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Determining the Concerns and Stress Levels of the Elderly Population About COVID-19: A Sectional Study

Yaşlı Nüfusun Covid-19 ile İlgili Endişeleri ve Stres Düzeylerinin Belirlenmesi: Kesitsel bir Çalışma

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ABSTRACT

Aim: *This study aims to determine the concerns and stress levels of individuals over the age of 65 towards COVID-19.*

Material and Method: *The data of this sectional study was collected both through an online survey and face-to-face between February 15 and March 13, 2022. Seven hundred and sixty nine surveys that met the criteria for data quality were included in the study. Both a questionnaire prepared by the researchers to determine the socio-demographic characteristics of older people and their concerns state during COVID-19 and the Perceived Stress Scale-10 were used. Statistical analysis of the results obtained in the study was carried out with the Statistical Package for Social Sciences (SPSS) for IBM 25 package program.*

Results: *49.9% of the participants were diagnosed with COVID-19. Additionally, 80.5% of the participants reported experiencing changes in their living circumstances as a result of the pandemic, while 88.2% reported feeling anxious during this period. The participants were seen to have an average score of 29.82±2.58 on the perceived stress scale. A statistically significant difference was seen in the average score of the perceived stress scale when comparing individuals based on their marital status, income, place of residence, presence of chronic condition (p <0.05).*

Conclusion: *The study revealed that the participants' reported stress level was moderate, with a significant number of persons experiencing anxiety.*

Key words: *elderly indidual; COVID-19; stress*

ÖZET

Amaç: *Bu araştırmada 65 yaş üstü bireylerin COVID-19'a yönelik endişelerinin ve stres düzeylerinin belirlenmesi amaçlanmıştır.*

Materyal ve Metot: *Kesitsel olarak planlanan bu araştırmanın verileri 15 Şubat – 13 Mart 2022 tarihleri arasında çevrimiçi anket ve yüz yüze toplanmıştır. Veri kalitesine uygun 769 anket çalışmaya dâhil edilmiştir. Verilerin toplanmasında araştırmacılar tarafından hazırlanan yaşlıların sosyodemorafik özelliklerini ve COVID-19 sırasında endişe durumlarını belirlemeye yönelik soru formu ile Algılanan Stres Ölçeği-10 kullanılmıştır. Araştırmada elde edilen sonuçların istatistiksel analizleri Statistical Package for Social Sciences (IBM 25 Sosyal Bilimlerde İstatistik Paket Programı –SPSS) paket programı ile yapılmıştır.*

Bulgular: *Araştırmadaki katılımcıların %49,9'u COVID-19 geçirmişlerdir. Katılımcıların %80,5'i pandemiden dolayı yaşam düzeninin değiştiğini, %88,2'si bu süreçte kendini endişeli hissettiğini ifade etmişlerdir. Katılımcıların algılanan stres ölçeğinden aldıkları toplam puan ortalaması 29,82±2,58'dır. Bireylerin medeni durum, gelir, kaldığı yer ve kronik hastalığın varlığı ile algılanan stress ölçeği puan ortalaması arasındaki fark istatistiksel olarak anlamlı bulunmuştur (p<0,05).*

Sonuç: *Bu araştırmada katılımcıların algılanan stress düzeyinin orta düzeyde olduğu saptanmış olup bireylerin çoğunun kendini endişeli hissettiği dikkat çekmektedir.*

Anahtar kelimeler: *yaşlı birey; COVID-19; stres*

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Introduction

The coronavirus disease (COVID-19) is an infectious disease caused by the SARS-CoV-2 virus[1,2]. Understanding the way it is transmitted is crucial for effectively reducing the spread. Individuals need to take necessary precautions to prevent the spread of infection. This includes maintaining a safe distance of at least 1 meter from others, wearing a mask correctly, and practicing good hand hygiene by washing hands frequently or using an alcohol-based sanitizer. Furthermore, it is crucial for individuals to be vaccinated and adhere to the guidance provided by local health authorities[3]. While most infected individuals experience mild or moderate respiratory symptoms and recover without any special medical intervention, some may become seriously ill, calling for treatment. The risk of severe illness is significantly higher for elderly individuals with chronic respiratory ailments, diabetes, or cancer. Based on data provided by WHO, an estimated 14.9 million deaths were attributed to the COVID-19 pandemic between January 1, 2020 and December 31, 2021[4]. Severe cases are often seen in older individuals or those with other underlying concomitant systemic disease[5]. As individuals age, they may experience a decline in physical, mental, and social well-being. Put simply, aging is a natural phenomenon that happens as time goes on in all living beings throughout the universe, affecting molecules, cells, tissues, organs, and systems in a way that brings about a decline in physical, functional, mental, and biopsychosocial abilities[6,7]. Based on data from the World Health Organization, the global population of individuals aged 60 and above is projected to reach 1.4 billion by 2030 and 2.1 billion by 2050. This increase will happen at a remarkable speed and will gain momentum primarily in developing countries[8]. In Türkiye, the number of elderly individuals has steadily increased over the past few years. In 2016, there were 6.651.503 elderly people, yet this number has grown by 24% in the last 5 years, reaching 9.7% of the total population in 2021. According to population projections, this trend is expected to continue, with the elderly population rate estimated to be 11.0% in 2025, 12.9% in 2030, 16.3% in 2050, and 22.6% in 2060[9]. This significant shift in the world's populations calls for adjustments in the organization of societies across various sectors, ranging from healthcare, social services, transportation, housing to urban planning. Efforts to create a more age-friendly world are crucial and time-sensitive, considering the shifting demographics[8]. Amidst the current COVID-19 pandemic, the daily routines of older individuals are being altered, along with the care and support they receive and how they are perceived. Elderly individuals are confronted with the necessity of spending increased time at home, the absence of physical contact with their loved ones, friends, and colleagues, temporary loss of employment, as well as heightened anxiety and stress[10]. When comparing the pandemic to other diseases, it stands out due to its unique stress direction. This can be described as a stress response to ongoing trauma, resulting in an increased reaction to danger that increases uncertainty about the future[11]. Even though complete psychological relief can only be achieved once the stressful pandemic ends, it is important to continue taking initiatives to ensure that elderly individuals feel more comfortable during this critical period. During the pandemic, it is also crucial to prioritize individual well-being and strive for a healthier lifestyle. Furthermore, it is essential to ensure that elderly individuals receive vaccinations and are educated on how to safeguard their health against the virus and also to provide them with access to local health resources, promoting awareness and timely psychosocial interventions.

It has been observed that the global prevalence of individual-level restrictions, as opposed to social-level restrictions, has grown increasingly widespread, which can be attributed to various factors, including the severity of the pandemic, the diminishing impact of the outbreak, and the widespread adoption of vaccination[12]. Nevertheless, it is crucial to acknowledge that the epidemic continues to be a significant psychological stressor in the present day. The hypothesis argues that elderly individuals in Türkiye experience elevated levels of stress related to COVID-19 as a result of variables such as severe isolation, feelings of loneliness, and insufficient social support[13–15]. Therefore, it is imperative to address how to examine and measure the psychological impact of the pandemic on elderly individuals, who are considered one of the most vulnerable groups in our society, providing insights into the present circumstances and facilitating the development of targeted interventions aimed at mitigating potential consequences on individuals' mental well-being. Additionally, it will also enable the evaluation and scrutiny of policies pertaining to pandemic management, as well as the establishment of mental health care provisions for future outbreaks. The objective of this study is to assess the levels of worry and stress experienced by adults aged 65 years and above in relation to the COVID-19 pandemic.

The research questions

1. Is there a difference between the sociodemographic characteristics of the elderly and COVID-19 stress levels?
2. What is the stress level of the elderly during the COVID-19 pandemic?

Material and Metod

Study Population

This sectional study was applied to individuals aged 65 and over living in Türkiye and utilized cross-sectional methods. The study data were collected between February 15 and March 13, 2022 using online and face-to-face survey methods. The online questionnaire form was sent via WhatsApp, e-mail, Instagram, and Facebook. Participants were able to fill in the questionnaires with desktop, laptop, tablet, or mobile devices. The sample size was calculated to include 769 elderly individuals who agreed to participate in the study, using the minimum sampling rate for an unknown population at 80% confidence interval, and a total of 769 individuals were included in the study.[16]

Inclusion Criteria for Research were 1) being able to communicate, 2) being over and 65 years old, 3) being literate, and 4) not having any psychological disorder.

Data Collection Tool

"Survey Form" and "Perceived Stress Scale (PSS-10)" were used as data collection tools.

Survey form: A total of 15 questions were applied, 6 of which included questions inquiring the sociodemographic characteristics such as gender, age, marital status, place of residence, having any child, chronic disease status, while 9 of which included questions inquiring their COVID-19 status, thoughts on social restrictions and lifestyle changes in an attempt to determine their attitudes and concerns about COVID-19.

PSS-10: The scale was developed by Cohen et al. in 1983 to measure how stressful individuals perceive certain situations.[17] The Turkish validity and reliability study of the scale was conducted in 2013 by Eskin et.[18] The scale consists of 4, 10, and 14-item forms, and the PSS-10 form was used in our study. The internal consistency coefficient for PSS-10 was calculated as 0.82 and the test-retest reliability coefficient as 0.88 for the PSS-10 by Eskin et al. In the scale, which consists of 10 items in total, the participants evaluate each item on a 5-point Likert-type scale ranging from "Never (0)" to "Very often (4)". 4 items (6,7,9,10) containing positive statements are scored in reverse. The score that can be obtained from the scale is between 0–40, and a high score indicates that the person has a high perception of stress[17]. In this study, the Cronbach's alpha coefficient of the perceived stress scale was 0.90.

Data Analysis

After the researchers coded the data, statistical analysis was made using IBM Statistical Package for Social Sciences (SPSS) program version 25.0 statistical program. Descriptive statistics were used in the analysis of the data. Since the data were suitable for normal distribution, t-test and ANOVA test were applied to independent groups from parametric tests. Scale Reliability Coefficient was determined in Cronbach's Alpha. In the evaluation of the results obtained, 95% confidence interval and $p<0.05$ error level were taken into consideration.

Ethics Approval of the Study

In order to carry out the study, the necessary permission was obtained from the TR Ministry of Health Scientific Research Platform (dated 25.10.2021) and ethical approval was obtained from the Batman University Ethics Committee (09.04.2021 Decision no: 2021/01-12).

Results

The distribution of the descriptive characteristics of the individuals participating in the research is given in Table 1.

56.2% of the elderly participants included in the study were women, 78.0% were within the age range of 65–74. Additionally, 40.2% of the participants resided in their residences, 61.9% were single, 45.1% said their income was sufficient to cover their needs, and 60.3% reported having a chronic disease.

The study revealed that 49.0% of elderly individuals reported having COVID-19 disease, while 80.5% indicated that the COVID-19 pandemic had a significant impact on their lifestyle.

The distribution of the participants' concerns about COVID-19 is presented in Table 2. According to Table 2, 88.2% of the elderly individuals are anxious

Table 1. *Distribution of elderly individuals by their sociodemographic characteristics*

Variables		n	%
Gender	Woman	432	56.2
	Male	337	43.8
Age	65–74 years	600	78.0
	75–84 years	125	16.3
	Over 85 years old	44	5.7
Marital status	Married	299	38.9
	Single	470	61.9
Place of stay	Relatives (children, nephews)	274	35.6
	Nursing home	36	4.7
	Other	150	19.5
	Own house	309	40.2
Income status	Income <Expense	347	45.1
	Income =Expense	305	39.7
	Income >Expense	117	15.2
Presence of chronic disease	Yes	464	60.3
	No	305	39.7

Table 2. *Distribution of concerns about the elderly towards COVID-19*

Variables		n	%
I'm worried about being infected with COVID-19	Yes	619	80.5
	No	150	19.5
I'm worried as I don't know how long the pandemic will last	Yes	702	91.3
	No	67	8.7
I'm worried about getting sick and transmitting it to family/friends/other people	Yes	711	92.5
	No	58	7.5
I'm worried as I don't know how long the pandemic will last	Yes	694	90.2
	No	75	7.5
I'm worried about social distancing	Yes	621	80.8
	No	148	19.2
I'm worried about social restrictions	Yes	630	81.9
	No	139	18.1

about getting infected, 92.5% catching the disease and transmitting it to other people, 90.2% not knowing how long the pandemic will last, 80.8% being away from the social environment and 81.9% are concerned about social restrictions.

91.3% of the elderly participants in the survey expressed the view that it is important to inform everyone about the locations of COVID-19 patients to stay away from them. Additionally, 91.3% of the participants agreed that infected individuals should be segregated from society. The study found a mean score of 29.82±5.58 from the perceived stress scale for elderly individuals participating in the study in addition to a median score of 30.00 (18–39).

The comparison of the descriptive characteristics of the elderly and the perceived stress scale mean scores are given in Table 3. The difference between the

Table 3. *Comparison of the descriptive characteristics of elderly individuals and the mean scores of the perceived stress scale*

Variables		Perceived stress scale	Statistics	p
Gender	Woman	29.94±2.55	t=0.762	0.901
	Male	29.96±2.55		
Age	65–74 years	29.89±2.43	F=0.764	0.466
	75–84 years	29.97±2.87		
	Over 85 years old	29.38±2.67		
Marital status	Married	29.07±2.47	t=2.85	**0.004**
	Single	30.07±2.54		
Place of stay	Relatives (children, nephews)	29.95±2.90	F=9.905	**0.001**
	Nursing home	29.03±2.22		
	Other	29.02±2.33		
	Own house	30.31±2.53		
Income status	Income <Expense	29.89±2.62	F=7.83	**0.001**
	Income =Expense	30.25±2.22		
	Income >Expense	29.88±2.67		
Presence of chronic disease	Yes	30.05±2.53	t=1.86	0.07
	No	29.64±2.51		

* p<0.05, t=independent t test, F=ANOVA

Table 4. *Comparison of COVID-19 concerns about of elderly individuals with the total score of the perceived stress scale*

Variables		X ± SS	Statistics	p
COVID-19 status	Yes	29.84±2.52	t=0.20	0.84
	No	29.81±2.63		
Has the COVID-19 process changed your lifestyle?	Yes	29.90±2.45	t=1.60	0.10
	No	29.52±3.03		
Locations of COVID-19 patients should be reported to everyone so others can stay away from them	Yes	29.87±2.55	t=1.61	0.10
	No	29.34±2.82		
People infected with COVID-19 should be isolated from society	Yes	29.83±2.57	t=0.348	0.72
	No	29.72±2.62		
I am worried about getting infected and infecting family/ friends/other people	Yes	29. 88±2.51	t=2.02	**0.04**
	No	29.17±3.27		
I'm worried as I don't know how long the pandemic will last	Yes	29.83±2.52	t=0.10	0.91
	No	29.80±3.11		
I'm worried about being infected with COVID-19	Yes	29.80±2.50	t=0.12	0.98
	No	29.82±3.11		
I'm worried about social distancing	Yes	29.87±2.48	t=0.94	0.34
	No	29.64±2.95		
I'm worried about social restrictions	Yes	29.83±2.49	t=0.48	0.96
	No	29.82±2.95		

*p<0.05, t=independent t test

participants' marital status and perceived stress scale total score averages was statistically significant. Single elderly individuals had higher mean scores than the married ones (p=0.004). On the other hand, the difference between the place of residence of the elderly and the mean perceived stress scale total score was statistically significant. The mean score of the elderly residing in their own house was higher than the elderly in the other group (p=0.001). When it comes to the difference between the income status of the elderly and the perceived stress scale total score averages, it was also found to be statistically significant. The mean score of the elderly individuals whose income level was equal to income/expenditure was higher than the individuals with low and high income status (p=0.001).

Table 4 compares the concerns and attitude states of elderly people who participated in the study regarding COVID-19 and their overall score on the perceived stress scale. Also, Table 4 indicates a statistically significant difference (p=0.04) between the anxiety levels of the elderly participants regarding contracting the disease and infecting their family/friends/other people and the overall mean scores of the perceived stress scale.

Discussion

It is seen in the literature that studies conducted on elderly individuals during the COVID-19 pandemic have addressed such aspects as mental problems, insomnia, anxiety, stress, depression, psychological distress, and loneliness[19–24].

The COVID-19 pandemic has led to changes in many life practices, such as daily routines, social relationships, and individual hygiene habits[10]. 80.5% of the elderly participants in the study stated that the COVID-19 process changed their lifestyle. The first restriction on individuals aged 65 and over in Türkiye started as of 20 March 2020, prohibiting people from going out of their residence, walking in open parks, and traveling by public transportation vehicles, with a ban on curfews[25]. Mental health problems may occur in those in isolation and quarantine, which may also exacerbate and trigger psychological and emotional distress[26]. It has been stated that the isolation process itself is likely to have adverse effects on the mental health of elderly individuals[27,28]. A study by Doğanay and Çopur[30] stated that the beginning of the curfew for individuals aged 65 and over and implementation of free-day practices paved the way for the intensification of negative emotions in the participants with their timing and framework.

It can be said that due to restrictions during the COVID-19 pandemic, some concerns have arisen in elderly individuals. The COVID-19 pandemic is thought to give rise to the concern to become infected and transmitting the infection to other people among elderly individuals. In this study, 88.2% of the elderly individuals stated that they were worried about being infected and 92.5% about transmitting the disease to other people. 90.2% stated that they did not know how long the pandemic would last, while 80.8% stated that they were worried about staying away from the social environment and 81.9% were worried about social restrictions. A study by Klaiber et al.[31] stated that young and middle-aged adults are more concerned about the threat caused by COVID-19 in multiple habitats than older adults. In a study by Amucucci et al.[23], it was stated that elderly individuals experienced anxiety. Still, when compared with younger individuals, no statistically significant difference was found in terms of the anxiety variable. Also, in the study by Rossi et al.[20], 20.8% of the participants reported severe anxiety symptoms, while in a study by Başer et al.[32], 3.8% of the participants aged 65 and over were found to have serious anxiety levels. In the study conducted by Yildirim et al.[13], the anxiety levels of elderly people aged 65–74, female and single were found to be very high. They reported that their family relationships were negatively affected during the pandemic, so they became lonely, bored, exhausted, and distressed during the pandemic, which increased their depression levels[33]. In the study by Vural et al., the relationship between geriatric anxiety and the age and marital status of the participants during the Covid 19 pandemic was found to be significant. It is stated that the risk of geriatric anxiety is higher in women aged 71–81 and single women[34].

It is noteworthy that the majority (91.3%) of the elderly individuals participating in the study expressed their concerns towards the location of COVID-19 patients, stating that their location should be reported to everybody. Again, as many as 91.3% of the participants expressed that the infected ones should be isolated from society.

The total mean score of the elderly individuals participating in the study in terms of the PCS was 29.82±5.58, and the median was 30.00 (min-max: 18–39). In the study by Limcaoco et al.[35], the mean perceived stress scale was 14.6 in individuals aged 60 and over. In a study by Amucucci et al.[23], on the other hand, the mean perceived stress in elderly individuals was determined

as 13.88±7.10. In a study by Nwachukwu et al.[22], the mean perceived stress of individuals aged 60 and over was found to be 16.65±6.77, and it was reported that they had lower stress levels compared to other age groups. A study by Rossi et al.[20] determined that older individuals displayed lower levels of perceived stress compared to young people. The stress level of elderly individuals was found to be 2.60 in a study by Klaiber et al.[31], which at the same time reported that elderly individuals had less control over their stressors compared to young adults, emphasizing more coping skills in those individuals, though. Fernandez et al.[36], on the other hand, found that individuals over 60 years of age had a lower acute stress level compared to individuals under the age of 60. Compared to other studies reporting that older individuals are less affected by stressors than younger individuals [36,37] and elderly individuals exhibit better resilience under difficult conditions, what we found in our study is the opposite[38]. As we hypothesized earlier, the perceived stress level of elderly individuals was found to be quite high in the study.

Negative lifestyle changes occurring in old age (such as relocation, loss of a safe environment, lack of caregivers) may cause stress and anxiety in elderly individuals[39]. Stress is among the negative factors associated with loneliness[40]. We can state that elderly individuals who live alone and do not have social support or who remain weak during the period of social restrictions in the COVID-19 process are highly likely to experience more stress. The studies in the literature also report that the elderly are more prone to experiencing loneliness than adults[41], and single elderly individuals feel more lonely[42]. Meng et al.[43] Also point out that single elderly people should be focused more during the COVID-19 process.

Living alone is an objective indicator of one's life pattern, while loneliness is a subjective emotional experience. Therefore, although living alone increases the risk of loneliness, not all elderly people living alone feel lonely and vice versa[44]. The difference between where the elderly reside and the mean total perceived stress scale scores was found to be statistically significant. In our study, the mean perceived stress scores of the elderly residing in their own home were found to be higher than the elderly in the other group. When this finding is evaluated together with the fact that the majority of the elderly individuals participating in the study are single, it suggests a lack of family support, social support or interaction between the elderly adults. Kasar and Karaman[45] reported in their studies that elderly individuals experienced social isolation and their degree of loneliness was adversely affected during the pandemic. Considering that elderly individuals in the Turkish family structure are generally in active interaction in crowded family structure, being away from family members during the COVID-19 and having to go through the isolation period can cause individuals living alone in their own home to experience higher stress levels.

Özmete[46] found in her study that as the income level rises and the health status remains good, the life satisfaction of the elderly individuals may tend to increase, and the kinship relations of the elderly experiencing financial insecurity turn negative. The pandemic can significantly lower the incomes and living standards of the elderly. What we encountered in our study was different in that the mean perceived stress was higher in elderly individuals whose income level was equal to income-expenditure rate compared to individuals with low and high income status.

COVID-19 has caused anxiety and fear in elderly individuals about contracting the disease and transmitting it to others or losing their lives[10]. The difference between the anxiety states of the elderly individuals about contracting the disease and transmitting it to their family/friends/other people and the mean total scores of the perceived stress scale was statistically significant. Based on this, we can say that the fear and anxiety experienced by individuals increase the level of stress they face.

Sharing the results obtained in studies addressing the effects of the pandemic on the elderly in various aspects will greatly contribute to the process and the following periods. In this study, the concerns of elderly individuals towards COVID-19 in terms of contracting and transmitting the infection are noteworthy. The study determined that the perceived stress levels of the elderly individuals were quite high.

The COVID-19 pandemic has revealed that public health policies, including how older individuals are treated, need to be reconsidered. In socially difficult times, practices should be carried out considering the rights of the vulnerable groups of the society as a priority without compromising basic human rights, which has once again been demonstrated by the pandemic process.

Individuals over the age of 65, who have always been in the fragile and risky group, experienced difficulties in participating in their daily life activities, physical activities and social lives due to restrictions during the Covid-19 period. The elderly individuals should be approached carefully in the crisis and recovery phases of COVID-19, having devastating social and economic impacts. On the other hand, we recommend the development of rapid supportive strategies aimed at elderly individuals which take their health and psychological status as priority risk groups into consideration in order to eliminate their stress and anxiety.

Limitations

The necessity of collecting some of the research data online may have prevented the collection of striking findings. In this study, the stress levels and anxiety states of the elderly were based on their self-reports.

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Conflicts of Interests

The authors report no conflicts of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Laser Therapy for Grade II and III Hemorrhoids: Three-year Clinical Experience

II. ve III. Derece Hemoroidlerde Lazer Tedavisi: Üç Yıllık Klinik Deneyim

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ABSTRACT

Aim: *Hemorrhoids are difficult to treat. Multiple treatment options are available, supported by heterogeneous evidence. In our study, we aimed to analyze laser therapy's clinical outcomes and effectiveness.*

Material and Method: *Our study was conducted on 1096 patients who underwent Hemorrhoidal Laser Procedure (HeLP) and were diagnosed with grade II and III hemorrhoids in our general surgery clinic between 2018 and 2021. The patients pre- and postoperative clinical data were obtained from patient files, electronic records, and telephone interviews.*

Results: *Bleeding and urinary retention were the most common complications in the early period. In the long term, the anal fissure was found to be the most common complication. We detected hemorrhoidal diseases 1.25 times more frequently in males. The patients presented to our clinic with the most common complaints of bleeding and hemorrhoidal syndrome.*

Conclusion: *The use of laser therapy is an appropriate procedure for grade II and grade III hemorrhoids that do not respond to conservative approaches, which require minimal analgesic use, less need for wound care and very short duration of pain and discomfort, with high patient satisfaction.*

Key words: *hemorrhoids; laser therapy; prognosis*

ÖZET

Amaç: *Hemoroidlerin tedavisi zordur. Heterojen kanıtlarla desteklenen birden fazla tedavi seçeneği mevcuttur. Çalışmamızda lazer tedavisinin klinik sonuçlarını ve etkinliğini analiz etmeyi amaçladık.*

Materyal ve Metot: *Çalışmamız, 2018–2021 yılları arasında genel cerrahi kliniğimizde evre II ve III hemoroid tanısıyla Hemoroidal Lazer Prosedürü (HeLP) uygulanan 1096 hasta üzerinde gerçekleştirildi. Hastaların ameliyat öncesi ve sonrası klinik verileri hasta dosyalarından, elektronik kayıtlardan ve telefon görüşmelerinden elde edildi.*

Bulgular: *Kanama ve idrar retansiyonu erken dönemde en sık görülen komplikasyonlardı. Uzun vadede anal fissürün en sık görülen komplikasyon olduğu bulundu. Hemoroidal hastalıkları erkeklerde 1,25 kat daha sık olduğu tespit edildi. Hastalar kliniğimize en sık kanama ve hemoroidal sendrom şikâyetleriyle başvurdu.*

Sonuç: *Lazer tedavisinin kullanımı, konservatif yaklaşımlara yanıt vermeyen, minimal analjezik kullanımı, daha az yara bakımı ihtiyacı ve çok kısa süreli ağrı ve rahatsızlık gerektiren, yüksek hasta memnuniyeti sağlayan II. ve III. derece hemoroidler için uygun bir prosedürdür.*

Anahtar kelimeler: *hemoroidler; lazer tedavisi; prognoz*

Introduction

Hemorrhoids affect millions of people around the world. The reported prevalence of hemorrhoids varies between 13–36%, depending on the research method. The most common symptoms are rectal bleeding, pain, anal irritation, and anal mass prolapse[1]. Hemorrhoids are difficult to treat. Multiple treatment options are available, supported by heterogeneous evidence. Evidence is conflicting for newer surgical techniques that are claimed to be less painful.

Conservative medical management, non-surgical treatments, and various surgical techniques are used in the treatment of symptomatic hemorrhoids. Traditionally, the most common open surgery is hemorrhoidectomy and the closed variant technique. These two methods are associated with a high risk of complications, postoperative pain and discomfort[2]. Because of these, clinicians have turned to less invasive solutions for less pain, better control of symptoms, and rapid recovery.

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Non-excisional laser treatments are emerging treatment modalities for Grade II and III hemorrhoidal disease. It is particularly useful in Grade I-II hemorrhoids where prolapse is less important[3]. It was reported in previous studies that the improvement of symptoms in Grade II and III hemorrhoids with laser treatments varies between 83.6% and 100%. The recurrence rates were reported as 5–11.3%[4]. In this context, non-excisional laser treatments are safe and effective in cases resistant to conservative treatments and Grade I, II, and III hemorrhoids[4,5]. The success rate of non-excisional laser treatments is low in Grade IV hemorrhoids, with a recurrence rate of 59.3%. Surgical methods are recommended for these cases. Conventional hemorrhoidectomy continues to be the main treatment for Grade IV hemorrhoids because of the presence of inductive prolapse and hypertrophic skin findings[6,7].

The hemorrhoidal laser procedure (HeLP) is a minimally invasive and painless procedure in which a special laser device diminishes and shrinks the terminal branches of the superior hemorrhoidal artery to treat symptomatic grade II and grade III hemorrhoids[8]. In our study, we aimed to analyze laser therapy's clinical outcomes and effectiveness.

Method

Our study was conducted on 1096 patients who underwent Laser hemorrhoidoplasty (LHP) diagnosed with grade II and III hemorrhoids in our general surgery clinic between January 2018 and December 2021. The patient's pre– and post-operative clinical data were obtained from patient files, electronic records, and telephone interviews. The inclusion criteria of the patients were determined as symptomatic grade II and grade III hemorrhoids whose symptoms persisted or recurred despite medical treatment. In our clinic, managing hemorrhoids depends on the type and severity of hemorrhoids, the preference of the patient and our clinical experience. It is primarily diet, lifestyle change, medical and conventional treatment for Grade I-II hemorrhoids. We primarily use local analgesics, anesthetic pomades and steroid-containing creams, suppository and laxative drugs in acute hemorrhoidal symptoms. Traditional methods are 15-minute hot water sitz baths 3–4 times daily and cleaning the perianal area with soapy water. Most commonly, oral flavonoids are used in our clinic [(Diosmin 450 mg+Hesperidin 50 mg), (Daflon®, Servier, France)] combined to control acute hemorrhoid symptoms 3000 mg/day for 4 days, 2000 mg/day for 3 days or calcium Dobesilate 1000 m/day. Our main target is to control the symptoms. The cases in which we failed with these treatment methods and Grade II and Grade III cases who failed with medical and conventional treatment in other clinics were included in the study. The LHP Procedure was applied to these cases. Low-grade hemorrhoids resistant to medical and conventional treatment, treatment non-compliance because of treatment duration and length of recovery (3–4 weeks), and relapse cases after medical treatment were determined as conservative treatment failure. Patients with liver cirrhosis, bleeding diathesis, chronic liver disease, inflammatory bowel disease, perianal abscess, patients younger than 18 years of age and those diagnosed with colorectal cancer and other malignancies were excluded from the study.

All patients were admitted on the morning of the operation day. Patients were allowed to eat and drink 8–10 hours before the operation. Bowel preparation was not deemed necessary. Two enemas were administered 2 hours before the intervention. The laser procedure was performed as a 1-day surgical procedure. After the detailed physical examination and proctoscopy, the LHP was performed using a 1470 nm diode laser. All surgical procedures were performed by the same surgeons experienced in coloproctological surgery. Spinal and/or local anesthesia was administered according to the clinical conditions of the patients. The LHP was performed in the lithotomy position. A disposable proctoscope was inserted into the anal canal. Standard five-six shots were made to each hemorrhoid pack with a 1470 diode laser probe. A hemorrhoid probe (a conical glass-tipped optical fiber) treats hemorrhoid pile with LHP. The glass tip of this probe provides energy transmission, while the distal, sharp tip helps to enter the hemorrhoidal tissue easily. Disposable optical fiber is used in these processes. The optical fiber is first connected to the laser unit (NeoLaser, HaEshel 7, 3088900, Caesarea Business Park, Israel). The laser unit is 980–1470 nm, 30–45J, 7–15.0 W/1–3 sec in this laser device. The tissues are energized homogeneously in 5–6 blows into each hemorrhoid pile. The energy dose for each pile of hemorrhoids was 50–100 J/cm in our clinic. In this way, each pile of hemorrhoids is sealed thermally. The hemorrhoid pile is cooled externally after the procedure, during which hemorrhoidal artery ligation is not performed simultaneously. The execution of the LHP process is shown in Figure 1. The patients were discharged 12–18 hours after the procedure. 1–3 months of follow-up data were analyzed regarding recovery, pain, return to normal

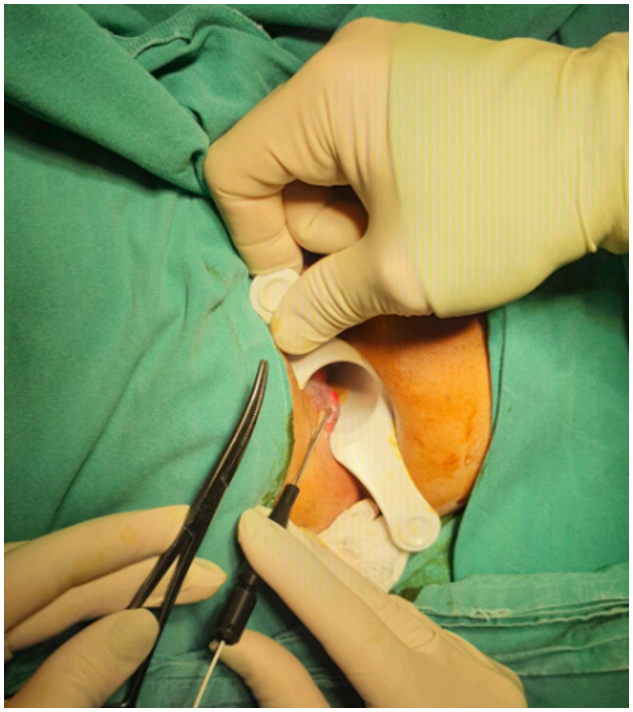

Figure 1. *The LHP process.*

life, and early complications. The patients were followed up for an average of 1.3±0.7 years regarding the success of the LHP method and late complications. The data were analyzed with statistical tests and presented with related tables and graphs. The present study was conducted in line with the ethical rules and the decision of the Medicana International Samsun Hospital Clinical Research Ethics Committee, dated 04.10.2021, with the number 7154.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). We compared chi-square statistics for categorical data, categorical variables (n) as percentages, and unpaired Student's t-test for continuous variables. Normally distributed variables were compared by the independent sample t-test, while non-normally distributed variables were compared by the Mann-Whitney test. The value of $p < 0.05$ was considered statistically significant. Data were analyzed using SPSS program software (IBM Statistical Package for the Social Sciences, version 22.0, Chicago).

Results

A total of 1096 (486 females, 610 males) patients were included in the study. The age of the patients was 48±11.4 years. We detected hemorrhoidal diseases 1.25 times more frequently in males. The most common clinical finding in the patients was found to be bleeding. The clinical complaints that brought the patients to the hospital were bleeding 77.5% (n=850), prolapse of the anal mucosa 39.5% (n=433), hemorrhoidal syndrome (pain, anal itching, discharge, anal fullness) 23.2% (n=was 255). Clinical complaints were not one single complaint, but these symptoms were present in many cases. The most common risk factors for hemorrhoids were constipation and pregnancy. Before the LHP, 16.1% of the patients needed analgesics. Demographic and pre-operative clinical data of the patients with grade II and III hemorrhoids are presented in Table 1.

