.Chorpita BF, Yim L, Moffitt C, Umemoto LA, Francis SE. Assessment of symptoms of DSM-IV anxiety and depression in children: A revised child anxiety and depression scale. Behav Res Ther 2000;38(8):835-55.

21.Gormez V, Kılıncaslan A, Orengul AC, et al. Psychometric properties of the Turkish version of the Revised Child Anxiety and Depression Scale–Child Version in a clinical sample. Psychiatry Clin Psychopharmacol 2017;27(1):84-92.

22.Uysal I, Kılıç A. Normal distribution dilemma. AJESI 2022;12(1):220-48.

23.Liu S, Yang L, Zhang C, et al. Correspondence online mental health services in China during the COVID-19 outbreak. Lancet Psychiatry 2020;0366:2019-20.

24.Cakmak G, Ozturk ZA. Being both a parent and a healthcare worker in the pandemic: who could be exhausted more? In Healthcare 2021;9(5):564.

25.Arpacıoglu S, Baltalı Z, Unubol B. Burnout, fear of Covid, depression, occupational satisfaction levels and related factors in healthcare professionals in the COVID-19 Pandemic. Cukurova Med J 2021;46(1):88-100.

26.Akdag B, Ege D, Goksuluk D, Ipekten F, Erdogan A, Onder A. The parental COVID-19 anxiety and emotional exhaustion in healthcare workers: exploring the roles of resilience, prosocialness, and optimism. Curr Psychol 2023;42(23):20042-51.

27.Wolicki SB, Bitsko RH, Cree RA, et al. Mental health of parents and primary caregivers by sex and associated

child health indicators. Advers Resil Sci 2021;2(2):125-39.

28.O'Sullivan T, Bourgoin M. Vulnerability in an Influenza Pandemic: looking beyond medical risk. Behav 2010;11:16.

29.Siegler RS. Children's learning. American Psychol 2005;60(8):769-78.

30.Hinde RA, Stevenson-Hinde J. Interpersonal relationships and child development. Developmental Rev 1987;7(1):1-21.

31.Keenan T, Evans S, Crowley K. An introduction to child development. London: SAGE Publications Ltd; 2016.

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ORIGINAL ARTICLE

Prognostic value of systemic immune-inflammatory index in hospitalized adolescent COVID-19 patients

Hastanede yatan adölesan COVID-19 hastalarında sistemik immün-inflamatuvar indeksin prognostik değeri

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ABSTRACT

Background: A new parameter called systemic immune-inflammatory index (SII), which is based on neutrophil-lymphocyte ratio (NLR) and platelet count, is used to examine the inflammatory and immune status of patients. The aim of this study was to evaluate the prognostic value of SII in adolescents diagnosed with COVID-19 and to compare SII with other biomarkers including C-reactive protein (CRP)/albumin (Alb) ratio, D-dimer, lactate and NLR.
Methods: The medical records of hospitalized adolescent COVID-19 patients between April 1, 2020, and March 31, 2022, were retrospectively reviewed. A cutoff value for SII was obtained to examine the predictive value of SII for intensive care unit (ICU) admission as the primary outcome.
Results: A total of 177 patients with a mean age of 165.89 ± 26.60 months were included in the study. 97 (54.8%) of the patients were male. The most common presenting symptom was fever (n = 102, 57.6%). Median (IQR) SII was 799 (951), lactate 1.9 (1.53), NLR 10.19 ± 6.77 and CRP/Alb ratio 1.55 (2.61). The cut-off value for SII in predicting ICU admission was ≥1111 (sensitivity, 78.6%; specificity, 75.2%; + likelihood ratio, 3.32; - likelihood ratio, 0.30; AUC: 0.768) (p < 0.001). While SII and CRP/Alb ratio were better than lactate in predicting ICU admission (p = 0.03 and p = 0.04, respectively), there was no statistical difference between SII and CRP/Alb ratio (p > 0.05).
Conclusion: The results of this study suggest that a high SII during hospitalization is associated with an increased likelihood of ICU admission in patients hospitalized with COVID-19. Although additional studies are needed to confirm and validate these findings, the evidence of this study supports that SII is a valuable prognostic predictor of hospitalized patients with COVID-19.

Keywords: Adolescent, COVID-19, prognoses, systemic immune-inflammatory index

ÖZ

Giriş: Nötrofil-lenfosit oranı (NLR) ve trombosit sayısına dayanan sistemik immün-inflamatuar indeks (SII) adı verilen yeni bir parametre, hastaların inflamatuar ve immün durumunu aynı anda değerlendirmek için kullanılmaktadır. Bu çalışmanın amacı COVID-19 tanısı alan adölesanlarda SII'nin prognostik değerini değerlendirmek ve SII'yi C-reaktif protein (CRP) / albümin (Alb) oranı, D-dimer, laktat ve NLR gibi diğer prognostik belirteçlerle karşılaştırmaktır.
Gereçler ve Yöntem: Hastanede yatan adölesan COVID-19 hastalarının 1 Nisan 2020 ve 31 Mart 2022 tarihleri arasındaki tıbbi kayıtları retrospektif olarak incelendi. Birincil sonlanım noktası olarak yoğun bakım ünitesine kabul kullanıldı. SII'nin yoğun bakım ünitesine kabul için öngörücü değeri hesaplandı ve diğer biyobelirteçler ile karşılaştırıldı.
Bulgular: Yaş ortalaması 165,89 ± 26,60 ay olan 177 hasta çalışmaya dahil edilmiştir. Hastaların 97 (54,8%) tanesi erkekti. En sık görülen başvuru semptomu ateşti (n = 102, %57,6). SII 799 (951), laktat 1.9 (1.53) mmol/L, NLR 10.19 ± 6.77 ve CRP/Alb oranı 1.55 (2.61) idi. Yoğun bakım kabulü öngörmede SII için cut-off değeri ≥1111 idi (sensitivite, 78,6%; spesivite, 75,2%; + likelihood ratio, 3,32; - likelihood ratio, 0,30; AUC: 0,768) (p < 0,001). SII ve CRP/Alb oranı yoğun bakıma kabulü öngörmede laktattan daha iyi iken (sırasıyla p = 0,03 ve p = 0,04), SII ve CRP/Alb oranı arasında istatistiksel fark yoktu (p > 0,05).
Sonuç: Bu çalışmanın sonuçları, COVID-19 ile hastaneye yatırılan adölesan hastalarda hastaneye yatış sırasında yüksek SII'nin artmış yoğun bakım kabulü ile ilişkili olduğunu göstermektedir. Bu bulguları doğrulamak ve geçerli kılmak için ek çalışmalara ihtiyaç duyulmasına rağmen, bu çalışmadan elde edilen kanıtlar, COVID-19 hastalarında hastane içi sonuçların değerli bir prognostik göstergesi olarak SII'nin potansiyel faydasını desteklemektedir.

Anahtar Kelimeler: adölesan, COVID-19, prognoz, sistemik immün-inflamatuvar indeks

Introduction

The past five years, COVID-19 caused more than 7 million deaths with approximately 750 million confirmed cases (1). In the early stages of the pandemic, COVID-19 was thought to affect mainly middle-aged and elderly people, and the incidence in children was lower. However, the incidence in children was underestimated due to low testing rate (2). Children with COVID-19 have with milder symptoms and are less likely to experience severe disease or death than adults (3,4). Obesity may worsen the prognosis of COVID-19 (5). It has also been shown that adolescents with the delta variant of COVID-19 require more oxygen support, have an increased need for endotracheal intubation, and experience prolonged hospital stays (6).

A new parameter called systemic immune-inflammatory index (SII), which is based on neutrophil-lymphocyte

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ratio (NLR) and platelet count, is used to assess the inflammatory and immune status of patients. In addition to cancer patients, SII has also been associated with poor outcomes and mortality in coronary artery disease, chronic heart failure, and intracranial hemorrhage (7-10). In a recent meta-analysis, Yuan et al. (11) highlighted the association between admission SII and the risk of in-hospital mortality in patients with COVID-19.

Age-related differences in the clinical course of COVID-19 are still under investigation; one hypothesis suggests that differences in immune system function and maturation in young children compared to adults (12). The aim of this study was to evaluate the prognostic value of SII in adolescents diagnosed with COVID-19 and to compare SII with other biomarkers including C-reactive protein (CRP)/albumin (Alb) ratio, D-dimer, lactate and NLR.

Methods

This study included patients aged 10-18 years who were diagnosed with COVID-19 and hospitalized between April 1, 2020 and March 31, 2022. The diagnostic criteria for COVID-19 were accepted a positive polymerase chain reaction (PCR) test and/or chest computed tomography (CT) findings indicative of viral pneumonia. Patients with missing data, patients aged >18 years or <10 years, those with hematologic or solid organ malignancy, those receiving immunosuppressive treatment for any reason, and those with any chronic disease were excluded from the study. The World Health Organization defined individuals between the ages of 10-19 as adolescents. We excluded patients aged 19 because admission to pediatric clinics is legally limited to 18 years old in Turkey (13). The local ethics committee approved the study (decision number 2024/5037).

Patient demographics, admission symptoms, laboratory results (CBC, C-reactive protein, D-dimer, lactate, albumin), SII score calculated as (neutrophil-to-lymphocyte ratio) x platelet count, CT findings (pleural effusion, ground-glass opacities, consolidation), hospital stay duration, intensive care unit (ICU) admission, and mortality were recorded.

Data analyses

Normality of the distribution was assessed using the Kolmogorov-Smirnov test. Continuous data were presented as mean ± standard deviation for variables with a normal distribution and as median and interquartile range (IQR) for variables with a non-normal distribution. Categorical data were presented as frequencies and percentages. The primary outcome was ICU admission. The effect of various factors on ICU admission was evaluated using chi-squared or Fisher's exact test for categorical variables and Student's t-test or Mann-Whitney U test for numerical variables. We analyzed the performance characteristics of CRP/Alb ratio, lactate, and SII levels in predicting ICU admission using receiver operating characteristic (ROC) curves. We determined cut-off values using Youden's index and compared them with DeLong's method. MedCalc statistical software (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org), version 20.110 was used for all analyses. A p-value of <0.05 was considered statistically significant.

Results

During the study period, 265 patients were hospitalized with a diagnosis of COVID-19 infection. Twelve patients were excluded due to hematologic malignancy, 2 patients due to solid organ malignancy, 5 patients due to immunosuppressive treatment, 27 patients due to asthma, 11 patients due to cerebral palsy, 8 patients due to diabetes mellitus, 7 patients due to epilepsy, 6 patients due to chronic renal failure, 4 patients due to congenital heart disease, 1 patient due to cystic fibrosis, and 5 patients due to missing data. Finally, 177 patients with a mean age of 165.89 ± 26.60 months were included in the study. Ninety-seven (54.8%) patients were male and 80 (45.2%) were female. The most common presenting symptom was fever (n = 102, 57.6%), followed by cough (n = 98, 55.4%) and weakness (n = 56, 31.6%). One hundred and fifty-eight (89.3%) patients had positive CT findings. The median (IQR) SII was 799 (951), lactate was 1.9 (1.53), and the CRP/Alb ratio was 1.55 (2.61). The mean ± SD NLR was 10.19 ± 6.77. Fourteen (7.9%) patients required ICU admission and 1 (0.6%) patient died. The demographic, clinical, and laboratory findings of the patients are summarized in Table 1.

There were significant differences in CRP (p = 0.021), albumin (p = 0.016), CRP/Alb ratio (p = 0.003), lactate (p = 0.043), and SII (p = 0.001) between patients in the inpatient ward and those in the ICU, while no significant differences were observed in age, sex, WBC, lymphocyte count, neutrophil count, NLR, and D-dimer (p > 0.05). The comparison between inpatient ward and ICU patients is summarized in Table 2.

Table 1. Demographic, clinical and laboratory findings of the study population

Number of patients	177
Age, months, mean ± SD	165.89 ± 26.60
Gender, n (%) Male Female	 97 (54.8) 80 (45.2)
Symptoms, n (%) Cough Fever Weakness Dyspnea Muscle pain Throat ache Diarrhea Anosmia Headache Vomiting Rhinorrhea Ageusia Rash	 98 (55.4) 102 (57.6) 56 (31.6) 37 (20.9) 48 (27.1) 49 (27.7) 21 (11.9) 29 (16.4) 22 (12.4) 16 (9) 18 (10.2) 17 (9.6) 5 (2.8)
Computed tomography findings, n (%) Negative Positive Pleural effusion Ground-glass opacity Consolidation	 19 (10.7) 158 (89.3) 25 (15.8) 129 (81.6) 65 (41.1)
White blood cell, 10^9/L, mean ± SD	12.68 ± 5.90
Neutrophil, 10^9/L, mean ± SD	10.55 ± 5.47
Lymphocyte, 10^9/L, mean ± SD	1.33 ± 0.73
Neutrophil/lymphocyte ratio, mean ± SD	10.19 ± 6.77
C reactive protein, mg/L, median (IQR)	89.8 (104.36)
Albumin, g/L, mean ± SD	36.91 ± 7.2
C reactive protein/Albumin ratio, median (IQR)	1.55 (2.61)
Lactate, mmol/L, median (IQR)	1.9 (1.53)
D-dimer, µg/mL mmol/L, median (IQR)	5.5 (8)
Systemic immune-inflammatory index, median (IQR)	799 (951)
Length of stay in hospital, days, median (IQR)	4 (3)
Intensive care unit admission, n (%)	14 (7.9)
Endotracheal intubation requirement, n (%)	3 (1.69)
Mortality, n (%)	1 (0.6)
IQR: interquartile range, n: number, SD: Standard Deviation	

Table 2. Comparison of inpatient ward and ICU patients

	Inpatient Ward (n=163, 92.1%)	ICU (n=14, 7.9%)	*p* value
Age, months, mean ± SD	165.07 ± 27.12	175.5 ± 17.59	0.058
Male gender, n (%)	92 (56.4)	5 (35.7)	0.166
White blood cell, 10^9/L, mean ± SD	12.65 ± 6.03	12.97 ± 4.28	0.846
Neutrophil, 10^9/L, mean ± SD	10.54 ± 5.55	10.69 ± 4.58	0.909
Lymphocyte, 10^9/L, mean ± SD	1.31 ± 0.71	1.44 ± 0.94	0.534
Neutrophil/lymphocyte ratio, mean ± SD	10.03 ± 6.51	12.04 ± 9.35	0.287
C reactive protein, mg/L, median (IQR)	71.86 (96.91)	140.1 (190.1)	**0.021**
Albumin, g/L, mean ± SD	37.29 ± 7.11	32.51 ± 6.7	**0.016**
C reactive protein/Albumin ratio, median (IQR)	1.46 (2.63)	4.38 (5.17)	**0.003**
Lactate, mmol/L, median (IQR)	1.9 (1.23)	3.1 (5.47)	**0.043**
D-dimer, µg/mL mmol/L, median (IQR)	5.2 (8)	9.8 (8)	0.232
Systemic immune-inflammatory index, median (IQR)	772 (884)	1728 (1797)	**0.001**
ICU:intensive care unit, IQR: interquartile range, n: number, SD: Standard Deviation			

The performance characteristics of SII, lactate, and the CRP/Alb ratio for predicting ICU admission were calculated (Table 3). The cutoff value for ICU admission was a SII of >1111 ($p < 0.001$). While a SII and CRP/Alb ratio were better than lactate in predicting ICU admission ($p = 0.03$ and $p = 0.04$, respectively), there was no statistical difference between SII and CRP/Alb ratio ($p > 0.05$) (Figure 1).

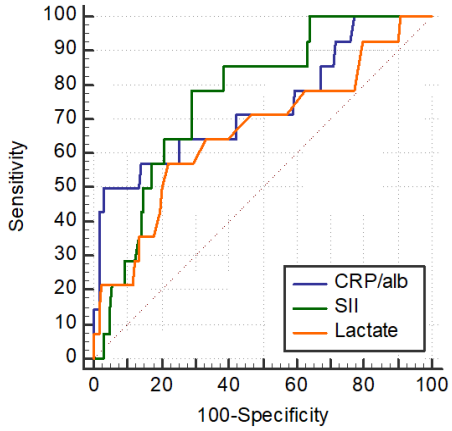

Figure 1. The ROC curves of SII, CRP/Alb ratio and lactate

Discussion

The COVID-19 pandemic was a global health issue that affected communities worldwide. Both therapeutic and predictive diagnostic management of COVID-19 are necessary to combat this problem. In this retrospective study, we evaluated the predictive value of SII determining the ICU admission in hospitalized adolescent patients with COVID-19. In cases when the SII calculated at the time of emergency department admission is >1111, there is an increased likelihood of ICU admission [+LR 3.32 (95% CI 2.4-4.5)]. While the SII was a better predictor than lactate, the predictive value was similar with CRP/Alb ratio. The findings of our study indicate that SII can serve as an indicator of inflammatory processes associated with the development of critical illness or ICU admission in patients hospitalized with COVID-19.

The SII comprises three peripheral blood parameters that provide a comprehensive summary of the immune and inflammatory status of patients. As ecpected, it has been previously identified as a prognostic biomarker in sepsis patients (14). In a recent study, Fois et al. (15) reported that patients with higher SII values exhibited significantly worse PaO□/FiO□ ratios and chest CT severity scores among those diagnosed with COVID-19. It was suggested that SII may serve as

Table 3. Comparison of ROC curves of SII, lactate and CRP/Alb ratio

	Sensitivity % (95% CI)	Specificity % (95% CI)	+LR % (95% CI)	-LR % (95% CI)	AUC % (95% CI)	*p* Value
SII (>1111)	78.6 (49.2-95.3)	75.2 (68.6-83.1)	3.32 (2.4-4.5)	0.30 (0.11-0.8)	0.768 (0.70-0.83)	<0.001
Lactate (>2.8mmol/L)	57.1 (28.9-82.3)	77.9 (70.8-84.0)	2.59 (1.5-4.4)	0.55 (0.30-1.0)	0.663 (0.59-0.73)	<0.05
CRP/Alb raito (>3.92)	69.7 (44.7-91.3)	95.3 (90.9-98.9)	3.31 (2.3-4.7)	0.52 (0.31-0.9)	0.738 (0.67-0.80)	<0.001

AUC: Area under the curve, CI: Confidence interval, LR: Likelihood ratio, SII: Systemic immune-inflammatory index, CRP/Alb: C-reactive protein/albumin

a marker of lung damage in patients with COVID-19 rather than a reflection of their overall clinical condition (16). While SII has been established as a prognostic marker in adults for various critical illnesses, our study is the first to investigate to delineate SII as a prognostic factor in adolescent patients.

Several mechanisms may explain the observed association between a high SII and an increased risk of ICU admission and worse prognosis in patients hospitalized for COVID-19. A high SII may reflect an increased inflammatory (elevated neutrophils) and thrombotic (elevated platelets) status along with worsening immune dysfunction (decreased lymphocytes). A study from China demonstrated that a high SII can effectively predict severe COVID-19 cases as defined by the National Guidelines for the Diagnosis and Treatment of COVID-19 (17). Furthermore, patients with a high admission SII were more likely to require ICU admission due to the severity of their disease (18). Finally, an elevated admission SII has been identified as a predictor of adverse in-hospital events in patients with COVID-19, including invasive mechanical ventilation, acute limb ischemia, and acute venous thrombotic events. These complications may collectively contribute to an increased risk of worsen prognosis (19-21).

The CRP/Alb ratio has been established as a prognostic biomarker in patients with septic shock, pancreatitis, and acute mesenteric ischemia (22). In a recent study, Yılmaz et al. (23) demonstrated that the CRP/Alb ratio is a valuable biomarker for predicting mortality in pregnant patients. Lactate is the primary end product of anaerobic metabolism. In the absence of oxygen, tissues typically exhibit increased lactate production, as pyruvate cannot be oxidized in the Krebs cycle due to oxygen deprivation and is instead converted to lactate. A systematic review of the literature revealed that patients with worse outcomes due to COVID-19 often exhibited higher blood lactate values than those with better outcomes at the early stages of the disease (24). In this study, both the CRP/Alb ratio and lactate were found to be associated with ICU admission, with results consistent with those reported in the literature.

The NLR is a reliable, readily available, and inexpensive biomarker that has been used as a prognostic indicator in numerous studies, including those examining sepsis, cardiovascular disease, and malignancy (25,26). NLR has been demonstrated to be a robust predictor of prognosis in patients diagnosed with COVID-19 (27,28). However, in this study, the NLR, which is a component of the SII, was unexpectedly not associated with ICU admission. This discrepancy may be attributable to our patient number, the relatively small sample size in our study compared to others, as well as the severity of SARS-CoV-2 infection, which was not evaluated in this study (25-28).

The major limitations of our study were that its single-center design, retrospective nature and unequal sample sizes between inpatient ward and ICU. Additionally, we were unable to evaluate the laboratory parameters after treatment. Other factors that may affect laboratory indices such as obesity, admission day, could not be assessed due to missing data. Prospective cohort studies are needed to confirm the reliability of SII.

The results of this study suggest that a high SII during hospitalization is associated with an increased likelihood of ICU admission in patients hospitalized with COVID-19. Although additional studies are needed to confirm and validate these findings, the evidence from this study supports the potential utility of SII as a valuable prognostic indicator for ICU admission outcomes in patients with COVID-19. Incorporating SII assessment into clinical practice may help identify patients at higher risk of adverse outcomes and facilitate more targeted and timely interventions to improve patient care and management.

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Author contribution statement

All authors have made substantial contributions to

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References

1.World Health Organization Coronavirus (COVID-19) Dashboard. https://covid19.who.int/ (Accessed August 1, 2024).

2.Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis. 2020;20(8):911-919.

3.Hoang A, Chorath K, Moreira M, Evans M, Burmeister-Morton F, Burmeister F, et al. COVID-19 in 7780 pediatric patients: a systematic review. EClinicalMedicine. 2020;24(100433).

4.Morand A., Fabre A, Minodier P, Boutin A, Vanel N, Bosdure E, et al. COVID-19 virus and children: What do we know? Arch Pediatr 2020;27(3):117-8.

5.Sperotto F, Friedman KG, Son MBF, VanderPluym CJ, Newburger JW, Dionne A. Cardiac manifestations in SARS-CoV-2-associated multisystem inflammatory syndrome in children: a comprehensive review and proposed clinical approach. Eur J Pediatr. 2021;180(2):307-322.

6.Çağlar HT, Pekcan S, Yılmaz Aİ, Ünal G, Metin Akcan Ö, Ünsaçar MZ, et al. Delta variant effect on the clinical course of adolescent COVID-19 patients. Pediatr Pulmonol. 2023;58(1):115-121.

7.Alifano M. Systemic immune-inflammation index and prognosis of advanced non-small cell lung cancer. Ann Transl Med. 2020;8(11):667.

8.Yang YL, Wu CH, Hsu PF, Chen SC, Huang SS, Chan WL, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest. 2020;50(5):e13230.

9.Trifan G, Testai FD. Systemic Immune-Inflammation (SII) index predicts poor outcome after spontaneous supratentorial intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2020;29(9):105057.

10.Seo M, Yamada T, Morita T, Frukawa Y, Tamaki S, Iwasaki Y, et al. Prognostic value of systemic immune-inflammation index in patients with chronic heart failure. Eur Heart J. 2018;39:ehy564.P589.

11.Yuan H, Tian J, Wen L. Meta-analysis of the systemic immune-inflammatory index and in-hospital mortality of COVID-19 patients. Heliyon. 2023;10(1):e23441.

12.Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics. 2020;145(6):e20200702.

13.World Health Organization. Adolescent health topics. https://www.who.int/health-topics/adolescent-health/#tab=tab_1 (Accessed Jan 10, 2025).

14.Lagunas-Alvarado M, Mijangos-Huesca FJ, Terán-González JO, Lagunas-Alvarado MG, Martinez-Zavala N, Reyes-Franco, et al. Systemic immune inflammatory index in sepsis. Med Interna Méx. 2017;33(3):303-309.

15.Fois AG, Paliogiannis P, Scano V, Cau S, Babudieri S, Perra R, et al. The Systemic Inflammation Index on Admission Predicts In-Hospital Mortality in COVID-19 Patients. Molecules. 2020;25(23):5725.

16.Karimi A, Shobeiri P, Kulasinghe A, Rezaeni N. Novel Systemic Inflammation Markers to Predict COVID-19 Prognosis. Front Immunol. 2021;12:741061.

17.Xia W, Tan Y, Hu S, Li C, Jiang T. Predictive Value of Systemic Immune-Inflammation index and Neutrophil-to-Lymphocyte Ratio in Patients with Severe COVID-19. Clin Appl Thromb Hemost. 2022;28:10760296221111391.

18.Zhao Y, Yu C, Ni W, Shen H, Qiu M, Zhao Y, et al. Peripheral blood inflammatory markers in predicting prognosis in patients with COVID-19. Some differences with influenza A. J Clin Lab Anal. 2021;35(1):e23657.

19.Halmaciu I, Arbănaşi EM, Kaller R, Mureşan AV, Arbănaşi EM, Bacalbasa N, et al. Chest CT Severity Score and Systemic Inflammatory Biomarkers as Predictors of the Need for Invasive Mechanical Ventilation and of COVID-19 Patients' Mortality. Diagnostics (Basel). 2022;12(9):2089.

20.Mureşan AV, Hălmaciu I, Arbănaşi EM, Kaller R, Arbănaşi EM, Budişcă OA et al. Prognostic Nutritional Index, Controlling Nutritional Status (CONUT) Score, and Inflammatory Biomarkers as Predictors of Deep Vein Thrombosis, Acute Pulmonary Embolism, and Mortality in COVID-19 Patients. Diagnostics (Basel). 2022;12(11):2757.

21.Arbănaşi EM, Halmaciu I, Kaller R, Mureşan AV, Arbănaşi EM, Suciu BA et al. Systemic Inflammatory Biomarkers and Chest CT Findings as Predictors of Acute Limb Ischemia Risk, Intensive Care Unit Admission, and Mortality in COVID-19 Patients. Diagnostics (Basel).

2022;12(10):2379.

22.Kaçer İ, Çağlar A, Akıllı NB. The Prognostic Value of C-Reactive Protein/Albumin Ratio in Acute Mesenteric Ischemia. Am Surg. 2023;89(5):1661-1667.

23.Yilmaz N, Tosun F, Comert E, Duran M, Tuna VD. The Relationship of CRP/Albumin ratio level and prognosis in pregnant COVID-19 patients. Niger J Clin Pract. 2022;25(10):1745-1750.

24.Carpenè G, Onorato D, Nocini R, Fortunato G, Rizk JG, Henry BM, et al. Blood lactate concentration in COVID-19: a systematic literature review. Clin Chem Lab Med. 2021;60(3):332-337.

25.Mei Z, Shi L, Wang B, Yang J, Xiao Z, Du P, et al. Prognostic role of pretreatment blood neutrophil-to-lymphocyte ratio in advanced cancer survivors: A systematic review and meta-analysis of 66 cohort studies. Cancer Treat Rev. 2017;58:1-13.

26.Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med. 2012;5(1):2.

27.Fu J, Kong J, Wang W, Wu M, Yao L, Wang Z, et al. The clinical implication of dynamic neutrophil to lymphocyte ratio and D-dimer in COVID-19: A retrospective study in Suzhou China. Thromb Res. 2020;192:3-8.

28.Liu J, Liu Y, Xiang P, Pu L, Xiong H, Li C, et al. Neutrophil-to-lymphocyte ratio predicts critical illness patients with 2019 coronavirus disease in the early stage. J Transl Med. 2020;18(1):206.

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ORIGINAL ARTICLE

Management Of Spontaneous Pneumomediastinum: Are Hospitalization And Prophylactic Antibiotic Treatment Necessary?

Spontan Pnömomediastinumun Yönetimi: Hastaneye Yatış Ve Profilaktik Antibiyotik Tedavisi Gerekli Midir?

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ABSTRACT

Aim: Spontaneous pneumomediastinum (SPM) is defined as the presence of free air in the mediastinum without concomitant disease. It is rare but usually benign and self-limiting. Usually, patients with SPM are hospitalized and sometimes prophylactic antibiotics are administered to prevent mediastinitis. The present study aims to describe the practices regarding the feasibility of outpatient treatment and follow-up of SPM and the necessity of prophylactic antibiotics.
Material and Method: Patients with SPM between August 2020 and December 2023 were retrospectively evaluated. Patients who showed free air in the mediastinum on chest radiography or thorax computed tomography were considered to have SPM and were included in the study. All case records were analysed for demographic data, symptoms, precipitating events, diagnostic studies, prophylactic antibiotic use, length of hospitalization and complications.
Results: Of 46 patients included in the study, 29 were male (63.1%) and 17 were female (36.9%). In terms of triggering events, 41.3% of patients (19 of 46) did not have a specific trigger (at rest). Suspected triggering events included asthma attacks, physical exercise, cough (with or without upper respiratory tract infection), sneezing, childbirth, shouting and sneezing. The mean duration of hospitalization was 2.4 days. Prophylactic oral antibiotherapy was administered to 18 patients. No patient developed complications such as tension pneumomediastinum, delayed pneumothorax, airway compromise and mediastinitis.
Conclusion: SPM is a benign condition seen primarily in young adults with uneventful recovery. Our study supports the feasibility of outpatient treatment and follow-up in stable patients. However, in patients where the underlying disease requires special treatment and the possibility of mediastinitis or organ perforation cannot be excluded, further diagnostic work-up, prophylactic antibiotics and inpatient treatment are required.

Keywords: Antibiotic, complication, hospitalization, spontaneous pneumomediastinum

ÖZ

Amaç: Spontan pnömomediastinum (SPM), eşlik eden bir hastalık olmaksızın mediastende serbest hava bulunması olarak tanımlanır. Nadirdir ancak genellikle iyi huyludur ve kendi kendini sınırlar. Genellikle SPM'li hastalar hastaneye yatırılır ve bazen mediastiniti önlemek için profilaktik antibiyotikler uygulanır. Bu çalışmanın amacı, spontan pnömomediastinumun ayakta tedavi ve takibinin uygulanabilirliği ve profilaktik antibiyotiklerin gerekliliği ile ilgili uygulamaları tanımlamaktır.
Gereç ve Yöntem: Ağustos 2020 ile Aralık 2023 arasında spontan pnömomediastinumlu hastalar retrospektif olarak değerlendirildi. Göğüs radyografisinde veya toraks bilgisayarlı tomografisinde mediastende serbest hava görülen hastalar SPM olarak kabul edildi ve çalışmaya dahil edildi. Tüm vaka kayıtları demografik veriler, semptomlar, tetikleyici olaylar, tanı çalışmaları, profilaktik antibiyotik kullanımı, hastanede kalış süresi ve komplikasyonlar açısından analiz edildi.
Bulgular: Çalışmaya dahil edilen 46 hastanın 29'u erkek (%63,1) ve 17'si kadındı (%36,9). Tetikleyici olay açısından hastaların %41,3'ünün (46'nın 19'u) belirli bir tetikleyicisi yoktu (dinlenme sırasında). Şüpheli tetikleyici olaylar arasında astım atağı, fiziksel egzersiz, öksürük (üst solunum yolu enfeksiyonu ile veya enfeksiyonu olmadan), hapşırma, doğum, bağırma ve hapşırma yer alıyordu. Ortalama hastanede kalış süresi 2,4 gündü. 18 hastaya profilaktik oral antibiyotik tedavisi uygulandı. Hiçbir hastada gerginlik pnömomediastinum, gecikmiş pnömotoraks, hava yolu tıkanıklığı ve mediastinit gibi komplikasyonlar gelişmedi.
Sonuçlar: SPM, esas olarak genç erişkinlerde görülen ve sorunsuz iyileşen iyi huylu bir durumdur. Çalışmamız, stabil hastalarda ayakta tedavi ve takibin uygulanabilirliğini desteklemektedir. Ancak, altta yatan hastalığın özel tedavi gerektirdiği ve mediastinit veya organ perforasyonu olasılığının dışlanamadığı hastalarda, daha ileri tanı çalışmaları, profilaktik antibiyotikler ve yatarak tedavi gereklidir.

Anahtar kelimeler: Antibiyotik, hastaneye yatış, komplikasyon, spontan pnömomediastinum

Introduction

Spontaneous pneumomediastinum (SPM) is defined as the presence of free air in the mediastinum without obvious comorbidity. It is rare, usually has a mild clinical course and is self-limiting. The pathophysiology of this disease is based on the pressure gradient between the alveoli and the lung interstitium. This pressure gradient can lead to alveolar rupture and consequent airflow into the interstitium. Once entering the lung interstitium, air flows along the pressure gradient between the lung periphery and mediastinum towards the hilum and mediastinum (1).

Patients with SPM classically present with chest pain and dyspnoea. Chest pain is typically behind the sternum and radiates to the back and/or neck. Chest pain increases

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with inspiration, sitting position and swallowing. Other frequently reported symptoms include cough, dysphonia, dysphagia and neck swelling. Chest X-ray is the first and most important investigation to be performed when a patient has symptoms and history suggestive of SPM. The role of chest computed tomography (CT) is not only to diagnose SPM but also, in many cases, to diagnose the underlying abnormality. Bronchoscopy or oesophageal endoscopy has an important diagnostic role in cases where tracheal or oesophageal pathology is considered (2).

Patients with SPM are generally, hospitalized, followed up and treated. Panacek et al. evaluated only three of 17 patients (17.6%) as outpatients (2). In retrospective studies on SPM, some authors reported a mean hospital stay of two to eight days (3,4). However, patients with benign and self-limiting SPM may not require hospitalization. Prophylactic antibiotics are occasionally administered to prevent mediastinitis in cases of SPM (5-7). However, prophylactic antibiotic coverage in SPM is a controversial issue. Therefore, the present study aimed to investigate the necessity of hospitalization and prophylactic antibiotic use in patients with SPM.

Materials and Method

We retrospectively evaluated 46 patients hospitalized in our thoracic surgery clinic between August 2020 and December 2023 in terms of SPM. Patients with free air in the mediastinum on chest radiography or thoracic CT were accepted as SPM and included in the study (Figures 1 and 2). Paediatric patients were also included. Patients with pneumomediastinum caused by tracheal or oesophageal perforation, iatrogenic factors (pneumomediastinum after thoracic or cardiac surgery), chest injuries, or any disease involving the neck or abdomen were excluded. All

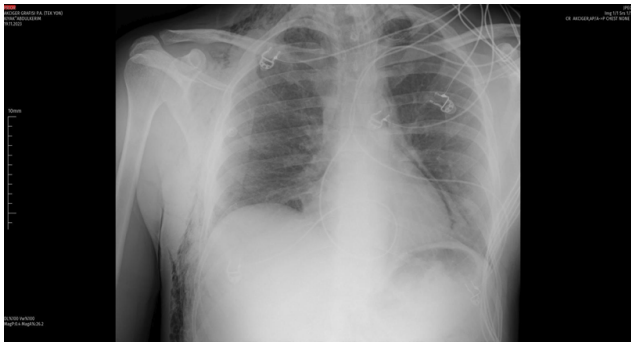

Figure 1. Pneumomediastinum on PA chest radiography

case records were carefully reviewed, taking into account demographic data, symptoms, precipitating events, diagnostic studies, prophylactic antibiotic use, length of hospital stay and complications. Complications included tension pneumomediastinum, pneumothorax, airway compression and mediastinitis.

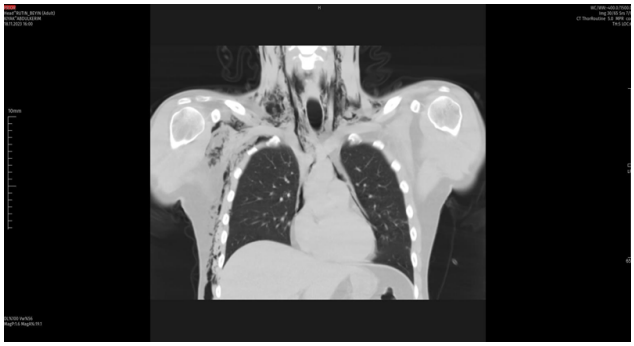

Figure 2. Pneumomediastinum on coronal section of Thorax Computed Tomography

Results

During the study period, 46 patients were included in the study [29 males (63.1%) and 17 females (36.9%)]; the mean age was found as 21.7 (13-36) years. All patients underwent chest radiography, while 34 (73.9%) patients underwent thoracic CT. Fibre optic bronchoscopy was performed in three patients and oesophagography in two patients, but no pathology was found in the oesophagus or tracheobronchial system. Chest pain was the most commonly reported symptom in 67.3% of patients (31 of 46), followed by dyspnoea in 26% (12 of 46) and sore throat in 19.5% (9 of 46). In terms of triggering events, 41.3% (19 of 46) of the patients did not have a specific triggering symptom (developed at rest). Asthma attack, physical exercise, cough (with or without upper respiratory tract infection), sneezing, labour, cold shower and sneezing were suspected triggering events. The mean duration of hospitalization was 2.4 (2-5) days. Eighteen of the patients (39.1%) received oral 1st generation cephalosporin (Cefazolin 1gr amp) type antibiotics due to asthma attacks and upper respiratory tract infection symptoms. Haemogram and biochemistry were performed on all patients during hospitalization. Infection parameters were also monitored in patients with an asthma attack and symptoms of upper respiratory tract infection. Mediastinitis was not observed clinically, laboratory and radiologically in any of the patients. None of the patients developed complications such as tension pneumomediastinum, airway pathology and mediastinitis. Minimal pneumothorax which did not require intervention developed in 2 patients. Recurrence was detected in

one of the patients on the 10th day after discharge, but since he was asymptomatic, he was followed up as an outpatient and no complication was detected (Table 1).

Table 1. Clinical and demographic characteristics of patients with spontaneous pneumomediastinum

Parameters	n (%)
Age (years)	21.7 (13-36)
Male	29 (63.1)
Symptoms	
Chest pain	31 (67.3)
Shortness of breath	12 (26.0)
Sore throat	9 (19.5)
Neck pain	5 (10.8)
Hoarseness	3 (0.6)
Triggering event	
At rest	19 (41.3)
Asthma attack	8 (17.3)
Exercise	8 (17.3)
Cough	5 (10.8)
Sneeze	2 (0.4)
Birth	2 (0.4)
Cold shower	1 (0.2)
No blowing the nose	1 (0.2)
Diagnostic examination	
PA chest radiograph	46 (100)
Thoracic CT	34 (73.9)
Bronchoscopy	3 (0.6)
Oesophagogram	2 (0.4)
Prophylactic antibiotics	18 (39.1)
Length of hospital stay	2.4 (2-4)
Complications	
Pneumothorax	2 (0.4)
Recurrence	1 (0.2)
Mortality	None

CT: Computed tomography, PA: Posteroanterior

Discussion

SPM was first described by Laennec in 1819 and further characterised in a case series by Hamman in 1939 (7). It is a rare condition with an incidence of 1:44,000 and usually follows a benign clinical course (4). SPM has been associated with triggering factors in approximately 75% of cases. The most common precipitating factors are cough, physical exercise and drug use (9). Triggering factors were present in 58.7% of our patients. Similar to previously reported cases, the most common triggers were asthma attacks, cough due to upper respiratory tract infection, and physical exercise.

There are several case series on SPM; however, only a few cases have shown poor outcomes. Takeda et al. suggest that two days may be an appropriate duration for observational hospitalization (5). On the other hand, Panacek et al. recommended outpatient treatment and follow-up in stable patients (2). In our study, the main reason for hospitalization was the severity of the underlying disease, such as a severe asthma attack. Therefore, our results support the feasibility of outpatient treatment and follow-up in stable patients, as recommended in previous studies (2,4,6). Considering the benign nature of this condition, cases where the diagnosis is doubtful or the underlying disease requires specialised treatment should be considered for further diagnostic work-up and hospitalization. This would be a cost-effective approach.

It may be difficult to differentiate SPM from pneumomediastinum secondary to oesophageal perforation. Age over 40 years, history of severe vomiting, abdominal tenderness on physical examination, high white blood cell count, and findings of pleural effusion, marked atelectasis, pneumopericardium or pneumoperitoneum on CT scan are considered high-risk factors; therefore, when these findings are observed, patients with pneumomediastinum may require further diagnostic work-up and hospitalization (10).

Only a few small studies have reported complications in SPM cases. In a case series of 47 patients, Perna et al. reported right tension pneumothorax, mediastinal shifting and tracheal compression in 1 case, requiring right thoracotomy to open the mediastinal pleura (11). Bakhos et al. reported a case series consisting of 49 patients and reported that only 1 patient required intubation because of a severe asthma attack. However, mortality was not recorded in the study population (10).

In some previous studies, prophylactic antibiotics were recommended to prevent mediastinitis (5,6,12). In the study by Koullias et al., prophylactic antibiotics were administered to all patients (6). In our study, we administered prophylactic antibiotics to only 18 of 46 patients. Despite this, no patient developed infectious complications including mediastinitis.

Our study has limitations such as being retrospective, lack of statistical analysis and small number of patients.

Conclusion

SPM is a benign condition occurring primarily in young adults and is characterised by uneventful recovery. The likelihood of complications is low. Our study supports the feasibility of outpatient treatment and follow-up in stable patients. However, in patients in whom the

underlying disease requires special treatment and the possibility of mediastinitis or organ perforation cannot be ruled out, further diagnostic work-up, prophylactic antibiotics and inpatient treatment are required.

References

1.Macklin MT, Macklin CC. Malignant interstitial emphysema of the lungs and mediastinum as an important occult complication in many respiratory diseases and other conditions: interpretation of the clinical literature in the light of laboratory experiment. Medicine 1944;23:281-358.

2.Panacek EA, Singer AJ, Sherman BW, Prescott A, Rutherford WF. Spontaneous pneumomediastinum: clinical and natural history. Ann Emerg Med 1992;21:122.

3.Miura H, Taira O, Hiraguri S, Ohtani K, Kato H. Clinical features of medical pneumomediastinum. Ann Thorac Cardiovasc Surg 2003;9:188-91.

4.Macia I, Moya J, Ramos R, Morera R, Morera R, Escobar I, Saumench J, et al. Spontaneous pneumomediastinum: 41 cases. Eur J Cardiothorac Surg 2007;31:1110-4.

5.Takada K, Matsumoto S, Hiramatsu T, Kojima E, Watanabe H, Sizu M, et al. Management of spontaneous pneumomediastinum based on clinical experience of 25 cases. Respir Med 2008;102:1329-34.

6.Koullias GJ, Korkolis DP, Wang XJ, Hammond GL. Current assessment and management of spontaneous pneumomediastinum: experience in 24 adult patients. Eur J Cardiothorac Surg 2004;25:852-5.

7.Hamman L. Spontaneous mediastinal emphysema. Bull Johns Hopkins Hosp 1939; 64:1-21.

8.Lang J, Dallow N, Lang A, Tetsworth K, Harvey K, Pollard C, et al. Inclusion of 'minor' trauma cases provides a better estimate of the total burden of injury: Queensland Trauma Registry provides a unique perspective. Injury 2014;45:1236-41.

9.Abolnik I, Lossos IS, Breuer R. Spontaneous pneumomediastinum: a report of 25 cases. Chest 1991;100:93-5.

10.Bakhos CT, Pupovac SS, Ata A, Fantauzzi JP, Fabian T. Spontaneous pneumomediastinum: an extensive workup is not required. J Am Coll Surg 2014; 219:713-7.

11.Perna V, Vilà E, Guelbenzu JJ, Amat I. Pneumomediastinum: is this really a benign entity? When it can be considered spontaneous? Our experience in 47 adult patients. Eur J Cardiothorac Surg 2010;37:573-5.

12.Sahni S, Verma S, Grullon J, Esquire A, Patel P, Talwar A. Spontaneous pneumomediastinum: time for consensus. N Am J Med Sci 2013;5:460-4.

13.Caceres M, Ali S, Braud R, Weiman D, Garrett Jr HE. Spontaneous pneumomediastinum: a comparative study and review of the literature. Ann Thorac Surg 2008;86:962-6.

14.Campillo-Soto A, Coll-Salinas A, Soria-Aledo V, Blanco-Barrio A, Flores-Pastor B, Candel-Arenas M, et al. Spontaneous pneumomediastinum: A descriptive study of our experience with 36 cases. Arch Bronconeumol 2005;41:528-31.

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ORIGINAL ARTICLE

Obsessive-Compulsive Personality Disorder Related Beliefs, Functional Impairment and Hopelessness in Medical Students: The Mediating Role of Depression

Tıp Öğrencilerinde Obsesif-Kompulsif Kişilik Bozukluğuyla İlgili İnançlar İşlevsellikte Bozulma ve Umutsuzluk: Depresyonun Aracı Rolü

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ABSTRACT

Background/Aims: To assess the associations of hopelessness, functional impairment, depression, anxiety, stress, and obsessive-compulsive personality disorder (OCPD) in medical students.
Methods: The Sheehan Disability Scale, Beck Hopelessness Scale (BHS), Depression Anxiety Stress Scale-21 (DASS-21), and OCPD subscale of Personality Belief Questionnaire-Short Form (PBQ-SF-OCPD) were administered. Participants with BHS scores ≥9 were considered hopeless. A mediation analysis was performed using the PBQ-SF-OCPD score as an independent variable, DASS-21 Depression, Anxiety, and Stress scores as mediator variables, and BHS score as a dependent variable.
Results: Of 164 medical students. 29.88% (n=49) showed hopelessness (BHS scores ≥9). Also, SDS work/school (p<0.001), SDS social life (p<0.001), SDS family life (p=0.001), SDS-total (p<0.001), DASS-21 depression (p<0.001), DASS-21 anxiety (p<0.001), DASS-21 stress (p<0.001) and PBQ-SF-OCPD scores (p=0.019) were significantly higher in the hopelessness group than in the group without. BHS score was positively correlated with SDS work/school (r=0.446, p<0.001), SDS social life (r=0.473, p<0.001), SDS family life (r=0.328, p<0.001), SDS total (r=0.461, p<0.001), DASS-21 depression (r=0.686, p<0.001), DASS-21 anxiety (r=0.484, p<0.001), DASS-21 stress (r=0.501, p<0.001) and PBQ-SF-OCPD scores (r=0.190, p=0.015). According to mediation analysis results, the indirect effect of PBQ-SF-OCPD score on BHS score via DASS-21 depression score was 0.119 (95% CI: 0.027-0.230) and the standardized indirect effect of PBQ-SF-OCPD score on BHS score via DASS-21 depression score was 0.153 (95% CI: 0.035-0.284). The DASS-21 depression score was found to be a full mediator of the PBQ-SF-OCPD score on the BHS score.
Conclusions: The high rate of hopelessness in medical students is noteworthy. Findings regarding hopelessness's association with functional impairment and OCPD beliefs need to be explored in the future. Medical students with hopelessness may be closely monitored regarding depression's mediating effect on OCPD beliefs. In the interventions to improve mental health in medical students, clinicians may focus on the mediating effect of depression between OCPD and hopelessness.

Keywords: Anxiety, depression, hope, obsessive-compulsive personality disorder, psychosocial functioning, stress psychological

ÖZ

Amaç: Tıp fakültesi öğrencilerinde umutsuzluk, işlevsellikteki bozulma, depresyon, anksiyete, stres ve obsesif-kompulsif kişilik bozukluğu (OKKB) özellikleri arasındaki ilişkileri değerlendirmeyi amaçladık.
Yöntem: Katılımcılara Sheehan Yeti Yitimi Ölçeği (SYYÖ), Beck Umutsuzluk Ölçeği (BUÖ), Depresyon Anksiyete Stres Ölçeği-21 (DASÖ-21), Kişilik İnanç Ölçeği-Kısa Formu'nun OKKB alt ölçeği (KİÖ-KF-OKKB) uygulandı. BUÖ puanı ≥9 olan katılımcılar umutsuzluğu var olarak kabul edildi. Bağımsız değişken olarak KİÖ-KF-OKKB puanı, aracı değişken olarak DASÖ-21 Depresyon, Anksiyete ve Stres puanları ve bağımlı değişken olarak BUÖ puanı kullanılarak bir aracılık analizi yapıldı.
Bulgular: Çalışmaya 164 tıp öğrencisi katılmıştır. Tıp öğrencilerinin %29,88'i (n=49) umutsuzluk göstermiştir (BUÖ skorları ≥9). Umutsuzluğu olan grupta SYYÖ iş/okul skoru (p<0,001), SYYÖ sosyal yaşam skoru (p<0,001), SYYÖ aile yaşamı skoru (p=0,001), SYYÖ toplam skoru (p<0,001), DASÖ-21 depresyon skoru (p<0,001), DASÖ-21 anksiyete skoru (p<0,001), DASÖ-21 stres skoru (p<0,001) ve KİÖ-KF-OKKB skoru (p=0,019) umutsuzluğu olmayan gruba göre anlamlı olarak daha yüksek bulunmuştur. BUÖ puanı, SYYÖ iş/okul puanı (r=0,446, p<0,001), SYYÖ sosyal yaşam puanı (r=0,473, p<0,001), SYYÖ aile yaşamı puanı (r=0,328, p<0,001), SYYÖ toplam puanı (r=0,461, p<0,001), DASÖ-21 depresyon puanı (r=0,686, p<0,001), DASÖ-21 anksiyete puanı (r=0,484, p<0,001), DASÖ-21 stres puanı (r=0,501, p<0,001) ve KİÖ-KF-OKKB puanı (r=0,190, p=0,015) ile pozitif korelasyon gösterdi. Aracılık analizi sonuçlarına göre, KİÖ-KF-OKKB puanının DASÖ-21 depresyon puanı aracılığıyla BUÖ puanı üzerindeki dolaylı etkisi 0,119 (95% CI: 0,027-0,230) ve KİÖ-KF-OKKB puanının DASÖ-21 depresyon puanı aracılığıyla BUÖ puanı üzerindeki standardize dolaylı etkisi 0,153 (95% CI: 0,035-0,284) olarak bulundu. DASÖ-21 depresyon puanının, KİÖ-KF-OKKB puanının BUÖ puanı üzerindeki etkisine tam aracılık ettiği bulundu.
Sonuç: Tıp öğrencilerindeki yüksek umutsuzluk oranı dikkate değerdir. Umutsuzluğun işlevsellikteki bozulma ve OKKB özellikleriyle ilişkisine ilişkin bulgular daha farklı çalışmalarla gelecekte araştırılabilir. Umutsuzluk yaşayan tıp öğrencileri depresyonun OKKB inançları üzerindeki aracılık etkisi açısından yakından izlenebilir. Ruh sağlığı çalışanları, tıp öğrencilerinde ruh sağlığını iyileştirmeye yönelik müdahalelerde, OKKB ve umutsuzluk arasındaki depresyonun aracılık edici etkisine önem verebilirler.

Anahtar Kelimeler: Anksiyete, depresyon, psikososyal işlevsellik, obsesif kompulsif kişilik bozukluğu, stres, umut

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Introduction

Being an undergraduate student in the faculty of medicine involves working with discipline, acquiring knowledge, and using it. Medical students experience challenging processes during their education. The stress of examinations, information overload, fear of failure, the intensity of the work schedule, and encountering terminally ill patients contribute to medical students' adverse emotions and cognitions (1).

Medical school students are faced with an intensive theoretical curriculum and a grueling clinical education. This challenging educational process requires a good level of functioning (5). Via the help of this functioning medical students can tackle the difficulties of medical education. Considering the professional negativities that medical students will experience in their functionality, the functionality of medical students is of great importance (6). Previously in an overview of systematic reviews, it was found that anxiety prevalence was between 7.04 to 88.30%, burnout between 7.0 to 86.0, depression between 11.0 to 66.5%, stress between 29.6 to 49.9% and suicidal ideation between 3.0 to 53.9% in medical students (7) As a consequence of the abovementioned prevalences of adverse psychiatric disorders among medical students, medical students may easily experience functional impairment difficulties (8).

Hope is a crucial aspect of the lives of individuals. Adaptation to harsh situations requires sufficient hope to cope with difficulties. Individuals often suffer from hopelessness in their daily lives. Unrealistic and pessimistic beliefs about the future are the core features of hopelessness. In hopelessness, assumptions that the problems will remain unresolved in the future are gaining ground. (9). Hopelessness was found to be associated with adverse consequences such as major depressive disorder, bipolar disorder, and suicide attempts (10, 11). Hopelessness and suicide behavior association is a significantly underscored issue in the literature (12, 13).

Dysfunctional personality disorder beliefs are the primary cognitive components that mainly characterize personality disorders in cognitive theory (14). Dysfunctional personality disorder beliefs include evaluations of oneself and others (15). Through the effects of dysfunctional personality disorder beliefs, personality disorders' main styles of attitudes are generated. So, dysfunctional personality disorder beliefs may supply explanations for personality disorder traits (16).

Obsessive-compulsive personality disorder (OCPD) is characterized by perfectionism, control demands in relationships, and preciseness (17). Via these core features of OCPD, individuals with high levels of OCPD beliefs suffer from increased stress and interpersonal functioning problems (18). OCPD was found to be associated with psychosocial functioning difficulties, quality of life impairments, anxiety disorders, and depression (19, 20). In a meta-analysis, OCPD features were found to be stable as antisocial and schizoid personality disorder features (21). Additionally, OCPD has a very high prevalence among all personality disorders (20).

As we mentioned above, medical students often suffer from psychiatric disorders. The associations of functional impairment difficulties, hopelessness, and OCPD features may yield clues to intervene in these adverse conditions in undergraduate medical students. So, in the present study, we mainly aimed to assess associations between levels of hopelessness, OCPD beliefs, functional impairment, anxiety, depression, and stress in undergraduate medical students. To the best of our knowledge, previously the association of functional impairment, hopelessness, and OCPD beliefs was not studied in undergraduate medical students.

The main hypotheses of the present study are as follows:

1) Medical students in the hopelessness group would show higher levels of functional impairment and OCPD beliefs than the medical students in the group without hopelessness;

2) Hopelessness levels of the medical students would be associated with functional impairment and OCPD beliefs

3) The effects of OCPD beliefs on hopelessness levels would be mediated by the depression, anxiety, and stress levels of the medical students.

Materials And Methods

Study design and participants

The study was conducted among the undergraduate medical students at Atatürk University between February

2023 and June 2023. The Local Ethical Committee approved the study (Date: 26/01/2023, Meeting number: 1, Decision number: 80). The samples consisted of students from the Medical Faculty of Atatürk University, and the participants were defined from the students' online groups and fifth-grade students attending psychiatry courses. The exclusion criterion for the study was only not being able to read and understand the questions in Turkish (considering foreign students continuing their education in the faculty of medicine). Being a medical student was sufficient for inclusion. The authors administered scales to evaluate levels of hopelessness, OCPD beliefs, functional impairment, depression, anxiety, and stress. Depression Anxiety Stress Scale-21, Beck Hopelessness Scale, OCPD subscale of Personality Belief Questionnaire-Short Form, and Sheehan Disability Scale were used in the study to evaluate levels of depression, anxiety, stress, hopelessness, OCPD beliefs, and functional impairment, respectively. A brief socio-demographic form generated for this study was administered to participants. Before filling out the scales via online forms by the participants, all the participants ticked a box to state their informed consent. One hundred and sixty-four undergraduate medical students constituted the sample of the study.