Table 1. *Demographic and pre-operative clinical data of patients with grade II and III hemorrhoids*

Parameters		**n (%) / Mean ± SD**
Sociodemographic information	**Sex, female**	504 (45.9)
	Age (years)	48±11.4
	Number of patients	1096
	Length of follow-up	1.3±0.7
Hemorrhoid symptoms of patients	Grade II hemorrhoids 262 (23.9%) n (%)	Grade III hemorrhoids 834 (76.0%) n (%)
Bleeding	167 (63.7)	683 (81.8)
Hemorrhoidal syndrome	47 (17.9)	208 (24.9)
Prolapsed hemorrhoid	0	433 (51.9)
Thrombosed hemorrhoid	0	85 (10.1)
Early pre-operative period analgesic need (nonsteroidal anti-inflammatory drugs, paracetamol)	11 (4.1)	166 (19.9)
Epidemiology and risk factors of hemorrhoids		
Constipation	148 (56.4)	522 (62.5)
Pregnancy	64 (24.4)	209 (25.0)
Diarrhea	5 (1.9)	17 (2.0)
Others (nutrition, socioeconomic level)	45 (17.1)	86 (10.3)

* whole cohort-n (%); SD: standard deviation.

Table 2. *Intra- and post-operative clinical data of patients with grade II and III hemorrhoids*

Parameters	**Mean ± SD**	
Duration of surgery, minutes ± SD	16.8±7.8	
Return to regular activity, days ± SD	11.2±4.8	
Distribution of patients according to grade II and III hemorrhoids	**Grade II hemorrhoids 262 (23.9%)**	**Grade III hemorrhoids 834 (76.0%)**
	n (%) / Mean ± SD	**n (%) / Mean ± SD**
Length of hospital stay (hours)	14.3±4	16.3±2
Need for blood transfusion	0	0
Early post-operative period analgesic need (nonsteroidal anti-inflammatory drugs, paracetamol, opioids) (days)	0–3	0–7
Relapse or recurrence	8 (3.0)	56 (6.7)
Urinary retention	6 (2.2)	42 (5.0)
Early complications		
Abscess	0	8 (0.9)
Bleeding	21 (8.0)	86 (10.3)
Long-term complications		
Anal fissure	4 (1.5)	32 (3.8)
Stenosis	0	2 (0.23)
Incontinence	0	2 (0.23)

* whole cohort-n (%); SD: standard deviation.

The LHP treatment time was 16.8±7.8 hours. The duration of analgesic use in all patients in the early post-operative period was 0–7 days. In the early period, bleeding was detected at 9.7%. Clinical follow-up of the patients was performed at 6-month intervals. The recurrence and/or recurrence rate during the follow-up was 5.8% (n=64). The mean time to relapse was 15.4±8.6 months. Recurrence was determined by considering the patient's examination and symptoms. Bleeding again was found in 16 of these patients, bleeding and prolapse in 24 patients, only prolapse in 14 patients, and hemorrhoidal syndrome findings in 10 patients. The predictive factor for recurrence was a thrombosed external hemorrhoid attack. The most common risk factors are constipation and inability to maintain a diet (intensive use of spices in meals). The relapse and/or recurrence rate at follow-up was 5.8%. Bleeding and urinary retention were the most common complications in the early period. In the long term, the anal fissure was found to be the most common complication. Intra- and post-operative late clinical data of the patients are shown in Table 2.

Discussion

Hemorrhoid disease is usually classified by the classic Goligher staging[9]. We used the Goligher staging in our study. We conducted the study on grade II and grade III hemorrhoids. Hemorrhoids can manifest with various symptoms, such as rectal bleeding and prolapse, anal pain, and anal itching. Rectal bleeding, usually painless and associated with defecation, is the most common symptom[10]. In our study, the most common complaint at admission to our clinic was rectal bleeding.

Risk factors for hemorrhoids are factors associated with excessive straining and/or increased intra-abdominal pressure (constipation, hard stools, pregnancy)[11]. Constipation and/or hard stools are believed to be the most common cause of hemorrhoids[12]. Some studies did not show a significant relationship between hemorrhoids and constipation[13]. Some reports asserted that diarrhea was a risk factor for the development of hemorrhoids[14]. It may predispose to symptomatic hemorrhoids during pregnancy. Many dietary factors were also blamed, including a low-fiber diet, spicy foods, and alcohol intake[11]. In our study, we determined that the risk for hemorrhoids was constipation and pregnancy, and less frequently, nutritional and dietary factors, socioeconomic level, and diarrhea.

Studies showed that laser hemorrhoid treatments were safe. Bleeding was reported to be the most common complication in the early period. It was shown in many different studies that bleeding occurred at 5.5–16.7% in treatment with the LHP. Total post-operative complications after the LHP were found to be 23.3%[15]. In our study, complications after the HeLP approach are consistent with the literature data. Bleeding was common in the early period at a rate of 9.7%. We found that all post-operative complications were 14.1%. In studies, relapse and/or recurrence rates were reported

as 5–9.4% in short-term follow-ups[16,17]. In long-term follow-up, the recurrence rate was 34% during a mean follow-up of 5.4 years[18]. Our study found a recurrence rate of 5.8% after 1.3±0.7 years of follow-up. It is observed in the studies that the complication rates of the HeLP method decrease, and the success performance increases as the clinical experience increases.

Urinary retention, one of the morbidities after the LHP, was found at a rate of 4.1–20.1% (18,19). In the early period, infection and/or abscess was 1%[19]. Our study found the frequency of urinary retention to be 4.3%. We showed that infection or abscess developed at a rate of 0.9% among the early complications. Among the long-term complications, it was shown in studies that anal fissure occurred at a rate of 1–2.6%, anal stenosis at a rate of 1%, and anal incontinence at a rate of 0.4%[3]. In our study, we found the frequency of long-term complications to be 3.2% for anal fissure, 0.2% for anal stenosis, and 0.2% for anal incontinence. When the literature is reviewed, short and long-term complications are observed to be very rare, as in our study. Our study and other studies show that the LHP method is new, non-excisional, mini-invasive, safe, and successful in patients with grade II and III hemorrhoids. It can be preferred as the first method when conservative treatments are unsuccessful.

Studies indicated the advantages of rapid return to normal life and low post-operative pain after the LHP[20,]. It is known that there are significant differences between post-operative analgesia studies[19,20]. In our study, the duration of post-operative analgesic use was 0–7 days, and many of our patients did not receive any analgesics. Return to regular activity after the LHP was 11.2±4.8 days.

The LHP technique is a minimally invasive, painless, safe and fast procedure with high efficacy, as in our study, in patients affected by grade II and III hemorrhoid disease. When our findings are compared with other methods in the literature, we think that the use of this technique is an appropriate procedure for grade II and grade III hemorrhoids that do not respond to conservative approaches, which requires minimal analgesic use, less need for wound care and very short duration of pain and discomfort, with high patient satisfaction.

Ethical Approval

This study was conducted in accordance with the ethical rules with the approval of Medicana International Samsun Hospital clinical research ethics committee (decision no 7154, 04.10.2021).

Patient's Consent

The study was carried out retrospectively by examining patient records with the approval of the institution.

Conflict of Interest

The authors declared no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Effect of Spirituality on Psychological Resilience in Women During the Pandemic Period

Pandemi Döneminde Maneviyatın Kadınlarda Psikolojik Sağlamlığa Etkisi

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ABSTRACT

Aim: *It was carried out to evaluate the effect of spirituality and spirituality on psychosocial resilience in women during the pandemic period.*

Material and Method: *It is a descriptive and cross-sectional study. The study sample consisted of 335 women who met the research criteria. The research was carried out between April 2022 and June 2022 in a province in the Eastern Anatolia Region of Türkiye. Personal data formula, Spirituality and Brief Psychological Resilience Scale were used to collect data.*

Results: *The average score women received from the spirituality scale was 108.21±13.81, and the average score they received from the short endurance scale was 19.84±4.65. Spirituality levels were statistically significant between those who spent the COVID-19 disease process in the hospital and those who spent it at home (p<0.05). As women's spirituality levels increased, their psychological resilience levels also increased (p<0.05). There is a positive relationship between women's spirituality levels and psychological resilience.*

Conclusion: *Women with high levels of spirituality have a higher potential to cope with challenges such as epidemics and pandemics.*

Key words: *COVID-19; pandemic; psychological resilience; spirituality; women*

ÖZET

Amaç: *Pandemi döneminde maneviyat ve maneviyatın kadınlarda psikososyal dayanıklılığa etkisini değerlendirmek amacıyla yapılmıştır.*

Materyal ve Metot: *Tanımlayıcı ve kesitsel bir çalışmadır. Araştırmanın örneklemini araştırma kriterlerini karşılayan 335 kadın oluşturmuştur. Araştırma, Türkiye'nin Doğu Anadolu Bölgesi'nde yer alan bir ilde Nisan 2022 ile Haziran 2022 tarihleri arasında gerçekleştirildi.*

Verilerin toplamasında kişisel veri formu, Maneviyat ve Kısa Psikolojik Sağlamlık Ölçeği kullanılmıştır.

Bulgular: *Kadınların maneviyat ölçeğinden aldıkları ortalama puan 108,21±13,81, kısa dayanıklılık ölçeğinden aldıkları ortalama puan ise 19,84±4,65'tir. COVID-19 hastalık sürecini hastanede geçirenler ile evde geçirenler arasında maneviyat düzeyleri istatistiksel olarak anlamlı bulundu (p<0,05). Kadınların maneviyat düzeyleri arttıkça psikolojik dayanıklılık düzeylerinin de arttığı tespit edildi (p<0,05). Kadınların maneviyat düzeyleri ile psikolojik dayanıklılıkları arasında pozitif bir ilişki bulunmaktadır.*

Sonuç: *Maneviyat düzeyi yüksek kadınların salgın ve pandemi gibi zorluklarla baş etme potansiyeli daha yüksektir.*

Anahtar kelimeler: *COVID-19; pandemi; psikolojik dayanıklılık; maneviyat; kadın*

Introduction

As in other disasters, the COVID-19 pandemic has triggered changes that have affected the daily routines of humanity[1–3]. In addition to the physical impacts of the uncertainties and challenges it has caused, the COVID-19 pandemic has also had considerable spiritual and psychological effects[4,5]. These effects include loneliness, anxiety, depression, stigma, fear of death, etc. such situations[2,4,6].

The pandemic period has created various concerns and fears in individuals, such as fears of contracting the disease, losing loved ones, feeling unsupported and lonely in the isolation process for treatment, and socio-economic problems[7–9]. The intensity of the reactions displayed against these concerns and fears varies from one individual to another. While some individuals can cope with their challenges, others are underwhelmed by these challenges[7,10,11].

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Psychological resilience is the ability of an individual to overcome a difficulty and adapt to it[12,13]. Individuals with high levels of psychological resilience have a stronger capability to cope with the challenges they encounter[12,14]. Psychological resilience, which means fighting against problems and recovering in difficult living conditions, has been especially important in the COVID-19 pandemic period[10].

Spirituality, which is a component of holistic midwifery care, is a factor that affects the recovery of individuals and their adaptation to situations such as health and disease[11,15]. In challenging life conditions, the person is attracted to spirituality to reach comfort and hope, overcome stress, anxiety, and fear, and feel powerful. Thus, through spirituality, individuals feel safe and maintain a healthy life[7,15,16]. In general, individuals need psychological resilience and spirituality when they feel insecure and cannot take the situation that is being experienced under control[5,17]. Thus, this study was carried out to evaluate the impact of women's spirituality and spirituality on their psychosocial resilience during the pandemic period, which is difficult to cope with.

Method

Research Design and Sample

It is a cross-sectional and descriptive study. The research was carried out between April 2022 and June 2022 in a province in the Eastern Anatolia Region of Türkiye. The study's sample size was determined using the formula of unknown sample population (n=t 2 pq/d2)[18]. The sample size was calculated as 246.335 people were included in the study.

Research Question

Does the COVID-19 pandemic have an impact on the spirituality and psychological resilience of women?

Inclusion Criteria

Being a woman over the age of 18 and having a minimum education level of primary school.

Instruments

Personal Data Form

It consists of 15 questions including, socio-demographic characteristics of women and information about the pandemic[12,26,31].

Spirituality Scale

A validity and reliability study was conducted by Şirin (2018). The measurement tool consists of 27 items, 3 of which (8, 13, 26) are reverse items. The scale was developed as a 5-point Likert. Scoring for each item is as follows: "Not applicable to me at all=1", "Not applicable to me=2", "Somewhat applicable to me=3", "Fairly applicable to me=4", Completely Applicable to me=5". The measurement tool consists of 7 sub-dimensions. These sub-dimensions; "Spiritual Coping" (9, 12, 20, 21, 23), "Transcendence" (19, 22), "Spiritual Experience" (3, 11, 24, 25, 27), "Seeking Meaning" (7, 14, 15, 17), "Spiritual Contentment" (6, 8, 13, 26), "Connection" (1,2,4,18) and "Harmony with Nature" (5, 10, 16). The total score that can be obtained on the scale varies between 27 and 135, and high scores indicate that the person has high spirituality; Low scores indicate that the person has low spirituality. The Cronbach's alpha coefficient of the scale is 0.9017. The Cronbach alpha coefficient of this study was found to be 0.87.

Brief Resilience Scale (BRS)

It was developed by Smith et al.[20] in 2008 to measure people's psychological resilience levels. A Brief Resilience Scale Turkish reliability and validity study was conducted by Doğan[21] in 2015. The scale is a self-report measurement tool consisting of 6 items, 3 of which are negative (items 2, 4 and 6). The scale consists of a single sub-dimension. The scale was developed as a 5-point Likert and from each item to the statement specified, "Not at all suitable=1", "Not suitable=2", "Somewhat suitable=3", "Appropriate=4", "Completely appropriate=5"." is asked to choose one of the options. The total score that can be obtained on the scale varies between 5 and 30, and high scores indicate high psychological resilience; Low scores indicate that the person has low psychological resilience. Cronbach's alpha coefficient of BRS is 0.81[21]. The Cronbach alpha coefficient of this study is 0.83.

Collection of Data

Research data were collected through face-to-face interviews with women who agreed to participate in the study voluntarily. A personal data form and the Spirituality and Brief Psychological Resilience scale were used to collect data. The collection time for each data set was between five and seven minutes.

Statistical Analysis

The analysis of the data obtained in the study was done using the IBM Statistical Package for Social Sciences (SPSS) program version 22.0. Normal distribution analyses of the study were performed. As a result of the analysis, Skewness and Kurtosis coefficients were evaluated, and it was determined that the data showed normal distribution[18]. For statistical analysis, one-way analysis of variance (ANOVA), independent sample t test, Pearson correlation, and post hoc (Tukey, LSD) were performed. The statistical significance level is $p<0.05$.

Ethics Principles of the Research

Ethics committee decision number B. 30.2. ATA. 0.01.00/138 was taken on 27.01.2022 by the Clinical Research Ethics Committee of Ataturk university to initiate and conduct the study. The women participating in the study were informed about the study. The women were informed that all data collected in this study would be kept confidential. Verbal and written consent was obtained from women who agreed to participate in the study.

Results

The mean age of the participants was 32.12±10.59. While 42.1% of the participants had a high school education, 41.2% had an income-generating job. It was found that 42.1% of the participants had contracted COVID-19. The average score of women on the spirituality scale was 108.21±13.81. Women's average score on the Brief Psychological Resilience Scale was determined as 19.84±4.65 (Table 1).

Regarding the pandemic-related experiences of the participants, a significant difference was determined in their Spirituality Scale scores concerning their statuses of needing spiritual support (p=0.024). It was found that the participants who needed spiritual support had a higher mean spirituality score (109.81±13.66). The COVID-19 pandemic was defined by 26.3% of the participants as "a punishment to humanity." The highest mean spirituality score was determined among the participants who defined the pandemic as a punishment. The post hoc analysis determined that the significance stemmed from the participants who called it "a punishment given to humanity". There is a significant difference between women's spirituality score averages according to their definition of the pandemic (p=0.011) (Table 2).

The mean general spirituality score of the participants was found to be high. The participants who stated they were not careful about the pandemic restrictions had a significantly lower mean spirituality score than those who stated they were careful about the restrictions and those who said they were sometimes careful (p=0.045). Similarly, considering the statuses of the participants to follow masking and social distancing measures, the lowest mean spirituality score (103.23±10.21) was

Table 1. *Sociodemographic characteristics and COVID-19 diagnosis statuses of the participants*

	$\bar{X}$ ± SD	Min-max
Age	32.12±10.59	18–64
Spirituality score	108.21±13.81	64–134
Brief resilience score	19.84±4.65	6–30
	n	%
Educational status		
Primary-secondary school	63	18.8
High school	141	42.1
University	131	39.1
Employment status		
Employed	138	41.2
Unemployed	197	58.8
History of COVID-19 diagnosis		
Yes	141	42.1
No	194	57.9

Table 2. *COVID-19-related behaviors of the participants and their mean spirituality scores*

Behaviors	n	%	$\bar{X}$ ± SD	Test and p-value
Needed psychological support				
Yes	93	27.8	109.58±14.26	t=1.120 p=0.264
No	242	72.2	107.69±13.62	
Received psychological support				
Yes	13	3.9	106.84±16.43	**t=0.389 p=0.697**
No	321	96.1	108.36±13.65	
Needed spiritual support				
Yes	179	53.4	109.81±13.66	**t=2.274 p=0.024**
No	156	46.6	106.39±13.79	
Defines the pandemic as punishment to humanity	88	26.3	109.10±13.57	
Natural disaster	26	7.8	100.42±14.34	f=4.603 p=0.011
Infectious disease	221	65.9	108.78±13.60	
Felt desperate				
Yes	63	18.8	106.95±15.24	
No	57	17	105.38±15.59	f=2.187 p=0.114
Sometimes	215	64.2	109.33±12.76	
Was concerned about the pandemic				
Yes	85	25.4	108.21±15.30	
No	49	14.6	107.34±14.66	f=0.121 p=0.886
Sometimes	201	60	108.43±12.97	

Table 3. *The effect of the attitudes of the participants towards protective measures on their spirituality levels*

Attitudes of the participants	n	%	$\bar{X}$ ± SD	Test and p-value
Was careful about pandemic-related measures				
Yes	175	52.2	107.32±14.39	
No	18	5.4	102.61±13.68	**f=3.121 p=0.045**
Sometimes	142	42.4	110.03±12.85	
Obeyed mask-wearing and social distancing rules				
Yes	219	64.4	107.58±14.42	
No	17	89.2	103.23±10.21	**f=2.670 p=0.071**
Sometimes	99	29.5	110.46±12.63*	
Has been vaccinated				
Yes	299	89.2	108.22±13.91	**t=0.036 p=0.702**
No	36	10.8	108.13±13.10	

* post hoc testi (LSD, Tukey)

Table 4. *The effect of the progress of the disease in the participants who had tested positive for COVID-19 on their spirituality*

Support requirement status	n	%	$\bar{X}$ ± SD	Test and p-value
Experienced COVID-19 at (n=141)				
Home	120	85.1	106.33±13.87	**t=2.418 p=0.017**
Hospital	21	14.9	114.61±17.67	
Needed psychological support				
Yes	54	38.3	109.14±14.65	t=1.004 p=0.317
No	87	61.7	106.58±14.78	
Needed spiritual support				
Yes	91	64.5	109.54±14.81	**t=2.184 p=0.031**
No	50	35.5	103.96±14.00	

found in those who did not follow mask-wearing and social distancing rules (p=0.071). It was determined that the difference between the groups stemmed from the women who answered sometimes (Table 3).

A significant difference was found between the spirituality levels of those who experienced COVID-19 at the hospital and those who experienced it at home (p=0.017). The spirituality scores of the participants who had tested positive for COVID-19 and were treated at the hospital were higher. Among women with positive COVID-19 test results, a statistically significant difference in spirituality scores was found between those who needed spiritual support and those who did not (p=0.031) (Table 4).

It was determined that as the spirituality levels of the participants increased, their psychological resilience levels also increased (p<0.001). Additionally, a significant correlation was found between all dimensions of the Spirituality Scale and psychological resilience (p=0.000) (Table 5).

Table 5. *The relationship between spirituality and psychological resilience*

	Psychological resilience	
Spirituality scale and dimensions	**r**	**p**
Spiritual coping	**0.306****	**0.000**
Transcendence	**0.117***	**0.032**
Spiritual life	**0.249****	**0.000**
Search for meaning	**0.218****	**0.000**
Spiritual satisfaction	**0.296****	**0.000**
Connection	**0.187****	**0.001**
Harmony with nature	**0.166****	**0.002**
Spirituality total	**0.337****	**0.000**

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed)

Discussion

In the present study, the effect of the COVID-19 pandemic on psychological resilience and spirituality in women was examined. The spirituality levels of the participants were found to be high in general. In Turkish culture and Islamic belief, spirituality is gained through experiencing certain challenges. This is because experiencing these challenges is considered valuable in God's eyes[22]. The spiritual levels of the participants of this study may have been found high as Turkish society is known for its commitment to its religious and cultural values; besides, it was stated that spirituality increases and deepens in situations such as difficult living conditions and traumas[23] (Table 1).

In this study, the spirituality levels of the participants who stated they needed spiritual support were high.

This may have resulted from the inclination of the participants towards spiritual support and their increased need for spiritual support to cope with the pandemic. In a metanalysis study, it was reported that spirituality provided support for mental relief in crises and times of danger[24]. Individuals have the capacity to use their spiritual values as a source of power in difficult processes such as disease and treatment[25]. The women who participated in this study may have desired to use this aspect of spirituality to cope with the stress that the COVID-19 pandemic caused them.

Spirituality is effective in many aspects of life. Therefore, health should be evaluated through a spiritual approach as a part of holistic midwifery care[25]. In a study conducted by Kımter[26] (2020), 46% of the participants stated that the COVID-19 pandemic was "God's test for humanity". In the present study, the participants with high levels of spirituality defined the pandemic as "a punishment to humanity", thus associating it with religion (Table 2).

Additionally, it was determined in the present study that the spirituality mean score of the women who did not practice the relevant measures and did not obey the rules regarding mask-wearing and social distancing was lower, while the spirituality mean score of those who obeyed these rules was higher. Studies examining the relationship between spirituality and health, have stated that spiritual practices protect individuals from harmful habits, provide them with a healthy living space, and guide them toward a regular life. Studies in the literature have reported that individuals with more established spirituality feel physically, socially, and emotionally healthier[25,27] (Table 3).

The mean spirituality score of the participants of this study who had been diagnosed with COVID-19 and recovered from it at the hospital was found to be higher. Spiritual values give hope to individuals. It is seen that the spiritual needs of individuals rise to peak levels in emergencies and unexpected situations such as disasters[22]. As the participants who experienced COVID-19 at the hospital went through a more difficult process compared to those who stayed at home, they may have benefited more from their spiritual emotions to hold on to life (Table 4).

There is a positive relationship between women's spirituality levels and psychological resilience. In this study, psychological resilience was found to have increased as the spirituality levels of the participants increased. The study conducted by Kasapoglu[28] (2020) reported that individuals with high spirituality levels had stronger psychological resilience. Gulerce and Maraj[29] (2021) stated that spirituality had a positive correlation with psychological resilience, and it had high value in terms of coping with situations such as desperation. In the study they conducted with African and American women during the COVID-19 pandemic, Barney et al.[30] (2021) found that they turned towards religious issues more and emphasized spirituality. The study by Killgore et al.[17] (2020) determined that those who prayed more frequently had higher levels of psychological resilience. Considering the results of the present study and other studies in the literature, it is seen that spiritual support provided in the pandemic period and other situations causing distress positively affects individuals' coping with problems and increases their psychological resilience levels (Table 5).

Conclusion

In this study, the general spirituality levels of the participants were found to be high. It was determined that spirituality was effective on the participants' psychological resilience during the COVID-19 pandemic, they paid more attention to the measures taken in this process, and developed positive behaviors. The spirituality levels of the participants who had tested positive for COVID-19 and been hospitalized were found to be higher. As the spirituality levels of the participants increased, so did their psychological resilience. Addressing the spiritual dimension of patient care and drawing the attention of healthcare professionals to this issue is important for both patients and families. Healthcare professionals should also consider spiritual support while providing holistic healthcare services.

Study Limitations

This study was conducted in a city in eastern Türkiye. Individuals living in other parts of the country may have given different answers.

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Declaration Conflict of Interest

The authors have no conflict of interest to declare.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Differences in *Lactobacillus spp.* Between Traditional and Industrial Vegetable Pickles

Geleneksel ve Endüstriyel Sebze Turşuları Arasındaki Lactobacillus Spp. Farklılıkları

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ABSTRACT

Aim: *This study investigates the content of Lactobacillus acidophilus, Levilactobacillus brevis and Lactiplantibacillus plantarum in traditional and industrially prepared cabbage and cucumber pickles.*

Material and Method: *Pickle samples were categorized according to the industrial (n=20) and traditional (n=38) production methods. The chemical compositions, including salt contents and pH of the pickles, were evaluated. The salt content of the pickles produced by the traditional method was recorded based on the manufacturer's declaration. Label information was assessed in industrially produced pickles. pH measurements were made using a desktop pH meter. Microbial load, including Lactobacillus acidophilus, Levilactobacillus brevis and Lactiplantibacillus plantarum counts of the pickles was carried out in a Real-time PCR device (RotorGene-Q, Germany) using the Diagen Real-time PCR Kit. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) program version 22.0.*

Results: *The pH values of the pickles produced by the traditional method had higher pH values than the industrial products ($p < 0.05$). Conventional and industrial pickles had similar salt content except for the industrial cabbage pickles (3.16 g/100 g, $p=0.002$). Lactobacillus acidophilus and Levilactobacillus brevis contents of traditional cucumber pickles (4.25±0.88 and 5.55±1.37 log_{10} cfu/g, respectively) were found to be significantly higher than those of industrial cabbage pickles (3.33±0.55 and 1.53±2.11 log_{10} cfu/g, respectively, $p < 0.05$).*

Conclusion: *This study's results, which found higher Lactobacillus spp. content in traditionally produced pickles than industrial ones, provide preliminary data for future studies investigating the bacterial community patterns and the proportions of predominant bacteria in pickles, which are fermented products consumed frequently in Türkiye.*

Key words: *industrial pickles; traditional pickles; cucumber; cabbage*

ÖZET

Amaç: *Bu çalışmanın amacı geleneksel ve endüstriyel olarak hazırlanan lahana ve salatalık turşularında Lactobacillus acidophilus, Levilactobacillus brevis ve Lactiplantibacillus plantarum içeriğini araştırmaktır.*

Materyal ve Metot: *Turşu örnekleri endüstriyel (n=20) ve geleneksel (n=38) üretim yöntemine göre sınıflandırılmıştır. Turşuların tuz içerikleri ve pH derecesi dâhil olmak üzere kimyasal bileşimleri değerlendirilmiştir. Geleneksel yöntemle üretilen turşuların tuz içerikleri üretici beyanı esas alınarak kayıt altına alınmış endüstriyel olarak üretilen turşularda ise etiket bilgileri değerlendirilmiştir. PH ölçümleri masaüstü pH metre kullanılarak yapılmıştır. Turşuların Lactobacillus acidophilus, Levilactobacillus brevis ve Lactiplantibacillus plantarum içeriği, Diagen Real-time PCR Kiti kullanılarak bir Realtime PCR cihazında (RotorGene-Q, Almanya) gerçekleştirilmiştir. İstatistiksel analiz IBM Sosyal Bilimlerde İstatistik Paket Programı (SPSS) sürüm 22.0 kullanılarak yapılmıştır.*

Bulgular: *Geleneksel yöntemle üretilen turşular, endüstriyel ürünlere göre daha yüksek pH değerlerine sahiptir ($p<0,05$). Geleneksel ve endüstriyel turşular, endüstriyel lahana turşuları dışında benzer tuz içeriğine sahipti (3,16 g/100 g, $p=0,002$). Geleneksel salatalık turşularının Lactobacillus acidophilus ve Levilactobacillus brevis içerikleri (sırasıyla 4,25±0,88 ve 5,55±1,37 log10 kob/g) endüstriyel lahana turşularına göre (sırasıyla 3,33±0,55 ve 1,53±2,11 log10 kob/g) önemli ölçüde yüksek bulunmuştur ($p < 0,05$).*

Sonuç: *Geleneksel olarak üretilen turşularda Lactobacillus spp içeriğinin endüstriyel olanlara göre daha yüksek olduğu tespit edilmiştir. Bu çalışma Türkiye'de sıklıkla tüketilen fermente ürünler arasında yer alan turşularda bulunan bakteri türlerinin, baskın bakteri oranlarının araştırıldığı ilerideki çalışmalara ön veri sağlayacaktır.*

Anahtar kelimeler: *endüstriyel turşu; geleneksel turşu; salatalık; lahana*

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Introduction

Pickling is one of the oldest historical methods of preserving various foods, including fruits, vegetables, meat, and fish. Pickling imparts unique and desirable changes in texture, color and flavor that take place over time in fermented pickles. In pickling food products, microorganisms (primarily Micrococcaceae, lactic acid bacteria, yeasts, Bacilli, and filamentous fungi) significantly impact the end product's quality and safety[1]. It has been revealed that especially *Lactobacillus* species are effective in the pickling process, which is widely applied to various fruits and vegetables today, and that these bacteria convert hexoses such as glucose and lactose to lactic acid and subsequently to acetic acid and also produce different metabolites including bacteriocins and exopolysaccharides, the positive effects of pickles on health are also investigated[1–3].

Pickle consumption is widespread in Türkiye, both as a method of preserving vegetables and traditionally in food consumption. Fermented pickles have often been homemade products manufactured by spontaneous fermentation in the traditional way, but they are still changing to solve difficulties with quality, safety, and mass production. Almost all investigations revealed that the dominant genus was Lactobacillus or Leuconostoc, regardless of the pickling duration, even though the microbiota in each variety of pickle is not the same[4].

In the studies carried out on most preferred pickles, cucumber and cabbage, the lactic acid bacteria found in the highest count as a result of the fermentation process[5–6] *Leuconostoc mesenteroides, Lactobacillus brevis, Enterococcus faecalis, Pediococcus pentosaceus, Lactobacillus pentosus, and Lactobacillus plantarum* are Lactic acid bacteria (LAB) that predominate in the medium during pickle fermentation. *L. plantarum* is the bacterium that completes fruit and vegetable fermentation because it has a higher acid tolerance than other LABs. The starter cultures of *L. plantarum and L. mesenteroides*[7] impact the quality of sauerkraut in low-salt conditions.

The fermentation stage is essential to pickle-making, with its health effects and unique characteristic flavor properties. However, there may be differences in the other steps applied in the pickling process. When traditionally produced, pickles are fermented by adding salt at 2–5% concentrations and sometimes acids such as vinegar or lemon juice; when commercially produced various preservatives such as potassium sorbate (E202) and sodium benzoate (E211) or acidity regulators such as acetic acid (E260) and citric acid (E330) can be added or pasteurization can be applied after fermentation to extend the storage period[1]. It has been shown that these additional processes, mainly used in some commercially produced pickles, affect the lactic acid bacteria content and that lactic acid bacteria are more dominant in traditionally produced pickles[8]. Certain species of lactic acid bacteria, such as *Lactiplantibacillus plantarum* and *Levilactobacillus brevis*, are mainly reported to be dominant in traditionally produced pickles, according to their tolerance levels of salt and acid concentrations[8–9].

Fermentation-produced lac improves the product's storage capacity by lowering the brine's pH, inhibiting the growth of acid-sensitive microorganisms. High-salinity brine is also used to enhance storability in the preparation of salt stock. Few halotolerant microorganisms can survive in brines with salinities up to 20%; therefore, salt stock preparation preserves vegetables rather than aiming for fermentation1. Pickling procedures remain crucial and are of great interest to scholars worldwide.

This study aimed to clarify the changes in microbial composition and concentrations of *Lactiplantibacillus plantarum*, *Levilactobacillus brevis* and *Lactobacillus acidophilus* by focusing on the processes method and salt stock preparation that have previously been overlooked. The results obtained from this study will help explain the effects of salinity and other pickling preservatives or natural additives like vinegar or lemon juice on the microbiota by comparing the results from the different processing conditions. This may provide valuable knowledge for improving pickle production.

Materials and Methods

Sample Collection

This study randomly obtained samples from significant retailers that produce industrially and traditionally produce pickles sold in Ankara, the capital of Türkiye. Within the scope of the study, 58 pickle samples (22 traditional cucumber pickles, 16 traditional cabbage pickles, 10 industrial cucumber pickles, and 10 industrial cabbage pickles) were collected by the researchers themselves (Fig. 1). While canned samples were presented in original containers without cooling, fresh samples were taken in their purchase containers

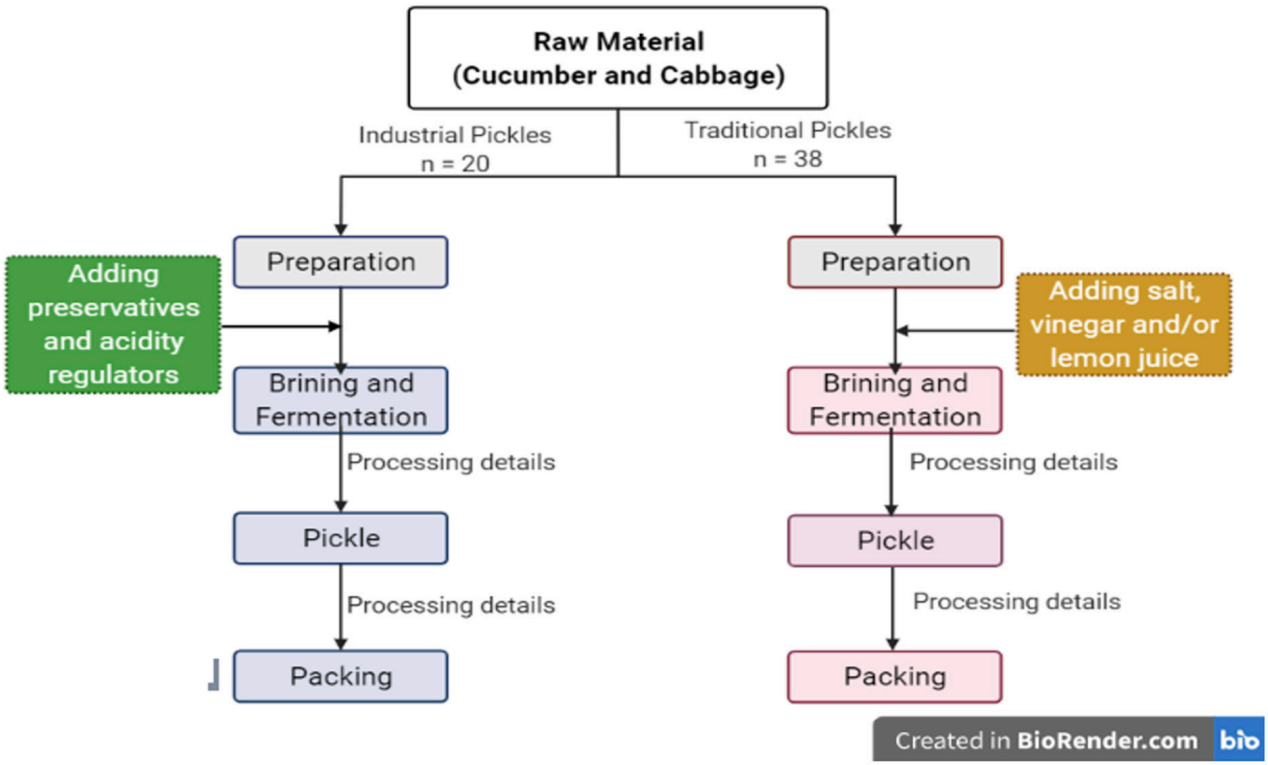

Figure 1. *The distinctions between industrial and traditionally produced pickles in the study.*

and transported to a laboratory in an insulated ice box (4±2°C) within two hours of collection. Upon arrival, all samples underwent quick biochemical and microbiological analysis. The categorization of traditional and industrially produced pickles was made as in Fig. 1. The study did not include pickles that have been pasteurized in industrial pickles. In the study, pickles evaluated within the scope of industrial pickles that contain preservatives and acidity regulators, while pickles produced by the traditional method, which do not contain preservatives and contain only lemon juice and/or vinegar in addition to salt, were evaluated.