Measures

Sheehan Disability Scale (SDS): Sheehan et al. developed the scale (22). The SDS is a self-report scale with three questions that evaluate functional impairment levels. This scale is composed of three subdimensions: Family life, social life, and work/ school life. Each subdimension is evaluated by one question. The sum of the three questions resembles overall functional impairment. High scores on this scale resemble levels of high functional impairment.

Depression Anxiety Stress Scale-21 (DASS-21): Developed by Lovibond (23), DASS-21 is a self-report scale with 21 questions. This scale includes three subdimensions: Depression, anxiety, and stress. Seven questions evalaute each subdimension. The total points of each subdimension resemble each subdimension level. The Turkish reliability and validity of the study were performed (24).

Personality Belief Questionnaire-Short Form (PBQ-SF): This self-report scale consists of 65 questions and was developed by Butler et al. (25). PBQ-SF evaluates dysfunctional beliefs associated with ten personality disorders. In cognitive theory, dysfunctional beliefs related to a personality disorder characterize that personality disorder (26). In the present study, only the OCPD subscale of the PBQ-SF (PBQ-SF-OCPD) was administered to participants to evaluate the beliefs specific to OCPD beliefs. High scores of PBQ-SF-OCPD mention high levels of OCPD beliefs. The Turkish reliability and validity of the study were performed (27).

Beck Hopelessness Scale (BHS): This scale was developed by Beck et al. (28) and is a self-report scale comprising 20 questions. High total scores for BHS indicate high levels of hopelessness. The Turkish reliability and validity of the study were performed by Durak and Palabıyıkoğlu (29). BHS scores of ≥9 are considered hopelessness

Statistical Analyses

All analyses were performed on IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). The conformity of the variables to normal distribution was evaluated using histogram and Q-Q plots. Descriptive statistics were presented using mean ± standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables. In the assessment of BHS, students were divided into two groups according to the cut-off point (BHS scores ≥9 considered hopelessness) of BHS (30). Between groups analysis of normally distributed continuous variables was performed using Student's t-test. Between groups, non-normally distributed continuous variables were analyzed using the Mann-Whitney U test. Between groups, categorical variables were analyzed using the chi-square test or Fisher-Freeman-Halton test. Relationships between variables were evaluated using the Spearman correlation coefficients. Mediation analysis was performed using the Hayes Process procedure. In the mediation analysis, the PBQ-SF-OCPD score was an independent variable, DASS-21 Depression, Anxiety and Stress scores were mediator variables, and the BHS score was a dependent variable. Two-tailed p-values of less than 0.05 were considered statistically significant.

Results

We included 164 students (97 females and 67 males) in the study. The mean age was 23.54±1.59 (range 20-30). The median Beck Hopelessness Scale (BHS) score was 5 (interquartile range 2.5-10, range 0-20). 29.88% (n=49) of the students had hopelessness (BHS scores ≥9) (Table 1).

Table 1. Summary of age, gender, grade, and scale/questionnaire scores

Age (years)	23.54±1.59
Gender	
Female	97 (59.15%)
Male	67 (40.85%)
Grade	
First	1 (0.61%)
Second	4 (2.44%)
Third	27 (16.46%)
Fourth	7 (4.27%)
Fifth	72 (43.90%)
Sixth	53 (32.32%)
SDS Score	
Work/School	3 (1-6)
Social Life	4 (1-6)
Family Life/Home Responsibilities	3 (1-5)
Total	10.5 (5-17)
BHS Score	5 (2.5-10)
≥9	49 (29.88%)
DASS-21 Score	
Depression	6 (2-9)
Anxiety	3.5 (1-7)
Stress	6 (4-9)
PBQ-SF-OCPD Score	12.30 ±6.23

Descriptive statistics are presented using mean±standard deviation for normally distributed continuous variables, median (25th percentile-75th percentile) for non-normally distributed continuous variables, and frequency (percentage) for categorical variables

We found no significant differences between BHS score groups (BHS scores ≥9) regarding age, sex, and grade. SDS Work/school score (p<0.001), SDS Social life score (p<0.001), SDS Family life score (p=0.001), SDS-Total score (p<0.001), DASS-21 Depression score (p<0.001), DASS-21 Anxiety score (p<0.001), DASS-21 Stress score (p<0.001) and PBQ-SF-OCPD score (p=0.019) were significantly higher in the hopelessness group than in the group without hopelessness (Table 2).

Table 2. Summary of age, gender, grade, and scale/questionnaire scores concerning BHS score

	BHS score		
	<9 (n=115)	**≥9 (n=49)**	p
Age (years)	23.63±1.57	23.33±1.63	0.256†
Gender			
Female	65 (56.52%)	32 (65.31%)	0.382§
Male	50 (43.48%)	17 (34.69%)	
Grade			
First	1 (0.87%)	0 (0.00%)	0.392¶
Second	3 (2.61%)	1 (2.04%)	
Third	17 (14.78%)	10 (20.41%)	
Fourth	3 (2.61%)	4 (8.16%)	
Fifth	50 (43.48%)	22 (44.90%)	
Sixth	41 (35.65%)	12 (24.49%)	
SDS Score			
Work/School	2 (1-5)	5 (3-6)	<0.001‡
Social Life	3 (1-5)	6 (4-7)	<0.001‡
Family Life/Home Responsibilities	2 (1-5)	4 (2-6)	0.001‡
Total	8 (3-15)	15 (11-18)	<0.001‡
DASS-21 Score			
Depression	4 (2-7)	11 (8-14)	<0.001‡
Anxiety	2 (1-5)	7 (4-11)	<0.001‡
Stress	5 (3-7)	9 (6-13)	<0.001‡
PBQ-SF-OCPD	11.56±6.03	14.04±6.38	0.019†

BHS Score was positively correlated with SDS Work/School score (r=0.446, p<0.001), SDS Social life score (r=0.473, p<0.001), SDS Family life score (r=0.328, p<0.001), SDS Total score (r=0.461, p<0.001), DASS-21 Depression score (r=0.686, p<0.001), DASS-21 Anxiety score (r=0.484, p<0.001), DASS-21 Stress score (r=0.501, p<0.001) and PBQ-SF-OCPD score (r=0.190, p=0.015) (Table-3).

Table 3. Correlations between scale/questionnaire scores

		BHS Score	DASS-21 Depression Score	DASS-21 Anxiety Score	DASS-21 Stress Score	**PBQ-SF-OCPD Score**
SDS Work/School score	r	0.446	0.531	0.515	0.459	0.057
	p	<0.001	<0.001	<0.001	**<0.001**	0.470
SDS Social Life Score	r	0.473	0.568	0.536	0.507	0.081
	p	<0.001	<0.001	<0.001	**<0.001**	0.305
SDS Family Life/Home Responsibilities Score	r	0.328	0.483	0.440	0.417	0.100
	p	<0.001	<0.001	<0.001	**<0.001**	0.202
SDS Total Score	r	0.461	0.584	0.559	0.513	0.093
	p	<0.001	<0.001	<0.001	**<0.001**	0.238
BHS Score	r	-	0.686	0.484	0.501	0.190
	p	-	<0.001	<0.001	<0.001	**0.015**
PBQ-S1 Obsessive-Compulsive score	r	0.190	0.202	0.223	0.287	-
	p	0.015	0.009	0.004	**<0.001**	-

Statistically significant p values are shown in bold. r: Correlation coefficient, SDS: Sheehan Disability Scale, BHS: Beck Hopelessness Scale, DASS-21: Depression, Anxiety and Stress Scale - 21 Items, PBQ-SF-OCPD: Personality Belief Questionnaire-Short Form Obsessive-Compulsive Personality Disorder subscale

SDS Work/School score was positively correlated with

DASS-21 Depression score (r=0.531, p<0.001), DASS-21 Anxiety score (r=0.515, p<0.001), and DASS-21 Stress score (r=0.459, p<0.001). SDS Social life score was positively correlated with DASS-21 Depression score (r=0.568, p<0.001), DASS-21 Anxiety score (r=0.536, p<0.001), and DASS-21 Stress score (r=0.507, p<0.001). SDS Family life score was positively correlated with DASS-21 Depression score (r=0.483, p<0.001), DASS-21 Anxiety score (r=0.440, p<0.001), and DASS-21 Stress score (r=0.417, p<0.001). SDS Total score was positively correlated with DASS-21 Depression score (r=0.584, p<0.001), DASS-21 Anxiety score (r=0.559, p<0.001), and DASS-21 Stress score (r=0.513, p<0.001) (Table-3).

PBQ-SF- OCPD score was positively correlated with DASS-21 Depression score (r=0.202, p=0.009), DASS-21 Anxiety score (r=0.223, p=0.004), DASS-21 Stress score (r=0.287, p<0.001), (Table 3).

We performed mediation analysis using the PBQ-SF-OCPD score as an independent variable, DASS-21 Depression, Anxiety, and Stress scores as mediator variables, and BHS score as a dependent variable. PBQ-SF-OCPD score was significantly associated with DASS-21 Depression score (b: 0.172, 95% CI: 0.053 - 0.291, p=0.005), DASS-21 Anxiety score (b: 0.190, 95% CI: 0.086 - 0.294, p<0.001) and DASS-21 Stress score (b: 0.223, 95% CI: 0.122 - 0.324, p<0.001). According to the multivariable model, the DASS-21 Depression score was the only variable significantly associated with the BHS score (b: 0.692, 95% CI: 0.518 - 0.866, p<0.001), although the PBQ-SF-OCPD score was significantly associated with BHS score (b: 0.163, 95% CI: 0.045 - 0.281, p=0.007) according to total effect model (Table 4).

The indirect effect of PBQ-SF-OCPD score on BHS score via DASS-21 Depression score was 0.119 (95% CI: 0.027 - 0.230) and the standardized indirect effect of PBQ-SF-OCPD score on BHS score via DASS-21 Depression score was 0.153 (95% CI: 0.035 - 0.284) (Table 5). According to mediation analysis results, the DASS-21 Depression score was found to be a full mediator of the PBQ-SF- OCPD score on the BHS score. In contrast, DASS-21 Anxiety and Stress scores were found to be non-significant mediators (Figure 1).

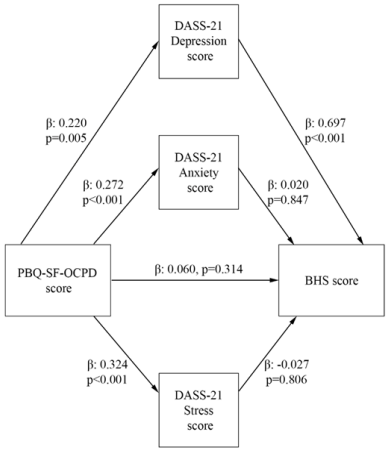

Figure 1. Mediation analysis results, Independent variable: Personality Belief Questionnaire - Short Form-Obsessive-Compulsive Personality Disorder subscale (PBQ-SF-OCPD) score, Mediator variables: Depression, Anxiety and Stress Scale - 21 Items (DASS-21) Depression, Anxiety and Stress scores, Dependent variable: Beck Hopelessness Scale (BHS) score, β: Standardized coefficient.

Table 4. Mediation analysis results

	Unstandardized coefficients (95% CI)	Standardized coefficients	p
Independent variables → Mediator variables			
PBQ-SF-OCPD Score → DASS-21 Depression Score	0.172 (0.053-0.291)	0.220	0.005
PBQ-SF-OCPD Score → DASS-21 Anxiety Score	0.190 (0.086-0.294)	0.272	<0.001
PBQ-S1-OCPD Score → DASS-21 Stress Score	0.223 (0.122-0.324)	0.324	<0.001
Multivariable Model			
PBQ-SF- OCPD Score → BHS Score	0.047 (-0.045-0.138)	0.060	0.314
DASS-21 Depression Score → BHS Score	0.692 (0.518-0.866)	0.697	<0.001
DASS-21 Anxiety Score → BHS Score	0.022 (-0.203-0.247)	0.020	0.847
DASS-21 Stress Score → BHS Score	-0.031 (-0.278-0.217)	-0.027	0.806
Total Effect Model			
PBQ-SF- OCPD Score → BHS Score	0.163 (0.045-0.281)	0.210	0.007

CI: Confidence interval, BHS: Beck Hopelessness Scale, DASS-21: Depression, Anxiety and Stress Scale - 21 Items, PBQ-SF-OCD: Personality Belief Questionnaire - Short Form Obsessive-Compulsive Personality Disorder subscale

Table 5. Indirect effects of PBQ-SF-OCPD score on BHS score

	Indirect effect (95% CI)	Standardized indirect effect (95% CI)
Total	0.116 (0.018-0.223)	0.150 (0.024-0.276)
Via DASS-21 Depression Score	0.119 (0.027-0.230)	0.153 (0.035-0.284)
Via DASS-21 Anxiety Score	0.004 (-0.055-0.057)	0.005 (-0.069-0.074)
Via DASS-21 Stress Score	-0.007 (-0.072-0.062)	-0.009 (-0.092-0.079)

CI: Confidence interval, BHS: Beck Hopelessness Scale, DASS-21: Depression, Anxiety and Stress Scale-21 Items, PBQ-S1: Personality Belief Questionnaire-Short Form

Discussion

In the present study, the mediation analysis revealed that depression levels were a full mediator of OCPD beliefs on hopelessness levels. One-third (29.88%) of undergraduate medical students showed hopelessness. In the group with hopelessness, levels of stress, anxiety, depression, functional impairment, and beliefs of OCPD were significantly higher than in the group without hopelessness. Additionally, the levels of hopelessness were significantly correlated with levels of functional impairment, anxiety, stress, depression, and OCPD beliefs.

In the present study, 29.88% of undergraduate medical students showed hopelessness. Previously, in Türkiye mild levels of hopelessness were found to be 54.4% among medical students (31). Another study from Türkiye revealed that only 30.6% of medical students had no hopelessness (32). In this study, 13.7% of the medical students had moderate hopelessness, and 7.3% of the medical students had severe hopelessness. Considering the high levels of hopelessness in the medical students in the mentioned studies, hopelessness may be considered a priority in mental health assessment in medical students.

In the present study, the medical student group with hopelessness had higher levels of overall functional impairment. In addition, considering subtypes of functional impairment (family life, social life, and work/school), the hopelessness group showed significantly higher levels than without the hopelessness group. In the correlation analysis, all subtypes of functional impairment and overall functional impairment levels were positively correlated with hopelessness. These associations between functional impairment and hopelessness in medical students warrant attention. To our knowledge, the present study is the first to reveal an association between hopelessness and functional impairment in medical students. Additionally, hopelessness levels were significantly associated with stress, anxiety, and depression levels. This finding is similar to previous findings (33-35).

Hopelessness levels of medical students were related to OCPD beliefs in the present study. The hopelessness and beliefs of the OCPD association are an underinvestigated issue, and to the best of our knowledge, this association was not previously explored in medical students. Perfectionism is also one of the core features of OCPD, and perfectionism is one of the maladaptive coping styles (36). Previously, perfectionism was found to be associated with hopelessness (37). Over-concerning orderliness, rigidity, and controlling demands in relationships are the core features of OCPD, too. As with perfectionism, these features may have contributed to the present study's finding regarding hopelessness and dysfunctional beliefs related to OCPD association.

In the present study, depression levels were found to mediate the effects of OCPD beliefs on hopelessness levels. To our knowledge, this is the first finding considering the mediating effects of depression-induced OCPD beliefs on hopelessness in a sample of medical students. Mental health problems, especially depression, are widespread among medical students (38). Depression is a mental disorder with deleterious serious effects on the daily lives of individuals, and this mediating effect sounds reasonable. (39). Additionally, hopelessness is one of the main risk factors for suicide behaviors (37, 40, 41). Besides, suicide is a crucial topic for medical students. Medical students show higher rates of suicide behaviors than the general population (42). In a meta-analysis, the prevalence of suicidal ideation was found to be 18.7%, and the prevalence of suicide attempts was found to be 5.5% in medical students (43). Thus, when medical students with high levels of OCPD beliefs experience depressive symptoms, they may be more carefully monitored regarding suicide behaviors. Also, it should be beneficial not to forget that OCPD is a personality disorder with a very high prevalence among personality disorders (20).

OCPD belief levels were positively associated with

anxiety, depression, and stress levels in the present study. Previously, in a large population-based study, OCPD was found to be associated with depression and anxiety (20, 44). In addition, OCPD features were found to be related to stress and stress-related exhaustion (18, 45). Considering the main characteristics of the OCPD, associations with depression, anxiety, and stress are not surprising.

The limitations of the present study are to be mentioned. First, the study was performed in a cross-sectional design. So, we should be cautious when evaluating the results. Second, assessing the main variables of the present study with a larger sample size would be better. Third, self-report measures were used in this study. Future trials may be conducted in medical students with clinical interviews regarding this study's topics. Fourth, medical students face harsh working conditions and experience high levels of mental health problems. So, the present study's findings can not be directly associated with the general population. Fifth, most of the participants of the study are from the fifth and sixth grades of medical faculty. It would be better if the participants were distributed homogeneously among the grades.

To our knowledge, the present study is the first to show the relationship between the mediating effects of depression levels and the effects of OCPD beliefs on hopelessness in medical students. Additionally, the present study first showed that the hopelessness levels of medical students were associated with levels of OCPD beliefs and functional impairment. A substantial proportion of the medical students suffer from hopelessness. This high proportion of hopelessness needs to be prioritized in the development of policies to improve medical students' mental health. Future clinical trials assessing the roles of personality disorder traits and psychosocial functioning in hopelessness would be performed to improve mental health in medical students.

Authors' Contributions

Conception: EFA. Design: EFA, OŞ, CÖ. Data collection and processing: EFA, OŞ, CÖ. Data analysis and interpretation: EFA, OŞ, CÖ. Writing: EFA. Critical review: EFA, OŞ, CÖ.

Conflict of Interest

The authors declare no conflict of interest

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References

1.Alshareef N, Fletcher I, Giga S. The role of emotions in academic performance of undergraduate medical students: a narrative review. BMC Med Educ. 2024;24(1):907.

2.Aljuwaiser S, Brazzelli M, Arain I, Poobalan A. Common mental health problems in medical students and junior doctors - an overview of systematic reviews. J Ment Health. 2023:1-37.

3.Watson M, Filia K, Stevens A, Cotton S, Nelson B, Ratheesh A. A systematic review and meta-analysis of global and social functioning among people at risk of bipolar disorder. J Affect Disord. 2023;321:290-303.

4.Rosa AR, Sánchez-Moreno J, Martínez-Aran A, Salamero M, Torrent C, Reinares M, et al. Validity and reliability of the Functioning Assessment Short Test (FAST) in bipolar disorder. Clin Pract Epidemiol Ment Health. 2007;3:5.

5.Huber A, Rabl L, Höge-Raisig T, Höfer S. Well-Being, Mental Health, and Study Characteristics of Medical Students before and during the Pandemic. Behav Sci (Basel). 2023;14(1).

6.Hall LH, Johnson J, Watt I, Tsipa A, O'Connor DB. Healthcare Staff Wellbeing, Burnout, and Patient Safety: A Systematic Review. PLoS One. 2016;11(7):e0159015.

7.Aljuwaiser S, Brazzelli M, Arain I, Poobalan A. Common mental health problems in medical students and junior doctors - an overview of systematic reviews. J Ment Health. 2024;33(6):779-815.

8.Vollmer-Conna U, Beilharz JE, Cvejic E, Macnamara CL, Doherty M, Steel Z, et al. The well-being of medical students: A biopsychosocial approach. Aust N Z J Psychiatry. 2020;54(10):997-1006.

9.da Silva AG, Malloy-Diniz LF, Garcia MS, Figueiredo CGS, Figueiredo RN, Diaz AP, et al. Cognition As a Therapeutic Target in the Suicidal Patient Approach. Front Psychiatry. 2018;9:31.

10.Abdoli N, Salari N, Darvishi N, Jafarpour S, Solaymani M, Mohammadi M, et al. The global prevalence of major depressive disorder (MDD) among the elderly: A systematic review and meta-analysis. Neurosci Biobehav Rev. 2022;132:1067-73.

11.Valtonen HM, Suominen K, Haukka J, Mantere O, Arvilommi P, Leppämäki S, et al. Hopelessness across phases of bipolar I or II disorder: a prospective study. J Affect Disord. 2009;115(1-2):11-7.

12.Hawton K, Casañas ICC, Haw C, Saunders K. Risk factors for suicide in individuals with depression: a systematic review. J Affect Disord. 2013;147(1-3):17-28.

13.Wenzel A, Beck AT. A cognitive model of suicidal behavior: Theory and treatment. Applied and preventive psychology. 2008;12(4):189-201.

14.Kart A, Yucens B. Personality Beliefs in Obsessive-Compulsive Disorder: How Are They Related to Symptom Severity? Psychiatry Investigation. 2020;17(8):822.

15.Beck AT, Butler AC, Brown GK, Dahlsgaard KK, Newman CF, Beck JS. Dysfunctional beliefs discriminate against personality disorders. Behav Res Ther. 2001;39(10):1213-25.

16.Ghahramanlou-Holloway M, Lee-Tauler SY, LaCroix JM, Kauten R, Perera K, Chen R, et al. Dysfunctional personality disorder beliefs and lifetime suicide attempts among psychiatrically hospitalized military personnel. Compr Psychiatry. 2018;82:108-14.

17.Pinto A, Teller J, Wheaton MG. Obsessive-Compulsive Personality Disorder: A Review of Symptomatology, Impact on Functioning, and Treatment. Focus (Am Psychiatr Publ). 2022;20(4):389-96.

18.Cain NM, Ansell EB, Simpson HB, Pinto A. Interpersonal functioning in obsessive-compulsive personality disorder. J Pers Assess. 2015;97(1):90-9.

19.Pinto A, Steinglass JE, Greene AL, Weber EU, Simpson HB. The capacity to delay reward differentiates obsessive-compulsive disorder and obsessive-compulsive personality disorder. Biol Psychiatry. 2014;75(8):653-9.

20.Grant JE, Mooney ME, Kushner MG. Prevalence, correlates, and comorbidity of DSM-IV obsessive-compulsive personality disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Psychiatr Res. 2012;46(4):469-75.

21.d'Huart D, Seker S, Bürgin D, Birkhölzer M, Boonmann C, Schmid M, et al. The stability of personality disorders and personality disorder criteria: A systematic review and meta-analysis. Clin Psychol Rev. 2023;102:102284.

22.Sheehan DV, Harnett-Sheehan K, Raj BA. The measurement of disability. Int Clin Psychopharmacol. 1996;11 Suppl 3:89-95.

23.Lovibond S. Manual for the depression anxiety stress scales. Psychology Foundation of Australia. 1995.

24.Sariçam H. The psychometric properties of the Turkish version of Depression Anxiety Stress Scale-21 (DASS-21) in health control and clinical samples. Journal of Cognitive Behavioral Psychotherapies and Research. 2018;7(1):19.

25.Butler AC, Beck AT, Cohen LH. The personality belief questionnaire-short form: Development and preliminary findings. Cognitive therapy and research. 2007;31:357-70.

26.Kart A, Yucens B. Personality Beliefs in Obsessive-Compulsive Disorder: How Are They Related to Symptom Severity? Psychiatry Investig. 2020;17(8):822-8.

27.Taymur İ, Türkçapar MH, Örsel S, Sargın E, Akkoyunlu S. Kişilik inanç ölçeği-kısa formunun (kiö-ktf) türkçe çevirisinin üniversite öğrencilerinde geçerlilik, güvenilirliği. Klinik psikiyatri. 2011;14:199-209.

28.Beck AT, Weissman A, Lester D, Trexler L. The measurement of pessimism: the hopelessness scale. Journal of consulting and clinical psychology. 1974;42(6):861.

29.Durak A, Palabıyıkoğlu R. Beck Umutsuzluk ölçeği geçerlilik çalişmasi. Kriz dergisi. 1994;2(2):311-9.

30.Gürgül S, Şeker FB. Tıp fakültesi öğrencilerinin depresyon, anksiyete, umutsuzluk ve endişe düzeylerinin belirlenmesi. Mersin Üniversitesi Sağlık Bilimleri Dergisi. 2022;15(2):361-9.

31.Coskun O, Ocalan AO, Ocbe CB, Semiz HO, Budakoglu I. Depression and hopelessness in pre-clinical medical students. The Clinical Teacher. 2019;16(4):345-51.

32.Kaygusuz TÖ, Erensoy A. Determination of hopelessness levels of final year students of the Faculty of Medicine. Tıp Eğitimi Dünyası. 2020;19(58):116-27.

33.Mert S, Peker Karatoprak A, Demirhan Y, Baydemir C, Çetinarslan B, Cantürk Z, et al. COVID-19, Anxiety, and Hopelessness: Quality of Life Among Healthcare Workers in Turkey. Eval Health Prof. 2022;45(1):97-107.

34.Momeni K, Salimi Y, Majzoobi MR, Ziapour A, Janjani P. Anxiety, coping style and hopelessness during COVID-19 pandemic: An Iranian population-based study. Health Sci Rep. 2023;6(5):e1233.

35.Demirtas AS, Yildiz B. Hopelessness and perceived stress: The mediating role of cognitive flexibility and intolerance of uncertainty. Dusunen Adam Journal of Psychiatry and Neurological Sciences. 2019;32(3):259.

36.Overholser J, Dimaggio G. Struggling with perfectionism: When good enough is not good enough. J Clin Psychol. 2020;76(11):2019-27.

37.Robinson A, Moscardini E, Tucker R, Calamia M. Perfectionistic Self-Presentation, Socially Prescribed Perfectionism, Self-Oriented Perfectionism, Interpersonal Hopelessness, and Suicidal Ideation in U.S. Adults: Reexamining the Social Disconnection Model. Arch Suicide Res. 2022;26(3):1447-61.

38.Pacheco JP, Giacomin HT, Tam WW, Ribeiro TB, Arab C, Bezerra IM, et al. Mental health problems among medical students in Brazil: a systematic review and meta-analysis. Braz J Psychiatry. 2017;39(4):369-78.

39.Özdemir PG, Ülkevan T, Işık M, Sütçü E. Circadian Preferences and Coping Styles for Stressful Life Events in Major Depressive Disorder. Van Tip Dergisi. 2024;31(3).

40.Balci V, Sevincok L. Suicidal ideation in patients with obsessive-compulsive disorder. Psychiatry Res. 2010;175(1-2):104-8.

41.Klonsky ED, May AM, Saffer BY. Suicide, Suicide Attempts, and Suicidal Ideation. Annu Rev Clin Psychol. 2016;12:307-30.

42.Blacker CJ, Lewis CP, Swintak CC, Bostwick JM, Rackley SJ. Medical Student Suicide Rates: A Systematic Review of the Historical and International Literature. Acad Med. 2019;94(2):274-80.

43.Kaggwa MM, Najjuka SM, Favina A, Griffiths MD, Mamun MA. Suicidal behaviors and associated factors among medical students in Africa: A systematic review and meta-analysis. Journal of Affective Disorders Reports. 2023;11:100456.

44.Grant BF, Hasin DS, Stinson FS, Dawson DA, Patricia Chou S, June Ruan W, et al. Co-occurrence of 12-month mood and anxiety disorders and personality disorders in the US: results from the national epidemiologic survey on alcohol and related conditions. J Psychiatr Res. 2005;39(1):1-9.

45.Gulin S, Ellbin S, Jonsdottir IH, Lindqvist Bagge AS. Is obsessive-compulsive personality disorder related to stress-related exhaustion? Brain Behav. 2021;11(6):e02171.

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ORIGINAL ARTICLE

The Diagnostic Role of Ultrasonography and Neutrophil-to-Lymphocyte Ratio in Acute Abdominal Pain in Children

Çocuklarda Akut Karın Ağrısında Ultrasonografi ve Nötrofil-Lenfosit Oranının Tanısal Rolü

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ABSTRACT

Background: Acute abdominal pain in children is typically a transient condition with age-dependent symptoms, but in some cases, it can lead to serious outcomes requiring urgent medical intervention. Early diagnosis and treatment are crucial to preventing complications. When physical examination alone is insufficient, diagnostic tools such as ultrasonography (USG) and laboratory tests, including the neutrophil-to-lymphocyte ratio (NLR), can enhance diagnostic accuracy.
Materials and Methods: This prospective study was conducted between January 2022 and December 2022 and included children aged 0 to 18 years presenting to the pediatric emergency department with acute abdominal pain lasting less than three days and underwent abdominal USG. Laboratory test results, ultrasound findings, and pathological examination results were recorded from the hospital database. The ultrasonographic criteria for diagnosing appendicitis were defined as an appendix larger than 6 mm or surrounded by a hypoechoic wall thicker than 2 mm.
Results: A specific diagnosis was established in 53.4% of the 504 patients. The most common diagnoses were mesenteric lymphadenitis, gastroenteritis, and appendicitis. In 46.6% of the cases, no specific diagnosis was made, and these were classified as nonspecific abdominal pain. Patients with organic abdominal pain had significantly higher NLR, white blood cell (WBC) counts, and C-reactive protein levels than those with nonspecific pain ($p<0.05$). Patients requiring surgery were older and had higher NLR, WBC, and neutrophil counts, and lower lymphocyte counts compared to those who did not require surgery ($p<0.05$). The sensitivity of USG in diagnosing appendicitis was 60.9%, with a specificity of 33.3%.
Conclusion: USG is a frequently used method in the diagnosis of acute abdominal pain in children; however, the inability to visualize the appendix may make diagnosis difficult. Neutrophil lymphocyte ratio increases diagnostic accuracy in cases requiring urgent surgical intervention, and the combined use of both methods allows faster and more accurate results.

Keywords: Acute abdominal pain, neutrophil-to-lymphocyte ratio, ultrasonography,

ÖZ

Giriş: Çocuklarda akut karın ağrısı, yaşa göre değişen belirtilerle genellikle kısa süreli bir durumdur. Bazı vakalarda acil müdahale gerektiren ciddi sonuçlar doğurabilir. Zamanında teşhis ve tedavi, morbiditeyi önlemek için kritik öneme sahiptir. Fizik muayenenin yeterli olmadığı durumlarda, ultrasonografi ve nötrofil lenfosit oranı gibi laboratuvar testleri tanısal doğruluğu artıran önemli araçlardır.
Metot: Bu çalışma, Ocak 2022 ile Aralık 2022 tarihleri arasında ani başlayan, üç günden kısa süren akut karın ağrısı ile çocuk acil kliniğine başvuran ve abdominal ultrasonografi çekilen 0-18 yaş arası çocukları kapsayan prospektif bir araştırmadır. Hastaların laboratuvar tetkikleri, abdominal USG incelemeleri ve patolojik inceleme sonuçları hastane veri tabanından kaydedildi. Ultrasonografik apandisit tanı kriterleri, 2 mm'den kalın hipoekoik duvarla çevrili veya 6 mm'den büyük apendiks varlığı olarak belirlendi.
Bulgular: 504 hastanın %53,4'üne tanı konuldu. En sık tanılar sırasıyla mezenter lenfadenit, gastroenterit ve apandisit olarak belirlendi, tanı konulamayan %46,6'lık grup ise spesifik olmayan karın ağrısı olarak değerlendirildi. Organik karın ağrısı olan hastalarda nötrofil lenfosit oranı ve lökosit ile CRP değerleri, spesifik olmayan ağrısı olanlara göre anlamlı şekilde yüksekti ($p<0,05$). Cerrahi müdahale gerektiren hastaların yaş, nötrofil lenfosit oranı, lökosit ve nötrofil sayıları, müdahale gerektirmeyenlere kıyasla daha yüksek, lenfosit sayıları ise daha düşüktü ($p<0,05$) Ultrasonografinin apandisit tanısındaki duyarlılığı %60,9, özgüllüğü %33,3 olarak belirlendi.
Sonuç: Ultrasonografi, çocuklarda akut karın ağrısının tanısında sıkça kullanılan bir yöntemdir; ancak apendiksin görüntülenememesi tanıyı zorlaştırabilir. Nötrofil lenfosit oranı, acil cerrahi müdahale gerektiren vakalarda tanısal doğruluğu artırmakta ve her iki yöntemin birlikte kullanımı, daha hızlı ve doğru sonuçlar elde edilmesine olanak tanımaktadır.

Anahtar Kelimeler: Akut karın ağırısı, nötrofil lenfosit oranı, ultrasonografi,

Introduction

Abdominal pain is a common complaint in children and may indicate conditions that require both medical and surgical approaches. Life-threatening conditions necessitating surgical intervention can also be the underlying cause of this pain. Particularly in the case of acute abdominal pain, the rapid exclusion of such serious conditions is of utmost importance. Acute abdominal pain is typically characterized by a clinical picture lasting less than three days, with causes, symptoms, and findings that vary according

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to age (1). The causes of acute abdominal pain may include surgical emergencies, intra-abdominal and extraintestinal issues, as well as systemic medical disorders. Timely diagnosis and initiation of treatment in a child with abdominal pain are critical to preventing morbidity (2,3).

A detailed physical examination in children may not always be feasible; therefore, laboratory tests and auxiliary imaging techniques play a significant role in enhancing diagnostic accuracy. When evaluating a child with abdominal pain, basic laboratory studies are often utilized. Leukocytosis, elevated C-reactive protein (CRP) levels, and the neutrophil-to-lymphocyte ratio (NLR) have been shown to increase the positive predictive value of diagnosis in cases of acute abdominal pain and contribute to the decision-making process in situations requiring surgical intervention (4). Ultrasonography (USG) is a commonly preferred imaging modality in pediatric emergency departments. The rapid, non-invasive, and radiation-free characteristics of USG make it a safe option for pediatric patients (5).

Appendicitis is the most common abdominal surgical condition encountered in pediatric emergency departments. Appendicitis is diagnosed in 1-8% of children presenting with acute abdominal pain (6). Due to the often nonspecific nature of symptoms in children, accurate diagnosis requires a combination of physical examination, blood tests, imaging techniques, and scoring systems. In 20-30% of acute appendicitis cases, the white blood cell (WBC) count may be normal or only mildly elevated. WBC, neutrophils, and CRP have wide ranges of specificity and sensitivity in predicting appendicitis (7). Some studies suggest that leukocytosis alone is insufficient to confirm or exclude a diagnosis of appendicitis and that the NLR may be a more sensitive test for diagnosing acute appendicitis (8).

USG is a commonly used method for diagnosing appendicitis. The accuracy of USG is particularly proportional to the experience of the operator. Additionally, the inability to visualize the appendix on USG is a frequently encountered issue. These factors limit the ability to achieve an accurate diagnosis using USG. This situation may necessitate a computed tomography (CT) scan, leading to radiation exposure for the patients (9).

The primary objective of this study is to ensure the rapid and accurate assessment of patients presenting to the pediatric emergency department with acute abdominal pain and to determine the effectiveness of USG and laboratory analyses in establishing a diagnosis.

Materials And Methods

The study included children aged 0-18 years who presented to the pediatric emergency department with acute abdominal pain lasting less than three days and underwent abdominal USG between January 2022 and December 2022. The research was conducted prospectively.

Patients undergoing abdominal USG without requested laboratory tests, those with abdominal pain who did not require a USG, and those who underwent USG for screening purposes due to trauma were excluded from the study.

All patients were evaluated by the physician on duty in the pediatric emergency department through history-taking and physical examination, and necessary laboratory tests were requested. The patients' sociodemographic information, presenting complaints, physical examination findings, laboratory results, abdominal USG and CT findings, surgical intervention status, and pathological examination results (if applicable) were recorded from the hospital data system. Patients were re-evaluated as needed through follow-up examinations. Laboratory tests included complete blood count, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, amylase, lipase, CRP, erythrocyte sedimentation rate, urinalysis, and urine culture results.

The Pediatric Appendicitis Score (PAS) for each patient presenting with acute abdominal pain was calculated separately by the physician on duty in the pediatric emergency department (Table 1). The score ranges were categorized as follows: ≤4 points: low risk, 5-7 points: moderate risk, ≥8 points: high risk (10).

Table 1. Pediatric appendicitis score (Total 10 points)

PAS Components	**Point Value**
Anorexia	1 Point
Nausea or vomiting	1 Point
Fever (≥38°C)	1 Point
Tenderness in the right lower quadrant	2 Points
Coughing/ percussion/ jumping at the right lower quadrant	2 Points

Migration of pain to the right lower quadrant	1 Point
Leukocytosis (≥10,000/mm³)	1 Point
Neutrophilia (when neutrophils constituted more than 75% of total leukocyte count)	1 Point

Abdominal USG examinations for all patients were performed using a Siemens ACUSON S3000 model ultrasound device. CT scans were conducted using a Siemens Somatom Go Up 64 model. The abdominal USG and CT evaluations were performed by a radiologist.

The ultrasonographic criteria used for diagnosing appendicitis included the presence of an appendix with a diameter greater than 6 mm or surrounded by a hypoechoic wall thicker than 2 mm under compression (11). The CT findings indicative of appendicitis included an enlarged appendix lumen greater than 6 mm and/or up to 80% thickening at the apex of the cecum (12). The pathological examination results of patients who underwent appendectomy were recorded from the hospital data system.

Statistical Analysis

Data entry and statistical analysis were performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA). The normality of the data distribution was examined using visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics for numerical data included arithmetic mean, standard deviation, and median (1st quartile-3rd quartile) values. Frequency distributions and percentages were used to summarize categorical data. The Mann-Whitney U test was used to compare non-normally distributed numerical data with categorical data. The Kruskal-Wallis test was employed for the evaluation of non-normally distributed numerical data across three or more groups. For pairs of groups found to be statistically significant in the Kruskal-Wallis test, post-hoc pairwise comparisons were conducted using the Mann-Whitney U test with Bonferroni correction. The chi-square test was used for comparing categorical data. Statistical significance was defined as $p<0.05$.

Results

In this study, which included a total of 504 patients, the median age was 9 years, with 51.0% being male and 49.0% female. The median age for males was 8 years, while for females it was 10 years, with the latter being significantly higher (p=0.001). Nausea was observed in 84.1% of the patients, and vomiting in 60.9%. A diagnosis was established in 53.4% (n=269) of the patients, with the most common diagnoses being mesenteric lymphadenitis (35.3%), gastroenteritis (27.5%), and appendicitis (18.2%). The remaining 46.6% of the group, for whom no specific diagnosis could be made, was classified as having nonspecific abdominal pain (Table 2). Among the patients initially suspected of gastroenteritis, USG revealed mesenteric lymphadenitis in 18.9%, appendicitis in 4.1%, intussusception in 2.7%, and gallstones and pancreatitis in 1.4%.

Table 2. Diagnosis status of patients and distribution of diagnosis types

Features	Number of Patients n=504
	n (%)
Diagnosis Status	
Nonspecific Abdominal Pain	235 (46.6)
Organic Abdominal Pain	269 (53.4)
Organic Causes of Abdominal Pain (n=269)*	
Mesenteric Lymphadenitis	95 (35.3)
Gastroenteritis	74 (27.5)
Appendicitis	49 (18.2)
Gallstone	20 (7.4)
Transaminase Elevation	16 (5.9)
UTI	14 (5.1)
Pancreatitis	12 (4.5)
Intussusception	10 (3.7)
Kidney Stone	7 (2.6)
Ovarian Cyst	4 (1.5)
Ileus	3 (1.1)
Ovarian Torsion	1 (0,4)

*Some patients have more than one diagnosis, UTI: Urinary tract infection

In our study, it was found that 17.3% of the patients underwent CT. Based on the CT results, at least one pathological finding was detected in 63.2% of these patients. The median WBC count for all patients was determined to be 11,060 /mm³, with a median neutrophil count of 7,155 /mm³, and the NLR was calculated as 3.52 (Table 3).

Table 3. Values of laboratory parameters of patients

Parameters	Number of patients n=504	
	Mean±SD	Median (1st-3rd Quartiles)
WBC (/mm³)	12376.44±5615.66	11060.00 (8052.00-15475.00)
Neutrophil (/mm³)	8567.55±5290.50	7155.00 (4612.00-11635.00)
Lymphocyte (/mm³)	2734.49±2134.33	2250.00 (1460.00-3220.00)
Platelets (10^3/mm³)	339.632±105.0	337.000 (271.000-387.750)
MPV (fL)	9.85±0.83	9.80 (9.30-10.40)
Aspartate Aminotransferase (u/L)	53.49±210.17	23.00 (18.00-30.00)

Alanine Aminotransferase (u/L)	39.41±163.50	13.00 (10.00-18.00)
Gamma Glutamyl Transferase (u/L) (n=258)	25.02±54.31	12.00 (9.00-18.00)
Amylase (u/L) (n=265)	108.26±297.31	63.00 (46.50-81.00)
Lipase (U/L) (n=264)	103.21±531.01	19.00 (16.00-26.00)
Urea (mg/dL)	24.39±8.85	22.00 (18.00-28.00)
Creatinine (mg/dL)	0.53±0.27	0.50 (0.41-0.63)
CRP (mg/L)	28.78±59.84	4.50 (0-26.00)
Sedimentation Rate (mm/h) (n=472)	15.39±10.30	13.00 (9.00-18.00)
Neutrophil-Lymphocyte Ratio	5.24±6.10	3.52 (1.55-6.81)
MPV Platelet rate	0.03±0.01	0.02 (0.02-0.03)

*MPV: Mean platelet volume, WBC: White blood cell, CRP: C-reactive protein, NLR: Neutrophil-lymphocyte ratio, SD: Standard deviation

WBC counts, neutrophil, CRP levels, and NLR in patients with organic abdominal pain were found to be significantly higher compared to those with nonspecific abdominal pain ($p<0.05$) (Table 4). Additionally, patients requiring surgical intervention had higher age, NLR, WBC, and neutrophil counts, and significantly lower lymphocyte counts compared to those not requiring surgery ($p<0.05$) (Table 5). The NLR was 4.14 in patients with organic abdominal pain, while it was 2.73 in those with nonspecific abdominal pain. Among patients requiring surgery, the NLR was 5.33, whereas it was 3.28 in those not requiring surgical intervention.

Table 4. Comparison of age and laboratory parameters in patients with acute abdominal pain

Features	Nonspecific Abdominal Pain (n=235)	Organic Abdominal Pain (n=269)	p*
	Median (1st-3rd Quartiles)	Median (1st-3rd Quartiles)	
Age (years)	9.0 (5.0-14.0)	9.0 (5.0-14.0)	0.748
WBC (/mm³)	9820.0 (7490.0-14370.0)	12430.0 (8800.0-16725.0)	**<0.001**
Neutrophil (/mm³)	6010.0 (4030.0-10600.0)	7920.0 (5255.0-12195.0)	**<0.001**
Lymphocyte (/mm³))	2280.0 (1420.0-3270.0)	2150.0 (1460.0-3175.0)	0.644
Platelets (10^3/mm³)	341.0 (269.0-388.0)	335.0 (271.0-386.0)	0.961
MPV (fL)	9.8 (9.2-10.3)	9.8 (9.3-10.4)	0.507
CRP (mg/L)	2.0 (0-17.0)	9.0 (1.0-40.5)	**<0.001**
Sedimentation Rate (mm/h)	12.0 (8.7-18.0)	14.0 (9.0-19.0)	0.140
NLR	2.73 (1.37-6.29)	4.14 (1.96-7.34)	**0.013**
MPV/Platelet	0.029 (0.024-0.037)	0.029 (0.025-0.037)	0.960

*Mann-Whitney U test. MPV: Mean platelet volume, CRP: C-reactive protein, NLR: Neutrophil-lymphocyte ratio, WBC: White blood cell

Table 5. Comparison of age and laboratory parameters of patients requiring and not requiring surgical approach

Features	Surgical Diagnoses		
	Yes (n=63)	No (n=206)	p*
	Median (1st-3rd Quartiles)	Median (1st-3rd Quartiles)	
Age (years)	11.0 (7.0-15.0)	8.0 (4.0-13.0)	**0.001**
WBC (/mm³)	13880.0 (11320.0-17380.0)	11360.0 (8492.5-16272.5)	**0.009**
Neutrophil (/mm³)	10820.0 (7870.0-14470.0)	6750.0 (4742.5-11700.0)	**<0.001**
Lymphocyte (/mm³))	1890.0 (1270.0-2540.0)	2255.0 (1527.5-3380.0)	**0.008**
Platelets (10^3/mm³)	321.0 (265.0-365.0)	338.0 (273.2-397.2)	0.153
MPV (fL)	9.9 (9.5-10.4)	9.8 (9.2-10.5)	0.155
CRP (mg/L)	10.0 (2.0-50.0)	8.5 (1.0-33.2)	0.155
Sedimentation Rate (mm/h)	14.0 (9.0-18.0)	14.0 (9.0-19.0)	0.858
NLR	5.33 (3.77-9.11)	3.28 (1.44-6.76)	<0.001
MPV/Platelet	0.029 (0.026-0.037)	0.028 (0.024-0.036)	0.109

*Mann-Whitney U test. MPV: Mean platelet volume, CRP: C-reactive protein, NLR: Neutrophil-lymphocyte ratio, WBC: White blood cell

The median age of patients diagnosed with appendicitis was significantly higher compared to those with mesenteric lymphadenitis and nonspecific abdominal pain ($p = 0.005$). Additionally, the proportion of patients with a pediatric appendicitis score of 8 or higher was markedly greater in those diagnosed with appendicitis ($p < 0.05$). The NLR was 7.1 in patients with appendicitis, compared to 4.2 in those with mesenteric lymphadenitis and 2.7 in those with nonspecific abdominal pain. Furthermore, both the NLR and CRP levels were significantly higher in patients with appendicitis than in those with mesenteric lymphadenitis and nonspecific abdominal pain ($p < 0.05$) (Table 6). In contrast, no significant differences were observed in mean platelet volume (MPV) or MPV-to-platelet ratios.

Table 6. Comparison of patients with appendicitis, mesenteric lymphadenitis, and non-specific abdominal pain

Features	Patients with Appendicitis (n=46)	Patients with Mesenteric Lymphadenitis (n=88)	Nonspecific Abdominal Pain (n=235)	p
Age* (years)	12.0 (8.7-15.0)	8.0 (6.0-12.0)	9.0 (5.0-14.0)	0.005[a]
Gender, n (%)				
Male	29 (63.0)	44 (50.0)	119 (50.6)	0.278[b]
Female	17 (37.0)	44 (50.0)	116 (49.4)	
WBC (/mm³)	14670.0 (12610.0-17925.0)	10775.0 (7845.0-15805.0)	9820.0 (7490.0-14370.0)	<0.001[a]

Neutrophil (/mm³)	11450.0 (9445.0-14910.0)	7115.0 (4812.5-12445.0)	6010.0 (4030.0-10600.0)	<0.001 [a]
PAS, n (%)				
≤4 points	1 (2.2)	33 (37.5)	143 (60.9)	<0.001
5-7 points	22 (47.8)	51 (58.0)	86 (36.6)	
≥8 points	23 (50.0)	4 (4.5)	6 (2.6)	
MPV	10.0 (9.5-10.4)	9.7 (9.2-10.4)	9.8 (9.2-10.3)	0.255
Platelets (10^3/mm³)	316.5 (264.7-358.2)	329.0 (283.5-388.7)	341.0 (269.0-388.0)	0.187
MPV/Platelet	0.03 (0.02-0.03)	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.127
NLR	7.1 (4.2-11.3)	4.2 (1.9-7.7)	2.7 (1.3-6.2)	<0.001 [a]
CRP*	13.0 (3.0-50.2)	13.0 (2.0-33.7)	2.0 (0-17.0)	<0.001 [a]

* Median (1st-3rd quartile values are given. a Kruskal Wallis H test; b Ki kare test. PAS: Pediatric appendicitis score, MPV: Mean platelet volume, CRP: C-reactive protein, NLR: Neutrophil-lymphocyte ratio, WBC: White blood cell

In 6.1% of the 49 patients who underwent surgery with a preliminary diagnosis of appendicitis, the pathological results were inconsistent with the initial diagnosis. In the USG analysis of patients who had undergone an appendectomy, the appendix was not visualized in 34.7% of the cases. In 4.1% of the patients, the appendix diameter was found to be less than 6 mm, while in 61.2%, it was greater than 6 mm (Table 7). Of the 30 patients whose USG was consistent with acute appendicitis, the pathological diagnosis confirmed acute appendicitis in 28 cases. In 17 patients (34.7%) who underwent an appendectomy, the appendix could not be visualized by USG, and 16 of these were pathologically diagnosed with appendicitis. The sensitivity of USG in diagnosing appendicitis was calculated as 60.9%, specificity as 33.3%, positive predictive value (PPV) as 93.3%, and negative predictive value (NPV) as 5.3%. In all 19 patients evaluated by CT, the appendix diameter exceeded 6 mm, and the sensitivity of CT was 100%. For patients diagnosed with appendicitis who had a PAS score of 5 or higher, the sensitivity was 97.8% and the PPV was 93.8% (Table 8).

Table 7. Distribution of ultrasound, CT, and pathology results in patients with a preoperative diagnosis of appendicitis

Features	Patients with Preliminary Diagnosis of Appendicitis N=49
	n (%)
USG Non-visualized <6 mm ≥6 mm	 17 (34.7) 2 (4.1) 30 (61.2)
CT (n=19) ≥6 mm	 19 (100.0)
Pathological Examination Results Normal Appendix Consistent with Appendicitis	 3 (6.1) 46 (93.9)

CT: Computed tomography, USG: Ultrasonography

Table 8. Evaluation of patient's CT, USG, and PAS results according to the diagnosis of pathological appendicitis

	Pathological Examination Results		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Features	**Normal Appendix**	**Consistent with Appendicitis**				
CT						
<6 mm	-	-	100.0	-	-	-
≥6 mm	-	19 (100.0)				
USG						
Non visualized/ ≤6mm	1 (33.3)	18 (39.1)	60.9	33.3	93.3	5.3
≥6 mm	2 (66.7)	28 (60.9)				
PAS						
PAS <5 point	-	1 (2.2)	97.8	0	93.8	0
PAS≥5 point	3 (100.0)	45 (97.8)				

PPV: Positive predictive value; NPV: Negative predictive value, PAS: Pediatric appendicitis score, CT: Computed tomography, USG: Ultrasonography

Discussion

Acute abdominal pain is typically categorized into two groups: cases where a clear diagnosis or structural problem can be identified immediately, and cases of acute non-specific abdominal pain. Non-specific abdominal pain accounts for 50-70% of cases (13). In Magnúsdóttir et al.'s study (14), this rate was found to be 40%, while Lee et al. (15) reported it as 45.4%. The most common causes identified were mesenteric lymphadenitis and appendicitis. In our study, 46.6% of the patients were diagnosed with non-specific abdominal pain, while 53.4% received a specific diagnosis.

Acute appendicitis occurs in approximately 1 in 1,000 individuals in the United States and is the most common surgical emergency in children, typically presenting in the second or third decade of life (7). The most frequent causes of acute abdominal pain in children are mesenteric lymphadenitis and acute appendicitis. Distinguishing between the symptoms of these two conditions can be challenging due to the children's ages and their ability to articulate symptoms. Mesenteric lymphadenitis is a significant clinical mimic of appendicitis and is frequently observed in negative surgical explorations (16). In our study, the most common diagnoses among our patients were mesenteric lymphadenitis, gastroenteritis, and appendicitis, with appendicitis identified as the most frequent surgical cause.

Acute gastroenteritis is a common condition in children and is one of the leading causes of hospitalization

in children under five years of age (17). In young children with acute abdominal pain, the first sign often associated with mucosal irritation is diarrhea (18). In our study, among patients with acute abdominal pain who underwent abdominal USG and were initially evaluated as having gastroenteritis, diagnoses of mesenteric lymphadenitis, appendicitis, and intussusception were made based on follow-up USG results. The possibility of an acute surgical condition should always be considered in patients presenting with symptoms of gastroenteritis.

Laboratory studies play a crucial role in the early diagnosis of patients presenting with acute abdominal pain. It has even been reported that certain laboratory tests can be beneficial in predicting outcomes in patients with diagnostic challenges. In the study by Harris et al. (19), it was found that WBC counts and CRP levels were significantly higher in patients with organic abdominal pain compared to those with non-specific abdominal pain. Similarly, Gurau et al. (4) demonstrated that increases in WBC and CRP levels, along with the NLR, enhanced the positive predictive value of the diagnosis in cases of acute abdominal pain and contributed to decision-making in situations requiring surgical intervention. In a meta-analysis conducted by Eun et al. (20) on 5,974 pediatric cases, the cut-off values for the NLR were reported to range between 2.5 and 6.14, while the study by Hajibandeh et al. (8) found that a ratio above 4.7 was a strong predictive factor for appendicitis. Furthermore, Toorenvliet et al. (21) noted higher WBC, neutrophil, and CRP levels in patients with appendicitis. However, in the study by Ozdamar and Karavaş (22), only the percentage of neutrophils was found to be significant, with no differences in WBC counts or CRP levels. In our study, patients with organic abdominal pain had significantly higher WBC, neutrophil, CRP levels, and NLR compared to those with non-specific abdominal pain. The NLR was found to be 5.33 in patients requiring surgical intervention and 3.28 in those not requiring surgery, with this difference being statistically significant. In patients diagnosed with appendicitis, the NLR was 7.1, significantly higher than in cases of mesenteric lymphadenitis and non-specific abdominal pain. Our findings align with the literature, suggesting that the neutrophil-to-lymphocyte ratio and leukocyte counts can be utilized in predicting the diagnosis of appendicitis.

In patients with acute appendicitis, the MPV is low, indicating platelet activation (23, 24). MPV levels should not be used to determine treatment options in pediatric patients, as no significant difference has been found compared to healthy controls (25). Biricik et al. (26) reported a negative correlation between platelet count and MPV, while Oktay et al. (27) suggested a weak relationship between leukocyte count and the MPV-to-platelet ratio, proposing that this ratio could be useful in diagnosing pediatric acute appendicitis. However, in our study, no significant differences were observed in MPV and the MPV-to-platelet ratio among patients diagnosed with appendicitis.

The diagnostic efficacy of USG in acute abdominal pain among children varies across different studies. Khalid et al. (28) reported that among patients evaluated with abdominal USG, the diagnosis rate was 45%, the rate of providing supportive information was 12%, and the overall efficacy was 57%. It has been determined that USG reduces the frequency of negative appendectomies, with negative appendectomy rates ranging from 5% to 10% (29). In our study, among the 49 patients operated on with a preliminary diagnosis of appendicitis, 6.1% had pathological findings that were inconsistent with the preliminary diagnosis. Baştuğ (30) found that in a study of 1,000 patients with acute abdominal pain evaluated with abdominal USG, the rate of CT scans was 4.5%, and the rate of pathological findings was 75.5%. Khan et al. (31) reported that in children presenting to emergency departments in the United States with abdominal pain, the CT scan rate was 14%, and the rate of pathological findings was 55.8%. In our study, 17.3% of patients underwent CT, and pathological findings were detected in 63.2% of these cases. The frequency of CT scans in our study exceeds the rates reported in the literature; we believe this may be attributed to the persistence of clinical suspicion despite the absence of pathological findings on USG, necessitating additional imaging methods to reach a diagnosis. Furthermore, due to the unavailability of pediatric surgery during off-hours, additional imaging techniques are utilized to confirm the diagnosis in patients with suspected surgical conditions.

Doria et al. (32) reported a sensitivity of 88% and specificity of 94% for USG in a meta-analysis involving 7,448 participants. Glass and Rangel (6) indicated that sensitivity rates ranged from 44% to 88%, while specificity varied between 90% and 97%. In another review, the sensitivity of US in children was found to be 96% with a specificity of 100% (33). Marcucci et al. (34) calculated the sensitivity of US at 52.8%, specificity at 83.3%, and PPV at 98.4%. In our study, the sensitivity of

USG for appendicitis was determined to be 60.9%, with a specificity of 33.3% and a PPV of 93.3%. The lower sensitivity and specificity levels of USG in our study compared to those in the literature may be attributed to factors such as the relatively small sample size and the experience of the USG operator.

In conclusion, the combined use of USG and the NLR plays a significant role in the accurate and timely diagnosis of acute abdominal pain in children. The findings of our study indicate that in cases where the appendix cannot be visualized via USG, leading to potential delays in the diagnostic process, the NLR and leukocytosis can serve as crucial biomarkers in situations requiring urgent surgical intervention.

Compliance with Ethicals Guidelines: The study was conducted with the approval of the Local Ethics Committee of the Ethics Committee of Necmettin Erbakan University, Faculty of Medicine (No: 2022/3685). All procedures performed in studies involving human participants were in accordance withunder the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Conflicts of Interest

There are no financial and nonfinancial conflicts of interest for any of the authors regarding specific financial interests that are relevant to the work conducted or reported in this manuscript.

Authors' Contributions

Conception: FA., AY,. and AOK.; Design: EB. and FA..; Supervision: EB., SB,. and FA..; Resource: FA., EB., AY., and AOK.; Materials: SB. and AA.., Data Collection and/or PProcessing: EB., FA., AOK,. and AA. ; Analysis and/or İlnterpretation: FA., EB,. and SB.; Literature RReview: FA., EB,. and SB.; Writinger: FA. and EB.; Critical Review: AY. and AA.

References

1. Kim JS. Acute abdominal pain in children. Pediatr Gastroenterol Hepatol Nutr. 2013;16:219-224.

2. Boyle JT. Abdominal pain. Pediatric gastrointestinal disease. 4th ed. Hamilton: BC Decker Inc. 2004. p.225-243.

3. Yang WC, Chen CY, Wu HP. Etiology of non-traumatic acute abdomen in pediatric emergency departments. World J Clin Cases. 2013;1:276-284.

4. Gurau G, Dinu CA, Earar K, Voicu DC, Botezatu D. Diagnostic Value of chemical and hematological markers in children acute abdominal pain. Rev. Chim (Bucharest). 2016;67:507-511.

5. Reust CE, Williams A. Acute abdominal pain in children. Am Fam Physician. 2016;93:830-836.

6. Glass CC, Rangel SJ. Overview and diagnosis of acute appendicitis in children. Semin Pediatr Surg. 2016;25:198-203.

7. Rentea RM, St Peter SD. Contemporary management of appendicitis in children. Adv Pediatr. 2017;64:225-251.

8. Hajibandeh S, Hajibandeh S, Hobbs N, Mansour M. Neutrophil-to-lymphocyte ratio predicts acute appendicitis and distinguishes between complicated and uncomplicated appendicitis: A systematic review and meta-analysis. Am J Surg. 2020;219:154-163.

9. D'Souza N, D'Souza C, Grant D, Royston E, Farouk M. The value of ultrasonography in the diagnosis of appendicitis. Int J Surg. 2015;13:165-169.

10. Samuel M. Pediatric appendicitis score. J Pediatr Surg. 2002;37:877-881.

11. Malia L, Sturm JJ, Smith SR, Brown RT, Campbell B, Chicaiza H. Predictors for Acute appendicitis in children. Pediatr Emerg Care. 2021;37:e962-e8.

12. Gunes Tatar I, Yilmaz KB, Sahin A, Aydin H, Akinci M, Hekimoglu B. Evaluation of clinical Alvarado scoring system and CT criteria in the diagnosis of acute appendicitis. Radiol Res Pract. 2016;2016:9739385.

13. Hayes R. Abdominal pain: general imaging strategies. Eur Radiol. 2004;14 Suppl 4:L123-137.

14. Magnúsdóttir MB, Róbertsson V, Þorgrímsson S, Rósmundsson Þ, Agnarsson Ú, Haraldsson Á. Abdominal pain is a common and recurring problem in pediatric emergency departments. Acta Paediatr. 2019;108:1905-1910.

15. Lee WH, O'Brien S, Skarin D, Cheek JA, Deitch J, Nataraja R, et al. Pediatric abdominal pain in children presenting to the emergency department. Pediatr Emerg Care. 2021;37:593-598.

16. Peng X, Gong Y. Value of high-frequency ultrasonography in the differential diagnosis of mesenteric lymphadenitis and acute appendicitis in children. Minerva Pediatr (Torino). 2022;74:389-391.

17. Hartman S, Brown E, Loomis E, Russell HA. Gastroenteritis in children. Am Fam Physician. 2019;99:159-165.

18. McCollough M, Sharieff GQ. Abdominal pain in children. Pediatr Clin North Am. 2006;53:107-137.

19. Harris BR, Chinta SS, Colvin R, Schnadower D, Tarr PI, Sayuk GS. Undifferentiated abdominal pain in children presenting to the pediatric emergency department. Clin Pediatr (Phila). 2019;58:1212-1223.

20. Eun S, Ho IG, Bae GE, Kim H, Koo CM, Kim MK, et al. The

neutrophil-to-lymphocyte ratio for the diagnosis of pediatric acute appendicitis: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2021;25(22):7097-7107.

21. Toorenvliet B, Vellekoop A, Bakker R, Wiersma F, Mertens B, Merkus J, et al. Clinical differentiation between acute appendicitis and acute mesenteric lymphadenitis in children. Eur J Pediatr Surg. 2011;21:120-123.

22. Özdamar MY, Karavaş E. Acute mesenteric lymphadenitis in children: findings related to differential diagnosis and hospitalization. Arch Med Sci. 2020;16:313-320.

23. Fan Z, Zhang Y, Pan J, Wang S. Acute appendicitis and mean platelet volume: A systemic review and meta-analysis. Ann Clin Lab Sci. 2017;47:768-772.

24. Shen G, Li S, Shao Z, Liu L, Liu Q, Yu H, et al. Platelet indices in patients with acute appendicitis: a systematic review with meta-analysis. Updates Surg. 2021;73:1327-1341.

25. Krishnan N, Anand S, Pakkasjärvi N, Bajpai M, Dhua AK, Yadav DK. Mean platelet volume in the diagnosis of acute appendicitis in the pediatric population: A systematic review and meta-analysis. Diagnostics (Basel). 2022;12(7):1596.

26. Biricik S, Narcı H, Dündar GA, Ayrık C, Türkmenoğlu M. Mean platelet volume and the ratio of mean platelet volume to platelet count in the diagnosis of acute appendicitis. Am J Emerg Med. 2019;37:411-414.

27. Oktay MM, Boğan M, Çolak ST, Sabak M, Gümüşboğa H, Eren SH. Evaluation of the diagnostic value of platelet indices in pediatric acute appendicitis. J Int Med Res. 2020;48:300060520946515.

28. Khalid M, Redhu N, Nazir B, Khalid S, Chana RS, Jha A. Diagnostic value of ultrasonography in evaluation and management of acute abdominal conditions in the pediatric age group. Afr J Paediatr Surg. 2012;9:198-201.

29. Malia L, Sturm JJ, Smith SR, Brown RT, Campbell B, Chicaiza H. Diagnostic accuracy of laboratory and ultrasound findings in patients with a non-visualized appendix. Am J Emerg Med. 2019;37:879-883.

30. Baştuğ BT. Distribution of causes of acute abdominal pain in children that presented to a state hospital radiology unit according to age, gender, and pathology origin. Eur Res J. 2019;5:510-514.

31. Khan HH, Subedi S, Kumar S, Lyons H. The Pattern of CT Scan Use in the Diagnosis of Abdominal Pain in Children Presenting to the Emergency Department of a Tertiary Community Hospital. Cureus. 2021;13:e19162.

32. Doria AS, Moineddin R, Kellenberger CJ, Epelman M, Beyene J, Schuh S, et al. US or CT for diagnosis of appendicitis in children and adults? A meta-Analysis. Radiology. 2006;241:83-94.

33. Téoule P, Laffolie J, Rolle U, Reissfelder C. Acute appendicitis in childhood and adulthood. Dtsch Arztebl Int. 2020;117:764-774.

34. Marcucci V, Yee S, Castillo RC, Fakhoury EN, Zuberi J. A retrospective comparison study of ultrasonography and computed tomography scan in diagnosis of acute appendicitis in the pediatric population. J Curr Surg. 2020;10:21-27

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ORIGINAL ARTICLE

Can the Systemic Immune-Inflammation Index Predict the Risk of Postoperative Atrial Fibrillation in Patients with Low Ejection Fraction Undergoing Coronary Artery Bypass Grafting?

Sistemik İmmün-İnflamasyon İndeksi, Düşük Ejeksiyon Fraksiyonuna Sahip Koroner Arter Baypas Greftleme Uygulanan Hastalarda Postoperatif Atriyal Fibrilasyon Riskini Öngörebilir mi?

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ABSTRACT

Aim: This study aimed to investigate whether the preoperative Systemic Immune-Inflammation Index (SII) can predict the development of postoperative atrial fibrillation (PoAF) in patients undergoing coronary artery bypass grafting (CABG) with low ejection fraction (EF).
Methods: Between January 2023 and January 2024, 100 patients undergoing CABG with low EF (<40%) were included in the study. Preoperative SII values of the patients, along with their demographic characteristics and operative variables, were compared.
Results: Among the 100 patients with reduced EJ included in the study, PoAF was identified in 10 cases. No significant differences were observed in the demographic and perioperative data of the patients. The SII levels were found to be higher in 10 patients developing PoAF, demonstrating a correlation (p=0.008). PoAF patients experienced a longer stay in the hospital although statistically insignificant (p=0.059).
Conclusion: Preoperative SII levels may be effective in predicting PoAF in coronary bypass patients with low EJ.

Keywords: Atrial fibrillation, cardiopulmonary bypass, coronary artery bypass, inflammation

ÖZ

Amaç: Bu çalışmanın amacı, düşük ejeksiyon fraksiyonu (EF) ile koroner arter baypas greftleme (CABG) uygulanan hastalarda, preoperatif dönemde belirlenen Sistemik İmmün-İnflamasyon İndeksi'nin (SII), postoperatif atriyal fibrilasyon (PoAF) gelişimini öngörmedeki potansiyel rolünü araştırmaktır.
Yöntem: Ocak 2023 ile Ocak 2024 tarihleri arasında düşük EF (%40'ın altında) ile CABG uygulanan toplam 100 hasta çalışmaya dahil edilmiştir. Çalışmada, hastaların preoperatif SII değerleri ile demografik özellikleri ve operasyonel değişkenleri karşılaştırılmıştır.
Bulgular: Düşük ejeksiyon fraksiyonuna sahip 100 hasta arasında, postoperatif atriyal fibrilasyon 10 olguda tespit edilmiştir. Demografik ve perioperatif değişkenlerde anlamlı bir farklılık saptanmamıştır. Bununla birlikte, PoAF gelişen 10 hastada SII seviyelerinin anlamlı derecede yüksek olduğu ve bu durumun bir korelasyon gösterdiği belirlenmiştir (p=0,008). PoAF gelişen hastaların hastanede kalış süresi, istatistiksel olarak anlamlı olmamakla birlikte, daha uzun bulunmuştur.
Sonuç: Preoperatif SII seviyelerinin, düşük ejeksiyon fraksiyonuna sahip koroner arter baypas greftleme uygulanan hastalarda postoperatif atriyal fibrilasyon gelişimini öngörmede potansiyel bir belirteç olarak işlev görebileceği düşünülmektedir.

Anahtar Kelimeler: Atriyal fibrilasyon, inflamasyon, kardiyopulmoner baypas, koroner arter baypas

Introduction

Postoperative atrial fibrillation (PoAF) is the most frequently observed heart rhythm disorder following cardiac surgery (1). Studies have shown that its occurrence rates widely vary from 10% to 65% (2,3). Despite this high incidence, PoAF has not typically been considered harmful due to its perceived reversibility. Evidence from prospective randomized trials suggests that most patients after coronary artery bypass grafting (CABG) surgery return to NSR within 60 days (4). In contrast, non-randomized studies have shown that PoAF can lead to adverse outcomes in the postoperative period, including cerebrovascular events, hemodynamic instability, prolonged hospital stays, renal failure, and both short- and long-term mortality (5,6). The pathophysiology of POAF after CABG is multifactorial, inflammation and oxidative stress play a significant role (7). Surgical revascularization exacerbates the systemic inflammatory response in the postoperative period, attributable both to surgical stress and the effects of the cardiopulmonary bypass (8).

The correlation between biochemical markers of systemic inflammation and PoAF has consistently been a focal point of scholarly interest. SII, a parameter gaining popularity recently, has been demonstrated through various studies to be associated with complications

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following cardiac surgery (8) and survival in cancer patients (9).

The primary objective of our study is to evaluate the prognostic value of preoperative SII indices in predicting the onset of PoAF in patients with low EF undergoing on-pump CABG.

Materials And Methods

After obtaining ethical approval from our institution (AEŞH-BADEK-2024-674), a retrospective examination was performed on a cohort of 1159 patients, during the period between January 2023 to January 2024, from which one hundred individuals with an EF equal or below 40% were selectively enrolled in the study. Exclusion criteria were; concomitant surgery, emergency surgery, off-pump surgery, chronic kidney disease, chronic liver disease, acute infection, and auto-immun disorders. SII was calculated from preoperative hemogram tests using the formula: platelet count x neutrophil count/lymphocyte count. PoAF is defined as the presence of atrial fibrillation rhythm for at least 30 minutes during the postoperative period in patients with preoperative normal sinus rhythm, necessitating pharmacological or electrical cardioversion. All patients diagnosed with POAF during the postoperative period were included in the study, regardless of whether the diagnosis was made through close monitoring in the intensive care unit, telemetry in the hospital unit, or based on symptomatic presentation. Only patients with normal sinus rhythm were included in the study.

The demographic characteristics of patients, along with data regarding CPB and cross-clamp durations, as well as SII values, were subjected to retrospective analysis through assessment of hospital records.

Statistical Analysis

Kolmogorov Smirnov test was used for analyzing the normal distribution of the data. Normally distributed continuous variables were expressed as mean ± SD, or median values if abnormally distributed. Categorical variables were expressed as numbers and percentages. Demographic characteristics and perioperative variables were compared using "independent samples t-test" or "Mann-Whitney-U test" for continuous variables and "chi-square test" or "Fisher's exact test" for categorical variables between patients PAOF and non-POAF after surgery. Patients were compared between groups in terms of demographic data, intraoperative data, postoperative data, and SI index. In all statistical tests, p-value <0.05 was accepted as significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (Armonk, NY: IBM Corp.).

Results

Data from 100 patients were analyzed in this study. The mean age of the patients was 62.16 8.52(42-78). There were no statistical differences in age between the groups. The demographic characteristics of the patients are detailed in Table 1. No statistically significant differences were observed in the demographic characteristics between the two groups. The perioperative characteristics of the patients are presented in Table 2. Although hospital stays were longer for the PoAF group, this difference was not statistically significant. No significant differences were identified between the two groups concerning other perioperative and postoperative characteristics. No valvular pathology requiring surgical intervention was observed in the patients. Additionally, there was no significant difference in left atrial diameters between patients with POAF and those without.

Table 1. Demographic Characteristics of the Patients

Demographic characteristics				
	All patients (n=100)	**PoAF (n=10)**	**No-PoAF (n=90)**	**p**
Age (years)	62.16±8.52 (42-78)	69.4±7.22 (57-78)	60.35±7.90 (42-77)	0.578
Gender				
Male	89 (89%)	8	81	0.338
Female	11 (11%)	2	9	
BSA (kg/m²)	1.92±0.16 (1.64±2.24)	1.92±0.16	1.93±0.17	0.086
Comorbidities				
Active Smoking	22 (22%)	3	19	0.198
HT	48 (48%)	3	45	0.676
DM	60 (60%)	5	55	0.851
COPD	16 (16%)	0	16	0.242
CVA	3 (3%)	0	15	0.762
CKD	8 (8%)	1	7	0.656
EF	33.5±2.73 (25-35)	33.2±2.29	32.2±2.59	0.264
STS score	7.77±5.29 (3.68-29.6)	6.19±2.88	8.36±5.70	0.111

BSA: Body surface area, HT: Hypertension, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CVA: Cerebrovascular accident, CKD: Chronic kidney disease, EF: Ejection fraction

Table 2. Perioperative characteristics of the patients.

Perioperative characteristics				
	All patients (n=100)	**PoAF (n=10)**	**No-PoAF (n=90)**	**p**
X-clamp time (min)	72.6±32.6 (23-218)	79.0±24.3	73.89±37.13	0.624
CPB time (min)	117.1±45.5 (42-313)	115.2±33.4	114.7±53.3	0.969
Duration of surgery (min)	232.4±50.30 (150-427)	240.3±57.3	230.4±48.9	0.216
IABP	23	1	22	0.428
Defibrillation after X-clamp	26	3	23	0.943
ICU stay (days)	5.04±5.0 (1-25)	2.71±1.11	6.27±6.02	0.123
Hospital stay (days)	5.66±8.51 (1-25)	8.5±5.12	5.4±2.7	0.184
Hospital mortality	7	2	5	0.862

CPB: Cardiopulmonary bypass, IABP: Intra-aortic balloon pump, ICU: Intensive care unit,

As demonstrated in Table 3, preoperative SII levels were found to be significantly elevated in patients developing PoAF (p=0.008).

Table 3. Correlation of SII levels and PoAF

	PoAF (n=10)	**No-PoAF (n=90)**	**p**
SII	1188±447	657±1137	0.008

PoAF: Postoperative Atrial Fibrillation, SII: Systemic Immune-Inflammation Index

Discussion

The main finding of our study is that preoperative SII values are directly associated with the development of PoAF in patients with reduced ventricular ejection fraction (EJ) undergoing CABG. In our analysis, traditional risk factors for PoAF, such as X-clamp time, age, and gender, did not show statistically significant associations, likely due to the study's relatively small sample size.

PoAF is the most commonly encountered supraventricular arrhythmia following open heart surgery, attributable to a multifactorial etiology (10). Despite advances in prophylactic measures and surgical techniques, PoAF remains the most frequent complication of cardiac surgery (11,12). CABG and valvular surgeries hold the greatest risk of developing POAF at 60–80%; they cause a greater scale of damage to the structural integrity of the heart via fibrosis and dilation of the valves and subsequently of the heart's chambers (13). Male gender, advanced age, hypertension, chronic obstructive pulmonary disease, and low EF are the well-known risk factors for PoAF (14). The occurrence of PoAF leads to extended ICU and hospital stays, resulting in increased healthcare costs. Although our study observed longer hospital stays among patients developing PoAF, no statistically significant difference was detected between the groups.

Moreover, contemporary research continues to propose new hypotheses regarding the pathophysiology of PoAF, which remains incompletely understood to date. The inflammatory response secondary to surgical trauma and the inflammatory effects of cardiopulmonary bypass frequently play a significant role in the pathophysiology of PoAF (10). However, these hypotheses still do not fully explain its occurrence. Therefore, researchers are investigating the effects of preoperative inflammatory status on the pathophysiology of PoAF as well. Originally utilized in oncological contexts, the Systemic Immune-Inflammation Index (SII) is a relatively new addition to prognostic inflammatory metrics and has more recently been investigated in cases of infective endocarditis, coronary artery disease, and various other cardiac pathologies (9,15). To our knowledge, limited research has explored the relationship between preoperative SII values and PoAF in CABG patients with low EJ.

It is well-established that patients' preoperative inflammatory status significantly influences the postoperative inflammatory response, which is an anticipated aspect of the surgical stress process (16). Additionally, the intensity of this inflammatory response has been associated with adverse postoperative outcomes, particularly arrhythmic complications (10). In this study, patients' preoperative inflammatory status was quantified using the SII. A comparative analysis revealed that patients developing PoAF had significantly elevated preoperative SII values, suggesting that inflammatory profiling could enable preoperative identification of patients at elevated risk for PoAF. This observation underscores a potential predictive role for elevated preoperative systemic inflammation in the pathogenesis of PoAF and indicates that patients with higher inflammatory markers are at increased risk of developing atrial fibrillation postoperatively.

Thus, identifying individuals with high preoperative SII levels could become an essential clinical strategy, potentially facilitating targeted interventions aimed

at modulating inflammatory responses before surgery. Such interventions may help reduce the incidence of PoAF, ultimately contributing to improved postoperative outcomes and a decreased healthcare burden associated with arrhythmic complications.

To mitigate the systemic inflammatory response, various strategies—such as the use of statins, vitamins, N-acetylcysteine, colchicine, and corticosteroids—have been explored in the preoperative period (17,18). Some studies have reported a reduced PoAF incidence, particularly in patients using statins for seven days before surgery (17). Nevertheless, further investigations are warranted to substantiate and broaden these findings in clinical practice.

Limitations

The retrospective design of the study and the relatively small sample size are the primary limitations. Furthermore, due to the retrospective nature of the study, additional analyses involving inflammatory markers, such as interleukin-6, could not be performed, constituting another limitation.

Conclusion

The levels of preoperative SII may effectively predict the development of PoAF in patients undergoing CABG with reduced EJ. Elevated SII values indicate an increased risk for PoAF, highlighting the potential for early identification of at-risk patients. This could facilitate targeted preoperative interventions aimed at improving postoperative outcomes. Further research is needed to clarify the relationship between preoperative inflammatory markers and PoAF and to explore strategies for mitigating this risk.

References

1.Woldendorp K, Farag J, Khadra S, Black D, Robinson B, Bannon P. Postoperative Atrial Fibrillation After Cardiac Surgery: A Meta-Analysis. Ann Thorac Surg [Internet]. 2021 Dec 1 [cited 2024 Nov 3];112(6):2084–93. Available from: https://pubmed.ncbi.nlm.nih.gov/33340521/

2.Wang MK, Meyre PB, Heo R, Devereaux PJ, Birchenough L, Whitlock R, et al. Short-term and Long-term Risk of Stroke in Patients With Perioperative Atrial Fibrillation After Cardiac Surgery: Systematic Review and Meta-analysis. CJC Open [Internet]. 2021 Jan 1 [cited 2024 Nov 3];4(1):85–96. Available from: https://pubmed.ncbi.nlm.nih.gov/35072031/

3.Shen J, Lall S, Zheng V, Buckley P, Damiano RJ, Schuessler RB. The persistent problem of new-onset postoperative atrial fibrillation: a single-institution experience over two decades. J Thorac Cardiovasc Surg [Internet]. 2011 Feb [cited 2024 Nov 3];141(2):559–70. Available from: https://pubmed.ncbi.nlm.nih.gov/20434173/

4.Gillinov AM, Bagiella E, Moskowitz AJ, Raiten JM, Groh MA, Bowdish ME, et al. Rate Control versus Rhythm Control for Atrial Fibrillation after Cardiac Surgery. N Engl J Med [Internet]. 2016 May 19 [cited 2024 Nov 3];374(20):1911–21. Available from: https://pubmed.ncbi.nlm.nih.gov/27043047/

5.Taha A, Nielsen SJ, Franzén S, Rezk M, Ahlsson A, Friberg L, et al. Stroke Risk Stratification in Patients With Postoperative Atrial Fibrillation After Coronary Artery Bypass Grafting. J Am Heart Assoc [Internet]. 2022 May 17 [cited 2024 Nov 3];11(10). Available from: https://pubmed.ncbi.nlm.nih.gov/35574947/

6.Mariscalco G, Klersy C, Zanobini M, Banach M, Ferrarese S, Borsani P, et al. Atrial fibrillation after isolated coronary surgery affects late survival. Circulation [Internet]. 2008 Nov 14 [cited 2024 Nov 3];118(16):1612–8. Available from: https://pubmed.ncbi.nlm.nih.gov/18824644/

7.Smukowska-Gorynia A, Perek B, Jemielity M, Olasińska-Wiśniewska A, Marcinkowska J, Stefaniak S, et al. Neopterin as a predictive biomarker of postoperative atrial fibrillation following coronary artery bypass grafting. Kardiol Pol [Internet]. 2022 [cited 2024 Nov 3];80(9):902–10. Available from: https://pubmed.ncbi.nlm.nih.gov/35698968/

8.Dey S, Kashav R, Kohli JK, Magoon R, ItiShri, Walian A, et al. Systemic Immune-Inflammation Index Predicts Poor Outcome After Elective Off-Pump CABG: A Retrospective, Single-Center Study. J Cardiothorac Vasc Anesth [Internet]. 2021 Aug 1 [cited 2024 Nov 3];35(8):2397–404. Available from: https://pubmed.ncbi.nlm.nih.gov/33046365/

9.Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. The systemic immune-inflammation index predicts the prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res [Internet]. 2014 Dec 1 [cited 2024 Nov 3];20(23):6212–22. Available from: https://pubmed.ncbi.nlm.nih.gov/25271081/

10.Qureshi M, Ahmed A, Massie V, Marshall E, Harky A. Determinants of atrial fibrillation after cardiac surgery. Rev Cardiovasc Med [Internet]. 2021 Jun 30 [cited 2024 Nov 3];22(2):329–41. Available from: https://pubmed.

ncbi.nlm.nih.gov/34258901/

11.Gudbjartsson T, Helgadottir S, Sigurdsson MI, Taha A, Jeppsson A, Christensen TD, et al. New-onset postoperative atrial fibrillation after heart surgery. Acta Anaesthesiol Scand [Internet]. 2020 Feb 1 [cited 2024 Nov 3];64(2):145–55. Available from: https://pubmed.ncbi.nlm.nih.gov/31724159/

12.Maesen B, Nijs J, Maessen J, Allessie M, Schotten U. Post-operative atrial fibrillation: a maze of mechanisms. Europace [Internet]. 2012 Feb [cited 2024 Nov 3];14(2):159–74. Available from: https://pubmed.ncbi.nlm.nih.gov/21821851/

13.Jagadish PS, Kirolos I, Khare S, Rawal A, Lin V, Khouzam RN. Post-operative atrial fibrillation: should we anticoagulate? Ann Transl Med [Internet]. 2019 Sep [cited 2024 Nov 3];7(17):407–407. Available from: https://pubmed.ncbi.nlm.nih.gov/31660306/

14.Uysal D, Aksoy F, Ibrişim E. The Validation of the ATRIA and CHA2DS2-Vasc Scores in Predicting Atrial Fibrillation after Coronary Artery Bypass Surgery. Braz J Cardiovasc Surg [Internet]. 2020 [cited 2024 Nov 3];35(5):619–25. Available from: https://pubmed.ncbi.nlm.nih.gov/33118725/

15.Magoon R. Evolving Spectrum of Prognostic Inflammatory Markers in Infective Endocarditis. J Cardiothorac Vasc Anesth [Internet]. 2020 Jul 1 [cited 2024 Nov 3];34(7):2001–2. Available from: https://pubmed.ncbi.nlm.nih.gov/32147322/

16.Weymann A, Popov AF, Sabashnikov A, Ali-Hasan-Al-Saegh S, Ryazanov M, Tse G, et al. Baseline and postoperative levels of C-reactive protein and interleukins as inflammatory predictors of atrial fibrillation following cardiac surgery: a systematic review and meta-analysis. Kardiol Pol [Internet]. 2018 Feb 16 [cited 2024 Nov 3];76(2):440–51. Available from: https://pubmed.ncbi.nlm.nih.gov/29354906/

17.Liakopoulos OJ, Kuhn EW, Slottosch I, Wassmer G, Wahlers T. Preoperative statin therapy for patients undergoing cardiac surgery. Cochrane Database Syst Rev [Internet]. 2012 Apr 18 [cited 2024 Nov 3];2012(4). Available from: https://pubmed.ncbi.nlm.nih.gov/22513959/

18.Chello M, Anselmi A, Spadaccio C, Patti G, Goffredo C, Di Sciascio G, et al. Simvastatin increases neutrophil apoptosis and reduces inflammatory reactions after coronary surgery. Ann Thorac Surg [Internet]. 2007 Apr [cited 2024 Nov 3];83(4):1374–80. Available from: https://pubmed.ncbi.nlm.nih.gov/17383342/

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ORIGINAL ARTICLE

Evaluation of Patients Presenting with Chronic Cough to the Pediatric Allergy Clinic According to Age Groups

Çocuk Alerji Polikliniğine Kronik Öksürük Nedeni ile Başvuran Hastaların Yaş Gruplarına Göre Değerlendirilmesi

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ABSTRACT

Background/Aims: Chronic cough is a prevalent issue in pediatric patients and is among the most common reasons for referral to pediatric allergists, significantly affecting quality of life and often necessitating specialized evaluation. This study aimed to analyze the clinical characteristics, etiologies, and management of chronic cough in children, providing insights into age-related prevalence.
Methods: Pediatric patients presenting with a chronic cough to our pediatric allergy clinic between 1st May 2023, and 31st May 2024 were included in this retrospective study. Patients previously diagnosed with allergic diseases or evaluated at other clinics were excluded. Medical records were reviewed for demographics, characteristics of cough, familial and environmental factors, and treatment regimes.
Results: Of 267 patients included, 54.7% were boys, and the median age was 6.99 [interquartile range (IQR) 4.47-11.54] years. Asthma (39%), protracted bacterial bronchitis (PBB) (25.8%), and upper airway cough syndrome (UACS) (22.1%) were the most common diagnoses. PBB was more prevalent in younger patients, whereas asthma was dominant in older age groups. Regardless of the cough etiology, antibiotic use was noted in 67.8% of patients before applying to the pediatric allergy outpatient clinic. Exposure to tobacco smoke was present in 40.1% of patients. The familial history of asthma was significantly more common in patients with asthma (p=0.03).
Conclusion: This study underscores the importance of distinguishing between chronic cough etiologies in children to prevent mismanagement and overuse of antibiotics. While asthma, PBB, and UACS were among the primary causes, many other potential diagnoses also warrant consideration. Comprehensive assessments are essential for accurate diagnosis, and a multi-disciplinary approach may enhance the outcomes of the management.

Keywords: Asthma, chronic cough, pediatric, protracted bacterial bronchitis.

ÖZ

Amaç: Kronik öksürük pediatrik hastalarda sık görülen bir sorundur ve pediatrik alerjistlere baş vurunun en sık nedenleri arasındadır. Çalışmamızda, çocuklarda kronik öksürüğün klinik özelliklerini, etiyolojilerini ve tedavi yönetimini analiz etmeyi ve yaşa göre prevalans farklılıklarına ilişkin bilgi sağlamayı amaçladık.
Gereç ve Yöntem: 1 Mayıs 2023-31 Mayıs 2024 tarihleri arasında kronik öksürük şikayetiyle pediatrik alerji polikliniğimize başvuran pediatrik hastalar retrospektif olarak taranarak çalışmaya dahil edildi. Önceden alerjik hastalık tanısı konulmuş veya başka bir çocuk alerji kliniğinde değerlendirilmiş olan hastalar çalışmaya dahil edilmedi. Tıbbi kayıtlardan hastaların demografik verileri, öksürük özellikleri, ailevi ve çevresel faktörler ile tedavileri değerlendirildi.
Bulgular: Çalışmaya 267 hasta dahil edildi. Hastaların %54,7'si erkek ve medyan yaşları 6,99 (çeyrekler arası aralık (ÇAA) 4.47-11.54) yıl idi. Hastalara en sık astım (%39), uzamış bakteriyel bronşit (UBB) (%25,8) ve üst solunum yolu öksürük sendromu (ÜSYÖS) (%22,1) tanıları koyuldu. UBB, daha çok küçük yaştaki hastalarda görülürken, astım ise daha büyük yaş gruplarında baskın tanı idi. Öksürük etiyolojisinden bağımsız olarak, hastaların %67,8'i çocuk alerji polikliniğine başvurmadan önce antibiyotik kullanmıştı. Hastaların %40,1'inde tütün dumanı maruziyeti tespit edildi. Ailede astım öyküsü, astım tanısı alan hastalarda diğer tanılara göre anlamlı derecede daha yüksek bulundu (p=0.03).
Sonuç: Çocuklarda kronik öksürük etiyolojisinin doğru bir şekilde belirlenmesi, yanlış tedavi ve gereksiz antibiyotik kullanımını önlemek için önemlidir. Astım, UBB ve ÜSYÖS çocuklarda kronik öksürüğün başlıca nedenleri olup göz önünde bulundurulması gereken birçok başka potansiyel tanı bulunmaktadır. Doğru teşhis için kapsamlı değerlendirme ve multidisipliner yaklaşım önemlidir.

Anahtar kelimeler: Astım, kronik öksürük, pediatri, uzamış bakteriyel bronşit.

Introduction

Chronic cough is a prevalent issue in pediatric patients and is among the most common reasons for referral to pediatric allergists. Defined as a cough lasting more than four weeks, chronic cough can significantly impact the quality of life (QoL) of both affected children and their families, often leading to disrupted sleep, impaired daily activities, and missed school days (1-3). Unlike acute cough, which usually arises from viral respiratory infections and typically resolves within a few weeks, chronic cough in children can be associated with a range of underlying etiologies, from common conditions like asthma and allergic rhinitis to more complex diseases such as cystic fibrosis, protracted bacterial bronchitis (PBB), and bronchiectasis (4).

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Early and accurate diagnosis is crucial to prevent the progression of potential diseases such as asthma, bronchiectasis, or foreign body aspiration, thereby improving long-term health outcomes. Clinical guidelines recommend a systematic approach to the evaluation of chronic cough in children, involving detailed history-taking, physical examination, and appropriate diagnostic tests to identify the underlying etiology (1,5,6).

In our study, the clinical characteristics, accompanying symptoms, family history, environmental exposures, chronic cough etiology according to age groups, and treatments of the patients applying to pediatric allergy clinics with chronic cough were evaluated. By analyzing the prevalence of chronic cough in children concerning its various etiologies, this study aimed to improve the understanding and guide the evidence-based management approaches, ultimately improving patient outcomes and reducing the burden of chronic cough on the pediatric population and healthcare systems.

Methods

Pediatric patients evaluated for chronic cough in the pediatric allergy outpatient clinic of our department between 1st May 2023 and 31st May 2024 were included in the study. Patients who had previously been diagnosed with an allergic disease and those who had previously been evaluated in other allergy clinics due to their chronic cough were excluded. The institutional ethics committee approval was obtained before the initiation of the study (2024/38).

When evaluating patients presenting with chronic cough, the duration and nature of the cough (dry/wet), the presence of nocturnal awakenings, whether it worsens with exertion, such accompanying symptoms as nasal congestion, mouth breathing, and snoring, previous treatments for the cough, family history of atopy, and environmental exposures were questioned in detail in the medical history.

The demographic and clinical characteristics, diagnoses, and treatments of the patients were evaluated retrospectively from their medical records. Duration and nature of the cough, accompanying symptoms, familial history of atopy, environmental exposures, physical examination findings of the patients, and skin prick test (SPT) results, if any, were recorded.

Chronic cough was defined as the presence of a daily cough of more than four weeks (1). The approach and treatment of chronic cough were based on the CHEST Guideline and Expert Panel Report (1).

As stated in the European Respiratory Society guidelines, patients with chronic wet or productive cough, without specific cough markers, and those responding between 2-4 weeks of appropriate antibiotic treatment were diagnosed with PBB (7). The diagnosis of upper respiratory tract cough syndrome (UACS) was performed primarily in conditions affecting the upper respiratory tract, such as rhinitis (allergic or non-allergic), sinusitis (acute or chronic rhinosinusitis), and other nasal or pharyngeal inflammatory disorders (8). If the patient had a cough lasting longer than three weeks but not exceeding eight weeks following an acute upper respiratory tract infection, the diagnosis of post-infectious cough was considered (8).

The patients were divided into four groups according to their age: 0–2 years (infants and toddlers), 2–5 years (preschoolers), 5–12 years (school-age children), and over 12 years of age (adolescents).

All analyses were performed using the Statistical Package for Social Sciences Statistics for Windows, version 27.0 (SPSS, IBM Corp, Armonk, New York). Descriptive statistics were expressed as mean (SD) or median (range) for continuous variables and as case numbers (percentage) for nominal variables. The values were presented as medians (interquartile range [IQR]) for the data showing no normal distribution. The chi-square ($\chi 2$) test was used to compare nonparametric data; the Mann-Whitney U test was used in comparisons with non-normally distributed continuous data and the independent-samples t-test for normally distributed continuous data. A p-value of <0.05 was considered statistically significant.

Results

The study included a total of 267 patients, and 54.7% (n=146) of the patients were boys. The median age of the patients was 6.99 (IQR 4.47-11.54) years. When patients were evaluated according to age groups, 6.4% (n=17) were infants and toddlers, 23.2% (n=62) were pre-schoolers, 46.8% (n=125) were school-age children, and 23.6% (n=63) were adolescents.

The median duration of cough was eight (IQR 6-12) weeks. Of all patients, 47.6% (n=127) had a dry cough, and 52.4% (n=140) had a wet/productive cough.

Cough occurred mostly at night in 48.7% (n=130) of the patients, and 25.1% (n=67) had both daytime and

nocturnal cough. Nocturnal wake-ups occurred in 55.8% (n=149) of the patients, and exercise-induced cough was present in 70.4% (n=188) of the patients. Of all participants, 22.8% (n=61) had loud snoring, and 36% (n=96) had nasal congestion and mouth breathing. There was no significant difference between night waking-ups and exercise-induced cough among those with dry and wet cough (p=0.052, p=0.99, respectively). Snoring and nasal congestion were significantly higher in those with wet cough (p=0.041, p =0.014 respectively).

Regardless of the cough etiology, 67.8% (n=181) of the patients had received antibiotic treatment before applying to the pediatric allergy outpatient clinic, and 64.6% (n=117) received a single course of antibiotic treatment (69.2% with amoxicillin clavulanic acid, 18.8% with clarithromycin, 3.4% with azithromycin, and 8.5% with cephalosporins) while the remaining (n=64) were administered multiple courses. There was no significant difference in terms of antibiotic use between patients presenting with wet cough (72.9% (n=102)) and dry cough (62.2% (n=79)) before applying to the pediatric allergy clinic (p=0.063). In those with wet cough, the use of antibiotics more than once was observed more frequently (44.1%, n=45), compared with those with dry cough (24.1%, n=19 and p=0.005). Among those receiving a single course of antibiotic treatment, 42.7% (n=50) were treated for less than seven days, 45.3% (n=53) for seven-10 days, and 11.1% (n=13) for 11-14 days. Only one patient received treatment lasting more than 14 days.

Exposure to tobacco smoke was present in 40.1% (n=107) of the patients, and 30% (n=80) and 6.7% (n=18) were found to be exposed to pet dander and mold. There was no significant difference in terms of exposure to tobacco smoke, having a pet, and mold exposure among those with dry and wet cough (p=0.44, p=0.83, and p=0.21). The characteristics of patients with wet and dry cough are presented in Table 1.

Table 1. Characteristics of patients with wet and dry cough

	Dry Cough (n=127) (%)	Wet Cough (n=140) (%)	p-value
Age (years)	8.38 ± 4.4	7.62 ± 4.38	0.16
Duration of cough (weeks)	10.4 ± 6.3	11.5 ± 9.4	0.26
Nocturnal wake-ups	63 (49.6)	86 (61.4)	0.052
Exercise-induced cough	89 (70.6)	99 (70.7)	0.99
Nasal congestion	36 (28.3)	60 (42.9)	**0.014**
Snoring	22 (17.3)	39 (27.9)	**0.041**
Antibiotic use before allergy visit	79 (62.2)	102 (72.9)	0.063
Antibiotic use more than once	19 (24.1)	45 (44.1)	**0.005**
Exposure to smoking	54 (42.5)	53 (37.9)	0.44
Exposure to animal dander	39 (30.7)	41 (29.5)	0.83
Exposure to mold	6 (4.7)	12 (8.6)	0.21

Asthma (n=104) was the most common diagnosis in patients with chronic cough, followed by PBB (n=69) and upper airway cough syndrome (UACS) (n=59). Diagnoses of patients are summarized in Table 2. When the patients in the infant and toddler age groups were evaluated, the most common cause of chronic cough was PBB, whereas asthma was more frequently observed in older age groups. Concerning age groups, the etiology of chronic cough is shown in Table 3.

Table 2. Diagnoses of patients with chronic cough (n=267)

Diagnoses	n (%)
Asthma	104 (39)
PBB	69 (25.8)
UACS	59 (22.1)
Post-infectious cough	18 (6.7)
Reflux cough	4 (1.5)
Tic cough	3 (1.1)
Wheezy infant	3 (1.1)
Pneumonia	2 (0.7)
Congenital heart disease	1 (0.4)
Primary ciliary dyskinesia	1 (0.4)
Dysfunction of swallowing	1 (0.4)
Cystic fibrosis	1 (0.4)
Bronchiolitis obliterans	1(0.4)

PBB: Protracted bacterial bronchitis, UACS: Upper airway cough syndrome

Table 3. Etiology of chronic cough according to age groups

	Infants and Toddlers (n=17) (%)	Preschoolers (n=62) (%)	School-age children (n=125) (%)	Adolescents (n=63) (%)
Asthma	-	20 (32.3)	51 (40.8)	33 (52.4)
PBB*	11 (64.7)	13 (21)	38 (30.4)	7 (11.1)
UACS**	-	17 (27.4)	27 (21.6)	15 (23.8)
Post-infectious cough	2 (11.8)	7 (11.3)	4 (3.2)	5 (7.9)
Reflux cough	-	2 (3.2)	1 (0.8)	1 (1.6)
Tic cough	-	1 (1.6)	-	2 (3.2)
Pneumoniae	-	1 (1.6)	1 (0.8)	-
Congenital heart disease	-	-	1 (0.8)	-
Primary ciliary dyskinesia	-	1 (1.6)	-	-
Dysfunction of swallowing	-	-	1 (0.8)	-
Cystic fibrosis	1 (5.9)	-		-
Bronchiolitis obliterans	-	-	1 (0.8)	-
Wheezy infant	3 (17.6)	-		-

PBB: Protracted bacterial bronchitis, UACS: Upper airway cough syndrome

A previous history of chronic cough was found in 22.5% of the patients (n=60). Additionally, 83 patients (31.1%) had a history of bronchiolitis, and 122 patients (45.7%) had used salbutamol at least once in their lifetime. Even so, 28.8% (n=30) of the asthmatic patients had a previous history of chronic cough, and this rate was 18.4% (n=30) in patients with other diagnoses. While a history of previous bronchiolitis was present in 38.5% (n=40) of asthma patients and 26.4% (n=43) of patients with other diagnoses, 52.9% (n=55) of the patients with asthma and 41.1% (n=67) of the patients with other diagnoses had previous use of salbutamol. The history of chronic cough and the rate of previous bronchiolitis were significantly higher in patients diagnosed with asthma, (p=0.046 and p=0.038, respectively). However, no significant difference was found regarding the previous use of salbutamol (p=0.06).

Of the patients diagnosed with PBB, 39.1% (n=27) used no antibiotics during their chronic cough. Among those prescribed antibiotics (n=42), 64.3% (n=27) were found to receive a single course of antibiotic treatment, and the treatment duration was less than 14 days in all those patients.

When the patients were evaluated in terms of the characteristics of familial atopy, 20.2% (n=54) and 24.7% (n=66) were detected to have had a family history of asthma and allergic rhinitis, respectively. Asthma was also present in the mothers of 26 patients, in the fathers of 16 patients, and in the siblings of 12 patients. In those diagnosed with asthma, the familial history of asthma (26.9%, n=28) was significantly higher, compared to those with other diagnoses (16%, n=26 and p=0.03). However, there was no difference in the frequency of allergic rhinitis in the families of asthma patients (24%, n=25) and those with other diagnoses (25.2%, n=41 and p=0.84).

SPT was performed on 165 (61.8%) patients. At least one aeroallergen sensitization was detected in 48.5% (n=80) of the patients, and the findings of aeroallergen sensitization are shown in Figure 1. Eighty-four (51%) of the SPTs were performed on patients diagnosed with asthma, 30 (18.2%) on PBB patients, and 37 (22.4%) on UCAS patients. According to diagnoses, aeroallergen sensitization status was 54.8, 46.7, and 43.2% for asthma, PBB and UCAS, respectively. No significant difference was found between diagnoses in terms of aeroallergen sensitization (p=0.45).

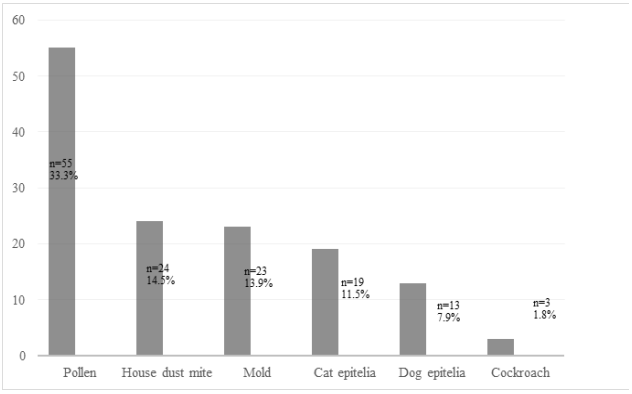

Figure 1. Aeroallergen sensitization of the patients

Physical examination findings of the patients are summarized in Table 4. The diagnosis of adenoid hypertrophy was carried out by ear nose and throat (ENT) specialists.

Table 4. Findings of physical examination of the patients

	n (%)
Oropharynx	
Tonsillar hyperemia/hypertrophy Postnasal drip	16 (6) 40 (15)
Ears	
Acute otitis media Serous otitis	8 (3) 3 (11.2)
Respiratory system	
Crackles Rhonchus Crackles and rhonchus	5 (1.9) 7 (2.6) 4 (1.5)
Cardiovascular system	
Cardiac murmur Situs in *versus* totalis	4 (1.5) 1 (0.4)
Pectus carinatum/excavatum Absence of pectoralis major	5 (1.9) 1 (0.4)
Adenoid hypertrophy	23 (8.6)

All patients with PBB were treated with antibiotics. The treatment of inhaled corticosteroids (ICSs) was initiated in 97.1% (n=101) of the patients with asthma. In other patients with asthma (n=3), treatment was started with montelukast. In addition to ICSs, 26 asthma patients also required antibiotics, 14 received antihistamines along with nasal steroids, four were treated with antihistamines and montelukast, and one patient was prescribed a proton pump inhibitor. In the treatment of UACS patients, antibiotics (n=23), antihistamines (n=42), nasal corticosteroids (n=32), and montelukast (n=19) were used in combinations. Two patients with confirmed pertussis infection were treated with macrolides; however, the other patients with post-infectious cough were followed up without treatment.

Discussion

The presented study provides a comprehensive analysis of pediatric patients presenting with chronic cough, highlighting the diverse etiologies, associated factors, and treatment approaches. In our study, the predominant diagnoses included asthma, PBB, and UACS.

In our study, asthma was identified as the leading cause of chronic cough among pediatric patients, accounting for 39% of the cases. Studies conducted in our country on chronic cough in children have also shown that asthma is the leading cause and responsible for 25 to 44% of chronic cough in pediatric patients (9-13). On the other hand, studies conducted by Marchant et al. and Chang et al. have identified PBB as the leading cause of chronic cough (14, 15). These discrepancies may be attributed to differences in study populations, diagnostic criteria, and regional variations in disease prevalence. Nonetheless, all studies emphasize the importance of considering multiple potential causes when evaluating chronic cough in pediatric patients.

In a large cohort study, Martinez et al. showed that recurrent wheezing in the first six years of life increased the risk of developing asthma later in childhood (16). Similarly, there was a significant association between the history of bronchiolitis and asthma in our study. In patients diagnosed with asthma, the familial history of asthma was significantly higher, compared to those with other diagnoses, which was an expected finding aligning with existing literature linking genetic predisposition to the development of asthma. Numerous studies have established that parental asthma significantly increases the likelihood of the condition in offspring.

PBB is a significant and often underrecognized cause of chronic wet cough in children responding typically to antibiotic treatment (17, 18). Although children with PBB are typically young, there have also been reports of children diagnosed with PBB at older ages (7, 19). PBB was also the second most common diagnosis in our study. Consistent with the literature, it was particularly prevalent in younger age groups while it was observed across all age groups.

Chang et al. demonstrated the importance of early antibiotic intervention in resolving symptoms of PBB and improving outcomes (20). In another study, it was emphasized that when PBB is left untreated, more severe conditions, such as bronchiectasis may occur (21). In our study, it was noteworthy that although about 70% of the patients with a chronic cough had received antibiotic treatment, a significant part of the patients with persistent bacterial bronchiolitis neither had prescribed antibiotic treatment nor received it for a short time.

The use of evidence-based antibiotic protocols has proven to be beneficial not only in resolving acute symptoms but also in enhancing the overall QoL for affected children and reducing healthcare utilization. Given the potential for serious complications, early recognition and treatment of PBB remain crucial, underscoring the need for healthcare providers to distinguish the condition from other causes of chronic cough and ensure that children receive the appropriate course and duration of antibiotics (18,22).

UACS, previously known as postnasal drip syndrome, is characterized by a cough resulting from nasal or sinus pathology leading to upper airway irritation. In children, UACS is a significant cause of chronic cough and is often associated with allergic, non-allergic rhinitis, sinusitis, or adenoid hypertrophy (23,24). In our study, UACS was found to be the third most common cause of chronic cough in all children and the second most common cause in preschoolers and adolescents. Management typically involves treating the underlying nasal or sinus condition, which may include the use of antihistamines, nasal corticosteroids, or antibiotics, depending on the etiology (23).

In our study, PBB was identified as the primary cause of chronic cough in younger age groups, while asthma was more common in older age groups. Similarly, the literature reports that PBB is predominantly observed in younger children, whereas asthma is more frequently diagnosed in older ages (4,9,14). These findings highlight the importance of considering age-specific etiological differences during the diagnostic and treatment process.

Environmental factors, particularly exposure to tobacco smoke, are well-known contributors to respiratory symptoms in children (25,26). Our study found that 40.1% of the patients were exposed to tobacco smoke; however, there was no significant difference in terms of exposure to tobacco smoke among those with dry and wet coughs. Such a feature aligns with the existing literature demonstrating the detrimental effects of passive smoking on respiratory health and the exacerbation of chronic cough (27) . The association between environmental irritants

and respiratory symptoms, even in the absence of significant differences between cough types, highlights the need for public health initiatives aiming at reducing children's exposure to tobacco smoke and other pollutants

A detailed evaluation of children presenting with chronic cough is crucial, as it ensures that less common but potentially serious conditions are not overlooked. While asthma, PBB, and UACS are frequent causes of chronic cough, numerous other potential diagnoses require consideration. These include gastroesophageal reflux disease, primary ciliary dyskinesia, congenital airway abnormalities, and even conditions such as aspiration syndromes or immunodeficiency disorders (1). Missing these diagnoses can lead to significant morbidity, prolonged symptoms, and delayed treatment, potentially resulting in long-term damage to the respiratory system (5). Therefore, a comprehensive assessment including a thorough history, physical examination, and appropriate diagnostic testing is essential to identify or rule out these conditions. This approach not only guides the targeted therapy but also helps prevent unnecessary treatments, such as the overuse of antibiotics or corticosteroids. Recognizing and treating the full spectrum of possible causes for chronic cough can markedly improve a patient's outcomes and overall QoL (1,5).

A multi-disciplinary approach, involving collaboration between the specialists of pediatric allergy, pulmonology, ENT, and gastroenterology, appears advantageous for chronic cough management, especially in cases with overlapping etiologies (3). This strategy allows for comprehensive assessment and can reduce the need for unnecessary antibiotic treatments, which is a common issue in chronic cough management. Integrating findings from a multi-disciplinary framework can improve diagnostic accuracy, support early intervention, and potentially reduce healthcare costs associated with repeated consultations and inappropriate treatments (3).

In conclusion, chronic cough in children is a complex condition with diverse etiologies that vary significantly according to age group and require a detailed history and systematic approach to ensure effective diagnosis and management. Environmental assessments are also important to improve outcomes for pediatric patients with chronic cough.

References

1.Chang AB, Oppenheimer JJ, Irwin RS; CHEST Expert Cough Panel. Managing Chronic Cough as a Symptom in Children and Management Algorithms: CHEST Guideline and Expert Panel Report. Chest. 2020;158(1):303-329. doi: 10.1016/j.chest.2020.01.042. PMID: 32179109.

2.Marchant JM, Newcombe PA, Juniper EF, Sheffield JK, Stathis SL, Chang AB. What is the burden of chronic cough for families? Chest. 2008;134(2):303-309. doi: 10.1378/chest.07-2236. PMID: 18641100.

3.Mukerji SS, Yenduri NJS, Chiou E, Moonnumakal SP, Bedwell JR. A multi-disciplinary approach to chronic cough in children. Laryngoscope Investig Otolaryngol. 2022;7(2):409-416. doi: 10.1002/lio2.778. PMID: 35434349; PMCID: PMC9008181.

4.Chang AB, Robertson CF, Van Asperen PP, Glasgow NJ, Mellis CM, Masters IB, Teoh L, Tjhung I, Morris PS, Petsky HL, Willis C, Landau LI. A multicenter study on chronic cough in children: burden and etiologies based on a standardized management pathway. Chest. 2012;142(4):943-950. doi: 10.1378/chest.11-2725. PMID: 22459773.

5.Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):260S-283S. doi: 10.1378/chest.129.1_suppl.260S. PMID: 16428719.

6.Morice AH, Millqvist E, Bieksiene K, Birring SS, Dicpinigaitis P, Domingo Ribas C, Hilton Boon M, Kantar A, Lai K, McGarvey L, Rigau D, Satia I, Smith J, Song WJ, Tonia T, van den Berg JWK, van Manen MJG, Zacharasiewicz A. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. Eur Respir J. 2020;55(1):1901136. Doi: 10.1183/13993003.01136-2019. PMID: 31515408; PMCID: PMC6942543.

7.Kantar A, Chang AB, Shields MD, Marchant JM, Grimwood K, Grigg J, Priftis KN, Cutrera R, Midulla F, Brand PLP, Everard ML. ERS statement on protracted bacterial bronchitis in children. Eur Respir J. 2017;50(2):1602139. Doi: 10.1183/13993003.02139-2016. PMID: 28838975.

8.Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, Brown KK, Canning BJ, Chang AB, Dicpinigaitis PV, Eccles R, Glomb WB, Goldstein LB, Graham LM, Hargreave FE, Kvale PA, Lewis SZ, McCool FD, McCrory DC, Prakash UBS, Pratter MR, Rosen MJ, Schulman E, Shannon JJ, Hammond CS, Tarlo SM. Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):1S-23S. doi: 10.1378/chest.129.1_suppl.1S. PMID: 16428686; PMCID: PMC3345522.

9.Asilsoy S, Bayram E, Agin H, Apa H, Can D, Gulle S, Altinoz S. Evaluation of chronic cough in children. Chest. 2008;134(6):1122-1128. doi: 10.1378/chest.08-0885. PMID: 18689594.

10.Karabel M, Kelekçi S, Karabel D, Gürkan MF. The evaluation of children with prolonged cough accompanied by American College of Chest Physicians guidelines. Clin Respir J. 2014;8(2):152-9. doi: 10.1111/crj.12052. PMID: 23981451.