DNA Extraction in Samples

The QuickGene (DNA extraction kit from tissue) extraction equipment was utilized for the extraction technique. Firstly, 250 µl of MDT (Tissue Lysis) solution and 50 mg of pickle samples were added to the homogenization tube. To homogenize, 15 mg of 0.1 mmø glass beads or 10 1.0 mmø zirconia beads were added to the tube. 2×120 seconds of application was made at 5000 rpm in the homogenizer. Twenty-five µl EDT (Proteinase K) solution was added after the sample had been homogenized, and it was incubated at 56°C for 60 minutes. Then, it was centrifuged at 5000 g for 5 minutes at room temperature. After centrifugation, 200 µl of supernatant was transferred to a 1.5 mL microtube. The microtube was filled with 180 µl of LDT (Cell Lysis) solution and vortexed for 15 seconds before being incubated at 70°C for 10 minutes. The following step involved adding 240 µl of 99% cold ethanol and vortexing it for 15 seconds. The QuickGene (Kurabo)[10] filtered cassette was filled with the complete contents of the microtube, and the instrument protocol was followed for performing washes and elutions. Three washes were performed using 750 µl of WDT (wash buffer) solution. As a result of the extraction process, genomic DNA diluted with 50 µl CDT (elution buffer) was obtained.

Determination of Lactiplantibacillus plantarum, Levilactobacillus brevis and Lactobacillus acidophilus counts by real-time PCR

Diagen Real-time PCR Kit was used for the analysis of *Lactobacillus acidophilus, Lactiplantibacillus plantarum* and *Levilactobacillus brevis* (catalog numbers were 3010–100, 3019–100, and 3017–100, respectively). The manufacturer's procedure carried out test

steps. The analyses were completed by performing the polymerase activation, denaturing and bonding/extension stages, respectively, and the changes in the time and temperatures to be applied depending on the Lactobacillus species to be analyzed. Studies were performed in a Real-time PCR device (RotorGene-Q, Germany) using 0.2 microcentrifuge tubes. As a result of the real-time PCR process, the device determined how many copies were in the samples by correlating the samples used as the standard according to the obtained ct values. The PCR reactions were conducted using the following program: 5 min of polymerase activation at 95°C, 10 s for denaturation at 95°C, 40 cycles of 30 s at 95°C, 30 s for elongation at 50°C and 60°C. PCR reactions were performed in 20 µL mixture containing five µL of *L. acidophilus* specific oligonucleotide mix, *L. plantarum* specific oligonucleotide mix, *L. brevis* specific oligonucleotide mix, ten µL of qPCR master mix (2×), five µL of Sample/Positive Control/Negative Control.

Chemical Composition

The pH was measured using a WTW Inolab pH 720 Desktop pH meter. The salt contents of traditional pickle samples were obtained by questioning the producers. Label information was used to record the salt content of industrial pickle samples.

Statistical Analysis

The microbial content of the pickles was expressed as cfu/g, and subsequently, $\log_{10}$ transformed before analysis. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) program version 22.0 (IBM Inc., Chicago, IL, USA). Data were expressed as the means ± standard deviation. The parameters, including Lactobacillus counts, pH values, and salt contents, were not normally distributed, so the Kruskal-Wallis tests were conducted to compare these parameters. The significance of pairwise differences was examined using the Mann-Whitney U test with the Bonferroni correction to account for multiple comparisons. The level of type-I error used to determine statistical significance was 5% overall[11].

Results

The microbiological and physicochemical properties of the pickles are shown in Table 1. The pH values of the pickles produced by the traditional method had higher pH values than the industrially produced alternatives ($p < 0.05$). In addition, the mean pH value of conventional cucumber pickles was statistically significantly higher than that of traditional cabbage pickles (3.66 and 3.49, respectively; $p < 0.05$), and a similar result was also obtained in industrial pickles, but the result in industrial pickles was not statistically significant. When the salt content of pickles was examined, traditional and industrial pickles had similar salt content except for industrial cabbage pickles. Industrial cabbage pickles had the lowest salt concentration, with a salt content of 3.16 g/100 g ($p=0.002$).

In traditional and industrial cucumber and cabbage pickles, *Lactiplantibacillus plantarum* was the most abundant species analyzed. The preparation techniques of the pickles (traditional or industrial) and types of the pickles (cucumber and cabbage) affected the microbial load pH characteristic of the pickles. The highest *Lactobacillus acidophilus* and *Levilactobacillus brevis* counts were observed in traditional cucumber (4.25±0.8 and 5.55±1.37 $\log_{10}$ cfu/g, respectively) and traditional cabbage pickles (4.78±0.50 and 6.16±1.37 $\log_{10}$ cfu/g, respectively; $p < 0.05$). Although there is no statistically significant difference between industrial production and traditional production in the counts of *Lactiplantibacillus plantarum* in both cucumber and cabbage, the mean *Lactiplantibacillus plantarum* counts of pickles made with conventional production are higher ($p > 0.05$). *Lactobacillus acidophilus* and *Levilactobacillus brevis*

Table 1. *Microbial load and physicochemical properties of pickles canned traditional and industrial*

Preparation technique	Types of pickles	N	pH	Salt (g/100 g)	*Lactobacillus acidophilus* ($\log_{10}$ cfu/g)	*Levilactobacillus brevis* ($\log_{10}$ cfu/g)	*Lactiplantibacillus plantarum* ($\log_{10}$ cfu/g)
Traditional	Cucumber	22	3.66 ± 0.20a	3.77 ± 0.16a	4.25 ± 0.88a,b	5.55 ± 1.37a,b	7.91 ± 0.86[a,b]
	Cabbage	16	3.49 ± 0.15b	3.77 ± 0.15a	4.78 ± 0.50a	6.16 ± 1.37a	7.98 ± 0.61[a]
Industrial	Cucumber	10	3.34 ±0.28b,c	3.74 ± 0.09a	3.43 ± 0.43b,c	1.23 ± 2.56b,c	5.95 ± 0.65[b]
	Cabbage	10	3.17 ± 0.18c	3.16 ±0.34b	3.33 ± 0.55c	1.53 ± 2.11c	7.10 ± 1.31[a,b]
			p = 0.000	***p*** = 0.002	***p*** = 0.002	***p*** = 0.000	***p*** = 0.002

Values are the mean (±standard deviation) of pickle samples. a-c means sharing different superscripts in each column significantly differs at $p < 0.05$. cfu means colony-forming unit. N: number of samples

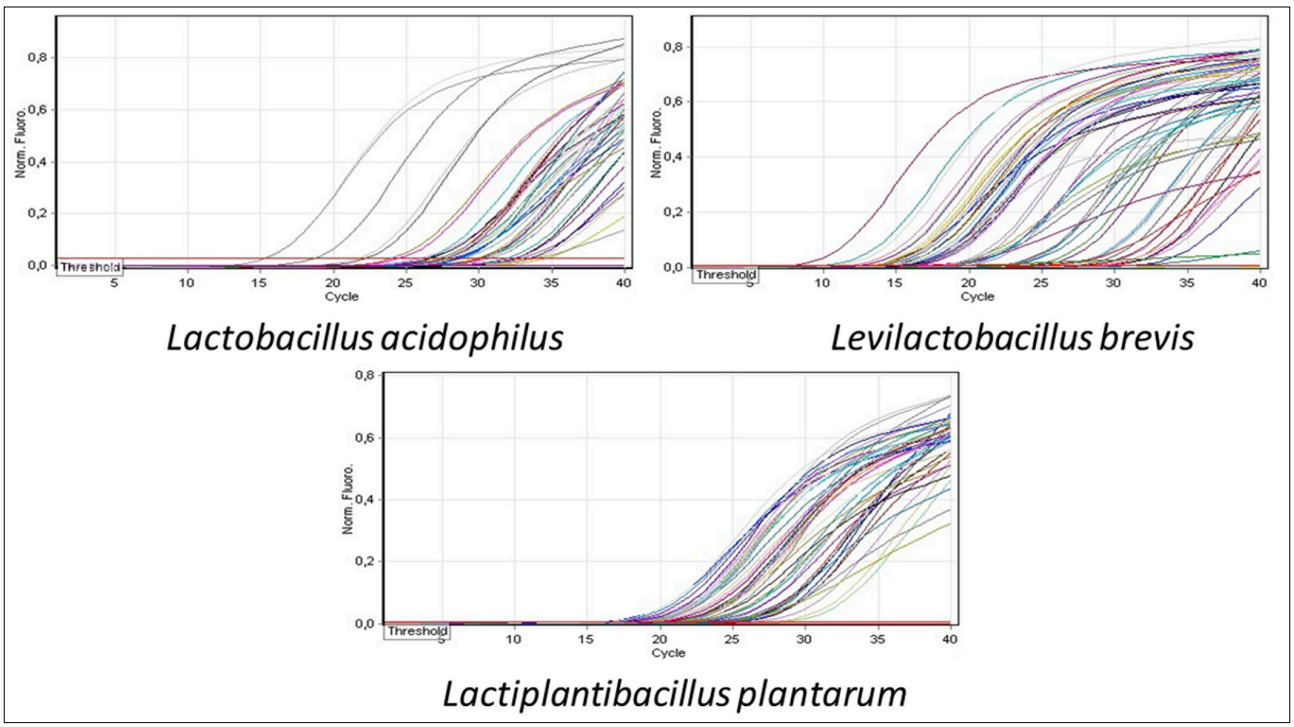

Figure 2. *Quantitation data for Cycling A. Green by quantitative PCR of pickle samples. Color lines represent the same samples indicated in Fig. 1, from the left to the right.*

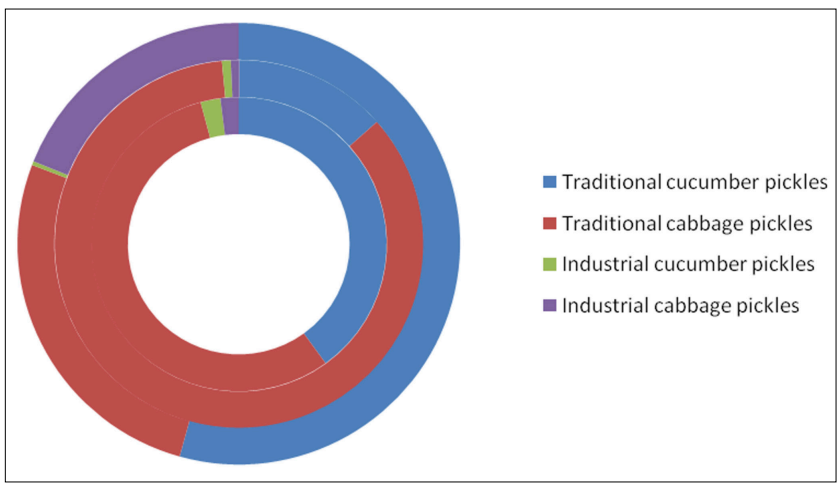

Figure 3. *Proportional distribution of Lactobacillus acidophilus, Levilactobacillus brevis and Lactiplantibacillus plantarum in pickles from inside to outside in rings, respectively.*

contents of traditional cucumber pickles (4.25±0.88 and 5.55±1.37 $\log_{10}$ cfu/g, respectively) were found to be significantly higher than those of industrial cabbage pickles (3.33±0.55 and 1.53±2.11 $\log_{10}$ cfu/g, respectively, $p < 0.05$). All three strains of bacteria analyzed in traditional cabbage were statistically significantly higher than in industrial cucumbers and cabbage ($p < 0.05$).

The results of real-time PCR demonstrated that the samples reached the amplification threshold beginning after cycle 13 for *Lactobacillus acidophilus*, cycle 8 for *Levilactobacillus brevis*, and cycle 16 for *Lactiplantibacillus plantarum* (Fig. 2). This finding could be due to the high quantity of specific DNA in pickle samples.

In Fig. 3, the varying ratios of *Lactobacillus acidophilus*, *Levilactobacillus brevis* and *Lactiplantibacillus plantarum* counts, respectively, from the inside to the outside in the rings, were presented according to the pickle and preparation techniques expressed in different colors.

As shown in Fig. 3, Lactiplantibacillus plantarum, expressed by the outermost ring, had the highest relative abundance in traditional cucumber pickles. In contrast, *Levilactobacillus brevis* (middle ring) and *Lactobacillus acidophilus* (innermost ring) had the highest relative abundance in traditional cabbage pickles. It is schematized that industrial cucumber pickles (purple color) contained all three bacterial species in minor relative abundance compared to the other pickle types.

Discussion

This study aimed to investigate and compare the bacterial communities of traditional and industrial production of cucumber and cabbage pickles. Pickles are an integral part of the diet, and various pickles are produced using different methods from different vegetables worldwide. Cucumber and cabbage pickles are most popular and frequently consumed in Türkiye and many countries around the world[12–13]. This study determined that traditional pickles had a higher microbial content than industrial pickles, and *Lactiplantibacillus plantarum* was the most abundant species analyzed.

Traditional fermented foods like cucumber and cabbage pickles are stored at room temperature and are abundant sources of LAB strains with unprecedented antimicrobial activity and probiotic characteristics[14]. Lactic acid bacteria are known to control serum cholesterol levels and also exhibit antiviral, antimutagenic, and antiplatelet aggregation attributes. The pickling process also helps effectively preserve and restore the natural bioactive compounds and antioxidant capacities of fruits and vegetables, which contain pigments such as anthocyanins, flavonoids, carotenoids, etc.[15]

With the changing pH, while the amount of some microorganisms decreases, other ones become more dominant[16]. Most *L. plantarum* and *L. brevis* strains showed more robust resistance to low pH17 than other LAB strains. Within the scope of the study, *L. brevis, L. blantarum and Lactobacillus acidophilus* species were evaluated in traditional and industrial pickles of cabbage and cucumber, and it was determined that all species were dominant, especially *L. plantarum* species that were resistant to low pH. In a study to identify the LABs of vegetable pickles, *Leu. mesenteroides, P. pentosaceus, L. brevis and L. plantarum* have been determined as the most frequently isolated species[18]. The study conducted by Boricha19 revealed that Lactobacillus strains isolated from pickles showed growth at pH three at the level of 6.2–7.7 log cfu/mL. In the study by Tokatlı et al. 17, the isolates obtained from pickle samples produced from different vegetables were examined regarding probiotic properties. As a result, it was stated that *P. ethanolidurans, L. plantarum,* and *L. brevis* remained viable at pH 2.5, and especially *L. brevis and L. plantarum* species could maintain their viability better at pH 2.5[17]. The average pH values of the pickles analyzed within the scope of this study were determined as 3.66 and 3.34 in cucumber pickles and 3.49 and 3.17 in cabbage. Similarly, *L. plantarum and L. previs* were dominant at low pH levels (Table 1).

It has been observed that the appropriate salt concentration for LAB growth is 2.5–10% NaCl[20]. The number of LAB cultures decreases with high salt concentration. LAB counts increase within 24 hours during fermentation when the salt concentration is below 5%[21], with salt's effect at the later fermentation stage, *Leu. mesenteroides, P. pentosaceus and L. plantarum* species become dominant[17]. In our study, salt content was determined to be 3.77 (g/100) in traditional cabbage and cucumber pickles, 3.16 (g/100) in industrial cabbage, and 3.74 (g/100) in cucumber pickles. The low salt concentration in pickles provides an opportunity for microbial diversity and load of strain.

The fermentation process of cabbage pickles is dominated by *L. mesenteroides*, which is salt tolerant. The acidic environment created by the growth of this microorganism not only inhibits the non-lactic competitive flora but also favors the development of other LABs. Thus, it is reported that with the decrease in the *Leuconostoc* population, other LABs, such as L. brevis and L. plantarum, become dominant[22]. Similarly, in our study, *L. brevis* and *L. plantarum* strains were the dominant species in all types of pickles. Ragul et al.[23] followed the development of LAB isolated from traditional brine pickles in the presence of 0.5% and 1% bile salt. According to this research, at 0.5% bile salt, none of the isolates' survival rates changed, and the isolates showed much greater tolerance to 1% bile salt than the reference strain. In a study conducted by Rao et al.[24] in China, *L. plantarum* strains were isolated from the traditionally produced pickle, and it was determined that the isolates survived in the presence of different bile salts.

It is stated that *L. plantarum* can be used as a probiotic starter for industrial pickle fermentation, and the pickled product may be utilized as a potential anti-Candida probiotic[24]. Considering the possible effects

of *L. plantarum*, which was determined as the dominant strain in our study, the beneficial effects of traditional pickles can be mentioned. Pickle manufacturers typically use non-iodized salt for fermenting pickles. It is hypothesized that iodine prevents fermentation by preventing the growth of LAB[25]. Traditional pickles produced in Türkiye mainly utilize non-iodized table salt to ferment cucumbers and cabbage; therefore, traditional pickles may have higher LAB content. In addition, the amount of salt in pickles has been reduced with the Sodium/Salt Reduction Guide, prepared by the Ministry of Health to minimize salt consumption[26].

Although fungus and bacteria contribute to the microbial variety in pickles, most studies on the microbial community of pickles have concentrated on bacteria, mainly lactic acid bacteria (LAB)[27]. The conditions for processing and storage differ in some ways between commercial and traditional pickle production. Traditional pickles are susceptible to various contaminants during manufacturing and storage, such as pathogens, pests, or cross-contamination, whereas industrial pickles are standardized with stringent control. Therefore, the traditional pickles made with household production methods also have richer microbial diversity[28]. Similarly, a richer microbial diversity was observed in our study, and *L. acidophilus*, *L. brevis*, and *L. plantarum* levels in traditional pickles were higher in both cucumber and cabbage pickles than in industrial pickles. The type of dominant species in naturally fermented vegetable pickles is slightly higher than in inoculation fermentation. However, the microbial diversity in naturally fermented vegetable pickles was more enriched than inoculated fermentation[29].

Food safety is increasing as a significant public health problem. Antibiotics are commonly used to reduce the harm caused by microbial contamination. As a result of excessive use of antibiotics, multidrug-resistant pathogens occurred. Therefore, finding favorable biological preservatives that are promising alternative antibiotics30 is essential. Fermentation by LAB is the best way of preserving and retaining natural ingredients while improving taste, aroma, and quality[31]. In addition to their probiotic functions, LAB can enhance food flavor and nutritional value by generating aromatic compounds 32. A study conducted by Çetin[5] revealed that adding *L. plantarum* as a starter culture into the pickles improved the taste and beneficial properties of the product. According to another study conducted by Al-Shaw[33], adding *L. acidophilus* as a starter culture into the pickles improved taste, flavor and odor. In this study, *L. plantarum* and *L. acidophilus* species in cucumber and cabbage pickles were higher in traditional pickles than in industrial pickles. Traditional homemade production is preferred instead of industrial output to obtain pickles' desired taste and flavor. The fact that conventional pickles are still produced in large quantities and stand out with their unique ingredients, production methods, and unique taste and flavor may be related to LAB contents.

A significant strength of the research is the analysis of a large sample of 58 different pickles. However, there are several significant limitations in this study. First, the process of making pickles could not be questioned in detail. Salt content, pH value, and fungal diversity in fermented pickles were necessary; no research has been done on these. This needs to be measured in future studies.

Conclusion

Pickle quality is affected by microbial diversity and the number of core microorganisms. Although a wide variety of microflora is involved in traditional and industrial vegetable pickles, traditional pickles have higher microbial content than industrial ones. This study result provides preliminary data for future studies investigating the microbiota of pickles. There are several health benefits thanks to the microorganisms contained in the pickled products. LABs found in pickled foods have been significantly associated with various probiotic properties, such as enhanced natural resistance to infectious disease in the gastrointestinal tract, prevention of urogenital infections, suppression of cancer, and improved digestion. It will be helpful in the food industry to develop pickles products by seriously following the process of traditional pickles, such as the raw material, production, storage and fermentation. This would help select specific microorganisms and create a standardized fermentation process to provide better microbial diversity and produce the characteristic flavor of industrial pickles. Further research is needed to understand the traditional community succession process of the core strains and how to develop the microbial diversity and flavor.

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Author contributions

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Comparison of KRAS Mutation, Microsatellite Instability and Histomorphologic Features in Metastatic Colorectal Carcinomas: Single Centre Experience

Metastatik Kolorektal Karsinomlarda KRAS Mutasyonu, Mikrosatellit İnstabilite ve Histomorfolojik Özelliklerin Karşılaştırılması: Tek Merkez Deneyimi

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ABSTRACT

Aim: *Microsatellite instability (MSI) and KRAS mutations change colorectal carcinoma (CRC) treatment protocols. Advanced examinations such as immunohistochemistry and polymerase chain reaction (PCR) are required to determine MSI and KRAS mutations. On the other hand, Crohn-like lymphoid reaction (CLR), tumor-infiltrating lymphocytes (TIL), tumor budding (TB), and desmoplastic response (DR) are histomorphologic features that can be determined only with routine hematoxylin-eosin (H&E) sections. Our study aimed to evaluate relationships between MSI, KRAS mutations, and histomorphologic features. It was thought that the relationships to be determined may be useful in predicting KRAS mutations and MSI by evaluating only H&E sections.*

Material and Method: *One hundred nine metastatic CRC cases were reviewed retrospectively. Polymerase chain reaction results were obtained from the molecular pathology report archive and performed on all cases for KRAS mutation detection upon clinical request during routine pathologic examinations. MLH1, MSH2, MSH6, and PMS2 immunohistochemistry, performed on 70 cases for MSI interpretation upon clinical request during routine pathological examinations, was re-evaluated for standardization. Routine H&E sections with tumors were examined for CLR, TIL, TB, and DR according to study-specific criteria.*

Results: *KRAS mutations were found in 35.77% (39/109), MSI in 24.28% (17/70), CLR in 32.11% (35/109), TIL in 44.95% (49/109), TB in 73.39% (80/109), DR in 84.40% (92/109) of the cases. CLR, TIL, DR, and KRAS mutations were higher in microsatellite stable (MSS) cases, and TB was higher in MSI cases. Crohn-like lymphoid reaction, TIL, DR, and MSI were higher in KRAS wild cases, and TB in KRAS mutant cases. Only the MSS-DR correlation was statistically significant.*

Conclusion: *The MSS-DR correlation was statistically significant in our study. However, desmoplasia was determined in 92.45% of MSS cases, and was also determined in 58.82% of MSI cases. Because DR is an expected feature in tumor stroma, its guidance in terms of MSI was limited. Also, no significant relationship was found between MSI and DR in Turkish or English literature. In our study, histomorphologic features were insufficient to predict MSI and KRAS mutations. It is vital to immediately refer patients with metastases evaluated in centers without immunohistochemistry and PCR facilities to an advanced center for MSI and KRAS mutation determination diagnosing CRC, especially for treatment selection.*

Key words: *colorectal cancer; KRAS protein; microsatellite instability*

ÖZET

Amaç: *Kolorektal karsinomlarda (KRK) mikrosatellit instabilite (MSİ) ve KRAS mutasyonu tedavi protokollerini değiştirir. Mikrosatellit instabilite ve KRAS mutasyonunu belirlemek için immünohistokimya ve PCR gibi ileri incelemeler gerekir. Diğer taraftan Crohn benzeri lenfoid reaksiyon (CBLR), tümörü infiltre eden lenfositler (TİEL), tümör tomurcuklanması (TT) ve desmoplastik yanıt (DY) yalnızca rutin hematoksilen-eozin (H&E) kesitlerle belirlenebilen histomorfolojik özelliklerdir. Çalışmamızda MSİ, KRAS mutasyonu ve histomorfolojik özellikler arasındaki ilişkilerin değerlendirilmesi amaçlanmıştır. Saptanacak ilişkilerin sadece H&E kesitler değerlendirilerek MSİ ve KRAS mutasyonunu öngörmede faydalı olabileceği düşünülmüştür.*

Materyal ve Metot: *Çalışmada 109 metastatik KRK olgusu retrospektif olarak incelenmiştir. Rutin patolojik inceleme yapılırken klinik istek üzerine KRAS mutasyonu tespiti için tüm olgulara uygulanmış olan PCR sonuçlarına moleküler patoloji rapor arşivinden ulaşılmıştır. Rutin patolojik inceleme yapılırken klinik istek üzerine MSİ yorumlaması için 70 olguya uygulanmış olan MLH1, MSH2, MSH6, PMS2 immünohistokimyaları standarizasyon amacıyla tekrar değerlendirilmiştir. Rutin tümörlü H&E kesitleri CBLR, TİEL, TT, DY açısından çalışma için oluşturulan kriterlere göre incelenmiştir.*

Bulgular: *Olguların %35,77'sinde (39/109) KRAS mutasyonu, %24,28'inde (17/70) MSİ, %32,11'inde (35/109) CBLR, %44,95'inde (49/109) TİEL, %73,39'unda (80/109) TT, %84,40'ında (92/109) DY saptanmıştır. Mikrosatellit stabil (MSS) olgularda CBLR, TİEL, DY, KRAS mutasyonu, MSİ olgularda ise TT daha sıktır. KRAS wild olgularda CBLR, TİEL, DY, MSİ, KRAS mutant olgularında TT daha sıktır. Sadece MSS-DY korelasyonu istatistiksel olarak anlamlı bulunmuştur.*

Sonuç: *Çalışmamıza göre MSS-DY korelasyonu istatistiksel olarak anlamlıdır. Ancak MSS olguların %92,45'inde saptanan desmoplazi, MSİ olguların da %58,82'sinde gözlenmiştir. Desmoplastik yanıtın tümör stromasında beklenen bir bulgu olması sebebiyle MSİ açısından yönlendiriciliğinin sınırlıdır. Ayrıca Türkçe ve İngilizce literatürler tarandığında MSİ ile DY arasında istatistiksel olarak anlamlı ilişki bulunamamıştır. Çalışmamızda histomorfolojik özellikler MSİ ve KRAS mutasyonunu öngörmede yetersiz kalmıştır. İmmünohistokimya ve PCR olanakları bulunmayan merkezlerde değerlendirilen hastaların KRK tanısı konulduktan sonra MSİ ve KRAS mutasyonu tayini için ivedilikle ileri bir merkeze sevk edilmesi tedavi seçimi açısından hayati önem taşımaktadır.*

Anahtar kelimeler: *kolorektal kanser; KRAS proteini; mikrosatellit instabilite*

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Introduction

Colorectal carcinomas (CRC) are third after female breast and lung cancers in terms of incidence and second after lung cancers in cancer-related deaths[1]. Surgical resection is the main treatment modality in CRC[2,3]. Chemotherapy, radiotherapy, targeted therapy, or immunotherapy are other treatment modalities that can be preferred when surgery cannot be performed or is insufficient. At this stage, the presence of microsatellite instability (MSI) or KRAS mutations in the patient will be decisive in terms of treatment selection because 5-fluorouracil (one of the classic chemotherapeutics) and anti-EGFR/VEGFR drugs are not preferred in the presence of MSI[3–5] and KRAS mutations,[3,6,7] respectively, due to low treatment response or profit/loss rates. In addition, anti-PD-1/PD-L1 drugs are a treatment option for patients with metastases in the presence of MSI[3,6,8].

Microsatellite instability is found in 15% of patients with CRC, which is a good prognostic factor. Early-onset disease, proximal colon localization, high histologic grade, mucinous or medullary differentiation, signet ring cell changes, Crohn-like lymphoid reaction (CLR), and tumor-infiltrating lymphocytes (TIL) are expected clinical and microscopic features in the presence of MSI[4–6,9,10]. Microsatellite instability is usually interpreted by evaluating MLH1, MSH2, MSH6, and PMS2 expressions in tumoral tissue using immunohistochemistry because it is more accessible. Loss of expression in any of them indicates MSI-high. However, it should be kept in mind that MSI can be detected using polymerase chain reaction (PCR) in 5% of patients who are MSI-low in immunohistochemistry[4,5]. KRAS mutations are evaluated using PCR and found in 30–45% of CRC cases[6,9,10]. KRAS mutations have been associated with poor prognosis in most studies[6].

Crohn-like lymphoid reaction, TIL, tumor budding (TB), and desmoplastic response (DR) are some of the histomorphologic features evaluated in CRC cases. Crohn-like lymphoid reaction and TIL have been associated with good prognosis, [11–15] whereas TB has been associated with poor prognosis[2]. The prognostic role of DR is unclear[16–20]. Among these features, only the TB has been clearly defined and standard criteria have been established for its evaluation[2].

We aimed to evaluate the relationships between MSI and KRAS mutations, which require immunohistochemistry or PCR for evaluation and histomorphologic features (CLR, TIL, TB, DR), which can be determined using just hematoxylin-eosin (H&E) sections. Knowledge of these relationships may be useful for predicting MSI or KRAS mutations in centers that do not have immunohistochemistry or PCR facilities, thus providing faster and cheaper access to treatment without advanced tests.

Materials and Methods

In our study, we reviewed 109 patients with metastases who were diagnosed as having carcinoma in colorectal resections at the pathology department of Karadeniz Technical University Medical Faculty between 2016 and 2019 retrospectively. Results of PCR, which had been performed on all cases for KRAS mutation detection upon clinical request during routine pathologic examinations, were obtained from the molecular pathology report archive. KRAS mutation analysis through PCR was performed on formalin-fixed, paraffin-embedded tumor tissue (Device: Qiagen Rotor-Gene Q real-time PCR device (Version 1.7.87), Kit: Easy® KRAS, Company: Diatech Pharmacogenetics, Detectable mutations: Codon 12–13–59–61–117–146). MLH1, MSH2, MSH6, and PMS2 immunohistochemistry, performed on 70 cases for MSI interpretation upon clinical request during routine pathological examinations, was re-evaluated by one pathologist for standardization. A Nikon Eclipse E200 microscope was used for evaluation. Immunohistochemistry had been performed on formalin-fixed, paraffin-embedded tumor tissue (Device: Ventana BenchMark ULTRA automated staining system, Clone (Respectively): M1, G219–1129, SP93, A16–4, Company: Ventana Medical Systems). Normal colonic mucosa contiguous to the tumors were available as an internal control in all cases. Nuclear staining was considered significant (Fig. 1). Despite positive internal control, complete negativity in tumor cells was considered a loss of expression. Loss of expression of at least one marker was considered MSI.