11.Gedik AH, Cakir E, Torun E, Demir AD, Kucukkoc M, Erenberk U, Uzuner S, Nursoy M, Ozkaya E, Aksoy F, Gokce S, Bahali K. Evaluation of 563 children with chronic cough accompanied by a new clinical algorithm. Ital J Pediatr. 2015;41:73. Doi: 10.1186/s13052-015-0180-0. PMID: 26444536; PMCID: PMC4595107.

12.Topal OY. Evaluation of Chronic Cough Etiologies in Children. Türkiye Çocuk Hast Derg. 2023;17(3):227-32. doi: 10.12956/tchd.1216596.

13.Ozsezen B. Evaluation of Patients with Chronic Cough Referred to Pediatric Pulmonology Outpatient Clinic. Türkiye Çocuk Hast Derg 17(1):62.7. Doi: 10.12956/tchd.1205598.

14.Marchant JM, Masters IB, Taylor SM, Cox NC, Seymour GJ, Chang AB. Evaluation and outcome of young children with chronic cough. Chest. 2006;129(5):1132-41. doi: 10.1378/chest.129.5.1132. PMID: 16685002.

15.Chang AB, Robertson CF, van Asperen PP, Glasgow NJ, Masters IB, Teoh L, Mellis CM, Landau LI, Marchant JM, Morris PS. A cough algorithm for chronic cough in children: a multicenter, randomized controlled study. Pediatrics. 2013;131(5):e1576-83. doi: 10.1542/peds.2012-3318. PMID: 23610200.

16.Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. N Engl J Med. 1995;332(3):133-8. doi: 10.1056/NEJM199501193320301. PMID: 7800004.

17.Di Filippo P, Scaparrotta A, Petrosino MI, Attanasi M, Di Pillo S, Chiarelli F, Mohn A. An underestimated cause of chronic cough: The Protracted Bacterial Bronchitis. Ann Thorac Med. 2018;13(1):7-13. doi: 10.4103/atm.ATM_12_17. PMID: 29387250; PMCID: PMC5772114.

18.Chang AB, Oppenheimer JJ, Weinberger MM, Rubin BK, Grant CC, Weir K, Irwin RS; CHEST Expert Cough Panel. Management of Children With Chronic Wet Cough and Protracted Bacterial Bronchitis: CHEST Guideline and Expert Panel Report. Chest. 2017;151(4):884-890. doi: 10.1016/j.chest.2017.01.025. PMID: 28143696.

19.Chang AB, Upham JW, Masters IB, Redding GR, Gibson PG, Marchant JM, Grimwood K. Protracted bacterial bronchitis: The last decade and the road ahead. Pediatr Pulmonol. 2016;51(3):225-42. doi: 10.1002/ppul.23351. PMID: 26636654; PMCID: PMC7167774.

20.Chang AB, Redding GJ, Everard ML. Chronic wet cough: Protracted bronchitis, chronic suppurative lung disease, and bronchiectasis. Pediatr Pulmonol. 2008;43(6):519-31. doi: 10.1002/ppul.20821. PMID: 18435475.

21.Chang AB, Marchant JM. Protracted bacterial bronchitis is a precursor for bronchiectasis in children: myth or maxim? Breathe (Sheff). 2019;15(3):167-170. doi: 10.1183/20734735.0178-2019. PMID: 31508153; PMCID: PMC6717611.

22.Wurzel DF, Marchant JM, Yerkovich ST, Upham JW, Petsky HL, Smith-Vaughan H, Masters B, Buntain H, Chang AB. Protracted Bacterial Bronchitis in Children: Natural History and Risk Factors for Bronchiectasis. Chest. 2016;150(5):1101-1108. doi: 10.1016/j.chest.2016.06.030. PMID: 27400908.

23.Pratter MR. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP evidence-based clinical practice guidelines. Chest. 2006;129(1 Suppl):63S-71S. doi: 10.1378/chest.129.1_suppl.63S. PMID: 16428694.

24.Gao F, Gu QL, Jiang ZD. Upper airway cough syndrome in 103 children. Chin Med J (Engl). 2019;132(6):653-8. doi: 10.1097/CM9.0000000000000118. PMID: 30855345; PMCID: PMC6416099.

25.Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. Pediatrics. 2012;129(4):735-44. doi: 10.1542/peds.2011-2196. PMID: 22430451.

26.Jones LL, Hashim A, McKeever T, Cook DG, Britton J, Leonardi-Bee J. Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: systematic review and meta-analysis. Respir Res. 2011;12(1):5. doi: 10.1186/1465-9921-12-5. PMID: 21219618; PMCID: PMC3022703.

27.Gibson PG, Chang AB, Glasgow NJ, Holmes PW, Katelaris P, Kemp AS, Landau LI, Mazzone S, Newcombe P, Van Asperen P, Vertigan AE; CICADA. CICADA: Cough in Children and Adults: Diagnosis and Assessment. Australian cough guidelines summary statement. Med J Aust. 2010;192(5):265-71. doi: 10.5694/j.1326-5377.2010.tb03504.x. PMID: 20201760.

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ORIGINAL ARTICLE

Immigrant Susceptibility to Hand Injuries in Industrial Work Environments: A Retrospective Analysis

Endüstriyel Çalışma Ortamlarında El Yaralanmalarına Karşı Göçmen Duyarlılığı: Retrospektif Bir Analiz

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ABSTRACT

Aim: To elucidate the prevalence and demographic characteristics of patients admitted to emergency departments (EDs) with work-related hand injuries and to determine the factors contributing to such injuries and have an impact on the severity of injuries.
Methods: The study spanned from January 2021 to January 2022 and involved patients seeking medical attention for hand injuries at a tertiary ED near an industrial area. Out of a total of 2,153 patients, 946 admitted due to work-related injuries were evaluated. Data on demographics, injury severity, the timing of injuries, the data on immigrant status, occupational hand injury prevalence in local and immigrant populations, and basic data on treatment methods were collected and analyzed.
Results: The study revealed that 31.9% of individuals with hand injuries were migrants. Injuries were more prevalent during the last working days of the week and in the 35-50 age group. The index finger exhibited the highest injury rate. Surgical interventions were required for 63.95% of patients with 32.72% of those identified as immigrants.
Conclusion: The study highlights that hand injuries are more common among immigrants and sheds light on their vulnerability in occupational settings. Factors such as increased risks in industrial jobs, language barriers, and social and cultural adaptation problems contribute to this increased sensitivity. To reduce these inequalities and increase workplace safety, special preventive measures, personal protection method training, as well as frequent repetition of language, social and cultural adaptation training will reduce the severity of hand injuries and injuries due to occupational accidents in the migrant population as well as in the general population.

Keywords: Emergency department, hand injuries, occupational, immigrants

ÖZ

Amaç: Bu çalışmanın amacı, çalışma kaynaklı el yaralanmaları ile acil servislere başvuran hastaların prevalansını ve demografik özelliklerini açıklamak ve bu yaralanmalara katkıda bulunan faktörleri ve yaralanmaların şiddeti üzerindeki etkilerini belirlemektir.
Gereç ve Yöntem: Çalışma, Ocak 2021 ile Ocak 2022 arasında endüstriyel bir bölgeye yakın üçüncü basamak bir AS'de el yaralanması nedeniyle tıbbi yardım talep eden hastaları kapsamıştır. Toplamda 2.153 hasta arasından, iş kazaları nedeniyle başvuran 946 hasta değerlendirilmiştir. Demografik veriler, yaralanma şiddeti, yaralanmaların zamanlaması, göçmenlik durumu, yerel ve göçmen popülasyondaki mesleki el yaralanması prevalansı ve temel tedavi yöntemleri hakkında veriler toplanıp analiz edilmiştir.
Bulgular: Çalışma, el yaralanması yaşayan kişilerin %31,9'unun göçmen olduğunu göstermiştir. Yaralanmaların haftanın son çalışma günlerinde ve 35-50 yaş grubunda daha yaygın olduğu belirlenmiştir. En yüksek yaralanma oranı subjelerin işaret parmağında görülmüştür. Hastaların %63,95'i cerrahi müdahale gerektirmiş ve bunların %32,72'sinin göçmen olduğu tespit edilmiştir.
Sonuç: Çalışma, göçmenler arasında el yaralanmalarının daha yaygın olduğuna dikkat çekmekte ve iş ortamlarında bu grubun hassasiyetini vurgulamaktadır. Endüstriyel alanlardaki artmış riskler, dil bariyerleri ve sosyal ve kültürel uyum sorunları bu hassasiyetin artışına katkıda bulunmaktadır. Bu eşitsizlikleri azaltmak ve iş yeri güvenliğini artırmak için özel önleyici tedbirler, kişisel koruma yöntemleri eğitimi ile dil, sosyal ve kültürel uyum eğitimlerinin sık sık tekrarlanması, hem göçmen popülasyonda hem de genel popülasyonda iş kazalarına bağlı el yaralanmalarının şiddetini azaltacaktır.

Anahtar Kelimeler: Acil Servis, el yaralanmaları, göçmenler, mesleki

Introduction

Hand injuries, which represent a common cause of admissions to the emergency departments (EDs), account for approximately 6.6% to 28.2% of the admissions (1,2). These injuries, which primarily affect young men with a marked tendency towards the dominant hand, are often caused by a variety of sources, including agricultural activities, industrial work accidents, household incidents, assaults, self-harm attempts, and traffic accidents (3,4). Hand injuries affecting agricultural and industrial workers fall within occupational hand injuries or work accidents, constituting a significant portion of cases seen in EDs, particularly in work-related incidents. At present, hand injuries stemming from work accidents constitute 41% of ED admissions for hand injuries (5). Hand injuries encompass a broad spectrum, ranging from minor skin

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cuts to intricate lacerations involving vessels, nerves, tendons, and bones, and in severe cases, even leading to amputations (2). Hand injuries occurring within domestic settings typically involve soft tissues and manifest as straightforward lacerations. Conversely, hand injuries resulting from work accidents tend to be more severe, resulting in complex injuries such as amputations (6,7).

The increasing immigrant population in recent years has simultaneously increased the representation of immigrants in the labor force, especially due to the increasing migration due to wars. Around the world, immigrants are vulnerable populations facing challenges (8). With the increase in the population of immigrants employed in the industrial sector, there has also been a noticeable increase in the number of immigrants admitted to EDs, especially due to hand injuries caused by work accidents. Because of barriers such as language barriers and adjustment problems they may experience in social and cultural adaptation, immigrants are particularly susceptible to potentially work-related hand injuries. Therefore, the present study aimed to reveal the demographic characteristics of patients admitted to the EDs with work-related hand injuries.

Materials And Methods

Design, population, and settings

The study was carried out complying with the Declaration of Helsinki, and approval was obtained from the local ethics committee of XXX University (Date: 02/03/2023, Protocol no: 03-43).

The study focuses on patients with hand injuries seeking medical attention in the ED of a tertiary trauma hospital located close to an industrial zone in Türkiye, where an average of 700 thousand patient admissions are recorded annually. The research period extends from January 2021 to January 2022. Non-occupational hand injuries due to home accidents were excluded from the study. As occupational hand injuries; Hand injuries caused by both agricultural equipment and industrial construction machinery were included in the study. Of the 2,153 patients who initially presented with hand injuries, 946 patients were included in the study as occupational hand injuries according to the inclusion criteria.

Data collection

A cohort of 946 patients was included in the study, and relevant data were extracted from patient files and the hospital's digital data archives. Additionally, injury prevalence in local and immigrant patients, injury severity, injuries in the dominant hand, timing and day of the injury, the number and specific fingers affected, and the frequency of injuries to particular fingers were examined.

An analysis of the patient's treatment methods was undertaken. Specifically, the focus was on determining whether hand injuries were addressed with simple interventions in ED or necessitated more extensive surgical procedures in the operating room. However, it is important to mention that the study does not provide a detailed breakdown of the specific types of surgeries performed.

Statistical analysis

All statistical analyses were conducted using the RStudio software (version 2023.09.0, RStudio, Inc., Massachusetts, USA). The significance level for the tests is set at 5%. The Chi-Square Homogeneity test is performed for equality of proportions, and the Bonferroni-corrected Chi-Square test is performed for pairwise comparisons.

Results

Only 6.5% of the total study population (62 out of 946) were female. Among the patients, 57.9% (548 out of 946) experienced injuries to their dominant hand. Upon scrutinizing the retrospective hospital registration data of the injured individuals, a notable finding emerged: 31.9% of them were identified as immigrant patients with diverse nationalities, constituting 302 out of the total 946 individuals in the study. Most affected individuals fell within the 35-50 age range, constituting 53.93% of the total study population. (Figure 1).

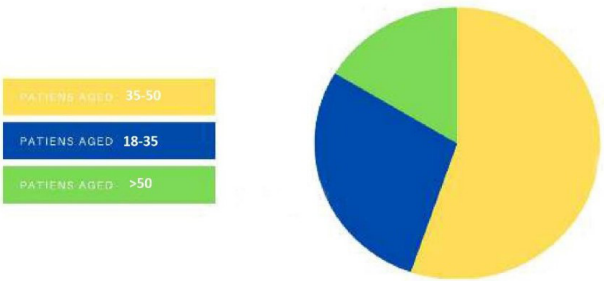

Figure 1. Distribution of patients based on age ranges.

Upon excluding immigrant patients and examining the educational backgrounds of the remaining 644 individuals who received education in Turkey, it was observed that 10.09% were illiterate, 82.45% had completed secondary school, and 6.52% were university graduates. The comparison between illiteracy and university graduation did not yield a significant difference. However, a noteworthy finding was the statistically significant prevalence (82.45%) of individuals with education levels at the secondary school level. Examining injury distribution concerning time intervals revealed that 52.80% of injuries occurred during morning hours. When the distribution of injuries according to time intervals was examined, it was seen that 52.80% of the injuries occurred in the morning hours. In the study, three shift work schedules, 8:00 am-4:00 pm, 4:00 pm-00:00, and 00:00-8:00 am were taken into consideration. When comparing the shift hours where the injury occurred according to the shift hours, the p-value for the chi-square homogeneity test = 0.0000. The injury rate in the 8:00 am-4:00 pm shift is the highest. In pairwise comparison The rate of hand injuries between 8:00 am-4:00 pm (p=0.5280899) and 00:00-8:00 am (p=0.3483146) shifts was significantly higher than the rate of hand injuries in the 4:00 pm-8:00 am (p=0.1235955) shift. (Table 1).

Table 1. Comparison of the time intervals when the injury occurred

The periods where injuries occurred	00:00 pm-8:00 am	08:00 am-4:00 pm	4:00 pm-00:00
Ratio	34.83% (0.3483146)	52.80% (0.5280899)	12.35% (0.1235955)
Dual Comparison	*A	*A	*B

*In comparison between shifts, a chi-square homogeneity test was used. The *p*-value for the chi-square homogeneity test, p=0.0000

In terms of weekly distribution, 51.79% of injuries occurred during the weekend (Friday-Saturday-Sunday), with injuries on Monday-Tuesday-Wednesday-Thursday accounting for 48.21% (Figure 2). Although the augmented workforce during weekdays, including administrative staff, the incidence of injuries was notably higher on weekends compared to weekdays.

The highest injury rate was index finder with 28.75%, followed by thumb with 27.27%. In the Binary comparison of the injury rates of each finger; According to the chi-square homogeneity test, the p-value was calculated as = 0.002724 and there was no significant difference between the thumb (0.2727273), index (0.28752079), middle (0.1522314) and little (0.1818182) fingers. However, the injury rate of the ring finger (0.1257020) was found to be significantly lower than the other fingers (Table 2).

Table 2. Comparison of the most injured fingers

Number of Injured Fingers	Thumb Finger	Index Finger	Middle Finger	Ring Finger	Little Finger
Ratio	27.27% (0.287507)	28.75% (0.2727273)	15.22% (0.1522314)	12.57% (0.125702)	18.18% (0.1818182)
Dual Comparison	*A	*A	*A	* B	*A

*In the Binary comparison of the injury rates of each finger. According to the chi-square homogeneity test, the *p*-value, p=0.002724

Strikingly, the percentage of immigrants presenting with hand injuries due to a work accident to all applicants with a work accident is approximately 31.9%. This indicates that the immigrant population is exposed to these injuries at a rate approximately six times higher.

Upon analyzing the treatment methods, it was observed that 63.95% of patients underwent surgery following consultation with the hand surgery department. Additionally, 22.30% received consultation from the same department, and intervention and treatment were administered by the relevant branch within EDs. Furthermore, 13.74% of patients underwent treatment by an emergency physician without consultation or hospitalization. (Figure 3). Notably, among the patients necessitating surgical intervention (n=604), 32.72% (n: 198) were identified as immigrant patients.

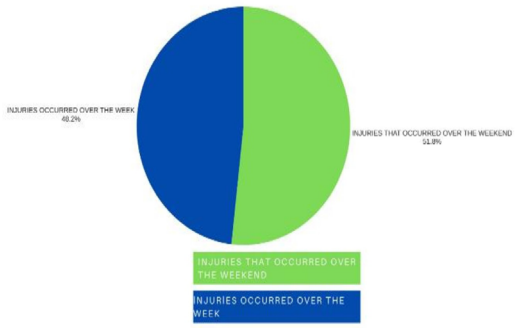

Figure 2: Distribution rate of injuries on days of occurrence (weekdays/weekends)

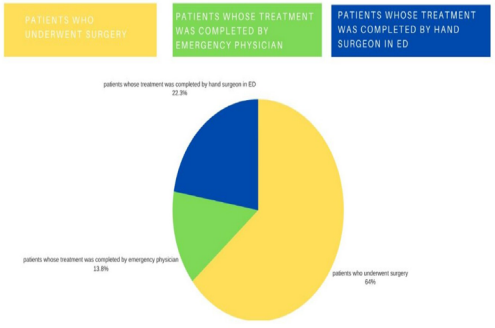

Figure 3. Distribution of treatment methods of patients

Discussion

In light of the data from our study, the observed higher frequency of injuries during the latter part of the week suggests a potential correlation with increased fatigue, underscoring the necessity for systematic rest periods to alleviate occupational hazards. The temporal clustering of injuries within the 08:00-16:00 timeframe corresponds with standard working hours, reflecting the operational patterns of most of the workforce. This observation accentuates the significance of integrating temporal considerations, such as work shift dynamics, when formulating comprehensive occupational safety strategies. While the proportion of female employees among the entire study population was around 46%, a notable finding was that only approximately 6.5% of those presenting with hand injuries were female. The reason for this intriguing discrepancy can be attributed to the fact that female workers are less employed since the patients included were working with heavy industrial machinery and in industries working in shifts. Another conceivable factor might be their more cautious approach when working in hazardous environments than their male counterparts. The key point in our data is that immigrant patients account for 31.9% of hand injuries. This strongly suggests that immigrants are more prone to hand injuries. Possible reasons could be their lack of experience with industrial work, challenges in understanding safety risks due to language issues, and a higher chance of working in risky jobs. However, it's important to note that these are just possible reasons; our data doesn't pinpoint the exact cause.

The heightened frequency of injuries in the dominant hand aligns with the expected outcome, given its primary utilization. Furthermore, the higher frequency of injuries to the thumb and index fingers indicates that these fingers are more vulnerable, likely due to increased usage during work. These findings underscore the importance of task-specific safety protocols and emphasize the necessity for tailored preventive measures aligning with the specific nature of tasks performed by employees.

Demographically, the incidence of hand injuries exhibits notable gender disparities, with a prevalence of 70-87.3% among males and 12.7-30% among females. It would be correct to attribute the reason for this inequality to differences in the employment sector. The age distribution of these injuries is most pronounced in the 21–30 age range, reflecting a demographic peak for occurrences (9-13). Gender ratios for hand injuries are typically in the range of 57-80% for males and 20-43% for females, and the frequency of incidents occurring in the 21-30 age group reflects the trends observed in our country (10-18). These data do not conflict with the data in our study An examination of the age distribution revealed that the most prevalent hand injuries occurred within the 35-50 age range, constituting 55.3% of cases, followed by the 18-35 age range at 28.4%.

Our data indicates that hand injuries occurred more frequently on weekends (Friday-Saturday-Sunday), compared to weekdays (monday-tuesday-wednesday-thursday), constituting 51.8% of cases. This observation aligns with findings from a comprehensive study conducted in China, which similarly concluded that work-related injuries exhibited a higher prevalence among weekend workers (19). The educational landscape of workers engaged in industrial machinery operations within the industrial zone aligns with global trends, where individuals typically attain education at the primary to secondary school level (3,16,20,21).

Despite the valuable insights from this study, some limitations warrant admission. The first limitation is a retrospective study. In particular, the lack of comprehensive data on patients' substance addictions such as smoking and alcohol is striking. Again, the retrospective nature of the study made it difficult to access data on the surgical technique used in patients with operated hand injuries. In addition, the study was restricted by the lack of information about postoperative rehabilitation processes and the duration of absence from work.

Conclusion

It is noteworthy that the incidence of the immigrant population and the severity of injury in the immigrant population are high in the case of admissions to EDs with hand injuries due to work accidents. In addition, the incidence of these injuries increases in the last working days of the week. These events are more common among individuals aged 35-50 years and are less frequent among women.

To reduce the difficulties faced by the immigrant population all over the world due to language barriers, and social and cultural adaptation problems, it is necessary to increase adaptation and training while being employed in risky business lines. To prevent such hand injuries, it is essential to implement preventive measures and provide more training to employees.

References

1. de Putter CE, Selles RW, Polinder S, Panneman MJM, Hovius SER, van Beeck E.F. Economic impact of hand and wrist injuries: health-care costs and productivity costs in a population-based study. J of Bone & J. Surg. 94(9): p e56, May 2, 2012.

2. Sahin F, Akca H, Akkaya N, Zincir ÖD, Işik A. Cost analysis and related factors in patients with traumatic hand injuryJ Hand Surg Eur Vol. 2013 Jul;38(6):673-679.

3. Gauchard GC, Chau N, Touron C, Benamghar L, Dehaene D, Perrin PhP. Individual characteristics in occupational accidents due to imbalance: a case-control study of the employees of a railway company. Occup Environ Med. 2003 May;60(5):330-335.

4. Larsen CF, Mulder S, Johansen AM, Stam C. The epidemiology of hand injuries in The Netherlands and Denmark. Eur J Epidemiol. 2004;19(4):323-327.

5. Leixnering M, Quadlbauer S, Szolarcz C, Schenk C, Leixnering S, Körpert K. Prevention of hand injuries-current situation in Europe. Handchir Mikrochir Plast Chir. 2013 Dec;45(6):339-343.

6. Frazier W. H., Miller M., Fox R. S., Brand D, Finseth F. Hand injuries: incidence and epidemiology in an emergency service. JACEP. 1978 Jul;7(7):265-268.

7. Smith M. E., Auchincloss J. A., Ali S. Causes and consequences of hand injury. J Hand Surg Br. 1985 Oct;10(3):288-292

8. Hemminki K. Immigrant health, our health. Eur J Public Health. 2014 Aug;24 Suppl 1:92-5.

9. Gupta A, Gupta AK, Uppal SK, Mittal RK, Garg R, Aggarwal N. Demographic profile of hand injuries in an industrial town of north India: a review of 436 patients. Indian J Surg. 2013 Dec;75(6):454-461.

10. Aslan A, Aslan İ , Özmeriç A , Atay T, Çaloğlu A, Konya MN. Acil El Yaralanmalarında Deneyimlerimiz: 5 Yıllık Verilerin Epidemiyolojik Değerlendirmesi. TAF Preventive Medicine Bulletin. 2013, Dec;12(5):563.

11. Sorock GS, Lombardi DA, Hauser RB, Eisen EA, Herrick RF, Mittleman MA. Acute traumatic occupational hand injuries: Type, location, and, severity. J Occup Environ Med. 2002 Apr;44(4):345-351.

12. Kleinert HE, Verdan C. Report of the Committee on Tendon Injuries (International Federation of Societies for Surgery of the Hand). J Hand Surg Am. 1983 Sep;8(5 Pt 2):794-798.

13. Oguz AB, Polat O, Eneyli MG. Gulunay B, Eksioglu M, Gurler S. The efficiency of bedside ultrasonography in patients with wrist injury and comparison with other radiological imaging methods: A prospective study. Am J Emerg Med. 2017 Jun;35(6):855-859.

14. de Putter CE, van Beeck EF, Polinder S, Panneman MJM, Burdorf A, Hovius SER. Healthcare costs and productivity costs of hand and wrist injuries by external cause: A population-based study in working-age adults in the period. Injury. 2016 Jul;47(7):1478-1482.

15. Rosberg HE, Carlsson KS, Cederlund RI, Ramel E, Dahlin LB. Costs and outcome for serious hand and arm injuries during the first year after trauma. A prospective study. BMC Public Health. 2013 May 24:13:501.

16. Chau N, Bhattacherjee A, Kunar BM; Lorhandicap Group. Relationship between job, lifestyle, age, and occupational injuries. Occup Med (Lond). 2009 Mar;59(2):114-119.

17. Chow CY, Lee H, Lau J, Yu IT. Transient risk factors for acute traumatic hand injuries: a case-crossover study in Hong Kong. Occup Environ Med. 2007 Jan;64(1):47-52

18. Davas Aksan A, Durusoy R, Ada S, Kayalar M, Aksu F, Bal E. Epidemiology of injuries treated at a hand and microsurgery hospital. Acta Orthop Traumatol Turc. 2010;44(5):352-360.

19. Wu Z, Guo Y, Gao J, Zhou J, Li S, Wang Z. The epidemiology of acute occupational hand injuries treated in emergency departments in Foshan City, South China. Ulus Travma Acil Cerrahi Derg. 2018 Jul;24(4):303-310

20. Sorock GS, Lombardi DA, Hauser R, Eisen EA, Herrick RF, Mittleman MA. A case-crossover study of transient risk factors for occupational acute hand injury. Occup Environ Med. 2004 Apr;61(4):305-311.

21. Hertz RP, Emmett EA. Risk factors for occupational hand injury. J Occup Med. 1986 Jan;28(1):36-41.

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ORIGINAL ARTICLE

Retrograde Pedal Artery Access versus Conventional Common Femoral Artery Access in Isolated Superficial Femoral Artery Lesions

İzole Yüzeyel Femoral Arter Lezyonlarında Retrograd Pedal Arter Erişimi ile Konvansiyonel Ortak Femoral Arter Erişiminin Karşılaştırılması

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ABSTRACT

Aim: The current study compared the efficacy and safety of retrograde pedal artery (PA) access versus conventional common femoral artery (CFA) access in managing isolated superficial femoral artery (SFA) occlusions or severe stenoses.
Method: A retrospective analysis was conducted on 34 patients treated between June 2020 and November 2023. The patients were categorized into two groups: 12 patients with PA access and 22 with CFA access. Technical success, complication rates, stent usage, procedure duration, and radiation doses were analyzed.
Results: Technical success was achieved in 92.8% of the patients in the PA access group and 84% of the CFA access group (p=0.636). Complications at the access site were significantly lower in the PA access group, with no hematomas or pseudoaneurysms observed, while both hematomas (32%) and pseudoaneurysms (16%) were noted in the CFA group (p=0.033). Stent usage was similar between the two groups (21.4% PA vs. 28% CFA, p=0.721). Median procedure durations were 43 minutes interquartile ranges (IQRs) 27.5-59) for PA and 47 minutes (IQR 29-64) for CFA (p=0.446). The median total air kerma dose was 280 mGy (IQR 166.5-326.75) for PA and 225 mGy (IQR 145-489) for CFA (p=0.826).
Conclusion: Retrograde PA access is a viable and safe alternative to CFA access, particularly for patients with complex femoral anatomy, offering similar efficacy with fewer access site complications.

Keywords: Balloon angioplasty, femoral artery, occlusion, pedal access, stenosis

ÖZ

Amaç: Bu çalışma, izole yüzeyel femoral arter (SFA) oklüzyonlarının veya ciddi stenozlarının yönetiminde retrograd yolla pedal arter (PA) erişimi ile konvansiyonel ortak femoral arter (CFA) erişiminin etkinlik ve güvenliğini karşılaştırmaktadır.
Yöntem: Haziran 2020 ile Kasım 2023 arasında tedavi edilen 34 hasta üzerinde retrospektif bir analiz yapıldı. Hastalar, PA erişimi ile tedavi edilen 12 hasta ve CFA erişimi ile tedavi edilen 22 hasta olmak üzere iki gruba ayrıldı. Teknik başarı, komplikasyon oranları, stent kullanımı, işlem süresi ve radyasyon dozları analiz edildi.
Bulgular: PA erişim grubundaki hastaların %92.8'inde, CFA erişim grubundaki hastaların ise %84'ünde teknik başarı elde edilmiştir (p=0.636). Girişim bölgesindeki komplikasyonlar PA akses grubunda anlamlı şekilde daha düşüktü; hematom veya psödoanevrizma gözlemlenmezken, CFA erişim grubunda hematom (%32) ve psödoanevrizma (%16) tespit edildi (p=0.033). Stent kullanımı iki grup arasında benzerdi (%21.4 PA vs. %28 CFA, p=0.721). Ortalama işlem süreleri PA erişim grubu için 43 dakika (IQR 27.5-59), CFA erişim grubu için 47 dakika (IQR 29-64) idi (p=0.446). Ortalama toplam hava kerma dozu PA erişim grubu için 280 mGy (IQR 166.5-326.75), CFA erişim grubu için ise 225 mGy (IQR 145-489) olarak ölçüldü (p=0.826).
Sonuç: Retrograd olarak PA erişimi, özellikle kompleks femoral anatomiye sahip hastalar için, benzer etkinlikle ve daha az komplikasyon oranıyla CFA erişimine göre uygulanabilir ve güvenli bir alternatiftir.

Anahtar Kelimeler: Balon anjiyoplasti, femoral arter, oklüzyon, pedal akses, stenoz

Introduction

Peripheral artery disease (PAD) of the lower extremities is a common condition that can lead to critical limb ischemia (CLI) and result in significant morbidity and mortality (1). Among the various arteries affected by PAD, the superficial femoral artery (SFA) is frequently involved, particularly in its proximal segment and within the Hunter's canal (2). Traditional endovascular treatments for SFA occlusions include approaches via the contralateral or ipsilateral common femoral artery (CFA) (3, 4). However, ipsilateral antegrade access can present with technical challenges and complications, especially in patients with anatomical variations such as a high level of CFA bifurcation or comorbid conditions such as obesity. Such conditions may make the procedure difficult and increase the risk of complications such as groin hematomas and bleeding. Additionally, in cases where the SFA ostium is affected, ipsilateral antegrade access becomes even more challenging (5). The contralateral retrograde approach often requires navigation through the

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aortoiliac bifurcation, which can be problematic due to angulation, iliac artery occlusions, or in the presence of bypass grafts or aneurysms. These factors can reduce the technical success rate and increase procedure-related morbidity. An alternative strategy with proven success involves accessing the vessel distal to the lesion and crossing the obstruction in a retrograde fashion. First advocated by Tonnesen et al., ipsilateral retrograde access is considered to be a safe approach for treating femoropopliteal lesions when CFA access fails (6). Retrograde access can be achieved through the distal SFA, popliteal artery, or the tibial or trans pedal arteries (7). Retrograde puncture is typically carried out under ultrasound, fluoroscopy guidance of ultrasound or fluoroscopy to minimize any complications due to bleeding. The most common complications associated with retrograde access are bleeding events, perforation of vessels, or damage to the vascular-nerve bundle (8).

The current study aimed to compare the efficacy and safety of retrograde access via the pedal arteries (PA) with conventional femoral access methods in the management of isolated SFA and CFA stenosis or occlusion. We aimed to provide insights into the potential benefits of the retrograde PA approach in PAD and CLI management by analyzing procedural success rates, complication profiles, and the need for re-intervention. Ultimately, this comparison will help guide future clinical practices by evaluating the advantages and limitations of each strategy.

Material And Methods

Patient Selection

The current retrospective study was approved by the local ethics committee (reference number: 2023-614), and informed consent was obtained from all patients before their participation. The study included all consecutive patients diagnosed with isolated chronic total occlusion (CTO) or severe stenosis of the SFA, who were treated with either retrograde PA access or conventional femoral access between June 2020 and November 2023.

Inclusion criteria were as follows: patients who had undergone pre-procedural computed tomographic angiography confirming chronic total occlusion or severe stenosis in the SFA, exhibited moderate to severe claudication (Fontaine Stage IIb), ischemic rest pain (Fontaine Stage III), and/or ulceration or gangrene (Fontaine Stage IV), and were ineligible for surgical revascularization due to lack of suitable venous conduit, absence of a distal non-diseased artery for anastomosis, or comorbid conditions precluding anesthesia. Patients with significant iliac artery disease and with no significant stenosis in the trifurcation arteries, as well as those eligible for bypass surgery, were excluded from the study.

Procedure

Endovascular revascularization was attempted for all study participants. The endovascular treatments for the patients included in the study were performed using a Philips Azurion Clarity IQ (Philips Medical Systems, Amsterdam, The Netherlands) angiography system. The access routes included ipsilateral common femoral or superficial femoral antegrade access, contralateral common femoral retrograde access, or retrograde access via the anterior or posterior tibial-pedal arteries. The decision regarding the revascularization technique was made by the treating physician and included one or a combination of the following: percutaneous transluminal angioplasty (PTA), drug-coated balloon (DCB) angioplasty, and bare-metal stent (BMS) placement.

An intravascular bolus of 70 U/kg heparin along with 300 µg of nitroglycerin was administered for antispasmodic effect, with nitroglycerin repeated every 30 minutes. If the duration of the procedure exceeded one hour, half of the initial heparin dose was administered again. Following the placement of a 5F sheath, a 4F vertebral catheter with either a 0.018-inch or 0.035-inch wire was used to cross the occlusion or stenosis. Balloon angioplasty was carried out on stenotic or occluded segments. In the event of greater than 30% residual stenosis or the presence of a dissection that prevented adequate flow following angioplasty, bail-out stenting was carried out. In case a 0.035-inch stent delivery system was required during PA access, a sheathless technique was utilized to minimize vessel trauma rather than switching to a 6F sheath. Lack of success in crossing the lesion or reentry into the true lumen entailed a switch to an alternative retrograde or antegrade approach. Examples of cases undergoing endovascular procedures via retrograde PA access are presented in the accompanying figures (Figures 1, 2, 3, and 4). Hemostasis at the pedal or femoral access site was achieved through manual compression. Patients were discharged on the same day after appropriate monitoring and Doppler ultrasound evaluation of the pedal or femoral artery.

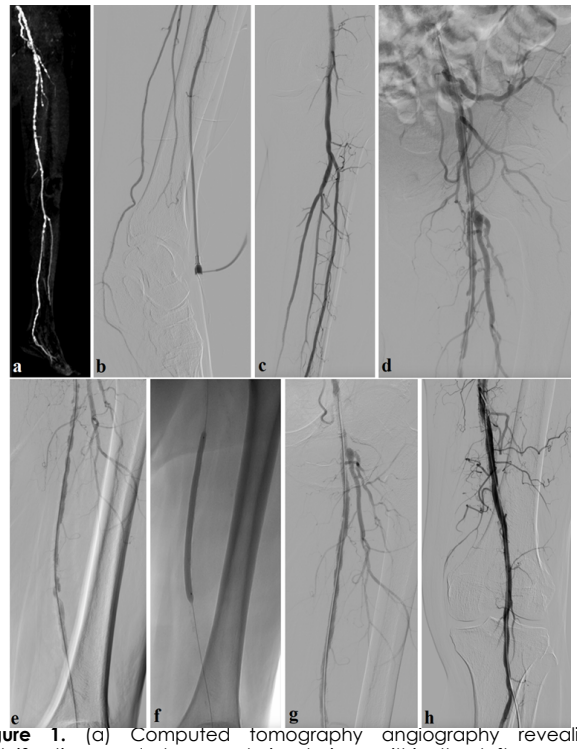

Figure 1. (a) Computed tomography angiography revealing calcifications and steno-occlusive lesions within the left common femoral artery and superficial femoral artery. (b, c) Initial digital subtraction angiography images, following retrograde placement of a 5F sheath in the anterior tibial artery, demonstrating patency of the trifurcation arteries and the popliteal artery. (d, e) Digital subtraction angiography images acquired after retrograde catheterization of the left external iliac artery using a diagnostic catheter and guidewire showing steno-occlusive lesions in the superficial femoral artery. (f) Balloon angioplasty was carried out on the stenotic and occluded segments within the superficial femoral artery. (g, h) Final angiographic images illustrating a complete revascularization of the superficial femoral artery.

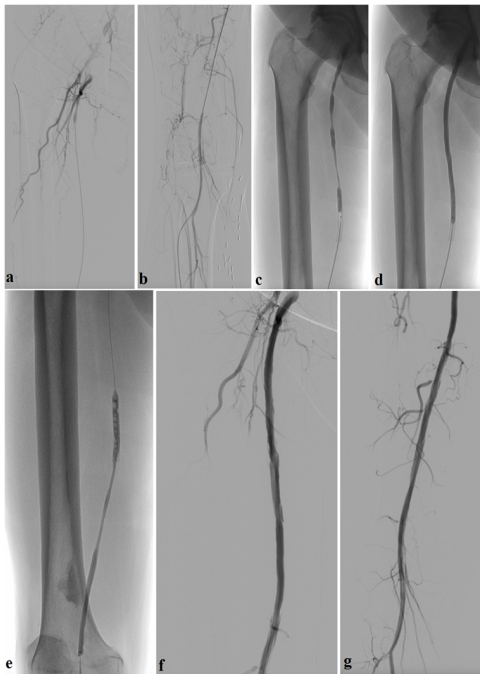

Figure 2. (a, b) Digital subtraction angiography images obtained from the right external iliac artery via retrograde access through the anterior tibial artery demonstrating a long-segment occlusion within the superficial femoral artery, including a previously deployed stent. (c, d, e) Sequential images of balloon angioplasty performed on the proximal segment of the SFA occlusion, followed by in-stent angioplasty and balloon dilation of the distal segment of the occluded superficial femoral artery. (f, g) Final angiographic images post-balloon dilation depicting successful recanalization of the superficial femoral artery.

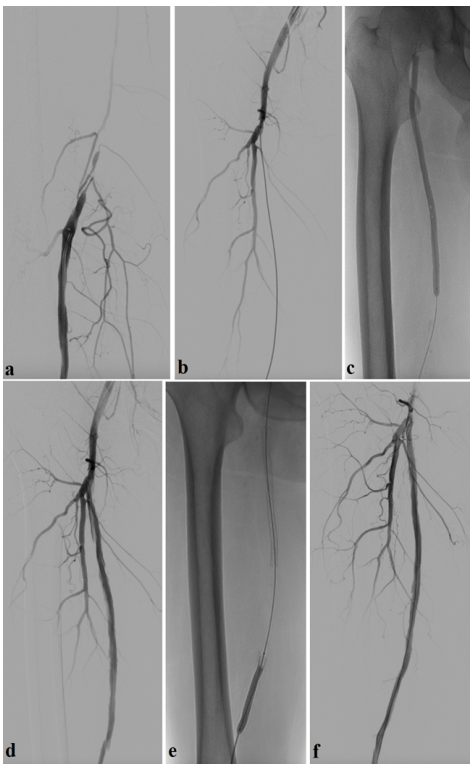

Figure 3: (a, b) Baseline angiography of the right superficial femoral artery via retrograde access through the posterior tibial artery revealing extensive occlusion of the superficial femoral artery with a patent popliteal artery. (c) Balloon angioplasty carried out on the occluded segment of the superficial femoral artery. (d) Post-percutaneous transluminal angioplasty angiogram showing flow-limiting dissections (indicated by arrows) in the proximal and distal segments of the superficial femoral artery. (e) Fluoroscopic image displaying stents placed to cover the dissected segments in the proximal and distal superficial femoral artery, followed by in-stent balloon angioplasty. (f) Final angiogram confirming a complete revascularization of the superficial femoral artery.

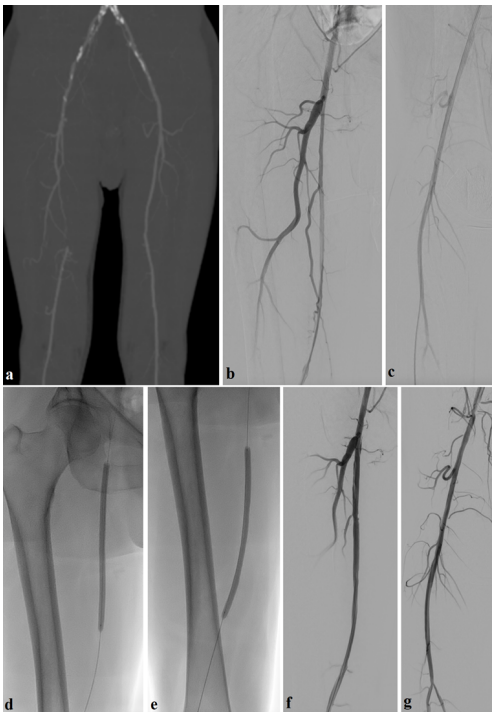

Figure 4: (a) CT angiography showing extensive calcifications in the bilateral iliac arteries, with an occlusion in the right superficial femoral artery. The bilateral common femoral arteries (CFA), left superficial femoral artery, and both popliteal arteries remained patent. (b, c) Following retrograde access through the right anterior tibial artery at the ankle level, a diagnostic catheter and guidewire were advanced to the right external iliac artery. Digital subtraction angiography images revealed areas of steno-occlusions within the superficial femoral artery. (d, e) Balloon angioplasty was carried out at the sites of steno-occlusions in the superficial femoral artery. (f, g) Final Digital subtraction angiography images post-balloon angioplasty indicating full patency of superficial femoral artery.

Outcome Measures

Technical success was defined as achieving revascularization with less than 30% residual stenosis, without the need for additional access. Any of the following events at the treated vessel or access site were considered as complications: arteriovenous fistula, thrombus formation, aneurysm, pseudoaneurysm, hematoma, infection, retroperitoneal bleeding, compartment syndrome, need for postprocedural blood transfusion, unplanned above-the-ankle amputation, embolization, dissection, and persistent vasospasm. In addition, the procedure duration and total radiation dose were compared between the patients undergoing retrograde PA access and those undergoing conventional femoral access.

Statistical Analysis

Data processing and analysis were carried out with SPSS Statistics, Version 25.0 (SPSS, Chicago, IL, USA). The normality of the distribution of the numerical variables was assessed quantitatively with the Kolmogorov-Smirnov test and visually via Q-Q plots. Descriptive statistics are presented as medians with interquartile ranges (IQRs). Due to a non-normal distribution, non-parametric tests were applied for comparative analyses. The Mann-Whitney U test was used to compare procedure duration and total air kerma dose between the two groups (retrograde PA access and CFA access), while Fisher's exact test was employed to analyze complication and technical success rates. A p-value of less than 0.05 was considered statistically significant for all tests.

Results

A total of 12 patients underwent retrograde access through the PA, including 10 males (83.3%) and two females (16.6%). Among the 12 cases, 12 (85.7%) had SFA occlusion, and two (14.3%) had severe SFA stenosis. Bilateral SFA intervention was conducted in two patients. The median age of the patients was 59 years (IQR, 55-62 years). Hypertension was present in nine patients (75%), diabetes mellitus (DM) in seven (58.3%), coronary artery disease in seven (58.3%), chronic renal failure (CRF) in three (25%), congestive heart failure (CHF) in one (8.3%), and a smoking history in eight patients (66.6%). The Fontaine stages were as follows: Stage IIb in two cases (14.3%), Stage III in three cases (21.4%), and Stage IV in nine cases (64.3%). Trans-Atlantic Inter-Society Consensus (TASC) II lesion classifications were as follows: TASC II B in five cases (35.7%), TASC II C in six cases (42.9%), and TASC II D in three cases (21.4%). Demographic data for the patients are presented in Table 1. Access via the anterior PA was used in eight procedures (57.1%), and access via the posterior tibial artery was used in six procedures (42.9%).

Table 1. Demographic Data of Patients

	Pedal Artery Access Group n=14	CFA Access Group n=25
Number of Patients	12	22
Male, n (%)	10 (83.3)	17 (77.3)
Female, n (%)	2 (16.6)	5 (22.7)
Age median (IQR)	59 (55–62)	62 (54–70)
SFA occlusion, n (%)	12 (85.7)	17 (68)
SFA severe stenosis, n (%)	2 (14.3)	8 (32)
Hypertension, n (%)	9 (75)	18 (81.8)
DM, n (%)	7 (58.3)	16 (72.7)
CAD, n (%)	7 (58.3)	16 (72.7)
CRF, n (%)	3 (25)	6 (27.7)
CHF, n (%)	1 (8.3)	2 (9)
Smoking History, n (%)	8 (66.6)	17 (77.3)
Fontaine Stage IIb, n (%)	2 (14.3)	5 (20)
Fontaine Stage III, n (%)	3 (21.4)	6 (24)
Fontaine Stage IV, n (%)	9 (64.3)	14 (56)
TASC II B, n (%)	5 (35.7)	9 (36)
TASC II C, n (%)	6 (42.9)	11 (44)
TASC II D, n (%)	3 (21.4)	5 (20)

CAD: Coronary artery disease, CHF: Congestive heart failure, CRF: Chronic renal failure, DM: Diabetes mellitus, SFA: Superficial femoral artery, TASC: Trans-Atlantic Inter-Society Consensus.

A total of 22 patients underwent CFA access, including 17 males (77.3%) and five females (22.7%). Among the 22 cases, 17 (68%) had SFA occlusion, and eight (32%) had severe SFA stenosis. Bilateral SFA intervention was performed in three patients. The median age was 62 years (IQR, 54-70 years). Hypertension was present in 18 patients (81.8%), DM in 16 (72.7%), coronary artery disease in 16 (72.7%), CRF in six (27.7%), CHF in two (9%), and a smoking history in 17 patients (77.3%). The Fontaine stages were as follows: Stage IIb in five cases (20%), Stage III in six cases (24%), and Stage IV in 14 cases (56%). TASC II lesion classifications were as follows: TASC II B in nine cases (36%), TASC II C in 11 cases (44%), and TASC II D in five cases (20%). Demographic data for the patients are presented in

Table 1.

Five procedures in the CFA access group (20%) were carried out via contralateral CFA retrograde access due to involvement of the SFA ostium or obesity, 17 procedures (68%) via ipsilateral CFA antegrade access, and three procedures (12%) via SFA antegrade access due to high CFA bifurcation.

Technical success was achieved in 13 procedures (92.8%) in the PA access group. In one case, the antegrade intervention was required after the failure of the retrograde recanalization, after which revascularization was successfully achieved. Technical success was achieved in 21 procedures (84%) in the CFA access group. Retrograde intervention was required in four cases following the failure of antegrade recanalization, and revascularization was successfully achieved. No significant difference in technical success rate was identified between the two groups (p=0.636) (Table 2). No hematomas or pseudoaneurysms were observed at the PA access sites. At the one-month follow-up, the pedal access artery remained patent in all patients, while eight patients (32%) in the CFA access group developed hematomas, and among these, four (16%) had pseudoaneurysms. A significant difference in access site complications was observed between the two groups (p=0.033).

Table 2. Comparison of procedural outcomes and complications between pedal artery and common femoral artery access groups.

	Pedal Artery Access Group n=14	CFA Access Group n=25	*p*-value
Technical Success, n (%)	13 (92.8)	21 (84)	0.636
Complications, n (%)	0 (0)	8 (32)	0.033
Stent Usage, n (%)	3 (21.4)	7 (28)	0.721
Procedure Duration time, minute, median (IQR)	43 (27.5-59)	47 (29-64)	0.446
Total Air Kerma Dose, mGy, median (IQR)	280 (166.5-326.75)	225 (145-489)	0.826

IQR: Interquartile range

Stents were used following balloon angioplasty in three procedures (21.4%) in the PA access group, and seven procedures (28%) in the CFA access group. The difference in stent usage between the two groups did not reach statistical significance (p=0.721).

The median procedure duration was 43 minutes (IQR 27.5-59) in the PA access group, with a median total air kerma dose of 280 mGy (IQR 166.5-326.75). The median procedure duration was 47 minutes (IQR 29-64) in the CFA access group and the median total air kerma dose was 225 mGy (IQR 145-489). The procedure duration and total air kerma dose were similar between the two groups (p=0.446 and p=0.826, respectively).

Discussion

The findings from the current study offer insights into the comparative effectiveness and safety of retrograde PA access versus conventional CFA access for treating isolated SFA occlusions or severe stenoses. Our study highlights the potential for PA access to be an effective alternative procedure, especially in patients with high CFA bifurcation, SFA ostium involvement, or obesity, where antegrade CFA access poses technical challenges. By exploring alternative access strategies, the current study contributes to the ongoing efforts to refine endovascular techniques for PAD, particularly in scenarios of challenging anatomical variations.

Our data demonstrated a comparable and high technical success rate in both PA and CFA access groups. Of note, PA access showed a lower incidence of access site complications, with no hematomas or pseudoaneurysms observed. This contrasted with the CFA group, where 32% of patients developed hematomas and 16% had pseudoaneurysms with a statistically significant difference from the PA access group. These findings suggest that retrograde PA access may be a safer option for minimizing access site complications, particularly in patients at high risk for such complications. These outcomes align well with prior studies that underscore the value of minimizing groin access in cases of complex SFA anatomy or increased bleeding risk.

A comparison of the current findings with existing literature suggests that retrograde pedal and tibial approaches may offer advantages over the traditional trans popliteal approach for accessing SFA lesions. Historically, the retrograde trans popliteal approach, as described by Leachman et al., required patients to be positioned prone, which can be challenging both technically and in terms of patient comfort (9). The close anatomical proximity of the popliteal artery to the vein in many cases increases the risk of complications, including fistula and hematoma formation, especially due to difficulties in achieving post-procedure compression. Studies have reported a higher rate of complications with this approach, with the overall complications dropping significantly when popliteal access in the prone position was excluded in favor of

pedal or tibial approaches. Additionally, the popliteal approach has been associated with a relatively high technical failure rate (10%-26%), often due to difficulties in re-entering the true lumen near the SFA origin, which can lead to excessive stenting and potential occlusion of the profunda femoris artery (6, 10). The outcomes of the current study are in good agreement with these findings, as PA access not only provided a safer alternative with fewer access site complications but also allowed successful revascularization without the need for extensive stenting in most cases. Furthermore, previously published studies suggest that lesion morphology and disease severity can influence technical success and outcomes, with complex lesions often requiring bidirectional access to improve the chances of intraluminal recanalization. Retrograde access is beneficial in crossing softer distal caps of CTO, which may enhance the technical success rate (11, 12). Consistent with these insights, our study demonstrated high technical success with retrograde PA access, particularly in patients with challenging lesion characteristics. Retrograde access supports better long-term patency by preserving a healthy distal landing zone and minimizing collateral damage which may improve outcomes if future surgical interventions are required (13).

The current study has some limitations that should be considered. As a retrospective analysis, it is inherently subject to selection bias, and the sample size was relatively small. Additionally, the study was conducted at a single institution, which may limit the generalizability of the findings. Prospective, multicenter studies with larger patient populations will provide a more comprehensive assessment of the effectiveness and safety of PA access compared to CFA access.

Retrograde PA access appears to be a safe and effective alternative to conventional CFA access, particularly for patients with challenging femoral anatomy. The retrograde PA access approach was associated with significantly fewer access site complications and therefore may improve procedural outcomes and expand treatment options for PAD patients with high-risk anatomical features.

Highlights

PA access achieved a high technical success rate (92.8%), comparable to CFA access (84%), for treating isolated SFA lesions.

Access site complications were significantly lower with PA access, with no hematomas or pseudoaneurysms, compared to higher rates in the CFA group (32% hematomas, 16% pseudoaneurysms).

PA access is particularly beneficial for patients with complex femoral anatomy, offering a safer alternative with fewer complications.

References

1.Varu VN, Hogg ME, Kibbe MR. Critical limb ischemia. J. Vasc. Surg. 2010;51:230-41.

2.Wiesinger B, Heller S, Schmehl J, et al. Percutaneous vascular interventions in the superficial femoral artery. A review. Minerva Cardioangiol. 2006;54:83-93.

3.Wheatley BJ, Mansour MA, Grossman PM, et al. Complication rates for percutaneous lower extremity arterial antegrade access. Arch. Surg. 2011;146:432-5.

4.Barbetta I, van den Berg JC, editors. Access and hemostasis: femoral and popliteal approaches and closure devices—why, what, when, and how? Semin Intervent Radiol.; 2014: Thieme Medical Publishers.

5.Sethi A, Arora RR. Medical management and cardiovascular risk reduction in peripheral arterial disease. Exp Clin Cardiol. 2008;13:113.

6.Tønnesen KH, Sager P, Karle A, Henriksen L, Jørgensen B. Percutaneous transluminal angioplasty of the superficial femoral artery by retrograde catheterization via the popliteal artery. Cardiovasc. Interv. Radiol. 1988;11:127-31.

7.Ye M, Zhang H, Huang X, et al. Retrograde popliteal approach for challenging occlusions of the femoral-popliteal arteries. J. Vasc. Surg. 2013;58:84-9.

8.Ueshima D, Ashikaga T, Shimura T, et al. The popliteal retrograde approach is effective and safe for superficial femoral artery chronic total occlusion. Ann. Vasc. Dis. 2015;8:220-6.

9.Leachman DR, Avedissian MG, Krajcer Z, Angelini P. Transluminal laser angioplasty of the femoropopliteal circulation by use of a percutaneous popliteal approach. Am J Cardiol. 1989;64:106-8.

10.Ko Y-G, Kim J-S, Choi D-H, Jang Y, Shim W-H. Improved technical success and midterm patency with subintimal angioplasty compared to intraluminal angioplasty in long femoropopliteal occlusions. J Endovasc Ther. 2007;14:374-81.

11.Saab F, Jaff MR, Diaz-Sandoval LJ, et al. Chronic Total Occlusion crossing approach based on Plaque cap morphology: the CTOP classification. J Endovasc

Ther. 2018;25:284-91.

12.Bazan HA, Le L, Donovan M, et al. Retrograde pedal access for patients with critical limb ischemia. J. Vasc. Surg. 2014;60:375-82.

13.Fanelli F, Lucatelli P, Allegritti M, et al. Retrograde popliteal access in the supine patient for recanalization of the superficial femoral artery: initial results. J Endovasc Ther. 2011;18:503-9.

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ORIGINAL ARTICLE

Advancing Surgical Outcomes in Extremity Vascular Trauma: Insights from Clinical Experience

Ekstremite Vasküler Travmasında Cerrahi Sonuçların Geliştirilmesi: Klinik Deneyimlerden Elde Edilen Görüşler

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ABSTRACT

Background/Aim: Extremity trauma is a major contributor to global morbidity and mortality, comprising up to 70% of trauma admissions. Vascular injuries associated with extremity trauma pose significant challenges as the delays in diagnosis may lead to acute limb ischemia, compartment syndrome, and limb loss. Timely diagnosis and surgical intervention are essential for optimizing patient outcomes.
Methods: This retrospective cohort study analyzed 85 patients with vascular extremity traumas treated at a tertiary care hospital from 2018 to 2023. Patients with isolated soft tissue injuries or chronic injuries were excluded. Data on demographics, injury mechanisms, clinical presentations, diagnostic imaging, surgical interventions, and outcomes were collected. Primary outcomes included limb salvage and mortality rates, while secondary outcomes evaluated complications and functional recovery.
Results: The cohort had a mean age of 33.7 years, with a predominance of male patients (87.1%). Lower extremity injuries were the most common, with gunshot wounds as the leading cause (31.8%). Most (90.6%) presented within 6 hours of injury, and 55.3% exhibited hemodynamic instability. In 91.8% of cases, surgical intervention was required, predominantly involving interposition vein grafting and primary repairs. Limb salvage was achieved in 92.9% of patients, though 15.3% experienced complications, primarily ischemia and necrosis. The rate of iatrogenic trauma was significantly higher in hemodynamically stable patients (18.4% vs 4.3%, p=0.007).
Conclusion: Early surgical intervention in extremity trauma is crucial for high limb salvage rates and favorable outcomes. Despite a notable complication rate, timely management can mitigate adverse effects. Future studies should focus on improving long-term functional outcomes and developing comprehensive rehabilitation protocols tailored to extremity trauma patients.

Keywords: Extremity trauma, limb salvage, trauma management, vascular injury

ÖZ

Giriş: Ekstremite travmaları, travma kaynaklı morbidite ve mortalitenin önemli bir nedeni olup, tüm travma yatışlarının %70'ine kadarını oluşturabilmektedir. Ekstremite travmalarına eşlik eden vasküler yaralanmalar, akut ekstremite iskemisi, kompartman sendromu ve uzuv kaybı gibi ciddi komplikasyonlara yol açabileceğinden dolayı önemli zorluklar teşkil etmektedir. Bu nedenle, tanının hızlı bir şekilde konulması ve cerrahi müdahalenin zamanında gerçekleştirilmesi hasta sonuçlarının iyileştirilmesinde hayati öneme sahiptir.
Yöntem: Bu retrospektif kohort çalışmasında, 2018-2023 yılları arasında bir üçüncü basamak hastanede vasküler ekstremite travması nedeniyle tedavi gören 85 hasta incelenmiştir. İzole yumuşak doku yaralanması veya kronik yaralanması olan hastalar çalışmaya dahil edilmemiştir. Demografik veriler, yaralanma mekanizmaları, klinik bulgular, görüntüleme yöntemleri, cerrahi müdahaleler ve sonuçlar gibi veriler toplanmıştır. Birincil sonuçlar arasında uzuv kurtarma ve mortalite oranları yer alırken, ikincil sonuçlar komplikasyonlar ve fonksiyonel iyileşme değerlendirilmiştir.
Bulgular: Kohortun ortalama yaşı 33,7 olup, hastaların %87,1'i erkekti. En sık karşılaşılan yaralanma alt ekstremite yaralanmaları olup, travmaların %31,8'i ateşli silah yaralanmalarıydı. Hastaların %90,6'sı travmadan sonraki ilk 6 saat içinde başvurmuş ve %55,3'ünde hemodinamik instabilite tespit edilmiştir. Olguların %91,8'inde cerrahi müdahale gerekli olmuş, en sık kullanılan yöntemler interpozisyon ven grefti ve primer onarımlar olmuştur. Uzuv kurtarma oranı %92,9 olarak bulunurken, hastaların %15,3'ünde iskemik ve nekrotik komplikasyonlar tespit edilmiştir. Hemodinamik olarak stabil hastalarda iyatrojenik travma oranı anlamlı derecede yüksek bulunmuştur (%18,4'e karşı %4,3, p=0,007).
Sonuç: Ekstremite travmalarında erken cerrahi müdahale, yüksek uzuv kurtarma oranları ve olumlu sonuçlar için kritik öneme sahiptir. Önemli bir komplikasyon oranı görülmesine rağmen, zamanında yönetim olumsuz etkileri azaltabilmektedir. Gelecekteki çalışmalar, uzun dönem fonksiyonel sonuçları iyileştirme ve ekstremite travmalarına yönelik kapsamlı rehabilitasyon protokolleri geliştirme üzerinde yoğunlaşmalıdır.

Anahtar Kelimeler: Damar yaralanması, ekstremite kurtarılması, ekstremite travmaları, travma yönetimi

Introduction

Extremity traumas, encompassing both upper and lower limb injuries, represent a significant portion of trauma cases worldwide and remain a leading cause of morbidity and mortality. Based on the World Health Organization (WHO), trauma is one of the most critical public health challenges, with over five million deaths annually attributed to injuries, and millions more suffering long-term disabilities (1). Among these, extremity trauma is particularly prevalent, accounting for up to 70% of all trauma admissions in emergency

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departments globally (2). The mechanisms of such injuries vary widely, ranging from road traffic accidents and falls to violence-related incidents such as gunshot and stab wounds, each presenting unique challenges in clinical management (3).

In high-energy trauma settings, the potential for concomitant vascular injury is a crucial consideration, as it can significantly affect limb viability and patient outcomes. Vascular injuries associated with extremity trauma can lead to devastating consequences, including acute limb ischemia, compartment syndrome, and, ultimately, limb loss if not promptly identified and managed (4). The presence of hard signs of vascular injury, such as pulsatile bleeding, expanding hematoma, and absent distal pulses, often necessitates immediate surgical exploration. In contrast, soft signs require a more nuanced approach involving advanced imaging modalities to confirm the extent of the injury. The timely and accurate diagnosis of these injuries is critical, as delays in treatment are associated with increased rates of amputation and mortality (5).

The management of extremity trauma involves a multidisciplinary approach including initial resuscitation, surgical intervention, and comprehensive postoperative care. The choice of surgical technique, such as primary repair, interposition vein grafting, or fasciotomy, is dictated by the type and severity of the injury. Early surgical intervention has been shown to improve outcomes significantly, particularly in cases of vascular injury where time to surgery is a critical determinant of limb salvage (6). Despite advances in surgical techniques and perioperative care, complications such as ischemia, necrosis, infection, and chronic pain remain significant concerns, often leading to prolonged hospital stays and repeated interventions (7).

Recent studies have highlighted the importance of a standardized approach to managing extremity trauma, emphasizing early identification of vascular injuries, appropriate surgical planning, and the use of advanced imaging techniques to guide treatment decisions (7). However, significant variability remains in clinical practice, particularly regarding the optimal timing of surgical intervention and the management of complications. Additionally, there is a paucity of data on the long-term functional outcomes of patients surviving extremity trauma, particularly in resource-limited settings where access to rehabilitation services may be restricted (7).

Given these gaps in the literature, this study aims to provide a comprehensive analysis of extremity trauma management in a tertiary care setting, focusing on the incidence and types of injuries, clinical presentations, surgical interventions, and outcomes, including limb salvage rates, complications, and long-term functional recovery. By examining a diverse cohort of patients over five years, we seek to identify key factors influencing outcomes and propose evidence-based recommendations for improving trauma care. The findings of this study will contribute to the growing body of evidence on extremity trauma and inform clinical guidelines, ultimately enhancing patient care and reducing the burden of trauma-related disabilities.

Methods

This retrospective cohort study was conducted in the cardiovascular surgery clinic of a tertiary university hospital between January 2018 and December 2023. The local ethics committee reviewed and approved the study protocol, and informed consent was obtained from all patients or their legal representatives. The study adhered to the ethical principles outlined in the Declaration of Helsinki.

Study Population

The study included a total of 85 patients presenting with extremity trauma. Inclusion criteria encompassed patients presenting with acute extremity trauma, defined as any injury involving the upper or lower extremities resulting from blunt, penetrating, or mixed mechanisms. Patients with major vascular injuries involving large vessels such as the aorta, vascular involvement of thoracic or abdominal organs, isolated soft tissue injuries without vascular involvement, chronic injuries, or those refusing to give consent were excluded from the study. Demographic data, including age, gender, and injury characteristics were obtained from electronic medical records of the hospital.

Clinical Assessment and Data Collection

Upon arrival at the emergency department, the trauma team thoroughly assessed all patients. This assessment included a detailed history, physical examination, and the evaluation of hemodynamic status. The clinical presentation was classified based on hard signs (e.g., pulsatile bleeding, absent distal pulses, cold, and pale limbs) and soft signs (e.g., non-pulsatile hematoma, reduced sensation) of vascular injury. The hemodynamic status was categorized as stable or unstable based on the initial vital signs and

the need for resuscitation.

The collected data included the time to clinical presentation defined as the interval between the injury and the initial presentation to the trauma center. It also included information about the mechanism of the injury (such as gunshot wounds, road traffic accidents, and stab wounds), as well as specific causes and related details about the injuries.

Imaging and Diagnostic Methods

Diagnostic imaging was used based on clinical need. All patients had X-rays to check for fractures and foreign objects. Computed tomography angiography was used to look for suspected vascular injuries, especially in cases where clear signs were not present. Duplex ultrasonography was used for patients suspected of having venous injuries or when immediate surgery was not needed. In unstable patients or those needing cardiopulmonary resuscitation, diagnosis relied only on physical examination. The choice of imaging was based on the patient's condition and available resources, as the emergency department physicians decided.

Surgical Interventions and Management

In cases of confirmed vascular injury or when conservative management was insufficient, surgery was necessary. The surgical procedure was determined based on the nature and severity of the injury. Options included interposition vein grafts, primary repair, fasciotomy, or a combination of these, as well as limb amputation when necessary. All surgeries took place in a dedicated cardiovascular surgery operating room equipped with full resuscitation capabilities and were performed by an experienced vascular team. Trauma teams were called in when required. The timing of surgery was recorded as either "less than six hours" or "more than six hours" post-injury, depending on the clinical urgency.

The type of anesthesia used, the length of the surgery, and any complications during surgery were carefully documented. After the surgery, standard trauma care procedures were followed, which included anticoagulation therapy, infection prevention, and close monitoring for signs of compartment syndrome or ischemia.

Outcome Measures

The study's main goals were to determine the rates of saving limbs, mortality, and the occurrence of major complications such as ischemia, necrosis, and infections. Secondary goals included the length of hospital stay, rates of readmission due to complications, and the need for blood transfusion. Long-term outcomes were evaluated using follow-up notes at the first, third, sixth, and 12th months after the discharge. Standardized scoring systems were used to assess full functional recovery and the presence of functional disabilities.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics, injury characteristics, and clinical outcomes. Continuous variables were expressed as mean ± standard deviation (SD) based on data distribution, while categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the chi-square test for categorical variables and the independent t-test for continuous variables. A p-value of <0.05 was considered statistically significant. All analyses were conducted using the Statistical Package for Social Sciences (SPSS) for Windows, software (version 29.0, IBM Corp., Armonk, NY, USA).

Results

Demographics and Injury Characteristics of Patients

The study included a total of 85 patients with extremity trauma. The mean age of the patients was 33.7 years, ranging from four to 84 years. Among the patients, 87.1% were male (n=74) and 12.9% were female (n=11). Most injuries affected the lower extremities, with the left lower extremity being the most frequently affected area (36.5%, n=31), followed by the right lower extremity (34.1%, n=29). In comparison, injuries to the upper extremities were less common, with 20% (n=17) involving the right upper extremity and 9.4% (n=8) affecting the left upper extremity (Table 1).

When examining the causes of injury, the most frequent reasons were gunshot wounds (31.8%, n=27), road traffic accidents (29.4%, n=25), and stab wounds (23.5%, n=20). Gunshot wounds stood out as the primary cause of injury (Table 1).

Of the gunshot-related injuries, 61.53% were shotgun and 38.46% were gunshot. Shotgun injuries had more extensive tissue damage and multiple vascular injuries than gunshot injuries and generally required more aggressive vascular repair and debridement.

Clinical Presentation and Hemodynamic Status

The majority of patients (90.6%, n=77) arrived at the healthcare facility within 6 hours of the injury. Upon admission, 55.3% (n=47) of patients were hemodynamically unstable, while 44.7% (n=38) were hemodynamically stable. In hemodynamically unstable patients, the rate of combined (arterial + venous) injuries was significantly higher compared to stable patients (59.6% vs 28.9%; p=0.013). Among the hemodynamically unstable patients, the most frequently observed hard signs were pulsatile bleeding (59.8%, n=49), absence of distal pulses (22.0%, n=18), and cold, pale extremities (18.3%, n=15). On the other hand, soft signs were found in 37.6% of the cases (n=32), with non-pulsatile hematoma and neurological deficits being the most common findings. The findings were similar in patients presenting with hard and soft signs. In hemodynamically stable patients, the incidence of iatrogenic trauma was significantly higher compared to unstable patients (18.4% vs 4.3%; p=0.007). (Table 1)

Table 1. Demographic and Injury Characteristics of Hemodynamically Stable and Unstable Patients

	HD Stable (n=38)	HD Unstable (n=47)	*p*-value
Age (years)	34.76±20.52	32.85±14.46	0.629
Gender			
Male	32 (84.2%)	42 (89%)	0.530
Related Extremities			
Right Upper Limb	11 (28.9%)	7 (14.8%)	0.293
Left Upper Limb	4 (10.5%)	3 (6.4%)	
Right Lower Limb	10 (26.3%)	19 (40.4%)	
Left Lower Limb	13 (34.2%)	18 (38.3%)	
Mechanism of Injury			
Gunshot Wounds	8 (21.1%)	19 (40.4%)	**0.007***
Road Traffic Collusion	8 (21.1%)	7 (14.9%)	
Stab Wounds	4 (10.5%)	11 (23.4%)	
Industrial or Heavy Machinery Trauma	3 (7.9%)	3 (6.4%)	
Blunt Injury	1 (2.6%)	0 (0.0%)	
Fall	1 (2.6%)	3 (6.4%)	
Glass-related Injury	6 (15.8%)	2 (4.3%)	
Iatrogenic Trauma	7 (18.4%)[a]	2 (4.3%)[b]	

*The p-value (p=0.007) indicates a statistically significant linear relationship between the injury mechanism and hemodynamic status. HD: Hemodynamically

In our cohort, multisystemic involvement was observed in 41.66% of patients with orthopedic injuries and 35.48% of patients with thermal or non-thermal nerve injuries, emphasizing the importance of a multidisciplinary approach in managing such complex traumas.

Surgical Interventions and Outcomes

Surgical intervention was performed on 91.8% of patients (n=78). The most common procedures were interposition vein grafts (52.9%, n=45), primary repairs (24.7%, n=21), and fasciotomies (22.4%, n=19). The vast majority of surgeries (97.6%, n=83) were done within the first 6 hours following the injury, highlighting the urgency of surgical intervention in traumatic vascular injuries. Limb salvage was achieved in 92.9% (n=79) of cases. Amputation was necessary for severe ischemia or non-viable limbs, and the decision was made either during the initial surgical procedure or during subsequent interventions following the first operation (Table 2).

Table 2. Distribution of Surgical Procedures Performed in Hemodynamically Stable and Unstable Patients

	HD Stable (n=38)	HD Unstable (n=47)	*p*-value
Interposition Vein Graft	18 (47.4%)	27 (57.4%)	0.213*
Interposition ePTFE Graft	1 (2.6%)	4 (8.5%)	
Primary Vascular Repair	17 (44.7%)	11 (23.4%)	
Ligation	1 (2.6%)	2 (4.3%)	
End-to-end Suturing	0 (0.0%)	1 (2.1%)	
Patch-plastic Repair	1 (2.6%)	0 (0.0%)	
Thrombectomy	0 (0.0%)	2 (4.3%)	

* The p-value (p = 0.213) indicates no statistically significant difference between the hemodynamically stable (HD Stable) and hemodynamically unstable (HD Unstable) groups regarding the distribution of surgical procedures.

Complications and Hospital Course

In 15.3% of cases (n=13), complications were observed, with the most common being ischemia (30.8%, n=4), necrosis (23.1%, n=3), and infections (15.4%, n=2). The average hospital stay was 8.5 days, ranging from 1 to 37 days. Additionally, 15.3% of patients (n=13) were readmitted due to the need for additional surgical procedures or infection management (Table 3).

Table 3. Complication Rates in Hemodynamically Stable and Unstable Patients Following Surgical Intervention

	HD stable	HD Unstable	*p*-value
No Complication	35 (92.1%)	37 (78.7%)	0.14
Compartment Syndrome	0 (0.0%)	2 (4.3%)	
Reperfusion Injury	0 (0.0%)	4 (8.5%)	
Bleeding on Surgical Site	1 (2.6%)	0 (0.0%)	
Disseminated Intravascular Coagulation	1 (2.6%)	0 (0.0%)	
Hematoma	0 (0.0%)	1 (2.1%)	
Ischemia	1 (2.6%)	0 (0.0%)	
Necrosis	0 (0.0%)	1 (2.1%)	
Osteomyelitis	0 (0.0%)	2 (4.3%)	

Blood Transfusion and Long-Term Outcomes

64.7% of patients (n=55) required a blood transfusion, with an average transfusion volume of 3.2 units per patient. In long-term follow-ups, 87.1% of patients (n=74) achieved full recovery without significant disability, while 12.9% (n=11) continued to experience functional disability due to nerve damage or other reasons.

Discussion

The current study provides valuable insights into the demographic characteristics, injury mechanisms, clinical presentations, surgical interventions, and outcomes of patients with extremity trauma. Our findings highlight several critical aspects of trauma care aligning with and expanding upon the existing literature, suggesting areas for continued improvement and future research. This discussion will contextualize our results within the broader scientific discourse, drawing comparisons with similar studies and emphasizing the implications for clinical practice.

In this cohort of 85 patients, the predominance of male patients (87.1%) and a mean age of 33.7 years reflect a demographic profile commonly reported in trauma studies worldwide. For instance, a systematic review by Kataria et al. (2023) noted that males are disproportionately affected by trauma due to greater involvement in high-risk activities such as driving, manual labor, and sports (8). Our findings are consistent with those of Sharifian et al. (2024), who also reported a high incidence of extremity injuries among young adult males, particularly in urban settings. The similar distribution of demographics highlights the persistent vulnerability of young males to trauma, suggesting the need for preventive strategies focused on this demographic. The observed gender disparity may be attributed to behavioral and sociocultural factors, necessitating targeted public health interventions to mitigate risks among these high-risk groups (4).

The distribution of injury mechanisms in our study, particularly the high incidence of gunshot wounds (31.8%), road traffic collisions (29.4%), and stab wounds (23.5%), mirrors global patterns reported in trauma literature. Gunshot wounds as a leading cause of injury are consistent with findings from urban trauma centers in the United States and South Africa, where firearm-related violence is prevalent. For instance, studies from the US urban centers have shown that firearms are responsible for a significant proportion of trauma cases, with over 80% of firearm-related injuries requiring hospitalization and a mortality rate of 10-13% depending on the number and severity of gunshot wounds (9-12). Our results also align with data from the WHO Global Status Report on Road Safety (2018), highlighting road traffic accidents as a leading cause of worldwide morbidity and mortality. The prevalence of violent injury mechanisms underscores the necessity for violence prevention programs and stricter firearm control measures to reduce trauma incidence.

Shotgun injuries usually lead to greater soft tissue damage and vascular disruption than gunshot injuries, necessitating more aggressive surgical repair or debridement and reconstructive procedures.

The substantial proportion of injuries resulting from violent mechanisms underscores the urgent need for comprehensive violence prevention programs and stricter firearm control policies, as advocated by recent public health studies (1, 9).

Clinically, the majority of our patients (90.6%) presented within 6 hours of injury, reflecting a commendable response time critical for favorable outcomes in trauma care. This is in line with the principles of damage control surgery and early resuscitation, which emphasize the importance of prompt surgical intervention to mitigate the effects of hemorrhagic shock and minimize secondary complications (13). The relatively high rate of hemodynamic instability (55.3%) upon admission in our cohort emphasizes the severity of injuries managed in this setting and necessitates preparedness for rapid intervention. The presence of hard signs of vascular injury, such as pulsatile bleeding (59.8%) and absent distal pulses (22.0%), necessitated immediate surgical exploration, which is consistent with current guidelines for managing vascular trauma (14).

The high rate of multisystemic involvement, including orthopedic and nerve injuries, highlights the need for a collaborative approach among vascular, orthopedic, and neurosurgical teams to optimize outcomes in extremity trauma patients.

The high rate of surgical intervention (91.8%) in our cohort, with interposition vein grafts and primary repairs being the most frequently performed procedures, reflects the complexity of managing extremity trauma, particularly when major vascular structures are involved. These findings are comparable to those of Feliciano et al. (2013), reporting similar surgical approaches in their analysis of vascular injuries (15). The frequent use of interposition vein grafts (47.4% in stable and 57.4% in unstable patients) underscores

the critical role of vascular grafting techniques in limb salvage efforts, particularly in complex trauma cases. The success of limb salvage in 92.9% of cases in our study is noteworthy and compares favorably with limb salvage rates reported in other contemporary trauma series (16). However, the 7.1% rate of amputation, although relatively low, underscores the challenges of managing severe vascular injuries and the critical importance of timely, definitive surgical care to optimize outcomes.

Complications were observed in 15.3% of our patients, with ischemia and necrosis being the most common. This complication rate is comparable to the one reported by Kontopodis et al. (2024), identifying similar postoperative complications in patients with complex extremity trauma (17). These findings underscore the importance of meticulous intraoperative technique and vigilant postoperative monitoring to promptly identify and address complications. Additionally, the significantly higher rate of iatrogenic trauma in hemodynamically stable patients (18.4% vs 4.3%; p=0.007) warrants attention. This finding may suggest that stable patients are subjected to more extensive diagnostic or interventional procedures, potentially increasing their risk of iatrogenic injury. Identifying the factors contributing to this higher rate of iatrogenic trauma could guide procedural refinements aimed at minimizing such complications. Moreover, our data indicate that a significant portion of patients required blood transfusions (64.7%), reflecting the substantial blood loss often associated with severe extremity trauma. This aligns with studies by Kontopodis et al. (2024), which underscore the necessity of robust transfusion protocols and the management of coagulopathy in trauma patients (17).

Long-term follow-up in our study revealed that while 87.1% of patients achieved full recovery, a notable 12.9% experienced functional limitations, primarily due to nerve damage or prolonged ischemia. These findings highlight the potential for significant long-term morbidity following extremity trauma, even in cases where initial limb salvage is successful. This is consistent with the work of Kontopodis et al. (2024), reporting persistent functional impairments in a subset of trauma survivors (17). The observed functional impairments underscore the importance of post-discharge rehabilitation and long-term follow-up to address residual disabilities and optimize recovery. Such outcomes underscore the need for comprehensive rehabilitation programs tailored to the needs of extremity trauma patients to enhance functional recovery and quality of life.

Conclusion

In summary, this study offers a comprehensive analysis of extremity trauma management, highlighting the importance of early diagnosis, prompt surgical intervention, and vigilant monitoring to optimize limb salvage and reduce complications. Our findings underscore the high success rate of limb salvage (92.9%) achieved through interposition vein grafts and primary repairs, alongside the challenges posed by complications such as ischemia and necrosis. The significantly higher rate of iatrogenic trauma in hemodynamically stable patients also suggests areas for targeted procedural improvements. These insights align with best practices in trauma care and emphasize the need for tailored rehabilitation programs to address long-term functional limitations. Future research should consider multi-center trials to validate these findings across diverse populations and explore novel strategies in trauma management further enhancing patient outcomes. By integrating these insights into clinical practice, we can advance the care of extremity trauma patients, ultimately improving both immediate and long-term outcomes.

References

1.Organization WH. Global status report on road safety 2018: World Health Organization; 2019.

2.Gosselin RA, Spiegel DA, Coughlin R, Zirkle LG. Injuries: the neglected burden in developing countries. Bull World Health Organ 2009; 87(4): 246-246a.DOI: 10.2471/blt.08.052290

3.Staudenmayer K, Wang NE, Weiser TG, Maggio P, Mackersie RC, Spain D, Hsia RY. The Triage of Injured Patients: Mechanism of Injury, Regardless of Injury Severity, Determines Hospital Destination. Am Surg 2016; 82(4): 356-361

4.Sharifian M, Marzban A, Beiranvand M, Mahboubi MJ, Garshasebi M. Vascular trauma injury evaluation in Khorramabad, Iran: a cross-sectional study. Ann Med Surg (Lond) 2024; 86(1): 109-114.DOI: 10.1097/MS9.0000000000001492

5.Derbel B, Mazzaccaro D, Krarti N, Miri R, Khadhar Y, Ben Mrad M, Righini P, Nano G, Denguir R. Penetrating Vascular Injuries of the Lower Limbs after Stab Wounds: Predictive Factors of Limb Loss and Mortality. J Clin Med 2023; 12(10). DOI: 10.3390/jcm12103476

6.Collaborators C-T. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): A randomized, placebo-controlled trial. Indian J Neurotraum 2012; 9(1): 3-14.DOI: 10.1016/j.ijnt.2012.05.001

7.Agarwal P, Kukrele R, Sharma D. Delayed revascularization of extremities following vascular injuries: Challenges and outcome. J Orthop 2023; 35: 31-36.DOI: 10.1016/j.jor.2022.10.016

8.Kataria H, Premkumar P, Samuel V, Selvaraj D, Stephen E. Factors Predicting the Outcome of Musculoskeletal Injuries Associated with Vascular Trauma at a Tertiary Care Trauma Centre in South India. Indian J Vascular En 2023; 10(1): 32-36. DOI: 10.4103/ijves.ijves_98_22

9.Harris KA, Yonclas P. Acute and Long-Term Complications of Gunshot Wounds to the Head. Curr Phys Med Rehab 2020; 8(4): 436-442.DOI: 10.1007/s40141-020-00301-4

10.Davoudi A, Woodworth L. The burden of firearm injuries on the hospital system, 2000-2020. Inj Epidemiol 2023; 10(1): 12.DOI: 10.1186/s40621-023-00420-1

11.Lumbard DC, Freese RL, Marek AP, Endorf FW, Richardson CJ, Nygaard RM. Firearm trauma: Race and insurance influence mortality and discharge disposition. J Trauma Acute Care Surg 2022; 92(6): 1005-1011.DOI: 10.1097/TA.0000000000003512

12.Hemenway D, Nelson E. The Scope of the Problem: Gun Violence in the USA. Curr Trauma Rep 2020; 6(1): 29-35.DOI: 10.1007/s40719-020-00182-x

13.Cannon JW, Khan MA, Raja AS, Cohen MJ, Como JJ, Cotton BA, Dubose JJ, Fox EE, Inaba K, Rodriguez CJ, Holcomb JB, Duchesne JC. Damage control resuscitation in patients with severe traumatic hemorrhage: A practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg 2017; 82(3): 605-617.DOI: 10.1097/TA.0000000000001333

14.Feliciano DV. Pitfalls in the management of peripheral vascular injuries. Trauma Surg Acute Care Open 2017; 2(1): e000110.DOI: 10.1136/tsaco-2017-000110

15.Feliciano DV, Moore EE, West MA, Moore FA, Davis JW, Cocanour CS, Scalea TM, McIntyre RC, Jr. Western Trauma Association critical decisions in trauma: evaluation and management of peripheral vascular injury, part II. J Trauma Acute Care Surg 2013; 75(3): 391-397.DOI: 10.1097/TA.0b013e3182994b48

16.Fox N, Rajani RR, Bokhari F, Chiu WC, Kerwin A, Seamon MJ, Skarupa D, Frykberg E, Eastern Association for the Surgery of T. Evaluation and management of penetrating lower extremity arterial trauma: an Eastern Association for the Surgery of Trauma practice management guideline. J Trauma Acute Care Surg 2012; 73(5 Suppl 4): S315-320.DOI: 10.1097/TA.0b013e31827018e4

17.Kontopodis N, Tosounidis T, Kehagias E, Kouraki A, Tzirakis K, Ioannou CV. Concomitant vascular and orthopedic trauma: 10 points to consider. J Clin Orthop Trauma 2024; 51: 102407. DOI: 10.1016/j.jcot.2024.102407

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ORIGINAL ARTICLE

Peripheral Blood Smear Findings and Clinical Significance in Pregnant Women with COVID-19

COVID-19'lu Gebe Kadıinlarda Periferik Yayma Bulguları ve Klinik Önemi

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ABSTRACT

Aim: Peripheral blood smear analysis is a cornerstone diagnostic tool in hematology. For pregnant women with coronavirus disease 2019 (COVID-19), this diagnostic technique assumes heightened significance. Our study aims to elucidate the peripheral smear findings in pregnant women with COVID-19.
Method: Our study participants comprise 50 pregnant women diagnosed with COVID-19 and 50 controls. Clinical findings, medications, peripheral blood smear, and complete blood count parameters are some of the variables examined here. The chi-square tests were employed to compare categorical measurements. Samples t-test was used for numerical measurements. The groups were compared in terms of complete blood count parameters. Significant differences were identified between the groups.
Results: The values of ferritin, C-reactive protein, procalcitonin, D-dimer, activated partial thromboplastin time (aPTT), and fibrinogen exhibited significant differences among the groups. The lymphocyte ratio in the COVID-19 group is lower, compared to the control group. The proportions of band cells, lymphocytes, monocytes, neutrophils, vacuolated monocytes, and hypersegmented neutrophils exhibit statistically significant differences between the groups. Peripheral blood abnormalities are prevalent in microbial infections, particularly in viral infections.
Conclusions: These abnormalities can provide insights into the underlying pathophysiological changes. In patients with COVID-19, no abnormalities have been observed in platelets and erythrocytes. However, compared to the controls, atypical monocytes and neutrophil hypersegmentation are significantly elevated in COVID-19 patients.

Keywords: Complete blood count, COVID-19, lymphocyte ratio, peripheral blood smear, pregnant women

ÖZ

Amaç: Periferik kan yayma analizi hematolojide temel bir tanı aracıdır. COVID-19'lu gebe kadınlarda, bu tanı tekniği daha da önem kazanmaktadır. Çalışmamız COVID-19'lu gebe kadınlarda periferik yayma bulgularını açıklamayı amaçlamaktadır.
Materyal ve Yöntemler: Çalışmamızın katılımcıları COVID-19 tanısı almış 50 gebe kadın ve 50 kontrolden oluşmaktadır. Klinik bulgular, ilaçlar, periferik kan yayması ve tam kan sayımı parametreleri incelenen değişkenlerden bazılarıdır. Kategorik ölçümleri karşılaştırmak için Ki-Kare testleri kullanıldı. Sayısal ölçümler için Örnek T-Testi kullanıldı. Gruplar tam kan sayımı parametreleri açısından karşılaştırıldı. Gruplar arasında anlamlı farklılıklar belirlendi.
Bulgular: Ferritin, CRP, prokalsitonin, D-dimer, aPTT ve fibrinojen değerleri gruplar arasında anlamlı farklılıklar gösterdi. COVID-19 grubunda lenfosit oranı kontrol grubuna göre daha düşüktür. Bant hücreleri, lenfositler, monositler, nötrofiller, vakuollü monositler ve hipersegmente nötrofillerin oranları gruplar arasında istatistiksel olarak anlamlı farklılıklar göstermektedir. Periferik kan anormallikleri mikrobiyal enfeksiyonlarda, özellikle viral enfeksiyonlarda yaygındır.
Sonuçlar: Bu anormallikler altta yatan patofizyolojik değişikliklere dair içgörüler sağlayabilir. COVID-19 hastalarında trombositlerde ve eritrositlerde anormallik gözlenmemiştir. Ancak kontrollerle karşılaştırıldığında atipik monositler ve nötrofil hipersegmentasyonu COVID-19 hastalarında önemli ölçüde yüksektir.

Anahtar Kelimeler: COVID-19, gebe kadınlar. lenfosit oranı, periferik kan yayması, tam kan sayımı

Introduction

Peripheral blood smear analysis is a cornerstone diagnostic tool in hematology, providing critical insights into the morphology and composition of blood cells (1). In the context of pregnant women with coronavirus disease 2019 (COVID-19), this diagnostic technique assumes heightened significance, given the unique hematologic changes during pregnancy and the additional impact of the viral infection on maternal and fetal health (2).

Pregnancy induces physiological alterations in the hematologic system, including increased plasma volume, dilutional anemia, and leukocytosis, complicating the interpretation of blood smears (3). The advent of COVID-19 introduces further complexities. SARS-CoV-2 infection has been associated with hematologic abnormalities, including lymphopenia, neutrophilia, thrombocytopenia, and atypical lymphocytes (4). These aberrations reflect the body's

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immune response to the virus and are pivotal in prognostication and therapeutic decision-making (4).

In pregnant women with COVID-19, a peripheral blood smear can reveal crucial data informing both maternal and fetal prognosis (5). For instance, severe lymphopenia might indicate a more aggressive disease course (6), necessitating closer monitoring and potentially more intensive therapeutic interventions. Moreover, detecting thrombocytopenia, especially in conjunction with elevated D-dimer levels (7), may suggest a predisposition to thromboembolic events, a recognized complication of COVID-19. This is particularly concerning in pregnancy, where hypercoagulability is already a physiological state, thus amplifying the risk of adverse outcomes such as venous thromboembolism (8).

Furthermore, the presence of fragmented red blood cells or schistocytes (9) on a blood smear could be indicative of microangiopathic hemolytic processes, which, in the setting of COVID-19, may suggest severe complications like disseminated intravascular coagulation or preeclampsia superimposed by viral infection (10). The differentiation of these conditions is crucial, as they have distinct management protocols and implications for maternal and fetal health (8-10).

The clinical significance of peripheral blood smear findings extends beyond immediate therapeutic implications (1). They can also provide prognostic information, guiding the need for intensive care and informing decisions regarding the timing and mode of delivery to optimize maternal and neonatal outcomes (11). In addition, serial blood smear examinations can help monitor the progression of the disease and the effectiveness of interventions, thereby enabling a dynamic and responsive approach to management (11).

In summary, peripheral blood smear analysis in pregnant women with COVID-19 is an invaluable diagnostic modality, offering profound insights into hematologic changes with significant clinical and prognostic implications. Its role in the comprehensive management of these patients underscores the importance of meticulous hematologic evaluation in the context of this complex interplay between pregnancy and viral infection. As the pandemic evolves, continued research into the hematologic manifestations of COVID-19 in pregnancy will be essential to refine diagnostic criteria and therapeutic strategies, ultimately enhancing maternal and fetal health outcomes. Our study aims to elucidate the peripheral smear findings in pregnant women with COVID-19 infection and determine their clinical significance.

Materials And Methods

Study Population

Our study's participants comprised 50 pregnant women diagnosed with COVID-19 presenting to a tertiary healthcare center in Adana, Türkiye, and 50 healthy pregnant women consenting to participate. The control group consists of healthy pregnant participants.

Power Analysis

A power analysis was employed to determine the sample size. The effect size was set at d=0.75, the power (1-β) at 0.90, and the allocation ratio at 1. Consequently, the minimum required sample size was 40 individuals per group.

Study Design and Participants

This is a prospective, controlled study. It included 100 participants diagnosed with COVID-19 between November 2021 and January 2022 at a tertiary facility in Adana in Türkiye. The researchers collected and analyzed the data about all participants.

Exclusion Criteria

Participants refusing to participate in the study,

Individuals outside the 18-45 age range.

Those using acetylsalicylic acid (ASA).

Groups

Group 1: Pregnant women diagnosed with COVID-19.

Group 2: Control group.

Examined Variables

Age, height, weight

Obstetric history (gravidity, parity, abortions, number of living children)

Previous surgeries

Comorbidities

Clinical findings (cough, dyspnea, fever, oxygen saturation)

Medications used

Gestational age

Week of delivery

Mode of delivery

APGAR score of newborns

Neonatal or maternal intensive care requirement

Duration of hospital stay

Peripheral blood smear

Complete blood count parameters

Ethics

Approval was obtained from the local ethics committee (Date and number: 11/11/2021-1623). Participation in the study was voluntary. Informed consent was obtained, stating that the participants' identities would remain confidential. The principles of the Declaration of Helsinki were adhered to throughout all stages of the research.

Statistical Analysis

In descriptive statistics, categorical measurements are presented as counts and percentages, while numerical measurements are expressed as means and standard deviations (and medians where necessary). The Chi-Square tests were employed to compare categorical measurements between groups. The Shapiro-Wilk test was utilized to analyze the normality of the distribution of numerical measurements. If the data conformed to a normal distribution, the Independent Samples T-Test was used for numerical measurements; otherwise, the Mann-Whitney U test was applied. The Statistical Package for Social Sciences for the Windows, version 20.0 software was employed for the statistical analysis of the data (SPSS, IBM Corp., Armonk, NY, USA). A statistical significance level of 0.05 was considered for all tests.

Results

The groups were compared in terms of age, pregnancy week, cough, dyspnea, fever, and oxygen saturation. Significant differences were identified between the groups concerning the data on pregnancy week, cough, dyspnea, and fever. The other variables were similar in both groups. In the control group, none of the participants exhibited cough, dyspnea, or fever symptoms.

The groups were compared in terms of complete blood count parameters. Significant differences were identified between the groups. The values of ferritin, C-reactive protein (CRP), procalcitonin, D-dimer, activated partial thromboplastin time (aPTT), and fibrinogen exhibited significant differences among the groups. These differences were statistically significant. The other parameters, however, were at similar levels across the groups. The CRP, procalcitonin, D-dimer, aPTT, and fibrinogen values were elevated in the COVID-19 group compared to the control group. Conversely, the ferritin level is lower (Tables 1 and 2) (Figure 1).

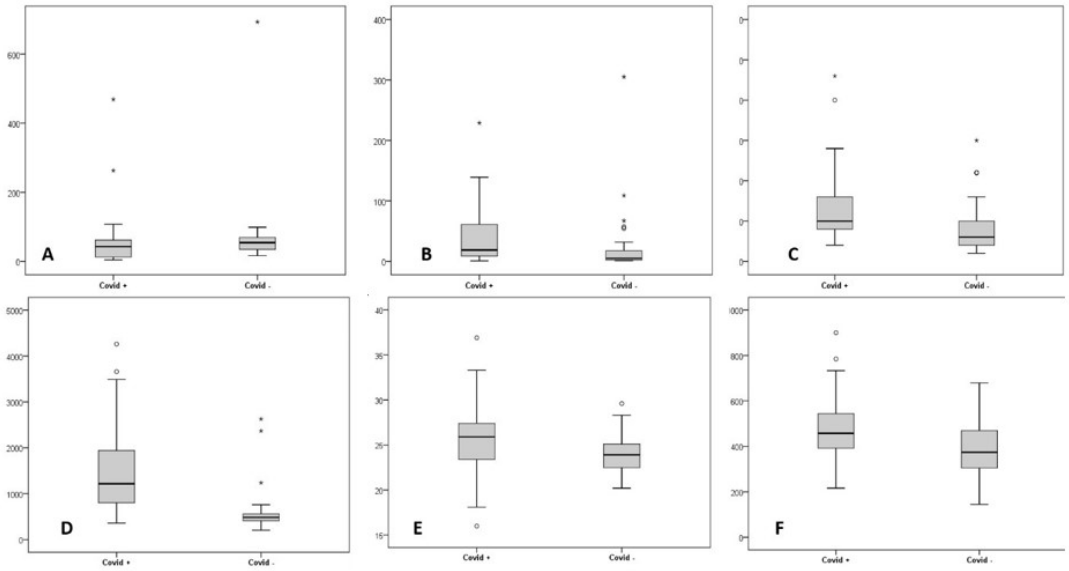

Figure 1. The values of ferritin, CRP, procalcitonin, D-dimer, aPTT, and fibrinogen. A. Ferritin, B. CRP, C. Procalcitonin, D. D-Dimer, E. aPTT, F. Fibrinogen

Table 1. Comparison of gestational weeks, cough, dyspnea, and fever between groups

Groups (Mean±SD)	COVID-19 Patients	Controls	p
Gestational Weeks	30.4±6.9	36.7±4	<0.001
Cough			<0.001
Yes	39 (78%)	0 (0%)	
No	11 (22%)	50 (100%)	
Dyspnea			<0.001
Yes	19 (38%)	0 (0%)	
No	31 (62%)	50 (100%)	
Fever			0.006
Yes	8 (16%)	0 (0%)	
No	42 (84%)	50 (100%)	
O_2 saturation	96.96±2.46	96.96±0.97	1

Table 2. Comparison of complete blood count between groups

	Groups		p
	COVID-19 Patients	Controls	
WBC*	8.8±2.9	9.8±4	0.150
RBC*	3.9±0.6	3.9±0.4	0.938
HGB*	10.9±1.4	10.7±1.6	0.502
PLT*	221.8±84.3	213.1±75.1	0.586
Ferritin**	42.6 (49.3)	54.5 (35.9)	0.025
CRP**	18.7 (53.9)	4.8 (15.8)	<0.001
Procalcitonin**	0.05 (0.04)	0.03 (0.03)	<0.001
Troponin*	4±2.4	3.8±2.4	0.739
D-Dimer**	1215 (1152)	483.5 (153)	<0.001
Prothrombin Time *	11.5±0.7	11.7±0.9	0.264
INR*	0.93±0.06	0.95±0.08	0.172
aPTT*	25.6±3.9	24.1±2.2	0.018
Fibrinogen*	483.2±136.9	392.9±108.5	<0.001

*Mean±SD, **Median. WBC: White blood cell, RBC: Red blood cell, HGB: Hemoglobin; PLT: Platelets; CRP: C-Reactive Protein; INR: International normalized ratio, aPTT: Activated partial thromboplastin time.

Peripheral blood smear results in our study indicate that the lymphocyte ratio in the COVID-19 group is lower compared to the control group, while other values are elevated. The proportions of band cells, lymphocytes, monocytes, neutrophils, vacuolated monocytes, and hypersegmented neutrophils exhibit statistically significant differences between the groups. The groups are similar in terms of Platelet Structure and Erythrocyte Structure. Vacuolated monocyte and hypersegmented neutrophil forms were observed exclusively in the COVID-19 group. The control group did not detect these forms (Table 3) (Figure 2).

Table 3. Findings of peripheral blood smear

	Groups		p
	COVID-19 Patients	Controls	
Band Cells (%)	20.5±4.3	5.7±2.1	<0.001
Lymphocytes (%)	12.7±4.5	37.7±6.9	<0.001
Monocytes (%)	7.3±2.6	5.4±2.1	<0.001
Neutrophils (%)	60±5.8	56.3±7.2	0.006
Platelet Structure			
Normal	36 (72%)	38 (76%)	0.245
Large	1 (2%)	4 (8%)	
Small	13 (26%)	8 (16%)	
Erythrocyte Structure			
Normochromic Normocytic	46 (92%)	47 (94%)	0.999
Hypochromic Microcytic	4 (8%)	3 (6%)	
Monocyte Structure			
Vacuolated	32 (64%)	0 (0%)	<0.001
Normal	18 (36%)	50 (100%)	
Neutrophil Structure			
Hypersegmentation	17 (34%)	0 (0%)	<0.001
Normal	33 (66%)	50 (100%)	

Discussion

In our study, the groups were compared based on complaints of cough, shortness of breath, fever, and oxygen saturation measurements. Significant differences were detected between the groups concerning the cough, shortness of breath, and fever data. Cough, shortness of breath, and fever are among the most common complaints of COVID-19. According to the analysis of studies, fever is observed in 81.2%, cough in 58.5%, and dyspnea in 26.1% of COVID-19 patients (12).

None of the participants in the control group exhibited symptoms of cough, shortness of breath, or fever. Oxygen saturation was similar in both groups, with values in the COVID-19 and control groups being relatively close to each other. This finding contradicts the information available in the literature (13-15).

Respiratory involvement is joint in COVID-19 (16). Different levels of low oxygen saturation can be detected, including clinical, subclinical, or asymptomatic presentations (17). The pathophysiological mechanisms of low oxygen saturation are multifactorial. The development of localized inflammatory damage progressing to interstitial lung edema and microvascular thrombosis are among the most critical mechanisms. Low oxygen saturation tends to be accompanied by impaired vasoregulation, dysregulated lung perfusion, and hypercoagulability. It is considered responsible for rapid clinical deterioration and mortality (18).

Some studies have found that the oxygen saturation values of COVID-19 patients correlate with their short-term outcomes and the severity of the disease (14). The situation detected in our study may be related to the severity of the diseases in our participants. The high oxygen saturation is correlated with the severity of the disease. The number of participants experiencing severe infection might be low, which could result in similar oxygen saturation values across the groups.

Significant differences in complete blood count

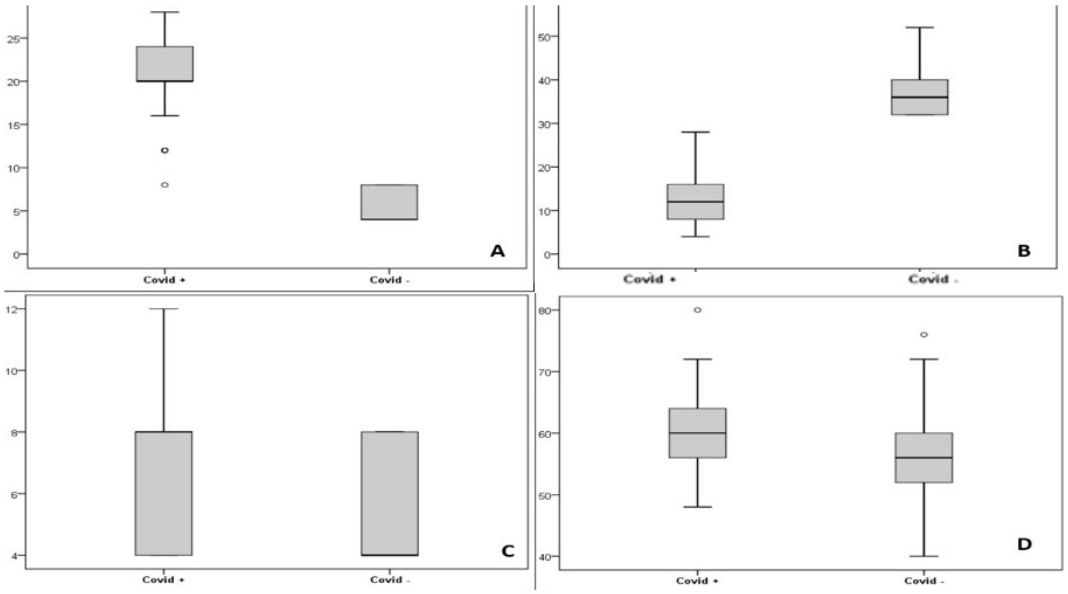

Figure 2. A. Band cells, B. Lymphocytes, C. Monocytes, D. Neutrophils

parameters were identified between the groups. Ferritin, CRP, procalcitonin, D-Dimer, aPTT, and fibrinogen levels demonstrated statistically significant variations among the groups. However, other parameters remained at similar levels across the groups. In the COVID-19 group, CRP, procalcitonin, D-dimer, aPTT, and fibrinogen levels were elevated compared to the control group, while ferritin levels were lower.

Laboratory abnormalities identified in COVID-19 include lymphopenia in approximately 50% of patients, leukopenia, eosinopenia, neutrophilia, and monocytosis (19-21). In the literature, lymphopenia is reported as the most significant hematological finding associated with COVID-19, known to indicate the severity of the disease (22). Various hypotheses have been proposed regarding the mechanism of lymphopenia. These include viral toxicity due to ACE-2 (Angiotensin-converting enzyme) receptor expression, lymphocyte apoptosis, and metabolic products causing lymphocyte inhibition (23).

In one study reporting absolute lymphopenia in 15% of participants, a decrease in absolute T cell count was detected in 90% of participants using flow cytometry analysis, and all participants with decreased T cell counts required mechanical ventilation (24). Disease activity is associated with changes in lymphocyte subpopulations in COVID-19 patients. Flow cytometry is often used as a sensitive method to detect these changes. A similar study reported that no specific complete blood count abnormalities were detected in COVID-19 cases compared with controls (25).

Significant differences were identified among the groups concerning complete blood count parameters.

In one study, ferritin levels were significantly higher in moderate and severe COVID-19 infections compared to mild infections. In the same study, ferritin levels were higher in those with complications, compared to those without. In addition, median ferritin levels were increased in those treated in intensive care units (26). In our study, ferritin levels of COVID-19-positive patients were lower than those of negative patients. This seemingly contradictory situation is due to the analysis of different data in the two studies.

The pathogenesis of COVID-19 is complex (27). The virus's entry into the body triggers the release of various cytokines and chemokines, initiating an adaptive immune response characterized by lymphopenia and neutrophilia (28). The increase in cytokines exacerbates the body's systemic inflammation (29). During this process, inflammatory biomarkers such as Interleukin-6, Lactate dehydrogenase, CRP, D-Dimer, and Ferritin rise; these biomarkers predict disease severity and response to treatment (30-32). Aside from

Ferritin, the data obtained from our study support these findings.

Only a limited number of studies in the literature investigating peripheral smear findings in COVID-19. One study on this subject reported the presence of monolobed neutrophils, neutrophilic granulation, abnormal platelet morphology, and apoptotic cells (33). The results of this study indicated that the abnormalities in neutrophils resolved following antiviral treatment (33).

The results of our study indicate the presence of hypersegmentation in neutrophils in 34% of COVID-19 cases. In this respect, our findings are consistent with the study above. Neutrophil hypersegmentation can be observed in anemic conditions such as vitamin B12 and iron deficiency, chemotherapy toxicity, and uremia (34-36). In our study, no other condition in the COVID-19 group could cause neutrophil hypersegmentation. In a study examining the peripheral smears of COVID-19 cases, hypersegmented neutrophils were detected in 84% (37). The same study reported the presence of giant platelets and atypical lymphocytes in all cases. The frequency of hypersegmented neutrophils in the control group was 25%, and no atypical lymphocytes or giant platelets were observed (37). In contrast to this study, the frequency of neutrophil hypersegmentation identified in our study was lower. Additionally, none of the controls exhibited hypersegmentation.

Peripheral blood abnormalities are prevalent in microbial infections, particularly in viral infections. These abnormalities can provide insights into the underlying pathophysiological changes. In patients with COVID-19, no abnormalities have been observed in platelets and erythrocytes. However, compared to controls, atypical monocytes and neutrophil hypersegmentation are significantly elevated in COVID-19 patients.

Our study has certain limitations. It is essential to evaluate our findings and their applicability critically. Firstly, although the sample size represents the population under investigation, ethnic groups underrepresented or populations with various comorbidities have not been considered. COVID-19 symptoms may manifest differently in these populations, potentially influencing the results. Additionally, our study focused on hospitalized patients, which may lead to inaccuracies when generalizing the findings to individuals with mild or asymptomatic disease courses. Another limitation lies in the rapidly evolving nature of COVID-19. The emergence of new variants and changes in public health interventions may affect the progression of the disease and the efficacy of treatments. Consequently, some of the study's outcomes may become less applicable to future outbreaks.

Data availability statement

The data are available upon reasonable request from the corresponding author.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Ethics Committee Approval

Ethical approvals were obtained from the ethics committees of the researchers' institutions. Participation in the study was voluntary. Informed consent was obtained, stating that the participants' identities would remain confidential. The principles of the Declaration of Helsinki were adhered to throughout all stages of the research.

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Declaration of Interests

The authors have no conflicts of interest to declare.

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References

1.Chase ML, Drews R, Zumberg MS, Ellis LR, Reid EG, Gerds AT, et al. Consensus recommendations on peripheral blood smear review: defining curricular standards and fellow competency. Blood Adv. 2023;7(13):3244–52.

2.Surekha M V, Suneetha N, Balakrishna N, Putcha UK, Satyanarayana K, Geddam JJB, et al. Impact of COVID-19 during pregnancy on placental pathology, maternal and neonatal outcome - A cross-sectional study on anemic term pregnant women from a tertiary care hospital in southern India. Front Endocrinol (Lausanne). 2023;14:1092104.

3.Chandra S, Tripathi AK, Mishra S, Amzarul M, Vaish AK. Physiological changes in hematological parameters during pregnancy. Indian J Hematol Blood Transfus Off J Indian Soc Hematol Blood Transfus. 2012;28(3):144–6.

4.Gajendra S. Spectrum of hematological changes in COVID-19. Am J Blood Res. 2022;12(1):43–53.

5. Erol Koç EM, Fındık RB, Akkaya H, Karadağ I, Tokalıoğlu EÖ,

Tekin ÖM. Comparison of hematological parameters and perinatal outcomes between COVID-19 pregnancies and healthy pregnancy cohort. 2021;49(2):141–7.

6.Ghizlane EA, Manal M, Abderrahim EK, Abdelilah E, Mohammed M, Rajae A, et al. Lymphopenia in Covid-19: A single-center retrospective study of 589 cases. Ann Med Surg. 2021;69:102816.

7. Nasif WA, El-Moursy Ali AS, Hasan Mukhtar M, Alhuzali AMH, Yahya Alnashri YA, Ahmed Gadah ZI, et al. Elucidating the Correlation of D-Dimer Levels with COVID-19 Severity: A Scoping Review. Anemia. 2022;2022:9104209.

8. Singhania N, Bansal S, Nimmatoori DP, Ejaz AA, McCullough PA, Singhania G. Current Overview on Hypercoagulability in COVID-19. Am J Cardiovasc Drugs [Internet]. 2020;20(5):393–403.

9. Elemam NM, Talaat IM, Bayoumi FA, Zein D, Georgy R, Altamimi A, et al. Peripheral blood cell anomalies in COVID-19 patients in the United Arab Emirates: A single-centered study. Front Med. 2022;9:1072427.

10. Aminimoghaddam S, Afrooz N, Nasiri S, Motaghi Nejad O, Mahmoudzadeh F. A COVID-19 pregnant patient with thrombotic thrombocytopenic purpura: A case report. J Med Case Rep. 2021;15(1):104.

11.Patel P, Balanchivadze N. Hematologic Findings in Pregnancy: A Guide for the Internist. Cureus. 2021;13(5):e15149.

12. Alimohamadi Y, Sepandi M, Taghdir M, Hosamirudsari H. Determine the most common clinical symptoms in COVID-19 patients: a systematic review and meta-analysis. J Prev Med Hyg. 2020;61(3):E304–12.

13.Cajanding R. Oxygen use and saturation targets in patients with COVID-19: Are we giving too much or aiming too low? Nurs Crit Care. 2022;27(2):282–5.

14. Inada-Kim M, Chmiel FP, Boniface M, Burns D, Pocock H, Black J, et al. Validation of oxygen saturations measured in the community by emergency medical services as a marker of clinical deterioration in patients with confirmed COVID-19: a retrospective cohort study. BMJ Open. 2024;14(1):e067378.

15.Galwankar SC, Paladino L, Gaieski DF, Nanayakkara KDPWB, Somma S Di, Grover J, et al. Management Algorithm for Subclinical Hypoxemia in Coronavirus Disease-2019 Patients: Intercepting the "Silent Killer". J Emerg Trauma Shock. 2020;13(2):110–3.

16.You J-S, Faner R, Sibila O, Sellarés J. COVID-19 and lung involvement. Vol. 17, Handbook of Systemic Autoimmune Diseases. 2022. p. 189–211.

17. Mehta OP, Bhandari P, Raut A, Kacimi SEO, Huy NT. Coronavirus Disease (COVID-19): Comprehensive Review of Clinical Presentation. Front public Heal. 2020;8:582932.

18. Swenson KE, Hardin CC. Pathophysiology of Hypoxemia in COVID-19 Lung Disease. Clin Chest Med. 2023;44(2):239–48.

19. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395(10223):497–506.

20. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet (London, England). 2020;395(10223):507–13.

21. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623.

22. Toori KU, Qureshi MA, Chaudhry A. Lymphopenia: A useful predictor of COVID-19 disease severity and mortality. Pakistan J Med Sci. 2021;37(7):1984–8.