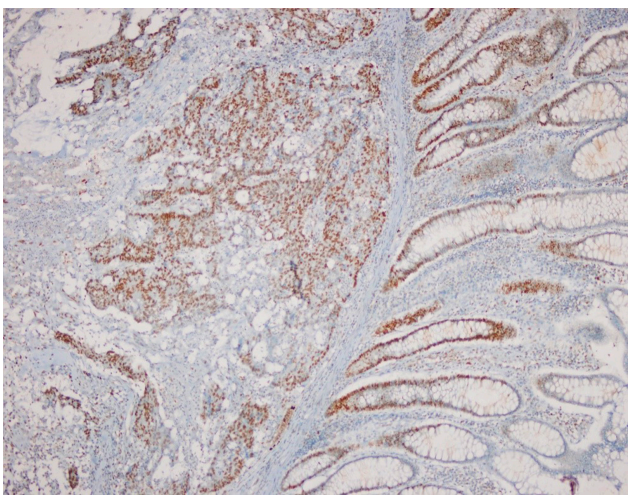

Figure 1. *Nuclear expression in tumor tissue (left) and normal colon mucosa as an internal control (right) (MLH1; ×100)*

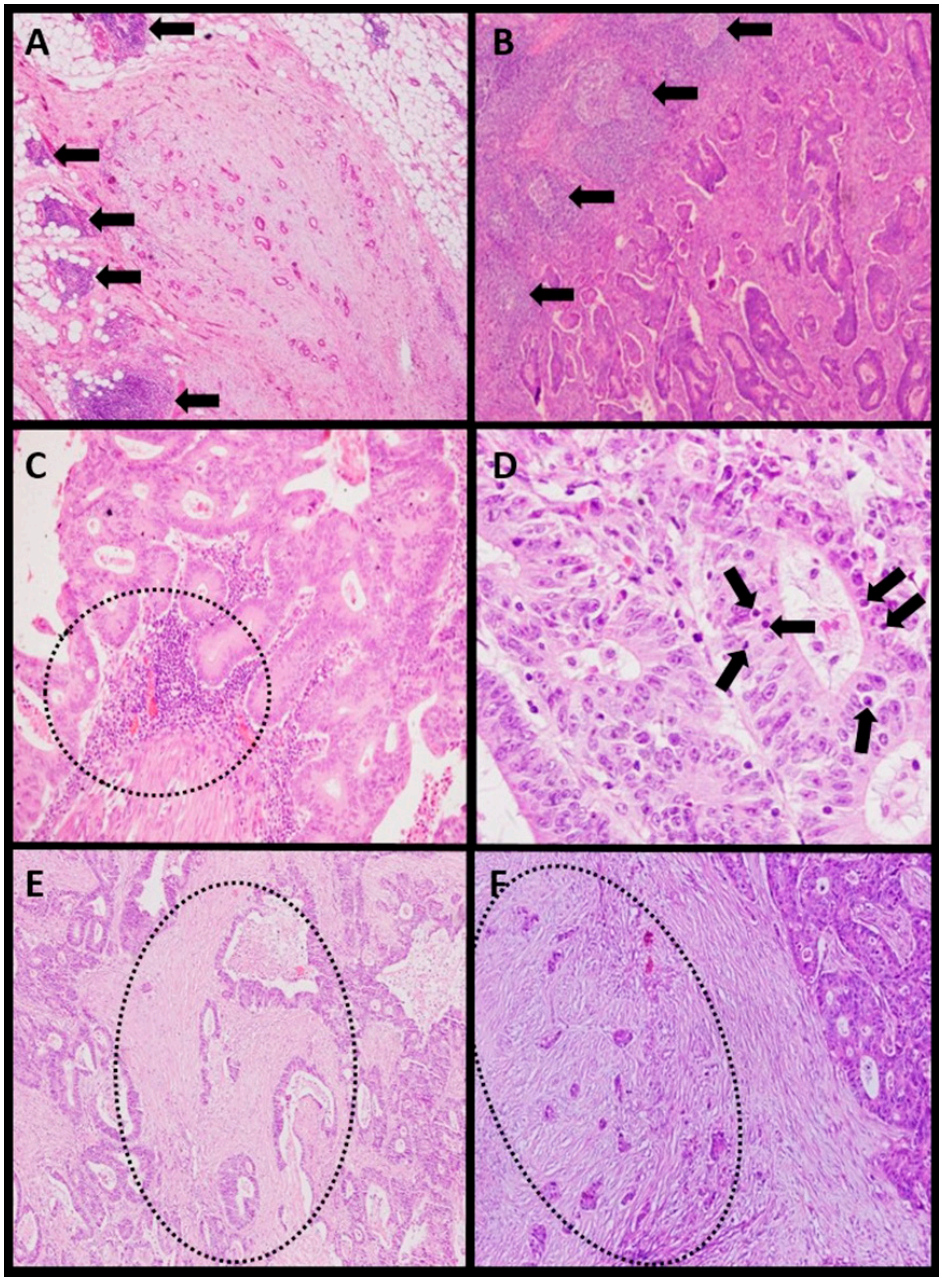

Figure 2. a–e. *Crohn-like lymphoid reaction (arrows, LA without germinal center) (H&E; ×40)*(a), *CLR (arrows, LA with the germinal center) (H&E; ×100)*(b), *Stromal lymphocytosis (ring, Cluster of lymphocytes spacing the glands) (H&E; ×200)* (c), *Intraepithelial lymphocytosis (arrows, Lymphocytes infiltrating gland epithelium) (H&E; ×400)*(d), *Desmoplastic response (ring, Dense fibrous connective tissue increase in the stroma) (H&E; X100)*(e), *TT (ring, Tumor buds progressing at the invasion margin) (H&E; ×100)*(e).

All H&E sections with tumors of all cases were evaluated for CLR, TIL, TB, and DR by one pathologist. There were standardized criteria for only TB in the English literature[2]. However, we established criteria for our study to evaluate features including TB. Lymphoid aggregates (LA) without a germinal center but with a diameter over 1 mm (Fig. 2a) or LA with a germinal center at the invasion margin of the tumor (Fig. 2b) were included in the calculation for CLR. The presence of CLR was accepted in cases with a mean LA count of ≥1 per section. When evaluating TIL, the density of stromal lymphocytes was given as the percentage of the one high-power field in the hotspot area, and a density of ≥10% was accepted as stromal lymphocytosis (Fig. 2c). The presence of only prominent lymphocytes infiltrating neoplastic glands was considered intraepithelial lymphocytosis (Fig. 2d). The presence of only stromal lymphocytosis, only intraepithelial lymphocytosis or both were accepted as TIL. Only prominent and diffuse fibrous connective tissue increase in the tumor stroma was accepted as DR (Fig. 2e). In our study, single tumor cells or less than five tumor cell groups at the invasion margin of the tumor were accepted as TBs as in the standard evaluation criteria. However, instead of being classified as low/medium/high according to the hotspot 0.785 mm^2 area, TB was accepted in cases with ≥1 bud in one high-power field of the hotspot area (Fig. 2f).

Table 1. *Clinical and microscopic features*

Clinical and microscopic features			Number (%)(N: 109)
Age	Maximum	85	
	Minimum	27	
	Average	60	
	≤60		47 (43.12%)
	>60		62 (56.88%)
Gender	Female		39 (35.78%)
	Male		70 (64.22%)
Tumor localization	Right colon		18 (16.51%)
	Left colon		57 (52.29%)
	Rectum		34 (31.20%)
Diagnosis	Adenocarcinoma		96 (88.07%)
	Mucinous carcinoma		13 (11.93%)
Histological grade	1		76 (69.72%)
	2		25 (22.93%)
	3		8 (7.35%)
Tumor diameter	Maximum	15 cm	
	Minimum	0.1 cm	
	Average	4 cm	
	≤4 cm		65 (59.63%)
	>4 cm		44 (40.37%)
Depth of invasion	Muscularis propria		10 (9.17%)
	Subserosa/adventisia		77 (70.64%)
	Serosa		22 (20.19%)
Lymphovascular invasion			43 (39.44%)
Perineural invasion			21 (19.26%)
Metastasis	Lymph node		67 (61.46%)
	Liver		100 (91.74%)
	Lung		15 (13.76%)
	Adrenal gland		6 (5.50%)
	Bone		2 (1.83%)
	Brain		1 (0.91%)
	Peritoneal carcinomatosis		11 (10.09%)

Table 2. *Histomorphologic features, MSI and KRAS mutation*

Parameters			Number (%)
Histomorphologic features (N: 109)	CLR		35 (32.11%)
	TIL		49 (44.95%)
	DR		92 (84.40%)
	TB		80 (73.39%)
MSI (N: 70)	MSI		17 (24.28%)
	Loss of expression	MLH1	10
		MSH2	1
		MSH6	8
		PMS2	14
	Combinations of expression losses	MLH1+PMS2	5
		MLH1+MSH6+PMS2	4
		Only PMS2	3
		Only MSH6	3
		MSH6+PMS2	1
		MLH1+MSH2+PMS2	1
KRAS mutation (N: 109)	KRAS mutation		39
	Codon-based mutations	Codon 12	30
		Codon 13	2
		Codon 61	2
		Codon 117	2
		Codon 146	3

CLR: Crohn-like lymphoid reaction, TIL: tumor-infiltrating lymphocytes, TB: tumor budding, DR: desmoplastic response, MSI: microsatellite instability, MSS: microsatellite stability

The hospital records of patients were reviewed. In all cases, there was at least one diagnosis of metastasis in magnetic resonance imaging (MRI), computed tomography (CT) or positron emission tomography (PET)/CT reports, and some were histopathologically correlated. None of the patients had a history of different malignancies, inflammatory bowel disease, colorectal cancer syndromes, or neoadjuvant chemotherapy.

Ethical approval for the study was obtained from the Ethics Committee of Karadeniz Technical University Medical Faculty (Number: 24237859-568, Date: 19.07.2019).

The IBM Statistical Package for Social Sciences (SPSS) program version 23.0 for Windows, was used for all statistical calculations. The Chi-square test was used to compare categorical data. P <0.05 was considered statistically significant.

Results

Clinical and microscopic features are given in Table 1, and histomorphologic features, MSI, and KRAS mutations are given in Table 2. The relationship between MSI, KRAS mutations, and histomorphologic features is given in Table 3 and Table 4.

Discussion

Microsatellite Instability and Histomorphologic Features

Crohn-like lymphoid reaction and TIL are histomorphologic features that are accepted to be related to MSI[4–6,9,10]. Different evaluation criteria for CLR have been established over time. In the semiquantitative Graham-Appelman criteria, cases with no LA are graded as '0' , cases with few LA with no germinal center are graded as '1' , and cases with many LA with germinal centers are graded as '2'[11]. In the Ueno criteria based on LA size, cases with LA with <1 mm maximum diameter are classified as 'inactive LA' , and cases with >1 mm diameter LA are classified as 'active LA'[12]. In the Vayrynen-Makinen criteria based on LA density, cases with <0.38 LA per mm^2 are graded as 'low CLR' , and those with >0.38 LA per mm^2 are graded as 'high CLR'[13]. Various semiquantitative criteria have

Table 3. *Relationship between MSI, KRAS mutation, and Histomorphologic features*

	MSI (N: 17)	MSS (N: 53)	KRAS mutant (N: 39)	KRAS wild (N: 70)
CLR (+)	5(23.81%) (29.41%)	16(76.19%) (30%)	11(31.42%) (28.20%)	24(68.58%) (34.28%)
CLR (-)	12(24.48%) (70.59%)	37(75.52%) (70%)	28(37.83%) (71.8%)	46(62.17%) (65.72%)
P value	0.951		0.515	
TIL (+)	7(20.58%) (41.17%)	27(79.42%) (50.94%)	14(28.57%) (35.89%)	35(71.43%) (50%)
TIL (-)	10(27.77%) (58.83%)	26(72.23%) (49.06%)	25(41.66%) (64.11%)	35(58.33%) (50%)
P value	0.483		0.156	
DR (+)	10(16.94%) (58.82%)	49(83.06%) (92.45%)	32(34.78%) (82.05%)	60(65.22%) (85.71%)
DR (-)	7(63.63%) (41.18%)	4(36.37%) (7.55%)	7(41.17%) (17.95%)	10(59.83%) (14.29%)
P value	0.030		0.613	
TB (+)	16(29.62%) (94.11%)	38(70.38%) (71.69%)	32(40%) (82.05%)	48(60%) (68.57%)
TB (-)	1(6.25%) (5.89%)	15(93.75%) (28.31%)	7(24.13%) (17.95%)	22(75.87%) (31.43%)
P value	0.940		0.778	

CLR: Crohn-like lymphoid reaction, TIL: tumor-infiltrating lymphocytes, TB: tumor budding, DR: desmoplastic response, MSI: microsatellite instability, MSS: microsatellite stability

Table 4. *Association between MSI and KRAS mutation*

	MSI	MSS	Total
KRAS mutant	4(16%) (23.52%)	21(84%) (39.62%)	25(100%)
KRAS wild	13(28.88%) (76.48%)	32(71.12%) (60.38%)	45(100%)
Total	17 (100%)	53 (100%)	P: 0.228

MSI: microsatellite instability, MSS: microsatellite stability

been used for TIL interpretation in different studies. The classifications were prepared according to the density and localization of lymphocytes (intraepithelial and stromal in the tumor, at the tumor invasion margin)[14,15]. However, standard criteria have not been established for CLR and TIL.

In the study of Ueno et al.,[12] active LA was present in 35.3% of the cases, and loss of expression of at least one of MLH1 and MSH2 was observed in immunohistochemistry. Thirteen percent of the cases that had preserved expression of both had active LA. Rozek et al.[21] evaluated MSI using PCR. While evaluating CLR, they accepted the presence of 3 LA per section as the cut-off value. Crohn-like lymphoid reaction was determined in 58.7% of instable cases and 45.3% of stable cases. Contrary to these studies, we found CLR slightly more frequently in MSS cases.

Rozek et al.[21] observed TIL in 56.3% of MSI cases and 22.6% of MSS cases. The correlation of MSI-TIL was statistically significant. In our study, TIL was present in 50.94% of MSS cases, and 41.17% of MSI cases. Contrary to expectations, TIL was found more frequently in MSS cases. Hu et al. evaluated TIL using a computerized system by immunohistochemistry. Tumor-infiltrating lymphocytes was grouped according to ITGAE and CD8 immunoreactivity as 'low' and 'high'. Tumor-infiltrating lymphocytes were found 'high' in 65.9% of MSS cases and 34.1% of MSI cases[22]. However, studies associating TIL with MSS, including our study, were not statistically significant.

Lymphocytic reactions (CLR and TIL), which have been proven to be correlated with MSI, were found more frequently in MSS cases in our study. All patients in our population had metastases. This may lead to the hypothesis of increased metastasis capacity in patients with MSI when the expected lymphocytic response does not accompany it. However, this hypothesis should be supported by new studies.

Fujiyoshi et al.[23] evaluated MSI using PCR. They found moderate/high TB using standard criteria in 42.79% of stable cases and 33.76% of instable cases. Graham et al.[24] evaluated MSI using PCR, and they classified TB as absent/low/high indicating that they had >10 TBs in a 0.95 mm^2 hotspot area. In these studies, TB was statistically significantly more frequent in MSS cases. By contrast, the frequency of TB was higher in MSI cases in our study.

We only found the DR-MSS correlation as statistically significant. However, desmoplasia, which was determined in 92.45% of MSS cases, was observed in 58.82% of MSI cases. Because DR is an expected finding in tumor stroma, its guidance in terms of MSI is limited. Also, no significant relationship was found between MSI and DR in the Turkish or English literature.

KRAS Mutation and Histomorphologic Features

In 212 patients with MSI, Kim et al.[11] found CLR more frequent in KRAS mutant cases using the Vayrynen-Makinen and Graham-Appleman criteria and in KRAS wild cases using the Ueno criteria. Lee et al.[25] evaluated cases for CLR according to possessing ≥1 mm peritumoral LA. They observed prominent CLR more frequently in KRAS wild cases, as in our study. Due to the different results and high p-values, CLR was not considered a predictive feature for KRAS mutation.

Lee et al.[25] classified TIL in terms of the density of peritumoral lymphocytes according to the 50%

cut-off value. High TIL was observed more frequently in KRAS wild cases, as in our study. Although the data were not statistically significant, they supported the KRAS-TIL inverse correlation.

Shin et al.[20] evaluated the maturation of tumor stroma and desmoplasia according to the structure of collagen fibers and cytomorphology of fibroblasts, and Akimoto et al.[26] examined the structure of collagen fibers and the presence of myxoid changes for desmoplasia interpretation; no significant relationship was found between DR-KRAS mutation in any study, including ours.

The results of Fujiyoshi et al.[23] and Lee et al.[25] demonstrated TB more frequently in KRAS wild cases. In contrast, Bonetti et al.[27] and Graham et al.[24] observed TB in KRAS mutant cases with higher rates, as in our study. Due to the different results and high p-values, TB was not considered a predictive feature for KRAS mutation.

Microsatellite instability and KRAS Mutation

Niu et al.[28] used immunohistochemistry for MSI interpretation. KRAS mutations were detected in 60% of MSI cases and 47.6% of MSS cases. The results statistically significantly supported the MSI-KRAS mutation correlation. However, in our study, MSI was observed in KRAS mutant cases at a rate of 16% and in KRAS wild cases at 28.88%. In addition, KRAS mutations were not determined in most MSI cases (76.48%). Although not statistically significant, there was an inverse correlation between MSI and KRAS mutations. In the study of 205 cases by Huang et al.[29], 20.3% of the cases in which KRAS or BRAF mutations were determined using PCR were MSI, and 79.7% were MSS. Microsatellite instability was observed statistically significantly less in mutant cases. KRAS mutation was determined in 14.2% of MSI cases and 38.3% of MSS cases in the N0147 study and 16.8% of MSI cases and 34.4% of MSS cases in the PETACC8 study. KRAS mutations were statistically significantly lower in MSI cases in these two studies with large populations, similar to our results[30]. In conclusion, studies in the English literature associated KRAS mutation with MSS or conversely with MSI with statistically significant results, as in our study.

In patients with metastases, histomorphologic features were insufficient to predict MSI and KRAS mutations. Therefore, it is vital to immediately refer patients who are evaluated in centers without immunohistochemistry and PCR facilities to an advanced center for MSI and KRAS mutation determination, with a paraffin block representing tumor tissue including normal mucosa preferably, after the diagnosis of CRC.

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Authors' Contribution

The authors share the responsibility for the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no potential conflicts of interest regarding this article.

Disclaimer

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Relationship Between Nonobstructive Coronary Arteries and Metabolic Parameters

Nonobstrüktif Koroner Arterlerle Metabolik Parametreler Arasındaki İlişki

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ABSTRACT

Aim: *The atherogenic index of plasma (AIP) and triglyceride-glucose (TyG) index are strongly associated with atherogenesis of the coronary artery. However, the relationship between these metabolic parameters and ischaemia with nonobstructive coronary artery diseases (INOCA) is unknown. Therefore, we aimed to investigate the relationship between AIP and TyG index and INOCA patients.*

Material and Method: *A total of 529 patients were enrolled in this study and assigned to the INOCA group (n=264) and control group (n=265). The clinical data and calculated AIP, TyG index, were collected. Multivariate logistic regression was set up to assess the AIP and TyG indices for INOCA.*

Results: *The optimal cut-off value of TyG for predicting INOCA was 8.87 with a sensitivity of 52.24% and a specificity of 70% ([AUC]: 0.634 [95% CI: 0.592–0.675, p=0.023]). The optimal cut-off value of AIP for predicting INOCA was 0.54 with a sensitivity of 45.15% and a specificity of 70.57% ([AUC]: 0.590 [95% CI: 0.547–0.632, p=0.025]). When the ROC curves of TyG and AIP are compared, it is seen that TyG is a better predictor ([Difference between areas]: 0.045 [95% CI: 0.0180–0.0711, p=0.001]).*

Conclusion: *AIP and TyG index were significantly higher in the INOCA group when compared to the control group. In addition, the main finding was that when the metabolic parameters TyG index and AIP were compared with each other, the TyG index provided a stronger prediction and was found to be an independent risk factor for INOCA.*

Key words: *atherogenic index of plasma; triglyceride-glucose index; ischaemia with no obstructive coronary arteries (INOCA); coronary artery disease*

ÖZET

Amaç: *Plazmanın aterojenik endeksi (AIP) ve trigliserit-glikoz (TyG) endeksi, koroner arter aterosklerozu ile güçlü bir şekilde ilişkilidir. Ancak bu metabolik parametreler ile nonobstrüktif koroner arter hastalıkları (INOCA) arasındaki ilişki bilinmemektedir. Bu nedenle AIP ve TyG endeksinin INOCA hastaları ile ilişkisini araştırmayı amaçladık.*

Materyal ve Metot: *Bu çalışmaya toplam 529 hasta dâhil edildi ve INOCA grubuna (n=264) ve kontrol grubuna (n=265) atandılar. Klinik veriler ve hesaplanan AIP, TyG endeksi kayıt edildi. INOCA için AIP ve TyG endekslerini değerlendirmek üzere çok değişkenli lojistik regresyon kullanıldı.*

Bulgular: *INOCA'yı öngörmek için TyG'nin optimal kesme değeri %52,24 duyarlılık ve %70 özgüllük ile 8,87 idi ([AUC]: 0,634 [%95 GA: 0,592–0,675, p=0,023]). INOCA'yı öngörmek için AIP'nin optimal kesme değeri, %45,15 duyarlılık ve %70,57 özgüllük ile 0,54 idi ([AUC]: 0,590 [%95 GA: 0,547–0,632, p=0,025]). TyG ve AIP'nin ROC eğrileri karşılaştırıldığında TyG'nin daha iyi bir öngörücü olduğu görülmektedir ([Alanlar arasındaki fark]: 0,045 [%95 GA: 0,0180–0,0711, p=0,001]).*

Sonuç: *AIP ve TyG endeksi INOCA grubunda kontrol grubuyla karşılaştırıldığında anlamlı derecede yüksekti. Ayrıca temel bulgu olarak, TyG endeksi ve AIP metabolik parametreleri birbirleriyle karşılaştırıldığında TyG endeksinin daha güçlü bir öngörü sağladığı ve INOCA için bağımsız bir risk faktörü olduğu tespit edildi.*

Anahtar kelimeler: *plazmanın aterojenik endeksi; trigliserit-glikoz endeksi; obstrüktif koroner arterlerin olmadığı iskemi (INOCA); koroner arter hastalığı*

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Introduction

Most individuals who have anginal symptoms do not have obstructive coronary artery disease (CAD)[1]. There are more women in this group than men. Up to 59–89% of these individuals referred to as "Ischaemia with No Obstructive Coronary Arteries (INOCA)" appear to have coronary vascular dysfunction, which includes both epicardial coronary vasospasm and coronary microvascular dysfunction[2,3]. While the exact pathophysiology of INOCA remains unknown, some research has shown that endothelial dysfunction and micro circular coronary anomalies are key factors[4].

Important components of atherogenesis include inflammation and abnormal glucose and lipid metabolism, which also serve as strong risk factors for cardiovascular disease[5,6]. Research has demonstrated that the triglyceride-glucose (TyG) index and atherogenic index of plasma (AIP) are novel indicators of inflammation, insulin resistance, and atherosclerosis, respectively[7,8].

Although the association of AIP and TyG index with coronary artery disease has been reported, its association with INOCA patients has not been reported in the literature. Therefore, we aimed to investigate the relationship between the atherogenic index of plasma (AIP) and TyG index to INOCA patients.

Method

Study Population

Of 529 patients: 264 were diagnosed with INOCA after coronary angiography at Kafkas University School of Medicine cardiology department between October 2020 and July 2023, and 265 patients were in the control group. Individuals who met the following criteria were classified as INOCA patients: normal coronary angiography, ischaemia on myocardial perfusion scintigraphy, and classic angina-like chest pain with normal 12-lead ECG at rest. Patients in the control group had similar demographics for age and sex, normal echocardiography, no signs of ischaemia during the treadmill exercise test or myocardial perfusion scintigraphy, and patients who had normal coronary angiography results after being suspected of having coronary artery disease.

The patients with coronary artery disease at coronary angiography and surgical or mechanical revascularization were excluded from the study.

Age, sex, hypertension, diabetes, smoking, and family history were recorded as baseline characteristics. The study protocol was approved by the local ethics committee (Ethics Committee of the Dean of the Faculty of Medicine of Kafkas University – numbered ethics committee approval numbered 80576354–050–99/216).

Blood Samples

Biochemical and complete blood counts were obtained retrospectively from intravenous blood samples before coronary angiography. Patients had fasted for twelve hours before the blood samples were taken in the morning. Blood samples were performed after 12 hours of fasting. Plasma total, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglycerides were determined using Cobas Integra 700/800 (F. Hoffmann-Laroche Ltd, Basel; Switzerland) or Cobas6000, module c501 (Roche Diagnostics, Basel, Switzerland) and blood cell count by ADVIA 120 or 2120 (Bayer Health Care, Tarrytown, NY, USA). The TyG index was calculated as ln [fasting triglycerides (mg/dL) × fasting glucose (mg/dL)/2]. The AIP was determined by the ratio of levels of TG and HDL-C relating to the logarithmic transformation as: log10 [TG (mmol/L)/HDL-C (mmol/L)][9].

Angiographic Analysis

Nitroglycerin was not utilized when performing coronary angiography (Siemens Medical Solutions, Erlangen, Germany) using the standard Judkins procedure. Two seasoned doctors who were blind to the study performed the examination of the angiograms. When evaluating angiograms, visually smooth contours devoid of any anomalies in the wall were regarded as normal.

Statistical Analysis

Version 18.0 of the IBM Statistical Package for Social Sciences (SPSS) program for Windows (IBM Inc., Chicago, IL) was utilized in the data analysis technique. The normality of the continuous variable distribution was examined using the Kolmogorov-Smirnov test. Continuous variables were denoted by averages, whereas categorical variables were indicated by standard deviations and percentages, respectively. The chi-square test was employed for categorical data, and independent sample t and Mann-Whitney U-tests were applied based on distribution patterns to determine

Table 1. *Clinical characteristics of subjects*

	Control group (n: 265)		INOCA group (n: 264)		All patients (529)		p
Age (years)	48	±11	55	±9	52	±11	0.001
Gender, n (%) (Female)	152	(57.4)	107	(39.9)	328	(61.5)	0.049
Smoking, n (%)	89	(33.6)	94	(44.3)	196	(36.8)	0.129
Family CAD history, n (%)	37	(14)	122	(45.7)	181	(34)	0.001
Hypertension, n (%)	59	(22.3)	89	(42.0)	179	(42.2)	0.001
Diabetes, n (%)	20	(7.5)	56	(20.9)	76	(14.3)	0.001
Hemoglobin (g/dL)	14.63	±1.72	14.91	±1.67	14.34	±1.70	0.001
Platelet (10^3/mL)	267.38	±72.35	250.79	±66.52	259.04	±69.90	0.003
Lymphocyte (10^3/mL)	2.42	±0.91	2.57	±0.875	2.494	±0.950	0.012
Eosinophil (10^3/mL)	0.160	(0.090–0.300)	0.160	(0.100–0.235)	0.160	(0.100–0.270)	0.945
Monocyte (10^3/mL)	0.470	(0.380–0.570)	0.510	(0.420–0.670)	0.490	(0.400–0.620)	0.001
Neutrophil (10^3/mL)	4.50	(3.53–5.57)	4.20	(3.50–5.24)	4.32	(3.50–5.40)	0.082
Glucose (mg/dL)	101	±28	114	±42	107	±36	<0.001
Total Cholesterol (mg/dL)	175	±39	195	±45	185	±43	<0.001
Triglyceride (mg/L)	120	(90–150)	145	(103–200)	134	(98–180)	<0.001
LDL-C (mg/dL)	102	±38	118	±46	110	±43	<0.001
HDL-C (mg/dL)	48	±12	47	±12	47	±12	0.348
Urea (mg/dL)	25	(17–31)	16	(11–24)	20	(13–29)	0.001
Creatine (mg/dL)	0.70	(0.60–0.84)	0.80	(0.68–0.90)	0.74	(0.64–0.94)	0.001
hsCRP (mg/L)	3	(1–5)	4	(3–8)	4	(2–7)	0.001
EF (%)	63.29	±5.57	60.90	±7.55	62.09	±6.74	0.001
AIP	0.41	(0.25–0.59)	0.50	(0.32–0.68)	0.45	(0.28–0.64)	<0.001
TyG index	8.68	±0.58	8.97	±0.61	8.83	±0.62	<0.001

INOCA: ischaemia with non-obstructive coronary arteries, CAD: coronary artery disease, LDL-C: low density lipoprotein cholesterol. HDL-C: high density lipoprotein cholesterol, hsCRP: high sensitive C-Reactive protein, EF: ejection fraction, AIP: atherogenic index of plasma, TyG: triglyceride-glucose.

differences in continuous variables across groups. Multivariate logistic regression analysis was used to identify factors whose p-value was less than 0.05. This allowed for the evaluation of the independent predictors of INOCA. As a result, the logistic regression model contained all significant factors following the univariate analysis.

Results

A total of 529 patients with an average age of 52±11 years (328[61.5%] patients were female) were included in the study. The patients were divided into two groups according to the diagnosis of INOCA. The baseline demographic, biochemical, and haematological data of the patients according to the groups are presented in Table 1.

Levels of triglyceride, glucose and AIP, TyG index were all greater in the INOCA patients. Smoking status, count of eosinophil and neutrophil, level of HDL-c did not significantly differ across the groups.

Familial coronary artery disease history was statistically significantly higher in INOCA patients than in the control group. From blood and biochemistry parameters; hemoglobin (Hgb), total cholesterol (TC), LDL-C, creatine, high sensitive C-reactive protein (hsCRP), counts of lymphocyte and monocyte were found to be statistically significant on the side of the INOCA group. On the other hand level of urea, count of platelet and ejection fraction (EF) were found to be higher on the side of the control group. While female gender was more in the control group, the INOCA group was older. Additionally, the presence of diabetes mellitus (DM) and hypertension (HT) was higher in the INOCA group.

Univariate logistic regression analysis revealed significant correlations between INOCA; age, HT, family CAD history, TyG, DM, hemoglobin, monocyte, platelet, urea, creatine and hsCRP (Table 2). Further analysis of these variables using the multivariate logistic regression analysis indicated that age (Odds Ratio [OR]: 1.070, 95% confidence interval [CI]: 1.048–1.093; p<0.001), HT (OR: 1.825, 95% CI: 1.176–2.833; p=0.007), family CAD history (OR: 2.276, 95% CI: 1.330–3.894; p=0.003) and TyG (OR: 1.577, 95% CI: 1.086–2.289; p=0.017) were independent predictors for the INOCA (Table 2).

Table 2. *Multivariate logistic regression model adjustment of INOCA*

	Univariate			Multivariate		
	Univariate OR, 95% CI		p	Multivariate OR, 95% CI		p
Age	1.072	(1.053–1.092)	0.001	1.070	(1.048–1.093)	<0.001
HT	2.938	(2.016–4.281)	0.001	1.825	(1.176–2.833)	0.007
Family CAD history	2.862	(1.858–4.410)	0.001	2.276	(1.330–3.894)	0.003
TyG index	2.311	(1.698–3.147)	<0.001	1.577	(1.086–2.289)	0.017
DM	1.157	(0.570–2.349)	0.687	-	-	-
Hemoglobin	1.000	(0.998–1.002)	0.998	-	-	-
Monocyte	3.218	(0.931–11.123)	0.065	-	-	-
Platelet	0.997	(0.994–1.000)	0.029	-	-	-
Urea	0.941	(0.922–0.960)	0.001	-	-	-
Creatine	1.948	(0.929–4.085)	0.078			
hsCRP	0.991	(0.970–1.013)	0.435			

OR: odds ratio, CI: confidence interval, HT: hypertension, CAD: coronary artery disease, TyG: triglyceride-glucose, DM: diabetes mellitus, hsCRP: high sensitive C-Reactive protein.

The optimal cut-off value of TyG for predicting INOCA was 8.87 with a sensitivity of 52.24% and a specificity of 70% ([AUC]: 0.634 [95% CI: 0.592–0.675, p=0.023]) (Fig. 1). The optimal cut-off value of AIP for predicting INOCA was 0.54 with a sensitivity of 45.15% and a specificity of 70.57% ([AUC]: 0.590 [95% CI: 0.547–0.632, p=0.025]) (Fig. 1). When the ROC curves of TyG and AIP are compared, it is seen that TyG is a better predictor ([Difference between areas]: 0.045 [95% CI: 0.0180–0.0711, p=0.001]).

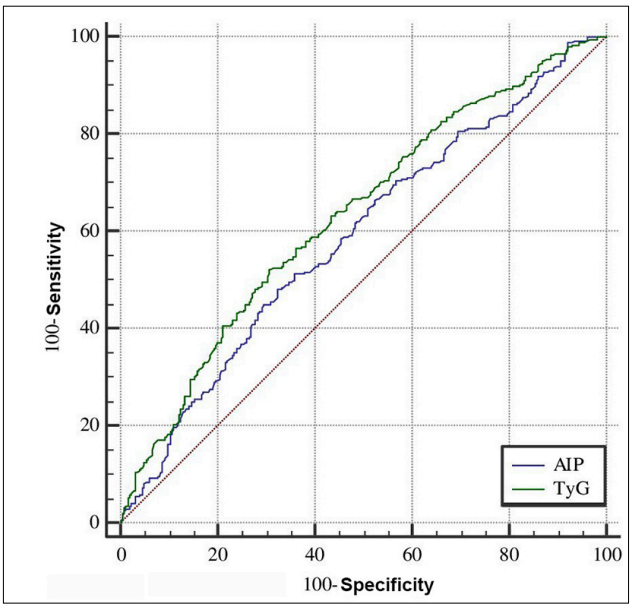

Figure 1. *Receiver operating characteristic curve analysis of AIP and Tyg to predict INOCA (AIP: atherogenic index of plasma, TyG: triglyceride-glucose index).*

Discussion

To our knowledge, this is the first study to determine the relationship between metabolic parameters such as AIP and TyG index and INOCA. We have found that AIP and TyG index were significantly higher in the INOCA group when compared to the control group. In addition, the main finding was that when the metabolic parameters TyG index and AIP were compared with each other, the TyG index provided a stronger prediction and was found to be an independent risk factor for INOCA.

Ischaemia with no obstructive coronary arteries appears to be caused by a variety of processes, some of which may operate alone or in combination[10]. While these may include, in some cases, congenital heart disease, myocarditis, hypertension, severe aortic stenosis, anemia, type II myocardial infarction, shunts, certain medications, heart failure or cardiogenic shock, Prinzmetal variant angina (coronary spasm), myocardial diseases, coronary anomalies, myocardial bridging, and other causes, the underlying mechanisms and appropriate diagnostic and management approaches are typically evident in these situations. One proposed mechanism contributing to INOCA is coronary microvascular dysfunction (CMD), defined as epicardial, microvascular endothelial or nonendothelial dysfunction that limits myocardial perfusion, most often detected as reduced coronary flow reserve (CFR)[11]. Coronary microvascular dysfunction can be iatrogenic, arise in the presence of cardiac disease or obstructive CAD but not in the absence of either. Patients even in the absence of flow-limiting stenosis are at risk of cardiac mortality if they have coronary vasomotor dysfunction[12].

Abnormal lipid metabolism, insulin resistance and the inflammatory response play important roles in the progression of coronary atherosclerosis, calcified plaque

formation and deterioration[6,13]. One significant risk factor for atherosclerosis is the plasma's atherogenic lipoprotein composition. The high and positive correlation between the AIP, cholesterol esterification rates, lipoprotein particle size, and residual lipoproteinemia has led to its proposal as a measure of plasma atherogenicity[14,15]. The AIP is a new comprehensive lipid index superior to LDL-C, HDL-C, TC, and triglyceride as a predictor for CAD[16]. Furthermore, previous studies have shown that AIP is more closely related to cardiovascular (CV) risk than individual lipoprotein cholesterol fractions or other atherogenic indices[17,18]. Foam cell production and the development of atherosclerotic plaque are aided by an increase in the AIP, which signifies a decrease in LDL particle diameter and an increase in the fraction of small dense LDL (sdLDL)[19].