23. Shen X-R, Geng R, Li Q, Chen Y, Li S-F, Wang Q, et al. ACE2-independent infection of T lymphocytes by SARS-CoV-2. Signal Transduct Target Ther. 2022;7(1):83.

24. Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang Y-Q, et al. Lymphopenia predicts disease severity of COVID-19: A descriptive and predictive study. Vol. 5, Signal transduction and targeted therapy. England; 2020. p. 33.

25. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, et al. Characteristics of Peripheral Lymphocyte Subset Alteration in COVID-19 Pneumonia. J Infect Dis. 2020;221(11):1762–9.

26. Kurian SJ, Mathews SP, Paul A, Viswam SK, Kaniyoor Nagri S, Miraj SS, et al. Association of serum ferritin with severity and clinical outcome in COVID-19 patients: An observational study in a tertiary healthcare facility. Clin Epidemiol Glob Heal. 2023 May-Jun;21:101295.

27. Bal A, Agrawal R, Vaideeswar P, Arava S, Jain A. COVID-19: An up-to-date review - from morphology to pathogenesis. Indian J Pathol Microbiol. 2020;63(3):358–66.

28. Catanzaro M, Fagiani F, Racchi M, Corsini E, Govoni S, Lanni C. Immune response in COVID-19: addressing a pharmacological challenge by targeting pathways triggered by SARS-CoV-2. Signal Transduct Target Ther. 2020;5(1):84.

29. D'Ardes D, Boccatonda A, Rossi I, Guagnano MT, Santilli F, Cipollone F, et al. COVID-19 and RAS: Unravelling an Unclear Relationship. Int J Mol Sci. 2020;21(8):3003.

30. Guan W-J, Ni Z-Y, Hu Y, Liang W-H, Ou C-Q, He J-X, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708–20.

31. Yitbarek GY, Walle Ayehu G, Asnakew S, Ayele FY, Bariso Gare M, Mulu AT, et al. The role of C-reactive protein in predicting the severity of COVID-19 disease: A systematic review. SAGE open Med. 2021;9:20503121211050756.

32. Zhao Y, Qin L, Zhang P, Li K, Liang L, Sun J, et al. Longitudinal COVID-19 profiling associates IL-1RA and IL-10 with disease severity and RANTES with mild disease. JCI insight. 2020;5(13): e139834.

33. Zini G, Bellesi S, Ramundo F, d'Onofrio G. Morphological anomalies of circulating blood cells in COVID-19. Am J Hematol. 2020;95(7):870–2.

34. Adewoyin AS, Nwogoh B. Peripheral blood film - a review. Ann Ibadan Postgrad Med. 2014;12(2):71–9.

35.Okazaki Y, Watabu T, Endo K, Oiwa H. Hypersegmented Neutrophils in Methotrexate Toxicity. Intern Med. 2018;57(7):1055–6.

36. Abuga KM, Muriuki JM, Williams TN, Atkinson SH. How Severe Anaemia Might Influence the Risk of Invasive Bacterial Infections in African Children. Int J Mol Sci. 2020;21(18):6976.

37. Salib C, Khattar P, Cheng J, Teruya-Feldstein J. Atypical Peripheral Blood Cell Morphology in COVID-19 (Sars-CoV-2) Patients from Mount Sinai Health System in New York City. Blood. 2020;136:26–7.

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ORIGINAL ARTICLE

Demographic Characteristics and Etiological Distributions of Poisoning Cases Admitted to Pediatric Emergency Clinic: A Retrospective Cross-Sectional Study

Çocuk Acil Kliniğine Başvuran Zehirlenme Vakalarının Demografik Özellikleri ve Etiyolojik Dağılımları: Retrospektif Kesitsel Çalışma

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ABSTRACT

Aim: Poisoning, defined as exposure to harmful substances leading to organ dysfunction, is a prevalent global health concern, particularly affecting children under the age of five. Understanding the demographics and etiological distributions of poisoning cases is crucial for effective diagnosis. We aimed to ascertain the demographic characteristics and etiological distributions of individuals presenting to the pediatric emergency due to acute poisoning.
Methods: This retrospective study evaluated the clinical data of patients aged 0-18 years admitted to the Pediatric Emergency Clinic at Konya Beyhekim Training and Research Hospital for poisoning between January 1st, 2023, and September 15th, 2024.
Results: Among the patients, 229 (88.4%) were asymptomatic, while 30 (11.6%) exhibited one or more symptoms (Median age: 3.9 years, interquartile range: 12 years). In cases of accidental poisoning, the most frequently ingested substances were caustic or corrosive agents (55 cases, 25.7%) and analgesic-antipyretic medications (36 cases, 16.8%). Gender-based comparisons revealed that the frequency of poisoning due to pharmacological agents was significantly higher in females (odds ratio [OR]: 2.837, 95% CI: 1.682-4.785, p<0.0001). Among the age groups, those aged 2-6 years showed a significantly higher prevalence of pharmacotoxic poisonings compared to other groups (p < 0.0001). Seasonal analysis indicated that summer had the highest occurrence of significant increases in cases (60 out of 162, 37%). Pharmacological agents, notably analgesics, were more frequently involved in poisonings, with a higher prevalence in females and preschool children. In contrast, non-pharmacological poisoning cases were more common in males and infants, particularly attributed to caustic substances.
Conclusions: This study highlights the significant prevalence of acute poisoning among children, particularly in preschool-aged individuals, with a notable increase in cases during the summer months. The majority of poisoning incidents were accidental and predominantly involved pharmacological agents, especially analgesics and antipyretics, while intentional poisonings were more common among female adolescents.

Keywords: Analgesic, child, infant, poisoning, season

ÖZ

Arka Plan/Amaçlar: Zehirlenme, zararlı maddelere maruz kalmanın organ disfonksiyonuna yol açması olarak tanımlanmakta olup, özellikle beş yaş altındaki çocukları etkileyen yaygın bir küresel sağlık sorunudur. Zehirlenme vakalarının demografik özelliklerini ve etiyolojik dağılımlarını anlamak, etkili tanı ve önleme stratejileri için kritik öneme sahiptir. Bu çalışmanın amacı, akut zehirlenme nedeniyle pediatrik acil servise başvuran bireylerin demografik özelliklerini ve etiyolojik dağılımlarını belirlemektir.
Yöntemler: Bu retrospektif çalışma, 1 Ocak 2023 ile 15 Eylül 2024 tarihleri arasında Konya Beyhekim Eğitim ve Araştırma Hastanesi Pediatrik Acil Kliniği'ne zehirlenme nedeniyle başvuran 0-18 yaş arası hastaların klinik verilerini değerlendirmiştir.
Bulgular: Hastaların medyan yaşı 3,9 yıl olup, interkuartil aralığı 12 yıldır. Hastaların %88,4'ü asemptomatik, %11,6'sı ise bir veya daha fazla belirti göstermiştir. Kazara zehirlenme vakalarında en sık alınan maddeler koroziv veya kostik ajanlar (55 vaka, %25,7) ve analjezik-antipiretik ilaçlar (36 vaka, %16,8) olmuştur. Cinsiyete dayalı karşılaştırmalar, farmakolojik ajanlardan kaynaklanan zehirlenme sıklığının kızlarda önemli ölçüde daha yüksek olduğunu ortaya koymuştur (Odds oranı [OR]: 2,837, %95 Güven Aralığı: 1.682-4.785, p <0.0001). Yaş grupları arasında, 2-6 yaş arası çocukların diğer gruplara kıyasla farmakotoksik zehirlenmelere maruz kalma sıklığı daha yüksektir (p <0.0001). Mevsimsel analiz, yaz aylarında vakalarda belirgin bir artış olduğunu göstermektedir (162 vaka arasından 60, %37). Farmakolojik ajanlar, özellikle analjezikler, zehirlenmelerde daha sık yer almakta olup, bu durum kız çocukları ve okul öncesi çocuklarda daha yaygındır. Farmakolojik olmayan zehirlenmeler ise erkek çocuklar ve bebeklerde daha sık görülmüş, bu vakalar özellikle kostik maddelere bağlı olarak tanımlanmıştır.
Sonuçlar: Bu çalışma, çocuklar arasında akut zehirlenmenin yüksek prevalansını, özellikle okul öncesi yaş grubunda ve yaz aylarında vaka sayısındaki belirgin artışı vurgulamaktadır. Zehirlenme olaylarının çoğu kazara gerçekleşmiş olup, genellikle analjezik ve antipiretik gibi farmakolojik ajanlarla ilişkilendirilmiştir; bunlara ek olarak, kasıtlı zehirlenmelerin kız ergenler arasında daha yaygın olduğu gözlemlenmiştir.

Anahtar Kelimeler: Analjezik, bebek, çocuk, mevsim, zehirlenme

Introduction

Poisoning is generally defined as exposure to a substance resulting in signs and symptoms of organ dysfunction (1). Acute poisoning is notably prevalent in children, presenting within 24-hour exposure, and remains a significant global health issue. It is among the leading causes of pediatric emergency department

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visits, contributing to both morbidity and mortality. The majority of these cases occur in children under the age of five (2).

In Türkiye, poisoning accounts for approximately 0.7-5% of pediatric emergency admissions (3). Such incidents often arise from the ingestion of medications and chemical substances. Notably, accidental poisoning is more frequently reported in early childhood, whereas intentional poisoning, typically associated with suicidal behaviors, is more common among adolescents. Education plays a vital role in preventing accidental poisonings (4).

The etiology of poisoning varies by country and across different socio-economic regions within the same nation. Understanding the types, characteristics, and severity of poisonings in specific areas is crucial for diagnosis, treatment, and the implementation of preventive measures (1). Previous studies have evaluated poisoning cases in pediatric emergency departments in Konya, identifying drug-related toxicity as the most common causal factor (5). Another study highlighted corrosive agents, followed by medications, as the primary types of poisonings observed (6). Our study aims to ascertain the demographic characteristics and etiological distributions of individuals presenting to the pediatric emergency department due to acute poisoning.

Materials And Methods

The study design was approved by the Karatay University Ethics Committee under approval number 2024/006, dated 31/10/2024. This retrospective study evaluated the clinical data of patients aged 0 to 18 years admitted to the Pediatric Emergency Clinic at Konya Beyhekim Training and Research Hospital for poisoning between January 1st, 2023, and September 15th, 2024. Inclusion criteria were based on a diagnosis of poisoning and the availability of complete clinical records, while patients with no prior history of poisoning or incomplete documentation were excluded.

Data were extracted from the automated information system of the hospital and included variables such as admission dates, demographic details, clinical signs and symptoms, clinical progression, treatment methods, and particulars regarding the nature of the poisoning and exposure circumstances. Cases of poisoning were classified into three distinct categories: pharmacological agents, non-pharmacological agents, and other substances as reported in a previous study (6). Additionally, patients were organized into four age groups: 0-2 years (infants), >2-6 years (preschool children), >6-12 years (school-aged children), and >12-18 years (adolescents). The resulting findings were subsequently analyzed by gender, age group, month, and season of admission.

Statistical Analysis

Numerical data were presented as counts and percentages. The Shapiro-Wilk and Kolmogorov-Smirnov tests were employed to assess the normality of distribution. Given that the parametric data did not conform to a normal distribution, they were expressed as median values with interquartile ranges [IQR]. Comparisons of non-normally distributed data were performed using the Mann-Whitney U test. The chi-square test was applied for binary comparisons of categorical data. A p-value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS), version 21.0 for the Windows software (IBM Corp., Armonk, NY, USA).

Results

Throughout the study period, 259 patients presented to the pediatric emergency clinic with a diagnosis of poisoning. Among these patients, 127 (49%) were male and 132 (51%) were female, resulting in a female-to-male ratio of 1.04:1. The overall median age of the patients was 3.9 years, with an IQR of 12 years, and ages varied from 0.6 to 17.9 years. For males, the median age was recorded at 3.2 years (IQR: 3.9 years; minimum-maximum: 0.6-17.9 years), whereas females had a higher median age of 5.5 years (IQR: 13.05 years; minimum-maximum: 1.1-17.9 years). The comparison of median ages between genders demonstrated a statistically significant difference, with females being older on average ($p<0.0001$). When categorized by age groups, there were 66 patients (25.5%) aged 0-2 years, 101 patients (39%) aged over two to under six years, 19 patients (7.3%) aged 6-12 years, and 73 patients (28.2%) aged over 12 to under 18 years. Monthly analysis revealed that presentations included 24 patients (9.3%) in January, 13 (5%) in February, 19 (7.3%) in March, 22 (8.5%) in April, 33 (12.7%) in May, 29 (11.2%) in June, 41 (15.8%) in July, 25 (9.7%) in August, nine (3.5%) in September, 10 (3.9%) in October, 10 (3.9%) in November, and 24 (9.3%) in December.

The seasonal distribution of poisoning cases revealed that the majority of presentations occurred during the summer months, with 97 cases (37.5%), followed by spring with 76 cases (29.3%), winter with 60 cases

(23.2%), and autumn with 26 cases (10%). Among the patients, 229 (88.4%) were asymptomatic, while 30 (11.6%) exhibited one or more symptoms. Specific symptoms recorded included abdominal pain in eight patients, nausea or vomiting in 21, difficulty swallowing in two, altered consciousness in seven, dizziness in seven, cramps in one, cough in one, palpitations in three, and coexisting psychiatric disorders in 13 patients. Notably, among those with psychiatric disorders, 11 (84.6%) were female and two (15.4%) were male, all within the 12-18 age group. The median time to hospital presentation following poisoning was 56 minutes (IQR, 60 minutes; range 7-593 minutes). When examining the hours of admission for children with poisoning to the pediatric emergency department, it was found that 113 cases (43.6%) occurred between 08:00 am and 04:00 pm, 121 cases (46.7%) occurred between 04:00 pm and 00:00, and 25 cases (9.7%) occurred between 00:00 and 08:00 am.

Regarding the classification of poisoning cases, 45 (17.4%) were identified as intentional, while 214 (82.6%) were categorized as accidental. Gender analysis indicated a significantly higher incidence of intentional poisoning among females (odds ratio [OR]: 5.793, 95% confidence interval [CI]: 2.576-13.028, p<0.0001). Furthermore, the age group of 12 to 18 years exhibited a significantly elevated rate of intentional poisoning compared to other age groups (p<0.0001). Among accidental poisoning cases, 66 patients (30.8%) were aged 0-2 years, 101 (47.2%) were aged over two to under six years, 18 (8.4%) were aged 6-12 years, and 29 (13.6%) were aged between over 12 and under 18 years. When examining gender distribution, one male patient (12.5%) with intentional poisoning was in the 6-12 age group, while seven (87.5%) were in the 12-18 age group. All 37 female patients with intentional poisoning were also in the 12-18 age group. Of the 45 cases of intentional poisoning, one (2.2%) was in the 6-12 age group and 44 (97.8%) were in the 12-18 age group, with no cases identified in those under 6 years of age. A significant difference was observed between age groups regarding intentional poisoning (p<0.0001).

In cases of accidental poisoning, the most frequently ingested substances were caustic or corrosive agents (55 cases, 25.7%) and analgesic-antipyretic medications (36 cases, 16.8%). In contrast, among patients with intentional poisoning, all but two cases were related to medication ingestion, with the most common cause being the intake of multiple medications (17 cases, 37.8%).

Among the total patient population, vital risk was identified in 144 (55.6%) patients, and forensic reports were prepared for 253 (97.7%) patients. Analysis of causative agents revealed that 162 cases (62.5%) involved pharmacological substances, 78 (30.1%) involved non-pharmacological agents, and 19 (7.3%) were attributable to other causes (Table 1). In gender-based comparisons, the frequency of poisoning due to pharmacological agents was significantly higher in females (OR: 2.837, 95% CI: 1.682-4.785, p<0.0001). Among the age groups, those aged >2-6 years showed a significantly higher prevalence of pharmacological poisonings compared to other groups (p<0.0001). In terms of specific pharmacological agents, incidents were most frequently associated with analgesic-antipyretics, polypharmacy, antipsychotics, and antidepressants. Monthly analysis indicated that July had the highest number of pharmacological poisonings (23/162, 14.2%). Seasonal analysis showed that summer contained the highest occurrences of pharmacological poisonings (60/162, 37%). However, no significant seasonal difference in pharmacological poisoning rates was identified (p>0.05).

Table 1. Distribution of poisoning agents

Pharmacological factors	**n**	**%**
Analgesics-Antipyretics	40	15.4
Multiple Drug Intake	25	9.7
Antipsychotics	18	6.9
Antidepressants	16	6.2
Vitamins	10	3.9
Gastrointestinal Drugs	10	3.9
Hormonal Preparations	8	3.1
Asthma Medications	6	2.3
Antihistamines	4	1.5
Antiarrhythmics	3	1.2
Iron Supplements	3	1.2
Antibiotic	3	1.2
Antivirals	2	0.8
Psychostimulant	2	0.8
Anticholinergics	2	0.8
Oral Antidiabetics	2	0.8
Zinc	1	0.4
Antiparkinsonian Medications	1	0.4
Colchicine	1	0.4
Myasthenia Gravis Medication	1	0.4
Aspirin	1	0.4
Antiepileptic	1	0.4
Muscle Relaxants	1	0.4
Antihypertensives	1	0.4
Non-Pharmacological Factors		

Caustic/Corrosive Substances	56	21.6
Hydrocarbons	7	2.7
Alcohols (Ethanol/Methanol)	4	1.6
Insecticides	2	0.8
Carbon Monoxide	2	0.8
Detergents	1	0.4
Antifreeze	1	0.4
Mercury	1	0.4
Naphthalene	1	0.4
Organophosphates	1	0.4
Thinners	2	0.8
Others	**19**	**7.3**
Total	**259**	**100**

In terms of gender comparison, instances of poisoning due to non-pharmacological agents were found to be significantly higher in males (OR: 0.352, 95% CI: 0.209-0.594, p<0.0001). When analyzed by age groups, the frequency of poisoning from non-pharmacological sources was significantly elevated in the under 2 years category (39/97, 40.2%) compared to other age groups (p<0.0001).

The most frequently identified non-pharmacological agents contributing to poisoning included caustic/corrosive substances, hydrocarbons, alcohol, and insecticides. Monthly data indicated that the highest frequency of non-pharmacological poisoning occurred in July (18/78, 23%). Seasonal analysis further revealed that summer showed the peak occurrence of non-pharmacological poisonings (37/78, 47.4%), although no statistically significant seasonal differences were found (p>0.05). Specifically, poisoning cases related to caustic/corrosive substances were most commonly reported in July (10/56, 17.9%) and were predominantly observed during the summer season (22/56, 39.3%).

Among all patients, a toxicology consultation was sought for 251 individuals (96.9%). Additionally, 85 patients (32.8%) underwent gastric lavage, while 98 patients (37.8%) received activated charcoal treatment.

Discussion

The findings from our study reveal that the majority of patients presenting with poisoning diagnoses were preschool children, with a notable increase in cases occurring in July during the summer months. Accidentally caused poisonings were identified as the most prevalent reason for these presentations. Furthermore, instances of intentional poisoning were found to be significantly higher among females and adolescents. Our analysis indicated that poisonings related to pharmacological agents occurred at a rate twofold higher than those associated with non-pharmacological substances. Notably, poisonings due to pharmacological agents were particularly elevated in preschool children and females. Within this category, analgesic and antipyretic medications emerged as the leading drugs. In contrast, non-pharmacological poisonings were notably higher in males and infants, with caustic and corrosive substances being the primary responsible agents. These insights underscore the need for targeted prevention strategies and educational efforts aimed at reducing the frequency of poisoning in vulnerable populations, particularly during the summer months.

The literature on the gender distribution of children presenting to emergency departments for poisoning reveals notable variability. A study in India identified a male-to-female ratio of 1.32:1 among pediatric poisoning cases (7). In contrast, a more recent report from the same region found a balanced ratio between females to males (8). An earlier investigation in Türkiye documented a male-to-female ratio of 1.39 (9), whereas another study from Türkiye noted comparable rates between genders (10). Additionally, a previous study in Konya found a ratio of 1.3 (5). Our findings show a gender distribution in poisoning cases aligning closely with these studies, suggesting that the proportions of males and females presenting to emergency departments are relatively equal. This consistency across different geographical contexts implies that while cultural and socio-demographic factors might shape the patterns of pediatric poisoning, they do not seem to significantly affect gender representation in emergency cases. Furthermore, a study conducted in India indicated that the average age of poisoned children was significantly higher in females compared to males (11). In line with this observation, our research similarly found that male patients were significantly younger than their female counterparts. These results underscore the importance of considering both age and gender in the assessment of children presenting with poisoning, as these factors may play a crucial role in understanding the epidemiology of such incidents.

Previous studies have demonstrated that most children presenting to emergency departments for poisoning do so within a few hours of exposure. For instance, Lee et al. (12) indicated that a significant proportion of pediatric patients arrived at the pediatric emergency department shortly after ingestion. Similarly, Dağ et al. (13) found that nearly two-thirds of poisoning cases

were reported within the first-hour post-exposure. The average time from poisoning to presentation was reported as 89 minutes in a study conducted by Yorulmaz et al. (5), with a range of 5 to 600 minutes. In our study, the time interval ranged from a minimum of 5 minutes to a maximum of 593 minutes, with a median of 56 minutes, aligning closely with findings from prior research. In the same study (5), the timing of pediatric emergency department visits due to poisoning was analyzed, revealing that 35.1% of cases occurred during daytime hours, while 52.6% occurred in the evening and 12.3% at night. Our findings align closely with this earlier work; we observed that 43.6% of presentations took place during the day, 46.7% in the evening, and 9.7% at night.

As established in earlier investigations, children may exhibit a range of symptoms after poisoning, although some may present asymptomatically. In a previous study conducted in Konya, it was noted that one-third of poisoned children exhibited no symptoms (5). The most common symptoms identified in that study were nausea and vomiting. Conversely, a recent analysis revealed that among poisoned children, 73.8% were asymptomatic, while symptomatic cases predominantly displayed gastrointestinal symptoms (13). In our findings, 88.4% of the poisoned children were asymptomatic, with only 8.1% exhibiting symptoms such as nausea and vomiting.

Accidental poisoning remains the most prevalent form of toxicity in children, particularly among those aged 5 months to 12 years, during which they display increased oral exploration and a limited grasp of potential dangers. This age group, especially infants and toddlers, is particularly at risk due to their developmental stage and susceptibility to toxic substances, often attracted by appealing packaging and enticing flavors. While the highest rates of accidental poisoning occur in children under 5, intentional poisoning incidents tend to rise during adolescence. Contributing factors include inadequate supervision and negligent behaviors exhibited by older family members (14). A study conducted in China analyzing the age distribution of 1,755 children with acute poisoning found that 34.6% were in early childhood and 37.3% were of preschool age (15). In Brazil, a study revealed that 48.7% of children presenting with poisoning were in the 1-4 age group, indicating a notable prevalence of incidents within this demographic (16). An Italian study by Berta et al. (17) identified that 72.9% of poisoning cases occurred in children aged 1-4 years. Additionally, Sahin et al. reported that 65.2% of children presenting with poisoning were younger than five (18). Our findings are in line with this literature, as we found that 64.5% of the reported poisoning cases involved children aged under 6, all of which were classified as accidental incidents. This evidence highlights the critical need for preventative measures across various age groups to mitigate the risks associated with pediatric poisoning.

Seasonality and monthly variations in pediatric emergency visits due to poisoning have also been documented in previous studies. In China, it was noted that poisonings predominantly occurred in the spring, suggesting that regional seasonal differences may influence incidence rates (15). A study in Egypt indicated that the summer and spring months recorded the highest incidence of pediatric poisonings (19). Furthermore, Sahin et al. found that poisoning cases peaked in January during the winter months (18). In a study conducted in Konya, the majority of pediatric poisonings were observed in the summer and spring (5). Moreover, previous research from Konya highlighted that non-pharmacological corrosive substances were mainly associated with poisonings in the spring and autumn (6). In our study, the most significant number of presentations to the pediatric emergency department occurred in July, specifically during the summer months, for both pharmacological and non-pharmacological agents. These findings emphasize the importance of considering regional characteristics when addressing the epidemiology of pediatric poisoning.

Poisoning in children predominantly occurs through oral ingestion, although other routes, such as inhalation, are also recognized. Öner et al. reported an oral poisoning rate of 97.3% among pediatric cases (20). Similarly, Dağ et al. found an oral ingestion rate of 97%, with inhalation accounting for 2.8% of cases (13). In our study, the rate of oral ingestion was even higher, at 99.2%, with only two patients (0.8%) diagnosed with inhalation-related carbon monoxide poisoning.

A multicenter study by Mintegi et al. reported that 68.5% of pediatric emergency visits for poisoning were due to accidental exposure, while intentional poisoning accounted for 13.8% (21). A recent study in Istanbul found a similarly high rate of accidental poisoning at 83.8%, with suicide attempts comprising 13.6% of cases (13). Our findings corroborate these results, as we identified accidental poisoning in 82.6% of cases, while intentional poisoning was present in 17.4%. In the context of adolescent suicide,

medication overdoses represent the most frequently employed method. Studies indicate that girls exhibit higher rates of suicide attempts, often utilizing less lethal means compared to boys, a trend linked to increased feelings of loneliness and hopelessness, as well as more severe psychopathological issues (9). Our analysis shows a notable prevalence of intentional poisoning among adolescent girls relative to their male peers. These findings are consistent with previous studies (9, 22). Additionally, a noteworthy proportion of the intentional poisoning cases in our study were associated with multidrug ingestion, with 13 cases having accompanying psychiatric disorders, the majority of whom involved female adolescents.

In a study conducted in Taiwan, poisoning due to pharmacological agents was detected in 42.2% of children, marking it as a leading cause of poisoning (12). Prior studies have implicated pharmacological agents in many poisoning cases, with analgesics and antipyretics being the most common culprits (23). Azab et al. conducted a comprehensive study reinforcing this trend across all age groups, identifying analgesics and antipyretics as the most frequently responsible medications (24). Furthermore, Dağ et al. reported that these agents accounted for 22.7% of poisoning cases (13). In line with earlier findings (9, 23), our study revealed that 15.4% of drug-related poisonings involved analgesics or antipyretics. Overall, 62.5% of poisoning cases in our cohort were attributable to pharmacological causes, with a significantly higher incidence of pharmacological poisonings observed among girls compared to boys. Notably, pharmacological poisonings were significantly elevated in preschool children, suggesting that preventive measures could be effectively implemented at this developmental stage.

In a study conducted in Italy, non-pharmacological agents were identified as the primary substances involved in childhood poisoning cases, accounting for 59% of incidents among children with a median age of 2.2 years; notably, 63% of these cases involved male subjects (17). Similarly, a study in Konya highlighted that non-pharmacological causes were the leading factors in pediatric poisonings, with caustic and corrosive substances responsible for 42.8% of cases (6). In our investigation, we observed that the proportion of poisonings attributable to non-pharmacological agents was 30.1%, while caustic and corrosive agents accounted for 21.6%. Our results align with previous findings, demonstrating a significantly higher incidence of non-pharmacological poisonings among males and infants.

The management of childhood poisoning can vary widely, particularly concerning the application of interventions such as gastric lavage and activated charcoal, depending on the type and rationale of poisoning. In the study by Dağ et al., gastric lavage was performed in 21.6% of cases, while activated charcoal was administered to 32.8% of patients (13). Conversely, another study reported gastric lavage in 34.7% of cases and activated charcoal in 42.8% (5). In our study, gastric lavage was utilized in 32.8% of poisoning cases, with activated charcoal applied in 37.8% of instances. These findings underscore the continued need for protocol optimization in the management of pediatric poisonings to enhance patient outcomes.

In conclusion, our study highlights the significant prevalence of acute poisoning among children, particularly in preschool-aged individuals, with a notable increase in cases during the summer months. The majority of poisoning incidents were accidental, predominantly involving pharmacological agents, especially analgesics and antipyretics, while intentional poisonings were more common among female adolescents. These findings underscore the critical need for targeted educational initiatives and preventive strategies aimed at reducing the incidence of poisoning, particularly in vulnerable age groups.

References

1.Molla YM, Belachew KD, Ayehu GW, Teshome AA. Acute poisoning in children in Ethiopia: a cross-sectional study. Sci Rep 2022; 12:18750

2.Tobaiqy M, Asiri BA, Sholan AH, Alzahrani YA, Alkatheeri AA, Mahha AM, et al. Frequency and Management of Acute Poisoning Among Children Attending an Emergency Department in Saudi Arabia. Pharmacy (Basel) 2020; 8:189

3.Kizilyildiz BS, Karaman K, Özen S, Üner A. Acute intoxications among Turkish children. Minerva Pediatr 2018;70:46–50

4.Kesapli M, Celik A, Isik I. Characteristic Features of Childhood and Adolescent Poisonings, in the Mediterranean Region over 6 Years. Iran J Public Health 2018;47: 1667-1674

5.Yorulmaz A, Akbulut H, Yahya İ, Aktaş R, Emiroğlu HH. Çocuk acil servisine zehirlenme nedeni ile başvuran olguların geriye dönük olarak değerlendirilmesi. J Pediatr Emerg Intensive Care Med 2017; 4:96-103

6.Kesebir F, Akın F, Yazar A, Kılıç AO, Akkuş A, Türe E. Çocuk Acil Servisine Başvuran Zehirlenme Vakalarının Retrospektif Olarak Değerlendirilmesi. Pediatr Pract Res 2024; 12:32-37

7.Tarvadi PV, Bakkannavar SM, Palimar V, Kumar GP, Shetty M, Badiger S. Gender differences in childhood poisoning. Journal of Health and Allied Sciences NU, 2013;3: 069-072

8.Naik IB, Vankayala H, Sailaja A, Kumari NG, Babjan S, Kumar PD. Clinical Profile, Socio-Demographic Factors and Outcome of Children Presenting with Poisoning or Intoxication, A Hospital Based Study. European Journal of Cardiovascular Medicine 2024; 14:158-168

9.Bulut M, Alemdar DK, Bulut A, Tekin E, Çelikkalkan K. Evaluation of accidental and intentional pediatric poisoning: Retrospective analysis in an emergency Department of Turkey. Journal of Pediatric Nursing 2022; 63:e44-e49

10.Kazanasmaz H, Kazanasmaz Ö, Çalık M. Epidemiological and sociocultural assessment of childhood poisonings. Turk J Emerg Med 2019;19(4):127-131

11.Ram P, Kanchan T, Unnikrishnan B. Pattern of acute poisonings in children below 15 years--a study from Mangalore, South India. J Forensic Leg Med. 2014; 25:26-29

12.Lee J, Fan NC, Yao TC, et al. Clinical spectrum of acute poisoning in children admitted to the pediatric emergency department. Pediatr Neonatol. 2019;60(1):59-67

13.Dağ ÖO, Yeşil Y, Özdemir AA. Acute poisoning in the pediatric emergency department: A 5-year analysis. Cerrahpaşa Med J. 2024. Published online July 31, 2024. doi: 10.5152/cjm.2024.23106

14.Biçer S, Sezer S, Çetindağ F, Kesikminare M, Tombulca N, Aydoğan G, Aldemir H. Evaluation of acute intoxications in pediatric emergency clinic in 2005. Marmara Medical Journal 2007; 20:12–20

15.Dai Q, Wang L, Gao X, Du D, Shuai P, Li L, et al. Clinical and Epidemiological Characteristics of Acute Poisoning in Children in Southwestern China: A Review of 1755 Cases from 2014 to 2020. International Journal of General Medicine 2022; 15:133–142

16.Rodrigues Mendonca D, Menezes MS, Matos MA, Reboucas DS, Filho JN, Assis RS, et al. Acute Poisoning in Children in Bahia, Brazil. Global Pediatric Health. 2016; 17:1-7

17.Berta GN, Di Scipio F, Bosetti FM, Mognetti B, Romano F, Carere ME, et al. Childhood acute poisoning in the Italian North-West area: a six-year retrospective study. Ital J Pediatr. 2020; 46:83

18.Sahin S, Carman KB, Dinleyici EC. Acute poisoning in children; data of a pediatric emergency unit. Iran J Pediatr. 2011;21(4):479-484

19.Kandeel F, El-Farouny R. Study of acute poisoning cases in children admitted to Menoufia Poison Control Center (MPCC) during the year 2016. A Prospective Study.Ain Shams Journal of Forensic Medicine and Clinical Toxicology 2017;29: 89-99

20.Öner N, İnan M, Vatansever Ü, Turan Ç, Çeltik Ç, Küçükuğurluoğlu Y, et al. Trakya bölgesinde çocuklarda görülen zehirlenmeler: orijinal araştırma. Türk Pediatr Ars 2004; 39:25-30

21.Mintegi S, Azkunaga B, Prego J, Qureshi N, Dalziel SR, Arana-Arri E, et al; Pediatric Emergency Research Networks (PERN) Poisoning Working Group. International Epidemiological Differences in Acute Poisonings in Pediatric Emergency Departments. Pediatr Emerg Care 2019;35(1):50-57

22.Günay A, Uğurlu Z, Ceylan A, Ayten N. A retrospective investigation of poisoning cases presented to the pediatric emergency Department of Başkent University Ankara Hospital between 2012 and 2017. Journal of Pediatrıc Emergency Intensive Care Medicine 2019; 6:13–17

23.Aygin D, Açıl H. The study of the intoxication cases of the patients (0–18 years) admitted to the pediatric emergency unit. The Medical Bulletin of Şişli Etfal Hospital 2014; 48:27–33.

24.Azab SM, Hirshon JM, Hayes BD, El-Setouhy M, Smith GS, Sakr ML, et al. Epidemiology of acute poisoning in children presenting to the poisoning treatment center at Ain Shams University in Cairo, Egypt, 2009-2013. Clin Toxicol (Phila) 2016; 54:20-26

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ORIGINAL ARTICLE

Comparison of the Clinical Effects of Early and Late Percutaneous Tracheostomy Timing in Intensive Care Unit Patients

Yoğun Bakım Hastalarında Erken ve Geç Perkütan Trakeostomi Zamanlamasının Klinik Etkilerinin Karşılaştırılması

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ABSTRACT

Background/Aims: Percutaneous tracheostomy (PT) is defined as early or late PT by the time from the patient's intubation to the day of the PT procedure. In this retrospective study, we aimed to evaluate the effects of early and late tracheostomy timing on the duration of mechanical ventilation (MV), duration of intensive care unit (ICU) stay, length of hospital stay, complications, and mortality.
Methods: The files of critically ill patients from hospital records undergoing tracheostomy during the treatment in the Anesthesiology and Reanimation ICU between 1st March 2023, and 31st May 2024 were retrospectively evaluated. Patients in whom tracheostomy was performed before the 10th day and on the 10th day of intubation were grouped as early tracheostomy, and those in whom tracheostomy was performed after the 10th day were grouped as late tracheostomy.
Results: The study included 90 patients. The early tracheostomy group (n=45) was significantly younger than the late tracheostomy group (n=45). The mean age of the early tracheostomy group was 62.42 ± 16.78, while that of the late tracheostomy group was 69.58±16.20 (p=.043). The median length of ICU stay was 32 days (range: 6-270 days) in the early tracheotomy group and 45 days (range: 16-270 days) in the late tracheotomy group; and the length of ICU stay in the early tracheotomy group was significantly shorter than the late tracheotomy group (p=.025). Besides, the number of MV days was significantly greater in patients in the late tracheotomy group compared with patients in the early tracheotomy group [32 days (range: 6-230 days)] vs [40 days (range: 16-265 days)] (p=.032).
Conclusions: Early tracheostomy procedure is important and beneficial for the treatment of elderly intensive care patients because it reduces the duration of ICU stay and reduces the duration of MV.

Keywords: Elderly, Intensive Care Unit, Mortality, Tracheostomy

ÖZ

Giriş/Amaçlar: Perkütan Trakeostomi (PT), hastanın entübasyonundan PT işleminin yapıldığı güne kadar geçen süreye göre erken veya geç PT olarak tanımlanır. Bu retrospektif çalışmada erken ve geç trakeostomi zamanlamasının mekanik ventilasyon süresi, yoğun bakım ünitesinde kalış süresi, hastanede kalış süresi, komplikasyonlar ve mortalite üzerindeki etkilerini değerlendirmeyi amaçladık.
Gereç ve Yöntem: Anesteziyoloji ve Reanimasyon Yoğun Bakım Ünitesi'nde (YBÜ) 1 Mart 2023-31 Mayıs 2024 tarihleri arasında tedavileri sırasında trakeostomi uygulanan kritik hastaların dosyaları ve hastane kayıtları retrospektif olarak değerlendirildi. Entübasyonun 10. gününde ve 10. günden önce trakeostomi yapılan hastalar erken trakeostomi, 10. günden sonra trakeostomi yapılan hastalar geç trakeostomi olarak gruplandırıldı.
Bulgular: Çalışmaya 90 hasta dahil edildi. Erken trakeostomi grubu (n=45) geç trakeostomi grubundan (n=45) anlamlı olarak daha gençti. Erken trakeostomi grubunun yaş ortalaması 62.42 ± 16.78 iken, geç trakeostomi grubunun yaş ortalaması 69.58 ± 16.20 idi], p=.043. Erken trakeostomi grubunun yaş ortalaması 62.42 ± 16.78 iken, geç trakeostomi grubunun yaş ortalaması 69.58 ± 16.20 idi], p=.043. Ortanca YBÜ kalış süresi erken trakeotomi grubunda 32 gün (dağılım: 6-270 gün) ve geç trakeotomi grubunda 45 gün (dağılım: 16-270 gün) idi ve erken trakeotomi grubunda yoğun bakım kalış süresi geç trakeotomi grubuna göre anlamlı derecede kısaydı (p=.025). Ayrıca, mekanik ventilasyon süresi geç trakeotomi grubundaki hastalarda erken trakeotomi grubundaki hastalara kıyasla anlamlı olarak daha fazlaydı (32 gün [dağılım: 6 - 230 gün] vs. 40 gün [dağılım: 16 - 265 gün], p=.032).
Sonuçlar: Erken trakeostomi prosedürü, yoğun bakım ünitesi kalış süresini ve mekanik ventilasyon süresini azalttığı için yaşlı yoğun bakım hastalarının tedavisi için önemli ve faydalıdır.

Anahtar kelimeler: Mortalite, Trakeostomi, Yaşlı, Yoğun Bakım Ünitesi

Introduction

Percutaneous tracheostomy (PT) is a common procedure in Intensive Care Units (ICU). Approximately 20-24% of critically ill patients intubated in the ICU undergo tracheostomy (1). Critically ill patients may require prolonged respiratory support due to respiratory failure. In such cases, tracheostomy is a common procedure that has been proven to shorten MV time, reduce the need for sedation, and improve pulmonary hygiene (2). Its biggest advantages are that it is performed at the bedside in the ICU, the patient does not need to be transported to the operating room, the complications are low and it is performed in a short time. It also allows the patient to be fed orally and enhances the patient's communication. (3).

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It is defined as early or late PT according to the time from the patient's intubation to the day of the PT procedure. There are different opinions among intensivists about the timing of these periods. While some physicians accept the first two and four days for the definition of early tracheostomy, others accept the 6th, 10th, 14th, and 21st days for the definition of late tracheostomy (1, 4-6). There is still no consensus on the timing of early and late tracheostomy.

In this retrospective study, we aimed to evaluate the effects of early and late tracheostomy timing on the duration of MV, duration of ICU stay, length of hospital stay, complications, and mortality in patients with PT in the Anesthesiology and Reanimation ICU.

Material and Methods

The study was conducted after obtaining the approval of the Local Ethics Committee of Selçuk University Faculty of Medicine. It was conducted under the World Medical Association Declaration of Helsinki. The files and hospital records of critically ill patients who underwent tracheostomy during their treatment in the 3rd level 48-bed Anesthesiology and Reanimation ICU of Selcuk University Faculty of Medicine between 1st March 2023, and 31st May 2024 were retrospectively evaluated. Informed consent was obtained for all tracheostomies. Patients over 18 years of age undergoing PT were included in the study. Patients in whom PT was performed were divided into two groups according to the timing of tracheostomy. Patients in whom tracheostomy was performed on the 10th day of intubation and before the 10th day were grouped as early tracheostomy, and patients in whom tracheostomy was performed after the 10th day were grouped as late tracheostomy. All percutaneous tracheostomies were performed at the bedside under visualization with a fiberoptic bronchoscope. A single-step dilation method known as the modified Ciaglia technique was used for tracheostomies. In this technique, a flexible, hard rubber, hydrophilic-coated special dilator is used to reduce complications such as posterior wall damage and bleeding that may occur during multiple dilatations. Instead of multiple dilatations as in the classical 'Ciaglia' method, single dilatation over the guide wire and guiding catheter can be performed with this dilator. All PT techniques were performed according to the Seldinger guidewire principle. At the end of the PT, chest radiography was performed at the bedside after listening to respiratory sounds.

Patient's demographic features: age, gender, body mass index [BMI (kg/m2), cachexia: <18,5 kg/m2, normal: 18,5-25 kg/m2, overweight: ≥25 kg/m2], smoking, comorbidities: history of diabetes mellitus, chronic kidney disease (defined as estimated glomerular filtration rate <30 mL/min/1.73 m2), chronic heart disease (defined as current or previous history of cardiac dysfunction), hypertension, malignancy, cerebrovascular disease (defined as stroke or hemoragy), chronic respiratory disease (defined as chronic obstructive pulmonary disease or asthma), diagnosis on admission, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, was collected.

Laboratory values in the last 24 hours before the tracheostomy procedure were recorded. White blood cell (K/uL), hemoglobin (g/dL), platelet count (K/uL), activated partial thromboplastin time (aPTT [sec]), international normalized ratio (INR) values of perioperative factors were recorded.

Early complications within 48 hours (wound site infection, subcutaneous emphysema, pneumothorax, minor bleeding, major bleeding, and mortality) were recorded.

Length of stay (LOS) in ICU (day), length of LOS at hospital (day), number of MV days, 30-day mortality, ICU mortality, ventilator-associated pneumonia (VAP), discharge, decanulation information, need for ventilator support at discharge were obtained from the patient's records.

Statistical Analysis

All statistical analysis was performed using R version 4.2.1 (www.r-project.org) statistical language. To check the normality of the data and homogeneity of the variance, Shapiro-Wilk's normality test and Levene test were used, respectively. Data were presented as mean ± standard deviation, median (range: min – max), or median [IQR: inter-quartile range] for numerical variables; and compared with student's t-test and Mann-Whitney U test. Data were described as count (n) and percentage (%); and compared with Pearson chi-square test, Fisher exact test, Chi-square test with Yates continuity correction, Fisher-Freeman-Halton test, and Two proportion Z-test according to the groups. A two-tailed p-value less than .05 was considered statistically significant.

Results

In our study, we found that PT was performed in 90 of 174 patients undergoing surgical and PT; of these

patients, 45 were in the early tracheostomy group and 45 (n=45) were in the late tracheostomy group (Figure 1). The mean age of 90 patients was 66±16.79

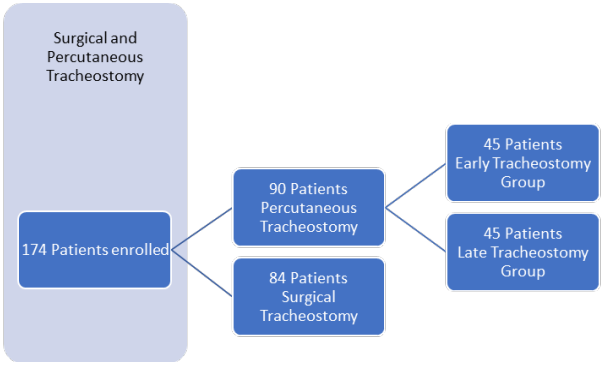

Figure 1. Flow diagram of patients in the study.

comorbidities, and diagnosis on admission were similar (Table 1).

Laboratory values in the last 24 hours before the tracheostomy procedure were the same in both groups (Table 2).

Tracheostomy-related complications included minor bleeding in 2 patients (66.7%) and wound site infection in 1 patient (33.3%) in the early tracheostomy group. In the late tracheostomy group, minor bleeding was observed in 2 patients (66.7%) and subcutaneous emphysema in 1 patient (33.3%). There was no difference between the two groups in terms of complications (Table 3).

Table 1. Baseline characteristics of patients at inclusion in the study.

	Total (*n*=90)	Early Tracheostomy (*n*=45)	Late Tracheostomy (*n*=45)	*p*-value
Demographical characteristics				
Age (years)	66±16.79	62.42±16.78	69.58±16.20	.043[1]
Gender (M/F)	56/34	29/16	27/18	.828[2]
BMI (kg/m²)				.102[3]
Normal	44 (48.9)	18 (40)	26 (57.8)	
Overweight	34 (37.8)	18 (40)	16 (35.6)	
Cachexia	12 (13.3)	9 (20)	3 (6.7)	
Smoking	30 (33.3)	13 (28.9)	17 (37.8)	.502[2]
Comorbidity				
Diabetes Mellitus	25 (27.8)	9 (20)	16 (35.6)	.158
Chronic Kidney Disease	12 (13.3)	3 (6.7)	9 (20)	.121[2]
Chronic Heart Disease	36 (40)	14 (31.1)	22 (48.9)	.132[2]
Hypertension	40 (44.4)	18 (40)	22 (48.9)	.525[2]
Malignancy	17 (18.9)	10 (22.2)	7 (15.6)	.591[2]
Cerebrovascular Disease	43 (47.8)	25 (55.6)	18 (40)	.205[2]
Chronic Respiratory Disease	18 (20)	9 (20)	9 (20)	>.999[2]
Diagnosis on Admission				
Post-cardiac arrest	8 (8.89)	4 (8.89)	4 (8.89)	>.999[6]
Neurological Diseases	34 (37.78)	21 (46.67)	13 (28.89)	.082[6]
Internal Diseases	30 (33.33)	13 (28.89)	17 (37.78)	.371[6]
Trauma	16 (17.78)	5 (11.11)	11 (24.44)	.098[6]
Dermatomyositis	2 (2.22)	2 (4.44)	0 (0)	.153[6]
APACHE II score	15.5 (3-64)	15 (3-60)	17 (5-64)	.278[7]

[1]Student's *t*-test; [2]Chi-square test with Yates continuity correction; [3]Pearson's chi-square test; [4]Fisher's exact test; [5] Fisher-Freeman-Halton test; [6]Two-proportion Z-test; [7]Mann-Whitney U test; Data were presented as mean±standard deviation, median (range: min-max) or median [IQR: Inter-quartile range] for numerical variables. Data were described as count (n) and percentage (%).

years. The early tracheostomy group was significantly younger than the late tracheostomy group. The mean age of the early tracheostomy group was 62.42 ± 16.78, while that of the late tracheostomy group was 69.58±16.20 (p=.043). Of the patients, 56 and 34 were males and females. APACHE II score, BMI, smoking,

The median ICU length of stay was 32 days (range: 6 – 270 days) in the early tracheostomy group and 45 days (range: 16 – 270 days) in the late tracheostomy group; and the ICU length of stay in the early tracheostomy group was significantly shorter than the late tracheostomy group (p=.025). Besides, the number of MV days was significantly greater in patients in the

Table 2. Comparison of pre-procedure laboratory values of the two groups.

	Total (n=90)	Early Tracheostomy (n=45)	Late Tracheostomy (n=45)	*p*-value
WBC (K/uL)	12.95±6.12	12.93±5.61	12.97±6.65	.976[1]
Hemoglobin (g/dL)	9.61±1.83	9.83±2.02	9.39±1.61	.253[1]
Platelet count (K/uL)	212.5 [155-322.75]	212 [152-296]	214 [166-335]	.623[7]
APTT (sec)	29.33±6.16	29.13±5.52	29.53±6.80	.759[1]
INR	1.18 [1.08-1.29]	1.15 [1.07-1.25]	1.22 [1.11-1.29]	.234[7]

WBC: White blood cell, APTT: Activated partial thromboplastin time, INR: International normalized ratio. [1]Student's t-test; [2]Chi-square test with Yates continuity correction; [3]Pearson's chi-square test; [4]Fisher's exact test; [5]Fisher-Freeman-Halton test; [6]Two-proportion Z-test; [7]Mann-Whitney U test; Data were presented as mean±standard deviation, median (range: min-max) or median [IQR: Inter-quartile range] for numerical variables. Data were described as count (n) and percentage (%).

Table 3. Comparison of complications of the two groups.

	Total (*n*=90)	Early Tracheostomy (*n*=45)	Late Tracheostomy (*n*=45)	*p*-value
Overall Complications	6 (6.7)	3 (6.7)	3 (6.7)	>.999[4]
Tracheostomy-related Complications				>.999[5]
Minor bleeding	4 (66.7)	2 (66.7)	2 (66.7)	
Wound Site Infection	1 (16.7)	1 (33.3)	0 (0)	
Subcutaneous emphysema	1 (16.7)	0 (0)	1 (33.3)	

[1]Student's *t*-test; [2]Chi-square test with Yates continuity correction; [3]Pearson's chi-square test; [4]Fisher's exact test; [5]Fisher-Freeman-Halton test; [6]Two-proportion Z-test; [7]Mann-Whitney U test; Data were presented as mean±standard deviation, median (range: min-max) or median [IQR: Inter-quartile range] for numerical variables. Data were described as count (n) and percentage (%).

Table 4. Comparison of the two groups by studied variables.

	Total (n=90)	Early Tracheostomy (n=45)	Late Tracheostomy (n=45)	*p*-value
ICU length of stay (days)	37 (6-270)	32 (6-270)	45 (16-270)	.025[7]
Hospital length of stay (days)	54 (6-270)	45 (6-270)	60 (16-270)	.088[7]
MV time (days)	35 (6-265)	32 (6-230)	40 (16-265)	.032[7]
30-days mortality	24 (26.7)	16 (35.6)	8 (17.8)	.095[2]
ICU mortality	68 (75.6)	34 (75.6)	34 (75.6)	>.999[2]
VAP After Tracheostomy	14 (15.6)	7 (15.6	7 (15.6)	>.999[2]
Patient Disposition				.677[5]
Discharge	4 (4.4)	3 (6.7)	1 (2.2)	
Palliative service	18 (20)	8 (17.8)	10 (22.2)	
Exitus	68 (75.6)	34 (75.6)	34 (75.6)	
Tracheostomy and MV status				>.999[5]
Tracheostomy with MV	9 (40.9)	4 (36.4)	5 (45.5)	
Tracheostomy without MV	2 (9.1)	1 (9.1)	1 (9.1)	
Decannulation before discharge	11 (50)	6 (54.5)	5 (45.5)	

ICU: Intensive care unit; LOS: Length of stay; VAP: Ventilator-associated pneumonia; MV: Mechanical ventilation.[1]Student's t-test; [2]Chi-square test with Yates continuity correction; [3]Pearson's chi-square test; [4]Fisher's exact test; [5]Fisher-Freeman-Halton test; [6]Two-proportion Z-test; [7]Mann-Whitney U test; Data were presented as mean±standard deviation, median (range: min-max) or median [IQR: Inter-quartile range] for numerical variables. Data were described as count (n) and percentage (%).

late tracheostomy group compared with patients in the early tracheostomy group (32 days [range: 6 – 230 days] vs. 40 days [range: 16 – 265 days], p=.032).

Hospital length of stay, 30-day mortality, ICU mortality, and VAP did not differ between the two groups. 68 (75.6%) patients died due to various reasons. Of the surviving patients, 4 (4.4%) were discharged from ICU and 18 (20%) were transferred to palliative service. Before discharge, 11 patients (32.3%) were decannulated who were breathing spontaneously and maintained airway protection. 2 patients (9.1%) were tracheostomized but didn't require a mechanical ventilator. 9 patients (40.1%) had tracheostomy and needed mechanical ventilators (Table 4).

Discussion

This study showed that LOS in ICU and MV days were significantly shorter in early PT patients than in late PT patients. While the mean age of the early group was significantly lower than the late group, the mean age in both groups was elderly critically ill patients over 60 years of age.

The appropriate timing for tracheostomy is still unknown and the evidence is still unclear. (4) The National Association of Medical Directors of Respiratory Care recommends that tracheostomy should replace endotracheal intubation in patients continuing to require MV three weeks after hospitalization. They stated that determining the optimal time for tracheostomy is one of the most important criteria when deciding to perform the procedure (7, 8). In a retrospective study by Bickenbach et al., early tracheostomies before 4th day of MV, intermediate tracheostomies between five to nine days, and late tracheostomies after 10 days were compared. There was a significant decrease in the incidence of VAP and sepsis in the early tracheostomy group compared to the late group. The late tracheostomy group had higher ventilator days and ICU length of stay. ICU mortality was significantly reduced in the late group compared to the early group, but not in the intermediate group (4). This study was conducted in a more specific surgical ICU and the patient population is different from our study. Our study was conducted in an ICU where not only surgical but also medical and surgical patients were admitted. The timing of the early and intermediate groups corresponds to the timing of our early group. Although the patient population was different, prolonged ICU length of stay and MV day decreased in the late tracheostomy group, similar to our study.

In a meta-analysis by Griffiths et al., they concluded that the duration of ICU stay and MV were significantly reduced in the early tracheostomy group compared to the late tracheostomy group. There was no difference in mortality rates (9). These results were similar in our study.

In a retrospective (case-control) study by Nasr et al., they grouped 1-10 days as early and 11-21 days as late tracheostomy group. While MV time and sedation time were found to be decreased, there was no difference in ICU length of stay, hospitalization time, and mortality. They concluded that patients who underwent early tracheostomy could be weaned from the mechanical ventilator rapidly (10). In our study, the duration of MV was also decreased.

Terragni et al. divided the patients into two groups early tracheostomy 6-8 days and late tracheostomy 13-15 days after MV support in their study including 419 patients. They reported that no significant difference in the incidence of VAP between the early and late tracheostomy group (7). Bickenbach et al. reported that; there was a significant decrease in the incidence of VAP and sepsis in the early tracheostomy group compared to the late group (4). In our study, we didn't find any difference in the incidence of VAP between the two groups.

Edipoglu et al. grouped the PT procedures in ICUs within one year as before and after 10 days. They found that the duration of ICU stay of the early tracheostomy group was significantly shorter than the late tracheostomy group, but they reported that there was no between-group difference in mortality (5). By these findings, we also found that the duration of ICU stay was significantly shorter in the early tracheostomy group, and similarly, we could not detect a significant difference in mortality.

Rumbak et al. showed that a tracheostomy performed within 2 days of hospitalization reduced the mortality rate, the occurrence of pneumonia, and length of ICU stay compared to a tracheostomy performed 14 to 16 days after endotracheal intubation (11). In our study, we didn't find any difference in the incidence of VAP and mortality rate between the two groups.

Tang et al. compared outcomes between early and late tracheostomy in Covid-19 ICU patients. They found that tracheostomies performed after 14 days were associated with increased mortality compared to early ones (12).

A recent study of 235 critically ill elderly patients found that the very early tracheostomy group had a shorter ICU stay and reduced hospital mortality, as well as a better postoperative survival rate. While the mean age of the three groups was over 60 years, the age in the very early tracheostomy group was significantly younger than that in the early tracheostomy group and the late tracheostomy group (6). In our study, the mean age in the early tracheostomy group was significantly younger than that in the late tracheostomy group. Similarly, the mean age was above 60 years in both groups. While the duration of ICU stay decreased, no difference was observed in mortality in early tracheostomy in our study, contrary to this study.