According to studies, the TyG index may be utilized as a predictor of CAD and adverse cardiovascular events and is a more accurate measure of insulin resistance than Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)[20,21]. In relation to coronary artery calcification, coronary artery stiffness, and the potential to predict the degree of coronary stenosis, the TyG index may have an impact on the development of atherosclerotic plaques at all stages of coronary artery disease (CAD) [22]. Furthermore, insulin resistance can change the way that systemic lipid metabolism functions. This can cause dyslipidemia, which aggravates vascular endothelial damage and inflammation as well as makes it more likely that susceptible plaques will burst[23]. Although our study does not claim that this relationship is stronger than obstructive coronary artery diseases, the relationship of these two indices, which have been proven to be related to atherosclerosis, was revealed for the first time in the literature with INOCA patients.

In conclusion, the TyG index was found to be a helpful indicator for INOCA prediction in the current investigation.

Limitations of the study

There are many restrictions on our investigation. We did not measure coronary flow velocity during cholinergic provocation in this single-center investigation with a limited sample size, and although the doppler wire evaluation is in accordance with recognized standards, it was not the basis for the diagnosis of microvascular spasm[24]. One of the most important limitations of our study is that we did not compare INOCA patients with obstructive coronary artery patients.

Conclusions

Ischaemia with no obstructive coronary arteries is a significant health issue that is linked to poor prognosis, insufficient therapy, and underdiagnosis. Multicenter research with a greater patient sample size is nonetheless required in this area. To address the unsolved concerns in the diagnosis and treatment of these individuals, prospective, well-designed, continuing research is required. Elevated TyG index may predict INOCA and independent risk factor. Although our study does not claim that this relationship is stronger than obstructive coronary artery diseases, the relationship of these two indices, which have been proven to be related to atherosclerosis, was revealed for the first time in the literature with INOCA patients.

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We thank all the health workers who participated in this study.

Authors' Contribution

The authors share the responsibility for the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no potential conflicts of interest regarding this article.

Disclaimer

The content is solely the responsibility of the authors

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of the Dietary Risk Factors in Calcium Oxalate Stone Forming Cases in Turkey

Türkiye'deki Kalsiyum Oksalat Taşı Vakalarının Diyet Risk Faktörleri Açısından Değerlendirilmesi

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ABSTRACT

Aim: *To evaluate the dietary content and evaluate the possible related risk factors in patients with calcium oxalate (CaOx) stones*

Material and Method: *A total of 2348 patients with CaOx stone disease and 1024 cases with no signs of stone disease were evaluated concerning the possible dietary content-related risk factors for stone formation. A well-prepared comprehensive questionnaire focused on the diet-related risk factors including fluid intake, sodium, animal protein, black tea, fruit juice, coffee, and vegetables was utilized. Urinary risk factors have been identified and additionally, the patient-related factors and possible effects of physical exercise, and smoking were also well evaluated.*

Results: *Evaluation of our findings demonstrated that 46.2% of study group cases consumed water less than 1 liter per day; black tea consumption was also found to be higher (28.9% consuming black tea >451 cc/day) in cases with CaOx stones. Similarly, consumption of daily coffee, protein, salt, and dairy products was higher in these cases than in the control group. Also, daily physical activity amounts were lower in this group of patients. Lastly, urinary stone-forming risk factors were common in patients with CaOx stone disease.*

Conclusion: *When comparing calcium-containing stones to others, our findings revealed that high salt, black tea, and animal protein consumption were the main stone-forming risk factors. These patients had higher levels of urinary risk factors than the general population.*

Key words: *calcium; oxalate; kidney; stone; diet*

ÖZET

Amaç: *Kalsiyum oksalat (CaOx) taşı olan hastalarda diyet içeriğini değerlendirmek ve ilişkili olası risk faktörlerini değerlendirmek*

Materyal ve Metot: *CaOx taş hastalığı olan toplam 2348 hasta ve taş hastalığı belirtisi olmayan 1024 vaka, taş oluşumu için diyet içeriğine bağlı olası risk faktörleri açısından değerlendirildi. Sıvı alımı, sodyum, hayvansal protein, siyah çay, meyve suyu, kahve ve sebzeleri içeren diyetle ilişkili risk faktörlerine odaklanan iyi hazırlanmış kapsamlı bir anket kullanıldı. Üriner risk faktörleri tanımlanmış ve ayrıca hastaya bağlı faktörler, fiziksel egzersiz ve sigara içmenin olası etkileri de iyi değerlendirilmiştir.*

Bulgular: *Bulgularımız değerlendirildiğinde, çalışma grubu vakalarının %46,2'sinin günde bir litreden az su tükettiği; CaOx taşı bulunan olgularda siyah çay tüketiminin de daha yüksek olduğu (%28,9 siyah çay tüketimi >451 cc/gün) saptanmıştır. Benzer şekilde bu olgularda günlük kahve, protein, tuz ve süt ürünleri tüketiminin kontrol grubu olgularına göre daha yüksek olduğu görüldü. Ayrıca bu hasta grubunda günlük fiziksel aktivite miktarları daha düşüktü. Son olarak CaOx taş hastalığı olan hastalarda üriner sistem taşı oluşturan risk faktörleri yaygındı.*

Sonuç: *Kalsiyum içeren taşları diğer taşlarla karşılaştırdığımızda bulgularımız yüksek tuz, siyah çay ve hayvansal protein tüketiminin taş oluşumuna neden olan ana risk faktörleri olduğunu ortaya koydu. Bu hastalarda genel popülasyona göre daha yüksek düzeyde üriner risk faktörleri vardı.*

Anahtar kelimeler: *kalsiyum; oksalat; böbrek; taş; diyet*

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Introduction

Urolithiasis prevalence has increased in several regions of the world, with significant changes in disease-related characteristics during the last three decades. In addition to significant changes in food habits and attitudes, developments in the identification and minimally invasive therapy of urinary stones in instances with urinary stones have also contributed to these changes[1–4].

Parallel to the increase in prevalence, reported data demonstrated that time-dependent stone recurrence rates also increased (31.5–50% for five and 72% in twenty years respectively)[5,6]. These observations regarding the increased risk of new stone formation have led urologists to focus not only on the minimally invasive management approaches to render the patients stone-free but also the efficient preventive measures (metaphylaxis) to limit new stone formation risk, particularly in recurrent stone formers. Regarding the possible underlying risk factors responsible for urinary stone formation and subsequent recurrences, changes in dietary habits, particularly in the younger generation, have been regarded to be highly important in this aspect[7–9]. Although limited, outcomes of some well-designed studies with an adequate number of cases have demonstrated that in addition to fluid intake, consumption of some other dietary constituents including calcium, oxalate, carbohydrate, sodium, protein, etc. were also found to affect the urinary composition by increasing the excretion of urinary risk factors and that of subsequent supersaturation[9–13] Related to the possible effects of dietary factors on stone formation although general evaluation and reported data seem to be useful, data derived from the local/regional epidemiological studies focusing on personal dietary and metabolic risk factors could be highly important to reflect the exact role of dietary habits in different parts of the world.

In this study, we wanted to examine the dietary risk factors that may be connected with the development of CaOx stones disease in a specific percentage of the Turkish population due to a lack of data on the prospective influence of various nutritional components on the risk of stone formation.

Method

To evaluate the possible relationship between dietary factors and the risk of calcium oxalate stone formation, a prospective observational study was conducted in 2348 adult patients (>18 years) with CaOx nephrolithiasis (Study group). From September 2019 to June 2022, a questionnaire survey was conducted on adult patients referring to pre-diagnosed CaOx stone disease. Data obtained in these cases were compared with the findings of 1024 cases referring to complaints of other diseases without any history and evidence (diagnosis) of stone disease (Control group). Patients presenting with certain pre-diagnosed kidney disease (s), active UTI, and other metabolic problems were excluded from the study program. Additionally, cases with a history of diet-related restriction, gout, hyperparathyroidism, nephrocalcinosis, gastrointestinal disease, renal tubular acidosis, urologic anatomical abnormalities, or chronic renal failure were also excluded.

Before the inclusion of patients into the study program no evidence of stone disease was confirmed in control group cases (n: 1024) with a detailed anamnesis and appropriate radiological evaluation. Stone-forming risk factors by performing a 24-hour urine analysis were performed in all cases in both groups. An informed consent has been obtained from all cases after describing the aim of the trial and the type, and content of evaluations to be made (urine, blood, and radiological).

In close collaboration with epidemiologists, our team developed a simple yet thorough questionnaire. Each form was completed by nurses and resident doctors on the urology units, who conducted face-to-face interviews with research participants in the urolithiasis and control groups. Gender, age, BMI values, dietary habits, smoking status, prior stone events, interventions, related co-morbidities, and exercise conditions were among the questions on documented risk factors for urinary calculi.

In addition to the basic demographic characteristics, daily exercise conditions, and family history, regarding the dietary habits of the cases, apart from daily fluid intake, frequency and type of consumption of salt, animal protein, carbohydrate, dairy products, coffee, black tea, soda water, fruit juice, vegetables were carefully asked and recorded. Last but not least, urinary stone-forming risk factors were identified in 24-hour urine samples obtained from both group cases.

Statistical Analysis

Utilizing IBM Statistical Package for Social Sciences (SPSS) program version 17.0 (IBM, Chicago, IL, USA), the obtained data in both case groups were examined. The values were assessed for significance using a chi-square test, and the independent risk factors for urolithiasis were examined using multivariate logistic analysis. For statistical significance, a p-value of less than 0.05 was used.

Results

Evaluation of the data regarding dietary consumption as well as urinary stone-forming risk factors obtained in 2348 cases with CaOx stone disease and 1024 cases without any evidence of urolithiasis revealed the following findings;

While the male/female ratio was 1.35 in the study group (1346 males, 1002 females) this value was 1.20 in control group cases (559 males, 465 females). Median age of the population was 42.7 (range: 15–69) years and 40.8 (range: 21–66) years in both groups respectively. Stone analysis data was identified as CaOx in all cases. Body mass index (BMI) values were above 30 in 31.3% of the cases in Group 1 and 29.1% of Cases in Group 2.

As the most important preventive parameter, evaluation of daily fluid consumption in our cases demonstrated that while nearly half of the population evaluated (1086 cases, 46.2%) consumed water less than 1 liter per day in Group 1. 42.8% of the cases consumed 1–2 liters per day and unfortunately only 10.8% of the patients consumed more than 2 liters per day. On the other hand, however, 39.0% of the cases in Group 2 were found to consume more than 2 liters of water per day.

Among the other constituents of diet dairy proteins (milk, yogurt, etc.) consumption rate (>3 days/week) was significantly higher in study group cases (46.2% vs 37.5%) than in control group. Similarly, the dietary content of sodium (salt) was prominently higher in cases suffering from stone disease compared to those in the control group (Consumption regularly at every meal 46.6% vs 30.9%).

Of the other diet-related parameters evaluation of black tea consumption demonstrated the common consumption where 28.9%, of the cases in Group 1 consumed more than 451 cc/day. This value was 21.5% in control group cases (p: 0.024). While 35.5% of the cases consumed more than 2 coupes of coffee/day in Group 1 cases, this value was 25.7% in cases without stone disease. There was no statistically significant difference between both groups regarding cola consumption (10.8% vs 7.9% consumption of more than 2 glasses of cola/day), cigarette smoking, soda water, and vegetable consumption (Table 1).

Evaluation of physical activity status in both groups of cases demonstrated a significant difference where patients with stone disease seemed to have less activity (36.7% of the cases had exercise 1–3 days/ week) compared with the cases in Group 2 (19.8%). All constituents of diet and their daily consumption rates are given in Table 1.

Last but not least, evaluation of stone-forming risk factors in both groups of cases revealed higher excretion of relevant constituents (Calcium, Uric acid, oxalate) in patients with CaOx stones.

A summary analysis of our findings revealed a statistically significant ($p<0.05$) difference between the two groups of cases concerning the 13 variables identified including physical activity, BMI values, fluid intake, sodium intake, animal protein and dairy products consumption, black tea, and coffee consumption.

Table 1. *Evaluation of dietary risk factors in both groups*

	Study group		Control group		
	N	%	N	%	P
Total number of cases	2348		1024		
Fluid consumption					
≤1 L/ day	1086	46.2	282	27.5	0.025
1–2 L/ day	1007	42.8	342	33.3	
≥2 L/ day	255	10.8	400	39.0	
Consumption of fruit					
Juice (1 glass=200 cc)					
None	1634	69.6	412	40.2	
≤200 cc/day	350	14.9	359	35.1	
≥200 cc/day	363	15.5	253	24.7	0.032
Consumption of black tea (1 tea glass: 50 cc, 1 large glass/coupe: 200 cc)					
None	218	9.3	108	10.6	0.25
≤150 cc/ day	700	29.8	327	31.9	0.024
151 – 450 cc /day	750	32.0	368	35.8	
≥451 cc/day	680	28.9	221	21.5	
Consumption of coffee					
None	481	20.5	394	38.7	
≤1 coupe/ day	1033	44.0	366	35.6	
≥2 coupe/ day	833	35.5	264	25.7	0.045
Consumption of cola (1 glass=300 cc)					
None	1213	51.7	716	69.9	
≤1 glass /day	880	37.5	227	22.2	
≥2 glasses/day	255	10.8	81	7.9	0.045
Consumption of soda water (1 glass=200 cc)					
None	662	28.2	217	21.2	0.023
≤1 glass /week	857	36.5	462	45.2	
≥2 glasses/week	829	35.3	345	33.6	
Consumption of water (L/day)					
≤1 L/ day	1086	46.2	282	27.5	0.025
1–2 L/day	1007	42.8	342	33.3	
≥2 L/day	255	10.8	400	39.0	0.01
Consumption of animal protein/day					
6–7 days/week	842	35.9	226	22.1	0.025
4–5 days/ week	576	24.5	349	34.1	
<3 days/week	930	39.6	449	43.8	

p<0.05 significant.

Discussion

Changing lifestyles and dietary habits in the population have caused a prominent increase in the prevalence of stone disease over the past decades[10]. This issue, the lifetime risk of urolithiasis has been observed to range from 1–5% in Asia, 5–9% in Europe, 10–15% in the United States, and 20–25% in the Middle East, with Greenland and Japan having the lowest frequency[5].

Although the underlying mechanisms involved in urinary stone formation are complex and multifactorial; data obtained in several studies have pointed out that the dietary habits and lifestyle of the major strategy for preventing the recurrence of urolithiasis-involved cases are important factors for close consideration[11,12]. If left untreated at least 50% of these individuals will have recurrent stone formation. It is well known that the composition of urine is highly important for stone formation and this factor is partly dependent on diet, including mainly the amount of fluid intake. When it comes to dietary risk factors for calcium-containing stones, the majority of stones are made of calcium oxalate, accounting for 40–60%. In contrast, the data regarding non-calcium-containing stones is rather sparse[13]. Daily diet management was shown to be a preventive approach and has gained more and more importance in recent years[14–16].

As stated above composition of daily diet plays a major role in the concentration of several urinary solutes and inhibitors involved in the formation and growth of urinary calculi. Determining the impact of one's diet on future stone risk begins with a dietary history and subsequent metabolic evaluation to outline the presence and impact of such factors. Regarding the dietary factors affecting the urinary levels of stone-forming risk factors and subsequent stone formation as a result, previous studies have demonstrated well that high fluid is highly important to reduce the risk of stone formation[17,18]. Increased urine volume has been demonstrated to lower the concentration of calcium oxalate in the urine and reduce the risk and recurrence rate of stone formation by 50% and 60–80%, respectively[19,20].

However, a number of randomized controlled studies evaluating the effects of fluid consumption on urinary risk factors as well as stone formation are highly limited and it is unknown whether all liquids (with different levels of hardness and constituents) have similar effects on the risk of stone formation. However, research has shown that some other liquids, such as orange juice, coffee, tea, wine, and beer, may lower the risk of stone development while carbonated and sugar-containing beverages may raise it[17,21].

In relation to this matter, it has been suggested that tea drinking may influence the excretion of risk factors for the development of stones, and prolonged tea drinking may raise the risk of stone formation by increasing oxalate intake. As a possible risk factor for hyperoxaluria, increased black tea consumption has been considered a risk factor particularly in recurrent stone-forming cases[22–24]. On the other hand, contradictory information from a few recent research has shown that drinking tea, especially green tea, can help prevent the development of stones[25–28].

In addition to the fluid intake, however, some other certain dietary components have also been found to be responsible for the formation and recurrence of calcium-oxalate calculi. Of these dietary components, high sodium intake was found to be responsible for elevated urinary sodium excretion levels which will in turn inhibit calcium absorption in the renal tubules. Higher calcium excretion will induce hyperuricemia resulting in increased risk for calcium oxalate crystal formation[29]. This topic is related to the findings of a study that examined the potential effects of sodium consumption levels on the formation of calcium oxalate stones in 210 patients. The study found that patients who present with hypercalciuric stones experience a significant decrease in calcium excretion when eating a low-salt diet (271 mg/day vs. 361 mg/day). This suggests that dietary salt intake may have an impact on the levels of calcium elimination and stone formation[30]. In another trial, Sorensen et al. evaluated the relationship between dietary content related kidney stone formation and they were able to show that elevated dietary sodium intake will prominently increase the risk of nephrolithiasis by 11–61%[31]. Similar studies have demonstrated the same correlation between higher salt consumption and urinary sodium and calcium excretion levels which has been reported to be linear[15,29,32].

Published data so far strongly emphasized that overconsumption of protein in daily diet, particularly animal protein, has been reported to be an important risk factor for new stone formation. Regarding this issue, in an animal model of increased protein intake, the authors were able to show that a high casein diet can cause a prominent increase in urinary calcium excretion where urinary citrate excretion and urinary pH were found to be relatively lower[33]. Other clinical

investigations by other authors also showed the protective benefits of limiting animal protein in a regular diet to lower the excretion of oxalate, phosphate, calcium, hydroxyproline, and uric acid. An increase in urine citrate excretion as a result of this dietary adjustment also reduced the incidence of stone formation[34,35].

As previously said, regulating fluid and nutritional consumption patterns is critical in the overall prevention of urolithiasis. Nonetheless, despite a huge amount of epidemiological data, high-quality prospective interventional research is scarce in this field. Taking this into consideration, the current observational study intended to investigate the underlying dietary risk factors in instances of urinary stones and compare the results to patients with no indications of stone illness.

Evaluation of the data obtained in our groups demonstrated the higher consumption of some well-established dietary stone-forming risk constituents in cases with urolithiasis. Patients with stone disease tended to consume more black tea, coffee, dairy products, salt, and animal protein than the cases without any evidence of stone disease. Physical activity was less in these cases with a more prominent sedentary life. Obesity was more common among the cases with urolithiasis and the rate of excreted urinary stone forming risk factors was significantly higher in these cases. Of these factors, higher excretion of oxalate and lower levels of citrate were the two common abnormalities noted in our group.

Based on all these factors, we may say such local, and regional epidemiological studies focusing on personal dietary and metabolic risk factors could be highly important in an attempt to derive valuable, predictive clinical implications to limit the risk of stone recurrence as well as lower the economic burden of the disease and outline the most rational treatment alternative.

Our study is not free of limitations. Number of patients evaluated may be limited. Again, some other certain dietary risk factors could be inquired and assessed. However, taking limited information regarding the epidemiological data on stone disease particularly in a regional evaluation-based manner, we believe our findings will be contributive enough on this aspect. Additionally, taking the endemic nature of the stone disease in our country, we believe that these values coming from a local regional part of a such country will give further insights into the epidemiologic features of the disease.

Conclusion

In the light of our current results and the published data so far confirm the importance of individual dietary factors in the development of calcium oxalate kidney stones. A well-evaluated dietary content is of paramount importance in an attempt to make the necessary modifications to lower the urinary excretion levels of stone-forming risk factors. Management of symptomatic urinary stones with minimally invasive stone removal procedures will not prove "complete" unless they are supported with metabolic evaluation-based dietary modification to reduce the urinary levels of stone-forming risk factors and subsequent stone formation.

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Authors' Contribution

The authors share the responsibility for the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no potential conflicts of interest regarding this article.

Disclaimer

The content is solely the responsibility of the authors.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Cardiac Mechanics in Asthmatic Female Patients During Exacerbation and After Stabilization: A Speckle-tracking Echocardiography Study

Astımlı Kadın Hastalarda Alevlenme Sırasında ve Stabilizasyon Sonrası Kalp Mekaniğinin Değerlendirilmesi; Speckle-tracking Ekokardiyografi Çalışması

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ABSTRACT

Aim: *There is a complex relationship between asthma and cardiac functions. According to speckle-tracking echocardiography studies, asthma, especially severe asthma, was associated with left and right ventricular subclinical dysfunction. The literature lacks data comparing the cardiac functions during exacerbations and stable periods in patients with asthma. In this study, we aimed to investigate cardiac functions using speckle-tracking echocardiography during exacerbations and in the stable phase in female patients with asthma.*

Material and method: *A total of 51 female adult asthma patients who were admitted to our center due to asthma exacerbations were included in this study. All participants had a previous diagnosis of asthma. Transthoracic echocardiography was performed both during hospitalization and after the asthma exacerbation was stabilized. Echocardiographic findings, including left ventricular longitudinal strain, in the two periods were compared. All patients were discharged in good condition after their asthma attacks stabilized.*

Results: *White blood cell count (WBC) and C-reactive protein (CRP) levels were significantly higher during exacerbation than in the stable phase. Regarding echocardiographical findings, isovolumetric contraction time (IVCT) was significantly longer and left ventricular global longitudinal strain (LVGLS) was significantly lower during exacerbation compared to the stable phase [median (IQR), 70 (61–76) msec vs. 66 (57–72) msec, p=0.011 and -12.9 (-13.8 – -12.1) vs. -14.2 (-14.8 – -13.2), p<0.001, respectively]. According to the multivariate analysis, IVCT, LVGLS, and WBC were independently associated with asthma exacerbation.*

Conclusion: *Our study showed that asthma exacerbations might have an oppressive and adverse impact on cardiac functions, particularly when analyzed by STE.*

Keywords: asthma; *asthma exacerbation; heart function; left ventricular longitudinal strain*

ÖZET

Amaç: *Astım ve kardiyak fonksiyonlar arasında karmaşık bir ilişki vardır. Yapılan speckle-tracking ekokardiyografy araştırmalarına göre, astım, özellikle şiddetli astım, sol ve sağ ventrikül subklinik disfonksiyonu ile bağlantılı olduğu tespit edilmişitir. Astımlı hastalarda alevlenme ve stabil dönemlerde kardiyak fonksiyonları karşılaştıran bir çalışma yoktur. Bu çalışmada, astımlı kadın hastalarda alevlenme sırasında ve stabil fazda speckle-tracking ekokardiyografi ile kardiyak fonksiyonları araştırmayı amaçladık.*

Materyal ve Metot: *Astım alevlenmesi nedeniyle ardışık olarak merkezimize yatırılan toplam 51 kadın yetişkin astım hastası bu çalışmaya dâhil edildi. Tüm katılımcılarda daha önce astım tanısı mevcut idi. Hastalara hem hastaneye yatış sırasında hem de astım atağı stabilize edildikten sonra transtorasik ekokardiyografi çekildi. Bu iki ekokardiyografik bulgular karşılaştırıldı. Tüm hastalar astım atağı stabil olduktan sonra iyi hal ile taburcu edildi.*

Bulgular: *Alevlenme sırasında beyaz kan hücresi sayımı (WBC) ve C-reaktif protein (CRP) seviyeleri stabil faza göre anlamlı derecede yüksekti. Ekokardiyografik bulgulara bakıldığında, stabil faza göre alevlenme sırasında izovolümetrik kontraksiyon süresinin (IVCT) anlamlı derecede uzun olduğu ve sol ventriküler global longitudinal strain'in (LVGLS) anlamlı derecede düşük olduğu görüldü.[medyan (IQR), sırasıyla, 70 (61–76) msn'ye karşılık 66 (57–72) msn, p=0,011 ve -12,9 (-13,8 – -12,1) vs. -14,2 (-14,8 – -13,2), p<0,001]. Çok değişkenli analize göre IVCT, LVGLS ve WBC bağımsız olarak astım alevlenmesiyle ilişkiliydi.*

Sonuç: *Çalışmamız astım alevlenmesinin özellikle speckle-tracking ekokardiyografi ile analiz edildiğinde kalp fonksiyonları üzerinde baskılayıcı ve olumsuz bir etkiye sahip olabileceğini gösterdi.*

Anahtar kelimeler: *astım; astım atağı; kalp fonksiyonu; sol ventrikül longitudinal strain*

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Introduction

Asthma is one of the most common diseases associated with morbidity and mortality, worldwide[1,2]. Asthma is considered a heterogeneous disease that manifestly differs by gender. While there is a higher preponderance of asthma in male teenagers, rates are higher in adult women compared with men[3].

Although there is plenty of data investigating the relationship and intercourse between chronic obstructive pulmonary disease (COPD) and cardiovascular disease, little is known about the interaction between asthma and cardiovascular disorders[4,5]. Some studies are showing biventricular subclinical dysfunction in asthma patients[5,6]. However, the literature lacks research comparing cardiac functions during exacerbations and stable periods, in patients with asthma. In our study, we aimed to investigate cardiac functions using conventional and speckle-tracking echocardiography (STE) measurements during exacerbation and in the clinically stable phase, in female patients with asthma.

Material and Method

A total of 51 female adult (>18 years) asthma patients hospitalized for asthma exacerbations were included in this observational case-control study between December 2019 and January 2021. All participants had a previous diagnosis of asthma. The admission hemogram and biochemical blood parameters of the patients were analyzed. Transthoracic echocardiography was performed within 12 hours of hospitalization and after the asthma exacerbation was stabilized. The initial (during asthma exacerbation) and follow-up (after clinical stability) echocardiographic findings were compared. All subjects received bronchodilator medications, including budesonide, ipratropium bromide, and salbutamol, as well as prednisolone. Those with heart failure (left ventricular ejection fraction <50), congenital heart disease, moderate or advanced heart valve disease, arrhythmia, renal failure (estimated glomerular filtration rate <60), malignancy, and thyroid dysfunction were excluded from the study.

Standard two-dimensional and Doppler echocardiographic evaluation

Philips HD 11 XE ultrasound machine (Andover, MA, USA) was used for echocardiography measurements. Left ventricle (LV), left atrial (LA), right ventricular (RV), and aortic root dimensions and LV wall thickness were measured according to the American Society of Echocardiography 2015 guideline[7]. Early (E) and late (A) wave velocities were measured from the mitral inflow profile. E/A values were calculated by dividing E to A. Tissue Doppler imaging (TDI) measurements were assessed in the apical four-chamber view. The myocardial systolic (s'), early diastolic (e'), and late diastolic (a') velocities were recorded at the lateral and septal mitral annulus by TDI in 3 consecutive beats. Mitral annular isovolumetric contraction time (IVCT) and isovolumetric relaxation time (IVRT) were also calculated. Modified Simpson's rule was utilized to calculate left ventricular ejection fraction (LVEF)[8].

2D-speckle tracking strain echocardiography

Analysis of STE was carried out per the recommendations of the American Society of Echocardiography and the European Association of Cardiovascular Imaging[9]. Speckle-tracking echocardiography analysis was performed per the Consensus Document of the EACVI/ASE/Industry Task Force to Standardize RV and LV myocardial Deformation Imaging[10]. Qlab13 (Philips Healthcare, Andover, Massachusetts) software was utilized for the calculation of LVGLS. End-diastole was specified as the peak R wave of the electrocardiogram and the end-systole was determined as aortic valve closure. The average of peak global longitudinal strain (GLS) values from apical two-chamber, apical three-chamber, and apical four-chamber images was estimated as left ventricular global longitudinal strain (LVGLS). During the end-systole, endocardial borders were detected automatically. Manually corrected when needed. left ventricular global longitudinal strain (LVGLS) change was expressed as percentages (%). Negative values of LVGLS represent myocardial contractility ability (the less negative value, the worse the LV systolic performance).

Statistical analyses

IBM Statistical Package for Social Sciences (SPSS) program version 20 (IBM Inc., Chicago, IL, USA) was used for statistical analysis. Continuous variables were represented as mean ± standard deviation (SD) or median [25–75 interquartile range (IQR)] according to normality and distribution characteristics. Comparisons were carried out using the student's *t*-test, or Mann–Whitney U-test. Categorical variables were shown with numbers and percentages. Categorical variables were compared using the χ^2 test or Fisher's exact test. A multivariate analysis was performed to indicate variables those are independently associated with asthma exacerbations. p-value under 0.05 was considered significant.

Results

The mean age of the patients was 53.33 (standard deviation 12.42). While 6 (11.7%) of the patients were smokers, 12 (23.5) were diagnosed with hypertension and 7 (13.7) were diagnosed with diabetes. The demographics, and laboratory findings of the patients during hospitalization (asthma exacerbation) and follow-up (after clinical stability of asthma exacerbation) are shown in Table 1. Levels of white blood cell count (WBC) and C-reactive protein (CRP) were significantly higher during exacerbation than in the stable phase.[median (IQR), 12.21 (9.22–13.77) vs. 10.41 (7.14–11.67), p=0.002 and 15 (3.03–36) vs. 4.26 (2.4–9.8), p=0.016, respectively]. The initial (during asthma exacerbation) and follow-up (after clinical stability of asthma exacerbation) echocardiographic evaluations of the study population are listed in Table 2. Isovolumetric contraction time was significantly longer during exacerbation than during the stable phase [median (IQR), 70 (61–76) msec vs. 66 (57–72) msec, p=0.011] (Fig. 1a). However, IVRT was similar in both recordings [median (IQR), 65 (60–69) vs. 66 (60–69), p=0.540]. Left ventricular global longitudinal strain by STE was significantly worse during the exacerbation than during the stable phase.[median (IQR), -12.9 (-13.8 – -12.1) vs. -14.2 (-14.8 – -13.2), p <0.001] (Fig. 1b). There was no significant difference in left ventricular end-diastolic, left ventricular end-systolic, septal thickness, posterior wall thickness, left atrial, right ventricular, and right atrial diameters. Left ventricular ejection fraction was similar between the first and second measurements. In addition, diastolic function parameters measured by echocardiography showed statistically similar values. Moreover, there was no significant difference in right ventricular systolic function measured by tricuspid annular plane systolic excursion (TAPSE) and tricuspid

Table 1. *Demographic, clinical, and laboratory characteristics*

	n=51
Age (years), mean ± SD	53.33±12.42
Smoking	6 (11.7)
Hypertension, n (%)	12 (23.5)
Diabetes, n (%)	7 (13.7)
Laboratory findings at admission	
Hgb (g/dL), median [IQR]	14.4 [13.1–15.1]
WBC (× 103/µL), median [IQR]	12.21 [9.22–13.77]
PLT (× 103/µL), median [IQR]	264 [212–325]
Albumin (mg/dL) median [IQR]	44.8 [39.5–46.2]
CRP (mg/L), median [IQR]	5.86 [2.96–12.3]
Creatinine (mg/dL), mean ± SD	0.64±0.14
Lymphocyte (× 103/µL), mean ± SD	2.45±1.01
Neutrophil (× 103/µL), mean ± SD	8.23±2.76

Hgb: hemoglobin; WBC: white blooc count; PLT: platelet; CRP: C-reactive protein

Table 2. *Comparison of echocardiographic characteristics during asthma exacerbation and after clinical stability*

Echocardiography features	During Exacerbation	After Stabilization	
LVDD (mm), mean ± SD	39±0.5	39±0.5	0.916
LVSD (mm), median [IQR]	28 [26–30]	27 [26–31]	0.898
IVS (mm), median [IQR]	9 [8–10]	9 [8.5–10]	0.756
PW (mm), median [IQR]	8 [7.2–8]	8 [7–8]	0.994
LA (mm), median [IQR]	31 [28.5–35]	30 [26.5–35]	0.793
RV (mm), median [IQR]	34 [31–37]	35 [31–37]	0.812
RA (mm), median [IQR]	30 [26–32]	28 [26–32]	0.783
Ejection Fraction (%), mean ± SD	60±6	60±5	0.856
E, mean ± SD	72.6±17.5	71.4±17.2	0.725
A, median [IQR]	80 [70–90]	77 [70–90]	0.234
E/A, median [IQR]	0.87 [0.79–1.13]	0.82 [0.70–1.01]	0.144
e’	8 [7–8.5]	7 [6–9]	0.095
E/e’, mean ± SD	9.25±2.60	10±2.73	0.161
TAPSE, median [IQR]	24 [19–25]	21 [19–25]	0.407
S’, mean ± SD	3.21±5.81	2.96±5.52	0.824
PASB (mmHg), median [IQR]	16.7 [15–18]	17 [15–20]	0.325
IVCT (ms), median [IQR]	70 [61–76]	66 [57–72]	0.011
IVRT (ms), median [IQR]	65 [60–69]	66 [60–69]	0.540
LVGLS, median [IQR]	-12.9 [-13.8 – -12.1]	-14.2 [-14.8 – -13.2]	<0.001

LVDD: left ventricle end-diastolic diameter; LVSD: left ventricle end-systolic diameter; IVS: interventricular septum thickness; PW: left ventricular posterior wall thickness; LA: left atrium diameter; RV: right ventricle diameter; RA: right atrium diameter; E: maximum flow velocity during early LV diastolic filling; A: maximum flow velocity during late diastolic LV filling; e’: mitral annulus systolic velocity; TAPSE: tricuspid annular plane systolic excursion; S’: tricuspid annulus systolic velocity; PASP: pulmonary arterial systolic pressure; IVCT: isovolumetric contraction time; IVRT: isovolumetric relaxation time; LVGLS: left ventricle global longitudinal strain.