In previous studies; early complications related to percutaneous dilatational tracheostomy techniques range from 9.7% to 15% (13, 14). In this study, although the complication rates associated with tracheostomy were similar between the two groups, the complication rate in the early tracheostomy group was lower than in previous studies.

The limitations of this study are that it was retrospective, conducted in a single center and a single ICU, the number of cases was small, and we could not evaluate the follow-up of long-term complications such as tracheoesophageal fistula, esophageal injury, and stenosis. There is a need for multicenter, prospective studies in which forward-looking and long-term complications will be followed up. The fact that our study population was elderly and had comorbid diseases poses an increased risk for mortality. Prospective studies in younger critically ill patients are needed.

Conclusion

We consider that the early PT procedure is important and beneficial for the treatment of elderly intensive care patients because it reduces the duration of ICU stay and reduces the duration of MV. At the same time, we think that the older age of the late group may be due to the waiting period after discontinuation of anticoagulants and anti-aggregants due to comorbidities, severe hypoxia, and late consent for tracheostomy by relatives of elderly patients.

Informed Consent

Informed consent was obtained from all of the participants included in the study.

Ethical Approval

The protocol of this study was approved by the Clinical Research Ethics Committee of Selcuk University, Konya (Number and date: 2024/436, 30th July 2024).

Author Contribution

Conceptualization: YSB; Methodology: YSB; Formal analysis: YSB; Investigation: YSB; Resources: YSB; Writing-original draft preparation: YSB; Writing_review and editing, YSB. All authors have read and approved the published version of the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Supporting Institution

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Main Points

PT is a common procedure in ICUs. It is defined as early or late PT according to the time from the patient's intubation to the day of the PT procedure. There are different opinions among intensivists about the timing of these periods.

Patients in whom tracheostomy was performed on the 10th day of intubation and before the 10th day were grouped as early tracheostomy, and patients in whom tracheostomy was performed after the 10th day were grouped as late tracheostomy.

Early PT procedure is important and beneficial for the treatment of elderly intensive care patients because it reduces the duration of ICU stay and reduces the duration of MV.

References

1.Tekin P, Bulut A. Tracheostomy Timing in Unselected Critically Ill Patients with Prolonged Intubation: A Prospective Cohort Study. J Clin Med 2024;13(10):2729.

2.Vudatha V, Alwatari Y, Ibrahim G, Jacobs T, Alexander K, Puig-Gilbert C, et al. Percutaneous Dilatational Tracheostomy in a Cardiac Surgical Intensive Care Unit: A Single-Center Experience. J Chest Surg 2023;56(5):346.

3.Marinaki C, Kapadochos T, Katsoulas T, Rubbi I, Liveri A, Stavropoulou A, et al. Early versus late Tracheostomy promotes weaning in intensive care unit patients. Acta Biomed 2022;93(Suppl 2).

4.Bickenbach J, Fries M, Offermanns V, Von Stillfried R, Rossaint R, Marx G, et al. Impact of early vs. late tracheostomy on weaning: a retrospective analysis. Minerva Anestesiol 2011;77(12):1176-83.

5.Edipoğlu İS, Özcan PE, Akıncı Öİ, Yornuk M, Orhun G, Şentürk E, et al. Yoğun Bakım Hastalarında Erken ve Geç Trakeostomi Uygulamalarının Değerlendirilmesi. J Turk Soc Intens Care. Türk Yoğun Bakım Derneği Dergisi 2013;11: 60-3.

6.Li C, Wang T, Sheng D, Zhang M, Zheng M, Li X. Association Between Timing of Percutaneous Dilatational Tracheotomy and Clinical Outcomes of Critically-ill Elderly Patients. J Coll

Physicians Surg Pak 2024;20:12.4.

7.Terragni PP, Antonelli M, Fumagalli R, Faggiano C, Berardino M, Pallavicini FB, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. Jama 2010;303(15):1483-9.

8.Plummer AL, Gracey DR. Consensus conference on artificial airways in patients receiving mechanical ventilation. Chest. 1989;96(1):178-80.

9.Griffiths J, Barber VS, Morgan L, Young JD. Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. Bmj. 2005;330(7502):1243.

10.Samiei Nasr D, Khoundabi B, Monshizadeh Azar G, Malekmohammad M, Jamaati H, Hashemian SM. Beneficial outcomes of early tracheostomy in patients requiring prolonged mechanical ventilation. TANAFFOS (Respiration). 2020;19(4):350-5.

11.Rumbak MJ, Newton M, Truncale T, Schwartz SW, Adams JW, Hazard PB. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. Crit Care Med. 2004;32(8):1689-94.

12.Tang Y, Wu Y, Zhu F, Yang X, Huang C, Hou G, et al. Tracheostomy in 80 COVID-19 patients: a multicenter, retrospective, observational study. Front Med (Lausanne). 2020;7:615845.

13.Añón JM, Gómez V, Escuela MP, De Paz V, Solana LF, De La Casa RM, et al. Percutaneous tracheostomy: comparison of Ciaglia and Griggs techniques. Crit Care. 2000;4:1-5.

14.Pietkiewicz P, Machała W, Kuśmierczyk K, Miłoński J, Wiśniewski T, Urbaniak J, et al. Early complications of Griggs percutaneous tracheotomy in own material. Otolaryngol Pol. 2012;66(3):196-200.

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ORIGINAL ARTICLE

Comparison of Histopathological Findings and Flap Survival Following Four Different Dermal Filler Material-Induced Vascular Occlusion

Dört Farklı Dermal Dolgu Maddesinin Neden Olduğu Damar Tıkanıklığı Sonrasında Histopatolojik Bulgular ve Flep Sağ Kalımının Karşılaştırılması

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ABSTRACT

Aim: To evaluate comparatively the damage, histopathological findings, and flap necrosis rates due to vascular occlusion caused by the intraarterial injection of dermal fillers calcium hydroxylapatite, polycaprolactone, agarose gel, hyaluronic acid, and serum physiologique.
Material and Methods: The study involved 100 rats, divided into five groups, and 40 arteries. Dermal fillers and serum physiologic were injected into the inferior epigastric arteries, with samples taken at various intervals. The study evaluated degeneration-necrosis, inflammation, fibroblast and collagen densities, thrombus presence, edema, polymorphonuclear leukocyte (PMNL), lymphocyte, mast cell, macrophage, and eosinophil percentages, and calcification. Additionally, 20 rats with 40 flaps created by the inferior epigastric arteries were divided into five injection groups to evaluate flap necrosis rates a week after injection.
Results: There was a statistically significant difference in the percentages of flap necrosis values between the groups. Post-HOC showed that the difference was due to the hyaluronic acid (HA) group with a higher necrosis percentage. Thrombus filling the whole lumen was observed to be higher in the HA group compared to the other groups at all hours and in the first week. Given intima and media degenerations, there was a statistically significant difference at all times and in all groups and a significant difference at certain times when examining the distribution of PMNL, lymphocyte, mast, and macrophage. When eosinophil measurement, inflammation, fibroblast and collagen densities, edema, and calcification findings were evaluated, no significant difference was found between the groups.
Conclusion: It was concluded that besides statistically significant histopathological differences between each filler within the artery, in particular, the HA group caused thrombus, completely occluding the lumen, significantly more than the other groups; accordingly, the flap necrosis rate was significantly higher than the non-HA filler groups. This result highlighted the importance of antithrombotic and thrombolytic therapy, especially in HA fillers.

Keywords: Agarose gel, calcium hydroxylapatite, hyaluronic acid, polycaprolactone, vascular occlusion

ÖZ

Amaç: Bu deneysel çalışma, intraarteriyel dermal dolgu maddeleri kalsiyum hidroksilapatit, polikaprolakton, agaroz jel, hyaluronik asit ve serum fizyolojik enjeksiyonu ile oluşan vasküler oklüzyona bağlı hasar, histopatolojik bulgular ve flep nekroz oranlarını karşılaştırmalı olarak değerlendirmek için tasarlanmıştır.
Gereç ve Yöntemler: 100 sıçan, beş gruba ve 40 atardamara bölünmüştür. Dermal dolgu maddeleri ve serum, alt epigastrik arterlere enjekte edilmiş ve çeşitli aralıklarla örnekler alınmıştır. Çalışmada dejenerasyon-nekroz, inflamasyon, fibroblast ve kollajen yoğunlukları, trombüs varlığı, ödem, PMNL, lenfosit, mast hücresi, makrofaj ve eozinofil yüzdeleri ve kalsifikasyon değerlendirilmiştir. Ek olarak, alt epigastrik arterler tarafından oluşturulan 40 flebe sahip 20 sıçan, enjeksiyondan bir hafta sonra flep nekroz oranlarını değerlendirmek için beş enjeksiyon grubuna ayrılmıştır.
Bulgular: Gruplar arasında flep nekroz yüzdesi değerinde istatistiksel olarak anlamlı bir fark vardı. Post-HOC, farkın daha yüksek nekroz yüzdesine sahip HA grubundan kaynaklandığını gösterdi. Tüm lümeni dolduran trombüsün HA grubunda diğer gruplara göre tüm saatlerde ve ilk haftada daha yüksek olduğu görüldü. İntima ve medya dejenerasyonları incelendiğinde tüm zamanlarda ve tüm gruplarda istatistiksel olarak anlamlı bir fark ve PMNL, lenfosit, mast ve makrofaj dağılımı incelendiğinde belirli zamanlarda anlamlı bir fark vardı. Eozinofil ölçümü, inflamasyon, fibroblast yoğunlukları ve kollajen yoğunlukları, ödem ve kalsifikasyon bulguları değerlendirildiğinde gruplar arasında anlamlı bir fark bulunmadı
Sonuçlar: Her bir dolgu maddesi arasında arter içinde istatistiksel olarak anlamlı histopatolojik farklılıkların yanı sıra, özellikle hyaluronik asit grubunun lümeni tamamen tıkayan trombüse diğer gruplardan anlamlı olarak daha fazla neden olduğu ve buna bağlı olarak flep nekroz oranının HA dolgusu olmayan gruplara göre anlamlı olarak daha yüksek olduğu sonucuna varıldı. Bu sonuç, özellikle hyaluronik asit dolgularında antitrombotik ve trombolitik tedavinin önemini vurguladı.

Anahtar Kelimeler: Agaroz jel, kalsiyum hidroksiapatit, hyaluronik asit, polikaprolakton, vasküler oklüzyon

Introduction

Dermal fillers have become increasingly popular in the field of aesthetic medicine, offering a non-surgical solution for addressing various cosmetic concerns, such as wrinkles, fine lines, and volume loss. The growing demand for these procedures can be attributed to the perceived benefits of a more youthful and rejuvenated appearance, as well as the relatively quick and minimally invasive nature of the treatments. However, the widespread use of dermal fillers has also been accompanied by a growing frequency of

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complications, some of which can be quite serious (1). It is of paramount importance for healthcare providers and patients to have a comprehensive understanding of the risks and considerations associated with these treatments.

Vascular complications, such as arterial occlusion and tissue necrosis, are considered the most serious and potentially devastating adverse events associated with dermal filler injections (1,2). The incidence of vascular complications is relatively low, but the consequences can be severe, ranging from temporary discoloration to permanent disfigurement, necrosis, or even blindness (1). Numerous studies have reported cases of vascular complications, highlighting the importance of understanding the underlying mechanisms and appropriate management strategies (3,4).

The pathophysiology of filler-induced vascular complications is complex, involving a cascade of inflammatory and thrombotic processes ultimately resulting in tissue ischemia and damage. Upon intravascular injection, the filler material can trigger an immediate inflammatory response, leading to the activation of platelets and the coagulation cascade (5,6). This can result in the formation of thrombi occluding the affected vessels, cutting off blood supply to the surrounding tissues. The severity of the inflammatory response is largely dependent on the specific properties of the dermal filler material, such as its viscosity, particle size, and biocompatibility (5).

The specific mechanisms by which different filler materials interact with the vascular system and trigger this cascade of events are still not fully elucidated, a better understanding of these processes is crucial for improving both prevention and management of these complications.

This experimental study was designed to comparatively evaluate the inflammatory and thrombotic processes and the damage caused by intraarterial injection of these four different structures of dermal fillers.

Material And Methods

This study was conducted using 120 male Wistar-Albino rats in 2023, following ethical approval from the Konudam Local Ethics Committee for Animal Experiments of Necmettin Erbakan University with the protocol number, 2002-047. Of 120 rats, 100 were used to observe the histopathological effects of fillers on the vessels. For this purpose, the animals were divided into five different groups, numbered one to five, to receive different filler injections. Group 1: Calcium hydroxylapatite (CaHa) Radiesse, Group 2: Polycaprolactone (PCL) Ellanse S, Group 3: Agarose gel (AG) Algeness 1.5%, Group 4: Hyaluronic acid (HA) Yvoire Classic 20mg/mL, Group 5: Serum Physiologique (SP)

Approximately 0.02 mL of dermal fillers were injected into both sides of inferior epigastric arteries following a 2-cm oblique incision under anesthesia. In this way, 40 arteries were used in each group, 200 in total. For each group, samples for histopathological examination were taken from eight vessels at hour 0, eight vessels at one hour, eight vessels at three hours, eight vessels at 24 hours, and eight vessels at the first week. Following the collection of biopsy samples, the relevant animals were sacrificed under the Care and Use of Laboratory Animals guidelines.

The biopsy samples obtained were evaluated by a single pathologist. Degeneration-necrosis, inflammation, fibroblast and collagen densities in the intima and media layers of the vessels, the presence of thrombus in the vessels, the presence of edema, polymorphonuclear leukocyte (PMNL), lymphocyte, mast cell, macrophage, and eosinophil percentages and the presence of calcification were evaluated (Figure 1).

The remaining 20 of the 120 experimental rats were also divided into five different injection groups and used for the evaluation of flap survival after inferior epigastric artery occlusion. Rats were anesthetized, and 40 flaps of 2 × 2 cm on both sides of the lower abdomen solely nourished by the inferior epigastric arteries were designed and elevated, The purpose of this flap design is to avoid feeding from surrounding tissue and collaterals. Then, approximately 0.02 mL of dermal fillers were injected into both sides of inferior epigastric arteries in each injection group (Figure 2). After the injections, the flaps were sutured back into place, and postoperative follow-up was started. Photographs of flaps in each group were taken at the end of the first week after injection. The percentage of the surviving area of each flap fig was measured with Digimizer Image Analysis Software (Ostend, Belgium) (Figure 2). Differences in flap necrosis occurrence rate and mean percentage of surviving flap area of each group were compared.

Statistical analysis

Data analysis was performed using the Statistics Package for Social Science (SPSS, Version 29.0,

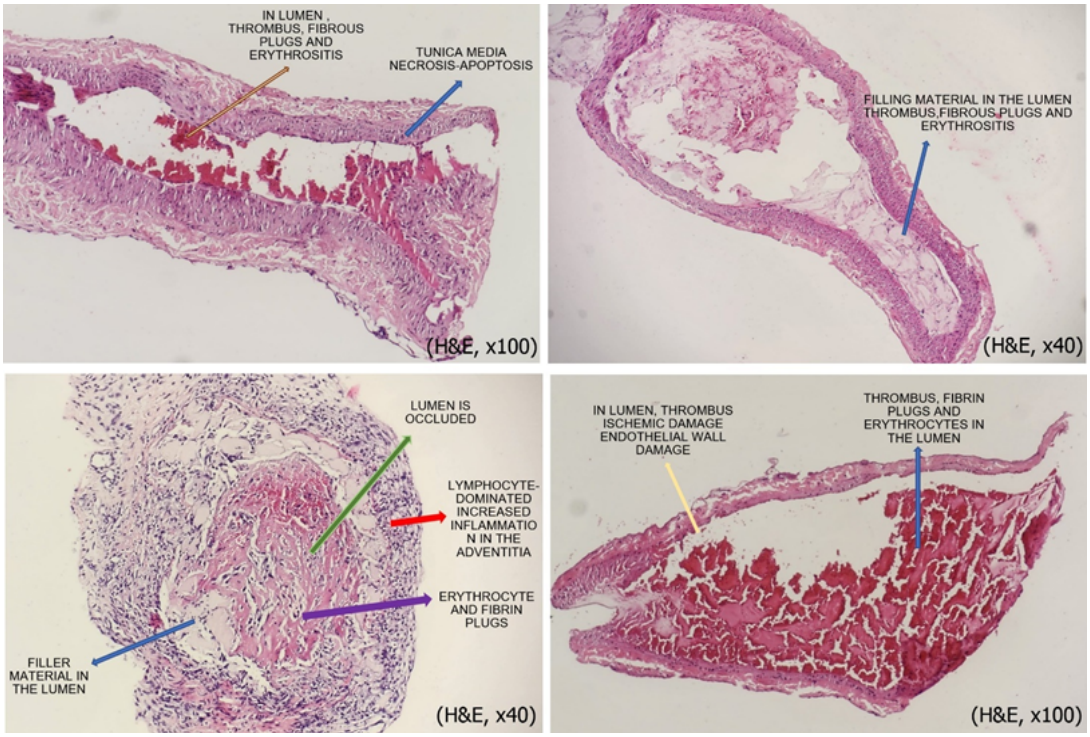

Figure 1. Degeneration-necrosis, inflammation, fibroblast and collagen densities in the intima and media layers of the vessels, the presence of thrombus in the vessels, the presence of edema, PMNL, lymphocyte, mast cell, macrophage and eosinophil percentages and the presence of calcification were evaluated histopathologically.

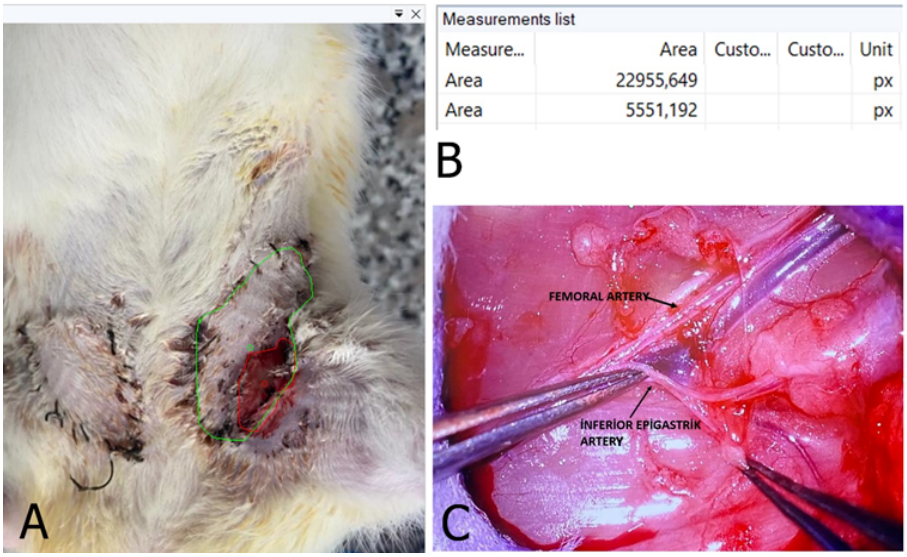

Figure 2. (A,B) The percentage of surviving area of each flap was measured with Digimizer Image Analysis Software, (C) inferior epigastric artery.

IBM Corp., NY, USA). Characteristics of patients, as n (percent) or median (minimum-maximum) for categorical and continuous variables, respectively, were reported. The Kruskal Wallis H test was used to compare the median of independent groups. Nominal variables were compared using a two-tailed chi-square or Fisher test. In pairwise comparisons between dependent measures, multiple tests were evaluated with the Bonferroni correction. A p-value was set at <0.05 for statistical significance.

Results

A total of 40 flaps in 20 rats were divided into five groups with eight flaps in each group. When the percentage of flap necrosis measured in the first week was examined, the mean values were 0.6% (min 0.3-max 13.7) in the CaHa Group 1, 1.7% (min 0.2-max 22.7) in the PLLA Group 2, 0.7% (min 0.2-max 12.6), in the AG Group 3, 25.4% (min 1.2-max 99.4)) in the HA Group 4 and 1.5% (min 0.5-max 5.9) in the SP Group 5 (p=0.036) (Table 1). It was determined that there

Table 1. Percentage of flap necrosis between the groups measured at the first week

Groups (n=40)	CaHa[1] (n=8)	PCL[2] (n=8)	AG[3] (n=8)	HA[4] (n=8)	SP[5] (n=8)	p	Post-HOC
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)		
Flap necrosis (%) (1st Week)	0.6 (0.3-13.7)	1.7 (0.2-22.7)	0.7 (0.2-12.6)	25.4 (1.2-99.4)	1.5 (0.5-5.9)	0.036	1-4;2-4;3-4

AG: Agarose gel, CaHa: Calcium hydroxylapatite, HA: Hhyaluronic acid, PCL: Polycaprolactone

was a statistically significant difference in flap necrosis value between the groups ($p<0.05$). Post-HOC test was performed to determine which groups caused the difference and determined that the differences were due to the HA group (group 4) in which the highest percentage of necrosis was detected.

In the histopathological examination of biopsy samples, the intima and media degenerations occurring in Groups 1-5 according to hours are summarized in Table 2. When the data were examined, it was seen that there was a statistically significant difference between the groups at all times and in all groups ($p<0.05$). At 24 hours, the highest intima damage in the vessels was in the CaHA group (group 1), while the highest media damage was in the HA group (group 4). At week 1, the highest intima and media damage was in the HA group (group 4).

whole lumen was seen at all times in the HA group, but it was seen in only one subject at the 24th hour in the PCL group and was not seen in the other groups.

The distribution of PMNL, lymphocyte, mast cell, macrophage, and eosinophil measurements by hours in Groups 1-5 is given in Table 4. When the table is examined, it was determined that there was a statistically significant relationship between the groups in PMNL measurements at the 1st and 24th hours and the 1st week, in all measurements except the initial measurement in lymphocytes, in mast measurements at the 24th hour and the 1st week, and in macrophage measurements only at the 1st week ($p<0.05$). No statistically significant relationship was observed between the groups in eosinophil measurements.

When inflammation, fibroblast and collagen densities, edema, and calcification findings were evaluated, no

Table 2. Intima and media degenerations that occurred in Groups 1-5 according to hours and distribution of degeneration-necrosis measurements among groups

Degeneration-Necrosis (%) (N=40)	CaHa[1] (n=8)	PCL[2] (n=8)	AG[3] (n=8)	HA[4] (n=8)	SP[5] (n=8)	p	Post-HOC
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)		
Intima							
Hour 0	10 (5-20)	0.5 (0-3)	2 (1-2)	0 (0-0)	0 (0-0)	<0.001	1-2;1-4;1-5;3-4;3-5
1st hour	35 (10-40)	12.5 (10-40)	60 (10-80)	7.5 (1-40)	0 (0-5)	<0.001	1-4;1-5;2-3;2-5;3-4;4-5
3rd hour	35 (20-60)	20 (10-40)	45 (20-60)	20 (15-40)	15 (0-30)	0.002	1-2;1-5;2-3;3-4;3-5
24th hour	55 (40-60)	40 (20-60)	45 (20-60)	35 (20-60)	2 (0-5)	<0.001	1-5;2-5;3-5;4-5
1st Week	30 (10-50)	20 (10-40)	22.5 (10-40)	40 (20-50)	5 (2-10)	<0.001	1-5;2-4;2-5;3-5;4-5
Media							
Hour 0	10 (3-20)	0.5 (0-3)	1 (1-2)	1 (0-2)	0 (0-0)	<0.001	1-2;1-3;1-4;1-5;3-5;4-5
1st hour	35 (30-40)	12.5 (10-20)	50 (30-70)	15 (2-50)	0 (0-2)	<0.001	1-2;1-5;2-3;3-4;3-5;4-5
3rd hour	40 (30-60)	30 (20-40)	50 (30-60)	35 (20-50)	25 (0-40)	0.002	1-2;1-5;2-3;3-5
24th hour	60 (30-70)	45 (10-70)	50 (20-70)	60 (30-70)	5 (2-10)	<0.001	1-5;2-5;3-5;4-5
1st Week	40 (30-60)	30 (20-40)	30 (20-80)	45 (20-60)	7.5 (0-10)	<0.001	1-5;2-5;3-5;4-5

AG: Agarose gel, CaHa: Calcium hydroxylapatite, HA: Hhyaluronic acid, PCL: Polycaprolactone

Thrombus formation within the artery after filler injection according to hours data in Groups 1-5 are summarized in Table 3. When the data were examined, it was seen that there was a statistically significant difference between the groups at all times and in all groups. ($p<0.05$). It was observed that thrombus filling the

significant difference was found between the groups.

Discussion

Dermal fillers have become increasingly prevalent in the field of cosmetic procedures, with a surge in demand over the past decade. The ease of use,

Table 3. Distribution of Thrombus Measurements Among Groups

Thrombus (n=40)	CaHa [1] (n=8)	PCL [2] (n=8)	AG [3] (n=8)	HA [4] (n=8)	SP (n=8)	p
	n (%)	n (%)	n (%)	n (%)	n (%)	
Thrombus (Hour 0)						0.002
None	3 (37.5)	8 (100)	8 (100)	6 (75)	8 (100)	
Lightly layered fibrin thrombus adhesive to the endothelium (+)	5 (62.5)	0 (0)	0 (0)	2 (25)	0 (0)	
Thrombus filling 50% of the lumen (++)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Thrombus filling the whole lumen (+++)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
Thrombus (1st hour)						<0.001
None	0 (0)	5 (62.5)	3 (37.5)	0 (0)	8 (100)	
Lightly layered fibrin thrombus adhesive to the endothelium (+)	6 (75)	3 (37.5)	2 (25)	1 (12.5)	0 (0)	
Thrombus filling 50% of the lumen (++)	2 (25)	0 (0)	3 (37.5)	2 (25)	0 (0)	
Thrombus filling the whole lumen (+++)	0 (0)	0 (0)	0 (0)	5 (62.5)	0 (0)	
Thrombus (3rd hour)						**<0.001**
None	5 (62.5)	8 (100)	2 (25)	0 (0)	5 (62.5)	
Lightly layered fibrin thrombus adhesive to the endothelium (+)	3 (37.5)	0 (0)	4 (50)	1 (12.5)	1 (12.5)	
Thrombus filling 50% of the lumen (++)	0 (0)	0 (0)	2 (25)	3 (37.5)	0 (0)	
Thrombus filling the whole lumen (+++)	0 (0)	0 (0)	0 (0)	4 (50)	2 (25)	
Thrombus (24th hour)						**<0.001**
None	0 (0)	3 (37.5)	2 (25)	0 (0)	8 (100)	
Lightly layered fibrin thrombus adhesive to the endothelium (+)	4 (50)	2 (25)	2 (25)	1 (12.5)	0 (0)	
Thrombus filling 50% of the lumen (++)	4 (50)	2 (25)	4 (50)	4 (50)	0 (0)	
Thrombus filling the whole lumen (+++)	0 (0)	1 (12.5)	0 (0)	3 (37.5)	0 (0)	
Thrombus (1st Week)						**<0.001**
None	0 (0)	8 (100)	2 (25)	1 (12.5)	8 (100)	
Lightly layered fibrin thrombus adhesive to the endothelium (+)	5 (62.5)	0 (0)	5 (62.5)	5 (62.5)	0 (0)	
Thrombus filling 50% of the lumen (++)	3 (37.5)	0 (0)	1 (12.5)	1 (12.5)	0 (0)	
Thrombus filling the whole lumen (+++)	0 (0)	0 (0)	0 (0)	1 (12.5)	0 (0)	

efficacy, and perceived safety of these treatments have contributed significantly to their popularity. However, despite their impressive safety profile, the growing prevalence of dermal filler injections has also been accompanied by a concerning rise in adverse events and complications, although proper patient selection, appropriate product selection, and meticulous injection techniques are crucial in minimizing the risk of adverse events (2).

Complications associated with dermal fillers can be broadly classified into early, occurring up to several days post-treatment such as injection site reactions, infection, hypersensitivity, lumps, asymmetries, vascular complications, and late complications occurring from weeks to years post-treatment such as atypical infection, biofilm, foreign body granuloma, migration (5). Although the probability of vascular injury caused by dermal fillers is reported to be less than 0.05%, when dermal fillers are accidentally injected into the blood vessels, they can lead to a range of serious complications, including persistent skin necrosis, ophthalmoplegia, permanent unilateral or bilateral vision loss, and stroke (7,8). It was reported that the most common vascular occlusion complication reported in patients undergoing facial filler was vision loss, and most cases resulting in blindness did not show complete recovery despite treatment due to the vulnerability of the retina to ischemia (7). In a previous review conducted by Beleznay et al., autologous fat was found to be responsible for 47.9% of cases of unilateral permanent blindness, followed by HA (23.5%), collagen (8.2%), poly-L-lactic acid (3.1%), and calcium hydroxylapatite (2%) (7).

Therefore, it is very important to have detailed knowledge about vascular complications that are more serious and require urgent intervention compared with other complications. To our knowledge, there is no study in the literature comparing the effects of different filler materials following intravascular injection. This experimental animal study was planned to investigate the rate of flap necrosis and histopathological changes developing within the artery following the intravascular injection of four different structural fillers.

In vascular complications, which can also be encountered as embolia cutis medicamentosa (ECM) in the literature, there may be an increase in vascular

Table 4. Distribution of PMNL, Lymphocytes, MAST Cells, Macrophage and Eosinophil Measurements among Groups

Variables (N=40) (%)	CaHa[1] (n=8)	PCL[2] (n=8)	AG[3] (n=8)	HA[4] (n=8)	SP[5] (n=8)	p	Post-HOC
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)		
PMNL							
Hour 0	0 (0-0)	0 (0-100)	0 (0-0)	0 (0-0)	0 (0-0)	0.406	
1st hour	0 (0-0)	0 (0-100)	0 (0-100)	100 (50-100)	100 (100-100)	<0.001	1-4;1-5;2-4;2-5;3-4;3-5
3rd hour	0 (0-98)	0 (0-100)	0 (0-100)	0 (0-50)	92.5 (0-100)	0.163	
24th hour	0 (0-50)	100 (99-100)	100 (95-100)	20 (20-40)	91.5 (80-96)	<0.001	1-2;1-3;1-5;2-4;2-5;3-4
1st Week	0 (0-3)	7.5 (0-100)	0 (0-2)	2 (0-10)	0 (0-0)	0.002	1-2;2-3;2-5;3-4;4-5
Lenfocytes							
Hour 0	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000	
1st hour	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-50)	0 (0-0)	0.013	1-4;2-4;3-4;4-5
3rd hour	0 (0-100)	0 (0-100)	0 (0-0)	100 (50-100)	0 (0-10)	<0.001	1-4;2-4;3-4;4-5
24th hour	25 (0-100)	0 (0-0)	0 (0-5)	75 (20-80)	5 (2-10)	<0.001	1-2;1-4;2-4;2-5;3-4
1st Week	69 (50-95)	80 (0-87)	77.5 (0-86)	73.5 (58-85)	100 (100-100)	<0.001	1-5;2-5;3-5;4-5
Mast							
Hour 0	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000	
1st hour	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000	
3rd hour	0 (0-2)	0 (0-2)	0 (0-0)	0 (0-0)	0 (0-0)	0.545	
24th hour	0 (0-0)	0 (0-1)	0 (0-0)	0 (0-0)	1 (0-10)	0.007	1-5;2-5;3-5;4-5
1st Week	0 (0-0)	1 (0-3)	2 (0-4)	0 (0-15)	0 (0-0)	<0.001	1-2;1-3;2-5;3-4;3-5
Macrophage							
Hour 0	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000	
1st hour	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000	
3rd hour	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000	
24th hour	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000	
1st Week	27 (0-40)	4 (0-10)	15 (10-20)	24 (0-40)	0 (0-0)	<0.001	1-2;1-5;2-3;2-4;3-5;4-5
Eosinophil							
Hour 0	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000	
1st hour	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000	
3rd hour	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	1.000	
24th hour	0 (0-2)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.406	
1st Week	1.5 (0-10)	0 (0-0)	0 (0-5)	0 (0-2)	0 (0-0)	0.058	

AG: Agarose gel, CaHa: Calcium hydroxylapatite, HA: Hhyaluronic acid, PCL: Polycaprolactone

problems depending on the amount of drug, and similarly, different fillers such as collagen (9), or fat (10).

While it is not clear why some fillers of the same amount cause a greater degree of vascular compromise, it may be due to the tendency of dermal fillers to activate the inflammatory process and/or the coagulation process resulting in the progression to irreversible necrosis of the involved tissues (1). For these reasons, it is important to know the structure, properties, tissue behavior of filling materials, and pathophysiology of vascular occlusions induced by dermal fillers.

Calcium Hydroxylapatite (CaHA)

CaHA consists of 30% calcium hydroxylapatite microspheres and 70% sodium carboxy-methylcellulose (CMC), after injection, the CMC gel is rapidly broken down while the CaHA microspheres act as a sort of platform for newly synthesized collagen (10). It is used in the face for mid-deep to deep wrinkles and folds and to correct volume loss and contours. Microscopically, CaHA is easily recognizable as 25- to 45- µm blue-gray, round-oval particles, surrounded by fibrin (11).

The onset of nodules is the most commonly reported adverse event, and its incidence was found to be 3% in a cohort study (12). In vitro analysis has shown limited reversibility of vascular compromise with calcium hydroxyapatite (13).

Polycaprolactone (PCL)

The PCL-based filler is composed of PCL microspheres (30%) suspended in an aqueous carboxymethyl cellulose (CMC) gel carrier (70%) (14). CMC gel is absorbed within the first 6-8 weeks, and the volume loss caused by the absorption of the gel is replaced by neocollagenesis caused by PCL (15).

Polycaprolactone (PCL) based fillers can rarely

cause complications such as nodules or granulomas. Nodule formation is a minor complication frequently associated with fillers, including HAs. In the periorbital region and very superficial applications, PCL-based fillers may very rarely cause xanthelasma-like products (16). It is reported in a study that, in 10 cases where PCL fillings caused vascular embolism complications, heparin and nitroglycerin treatment resulted in significant improvement in blood flow and reduction in ischemia (17).

Agarose Gel (AG)

Agarose is a saccharide polymer (D-galactose and 3,6-anhydro-L-galactopyranose sugars) extracted from red algae (Rhodiphyta) (18). AG is viscous-elastic at temperatures below 45C°. It is slowly degraded by macrophages, and intracellular metabolism through the pentose cycle (19). It is hydrocolloid and nonhydrophilic and causes no mid-term or long-term edema in the surrounding tissues (18). It contains no chemical cross-linking materials such as BDDE, or polyethylene glycol (PEG), which are found in crosslinked HA fillers.

Although there is no reported case of vascular occlusion in the literature, in an experimental study conducted on rats, it was determined that the mean flap survival rate was 92% after the urokinase treatment of arterial occlusion created with agarose gel (20).

Hyaluronic Acid (HA)

The use of cross-linked HA fillers has become the most commonly used filling material in aesthetic practices. Cross-linking is a process that modifies the molecular structure of HA, making it more resistant to degradation and increasing its durability within the skin. Among the various crosslinking agents, 1,4-Butanediol diglycidyl ether (BDDE) has emerged as a widely used option due to its versatility and effectiveness. Different brands have different crosslinking technologies, the degree of modification ranging from 1 to 10%, the molecular weight of 100-600 kDa, and HA concentrations (HAC) ranging from 15 to 24 mg/mL with different shear elastic moduli (G') (21,22). Cohesivity or the capacity to resist fragmentation and dispersal, MoD, and the ability of a gel to take up water (swelling factor) may be important in the intravascular behavior of dermal fillers and their response to reversal agents (22,23).

The vaso-occlusive process induced by intravascular injection of HA gel may further increase the size of the plug, creating a prothrombotic state (24). HA platelet interaction appears to trigger hemostasis and platelet aggregation. Experimental studies on murine have shown that the platelet-rich white thrombus within the gel plug subsequently forms a fibrin-rich red thrombus (25). This rapid process suggests an inflammatory process initiated by the HA bolus rather than anoxic endothelial damage, and the nature of the early white thrombus points to a direct role in platelet interaction with intravascular HA (26). The pro-inflammatory, platelet-activating effect of HA, which begins with platelet-derived hyaluronidase 2 and leukocyte binding, has been described in many studies (27).

In a comparative study showing that HA induces a thrombotic response, thrombus formation was evident in rabbit ears after Restylane (HA) injection and showed a higher rate of total, irreversible vessel occlusion compared with injections of lower viscosity, small-particle polymethylmethacrylate (PMMA) filler whereas this effect was not seen (28).

Besides the thrombogenicity of vasoinoculated HA gels, it is considered an advantage in terms of safety that HA fillers are reversible with hyaluronidase and can be applied around the affected blood vessels. In animal studies a significant flap survival benefit has been shown in animals treated with dual therapy—featuring thrombolytic agents (urokinase or alteplase) combined with hyaluronidase when compared with hyaluronidase alone (25). Cavallini et al showed in animal models that immediate intervention within the first 4 hours after a vascular event significantly reduced ear skin necrosis (29).

In our study, it was observed that the thrombus filling the entire lumen was significantly higher in the HA group than in the non-HA groups, starting from the first hour at all times. It was also observed that this finding was reflected in the flap necrosis rates that there was a significant difference in favor of the HA group compared to the non-HA filler groups, and that this was consistent with the thrombus formation potential of HA.

To our knowledge, there is no similar study in the literature. It is noteworthy that the rate of flap necrosis and thrombus formation completely occluding the vessel lumen was statistically significantly higher in the HA group (Group 4) than in the other groups. The low percentages of flap necrosis in Groups 1, 2, and 3, despite no treatment, are worth evaluating in terms of questioning the flap model or the amount of filler injected. The main limitations of our study are the use

of a limited number of rats for the measurement of flap necrosis percentages and the exclusion of the effects of hyaluronidase and antithrombotic and thrombolytic therapies.

Conclusion

It was concluded that besides statistically significant histopathological differences between each filler within the artery, in particular, the HA group caused thrombus, occluding completely the lumen, significantly more than the other groups, and accordingly, the flap necrosis rate was significantly higher than the non-HA filler groups. This result highlighted the importance of antithrombotic and thrombolytic therapy, especially in HA fillers.

References

1.DeLorenzi C. Complications of Injectable Fillers, Part 2: Vascular Complications. Aesthetic Surgery Journal. 2014 May 1;34(4):584–600.

2.COHEN JL. Understanding, Avoiding, and Managing Dermal Filler Complications. Dermatologic Surgery. 2008 Jun;34(s1): S92–9.

3.Hsieh YH, Lin CW, Huang JS, Yeh PT. Severe ocular complications following facial calcium hydroxylapatite injections: Two case reports. Taiwan Journal of Ophthalmology. 2015 Mar;5(1):36–9.

4.Pavicic T, Funt D. Dermal fillers in aesthetics: an overview of adverse events and treatment approaches. Clinical, Cosmetic, and Investigational Dermatology. 2013 Dec; 6:295.

5.Halepas S, Peters SM, Goldsmith JL, Ferneini EM. Vascular Compromise After Soft Tissue Facial Fillers: Case Report and Review of Current Treatment Protocols. Journal of Oral and Maxillofacial Surgery. 2020 Mar;78(3):440–5.

6.Beleznay K, Carruthers JDA, Humphrey S, Jones D. Avoiding and Treating Blindness From Fillers. Dermatologic Surgery. 2015 Oct;41(10):1097–117.

7.Chen Y, Wang W, Li J, Yu Y, Li L, Lu N. Fundus artery occlusion caused by cosmetic facial injections. Chinese medical journal. 2014;127(8):1434–7.

8.Shier MR, Wilson RF. Fat embolism syndrome: traumatic coagulopathy with respiratory distress. Surgery annual. 1980; 12:139–68.

9.Jacovella PF. Calcium Hydroxylapatite Facial Filler (RadiesseTM): Indications, Technique, and Results. Clinics in Plastic Surgery. 2006 Oct;33(4):511–23.

10.Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L. Adverse reactions to injectable soft tissue fillers. Journal of the American Academy of Dermatology. 2011 Jan;64(1):1–34.

11.Kadouch JA. Calcium hydroxylapatite: A review on safety and complications. Journal of Cosmetic Dermatology. 2017 Mar 1;16(2):152–61.

12.Yankova M, Pavicic T, Frank K, Schenck TL, Beleznay K, Gavril DL, et al. Intraarterial Degradation of Calcium Hydroxylapatite Using Sodium Thiosulfate – An In Vitro and Cadaveric Study. Aesthetic Surgery Journal. 2021 Feb 5;41(5):NP226–36.

13.Christen MO, Vercesi F. Polycaprolactone: How a Well-Known and Futuristic Polymer Has Become an Innovative Collagen-Stimulator in Esthetics. Clinical, Cosmetic, and Investigational Dermatology. 2020 Jan; Volume 13:31–48.

14.Kim JA, Van Abel D. Neocollagenesis in human tissue injected with a polycaprolactone-based dermal filler. Journal of Cosmetic and Laser Therapy. 2014 Oct 27;17(2):99–101.

15.Lin S, Christen M. Polycaprolactone-based dermal filler complications: A retrospective study of 1111 treatments. Journal of Cosmetic Dermatology. 2020 Jun 18; Aug;19(8):1907-1914

16.Khan A, Wang T, Zhang P, Qi L, Gong L, Cui H. The Efficacy of Heparin and Nitroglycerin in Managing Vascular Embolism Complications from Polycaprolactone (PCL) Fillers: A Clinical Study. Aesthetic plastic surgery 2025 Feb;10.1007/s00266-02404608-8.

17.Scarano A, Carinci F, Piattelli A. Lip augmentation with a new filler (agarose gel): a 3-year follow-up study. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics. 2009 Aug 1; 108(2):e11-15.

18.CHRISTENSEN LH. Host Tissue Interaction, Fate, and Risks of Degradable and Nondegradable Gel Fillers. Dermatologic Surgery. 2009 Oct; 35:1612–9.

19.Buhsem O, Aksoy A. Omer Buhsem et al. The Effectiveness of Urokinase and Vitamin C in the Treatment of Arterial Occlusion Caused by Agarose Gel Injection 7248 Tob Regul Sci.TM 2021;7(6-1): 7248-7253. Tobacco Regulatory Science. 2023 Jul 27;2021;7(6-1):7248–53.

20.Rohrich RJ, Bartlett EL, Dayan E. Practical Approach and Safety of Hyaluronic Acid Fillers. Plastic and Reconstructive Surgery - Global Open. 2019 Jun;7(6): e2172.

21.Edsman K, Nord LI, Öhrlund Å, Lärkner H, Kenne AH. Gel Properties of Hyaluronic Acid Dermal Fillers. Dermatologic Surgery. 2012 Jul;38(7pt2):1170–9.

22.Hee CK, Shumate GT, Narurkar V, Bernardin A, Messina DJ. Rheological Properties and In Vivo Performance Characteristics of Soft Tissue Fillers. Dermatologic Surgery. 2015 Dec;41(Supplement 1): S373–81.

23.Chiang C, Zhou S, Liu K. Intravenous Hyaluronidase with Urokinase as Treatment for Arterial Hyaluronic Acid Embolism. Plastic and reconstructive surgery. 2016 Jan;137(1):114–21.

24.Chen Y, Zhang Y, Luo SK. Experimentally Induced Arterial Embolism by Hyaluronic Acid Injection. Plastic and Reconstructive Surgery. 2019 Apr;143(4):1088–97.

25.Tan KT, Lip GYH. Red vs white thrombi: treating the right clot is crucial. Archives of internal medicine. 2003 Oct;163(20):2534–5.

26.de la Motte C, Nigro J, Vasanji A, Rho H, Kessler S, Bandyopadhyay S, et al. Platelet-Derived Hyaluronidase 2 Cleaves Hyaluronan into Fragments that Trigger Monocyte-Mediated Production of Proinflammatory Cytokines. The American Journal of Pathology. 2009 Jun;174(6):2254–64.

27.Nie F, Xie H, Wang G, An Y. Risk Comparison of Filler Embolism Between Polymethyl Methacrylate (PMMA) and Hyaluronic Acid (HA). Aesthetic Plastic Surgery. 2019 Mar 1;43(3):853–60.

28.Cavallini M, Gazzola R, Metalla M, Vaienti L. The Role of Hyaluronidase in the Treatment of Complications from Hyaluronic Acid Dermal Fillers. Aesthetic Surgery Journal. 2013 Nov 1;33(8):1167–74.

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REVIEW ARTICLE

Overview of Cryptosporidium spp.

Cryptosporidium spp.'ye Genel Bakış

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ABSTRACT

Cryptosporidium spp., the causative agent of Cryptosporidiosis, is an obligate intracellular and extracytoplasmic protozoan. Cryptosporidium spp. emerges as a public health problem transmitted by contaminated water and food due to its features such as the widespread occurrence of oocysts in nature, low infective doses, ability to pass through the filters of treatment plants, resistance to disinfectants, and ability to survive in water and soil for months at appropriate humidity and temperature. Transmission to humans usually occurs through the fecal-oral route by ingestion of oocysts. However, endogenous auto-infection can occur. Respiratory transmission has been reported. Cryptosporidium spp. infections may lead to serious life-threatening clinical conditions in children under two years of age and immunosuppressed patients. To prevent water and foodborne cryptosporidiosis outbreaks and protect public health, the causes of Cryptosporidium oocysts contaminating these resources should be determined, necessary precautions should be taken and combat methods should be determined. In this review, information on the life cycle, epidemiology, clinical findings, diagnosis, protection, and control of Cryptosporidium spp. is presented.

Keywords: Cryptosporidium, immunosuppressive, protozoan

ÖZ

Cryptosporidiosis etkeni olan Cryptosporidium spp., zorunlu intrasellüler ve ekstrasitoplazmik bir protozoondur. Cryptosporidium spp., ookistlerinin doğada yaygın olarak bulunması, enfektif dozlarının düşük olması, arıtma tesislerinin filtrelerinden geçebilmeleri, dezenfektanlara karşı dirençli olmaları, su ve toprakta uygun nem ve sıcaklıkta aylarca canlı kalabilmeleri şeklinde sıralanabilecek özellikleriyle kontamine su ve gıda ile bulaşan bir halk sağlığı problemi olarak karşımıza çıkmaktadır. İnsanlara bulaş genellikle ookistlerin fekal oral yolla alınmasıyla gerçekleşir. Ancak endojen oto-enfeksiyon da gelişebilmektedir. Respiratuvar bulaş bildirilmiştir. Cryptosporidium spp. enfeksiyonları iki yaş altı çocuklarda ve immünsupresif hastalarda hayatı tehdit eden ciddi klinik tablolara neden olabilmektedir. Su ve gıda kaynaklı cryptosporidiosis salgınlarının önlenmesi ve halk sağlığının korunması için Cryptosporidium ookistlerinin bu kaynakları kontamine etme nedenleri belirlenerek gerekli önlemlerin alınması ve mücadele yöntemlerinin belirlenmesi gerekmektedir. Bu derlemede Cryptosporidium spp.'nin yaşam döngüsü, epidemiyolojisi, klinik bulguları, tanısı, korunma ve kontrolü ile ilgili bilgilere yer verilmiştir.

Anahtar Kelimeler: Cryptosporidium, immünsupresif, protozoon,

Introduction

Cryptosporidium spp. is an opportunistic parasitic agent transmitted through oocysts in contaminated water and food. It can infect mainly the intestines and many organs, such as the lungs, pancreas, and gall bladder (1). Along with Giardia, it is the most common parasite in humans worldwide (2).

Cryptosporidium species were first described by Clarke in 1885 as spore clusters on the epithelium of a mouse stomach. In 1905, Ernest Edward Tyzzer demonstrated them in the gastric mucosa cells of mice and named them Cryptosporidium, which means hidden sporocysts in ancient Greek, because they do not have sporocysts in their oocysts, unlike other Coccidia species. The disease it causes has been called Cryptosporidiosis (3). Cryptosporidium spp., the agent of Cryptosporidiosis, is an obligate, intracellular, and extracytoplasmic protozoan (4).

Cryptosporidium species are included in the Apicomplexa group, Sporozoasida class, Coccidiasina subclass, Eucoccidiorida order, Eimeriorina suborder, and Crptosporidiidae family (5). There are approximately 22 species of Cryptosporidium spp., which are either zoonotic or anthroponotic. While the zoonotic species of the agent, Cryptosporidium parvum, infects both humans and animals, the anthroponotic species Cryptosporidium hominis is only a pathogen for humans (6). Additionally, C. canis, C. felix, C. meleagridis, and C. muris can also cause human infection (7).

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Life Cycle

The life cycle of Cryptosporidium spp., characterized by six stages, the alternation of sexual and asexual fertilization, is completed in a single host. The only stage the parasite spends outside the host is the oocyst stage (8).

In the first stage of the life cycle (excystation), four infective sporozoites are released from the oocyst ingested by the host as a result of opening in the small intestine. These sporozoites enter the intestinal epithelial cells. The intestinal microvilli folds surround the parasite to form a membrane sac. In this way, the parasite shows an intracellular-extracytoplasmic settlement in the intestinal epithelial cells of the host (9). In the second stage of the life cycle (merogony), sporozoites first transform into trophozoites and then into type 1 meronts by asexual reproduction. 6-8 merozoites are formed from type 1 meronts. These merozoites enter new cells and begin sexual reproduction by reproducing asexually and transforming into either type 1 or type 2 meronts (4 merozoites). The third stage of the life cycle of Cryptosporidium spp. is gametogony. Merozoites formed from type 2 meronts transform into macro and microgametocytes, and then into either macro or microgametes. In the fourth stage of the life cycle (fertilization), microgametes fuse with macrogametes to form an oocyst (zygote). In the fifth stage, the oocyst wall is formed. While a two-layered oocyst wall is formed in approximately 80% of oocysts, a thin-walled structure is formed in 20%. The final stage of development, the sporogony stage, takes place inside the parasitic vacuole. After meiosis, four sporozoites are formed inside the thin-walled oocysts. These oocysts are ejected into the intestinal lumen and hatch there without leaving the host (5). This process is responsible for the recurrence of infection in the host, which is called autoinfection (4). Chronic cryptosporidiosis is observed in cases where the host cannot destroy this parasite. Thick-walled type 2 oocysts are sporulated and excreted with the host feces. Thus, the life cycle is completed in a single host (monoxen). Oocysts shed in the environment penetrate new hosts and begin a new life cycle (5).

Epidemiology

Cryptosporidium oocysts are widely found in nature due to their ubiquitous properties (10). In recent years, Cryptosporidium spp. has come to the forefront as a public health problem transmitted through contaminated water and food due to its characteristics, such as low infective doses of its oocysts, no necessity for a new host or maturation process, long incubation period, the ability of oocysts excreted in feces contaminating the environment for up to 60 days even if clinical symptoms are not seen, being able to pass through the filters of treatment plants with their 4-6 µm size, being able to be transported in air and water for long distances due to their small size, being resistant to disinfectants (e.g., chlorine), and being able to survive in water and soil for months at appropriate humidity and temperature (11-13). Therefore, waterborne outbreaks caused by Cryptosporidium spp. have been reported in history. This agent has been included in the category B pathogen list by the Centers for Disease Control and Prevention (CDC) (14).

Outbreaks caused by this parasite, particularly those from swimming pools, have been reported since the 1990s in many developed countries, including the United States (US), Canada, England, Scotland, and Japan. However, the most important of these occurred in Milwaukee, USA, in the spring of 1993, where 403,000 cases were reported (15). The Milwaukee outbreak is the largest waterborne outbreak on record, and during the outbreak, the presence of Cryptosporidium oocysts was shown in 90% of sewage samples, 75% in river water samples, and 28% in drinking water samples. Also in 1984, an outbreak of cryptosporidiosis occurred in two separate locations in a residential area with 5,900 people in Texas. It was determined that the drinking water for these two centers was supplied from the same artesian well, that the water was circulated without being filtered, while it was chlorinated just before being released to the network. After the outbreak, dye tests were used to definitively establish that sewage effluents were mixed with drinking water and that this mixing occurred at irregular intervals. However, the location where sewage effluents are mixed with drinking water could not be determined. In 1987, in an outbreak in West Georgia where an estimated 13,000 people were affected, it was determined that drinking water criteria met federal and state standards at the time, but when the stools of 489 people were examined, 61% were found to be positive for Cryptosporidium. Of the 322 people using alternative drinking water, 20% were found to be Cryptosporidium positive (3). When the national literature was examined, in a study conducted in the water resources of Mardin, the presence of Cryptosporidium spp. was determined to be 8.92% with the Kinyoun acid-fast staining method (16). In Iğdır

province, in the analysis of 69 spring water samples using native-Lugol, modified acid-fast staining, and nested polymerase chain reaction (nPCR) methods, Cryptosporidium spp. was found to be positive in 1 sample (1.4%) (17).

Access to clean and adequate water and food is currently a problem in underdeveloped countries. It is estimated that the inability of non-industrialized countries to keep up with population growth and the inability to meet the increasing demand for clean and safe drinking water due to migration to urban areas will continue to affect the spread of diseases (18). Therefore, the prevalence of Cryptosporidium spp. infection is higher in developing countries (10). Cryptosporidiosis is reported to occur at an incidence of 1-9% in people with a healthy immune system in developed countries and at an incidence of 7-20% in developing countries (19).

Epidemiological studies reveal that the geographical distribution of Cryptosporidium spp. varies around the world. Studies have reported that C. parvum and C. hominis are responsible for 90% of cryptosporidiosis cases (5). While C. hominis is common in North and South America, Australia, China, Japan, and Africa, C. parvum is more common in Europe and New Zealand, especially in the UK (20).

Cryptosporidium spp. infections can cause serious life-threatening clinical conditions in children under two years of age (19). This age group may pose a risk for prolonged Cryptosporidium spp. infection even if immunodeficiency tests are normal because there may be defects in the natural immune system and lymphocyte functions (21). When international data are examined in the literature, the Cryptosporidium positivity rate in children presenting with diarrhea varies between 10 and 25% (22). In studies conducted in our country, in Van and Izmir, among children presenting with acute diarrhea, the presence of Cryptosporidium spp. oocysts in stool samples were reported at a frequency of 2.2% and 13.5% (19). In another study, it was observed that the prevalence of Cryptosporidium spp. was higher in children, especially in prolonged diarrhea (23).

Cryptosporidium spp. can cause severe infection, especially in immunocompromised individuals, due to its intracellular location and its ability to cause autoinfection (6). The rate of Cryptosporidium infection in HIV-positive patients is 14% in developed countries and 24% in developing countries. In studies conducted on immunocompromised individuals in Türkiye, the prevalence of Cryptosporidium spp. has been reported to be between 0-35.5% (5).

The parasite is transmitted through infected food and drinks, contaminated water (swimming pools, hot springs, jacuzzis, lakes, rivers, and streams) with human or animal feces, and uncooked consumption of contaminated food (19). In recent years, transmission through unpasteurized fruit juices has been frequently mentioned (7). People are usually infected by ingesting oocysts via the fecal-oral route (6). However, endogenous autoinfection can also occur. The transmission route of oocysts can be summarized as human to human, animal to human, and environment to human. This parasite can pass from the waste of infected animals to drinking water sources during periods of heavy rainfall (7). Respiratory transmission has also been reported (24).