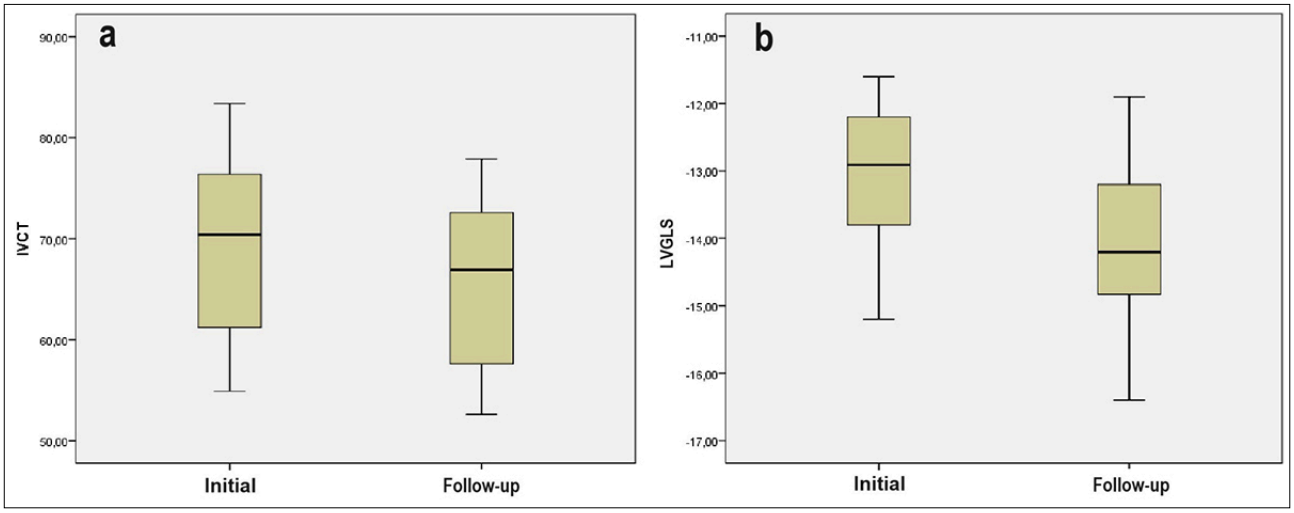

Figure 1. a, b. *Distribution of IVCT* ***(a)*** *and LVGLS* ***(b)*** *during asthma exacerbation (initial) and after stabilization (follow-up)(IVCT, isovolumetric contraction time; LVGLS, left ventricular global longitudinal strain).*

Table 3. *Univariate and multivariate regression analysis*

	Univariate		Multivariate	
	OR (95% CI)	p value	OR (95% CI)	p value
IVCT	0.942 (0.898-988)	**0.013**	0,914 (0.848-0.986)	**0.019**
LVGLS	0.358 (0.226-0.568)	**<0.001**	0,194 (0.087-0.428)	<0.001
CRP	1.016 (1.001-1.031)	**0.042**	1,005 (0.984-1.026)	**0.634**
WBC	1.324 (1.111-1.577)	**0.002**	1,450 (1.144-1.839)	**0.002**

CI, confidence interval; CRP, C-reactive protein; IVCT, isovolumic contraction time; LVGLS, left ventricular global longitudinal strain; OR, odds ratio; WBC, white blood count

annular systolic velocity (S') between the initial and follow-up recordings [median (IQR), 24 (19–25) vs. 21 (19–25), p=0.407 and (avarage ± SD), 3.21±5.81 vs. 2.96±5.52, p=0.824, respectively]. Pulmonary artery systolic pressure (PASB) measured from tricuspid valve regurgitation was also similar between initial and follow-up recordings [median (IQR), 16.7 (15–18) vs. 17 (15–20), p=0.325]. According to the multivariate analysis, IVCT, LVGLS, and WBC were independently associated with asthma exacerbation [OR (95% CI), 0.914 (0.848–0.986), p=0.019, 0.194 (0.087–0.428), p<0.001 and 1.450 (1.144–1.839, p=0.002, respectively] (Table 3).

Discussion

In our study, we compared conventional and STE examinations during asthma exacerbation and clinically stable periods, in female patients with asthma. The main findings were as follows: The IVCT of the left ventricle was prolonged during asthma exacerbation compared to the clinically stable period. More importantly, based on the STE measurements the left ventricular systolic function during asthma exacerbation was more impaired than during the stable period. To the best of our knowledge, it is the first time the current study established a comparison of cardiac function during asthma exacerbation and stable phase in patients with asthma.

Previous studies showed a variety of cardiac dysfunction in patients with asthma[5,6,11]. De-Paula et al. found lower pulmonary acceleration time and higher PSAP in asthma children and adolescents compared to age-matched healthy control[6]. Another study showed that asthma was associated with an increased occurrence of subclinical biventricular dysfunction[5]. However, the literature lacks data investigating the comparison of cardiac functions during exacerbation and stable phase in asthma patients. The current study aimed to address this gap.

According to previous reports, IVCT was significantly associated with heart failure (HF) and provides important prognostic information for the risk of future HF in the general population[12,13]. According to Alhakak et al., the risk of HF increased by 24% per 10 msec increase in IVCT (per 10 msec increase: HR 1.24;

95% CI (1.14–1.36), p<0.001)[12]. Myocardial fibers start to contract during the IVCT, increasing LV pressure without changing ventricular volume[14]. Thus, no blood is ejected and only internal work is performed. The cardiac efficiency is zero. However, during the ejection, external work is performed and cardiac efficiency improves. As myocardial function deteriorates, the IVCT is prolonged, increasing the internal work. Furthermore, the ejection time is shortened, decreasing the external work[15]. In a study consisting of mild-to-moderate HF patients, the ejection time was dramatically reduced and the IVCT was significantly extended[16]. Similarly, we found longer IVCT during exacerbation compared to the stable period. Mentioned phenomena could explain the prolongation of IVCT during asthma exacerbations. This prolongation possibly indicates that asthma exacerbation implements additional oppression on cardiac functions through varied substances produced during the exacerbation. It should be kept in mind that bronchodilator treatment also might have deteriorated the cardiac function. We also examined IVRT, which may be prolonged in HF and some diseases[14,17]. No significant prolongation of IVRT was observed during exacerbation in asthma patients compared to the stable period.

LVGLS, a measure of systolic myocardial deformation over the longitudinal axis, has proven effective in detecting subtle LV systolic dysfunction when LV ejection fraction is still preserved. Furthermore, it does not only reveal the subclinical LV systolic dysfunction but also predicts worse outcomes in many diseases[18]. Tuleta et al. investigated the LVGLS in mild-to-severe asthma patients[5]. Left ventricular global longitudinal strain values were reduced significantly in severe and mild-to-moderate asthma patients compared to the control group [avarage ± SD, -12.91±0.84% and -13.92±1.55%, p<0.05). Özkan et al. showed the adverse impact of asthma on ventricular contractility and that cardiac systolic function was impaired, in children with asthma[19]. In our study, according to the STE measurements left ventricular systolic function during asthma exacerbation was more impaired than during the stable period. The deterioration of LV systolic function during an asthma exacerbation is presumably due to some non-cardiac circumstances that implement oppression on cardiac function.

Asthma is mostly characterized by reversible obstruction of proximal and distal airways in response to various triggers. When compared to COPD, oxidative stress, neutrophil dominancy, and traditional systemic inflammation with specific pro-inflammatory mediators like tumor necrosis factor-alpha, interleukin-8, etc. —generally seem to be less prominent in the context of asthma[20]. Conversely, asthma is essentially defined by mast cells and eosinophils in the airways, which produce particular bronchoconstrictor chemicals such as histamine. Nevertheless, there is probably some overlap between the eosinophilic and neutrophilic pathways in these two situations[21]. During an asthma exacerbation, not only a variety of non-cardiac clinical scenarios such as hypoxemia, tachycardia, and bronchodilator therapy but also pro-inflammatory mediators might account for the depression of cardiac functions.

Conclusion

Our study showed that asthma exacerbation might have an oppressive and adverse impact on cardiac functions, particularly when analyzed by STE. Therefore, maximum efforts should be made to prevent asthma attacks and treat exacerbations without delay. Prospective studies with a larger number of patients are needed in this area.

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Authors' Contribution

The authors share the responsibility for the manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no potential conflicts of interest regarding this article.

Disclaimer

The content is solely the responsibility of the authors.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Investigation of Possible Antenatal and Perinatal Risk Factors in Patients with Congenital Epiphora

Konjenital Epiforalı Hastalarda Olası Antenatal ve Perinatal Risk Faktörlerinin Araştırılması

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ABSTRACT

Aim: *We aimed to investigate the effective factors to increase treatment options in patients with congenital nasolacrimal duct obstruction (LDO).*

Materyal and Methods: *Our study was planned retrospectively. The patients admitted to Erzurum Regional Training and Research Hospital Family Medicine Outpatient Clinic with symptoms such as watering, burring, swelling in the sac area, chronic conjunctivitis < In 200 children under 4 years of age, information on maternal age, mode of conception, gender, birth weight, mode of delivery, presence of multiple pregnancies, sibling history, duration of hospitalization, need for invasive mechanical ventilation, maternal pre-eclampsia, gestational DM, and bilateral or unilateral occlusion, need for surgery, number of surgeries, presence of anisometropia, when epiphora started and when it ended were collected and evaluated.*

Results: *Of the children included in the study, 52% (n=103) were male and 48% (n=95) were female. It was shown that complaints such as watering, redness, and burring due to congenital nasolacrimal duct obstruction mostly started in the first weeks (7.1%), and most of these complaints were relieved by massaging the sac area and topical drops (90.3%) without surgical intervention. There were no significant statistical differences between children with and without congenital epiphora in terms of gender, multiple pregnancies, mode of delivery, delivery week, need for postnatal intensive care, mother's mode of conception, maternal age and chronic diseases (p>0.05). Significant differences were found in birth weight and the presence of positive sibling history (p<0.05).*

Conclusion: *This study was conducted to evaluate the association of congenital epiphora with possible antenatal and perinatal risk factors. It was concluded that low birth weight and positive sibling history may be involved in the etiopathogenesis of epiphora, but it was concluded that studies on this subject should be conducted by reaching large populations.*

Key words: *Epiphora, Caesarean section, Hasner's valve, Lacrimal Duct Embryology*

ÖZET

Amaç: *Konjenital nazolakrimal kanal tıkanıklığı (LDO) olan hastalarda tedavi seçeneklerinin artırılması için etkili faktörlerin araştırılması amaçlanmıştır.*

Materyal ve Metot: *Çalışmamız retrospektif olarak planlanmıştır. Erzurum Bölge Eğitim ve Araştırma Hastanesi Aile Hekimliği Polikliniğine başvuran daha önce sulanma, çapaklanma, kese bölgesinde şişlik, kronik konjonktivit gibi bulguları olan < 4 yaş altı 200 çocuğun anne yaşı, gebe kalma şekli, cinsiyet, doğum ağırlığı, doğum şekli, çoğul gebelik varlığı, kardeş öyküsü, hastanede yatış süresi, invaziv mekanik ventilatör ihtiyacı, annede preeklampsi, gestasyonel DM gibi faktörler ve tıkanıklığın her iki taraflı yada tek taraflı olması, cerrahi gereksinimi, cerrahi sayısı, anizometropi varlığı, epiforanın ne zaman başlayıp hangi zamanda sonlandığı gibi bilgileri toplanıp değerlendirilmiştir.*

Bulgular: *Çalışmaya alınan çocukların %52'si (n=103) erkek, %48'i (n=95) kadın idi. Konjenital nazolakrimal kanal tıkanıklığına bağlı sulanma, kızarıklık, çapaklanma gibi şikayetlerin çoğunlukla ilk haftalarda (%7,1) başladığı, bu şikayetlerin çoğunun da cerrahi müdahale olmaksızın, kese bölgesine masaj ve topikal damlalarla (%90,3) giderildiği gösterildi. Konjenital epiforası mevcut olan ve olmayan çocuklar arasında cinsiyet, çoğul gebelik, doğum şekli, doğum haftası, doğum sonrası yoğun bakım ihtiyacı, annenin gebe kalış şekli, anne yaşı ve kronik hastalıkları açısından önemli istatistiksel farklılıklar bulunmadı (p>0,05). Doğum kilosu ve pozitif kardeş öyküsü varlığı konusunda ise anlamlı farklılık saptandı (p<0,05).*

Sonuçlar: *Bu çalışma konjenital epiforanın olası antenatal ve perinatal risk faktörleriyle ilişkisinin değerlendirilmesi için yapılmıştır. Düşük doğum kilosu ve pozitif kardeş öyküsünün epifora etiyopatogenezinde yer alabileceği sonuçlarına ulaşılmıştır ancak bu konudaki çalışmaların geniş kitlelere ulaşılarak yapılması kanaatine varılmıştır.*

Anahtar kelimeler: *Epifora, Sezaryen doğum, Hasner valvi, Lakrimal kanal embriyolojisi*

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Introduction

Epiphora is one of the common ocular disorders found in newborns starting from the first hours of birth. The first symptom is ponding and outflow of tears around the free edge ofthe lower eyelid and in the medial canthal region, and later, with the progression of symptoms,mucoid secretion reflux with pressure on the nasolacrimal sac, recurrent and persistent conjunctivitis attacks, It is an important clinical entity that manifests itself with a mucoid sticky secretion, discharge and burring at the eyelash margins in the morning or after crying attacks and may cause serious ocular morbidity such as acute dacryocystitis, preseptal and orbital cellulitis in case of development of secondary infection, although there is usually no evidence of serious inflammation[1].

Epiphora is more common in the first years of life and is found in one out of every 5 children[1]. In newborns, incomplete canalization at birth is common. Although it may also beassociated with various agenesic conditions, obstruction-related conditions are usually partial and transient[2,3]. In the majority of infants, it resolves spontaneously with fasciocranial growth until the age of one year[4]. The need for surgical operation is approximately 2 to 5% of children with persistent symptomatic epiphora[5].

Lacrimal duct development is complex. First, nasolacrimal duct growth continues throughout all stages of embryo development. At 32 days of embryo development, the maxillaryand frontonasal processes begin to appear. As these processes grow and expand, a groove forms between them. Simultaneously, the epithelial cord invades the upper and lower eyelid margins to form canaliculi, which fuse to form the nasolacrimal drainage system. Canalization of the epithelial cord begins simultaneously along the entire cord at 4 months. Epithelial remnants inthe cord do not show continuity and form valvula-like folds[6].

Understanding the diseases of the nasolacrimal system is only possible by explaining the histopathologic developmental stages of the duct. Punctal membranes are usually completely open at full term. However, it has been observed that Hasner's Valve is not perforated in 70% of newborns[6]. Understanding the diseases of the nasolacrimal system canonly be possible by explaining the histopathologic developmental stages of the duct and the factors affecting them.

The spontaneous improvement of the condition in children with epiphora <1 year of ageor the differences in its presence between children of the same chronologic age is a subject in need of research. The female predominance of congenital epiphora cases and differences in racial preference suggests a potential hereditary predisposition to nasolacrimal system obstruction[7]. There are also studies showing the effect of antenatal factors such as mode of delivery. These cases may be coincidental; therefore, further studies are necessary to confirm whether there is indeed a correlation.

In summary, the issue of a genetic or environmental predisposition to the occurrence ofcongenital epiphora remains an open one. Through ophthalmologic and otolaryngologic collaboration, such familial and non-hereditary assessments could potentially lead to a better understanding and prevention of the potential complications and ultimately economic costs of conditions related to nasolacrimal system development. Studies on this subject may help support and counsel the activities of family physicians. In our study, we aimed to determine theeffect of antenatal and perinatal factors on this condition and to evaluate the results.

Materials and Methods

Study Design, Population, and Clinical Assessment

Our study was planned retrospectively. According to the power analysis performed with the *Power 3.1.9.4* program, the number of participants required for the study was determined as 200 with a type 1 error of 0.05, 80% confidence interval and medium effect size (q=0.3). Thepopulation of our study consisted of 200 children < 4 years of age with symptoms such as watering, burring, swelling in the sac area, and chronic conjunctivitis who applied to Erzurum Regional Training and Research Hospital Family Medicine Polyclinic. Patients who did not agree to participate voluntarily and did not sign the informed consent or whose parents/legal representatives did not agree to participate in the study and patients >4 years of age were excluded from the study. Factors such as maternal age, mode of conception, gender, birth weight, mode of delivery, presence of multiple pregnancies, sibling history, duration of hospitalization, need for invasive mechanical ventilation, maternal pre-eclampsia, gestational DM, and bilateral or unilateral occlusion, need for surgery, number of surgeries, presence of anisometropia when epiphora started and when it ended were collected and evaluated.

Ethical Approval

For this study, permission was obtained from Atatürk University Faculty of Medicine Internal Medicine Sciences Board and Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Ethics committee meeting date and number: 24.06.2021/05-24).

Statistical Analysis

SPSS 20 package program was used for statistics and analysis. Descriptive statistics were presented as frequency and percentage for categorical data and mean and standard deviation for numerical data. The compatibility of numerical variables with normal distribution was examined by the Kolmogorov-Smirnov test. One-way ANOVA was applied for normally distributed variables and the Kruskal-Wallis test was applied for variables that did not show normal distribution. Statistically, the significance limit of $p<0.05$ was accepted.

Results

The data of 198 participants in the study were analyzed. Of the children included in the study, 52% (n=103) were male and 48% (n=95) were female. The mode of delivery was normaldelivery in 37.4% (n=74) and cesarean delivery in 62.6% (n=124), and the rate of spontaneous vaginal delivery without intervention was 81.1%. The mean birth weight was 2562 ± 291.9 g. Spontaneous conception and singleton pregnancy rates of the participating mothers were 97%.The need for intensive care in postpartum children was 84.8% and the need for mechanical ventilation in those who needed intensive care was 23.3%. Among children diagnosed with epiphora by an ophthalmologist or paediatrician, both eyes were involved (n=12). It was shown that complaints such as watering, redness, and burring due to congenital nasolacrimal duct obstruction mostly started in the first weeks (7.1%), and most of these complaints were relievedby massaging the sac area and topical drops (90.3%) without surgical intervention. There wereno significant statistical differences between children with and without congenital epiphora in terms of gender, multiple pregnancies, mode of delivery, delivery week, need for postnatal intensive care, mother's mode of conception, maternal age and chronic diseases ($p>0.05$). Significant differences were found in birth weight and the presence of positive sibling history ($p<0.05$).

Discussion

Epiphora is a common ocular disorder found in newborns starting from the first hours of birth. Congenital epiphora is a common condition, with an incidence ranging from 1.2% to20% in infants. In general, anatomical anomalies in the lacrimal passage should be considered in the approach to infants with epiphora. Tears drain along the lacrimal passage from the level of the punctum canaliculus to the meatus nazi inferior. Absence, stenosis or stenosis may be observed at different levels of the lacrimal passage[8]. Congenital dacryostenosis is the most common cause of watery eyes in childhood. However, although rare, congenital malformationsof the lacrimal drainage system may occur[9-11].

Understanding the diseases of the nasolacrimal system is only possible by explaining the histopathologic developmental stages of the duct. Punctal membranes are usually completely open at full term. Lacrimal stenosis can be defined as a congenital defect of any component of the nasolacrimal drainage system. Failure of normal development at any point inthis embryologic process due to genetic or intrauterine factors can cause pathologies in the lacrimal drainage system.

An imaging study showed that the distal part of the lacrimal duct junction was an anthropometric site of obstruction in all patients. In these studies, it was reported that lacrimal duct obstructions are mainly caused by thickening of the bony wall distal to the NLD that narrows the lumen, pathologic persistence of a membrane distal to the NLD, and narrowing ofthe distal duct by abnormal proliferation and apposition of the nasal mucosa. All of these mechanisms are thought to represent different stages in the developmental process that are necessary for continuity between the lacrimal duct and the meatus nasi inferior[12].

Vertical epithelialization and proliferation of the distal portion and its interactions with surrounding mesenchymal tissues determine the shape of the distal lacrimal duct. The presenceof membranous bone tissue or bone canal stenosis distal to the lacrimal duct may be evidence of abnormal inductive interactions.

Another issue is the presence of a nasal mucosa-derived membrane that is in harmony with the LD epithelium, which is detected even in histologic examinations performed in healthy newborns[13]. This membrane causes especially the distal parts of the LD to become more resistant to dilation and is balanced by the hydrostatic pressure, which is highest in the

Table 1. *Demographic characteristics of the participants, various risk situations and statistical comparisons of children with and without LDO diagnosis*

	Frequency %		Sign
	LDO – (n: 105)	LDO + (n: 93)**	P
Gender			
Male	63 (31%, 8)	48 (24%, 2)	0.129*
Woman	42 (21%.21)	45 (22%, 7)	
Multiple pregnancy			
Yes	4 (2%, 02)	2 (1%, 01)	0.238†
No	101 (51%, 01)	91 (45%, 95)	
Mother's mode of conception			
Natural	96 (48%, 5)	87 (43%, 9)	0.238†
IVF – Embryo transfer	9 (4%, 54)	6 (3%, 03)	
Presence of chronic disease in the mother			
There is	14 (7%, 07)	6 (3%, 03)	0.745†
No	91 (45%, 95)	87 (43%, 93)	
Birth week			
Miad 36–40 weeks	88 (44%, 4)	69 (34%, 84)	
Postmature >40 weeks	6 (3%, 03)	6 (3%, 03)	0.724†
Prematurity <36 weeks	11 (5%, 6)	18 (9%, 09)	
Mode of birth			
Normal birth	53 (26%, 8)	21 (10%, 6)	0.064*
Cesarean section (C/S)	52 (26%, 3)	72 (36%, 4)	
Intervention in normal birth			
No intervention	45 (60%, 9)	15 (20%, 3)	0.130†
Intervention/ forceps	8 (10%, 8)	6 (8%, 1)	
The need for intensive care for the child after birth			
Yes	12 (6%, 06)	18 (9%, 1)	0.584†
No.	93 (46%, 9)	75(37%, 9)	
Need for mechanical ventilator if in the intensive care unit.			
Yes	4 (13%, 4)	3 (10%, 0)	0.646†
No.	17 (56%, 7)	6 (20%, 0)	
If you have siblings or multiple pregnancies (twins, triplets. . .), did they have the same complaints?			
Yes	≠	19 (67%, 8)	**<0.001†**
No.	≠	9 (32%, 2)	
Birth weight, gr, mean ± sd	3259.1±628.6	3023.4±479.1	**0.049‡**
Age of mother, years, mean ± sd	31.1±4.6	32±4.3	0.307‡

* Pearson Chi-Square test, † Fisher's Exact test, ‡ Student's t-test
* *LDO: Participants diagnosed with lacrimal duct obstruction by an ophthalmologist

distal part and increases with postnatal lengthening of the LD[14]. It is thought to cause spontaneous perforations when the tensile strength of the membrane is exceeded by hydrostatic pressure, which increases with the accumulation of tears with the mechanical effect of the lids and the pressure created by the opening and closing of the eyelids. The persistence of the obstruction can be explained by the fact that the hydrostatic pressure effect is less or the mucosal membrane is more fibrotic with developmental anomalies. It has been observed that Hasner's Valve is not perforated in 70% of newborns and this explains the more frequent occurrence of epiphora in premature babies compared to term babies[6].

The respiratory efforts of the newborn during labour usually cause perforation of this membrane and provide LD patency[15]. The reason why lacrimal duct obstruction is less common in vaginal deliveries compared to cesarean deliveries may be due to possible physiologic effects of normal vaginal delivery. It is known that the pressure in the birth canal increases excessively during normal vaginal delivery. This is thought to increase the hydrostatic pressure, especially in the body cavities, leading to perforation of membranous structures. It is thought that the frequency of LCO due to lower external pressure will increase in children born by cesarean delivery or even after the first delivery due to weakening of the pelvic muscles[16–20]. In addition, it

has been reported that the amount of various enzymes in favour of collagen destruction increases in the amniotic fluid during vaginal delivery and this may lead to the destruction of membranous structures similar to Hasner's valve[16]. For these reasons, the belief that vaginal delivery may prevent epiphora in newborns has gained weight. In our study, no statistical difference was found between the mode of delivery and LDO.

Another risk factor we examined in our study was gestational age. Although the numberof premature babies was low in our study, it was observed that epiphora complaints started earlier and lasted longer in babies with low gestational age and low birth weight among term babies. As known, the incidence of congenital nasolacrimal duct obstruction in premature infants may be affected by lacrimal duct immaturity. Sathiamoorthi et al. suggested that the lacrimal duct shows partial intrauterine development until the 32nd week and the canalization is not completed[21]. The results of our study show that lacrimal duct maturation continues even after birth depending on gestational age.

According to the results of our study, there was a statistical difference between siblingsin terms of the incidence of LDO. As stated in previous studies on lacrimal duct obstruction, female gender and Caucasian race suggest a potential hereditary predisposition to the lacrimal duct system[22]. Another study with varying demographic characteristics reported a familial involvement of approximately 11% in a series of dacryocystitis cases[23]. In another more recent study, familial cases reported belonged to the findings of siblings with craniofacial developmental anomalies[24]. Even though the results of our study suggest that there is a significant difference, the possibility of underreporting familial cases is high, especially because the disease progresses with subclinical findings in some individuals and only severe cases are referred to medical professionals. Therefore, we think that more studies are needed toconfirm whether there is indeed a familial correlation.

According to the results of our study, no significant association was found between lacrimal duct obstruction and maternal age, history of drug use, preeclampsia, presence of maternal infection, gestational diabetes, smoking, educational status and occupation. Although there are limited studies on this subject in the literature, Aldahash et al. reported that maternal infections may be a risk factor for lacrimal duct obstruction[25].

The retrospective design of the study has some limitations as it may lead to incompletedocumentation and misrepresentation. The actual incidence in the population may be overestimated or underestimated as clinical findings may be confounded with other ocular infections and allergic conditions. In addition, some infants with LDO may be asymptomatic in the first months, then improve after some time and ultimately go unnoticed by the patient'scaregiver or physician.

In summary, epiphora, which is frequently observed in the neonatal and early childhood periods, usually occurs due to LDO. The results suggest that the disease may be hereditary and many authors consider it to be due to acquired sporadic embryologic factors. Several factors have been suggested to play a role in the aetiology of LDO, including genetics, maternal infections, radiation exposure, medications or certain occupational hazards during pregnancy. Since LDO carries a risk of acute dacryocystitis and amblyopia even with minimal frequency, screening and vigilance in individuals with risk factors should be performed[26]. Understanding these factors is crucial for developing effective strategies for the prevention andmanagement of CNLDO in infants.

Conclusion

This study was conducted to evaluate the association of congenital epiphora with possible antenatal and perinatal risk factors. It was concluded that low birth weight and positivesibling history may be involved in the etiopathogenesis of epiphora, but it was concluded that studies on this subject should be conducted by reaching large populations.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Relationship of Serum Beta Defensin-2 and Surfactant Protein A and B Levels with the Clinical Course and Prognosis of COVID-19 Infection

Serum Beta Defensin-2 ve Sürfaktan Protein A ve B Düzeylerinin COVID-19 Enfeksiyonunun Klinik Seyri ve Prognozu ile İlişkisi

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ABSTRACT

Aim: *Defensin and surfactant-related peptides are antimicrobial peptides that play an essential role in the natural host defense against micro-organisms. The objective is to compare the serum beta-defensin 2 (ß-def2), serum surfactant protein-A (sSPA) and B (sSPB) levels and respiratory surfactant protein A (rSPA) and B (rSPB) levels in patients with clinically mild and severe COVID-19 pneumonia.*

Material and Method: *On presentation at the hospital before any treatment, venous blood samples and a nasopharyngeal smear sample were taken for rSPA and rSPB. The ß-def2, SPA, and SPB levels were advanced and analyzed using the ELISA method.*

Results: *The levels of acute phase reactants of ß-def2, sSPA, sSPB and white blood cell (WBC), neutrophil count, ferritin, procalcitonin, and C-reactive protein (CRP) were determined to be higher in the clinically and radiologically severe patients. The rSPA and rSPB levels showed a tendency to be lower in this patient group but not to a statistically significant level. The ß-def2, sSPA and sSPB values were determined to be positively correlated with WBC, neutrophil count, NLR, ferritin, procalcitonin, and CRP levels and negatively correlated with the albumin level.*

Conclusion: *ß-def2, sSPA, and sSPB, which play a role in the natural host defense, are correlated with the acute phase reactants of the clinical and radiological severity of COVID-19:WBC, neutrophil count, NLR, ferritin, procalcitonin, and CRP. In patients with severe disease, rSPA and rSPB levels tended to be low, although not statistically significant, and further studies on this subject could guide the use of surfactants in treatment.*

Keywords: *beta defensin-2; COVID-19; surfactant protein A; surfactant protein B*

ÖZET

Amaç: *Defensin ve sürfaktan, mikroorganizmalara karşı doğal konak savunmasında önemli rol oynayan antimikrobiyal peptitlerdir. Bu çalışmanın amacı, klinik olarak hafif ve şiddetli COVID-19 pnömonisi olan hastalarda serum beta-defensin2 (ß-def2), serum sürfaktan protein-A (sSPA) ve B (sSPB) seviyeleri ile respiratuvar sürfaktan protein A (rSPA) ve B (rSPB) seviyelerini karşılaştırmaktır.*

Materyal ve Metot: *Herhangi bir tedaviye başlamadan önce hastaneye başvurduklarında venöz kan örnekleri alındı ve rSPA ve rSPB için nazofarengeal sürüntü örneği alındı. ß-def2, SPA ve SPB seviyelerinin ileri analizi ELISA yöntemiyle yapıldı.*

Bulgular: *Akut faz reaktanları olan ß-def2, sSPA, sSPB ve beyaz kan hücresi (WBC), nötrofil sayımı, ferritin, prokalsitonin ve C-reaktif protein (CRP) seviyelerinin, klinik ve radyolojik olarak şiddetli hastalarda daha yüksek olduğu belirlendi. rSPA ve rSPB seviyelerinin bu hasta grubunda istatistiksel olarak anlamlı olmayacak şekilde daha düşük olduğu eğilimi gösterdi. ß-def2, sSPA ve sSPB değerleri, WBC, nötrofil sayımı, NLR, ferritin, prokalsitonin ve CRP seviyeleri ile pozitif korelasyon gösterirken albümin seviyesi ile negatif korelasyon gösterdiği belirlendi.*

Sonuç: *Doğal konak savunmasında rol oynayan ß-def2, sSPA, sSPB, WBC, nötrofil sayımı, NLR, ferritin, prokalsitonin ve CRP gibi klinik ve radyolojik şiddetin akut faz reaktanları ile korele olup, şiddetli hastalığı olan hastalarda rSPA ve rSPB seviyelerinin istatistiksel olarak anlamlı olmasa da düşük olduğu eğilimindedir ve bu konu üzerinde daha fazla çalışma, tedavide surfactant kullanımı için rehberlik edebilir.*

Anahtar kelimeler: *beta defensin-2, COVID-19, yüzey aktif madde protein A, yüzey aktif madde protein B*

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Introduction

Antimicrobial peptides (AMP) in the mucosa, a component of primary host defense, are produced by epithelial cells and cells in the natural immune system and play a role as modulators of the natural immune system in the defense against infections[1]. Defensin is an AMP found in many organisms, including mammals, insects, and plants. In mammals, β-defensins are produced by epithelial cells and leukocytes, then stored as bioactive molecules in neutrophils in circulation[2]. These peptides have an essential role in the fight against infections caused by bacteria and viruses such as Haemophilus influenzae by activating immature dendritic cells[3,4]. They also show a chemotactic effect for monocytes, polymorphonuclear leukocytes and T-cells, and strengthen the acquired immune response[5,6].

The capability of a virus to resist natural antiviral immunity is related to the pathogenicity of the virus, which affects the severity of the disease[7]. Cytokines such as Type 1 interferon (IFN) play an essential role in the natural antiviral immune response by regulating immune cells and producing proteins[8]. However, some viruses, including Middle East respiratory syndrome coronavirus (MERS-CoV), inhibit the induction pathways of cytokines such as type 1 IFN[9]. This is related to immune avoidance mechanisms such as T-cell inactivation with the downregulation of antigen presentation and the induction of macrophage apoptosis[10].

Surfactant proteins, such as serum surfactant protein-A (SPA) and Surfactant protein D (SPD), found within pulmonary surfactant in the lungs, have a role in host defense and the regulation of inflammation[11,12]. Previous studies have suggested that SPA plays a role in regulating hBD3 (human β defensin 3)-mediated activation of mast cells[13,14]. Defensins and surfactant proteins are essential in early host defense against gram-positive and gram-negative bacteria, mycobacteria, and fungi. Moreover, several studies have documented the activities of the antiviral characteristics of defensins against both enveloped and non-enveloped viruses[5].

Acute phase reactants (APR) are a heterogenous plasma protein group that increases or decreases in response to inflammatory stimuli such as infections, trauma, acute arthritis, systemic autoimmune disorders and neoplasms[15]. The production of APRs in response to infection is stimulated by the liver and mediated by proinflammatory cytokines produced by macrophages, monocytes, and other cells participating in the inflammatory response. C-reactive protein (CRP), procalcitonin (PCT), and serum ferritin are among the most essential APRs. The albumin level decreases as a response to inflammation and is therefore known as a negative APR[16].

The novel coronavirus disease (COVID-19) emerged in Wuhan, China, in December 2019 and, with its rapid spread across the world, was declared a global pandemic within a few months as a disease primarily affecting the respiratory system and lungs and causing thousands of deaths[17]. Although there are several studies in literature related to COVID-19, to the best of our knowledge, no study has examined defensin and surfactant levels. This study aimed to compare the serum beta-defensin2 (ß-def2), serum surfactant protein A (sSPA) and B (sSPB) levels and respiratory surfactant protein A (rSPA) and B (rSPB) levels on nasopharyngeal swabs in patients with clinically mild COVID-19 and patients with clinically severe COVID-19 pneumonia. The comparisons of these parameters aimed to determine their role in the clinical course and prognosis of COVID-19 and contribute to the understanding of the disease course.

Materials and Methods

The Ethics approved this study of Committees of the University of Health Sciences, Bakirköy Dr. Sadi Konuk Training and Research Hospital (approval number: 2020/197) and conducted by the principles of the Declaration of Helsinki and its later amendments or comparable ethical standards.

The hospital Ethics Committee granted approval for this observational, descriptive, cross-sectional study and all procedures were applied in compliance with the principles of the Helsinki Declaration. The study included patients diagnosed with COVID-19 with positivity in Real-Time Polymerase Chain Reaction (RT-PCR) analysis of nasal and pharyngeal smear samples, who were admitted and followed up in the hospital between 01.06.2020 and 01.08.2020. Patients were excluded from the study if they were aged <18 years, did not consent to participate in the study, received immunosuppressive treatment, had congenital immune suppression, or had received anti-inflammatory or mucolytic treatment within the previous 15 days.