Family members, daycare centers, pre-school, and similar institutions constitute an important source of direct transmission from person to person. It has been reported that the infection rate is high in some occupational groups (veterinarians, livestock breeders, and farm workers), those traveling to endemic areas, and those in close contact with infected people (25). Farm animals are an important source of transmission. Cattle, sheep, goats, and pigs play a role as reservoirs in the transmission of the disease agent (26). Contamination of the product with manure during production, irrigation water, agricultural workers, food processors, kitchen workers, washing water, kitchen counters, and tools and equipment constitute a potential source of cryptosporidiosis outbreaks. In a study conducted on food industry workers in the Van region, the rate of the asymptomatic carrier was determined as 1.27% (27). Vegetables, fruits, and salads consumed raw without a heating process, unpasteurized milk and apple juice, dairy products, meat, offal, and various seafood (mussels, oysters) are foods that carry a risk in cases of cryptosporidiosis (5,28). In India, the rate of Cryptosporidium spp. was determined as 6% in fresh vegetables (coriander, lettuce, tomatoes, cucumbers, cabbage, red pepper, mint, carrots, and radishes) purchased from different sales points (29).

Clinical Findings

The incubation period of infections caused by Cryptosporidium varies from 5 to 28 days (3). Cryptosporidiosis causes abdominal pain, nausea,

vomiting, diarrhea, weight loss, and anorexia in humans (30). Diarrhea can be acute or chronic, transient, intermittent or continuous, in severe diarrhea, fluid loss can be up to 25 L/day (21).

Infection usually limits itself in immunocompetent individuals and resolves within a few weeks (30). In immunocompromised individuals, the course of infection can be short-term and rapidly resolving diarrhea or chronic diarrhea resulting in life-threatening cholera-like diarrhea, malabsorption, and malnutrition. Symptoms are particularly severe in patients with acquired immunodeficiency syndrome (AIDS), viral diseases such as measles, leukemia, gammaglobulinemia, insulin-dependent diabetes, renal failure, solid organ transplantation, and cancer treatment. In these patients, diarrhea may last longer than two months, and oocyst excretion with feces, severe dehydration, weight loss, and malnutrition may be observed throughout the infection (2,31). Although the main location of Cryptosporidium spp. is the intestines, extraintestinal involvement (bile ducts, pancreas, stomach, respiratory system, kidney) may also be seen in immunocompromised patients. When systematic screening is performed, it has been reported that Cryptosporidium spp. colonization is up to 70%, especially in patients with hyperimmunoglobulin M syndrome, among primary immunodeficiencies, and this leads to serious problems ranging from sclerosing cholangitis to hepatitis and end-stage liver disease (21). It has been reported that biliary system involvement may be seen in 10-30% of patients diagnosed with AIDS from secondary immune deficiencies, that is, it may occur as acalculous cholecystitis, sclerosing cholangitis, and pancreatitis (19). Pulmonary cryptosporidiosis is characterized by cough (10). Intestinal symptoms and fever are frequently observed and may be fatal (7).

Diagnosis

In the diagnosis of Cryptosporidium infections, stool, sputum, or bile samples are evaluated with microscopic, molecular, serological, histopathological, and culture methods (11,32,33).

However, it is difficult to evaluate Cryptosporidium oocysts in direct microscopic examinations due to their small size. Microscopic examination after acid-fast staining is accepted as the minimum method for diagnosis (34). However, it has been reported that the sensitivity of microscopic methods is low, the workload is high and is prone to personnel mistakes (35).

In recent years, with the widespread use of molecular methods, it has been reported that the detection rate of Cryptosporidium spp. in foods has increased, and the sensitivity and specificity of the method are high. (36). Additionally, thanks to genomic studies, detailed information about the biology of the parasite has been obtained. These studies have also helped to understand the antimicrobial resistance mechanism of the parasite (37). Although polymerase chain reaction (PCR) is a fast and highly sensitive method, there are many limiting factors for the method. First of all, an appropriate extraction method should be used for DNA isolation. Bile salts, bilirubin, complex polysaccharides, and other components in stool are structures that can exhibit inhibitory properties in the PCR technique. Therefore, to use the PCR technique routinely in stool-based studies, the risk of contamination should be eliminated and oocysts should be meticulously isolated from the sample. Also, the selection of appropriate primers in terms of the reliability of the test is very important for the sensitivity of the study (5).

In the Enzyme-Linked ImmunoSorbent Assay (ELISA) method, one of the serological diagnostic methods, the stool sample is emulsified with the sample dilution fluid. The diluted stool sample and the conjugate with the monoclonal antibody specific to the parasite antigen are put in the wells of the microplates. These wells contain polyclonal antibodies that will bind to the Cryptosporidium oocyst antigen. If oocysts are present in the stool sample, the polyclonal antibodies in the microplates and oocyst-specific monoclonal antibodies in the conjugate bind. Nonspecific combinations are removed by washing. When the substrate is added, color formation occurs due to the enzyme-antibody-antigen complex (38). The sensitivity of ELISA methods is higher than microscopic methods. However, cross-reaction with other microorganisms limits the use of the method (39).

The direct fluorescent antibody (DFA) method is another serological diagnostic method, which detects the surface antigens of the parasite. This method is more sensitive (99%) and specific (100%) compared to microscopic examinations and is accepted as the reference method. With DFA, the stool sample in which the agent is sought is put on a slide and fixated, and fluorescein isothiocyanate (FITC)-labeled monoclonal antibodies are used. Oocysts are detected by examination using a fluorescence microscope (40).

Histopathological methods were used in the diagnosis

of Cryptosporidium spp. before the 1980s. In intestinal biopsies, eosin and hematoxylin stains were used to search for small and round parasite oocysts in microvilli, but species differentiation could not be made. It is not preferred today because it is an invasive method, requires rapid evaluation of biopsies, is not economical, and requires a long time to process (41).

With culture methods, in colon cancer cells and iliocecal adenocarcinoma cells, it is possible to detect infective oocysts of Cryptosporidium spp. resistant to the effects of inhibitors in water samples. It has also been reported that cell culture methods detect the concentration of Cryptosporidium spp. oocysts. In addition to these positive sides, there are also negative sides, such as the need for various materials for culture and the need for 1-3 days to observe oocyst morphology (42).

Treatment

An effective treatment approach against Cryptosporidium has not yet been established because its basic biology is not fully understood. For this reason, the infection can become chronic and reach life-threatening levels (43-45).

Lack of knowledge about biochemical and metabolic pathways underlies treatment limitations. Studies show that Cryptosporidium does not have functional mitochondria and lacks the active Krebs cycle, but notes that it encodes all glycolytic enzymes. Since the parasite primarily uses anaerobic oxidation of glucose in energy metabolism, enzymes and other products involved in the glycolytic pathway may be potential targets for anticryptosporidial drugs. Other studies conducted with apicomplexan parasites have shown that antiparasitic treatment can be achieved by inhibiting glycolysis (43,45).

ATPases are a family of proteins that actively transport ions and aminophospholipids across the membrane. Studies indicate that Cryptosporidium requires a P-ATPase family to maintain homeostasis during its passage through intracellular and extracellular environments. Additionally, a new P-ATPase (CpATPase3) of this agent has been characterized. It is thought that these pathways can be used for drug development (46).

Some research suggests that essential oils may be effective against C. parvum. It is known that essential oil molecules such as carvacrol, linalool, thymol, and eugenol have antimicrobial effects, but no detailed study has been conducted on their antiprotozoal activities (47).

In the immunocompetent patient group, water and electrolyte replacement therapy is usually sufficient (22). An effective chemotherapeutic agent is needed because it causes life-threatening clinical symptoms in the immunocompromised patient group (44). Paromomycin, rifampicin, rifabutin, HIV protease inhibitors, macrolides, and nitazoxanide are the agents used for treatment in these patients (22,48). Halofuginone and toltrazuril are among the agents whose therapeutic properties are evaluated (49).

A study found that heparin sulfate is effective against this agent. It has been noticed that the effect of Cryptosporidium is inhibited when the C.parvum elongation factor 1a protein (CpEF1a), which is responsible for the spread of this parasite, interacts with heparin. For this reason, it is thought that heparin sulfate may be a promising agent in the treatment of Cryptosporidium (50).

Protection and Control

Consumption of water determined not to comply with drinking water standards leads to serious health problems regarding public health (13). Therefore, Cryptosporidium, which is considered a potential bioterrorism agent resistant to standard water disinfectants, must be purified from water (7). Chlorination alone is not effective in eliminating Cryptosporidium oocysts. Removal of oocysts from drinking water by coagulation, sedimentation, filtration, and disinfection methods are the primary procedures that should be performed in cases of waterborne cryptosporidiosis. Correct application of these traditional processing techniques ensures a success rate of 99% or more. Following the critical times when oocysts can pass through the filtration barrier, a backwash process that ensures the filtration of waste should be applied. The addition of a coagulant or the frequency of the backwash process minimizes the passage of oocysts (6,51,52).

Besides, water inspections should be carried out by relevant institutions, water should be analyzed at regular intervals, and contamination of natural resources or canal systems with agricultural, domestic, and industrial waste should be prevented. Especially in provincial and district centers, it may be appropriate to provide water from the network system to fountains that cannot be supplied with quality source water (13).

Although most parasitic infections can be treated, several control programs should be implemented to reduce infection rates. People should be informed and hygiene conditions should be provided. In case of an outbreak, cooperation should be established between different centers, health authorities and academicians should act together, cases and their contacts should be quickly identified, necessary precautions should be taken and the outbreak should be brought under control in a short time (15).

Conclusion

To prevent water and foodborne cryptosporidiosis outbreaks and protect public health, the causes of Cryptosporidium oocysts contaminating these resources should be determined, necessary precautions should be taken and combat methods should be determined.

Author's Contribution:

DB conducted the literature review and wrote the article.

References

1. Laksemi DA, Suwanti LT, Mufasirin M, Suastika K, Sudarmaja M. Opportunistic Parasitic Infections in Patients with Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome: A Review. Vet World 2019; 13(4): 716-25.

2. Leder K, Weller PF. Epidemiology, clinical manifestations, and diagnosis of cryptosporidiosis. Available from:URL:https://www.uptodate.com/contents/epidemiology-clinical-manifestations-and-diagnosis-ofcryptosporidiosis.

3. Yalçın S, Doğan NY. Determination of Cryptosporidium spp. by Molecular Methods in Different Water Resources of Erzincan Province. Erzincan University Journal of Science and Technology 2019; 12(1): 1-13.

4. Wang P, Li S, Zou Y, Du ZC, Song DP, Wang P, et al. The Infection and Molecular Characterization of Cryptosporidium spp. in Diarrheic Pigs in Southern China. Microb Pathog 2022; 165: 105459.

5. Şahin S, Ağaoğlu S, Alemdar S. Cryptosporidium ve Cryptosporidiosis. Türkiye Klinikleri; 2018; 35-41.

6. Ulusan Bağcı Ö, Caner A. miRNA Expression Profile in Ileocecal Adenocarcinoma Cells Infected with Cryptosporidium. Mikrobiyol Bul 2022; 56(3): 449-465.

7. Aksoy Ü. Bioterorism, Prasites as Potential Bioterrorism Agents and Biosecurity studies. Mikrobiyol Bul 2006; 40: 129-139.

8. Fayer R. General biology. In: Fayer R, Xiao L. eds. Cryptosporidium and Cryptosporidiosis. Boca Raton: CRC Press; 2008; 1-42.

9. Chalmers RM, Davies AP. Clinical cryptosporidiosis. Exp Parasitol 2010; 124(1): 138- 46.

10. Caccio SM, Putignani L. Epidemiology of Human Cryptosporidiosis. In: Caccio S, Widmer G, eds. Cryptosporidium: parasite and disease. Vienna: Springer; 2014; 43-79.

11. Ryan U, Hijjawi N, Xiao L. Foodborne cryptosporidiosis. Int J Parasitol 2018; 48(1): 1-12.

12. Vanathy K, Parija SC, Mandal J, Hamide A, Krishnamurthy S. Cryptosporidiosis: A mini-review. Trop Parasitol 2017; 7(2): 72-80.

13. Atasever M, et al. Investigating the Quality of Public Fountain Water in Gümüşhane Province and the Presence of Cryptosporidium spp. Using the PCR Method. Turkish Journal of Agriculture-Food Science and Technology 2024; 12(9): 1530-1538.

14. Tin D, Sabeti P, Ciottonea GR. Bioterrorism: An Analysis of Biological Agents Used in Terrorist Events. Am J Emerg Med 2022; 54: 117-121

15. Ruh E, Özkan AT. Outbreaks Due to Parasites: Examples from the World and Türkiye. Mikrobiyol Bul 2023, 57(2): 317-329.

16. Çuhadar V, Şengül M, Mete E. Investigation of Cryptosporidium parvum in Water Resources in Mardin Province. Turk Mikrobiyol Cemiy Derg 2023; 53(3): 156–162.

17. Akkaş Ö, Gürbüz E, Aydemir S, Şahin M, Ekici A. Investigation of Giardia spp., Cryptosporidium spp. and Cyclospora cayetanensis in Samples Collected from Different Spring Waters Iğdır, Türkiye. Turkiye Parazitol Derg 2023;47(2):71-7.

18. Macpherson CN, Gottstein B, Geerts S. Parasitic food-borne and water-borne zoonoses. Rev Sci Tech 2000; 19(1): 240-58.

19. Şen ZS, et al. A Rare Complication of Acute Diarrhea Caused by Cryptosporidium: Possible Hepatobiliary System Involvement in a Child without Immunodeficiency. Mikrobiyol Bul 2019; 53(4): 464-471.

20. Shrivastava AK, Kumar S, Smith WA, Sahu PS. Revisiting the global problem of cryptosporidiosis and recommendations. Trop Parasitol 2017;7(1):8-17.

21. Rodrigues F, Davies EG, Harrison P, McLauchlin J, Karani J, Portmann B, et al. Liver disease in children with primary immunodeficiencies. J Pediatr 2004; 145(3): 333-9.

22. Miman Ö, Saygı G. Temel Tibbi Parazitoloji. Istanbul: Istanbul Bookstore. 2018:241-248.

23. Dabas A, Shah D, Bhatnagar S, Lodha R. Epidemiology of Cryptosporidium in pediatric diarrheal illnesses. Indian Pediatrics 2017; 54(4): 299-309.

24. Bensen R, Fuentebella J, Fridge JL, Bass DM. Enteric parasites, pp: 463-77. In: Wyllie R, Hyams JS, Kay M (eds), Pediatric Gastroenterology and Liver Disease. 2016, 5th ed. Philadelphia: Elsevier Inc.

25. Usluca S, Aksoy Ü. A Waterborn Parasite: Cryptosporidium. Dokuz Eylül Üniv Tıp Fakültesi Derg 2006; 20(1): 65-74.

26. Çiçek M, Körkoca H, Gül A. Investigation of Cryptosporidium spp. in Workers of the Van Municipality Slaughterhouse and in Slaughtered Animals. Türkiye Parazitol Derg 2008; 32(1):8-11.

27. Körkoca H, Göz Y, Ataş AD, Kurtoğlu MG, Ekici K, Berktaş M. Prevalence of Cryptosporidium spp. in asymptomatic food workers. Türkiye Parazitol Derg 2013; 37(4): 241-4.

28. Ryan U, Fayer R, Xiao L. Cryptosporidium species in humans and animals: current understanding and research needs. Parasitology 2014; 141(13): 1667-85.

29. Utaaker KS, Kumar A, Joshi H, Chaudhary S, Robertson LJ. Checking the details in retail: occurrence of Cryptosporidium and Giardia on vegetables sold across different counters in Chandigarh, India. Int J Food Microbiol 2017; 263:1-8.

30. Aydemir S, et al. Investigation of the Effect of Pasteurization on the Viability of Cryptosporidium parvum in Cow's Milk by Propidium Monoazide qPCR. Mikrobiyol Bul 2023; 57(4): 660-666.

31. Cryptosporidium, pp: 312-5. In: Kimberlin DW, Brady MT, Jackson MA, Long SS, eds. Red Book: 2015 Report of the Committee on Infectious Diseases. 2015, 30th ed. Elk Grove Village, IL: American Academy of Pediatrics.

32. Karabey M, Can H, Öner TÖ, et al. Cryptosporidium spp. during chemotherapy: a cross-sectional study of 94 patients with malignant solid tumor. Ann Saudı Med 2021; 41(5); 293-298.

33. Robertson LJ. Cryptosporidium as a Foodborne Pathogen. 1st ed. New York: Springer; 2014; 1-10.

34. Usluca S, Babur C, Kilic S. Current Status in Intestinal Parasitic Infections: A Reference Laboratory Results. KLIMIK Derg 2020; 33(3): 307-314.

35. McHardy IH, Wu M, Shimizu-Cohen R, Couturier MR, Humphries RM. Detection of intestinal protozoa in the clinical laboratory. J Clin Microbiol 2014;52(3): 712-20.

36. Checkley W, White AJ JR, Jaganath D, Arrowood MJ, Chalmers RM, Chen XM. et al. A review of the global burden, novel diagnostics, therapeutics, and vaccine targets for Cryptosporidium. Lancet Infect Dis 2015;15(1):85- 94.

37. Donato B. Tuft Veterinary School scientists decode Cryptosporidium genome. 2004; http:/www./vet. tufts.edu/

38. Control and Prevention Diagnostic Procedures for Stool Specimens. 2004. Available from: URL https://www.cdc.gov/dpdx/diagnosticprocedures/index.html

39. Roellig DM, Yoder JS, Madison-Antenucci S, Robinson TJ, Van TT, Collier SA. et al. Community laboratory testing for Cryptosporidium: multicenter study retesting public health surveillance stool samples positive for Cryptosporidium by rapid cartridge assay with direct fluorescent antibody testing. PLoS One 2017; 12(1): e0169915

40. Yavuz U, Özkan AT. Antigen Detection Methods in Diagnosis of Amebiasis, Giardiasis, and Cryptosporidiosis. Türkiye Parazitol Derg 2009; 33 (2): 140-150.

41. Fayer R. Ungar BL. Cryptosporidium spp. and cryptosporidiosis. Microbiol Rev 1986; 50(4): 458-483

42. Barrett TJ. Molecular subtyping for epidemiology: issues in the comparability of patterns and interpretation of data In D. H. Persing et al. (ed.), Molecular microbiology, diagnostic, principles, and practice. ASM Press, Washington, DC. 2004: 259-268.

43. Üner A, Tanrıverdi S, Caner A, Değirmenci A. Cryptosporidium'larda moleküler biyolojik yapı ve çalışmalar. Özcel A, Tanyüksel M, Eren H (eds). Moleküler Parazitoloji Books. 2009; 22: 631-47.

44. Köreng B. Entamoeba histolytica/Entamoeba dispar, Giardia lamblia ve Cryptosporidium spp. tanısında mikroskobi, TRIAGE ve ELISA yöntemlerinin karşılaştırılması. Yüksek Lisans Tezi, Çukurova Üniversitesi, Sağlık Bilimleri Enstitüsü, Parazitoloji Anabilim Dalı, 2011.

45. Cook WJ, Senkovich O, Hernandez A, Speed H, Chattopadhyay D. Biochemical and structural characterization of Cryptosporidium parvum Lactate dehydrogenase. Int J Biol Macromol 2015; 74: 608-619.

46. LaGier MJ, Keithly JS, Zhu G. Characterisation of a novel transporter from Cryptosporidium parvum. Int J Parasitol 2002; 32(7): 877–87.

47. Dominguez-Uscanga A, Aycart DF, Li K, Witola WH, Andrade Laborde JE. The anti-protozoal activity of thymol and a thymol ester against Cryptosporidium parvum in cell culture. Int J Parasitol Drugs Drug Resist 2021; 15: 126–33.

48. Xiao L, Fayer R, Ryan U, Upton SJ. Cryptosporidium taxonomy: recent advances and implications for public health. Clin Microbiol Rev 2004; 17(1): 72-97.

49. Büget E, Büyükbaba-Boral Ö, Kırkoyun-Uysal H, Nazlıcan Ö, Öğüt T, Şengür G. Türkiye'de bir AIDS hastasında ilk mikrosporidiyaz ve solunum sistemini tutan ilk kriptosporidiyaz olgusu. Türk Mikrobiyol Cem Derg 2000; 30(3-4): 166-70.

50. Inomata A, Murakoshi F, Ishiwa A, Takano R, Takemae H, Sugi T, et al,. Heparin interacts with elongation factor 1a of Cryptosporidium parvum and inhibits invasion. Sci Rep 2015; 5: 11599.

51. Xiao L, Cama VA. Cryptosporidium and Cryptosporidiosis. In: Ortega YR, ed. Foodborne Parasites. Food Microbiology and Food Safety. Newyork, USA: Springer; 2006; 57-86.

52. Sudradjat A, Sandhyana Angga M, Barlian K, Nastiti A. Assessing Log Reduction Values of Conventional Water Treatment Plants with Microbially Highly Polluted Raw Water Sources. J Eng Technol Sci 2022; 54(1): 220101.

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LETTER TO THE EDITOR

Myeloid/Lymphoid Neoplasms With Eosinophilia And Specific Gene Rearrangements: A Genetic Approach

Eozinofilisi ve Spesifik Gen Yeniden Düzenlenmeleri Olan Miyeloid/ Lenfoid Neoplazmalara Genetik Yaklaşım

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ABSTRACT

Eosinophils are granular leukocytes derived from a pluripotent stem cell in the bone marrow. An increase in the number of eosinophils in the blood and/or tissues requires a multifaceted clinical approach. It is important to determine the cause of the increase in order to make a correct diagnosis. Myeloid/lymphoid neoplasms with eosinophilia and specific gene fusions involve abnormal tyrosine kinase or cytokine receptor activity. Due to the similarity and heterogeneity of clinical findings, there may be diagnostic confusion in this group of diseases. Confirmation of the diagnosis is possible with genetic testing. This article briefly summarises the genetic approach to myeloid/lymphoid neoplasms with eosinophilia and tyrosine kinase gene fusions.

Keywords: Eosinophilia, hematological neoplasm, myeloid/lymphoid neoplasm with eosinophilia

ÖZ

Eozinofiller kemik iliğinde pluripotent bir kök hücreden köken alan granüler lökositlerdir. Eozinofillerin sayısında, kan ve/veya dokuda artış gözlemlenmesi, klinik açıdan çok yönlü bir yaklaşım gerektirir. Doğru tanı için bu artışın sebeplerini belirlemek önemlidir. Eozinofilisi olan ve spesifik gen füzyonlarının eşlik ettiği miyeloid/lenfoid neoplazmalar da, anormal tirozin kinaz veya sitokin reseptörü aktivitesi söz konusudur. Klinik bulguların benzerliğinden ve heterojenitesinden dolayı , bu grup hastalıklarda tanı karmaşası söz konusu olabilmektedir. Tanıyı doğrulamak genetik testler ile mümkündür. Bu yazıda, eozinofilisi ve tirozin kinaz gen füzyonları olan miyeloid/lenfoid neoplazmalar, hakkında genetik yaklaşım kısaca özetlenmiştir.

Anahtar Kelimeler: Eozinofili, hematolojik neoplazma, eozinofilisi olan miyeloid/lenfoid neoplazmalar

Eosinophils originate from a pluripotent stem cell in the bone marrow. An increased number of eosinophils requires a multifaceted approach in the clinic. The causes of such an increase must be established to make an accurate diagnosis. Depending on the cause, eosinophilia can be classified as familial, secondary, primary, or of unknown significance. Primary eosinophilia is characterized by the presence of a malignant clone of eosinophils in myeloid/stem cell neoplasms (1). According to the World Health Organization (WHO) classification (2), eosinophilia is classified in four groups [Platelet-derived growth factor receptor alpha (PDGFRA); Platelet-Derived Growth Factor Receptor-β (PDGFRB); Rearrangements of the fibroblast growth factor receptor-1 (FGFR1); Pericentriolar material-1::The Janus kinase-2 (PCM1::JAK2)]; according to the International Consensus Classification (ICC) (3), myeloid/lymphoid neoplasms (MPN) with eosinophilia and tyrosine kinase gene fusions are classified in six groups [PDGFRA; PDGFRB; FGFR1; The Janus kinase-2 (JAK2); Fms-related receptor tyrosine kinase-3 (FLT3); ets variant 6:: v-abl Abelson murine leukemia viral oncogene homolog-1 (ETV6::ABL1)].

Myeloid/lymphoid neoplasm with PDGFRA rearrangement: The PDGFRA gene is located at 4q12 and encodes a receptor protein involved in cell division. The most common fusion is the FIP1L1-PDGFRA, caused by the deletion of Cysteine Rich Hydrophobic Domain 2 (CHIC2) due to an 800-kb deletion at 4q12

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(4). Patients with this fusion respond to imatinib, but the T674I mutation causes resistance. T674I and D842V mutations were reported to cause resistance to imatinib, sorafenib, and dasatinib (5).

Myeloid/lymphoid neoplasm with PDGFRB rearrangement: The PDGFRB gene is located at 5q32 and encodes a tyrosine kinase receptor protein that plays a role in cell growth and differentiation. Among the numerous part genes, the most common is the PDGFRB-ETV6 fusion, which results from t(5;12) (q32;p13.2). Response to imatinib treatment is favorable (1, 6).

Myeloid/lymphoid neoplasm with FGFR1 rearrangement: The FGFR1 gene on 8p11 has been observed with different partners (4). The FGFR1 rearrangement is linked to an aggressive clinical course in patients. Transformation can lead to acute leukemia or lymphoma. In the absence of a targeted inhibitor, allogeneic transplantation may be an option. The most common fusion partners in patients with FGFR1 rearrangement are ZMYM2(13q12), BCR(22q11), CNTRL(9q33), and FGFR1OP(6q27) (1). Patients with BCR fusion may be misdiagnosed due to similarities to those with chronic myeloid leukemia (CML). A cytogenetic analysis is crucial (7).

Myeloid/lymphoid neoplasm with JAK2 rearrangement: The JAK2 gene on chromosome 9p24 synthesizes a tyrosine kinase involved in cell proliferation. Translocations are uncommon and involve different fusion partners. The most common PCM1-JAK2 fusion is the result of a t(8;9) translocation. The other partners are ETV6-JAK2 and BCR-JAK2, exhibiting a similar clinical picture (8).

Myeloid/lymphoid neoplasm with FLT3 rearrangement: The FLT3 gene plays a key role in regulating cell differentiation, proliferation, and survival. It is a tyrosine kinase receptor localized to 13q12. While mutations are common in hematological neoplasms, translocations involving this gene are rare. The most prevalent is the FLT3::ETV6 translocation (1, 9).

Myeloid/lymphoid neoplasm with ETV6::ABL1: The ABL1 gene at 9q34.12 encodes a tyrosine kinase

Table. Clinical findings, genetic characteristics, and treatment options in myeloid/lymphoid neoplasms with eosinophilia and specific gene rearrangements

Gene	Fusion Partners	Genetic Method	Clinical Findings	Diagnostic Confusion	Therapy	Resistance Mutations
PDGFRA (4q12)	**FIP1L1(4q12)*** STRN (2p24), FOXP1 (3p14), CDK5RAP2 (9q33), KIF5B (10p11), TNKS2 (10q23), ETV6 (12p13), BCR (22q11)	Chromosome Analysis, FISH, PDGFRA-FIP1L1 fusion RT-PCR	Eosinophilia	Blastic phase MPN / AML associated with eosinophilia / T-cell lymphoblastic lymphoma	Imatinib (Allo-SCT in the presence of resistance mutation	T674I D842V
PDGFRB (5q31- 33)	**ETV6 (12p13)*** TPM3 (1q21), PDE4DIP (1q22), SPTBN1 (2p16), SPDR (2q32), WDR48 (3p22), GOLGA4 (3p22), GOLGB1 (3q12), PRKG2 (4q21), DIAPH1 (5q31), TNIP1 (5q33), CEP85L (6q22), HIP1 (7q11), KANK1 (9p24), CCDC6 (10q21), GPIAP1 (11p13), ERC1 (12p13), BIN2 (12q13), CPSF6 (12q15), SART3 (12q23), GIT2 (12q24), NIN (14q24), CCDC88C (14q32), TRIP11 (14q32), TP53BP1 (15q22), NDE1 (16p13), SPECC1 (17p11), MPRIP (17p11), RABEP1 (17p13), NDEL1 (17p13), MYO18A (17q11), DTD1 (20p11)	Chromosome Analysis, FISH, maybe NGS	Eosinophilia, sometimes monocytosis or neutrophilia	MPN/eosinophilia MDS/MPN, AML/ALL	Imatinib	
FGFR1 (8p11)	**ZMYM2 (13q12)* BCR (22q11)* CNTRL (9q33)* FGFR1OP (6q27)*** TPR1 (1q25), RANBP2 (2q13), LRRFIP1 (2q37), TFG (3q12), SQSTM1 (5q35), CUX1 (7q22), TRIM24 (7q34), PCM1 (8p21), FGFR1OP2 (12p11), CPSF6 (12q15), MYO18A (17q11), HERV-K (19q13)	Chromosome Analysis, FISH	Eosinophilia, sometimes monocytosis or neutrophilia	MPN, lymphoblastic lymphoma, acute leukemia, myeloid, lymphoid, or mixed-lineage disease	Pemigatinib, Futibatinib Midostaurin, Ponatinib (Allo SCT)	
JAK2 (9p24)	**PCM1(8p21)*** ETV6 (12p13) BCR (22q11)	Chromosome Analysis, FISH	Eosinophilia	MPN, MDS/MPN, ALL, de-novo AML, T-cell lymphoma	Ruxolitinib, Fedratinib Pacritinib, Momelotinib (Allo SCT)	
FLT3 (13q12)	**ETV6 (12p13)*** BCR (22q11), SPTBN1 (2p16), GOLGB1 (3q12), LYN (8q12), MYO18A(17q12), SYK (9q22), TRIP11 (14q32), NTRK3 (15q25), ZMYM2(13q12)	Chromosome Analysis, FISH, ETV-FLT3 fusion nested RT-PCR	Eosinophilia	MPN, B/T-ALL, AML.	Gilteritinib, Midostaurin Sorafenib, Sunitinib	
ABL1 (9q34)	ETV6 (12p13)*	Chromosome Analysis, FISH	Eosinophilia Basophilia	CML, AML, Ph-like B-ALL.	Dasatinib, Nilotinib Imatinib, Bosutinib Ponatinib, Asciminib	

*The most common gene partner FISH=Fluorescence *in situ* hybridization, RT-PCR: Reverse transcription-polymerase chain reaction, NGS: Next Generation Sequencing, AML: Acute Myeloid Leukemia, MDS: Myelodysplastic Syndrome, ALL: Acute Lymphoblastic Leukemia, Allo-SCT: Allogeneic Stem Cell Transplantation

protein regulating cell proliferation and apoptosis. The fusion of ABL1 and ETV6 results in the activation of the tyrosine kinase, as observed in BCR-ABL1. Clinical manifestations are similar to those in chronic phase CML, but often with eosinophilia and basophilia (1, 5).

Myeloid/lymphoid neoplasms with eosinophilia and specific gene rearrangements are difficult to classify. The following table summarises the fusion partners of each specific gene rearrangement, the genetic methods that can be used to identify them, the clinical findings, and the treatment options (4, 10). The genetic tests selected based on the preliminary diagnosis help clinicians confirm the diagnosis and identify and implement treatment options accurately and quickly.

References

1.Morales-Camacho RM, Caballero-Velázquez T, Borrero JJ, Bernal R, Prats-Martín C. Hematological Neoplasms with Eosinophilia. Cancers (Basel). 2024;16(2):337. Published 2024 Jan 12. doi:10.3390/cancers16020337

2.Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405. doi:10.1182/blood-2016-03-643544

3.Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228. doi:10.1182/blood.2022015850

4.Kim AS, Pozdnyakova O. SOHO State of the Art Updates and Next Questions | Myeloid/Lymphoid Neoplasms with Eosinophilia and Gene Rearrangements: Diagnostic Pearls and Pitfalls. Clin Lymphoma Myeloma Leuk. 2022;22(9):643-651. doi:10.1016/j.clml. 2022.03.008

5.Lierman E, Michaux L, Beullens E, et al. FIP1L1-PDGFRalpha D842V, a novel pan-resistant mutant, emerging after treatment of FIP1L1-PDGFRalpha T674I eosinophilic leukemia with single agent sorafenib. Leukemia. 2009;23(5):845-851. doi:10.1038/leu.2009.2

6.Di Giacomo D, Quintini M, Pierini V, et al. Genomic and clinical findings in myeloid neoplasms with PDGFRB rearrangement. Ann Hematol. 2022;101(2):297-307. doi:10.1007/s00277-021-04712-8

7.Bayrak, A.G., Ucur, A., Daglar Aday, A., et al. A case mimicking chronic myeloid leukemia with t(8;22)(p11;q11)/BCR-FGFR1 and sequential transformation to B-acute lymphoblastic leukemia and acute myeloid leukemia. J Hematopathol 2021; 14:151–156. doi:10.1007/s12308-020-00429-1

8.Kaplan HG, Jin R, Bifulco CB, Scanlan JM, Corwin DR. PCM1-JAK2 Fusion Tyrosine Kinase Gene-Related Neoplasia: A Systematic Review of the Clinical Literature. Oncologist. 2022;27(8):e661-e670. doi:10.1093/oncolo/oyac072

9.Tang G, Tam W, Short NJ, et al. Myeloid/lymphoid neoplasms with FLT3 rearrangement. Mod Pathol. 2021;34(9):1673-1685. doi:10.1038/s41379-021-00817-7

10.Gotlib J. Available and emerging therapies for bona fide advanced systemic mastocytosis and primary eosinophilic neoplasms. Hematology Am Soc Hematol Educ Program. 2022;2022(1):34-46. doi:10.1182/hematology.2022000368

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ERRATUM - DÜZELTME

ERRATUM: Evaluation of Systemic Inflammatory Marker in Patients with Laryngopharyngeal Reflux

DÜZELTME: Larengofaringeal Reflüsü Olan Hastalarda Sistemik İnflamatuar Belirteçlerin Değerlendirilmesi

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ORIGINAL ARTICLE

Evaluation of Systemic Inflammatory Marker in Patients with Laryngopharyngeal Reflux

Larengofaringeal Reflüsü Olan Hastalarda Sistemik İnflamatuar Belirteçlerin Değerlendirilmesi

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ABSTRACT

Aim: It was aimed to investigate whether systemic inflammation markers have diagnostic value in laryngopharyngeal reflux disease.
Materials and Methods: This retrospective study was conducted including 32 patients with laryngopharyngeal reflux and 27 subjects with vocal cord nodules. Patients with laryngopharyngeal reflux were evaluated as Group 1, and subjects with vocal cord nodules as Group 2. Patient files were scanned. Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic inflammation index values were calculated. In addition, the previously filled Reflux symptom index and the Reflux sign scores performed by videoendoscopic examination were noted.
Results: While the mean age was 43.21±13.26 years in Group 1, it was 38.04±10.39 years in Group 2. While there were 12 male and 20 female patients in Group 1, there were 12 male and 15 female patients in Group 2. When Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic inflammation index values were examined, no statistically significant difference was found between Group 1 and Group 2 ($p>0.05$). Reflux symptom index and Reflux sign scores were significantly higher in Group 1 ($p<0.05$). There was a significant positive correlation between the Reflux symptom index and Reflux sign scores.
Conclusion: In our study, no significant difference was found in the Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and systemic inflammation index values used in the follow-up of many diseases compared to the control group in laryngopharyngeal reflux patients and had no diagnostic value. While the Reflux symptom index and Reflux sign scores were found to be significantly higher in laryngopharyngeal reflux patients compared to the control group, they were significantly positively correlated with each other.

Keywords: Laryngopharyngeal Reflux, Lymphocyte, Neutrophil, Reflux Symptom Index, Reflux Finding Score

ÖZ

Amaç: Laringofaringeal reflü hastalığında sistemik inflamasyon belirteçlerinin tanısal değeri olup olmadığının araştırılması amaçlandı.
Gereç ve Yöntemler: Bu retrospektif çalışma laringofaringeal reflüsü olan 32 hasta ve vokal kord nodülü olan 27 olgu dahil edilerek yapıldı. Laringofaringeal reflü hastaları Grup 1, vokal kord nodülü olan olgular Grup 2 olarak değerlendirildi. Hasta dosyaları tarandı. Nötrofil/lenfosit oranı, trombosit/ lenfosit oranı ve sistemik inflamasyon indeksi değerleri hesaplandı. Ayrıca daha önce doldurulmuş olan Reflü semptom indeksi ve videoendoskopik muayene ile yapılan Reflü belirti skorları not edildi.
Bulgular: Grup 1'de yaş ortalaması 43.21±13.26 iken, Grup 2'de 38.04±10.39 bulundu. Grup 1'de 12 erkek ve 20 kadın hasta bulunurken, Grup 2'de ise 12 erkek ve 15 kadın hasta mevcuttu. Nötrofil/ lenfosit oranı, platelet/ lenfosit oranı ve sistemik inflamasyon indeksi değerleri incelendiğinde Grup 1 ve Grup 2 arasında istatistiksel olarak anlamlı fark saptanmadı $p>0.05$). Reflü semptom indeksi ve Reflü bulgu skorları Grup-1'de anlamlı olarak daha yüksek bulundu ($p<0.05$). Reflü semptom indeksi ve Reflü bulgu skorları arasında önemli ölçüde pozitif korelasyon mevcuttu.
Sonuç: Bizim çalışmamızda Laringofaringeal reflü hastalarında, birçok hastalığın takibinde kullanılan nötrofil/lenfosit oranı, platelet/lenfosit oranı ve sistemik inflamasyon indeksi değerlerinde kontrol grubuna göre anlamlı fark saptanmadı ve tanısal değeri yoktu. Reflü semptom indeksi ve Reflü bulgu skorları, laringofaringeal reflü hastalarında kontrol grubuna göre anlamlı yüksek bulunurken, birbirleri ile önemli ölçüde pozitif korele bulundular.

Anahtar Kelimeler: Laryngopharyngeal Reflux, Lymphocyte, Neutrophil, Reflux Symptom Index, Reflux Finding Score

Introduction

The inflammatory state caused by the reflux of gastric contents into laryngeal and pharyngeal tissue is known as laryngopharyngeal reflux (LPR). Although the prevalence of LPR is still unclear, it is a frequently encountered entity in ear, nose, and throat (ENT) clinical practice. It causes symptoms of a tickling sensation in the throat, voice disorders, difficulty in swallowing, chronic cough, and globus pharyngeus. These symptoms result from laryngeal epithelial damage caused by the reflux content or vagal nerve-mediated stimulation of laryngeal reflexes (1). The laryngopharynx has been reported to be potentially more sensitive to reflux content than the esophagus (2).

The diagnosis of LPR was difficult. The methods employed in diagnosis included the Reflux Finding Score (RFS) (Table 1) and were evaluated using the video laryngoscopic examination and the Reflux Symptom

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Index (RSI) (Table 2) (3,4). The RSI scores over 13 are regarded as pathological, and the RFS scores over 7 were interpreted in favor of LPR.

Table 1. Reflux Finding Scores

Reflux Finding Scores	
Subglottic edema	0 Absent
	2 Present
Ventricular Obliteration	0 Absent
	2 Partial
	4 Complete
Erythema/hyperemia	0 Absent
	2 Arytenoids
	4 Diffuse
Vocal fold edema	0 Absent
	1 Mild
	2 Moderate
	3 Severe
	4 Polypoid
Diffuse laryngeal edema	0 Absent
	1 Mild
	2 Moderate
	3 Severe
	4 Obstructing
Posterior commissure hypertrophy	0 Absent
	1 Mild
	2 Moderate
	3 Severe
	4 Obstructing
Granuloma/granulation tissue	0 Absent
	2 Present
Thick endolaryngeal mucus	0 Absent
	2 Present

RSF >7 = Laryngopharyngeal Reflux

Neutrophil/lymphocyte ratio (NLR), platelet/ lymphocyte ratio (PLR), and systemic inflammation index (SII) can be easily calculated by peripheral complete blood count. NLR and PLR have been identified as potential markers of systemic inflammation (5-7). It is known that NLR, PLR, and SII, which are widely studied especially in cardiovascular diseases, can be used as classical inflammatory markers (8,9). The prognostic value of the systemic inflammation index (SII), neutrophil/lymphocyte ratio (NLR), and platelet/ lymphocyte ratio (PLR) have been demonstrated in many inflammatory diseases, particularly cancer (10,11).

Based on the literature, we encountered no studies investigating the relationship between LPR and SII in the literature search. This study aimed to examine the relationship between LPR, a disease frequently encountered in ENT medicine, and systemic inflammatory markers.

Table 2. Reflux Symptom Index

Within the last Month, how did the following problems affect you?	(0=No problem-5=Severe problem)					
Hoarseness or a problem with your voice	0	1	2	3	4	5
Clearing your throat	0	1	2	3	4	5
Excess throat mucus or postnasal drip	0	1	2	3	4	5
Difficulty swallowing food, liquids, or pills	0	1	2	3	4	5
Coughing after you ate or after lying down	0	1	2	3	4	5
Breathing difficulties or choking episodes	0	1	2	3	4	5
Troublesome or annoying cough	0	1	2	3	4	5
Sensation of something sticking in your throat, or a lump in your throat	0	1	2	3	4	5
Heartburn, chest pain, indigestion, or stomach acid coming up	0	1	2	3	4	5

RSI>13=Abnormal

Material And Method

The study was carried out under the Declaration of Helsinki and with the approval of the Non-Interventional Ethical Committee of Siirt University (Date:19.03.2021, Decision 2021-KAEK-6934). Since the data in the research was obtained from electronic records of the patients, consent from the patients was not obtained.

The study was planned retrospectively. Thirty-two patients presenting to the ENT clinic between 1st October 2020 and 1st March 2021, diagnosed with LPR, and with no additional systemic disease were included in the study. These were assigned to Group 1, while 27 subjects with vocal cord nodules constituted Group 2.

Once the patient's age and sex distributions had been determined, RFS and RSI forms routinely applied in ENT clinics to assist in the diagnosis of LPR were scanned from the files. The Turkish language versions of both forms had previously been validated (12,13).

Hemoglobin values and neutrophil, platelet, and lymphocyte counts were retrieved from complete blood counts (CBC) performed for other reasons during the previous three months. CBC parameters were calculated with an automated hematologic analyzer (XN-1000-Hematology-analyzer-Sysmex Corporation,

Japan). NLR, PLR, and SII values were calculated by formula. SII (platelet×neutrophil/lymphocyte), NLR, and PLR analyses were also performed. The groups were then compared based on these values.

The study assessed patients aged 18 to 60 diagnosed with gastroesophageal reflux who followed a reflux diet for at least one month without taking medication. An ENT physician then examined these patients. A single otolaryngologist with ten years of experience obtained a thorough medical history from the study participants, and a flexible endoscopic examination of the larynx revealed laryngopharyngeal reflux. The control group consisted of subjects with vocal cord nodules with similar age and gender characteristics as the study group. This study group presented to the ENT outpatient clinic with a complaint of dysphonia but no complaints or symptoms of reflux.

Patients at the age of <18 years or >60 years, those consistently taking medications for any reason, those with blocked nasal air passages such as septum deviation, allergic rhinitis, and turbinate hypertrophy, those with postnasal purulent discharge, those smoking and consuming alcohol, those with such disorders as coronary artery disease, hypertension, diabetes mellitus, hyperlipidemia, chronic obstructive pulmonary disease, chronic liver disease, acute and chronic renal diseases, and those with previous interventional procedures or surgery in the laryngopharyngeal area, and those choosing not to participate in the study were excluded from the study.

Statistical Analysis

Statistical analyses were performed on the Statistical Package for Social Sciences (SPSS) for Windows, version 21.0 software (IBM SPSS Inc., Chicago, IL, USA). Mean±standard deviation and descriptive statistics were employed. The normality of distribution was evaluated using the Kolmogorov–Smirnov test. NLR and PLR values were not normally distributed in Group 1, and NLR, PLR, RSI, and RFS values were not normally distributed in Group 2. Normally distributed data were compared between the groups using the independent samples t-test. The Mann–Whitney U test was applied in the comparison of non-normally distributed variables between the groups. The correlation between RSI and RFS was investigated using Spearman's correlation test. A p-value of <0.05 was considered statistically significant. The Cronbach's alpha test was used to assess the intra-rater reliability. The value is 0.731.

Results

Group 1 consisted of 20 (62.5%) women and 12 (37.5%) men, and Group 2 of 15 (55.6%) women and 12 (44.4%) men. Mean ages were 43.21±13.26 years in Group 1 and 38.04±10.39 in Group 2. No significant differences were observed between the groups in terms of age (p=0.178) or sex (p=0.783).

Platelet counts, hemoglobin values, lymphocyte counts, neutrophil counts, and NLR, PLR, and SII values in groups 1 and 2 are shown in Table 3. No significant differences were observed between the groups in terms of the values shown in Table 3 (p>0.05).

Table 3. Age, platelet count, hemoglobin, lymphocyte count, neutrophil count and NLR, PLR and SII values of the groups

	Group 1	Group 2	P value
Age (years) (mean±SD)	43.21±13.26	38.92±10.39	0.178*
Platelet Count (x1000 uL) (mean±SD)	244.78±51.40	265.29±48.07	0.121*
Hemoglobin (mean±SD)	14.59±1.59	15.15±1.77	0.205*
Lymphocyte Count (mean±SD)	2.30±0.73	2.54±0.81	0.236*
Neutrophil Count (mean±SD)	5.06±1.95	4.83±1.73	0.627*
NLR [median (IQR)]	1.94 (1.38-2.32)	2.10 (1.40-3.07)	0.338¥
PLR [median (IQR)]	105.93 (80.00-139.52)	109.19 (86.33-138.91)	0.831¥
SII (mean±SD)	579.83±293.15	549.17±263.76	0.677*

*: Independent Sample t test was used. ¥: Mann-Whitney U test was used. NLR: Neutrophil/Lymphocyte ratio,

PLR: Platelet/ Lymphocyte ratio, SII: Systemic Inflammation Index, IQR: Interquartile Range

RSI and RFS values in groups 1 and 2 are shown in Table 4. RSI and RFS values were significantly higher in the LPR group than in the control group (Table 4) (p<0.05). A significant positive correlation was observed between RSI and RFS (p=0.000).

Table 4. RSI and RFS values of groups.

	Group 1 [median (IQR)]	Group 2 [median (IQR)]	*p*-value
RSI	1.00 (0.00-6.00)	15.50 (12.25-19.50)	0.000¥
RFS	0.00 (0.00-2.00)	7.00 (4.00-9.00)	0.000¥

¥: Mann-Whitney U test was used. RSI: Reflux Symptom Index, RFS: Reflux Finding Scores,

IQR: Interquartile Range

Discussion

LPR is an inflammatory disease caused by the reflux of gastroduodenal contents. It causes non-specific symptoms such as a tickling sensation in the throat and voice disorders. Its association with chronic pharyngitis,

premalignant lesions of the larynx, and squamous cell carcinoma has also been reported (14,15). Gastroesophageal reflux disease is observed in 57-80% of patients with clinical symptoms of LPR (16). However, LPR patients may not have gastroesophageal reflux findings.

Although the main diagnostic test for LPR is 24-hour pH monitoring, more rapid tests have begun entering into use. Belafsky et al. defined the RSI and RFS forms (3,4). RSI exceeding 13 is compatible with LFR, while RFS above seven indicates LPR with a likelihood of 95% (3,4). RFS in the LPR group in the present study was 15.65±5.82, while RSI was 7.03±3.37.

The RSI and RFS forms are practical for the diagnosis of LPR and observing the response to treatment (3). Karakaya et al. showed that RSI and individual variables in RFI were correlated in LPR, except for posterior commissure hypertrophy (12). In agreement with the previous literature, a significant correlation was observed between RSI and RFS in the present study, and both were significantly higher in the LPR group than in the control group.

Increasing platelet and decreasing lymphocyte counts during inflammation allows the PLR to be employed as an inflammatory marker. The NLR and PLR can be used to predict prognosis in several cancers and in the evaluation of inflammation in diseases such as diabetes, hypertension, rheumatoid arthritis, and acute coronary syndrome (17,18). Ateş et al. showed that NLR values may rise in gastroesophageal reflux-related erosive esophagitis and non-erosive esophagitis (19). Arslan et al. found that PLR was significantly higher in patients with LPR than in the control group, but NLR did not differ significantly. They also suggested that the mean platelet volume value has prognostic significance in treating LPR (8). No significant difference in PLR and NLR values was observed between the LPR and control groups in the present study.

The systemic inflammation index (SII), consisting of three cell types (neutrophils, platelets, and lymphocytes), was developed by Hu et al. in 2014 (20). The SII can provide a clearer picture of immune and inflammatory conditions (21,22). It has also been shown to be a useful marker in predicting clinical outcomes in tumors and several inflammatory diseases (21-23). Our search of the literature revealed no studies investigating the relationship between LPR and the SII. In the present study, SII values were lower in the control group than in the LPR group, although no significant difference was found between the two groups.

The principal limitations of this study are its retrospective nature and the low case number. The fact that more objective tests for LPR were not used is another limitation.

LPR is a common condition frequently encountered in otolaryngology practice. Regarding the prevalence of LPR, it is clear that it is impractical to perform objective diagnostic tests on every patient. The RSI and RFS forms are practical and valuable for the initial assessment and subsequent evaluation of treatment. SII, NLR, and PLR are biomarkers that can be used to assess inflammation.

Conclusion

Our study indicated that patients with LPR exhibited significantly elevated levels of RSI and RBS, diagnostic markers for LPR. The analysis found no significant correlation between the markers SII, NLR, and PLR, extensively studied in recent years, and LFR. Prospective studies can be designed to include more patients and assess these markers before and after treatment.

Ethics Committee Approval

The study was carried out in accordance with the Declaration of Helsinki and with the approval of the Siirt University Non-Interventional Ethical Committee (Date:19.03.2021, Decision 2021-KAEK-6934). Written informed consent was obtained from all participants.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception: MY. Design: MY, BMT. Resource: MY, BMT. Materials: MY, BMT. Analysis: MY. Literature Review: MY. Critical Review: MY, BMT. Supervision: MY. Resource: MY, BMT. Data Collection and Processing: MY, BMT. Writer: MY. Critical Review: MY, BMT.

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References

1. Hutnik R, Zlatopolsky A, Mehraban-Far S, Alrassi J, McMillan N, Amadi C, et al. Laryngopharyngeal reflux: Comparing improvements in reflux symptom index with reflux finding score. Am J Otolaryngol. 2020;41(6):102730.

2. Axford SE, Sharp N, Ross PE, Pearson JP, Dettmar PW, Panetti M, et al. Cell biology of laryngeal epithelial defenses in health and disease: preliminary studies. Ann Otol Rhinol Laryngol. 2001;110(12):1099-108.

3. Abraham ZS, Kahinga AA. Utility of reflux finding score and reflux symptom index in diagnosis of laryngopharyngeal reflux disease. Laryngoscope Investig Otolaryngol. 2022 Jun; 7(3): 785–789.

4. Belafsky PC, Postma GN, Koufman JA. Validity and reliability of the reflux symptom index (RSI). J Voice. 2002;16(2):274-7.

5. Balta S, Demirkol S, Unlu M, Arslan Z, Celik T. Neutrophil to lymphocyte ratio may be predict of mortality in all conditions. Br J Cancer. 2013 Dec 10;109(12):3125-6.

6. Atan D, İkincioğulları A, Köseoğlu S, Özcan KM, Çetin MA, Ensari S, et al. New Predictive Parameters of Bell's Palsy: Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio. Balkan Med J. 2015 Apr;32(2):167-70.

7. Torun S, Tunc BD, Suvak B, Yildiz H, Tas A, Sayilir A, et al. Assessment of neutrophil-lymphocyte ratio in ulcerative colitis: a promising marker in predicting disease severity. Clin Res Hepatol Gastroenterol. 2012 Oct;36(5):491-7.

8. Arslan H, Çandar T, Kuran S, Akmansu ŞH, Kocatürk S. New inflammatory parameters in laryngopharyngeal reflux. J Laryngol Otol. 2016 Sep;130(9):878-82.

9. Bhat T, Teli S, Rijal J, Bhat H, Raza M, Khoueiry G, Meghani M, et al. Neutrophil to lymphocyte ratio and cardiovascular diseases: a review. Expert Rev Cardiovasc Ther. 2013 Jan;11(1):55-9.

10. Yao C, Zhang Z, Yao Y, Xu X, Jiang Q, Shi D. Predictive value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio for acute deep vein thrombosis after total joint arthroplasty: a retrospective study. J Orthop Surg Res. 2018 Feb 27;13(1):40.

11. Sun H, Que J, Peng Y, Ye H, Xiang H, Han Y, et al. The neutrophil-lymphocyte ratio: A promising predictor of mortality in coronary care unit patients - A cohort study. Int Immunopharmacol. 2019 Sep;74: 105692.

12. Karakaya NE, Akbulut S, Altıntaş H, Demir MG, Demir N, Berk D. The reflux finding score: reliability and correlation to the reflux symptom index. J Acad Res Med. 2015;5(2):68-74.

13. Akbulut S, Aydinli FE, Kuşçu O, Özcebe E, Yilmaz T, Rosen CA, et al. Reliability and Validity of the Turkish Reflux Symptom Index. J Voice. 2020;34(6):965. e23-965.e28.

14. Koufman JA. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24-hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. Laryngoscope. 1991;101(4 Pt 2 Suppl 53):1-78.

15. Parsel SM, Wu EL, Riley CA, McCoul ED. Gastroesophageal and laryngopharyngeal reflux associated with laryngeal malignancy: A systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2019 Jun;17(7):1253-1264.e5.

16. Ulualp SO, Toohill RJ. Laryngopharyngeal reflux: state of the art diagnosis and treatment. Otolaryngol Clin North Am. 2000;33(4):785-802.

17. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med. 2012;5(1):2.

18. Cao W, Yu H, Zhu S, Lei X, Li T, Ren F, et al. Clinical significance of preoperative neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in the prognosis of resected early-stage patients with non-small cell lung cancer: A meta-analysis. Cancer Med. 2023 Mar;12(6):7065-7076.

19. Ateş F, Yaraş S, Sarıtaş B, Altıntaş E, Sezgin O, Orekici G. Does neutrophil to lymphocyte ratio in peripheral blood predict endoscopic erosive esophagitis. Endoscopy. 2011;19(3):88-90.

20. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. The systemic immune-inflammation index predicts the prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212-22.

21. Fest J, Ruiter R, Mulder M, Groot Koerkamp B, Ikram MA, Stricker BH, et al. The systemic immune-inflammation index is associated with an increased risk of incident cancer in a population-based cohort study. Int J Cancer. 2020;146(3):692-698.

22. Furuncuoğlu Y, Tulgar S, Dogan AN, Cakar S, Tulgar YK, Cakiroglu B. How obesity affects the neutrophil/lymphocyte and platelet/lymphocyte ratio, systemic immune-inflammatory index and platelet indices: a retrospective study. Eur Rev Med Pharmacol Sci. 2016;20(7):1300-6.

23. Atalay F, Kars A, Topal K, Yavuz Z. Systemic immune inflammation index in patients with recurrent aphthous stomatitis. Braz J Otorhinolaryngol. 2022 Jul-Aug; 88(4): 621–624.