At the time of presentation at the hospital, before administering any antiviral or immune suppressive treatment, including steroids, a 1 cc venous blood sample was withdrawn into a yellow-top tube and nasal and pharyngeal smear samples were taken. The venous blood sample was centrifuged and then stored at -80°C, and the smear samples were stored directly. Analysis of the

ß-def2 (DEFB2 ELISA kit KTE62104, Abbkine), SPA (SP-A ELISA kit KTE60675 Abbkine) and SPB (SP-B ELISA kit KTE60674 Abbkine) levels was performed in the advanced analysis laboratory of the hospital with the ELISA (Enzyme-Linked Immunosorbent Assay) method. In the ELISA method, microplates provided in the kits are pre-coated with antibodies specific to the protein sought. First, standards and samples were added, and then protein-specific biotin-conjugated antibody was added to the appropriate microplate wells. Avidin conjugated to Horseradish Peroxidase (HRP) was then added to each microplate well and incubated. After the substrate solution was added, only the wells containing the sought protein-specific biotin-conjugated antibody and enzyme-conjugated Avidin showed a color change. The enzyme-substrate reaction was terminated by adding sulfuric acid solution, and the color change was measured spectrophotometrically at a wavelength of 450nm ±10nm. Protein concentrations in the samples were then evaluated by comparing sample O. D. s to the standard curve.

In the hospital laboratory, the reference ranges were taken as 3.7–10.1/μm^3 for leukocytes, 1.63–6.96 μm^3 for neutrophils, 1.09–2.99 μm^3 for lymphocytes, 12.9–15.9 g/dl for hemoglobin, and 35–52 g/l for albumin. The upper limit for PCT was defined as 0.5ng/ml, and for CRP, 5 mg/l. Internal quality control and external quality reliability were applied to ensure the accuracy of the tests. For the albumin, CRP, and ferritin levels, a Beckman Coulter AU5800 clinical chemistry analyzer was used (Beckman Coulter, Brea, CA, USA). An ADVIA 2120 hematology autoanalyzer (Siemens Healthcare Diagnostics, Erlangen, Germany) was used for the complete blood count (CBC).

For the classification of lung involvement of the patients, a semi-quantitative scoring system was used on the thoracic computed tomography (CT) images. Each of the five lobes of the lungs was scored from 0–5 as follows: 0:no involvement, 1: <5% involvement, 2:25% involvement, 3:26%-49% involvement, 4:50%-74% involvement, 5: >75% involvement[18]. In this study, the patients were separated into three groups: mild involvement (<25%), moderate level involvement (26–74%), and severe involvement (>75%).

The patients were grouped according to the clinical condition as mild, moderate, and severe. Patients with mild symptoms and oxygen saturation within normal limits (>98%) were accepted as mild disease. Patients with clinical or radiographic evidence of lower respiratory tract disease and blood oxygen saturation ≥94% in room air were accepted as moderate disease. The signs of severe disease were accepted as evident tachypnea (respiratory rate ≥30 breaths per min), hypoxemia (oxygen saturation ≤93%, breathed oxygen fraction rate of partial arterial oxygen pressure <300), and pulmonary leakage (>50% involved lung area within 24–48 hours)[19].

Statistical Analysis

Data obtained in the study were analyzed statistically using Number Cruncher Statistical System vn—2007 software (NCSS, Kaysville, Utah, USA). In comparing two groups of quantitative data showing normal distribution, the student's t-test was applied; for data not showing normal distribution, the Mann-Whitney U-test was used. The One-Way ANOVA test was applied to comparisons of three or more groups showing normal distribution, and the Bonferroni test was applied to paired comparisons. For data not conforming to a normal distribution, the Kruskal Wallis test was applied to three groups or more comparisons, and the Bonferroni Dunn test to paired comparisons. Spearman's correlation analysis was used in the evaluation of relationships between variables. A value of $p<0.05$ was accepted as statistically significant.

Results

Evaluation was made of 94 patients in this prospective study, comprising 57 (60.6%) males and 37 (39.4%) females with a mean age of 53 years (range 19–86 years). Demographic and clinical characteristics are given in Table 1. The WBC, neutrophil, NLR, ferritin, PCT,

Table 1. *Demographic and clinical characteristics of the patients*

		n	%
Age (year)	*Min-Max (Median)*	19–86 (55)	
	Mean ± SD	53.18±15.14	
Gender	Female	37	39.4
	Male	57	60.6
Comorbid diseases	Diabetes Mellitus	27	28.7
	Hypertension	28	29.8
	CAD	12	12.8
	COPD	12	12.8
	Others	4	4.3
Clinical condition	Mild	48	51.1
	Moderate + Severe	46	48.9
Thoracic CT	Mild	29	30.9
	Moderate	33	35.1
	Severe	32	34
Stay in ICU	Non	86	91.5
	Yes	8	8.5
Length of hospital stay (days)	*Min-Max (Median)*	3–50 (9)	
	Mean ± SD	12.21±9.63	
Survival status	Survivor	88	93.6
	Nonsurvivor	6	6.4

• Multiple diseases are seen.
CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, CT: computed tomography, ICU: intensive care unit

and CRP values were higher in the patients with severe thoracic CT findings than those with mild and moderate CT findings. The lymphocyte and albumin values were lower in the patients with severe thoracic CT findings than those with mild and moderate CT findings. In the patients with moderate and severe clinical status, the lymphocyte and albumin measurements were lower (p=0.001), and the neutrophil, NLR (p=0.001), ferritin, PCT, and CRP values (p<0.01) were determined to be higher than those of clinically mild patients (Table 2).

When the patients were grouped according to clinical severity, the ß-def2, sSPA and sSPB measurements in the moderate and severe groups were statistically significantly higher than those of the clinically mild patients (p=0.017, p=0.044, respectively). No difference was determined between the groups of clinical severity with respect to the rSPA and rSPB measurements (p>0.05) (Table 3).

A statistically significant difference was determined between the cases according to thoracic CT findings in respect of β-def2 measurements. The β-def2 values of the patients with severe thoracic CT findings were higher than those of patients with mild and moderate findings (p=0.001).

The sSPA measurements were statistically significantly higher in the cases with severe CT findings compared

Table 2. *Laboratory findings according to CT involvement and clinical condition*

		Thoracic CT				Clinical condition		
		Mild (n=29)	Moderate (n=33)	Severe (n=32)	*p*	Mild (n=48)	Moderate + Severe (n=46)	*p*
WBC (per µm³)	***Min-Max (Median)***	3.1–9.7 (5.5)	2.6–8.3 (5.7)	2.8–15.6 (6.8)	[a]***0.020****	3.1–9.7 (5.5)	2.6–15.6 (6)	[c]***0.068***
	Mean ± SD	5.50±1.51	5.58±1.53	7.66±3.51		5.60±1.54	6.96±3.20	
Lymphocyte (per µm³)	***Min-Max (Median)***	0.8–2.7 (1.6)	0.7–3 (1.4)	0.4–3.1 (1.1)	[a]***0.001****	0.8–3 (1.6)	0.4–3.1 (1.1)	[c]***0.001****
	Mean ± SD	1.62±0.56	1.54±0.57	1.11±0.50		1.64±0.58	1.18±0.50	
Neutrophil (per µm³)	***Min-Max (Median)***	0.7–7.4 (3.2)	1.5–5.7 (3.4)	1.6–14.1 (5.2)	[a]***0.001****	0.7–7.4 (3.2)	1.5–14.1 (4.5)	[c]***0.001****
	Mean ± SD	3.31±1.42	3.50±1.19	5.98±3.36		3.39±1.34	5.22±3.08	
NLR	***Min-Max (Median)***	0.3–9.3 (2)	0.9–5.2 (2.2)	1.8–33.3 (4.9)	[a]***0.001****	0.3–9.3 (2)	1.2–33.3 (3.9)	[c]***0.001****
	Mean ± SD	2.45±1.84	2.52±1.15	6.70±6.75		2.40±1.56	5.51±5.92	
Albumin (g/L)	***Min-Max (Median)***	27.6–48.3 (40.6)	15.2–46 (38.9)	27.8–45 (36)	[b]***0.001****	15.2–48.3 (39.8)	27.8–45 (36.3)	[d]***0.001****
	Mean ± SD	40.59±4.22	38.15±5.07	36.14±3.72		39.61±5.22	36.76±3.58	
Ferritin (µg/L)	***Min-Max (Median)***	3–674 (108)	6.5–1499 (177)	22.4–1631(376.5)	[a]***0.002****	3–1070 (105.5)	22.4–1631 (359.5)	[c]***0.001****
	Mean ± SD	164.26±161.83	283.28±350.41	400.04±335.15		161.60±179.49	416.44±363.66	
PCT (ng/ml)	***Min-Max (Median)***	0–0.4 (0)	0–0.7 (0.1)	0–6.4 (0.1)	[a]***0.001****	0–0.4 (0)	0–6.4 (0.1)	[c]***0.001****
	Mean ± SD	0.07±0.08	0.09±0.12	0.40±1.11		0.06±0.06	0.32±0.93	
CRP (mg/dl)	***Min-Max (Median)***	1–165 (12)	2–148 (27)	14–375 (98.5)	[a]***0.001****	1–165 (16.4)	6.1–375 (83.5)	[c]***0.001****
	Mean ± SD	34.28±41.62	36.99±35.97	116.68±77.89		30.99±34.69	96.97±75.66	

[a]Kruskal-Wallis Test, [b]Oneway ANOVA Test, [c]Mann-Whitney U Test, [d]Student t Test; *p<0.05, **p<0.01.
WBC: white blood cells, NLR: neutrophil to lymphocyte ratio, PCT: procalcitonin, CRP: C-reactive protein.

Table 3. *Comparison of parameters according to clinical condition*

		Clinical condition		*p*
		Mild (n=48)	Moderate + severe (n=46)	
ß-def2 (pg/ml)	***Min-Max (Median)***	9.4–149.8 (29.3)	9.4–130 (43.2)	***0.017****
	Mean ± SD	36.06±23.6	57.42±38.27	
sSPA (pmol/L)	***Min-Max (Median)***	11.8–202.7 (43.1)	18.2–122.8 (52.8)	***0.044****
	Mean ± SD	48.40±28.91	57.23±25.52	
sSPB (ng/L)	***Min-Max (Median)***	65.2–448.9 (159.7)	58.3–457.1 (223.7)	***0.009****
	Mean ± SD	165.73±64.8	230.95±113.28	
rSPA (pmol/L)	***Min-Max (Median)***	0.7–41.4 (13.5)	0.4–39.6 (11.7)	***0.846***
	Mean ± SD	16.65±12.6	15.53±11.17	
rSPB (ng/L)	***Min-Max (Median)***	24.4–135.5 (57.5)	22.7–134.4 (56.5)	***0.676***
	Mean ± SD	70.18±32.19	65.32±29.45	

Mann-Whitney U Test, *p<0.05, **p<0.01.
ß-def2:beta-defensin2, sSPA: serum surfactant protein A, sSPB: serum surfactant protein B, rSPA: respiratory surfactant proteinA, rSPB: respiratory surfactant proteinB.

Table 4. *Comparison of parameters according to thoracic CT involvement*

		Thoracic CT			*p*
		Mild (n=29)	**Moderate (n=33)**	**Severe (n=32)**	
ß-def2 (pg/ml)	***Min-Max (Median)***	15.1–149.8 (32.8)	9.4–92.7 (26.9)	10.4–130 (61.7)	***0.001****
	Mean ± SD	40.69±26.3	32.39±19.59	67.28±40.75	
sSPA (pmol/L)	***Min-Max (Median)***	19–202.7 (46.3)	17.1–82.3 (41.7)	11.8–122.8 (59.5)	***0.005****
	Mean ± SD	55.23±33.35	41.72±15.96	61.94±28.07	
sSPB (ng/L)	***Min-Max (Median)***	79.1–448.9 (175.2)	58.3–245.8 (142.8)	85.5–457.1 (284.9)	***0.001****
	Mean ± SD	184.57±75.84	146.05±47.08	263.74±115.55	
rSPA (pmol/L)	***Min-Max (Median)***	1.2–39.6 (14.4)	0.4–35.9 (11.6)	0.7–41.4 (9.5)	***0.656***
	Mean ± SD	16.64±10.42	15.81±12.02	15.8±13.35	
rSPB (ng/L)	***Min-Max (Median)***	24.4–135.5 (60.4)	22.7–134.4 (57.5)	33–129 (45.3)	***0.447***
	Mean ± SD	71.36±30.95	66.91±32.36	64.89±29.93	

Kruskal-Wallis Test *p<0.05, **p<0.01.
CT: computed tomography, ß-def2:beta-defensin2, sSPA: serum surfactant protein A, sSPB: serum surfactant protein B, rSPA: respiratory surfactant proteinA, rSPB: respiratory surfactant protein B.

Table 5. *Relationship between parameters and laboratory findings*

		ß-def2 (pg/ml)	**sSPA (pmol/L)**	**sSPB (ng/L)**	**rSPA (pmol/L)**	**rSPB (ng/L)**
WBC (per µm^3)	r	0.245	0.276	0.312	-0.035	-0.014
	p	***0.021****	***0.008*****	***0.002*****	***0.745***	***0.897***
Lymphocyte (per µm^3)	r	-0.072	-0.057	-0.106	-0.101	0.022
	p	***0.505***	***0.585***	***0.312***	***0.338***	***0.835***
Neutrophil (per µm^3)	r	0.293	0.271	0.341	0.019	-0.013
	p	0.005**	0.009**	0.001**	0.860	0.904
NLR	r	0.264	0.242	0.322	0.090	-0.013
	p	***0.013****	***0.020****	***0.002*****	***0.394***	***0.902***
PLT	r	0.120	-0.114	-0.115	0.152	0.245
	p	***0.264***	***0.283***	***0.273***	***0.145***	***0.018****
Albumin (g/L)	r	-0.399	-0.243	-0.284	-0.003	0.046
	p	0.001**	0.019*	***0.006*****	***0.976***	***0.661***
Ferritin (µg/L)	r	0.148	0.159	0.158	0.069	0.191
	p	***0.167***	***0.128***	***0.130***	***0.518***	***0.068***
PCT (ng/ml)	r	0.244	0.250	0.256	0.061	0.111
	p	***0.021****	***0.016****	***0.013****	***0.568***	***0.292***
CRP (mg/dl)	r	0.328	0.205	0.307	-0.005	-0.074
	p	0.002**	0.049*	0.003**	0.966	0.485

r: Spearman's correlation coefficient *p<0.05, **p<0.01.
ß-def2:beta-defensin2, sSPA: serum surfactant protein A, sSPB: serum surfactant protein B, rSPA: respiratory surfactant proteinA, rSPB: respiratory surfactant proteinB, WBC: white blood cells, NLR: neutrophil to lymphocyte ratio, PLT: platelet, PCT: procalcitonin, CRP: C-reactive protein.

to those with moderate CT findings (p=0.004). The sSPB measurements of the group with severe CT findings were higher than those of the patients with mild and moderate CT findings (p=0.044, p=0.001, respectively).

According to the thoracic CT findings, no statistically significant difference was determined between the cases in respect of the rSPA and rSPB measurements (p>0.05) (Table 4).

A positive very weak correlation was determined between the ß-def2 measurement and the WBC and PCT measurements (r=0.245; r=0.244; p<0.05), and a positive weak correlation between the ß-def2 measurement and neutrophil, NLR, and CRP values (r=0.293; r=0.264; r=0.328; p<0.05). A negative, weak correlation was determined between the ß-def2 measurement and the albumin value (r=-0.399; p<0.05).

The sSPA measurement was determined to be very weakly positively correlated with the NLR, PCT, and CRP values (r=0.242; r=0.250; r=0.205; p<0.05), weakly positively correlated with the WBC and neutrophil values (r=0.276; r=0.271; p<0.05), and very weakly negatively correlated with the albumin measurement (r=-0.243; p<0.05).

A weak positive correlation was determined between the sSPB measurement and the WBC, neutrophil, NLR, and CRP values (r=0.312; r=0.341; r=0.322; r=0.307; p<0.05), and a very weak positive correlation was determined between sSPB and the PLT and PCT values (r=0.245; r=0.256; p<0.05). There was determined to be a very weak negative correlation between sSPB and the albumin value (r=-0.284; p<0.05). No significant correlation was detected between ß-def2, sSPA, sSPB, rSPA, rSPB measurements and lymphocyte and ferritin levels (Table 5).

Discussion

The results of this prospective study demonstrated a positive correlation between elevated levels of natural immunity proteins (β-def2, sSPA, sSPB) and the known positive acute phase reactants of CRP, PCT, and ferritin in COVID-19 patients defined as clinically and radiologically severe at the time of first presentation at the hospital before the administration of any treatment which could affect the immune system, immune response, or the production of surfactant.

The cytokine storm is known to play a significant role in the clinical status of COVID-19. The development of a cytokine storm is a potentially fatal immune condition characterized by the over-production of more than 150 inflammatory cytokines and chemical mediators expressed by immune or non-immune cells and the rapid proliferation and hyperactivation of T-cells, macrophages, and natural killer cells[20]. Increasing serum levels of ferritin, PCT, and CRP, known to be proinflammatory molecules and correlate with infection severity, were seen in the current study to be statistically significantly higher in patients with a more severe clinical and radiological disease course. Albumin, accepted as a negative acute phase reactant, was significantly lower in the clinically and radiologically more severe COVID-19 patients. As shown in several previous studies, the lymphocyte ratio was lower in the current study of patients classified clinically and radiologically as more severe[21,22].

When an organism faces an endogenous or exogenous threat, the first line of defense is natural immunity[23]. Previous studies have shown that defensins are antibacterial effectors of the natural immune response and function as antiviral peptides[24]. The antibacterial mechanism of antimicrobial peptides, such as defensin, depends on the pathogen being rendered inactive through disrupting the pathogen membrane stability by cationic peptides. In one of the first studies to show this, Daher et al. suggested that the ability of defensin to directly inactivate HSV and other enveloped viruses, including influenza A virus, could be due to the ability of defensin to destabilize viral envelopes[25]. In a study by Kerget et al., which examined the role of defensin in COVID-19, the alpha-defensin level in COVID-19 patients with pulmonary involvement and clinical acute respiratory distress syndrome (ARDS) was higher than in healthy individuals[26]. ARDS is a life-threatening lung injury that allows fluid to leak into the lungs. In the current study, the β-def2 level was significantly higher in clinically severe patients and those with severe radiological involvement.

SPD, a part of the natural immune system, is one of the collectin protein families synthesised by Type 2 alveolar epithelium. In addition to SPD, SPA and SPB target alveolar macrophages, dendritic cells, and T-cells and play an essential role in agglutination, optimisation, and modulation. Previous studies have shown that serum SPD levels increase with disease severity in patients infected with SARS-CoV, a coronavirus similar to that responsible for severe acute respiratory syndrome (SARS)[27–31]. Similarly, in the current study, sSPA and sSPB levels were determined to be high in patients with more severe disease, both clinically and radiologically. In ARDS, there is known to be a disruption in lung surfactant activity and a reduction in content and components of active large surfactant aggregates[32]. In COVID-19 with pulmonary involvement, there is consumption of surfactant with ARDS, the formation of hyalin membrane[33], together with virus-origin lysis of Type II pneumocytes, the formation of ground-glass opacities and bilateral infiltrates radiographically, reduced pulmonary compliance and refractory hypoxemia occurs[34]. Surfactant activity deficiencies can be weakened with an increase in active surfactant concentration[35]. The appropriate administration of exogenous surfactant has proven effective in premature infants with ARDS[36]. There are recommendations for the use of surfactants in the treatment of COVID-19, especially in patients who have developed clinically severe ARDS[37].

In the current study, rSPA and rSPB tended to be lower, although not at a level of statistical significance, in clinically severe patients and those with severe radiological involvement. The reason for this could be that the alveolar surfactant level was examined at the time of diagnosis, that no sample was taken when the

clinical status of ARDS progressed and that samples taken were not entirely from the alveoli (a method such as bronchoalveolar lavage was not used).

This study had some limitations, primarily that samples were only taken on presentation before administering any medication or treatment that could affect cytokines and blood levels. Therefore, changes in the parameters examined at advanced stages of the disease were unknown. One of the limitations of our study was that there was no COVID-negative control group. The whole world has been affected by COVID-19 for nearly two years, and for new developments in the treatment and prevention of COVID-19, real-life data would be of help in determining the pathways which play a role in the pathogenesis of the disease. Therefore, there is a need for furthermore extensive studies in this area.

In conclusion, the results of this study demonstrated that ß-def2, sSPA, and sSPB values were significantly higher in clinically severe patients and those with severe pulmonary involvement. In patients with severe disease, rSPA and rSPB levels showed a tendency to be lower, although not statistically significant. When it is considered that the serum surfactant level is low in an ARDS table and it is even recommended to administer surfactant to patients in treatment, that the rSPA and rSPB values were not statistically significantly low could be a sign that they could fall further in advanced stages of the disease.

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Authors' Contributions

Constructing an idea or hypothesis for the research and literature review: GSE, NI; Designing and planning methodology: GSE, NI; Providing material and environmental supports and data collection: RK, KKY, MEI, PK, TST; Analysis and interpretation: GSE, NI, PK, SKT, TST; Writer, supervision and critical review: GSE, PK, TST, RK, MEI, SKT, KKY, NI.

Conflict of Interest

We declare that there is no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Food Neophobia and Disgust Sensitivity in Medical Students

Tıp Fakültesi Öğrencilerinde Gıda Neofobisi ve Tiksinme Duyarlılığı

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ABSTRACT

Aim: *Food neophobia, the avoidance of trying new flavours, is increasingly observed in the globalised world. There may be different reasons underlying food neophobia, which can be considered both as a personality trait and a symptom. In our study, we aimed to explore the relationship between food neophobia and disgust sensitivity in medical students.*

Material and Method: *A total of 163 Recep Tayyip Erdoğan University Faculty of Medicine students who were continuing their education in the 2022–2023 academic year between 01.04.2023 and 01.07.2023 were included in the research. Sociodemographic data form, Food Neophobia Scale (FNS), Disgust Sensitivity Scale Revised Form (DSS-R) were applied online to all participants*

Results: *DSS-R (mean=48.07±10.447) in females was statistically significantly higher than male gender (mean=43.8±9.57). (p=0.01). There was no significant difference between the FNS levels of the female and male genders (p=0.911). A significant positive correlation was found between DSS-R and FNS (p=0.08 r=0.208).*

Conclusions: *There is a positive relationship between disgust sensitivity and food neophobia. It is important to explore the underlying factors of food neophobia, which may lead to significant nutritional problems. Disgust sensivity can be a cause of food nephobia. New research is needed on food neophobia leading to malnutrition and obesity in older age.*

Keywords: *food neophobia; disgust sensitivity; medical students*

ÖZET

Amaç: *Yeni tatları denemekten kaçınma olarak tanımlanan gıda neofobisi küreselleşen dünya ile birlikte giderek daha fazla gözlenmektedir. Hem bir kişilik özelliği hem de bir semptom olarak ele alınabilecek olan gıda neofobisinin altında yatan farklı sebepler bulunabilir. Araştırmamızda tıp fakültesi öğrencilerinde gıda neofobisi ile tiksinme duyarlılığının ilişkisinin araştırılması amaçlanmıştır.*

Materyal ve Metot: *Araştırmaya 01.04.2023 – 01.07.2023 tarihleri arasında 2022–2023 eğitim ve öğretim döneminde eğitimlerini sürdürmekte olan toplam 163 Recep Tayyip Erdoğan Üniversitesi Tıp Fakültesi öğrencisi dâhil edilmiştir. Tüm katılımcılara Sosyodemografik özellikler veri formu, Gıda Neofobisi Ölçeği (GNÖ), Tiksinme Duyarlılığı Ölçeği Revize Formu (TDÖ-R) çevrimiçi olarak uygulanmıştır*

Bulgular: *Kadın cinsiyette TDÖ-R (ort=48,07±10,447) erkek cinsiyetten (ort=43,8±9,57) istatistiksel olarak anlamlı olarak yüksek saptanmıştır. (p=0,01). Kadın ve erkek cinsiyette GNÖ düzeyleri arasında anlamlı farklılık elde edilmemiştir (p=0,911). TDÖ-R ile GNÖ arasında pozitif yönde anlamlı bir ilişki saptanmıştır (p=0,08 r=0,208).*

Sonuç: *Tiksinme duyarlılığı ile gıda neofobisi arasında pozitif bir ilişki mevcuttur. Önemli beslenme sorunlarına yol açabilecek olan gıda neofobisinin altta yatan faktörlerinin araştırılması önemlidir. Tiksinme duyarlılığı gıda nefobisinin bir nedeni olarak ele alınabilir. Özellikle yetişkinlik döneminde beslenme yetersizliği, obezite gibi sağlık sorunlarına yol açabilen gıda neofobisi ile ilgili yeni araştırmalara ihtiyaç duyulmaktadır.*

Anahtar kelimeler: *gıda neofobisi; tiksinme duyarlılığı; tıp öğrencileri*

Introduction

Food neophobia (FN) is defined as the fear of trying new foods. People with FN avoid trying new and unfamiliar foods[1]. Humans are classified as both carnivores and herbivores. People who are defined as omnivores always tend to reject new foods. This may be due to factors such as the appearance, colour, smell, shape of the food source, as well as the possibility that it may be harmful. These factors create an emotion towards the food source, which leads to the acceptance or rejection of the food[2]. However, in addition to these feelings, omnivores also desire to feed and have the instinct to maintain the continuity of life. This has been described as the 'omnivore' s paradox', which is the desire

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to avoid new foods as well as the desire to find new foods[3]. FN is observed in its most severe form between 2–6 years of age. It is common for babies to exhibit negative attitudes towards new flavours, especially when they are weaned from breast milk and switched to additional foods. These negative attitudes decrease with age. Sometimes, however, rejection of new foods can persist into adulthood. Although FN is frequently observed in childhood, it may also be encountered as a nutritional problem in adulthood[4]. Knowledge about the aetiology of FN is still limited. Although it is defined as a personality trait, it has been suggested that genetic factors also play a role in its aetiology[5]. There are no specific diagnostic criteria for FN and it is not included in any diagnostic system. For this reason, it increases the risk of FN being overlooked[6,7].

Disgust sensitivity can be defined as the feeling of discomfort and disgust when a person comes into contact with a certain situation or object[8]. This feeling protects people from the unknown, such as neophobia. It is more related to physical transmission. It is caused by stimuli such as odour, food, body parts, insects, sexuality. However, in addition to physical contamination, there was also a social and moral aspect[9]. Disgust sensitivity has been associated with mental illnesses, mostly eating disorders. This disturbing unpleasant feeling can affect food preferences[10]. There are studies indicating that there is a relationship between FN and disgust sensitivity. In a recent study, factors related to the decision to taste a new food were examined. Accordingly, emotional, sensory and cognitive factors associated with FN were identified. It has been suggested that reactions to food are combined with cognitive associations based on negative memories and negative beliefs[4]. Food neophobia has been well explored in children but not sufficiently in adults. Studies on FN have mostly been carried out with children in the early age group, and information on adulthood is limited in the literature[4,11,12]. In recent studies conducted with different countries and groups, it is remarkable that FN has increased rapidly[13,14].

Food neophobia may cause nutritional problems, depressive symptoms, inability to participate in tourism activities, inability to visit new places to try new flavours. While the increase in gastronomy tourism provides the opportunity to meet different flavours for many people, this situation is considered as a limitation for people with FN[15]. On the other hand, the global population, which is expected to reach 10 billion by 2050, climate crisis, scarcity of resources for natural food production have led to changes in nutrition and lifestyle[16]. Especially with the development of gastronomy science, eating habits are changing daily. However, it is not clear whether consumers are ready for changes in the food industry. To date, there are studies investigating FN involving tourism and hotel management students and tourists[17,18]. Therefore, there is a need for studies investigating the attitudes and behaviours of different professional and cultural groups towards FN.

In our study, we hypothesized that there might be a relationship between GN and disgust sensitivity. Faculty of Medicine students were preferred as the research sample. It is assumed that medical faculty students are more open to innovation, use more social media, and interact more with the world. Also health-related lectures may influence food choices[19,20]. As far as we know, although there are studies conducted with similar samples in the world, our research is a first in Türkiye[21]. The study is thought to will significantly contribute to the literature on FN, which is a new definition and of increasing importance.

Material and Method

Our study was conducted at Faculty of Medicine between 01.04.2023 and 01.07.2023. A total of 163 students studying in the 2022–2023 academic year were included in the study. An online form containing the scales to be used in the study was sent to the medical faculty students together with a consent document indicating that they approved to participate in the study. The students approved to participate in the study and filled out the forms online. People with any mental illness, alcohol and substance abuse, chronic internal diseases such as diabetes and hypertension were excluded from the study. Four students were excluded from the study because they reported a diagnosis of mental illness. The ethics committee approval of the research was obtained. In addition, all practices in the study were conducted in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its subsequent revisions or comparable ethical standards.

Data Collection Tools

Sociodemographic Data Form: It is a form created by the researchers that questions basic sociodemographic data such as name, age and gender. In addition to sociodemographic data, medical information such as the

presence of mental illness, medication use, family history of mental illness, presence of chronic illness and regular medication use were also questioned.

Food Neophobia Scale (FNS): It is a Likert-type scale consisting of 10 items developed to determine the level of food neophobia. Scale answers are scored as "strongly disagree" 1 and "strongly agree" 5. Increasing scores were considered as increasing level of food neophobia and developed by Pliner and Hobden in 1992[22]. Turkish validity and reliability was performed by Duman et al. In the validity and reliability analysis conducted in the Turkish sample, Cronbach's alpha value was found to be 0.614 and the scale was reported usable in the Turkish sample. In our research sample, the Cronbach's alpha value of the scale was calculated as 0.72[23].

Disgust Sensitivity Scale Revised Form (DSS-R): It is a 16-question scale developed by Overveld et al. to examine the feeling of disgust and the level of reaction. It is calculated as never 1 point, rarely 2 points, sometimes 3 points, often 4 points and always 5 points. Increasing scores are associated with increasing levels of disgust sensitivity[24]. Turkish validity and reliability was performed by Arusoğlu and Cronbach's alpha was calculated as 0.916 in the Turkish sample. In our sample, Cronbach's alpha value was calculated as 0.82[25].

Statistical Analysis

Statistical evaluation of the research data was performed with IBM Statistical Package for Social Sciences (SPSS) program version 25. Descriptive statistics are presented with mean and standard deviation values and percentages, minimum maximum values. The normality of the data was evaluated by Kolmogorow Smirnow test. The comparison between two normally distributed groups was evaluated by Independent Sample t test. The comparison between more than two not normally distributed groups was evaluated by kruskal wallis test. Spearman Correlation test was performed in the correlation of continuous data that are not normally distributed and statistical significance level was accepted as $p<0.05$.

Results

A total of 163 participants, 103 (63.2%) female and 60 (36.8%) male, were included in the study and all participants were medical faculty students. The research sample consists of 57 (35%) term 1, 29 (17.8%) term 2, 9 (5.5%) term 3, 24 (14.7%) term 4, 18 (11%) term 5, 26 (16%) term 6 students. One hundred thirty seven (84.1%) participants had no family history of mental illness, while 26 (15.9%) participants had a family history of mental illness (Table 1). When the relationship between the sociodemographic data of the participants and the scale scores was analysed, FNS total score of the female gender (mean=48.07±10.447) was statistically significantly higher than the total score of the male gender (mean=43.8±9.57) (p=0.01). No statistically significant relationship was found between other sociodemographic data and scale scores (Table 2). When the relationship between DSS-R and FNS scores is analysed, there is a significant positive relationship between the total scores obtained from DSS-R and total scores obtained from FNS (p=0.008; r=0.208). While there was a significant positive correlation between the total scores obtained from the DSS-R and the scores obtained from the FNS-confidence new foods subdimension (p=0.001; r=0.269), no significant correlation was found between the scores obtained from the DSS-R and the FNS-willingness to try new foods subdimension (p=0.25; r=0.091) (Table 3).

Discussion

In our study, the relationship between FN and disgust sensitivity in medical school students was explored. 63.2% of the participants are female. While the sensitivity of disgust was found to be higher in women, there was no difference in FN levels between male and

Table 1. *Sociodemographic data of participants*

		min-max	med ± SD
Age		18–26	21.39±1.9
		n	%
Gender	Female	103	63.2
	Male	60	36.8
Term	Term 1	57	35
	Term 2	29	17.8
	Term 3	9	5.5
	Term 4	24	14.7
	Term 5	18	11
	Term 6	26	16
Presence of mental illness in the family	No	137	84.1
	Yes	26	15.9
Diagnosis of mental illness in the family	Depression	10	6.1
	Anxiety disorder	9	5.5
	Schizophrenia	1	0.6
	Bipolar disorder	3	1.8
	Obsessive-compulsive disorder	3	1.8
Total		163	100

Table 2. *Relationship between sociodemographic characteristics and scale scores*

			FNS Total	FNS confidence new foods	FNS willingness to try new foods	FNS Total
Age		r	-0.098	-0.09	-0.057	-0.053
		p	0.212	0.254	0.469	0.499
Gender	Female	n	103	103	103	103
		Mean ± SD	28.03±4.94	16.77±2.78	11.26±2.762	48.07±10.447
	Male	n	163	163	163	163
		Mean ± SD	28.12±4.574	16.72±2.669	11.4±2.546	43.8±9.57
		Test stat.	-0.112	0.113	-0.316	2.593
		p	0.911	0.91	0.752	**0.01***
Presence of mental illness in the family	Yes	n	26	26	26	26
		Mean ± SD	27.96±5.024	16.81±2.994	11.15±3.029	48.96±9.084
	No	n	137	137	137	137
		Mean ± SD	28.08±4.768	16.74±2.691	11.34±2.616	46.03±10.494
		Test stat.	0.115	-0.12	0.329	-1.332
		p	0.908	0.904	0.742	0.185
Term	1	n	57	57	57	57
		med (IQR)	28(6)	17(4)	12(3)	46(15)
	2	n	29	29	29	29
		med (IQR)	29(5)	18(4)	11(3)	47(15)
	3	n	9	9	9	9
		med (IQR)	25(10)	17(6)	11(5)	54(19)
	4	n	24	24	24	24
		med (IQR)	30(8)	17.5(3)	11.5(4)	48(16)
	5	n	18	18	18	18
		med (IQR)	26.5(7)	16(4)	11(3)	45(13)
	6	n	26	26	26	26
		med (IQR)	26(7)	15.5(4)	11(2)	45.5(15)
		test stat.	6.125	4.68	2.899	1.774
		p	0.294	0.456	0.716	0.879

Independent sample t-test, Kruskal-Wallis test, Spearman Correlation, *p<0.05.
FNS: Food Neophobia Scale, IQR: Interquartile range

Table 3. *The relationship between disgust sensitivity and food neophobia*

		FNS total	FNS confidence new foods	FNS willingness to try new foods
DSS-R total	r	**0.208**	**0.269**	0.091
	p	**0.008***	**0.001***	0.25

Spearman Correlation, *p<0.01.
FNS: Food Neophobia Scale, DSS-R: Disgust Sensitivity Scale Revised Form

female genders. In studies similar to our study, a higher level of disgust sensitivity was found in the female gender. While disgust sensitivity in women is more associated with eating disorders, it has also been suggested that another reason why disgust sensitivity is higher than in men may be related to progesterone[26,27]. When studies investigating the relationship of GN with sociodemographic characteristics and gender are examined in the literature, there are inconsistencies between genders. In a study by Smith et al., higher FN levels were found in women[28]. In another study conducted in the same way, higher levels of FN were reported in women [21]. Although studies are reporting that men have high levels of avoidance of new foods, there are also studies stating that there is no relationship between FN and gender[29,30]. However, it has been suggested that women may be genetically predisposed to FN to protect their offspring from foreign foods since they are evolutionarily carrying and nurturing the offspring[31]. Our study, no relationship was found between age and FN and disgust sensitivity. As a result of research, it is thought that FN symptoms decrease with increasing age[32,33]. In a study by Sahrin et al., it was stated that age did not affect FN levels[21]. In another study conducted in the

same way, no relationship was found between age and FN[30]. These results are consistent with our research. Although data such as economic level, education level, and living space are found to be related to FN in studies, there are also data indicating that FN may have a genetic basis[5,34,35]. However, these parameters were not analysed in detail in our study. In this case, it was thought that FN might also be associated with a mental disorder. The mental disorder in which FN was most explored as a symptom was autism spectrum disorders (ASD). In many studies, FN was found to be high in individuals with ASD[12,36,37]. Individuals diagnosed with ASD have common eating problems, including refusal to eat, dietary restrictions, and behavioral problems while eating. It has been reported that individuals with ASD and FN prefer spices, candies with a strong mint flavor, and foods with a similar texture such as applesauce, cheese, peanut butter. In addition, individuals with a diagnosis of ASD with FN had a lower daily living skill score than individuals with a diagnosis of ASD without a FN. Another study showing that children with ASD are more selective than other children stated that FN seems to be a sensory feature most associated with atypical oral sensitivity, eating disorders[34]. Another medical condition for which FN has been explored is obesity. Food neophobia is considered both a cause and a consequence of the development of obesity. Obese individuals have higher FN levels and obese men have lower taste sensitivity. Obese individuals with high FN levels prefer to consume traditional foods with high energy density compared to individuals with normal weight, and this results in weight gain. Although FN reduces diet diversity, it increases the risk of obesity, especially due to vitamin and mineral deficiencies. Obese individuals are also more prone to foods high in fat and sugar. As a result of obesity, individuals preferred traditional high-calorie foods and decreased their desire to try new foods and developed FN[35,36].

In our study, a significant positive correlation was also found between FN and disgust sensitivity. In the studies conducted, a positive correlation was found between FN and disgust sensitivity, similar to our study[37,38]. Food neophobia is associated with sensory responses to foods that are considered particularly repulsive. In addition, individuals with high levels of disgust are more cautious about new foods[39]. In the light of all the literature, it can be thought that the sensitivity of disgust plays an important role in the development of FN. The appearance, colour and smell of food affect the disgust sensitivity. In adults, the sense most strongly involved in the development of FN is smell. People with FN are less developed than the general population to perceive odors (either related to food or not) as pleasant and intense. There are also studies that mention possible relationships between FN olfactory performances and oral microbiota[40].

Food neophobia can cause nutritional deficiencies or social exclusion. It is known that individuals with high FN levels prefer less healthy foods such as fruits, vegetables, protein and have low dietary quality. This can cause serious nutritional disorders over time. Food neophobia in adults appears to be affected by different factors. Delayed perception of satiety in adults is associated with failures in the regulation of energy intake. Dietary diversity and fruit and vegetable consumption decrease with FN[15]. Investigation of FN, which can cause important nutritional problems, systematization of its clinical findings, is valuable in terms of symptom recognition.

In our study, the relationship between FN and disgust sensitivity was explored in a specific population. Geography of individuals, culinary culture, eating habits, experiences and country conditions affect FN levels and may cause changes in FN levels. In the globalizing world, people are now able to reach much more new tastes. Food neophobia may also cause situations such as not preferring more sustainable and ecological foods developed with the help of technology. Attitudes towards a new food; Although FN is characterized as an individual condition that can affect food choice and consumption, FN can also be considered as a symptom of mental disorders. Studies investigating the relationship between mental disorders and FN are limited in the literature. In particular, its relationship with mental disorders still remains confidential.

Our study has some limitations. The findings of the study cannot be generalized to all medical school students since the participants were selected from only one medical school. In addition, the relatively small sample size, the online application of questionnaires and scales to the participants, and the lack of structured psychiatric interviews are also among the limitations of the study. In addition, not questioning the body mass index, eating habits and food preferences of the participants can also be considered as a limitation. However, the fact that the relationship between FN and disgust sensitivity was explored in a specific group

is the strength of the study and may guide future studies in terms of its results.

As a result, FN, which is generally observed as fear, withdrawal and reluctance to try new foods in individuals, is increasing rapidly all over the world. Although fear of novelty in food protects the individual against the potential harms of the new food, over time it can limit the individual's nutritional cycle and cause serious nutritional problems and psychosocial problems. More research is needed to elucidate the cultural, genetic aspects, risk factors and neurobiology of FN. Studies investigating whether FN is associated with certain food groups and its relationship with developmental periods will provide a better understanding of the subject. In addition, it is important to be noticed about prevention and precautions, especially in childhood, to make the necessary appropriate interventions, to inform individuals about food, and to increase the awareness of those working in the food sector about FN. Providing adults with education on FN and quality of life can prevent FN behavior disorder and gain a wide range of dietary habits.

Author Contributions

Idea: ÇH, MP; Design And Design: ÇH, MP, BAT; Counselling: MP, BAT; References: MP, MB; Data Collection: BAT; Analysis And Comment: MP, BAT, ÇH; Literature Review: MP, ÇH; Final Review: MP, ÇH

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Unpleasant Traumas of Orthopedics: Firearm Wounds

Ortopedinin Sevimsiz Travmaları: Ateşli Silah Yaralanmaları

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ABSTRACT

Aim: *This study aimed to examine the clinical outcomes of patients presenting with gunshot wounds who were hospitalized in the orthopedic clinic in the last five years.*

Material and Method: *The study is a retrospective study with 41 patients. Gender, age, length of hospitalization, injured extremities and regions, presence of fractures and distribution of fractured bones, need for surgery, need for other specialties, distribution of different specialties, additional injuries and complications, and their distribution were investigated.*

Results: *The mean age of the patients was 39.76±12.77. 92.70% (n=38) of the patients were male, and 7.30% (n=3) were female. The mean duration of hospitalization among the patients was 5.68±3.38 days. It was observed that 80.50% (n=33) of the patients had the most injuries in the lower extremities. 70.70% (n=29) of the patients had a fracture accompanying the firearm injury. The femur was the most commonly fractured bone. Surgery was required in 82.90% (n=34) of the patients. 53.70% (n=22) of the patients had additional injuries and complications.*

Conclusion: *Firearm injuries are an increasingly frequent and severe orthopedic injury, especially with the increase in individual armament. Therefore, emergency and orthopedic physicians should be equipped for early and effective intervention.*

Key words: *gunshot wounds; orthopedics; trauma*

ÖZET

Amaç: *Bu çalışmada son beş yılda ortopedi kliniğinde yatarak tedavi gören ateşli silah yaralanması olan hastaların klinik sonuçlarının değerlendirilmesi amaçlandı.*

Materyal ve Metot: *Araştırma 41 hasta ile yapılan tanımlayıcı bir çalışmadır. Hastaların cinsiyetleri, yaş ve hastanedeki yatış süreleri, yaralanan ekstremiteler ve bölgeler, kırık varlığı ve kırık tespit edilen kemiklerin dağılımları, cerrahi gereksinim varlığı, diğer branşlara gereksinim varlığı, gereksinim duyulan diğer branşların dağılımları, ek yaralanma ve komplikasyon durumları ve dağılımları incelenmiştir.*

Bulgular: *Hastaların %92,70'i (n=38) erkek iken, %7,30'u (n=3) kadındır. Hastaların yaş ortalaması ve standart sapması 39,76±12,77 yıldır. Hastaların yatış sürelerinin ortalaması ve standart sapması 5,68±3,38 gündür. Hastalarda en fazla yaralanmanın %80,50'si (n=33) alt ekstremite bölgesinde olduğu görülmüştür. Hastaların %70,70'inde (n=29) ateşli silah yaralanmasına eşlik eden kırık mevcuttur. En fazla kırılan kemiğin femur olduğu görülmüştür. Hastaların %82,90'nında (n=34) cerrahi gereksinim duyulmuştur. Hastaların %53,70'inde (n=22) ek yaralanma ve komplikasyon mevcuttur.*

Sonuç: *Ateşli silah yaralanmaları günümüzde özellikle bireysel olarak silahlanmanın artması ile sıklığı giderek artan ve ciddi ortopedik yaralanmaya sebep olan bir yaralanmadır. Bu sebeple acil servis ve ortopedi hekimleri erken ve etkili müdahale için donanımlı olmalıdır.*

Anahtar kelimeler: *ateşli silah yaralanmaları; ortopedi; travma*

Introduction

Firearm injuries (FAI) are a preventable forensic public health issue worldwide, and since firearms are readily available, these types of injuries have significantly increased in recent years[1,2]. Firearms are frequently used for purposes such as hunting, defense, assault, terrorism, security, etc. in today's world. Firearms are classified as short-barreled and long-barreled, while injuries caused by them are categorized as low-energy and high-energy injuries. Firearm injuries that are contaminated and high-energy injuries are related to more excellent rates of death and disability. In the United States (US), these cases are the second most prevalent cause of mortality in the second decade of a person's life following traffic accidents[3]. In a similar epidemiological study, it is stated that the number of cases resulting in death after FI in the US reaches 100.000 annually, and nearly more than 50% of these cases have extremity injuries[4]. In Türkiye,

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FAI is a significant cause of deaths and morbidities as a result of the fight against terrorism and personal injuries. Every year in Türkiye, more than 2000 people die, and more than 3000 people are injured by firearm injuries[5]. Firearm injuries is most prevalently encountered in the extremities and most frequently in soft tissue injuries in the body[6]. Although they are not as mortal as head and neck injuries, the risk of causing sequella in extremities is higher. The severity of the injury can vary based on the type of firearm, the distance from which the shot was fired, and the characteristics of the bullet and the affected region. Depending on the severity of the injury, extensive soft tissue injuries, neurovascular injuries, joint injuries, and fragmented, segmental, or defective fractures may occur in the extremities. The treatment of FAI requires a multidisciplinary approach. Treating high-energy and contaminated FAI is very difficult, and the process may be lengthy and costly. The treatment aims to prevent bone and soft tissue infections, ensure union if there is a fracture, and promote early mobilization and functional recovery. Irrigation, debridement, and antibiotic prophylaxis are employed to prevent diseases, while external fixation methods are used in fracture fixation, but internal fixation methods are also applied. Complications may be inevitable in complex, high-energy, and contaminated cases, even with the most optimal treatment methods. Complications such as neurovascular injuries, osteomyelitis, pseudoarthrosis, osteoarthritis, amputation, and posttraumatic stress disorder may develop. This study aims to investigate the clinical outcomes of cases presenting with firearm injuries who have received in-patient treatment at the orthopedic clinic in the last five years.

Materials and Methods

The research is a retrospective study conducted with 41 cases who were admitted to the Department of Orthopedics and Traumatology at the Medical Faculty Hospital of Kafkas University due to firearm injuries between January 2017 and January 2022. Forensic cases without firearm injuries, those not admitted to the Orthopedics and Traumatology Department, and the data of patients who died were not included in the analyses. The study examined the gender, age, and hospitalization of the patients, injured extremities and regions, presence of fractures and distribution of fractured bones, need for surgery, need for other branches, distribution of other branches needed, additional injuries, and the occurrence and distribution of complications.

The study utilized frequency (n) and percentage values for qualitative (categorical) variables. At the same time, mean, standard deviation, median, 1st and 3rd quartiles, and minimum and maximum values were used for quantitative (continuous) parameters. The statistical analyses were conducted with the Statistical Package for the Social Sciences (SPSS –IBM Statistical Package for Social Sciences program, version 21).

All patients gave informed consent. The Ethics Committee of Kafkas University Faculty of Medicine approved the study in session number 02, dated 23/02/2022, with protocol number 80576354-050-99/22. The study was conducted in compliance with the Declaration of Helsinki.

Results

The study sample included 41 patients in total. While 92.70% (n=38) of the patients were male, 7.30% (n=3) were female. The mean age of the cases was 39.76±12.77, the median and 1st Quartile – 3rd Quartile was 39.00 [28.00–48.50] years, the youngest age was 21.00 years and the oldest age was 69.00 years. Of the hospitalization duration of the patients, the mean and standard deviation were 5.68±3.38 days, the median and 1st Quartile-3rd Quartile were 4.00 [3.00–7.00] days, the shortest one was 3.00 days, and the longest one was 17.00 days (Table 1).

80.50% (n=33) of the patients were injured in the lower extremity and 19.50% (n=8) in the upper extremity. When the injured regions were examined, it was observed that 36.60% (n=15) of the patients had injuries in the femur, 29.30% (n=12) in the cruris, and 12.20% (n=5) in the arm region (Table 2).

In 70.70% (n=29) of the patients, there was a fracture accompanying the firearm injury. In the examinations

Table 1. *Characteristics of the patients who have received in-patient treatment due to firearm injuries*

Variables	n (%)
Gender	
Female	3 (7.30)
Male	38 (92.70)
Age (Years)	
Mean ± Standard deviation	39.76±12.77
Median [1st Quartile-3rd Quartile]	39.00 [28.00–48.50]
Minimum-maximum	21.00–69.00
Duration of hospitalization (days)	
Mean ± Standard deviation	5.68±3.38
Median [1st quartile – 3rd quartile]	4.00 [3.00–7.00]
Minimum-maximum	3.00–17.00
Total	41 (100.0)

Table 2. *Extremity injuries of the patients who have received in-patient treatment due to firearm injuries and the distribution of the injured regions*

Variables	n (%)
Injured extremity	
Upper extremity	8 (19.50)
Lower extremity	33 (80.50)
Injured regions*	
Shoulder	3 (7.30)
Arm	5 (12.20)
Elbow	2 (4.90)
Forearm	3 (7.30)
Wrist	1 (2.40)
Inguinal region	1 (2.40)
Hip	2 (4.90)
Gluteal region	2 (4.90)
Femur	15 (36.60)
Knee	3 (7.30)
Cruris	12 (29.30)
Ankle	4 (9.80)
Foot	2 (4.90)

Table 3. *Presence of accompanying fracture in the patients who have received in-patient treatment due to firearm injuries and distribution of bones with fractures*

Presence of fracture	
Yes	29 (70.70)
No	12 (29.30)
Bone with fracture*	
Femur	8 (19.50)
Tibia	7 (17.10)
Fibula	4 (9.80)
Calcaneus	1 (2.40)
Talus	1 (2.40)
Navicula	1 (2.40)
Metatarsus	1 (2.40)
Scapula	1 (2.40)
Humerus	7 (17.10)
Ulna	2 (4.90)
Radius	3 (7.30)

* There are patients with fractures in more than one bone.

of bones with fractures, it was observed that the femur was affected in 19.50% (n=8) of the patients, tibia in 17.10% (n=7), and fibula in 9.80% (n=4) (Table 3).

Surgery was required in 82.90% (n=34) of the patients. Other branches were needed in 12.20% (n=5) of the patients. The most frequently required other branches were general surgery and cardiovascular surgery (Table 4).

There were additional injuries and complications in 53.70% (n=22) of the patients. In the examinations of these additional injuries and complications, it was seen that osteoarthritis developed in 29.30% (n=12) of the patients with firearm injury, joint injury caused by the firearm injury was detected in 24.40% (n=10), and nonunion was detected in 12.20% (n=5). Brachial artery injury was detected in one patient, and amputation was performed (Table 5).

Table 4. *Need for surgery and other branches for the patients who have received in-patient treatment due to firearm injuries and distribution of other branches needed*

Variable	n (%)
Need for surgery	
Yes	34 (82.90)
No	7 (17.10)
Need for other branch	
Yes	5 (12.20)
No	36 (87.80)
Other branches needed*	
General surgery	3 (7.30)
Cardiovascular surgery	3 (7.30)
Urology	2 (4.90)
Plastic, reconstructive and aesthetic surgery	2 (4.90)
Brain and nerve surgery	1 (2.40)

* There are patients with fractures in more than one bone.

Table 5. *Additional injuries and complication distribution of the patients who have received in-patient treatment due to firearm injuries*

Variables	n (%)
Additional injury and complication	
Yes	22 (53.70)
No	19 (46.30)
Additional injuries and complications*	
Tendon injuries	2 (4.90)
Osteomyelitis	2 (4.90)
Osteoarthritis	12 (29.30)
Joint damage caused by the injury	10 (24.40)
Non-union	5 (12.20)
Arterial injury	2 (4.90)
Ulnar nerve injury	4 (9.80)
Median nerve injury	3 (7.30)
Radial nerve injury	3 (7.30)
Amputation	1 (2.40)

* There are patients with fractures in more than one bone.

Discussion

Firearms have always attracted humankind's attention. Today, various types of weapons are used for defense, attack, and hunting[7]. As it becomes easier to obtain firearms, the cases of injuries and deaths caused by firearms are observed more frequently[8].

The gender, age, and hospitalization duration of the patients with firearm injuries who have received in-patient treatment at the orthopedic clinic in the last five years, injured extremities and regions, presence of fractures and distribution of fractured bones, need for surgery, need for other branches, distribution of other branches needed, additional injuries, and the occurrence and distribution of complications were examined in this study.

It has been reported that firearm injuries are observed chiefly in males and usually in the lower extremities[9]. In their study evaluating 112 cases of FAI over a decade of

experience, Dodge et al. reported that the most common etiological cause was suicide (31%), 20% of the cases resulted in death, and the rate of lower extremity injury (25%) was higher than that of upper extremity injury (25%)[10]. Halanski and Corden reported that orthopedic treatment was required in 79% of the cases, and 95% of the cases were male. Their study included 24 cases with ISS scores ranging from 1–50 about FAI during the hunting season[11]. In their study in which they evaluated 60 civilian patients regarding extremity FAI, Burg et al. reported that bone fractures were observed in 36 patients, and 75% of these fractures were in the lower extremities[12]. In their study in which they evaluated 38 FAI patients, Özerdemoğlu et al. reported that male patients (95%) were more common, and 56% of the injuries were in the lower and 46% in the upper extremities[13]. In our study, according to the literature, the patients were predominantly male (92.7%), and lower extremity injuries were more common (80.5%).

Depending on the type and severity of the injury, extremity FAI injuries are associated with isolated soft tissue injury, bone fracture, neurovascular injury, and complications up to amputation[14]. Type 3 injuries, which generally cause serious problems, are more frequently observed, and fractures and other associated injuries are often seen in type 3 injuries, usually resulting in poor functional recovery[12]. Özerdemoğlu et al. reported encountering infections in six cases and union-related problems in 12 cases among the 38 patients they studied[13].

The extremity preservation rate in the literature is reported to be between 81–97%[13]. Arterial injuries lead to high morbidity and amputation rates. In this type of injury, the presence of additional pathologies in patients, accompanying bone pathologies, and late delivery of patients to the hospital may increase these rates. It is reported that they lead to amputation by 27–54% in popliteal artery injuries[15]. On the other hand, aggressive wound debridement, irrigation, examination of the wound for pellet and stopper (plugs, felt), and adequate fracture fixation should be ensured in the early period due to the high incidence of infection and nonunion in FAI[13]. Esenkaya et al. emphasized the significance of removing the stopper in FAI[16].

Following the initial evaluation in the emergency department, we applied wound irrigation, broad-spectrum antibiotics, tetanus prophylaxis, and adequate debridement of devitalized tissues to all patients we followed in our study. It tried to explore and remove as many pellets, plugs, felt, and bullets as possible. Plugs were identified in two of the three cases where infections developed. The extremity preservation rate we found was 97.5%, higher than the one reported in the literature. On the other hand, one patient with an arterial injury was amputated at the elbow level. Additionally, the most significant factors that prolong the duration of hospitalization were identified as infections and arterial injuries.

Stucky et al. reported that there were 29 bone fractures in 37 cases injured by firearms; two of them developed superficial wound infections, and all patients recovered except those who encountered undesirable conditions[17]. In our study, 70.70% (n=29) of the patients had fractures accompanying firearm injuries. When the injured areas were examined, it was observed that the femur was affected in 36.60% (n=15) of the patients, the cruris in 29.30% (n=12), and the arm region in 12.20% (n=5) (Table 2). When the bones with fractures were examined, it was found that the femur was affected in 19.50% (n=8) of the patients, tibia in 17.10% (n=7), and fibula in 9.80% (n=4) (Table 3).

In firearm injuries, the high velocity of the arms creates problematic fractures in the human body. Many studies have reported favorable outcomes for treating fractures and pediatric extremity injuries[18]. In their research, Washington et al. reported that wound infection developed in only five patients, osteomyelitis did not occur, and all recovered, although one of the cases was grafted[17]. In our study, 53.70% (n=22) of the patients had additional injuries and complications. When these additional injuries and complications were examined, it was seen that osteoarthritis developed in 29.30% (n=12) of the patients with firearm injury, joint injury caused by the firearm injury was detected in 24.40% (n=10), and nonunion was detected in 12.20% (n=5). Brachial artery injury was detected in one patient, and amputation was performed (Table 5).

Advanced tissue damage may not be seen in injuries frequently encountered in the upper extremities. While fractures and joint damage are commonly observed in hand injuries, vascular and nerve injuries are relatively less common[19]. However, most of the amputations in the upper extremity are traumatic amputations[20]. In our study, one patient was amputated at the elbow level due to brachial artery injury.

In the study by Khatri et al. that included 29 patients, all cases were male patients with a mean age of 33 years (22–48). The mechanism of injury in all cases was

high-velocity firearm injury; 3 of 29 patients had arterial injuries (2 with popliteal artery, 1 with posterior tibial artery), and two patients had peroneal nerve injuries. Three patients underwent skin grafting. Union was achieved in all fractures, but secondary procedures were required to achieve union in 6 cases. In 23 patients, the union was completed between 16–22 weeks; the delayed union was detected in 5 patients at 6-month follow-up. An autologous iliac bone graft was applied to three patients without removing the implant (intramedullary nail in one patient, locking plate in two patients). Two patients received a carved nail, and an external fixator was applied to one patient. In 6 months, union was also achieved in these cases[21]. In our study, surgery was required in 82.90% (n=34) of the patients. Other branches were needed in 12.20% (n=5) of the patients. One of our patients had radial nerve symptoms and completely recovered in the follow-ups. The most frequently required other branches were general surgery and cardiovascular surgery (Table 4).

In a study conducted in Türkiye, 19.7% of 56 open tibial fractures were caused by FAI; 35 (68.6%) of the patients were male, 16 (31.4%) were female, and the average age of those male and female patients was 34.2 (ranging from 17 to 56 years)[22]. In our study, the mean age of the patients was 39.76±12.77, the median and 1st Quartile-3rd Quartile was 39.00 [28.00–48.50] years, the youngest age was 21.00 years, and the oldest age was 69.00 years. Of the hospitalization duration of the patients, the mean and standard deviation were 5.68±3.38 days, the median and 1st Quartile-3rd Quartile were 4.00 [3.00–7.00] days, the shortest one was 3.00 days, and the longest one was 17.00 days (Table 1).

The study's limitation is the relatively small sample size from a single center. Conducting multi-center studies with more patients could contribute more significantly to the literature.

Conclusion

We often encounter FAI cases in orthopedic clinics. Especially in our region, due to the prolonged conflict environment, increasing firearm usage habits, and factors such as "terrorism, customs, and honor," it is observed that people, regardless of age, are exposed to firearm injuries and death incidents. In conclusion, as physicians, it would be prudent to minimize the damage that may occur by increasing our knowledge and expertise in the diagnosis, treatment, follow-up, and rehabilitation of FAI cases.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Relationship Between Primary Ventricular Arrhythmias and In-hospital Mortality and Resuscitated Cardiopulmonary Arrest in Patients with Acute ST Segment Elevation Myocardial Infarction

ST Segment Yükselmeli Miyokard Enfarktüsü ile Gelen Hastalarda Gelişen Primer Ventriküler Aritmilerin Hastane İçi Ölüm ve Resüsitasyon Yapılmış Kardiyopulmoner Arrest ile İlişkisi

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ABSTRACT

Aim: *Arrhythmic complications in patients with acute coronary syndromes during hospitalization are not uncommon in cardiology practice. In our retrospective study, we investigated the effect of primary ventricular arrhythmias occurring within the first 48 hours from the time of hospitalization on cardiovascular mortality and resuscitated cardiopulmonary arrest in patients with ST-segment elevation myocardial infarction.*

Introduction: *Although the rate of myocardial infarction has decreased over the years, it is responsible for hundreds of thousands of deaths worldwide. Arrhythmic complications take an essential place for morbidity and mortality in the course of myocardial infarction. Ventricular arrhythmias play a pivotal role in terms of mortality in acute terms of myocardial infarction.*

Material and Method: *In our single center and retrospective study, 18-year-old and older patients who presented to Sağlık Bilimleri University Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital emergency department with ischemic symptoms and were admitted to hospital with the diagnose of ST-segment elevation myocardial infarction were enrolled. The primary endpoint was in-hospital mortality and resuscitated cardiopulmonary arrest.*

Results: *1,137 patients were included in the study. Primary VT/VF which occurred within the first 48 hours from the time of hospitalization was observed in 8.2% of patients (n: 93). Previous MI history (3.47 OR, 95% CI 1.41–8.55 p=0.0068, LASSO: 0.388), KILLIP class at the time of admission (1.52 OR, 95% CI 0.94–2.45 p=0.0813, LASSO: 0.627), Primary VT/VF (4.02 OR, 95% CI 1.44–11.21 p=0.0077, LASSO: 0.440), left ventricle ejection fraction calculated by transthoracic echocardiography (0.88 OR, 95% CI 0.78–0.99 p=0.0444, LASSO: -0.032) and serum CRP level (1.81 OR, 95% CI 0.22–14.53 p=0.57, LASSO: 0.036) were independent predictors of MACE including in-hospital mortality and resuscitated cardiopulmonary arrest.*

Conclusion: *Primary VT and VF are independent predictors of in-hospital mortality and resuscitated cardiopulmonary arrest events in patients with ST-segment elevation acute MI.*

Key words: *myocardial infarction, STEMI, ventricular arrhythmias, in-hospital mortality*

ÖZET

Amaç: *Akut koroner sendrom hastalarının hastanede yatış sürecinde gelişen aritmik komplikasyonlar kardiyoloji pratiğinde nadir karşılaşılan durumlar değildir. Retrospektif çalışmamızda ST yükselmeli miyokard infarktüsü ile gelen hastaların hastaneye yatışı sonrası ilk 48 saatte gelişen primer ventriküler aritmilerin kardiyovasküler mortalite ve resussite kardiyopulmoner arrest üzerine etkilerini araştırdık.*

Materyal ve Metot: *18 yaş ve üzeri iskemik semptomlarla Sağlık Bilimleri Üniversitesi Dr. Siyami Ersek Göğüs Kalp ve Damar Cerrahisi Eğitim ve Araştırma Hastanesi'ne başvuran ve ST yükselmeli miyokard enfarktüsü tanısı ile hastaneye yatışı yapılan hastalar tek merkezli ve retrospektif çalışmamıza alındı. Birincil sonlanım noktası hastane içi ölüm ve resussitasyon yapılmış kardiyopulmoner arrest olarak belirlendi.*

Bulgular: *Çalışmamıza 1.137 hasta dâhil edildi. Hastaneye yatış sonrası ilk 48 saatte gelişen Primer VT/VF oranı %8,2 (93 hasta) idi. Miyokard enfarktüsü öyküsü (3,47 RR, %95 GA 1,41–8,55 p=0,0068, LASSO: 0,388), başvuru esnasındaki KILLIP sınıflaması (1,52 RR, %95 GA 0,94–2,45 p=0,0813, LASSO: 0,627), Primer VT/VF (4,02 RR, %95 GA 1,44–11,21 p=0,0077, LASSO: 0,440), transtorasik ekokardiyografide hesaplanan sol ventrikül ejeksiyon fraksiyonu (0,88 RR, %95 GA 0,78–0,99 p=0,0444, LASSO: -0,032) ve serum CRP düzeyi (1,81 RR, %95 GA 0,22–14,53 p=0,57, LASSO: 0,036) hastane içi ölüm ve resussitasyon yapılmış kardiyopulmoner arrestti de içeren majör kardiyovasküler olumsuz olayların bağımsız öngördürücüleri olarak belirlendi.*

Sonuç: *ST yükselmeli miyokard enfarktüsü hastalarında Primer VT/VF, hastane içi ölüm ve resussitasyon yapılmış kardiyovasküler arrest olaylarının bağımsız öngördürücüleridir.*

Anahtar kelimeler: *miyokard enfarktüsü, STYME, ventriküler aritmiler, hastane içi ölüm*

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Introduction

Although myocardial infarction (MI) and its mortality rates showed a trend of decline in the last decades, myocardial infarction with ST-segment elevation (STEMI) has similar mortality rates when compared with rates of the early 2000 s[1]. Similarly, although the rates of life-threatening ventricular arrhythmias (VAs) seem to decline over time, ventricular tachycardia (VT) and ventricular fibrillation (VF) can complicate the course of MI with relatively high rates of up to 5–7.5%[2–5].

Whether VAs adversely impact both short- and long-term outcomes in patients suffering from MI has long been investigated[3,5–8]. Data from the literature reveals that the vast majority of VAs tend to occur within the first 48 hours of the index event[5,8,9]. As understood from the study results, the prognostic significance of VAs developing in the early stage of MI on in-hospital, short- and long-term survival is still unclear[3,7,8,10,11].

This study aims to investigate whether primary VF and VT in the setting of STEMI impact in-hospital mortality in patients undergoing primary percutaneous coronary intervention (pPCI).

Material and Method

Study Population

Our study was designed as a retrospective and single-center study. Between January 2017 and July 2018, 1,137 patients admitted to tertiary centers with acute onset chest pain accompanied by ≥1 mm persistent ST-segment elevation at least two consecutive leads on surface electrocardiogram (ECG) were included in the study. Patients with structural heart disease or channelopathies, patients with a history of VT/VF and implantable cardioverter defibrillator (ICD) implantation, patients with previously known left ventricular ejection fraction (LVEF) 30% or less and patients under 18 years of age were excluded from the study population. The local ethical committee of the hospital approved the study protocol.

Data Ascertainment

Peripheral venous blood samples were obtained on admission for complete blood count and biochemical parameters. Hematologic parameters were studied with Cell-Dyn 37000 Hematology Analyzer (Abbott Diagnostic Division, Wiesbaden, Germany) and biochemical parameters such as serum creatinine and C-reactive protein (CRP) levels were studied with Architect Plusci 4100 (Abbott Laboratories, Abbott Park, Illinois).

Clinical data, laboratory parameters, electrocardiography and transthoracic echocardiographic measurements were retrospectively obtained from the hospital information system.

Definitions

Ventricular tachycardia was defined as a tachycardia (rate >100 beats per minute) with three or more consecutive beats originating from ventricles independent of atrial or atrioventricular nodal conduction. If the QRS complexes were similar in the configuration from beat to beat, they were classified as monomorphic; if the QRS configurations changed from beat to beat, they were classified as polymorphic VT[12].

Ventricular fibrillation was defined as a chaotic rhythm on the surface ECG characterized by irregular undulations in both timing and morphology without discrete QRS complexes[12].

Hypertension (HTN) was defined as the use of antihypertensive medication or systolic blood pressure (SBP) values ≥140 mmHg and/or diastolic blood pressure (DBP) values ≥90 mmHg[13].

Primary VT/VF was defined as VT/VF occurring within the first 48 hours after admission to the hospital.

Diabetes mellitus (DM) was defined as random plasma glucose ≥200 mg/dl with symptoms or glycated hemoglobin level ≥6.5% or using antidiabetic medications[14].

KILLIP classification at admission assessed the presence and severity of heart failure signs and symptoms[15].

Statistical Analysis

Mean and standard deviation, median and interquartile range were used to present numerical parameters, and the percentage and number of patients were used to represent categorical parameters.

Endpoint

The primary endpoint was in-hospital major adverse cardiovascular events (MACE), which was a composite of in-hospital mortality and aborted cardiopulmonary arrest (aCPA).

Candidate Predictors

Predictors were identified a priori and informed by clinical expertise and literature review. The candidate predictors must be moderately/strongly associated with in-hospital MACE. We pre-specified candidate predictors according to these principles. As candidate predictors, age, gender, HTN, DM, previous MI, smoking history, KILLIP classification at the time of admission, SBP, heart rate, VT and VF, in-hospital atrial fibrillation (AF), in-hospital supraventricular tachycardia (SVT), atrioventricular block (AVB), MI related artery (LAD versus non-LAD), LVEF, CRP, hemoglobin level, serum creatinine and potassium level have been determined. Our model did not include Variables with very low or very high frequencies. Finally, we included 19 candidate predictors in our study model.

Sample Size Calculation

A clinical prediction model requires a sufficiently large sample size and a sufficiently conservative number of predators. Specifically, at least ten patients should have the primary endpoint for each candidate predictor (endpoint/variable >10). In our clinical model, 119 patients had the primary outcome. However, 19 candidate predictors were identified (119/19=6.3). Therefore, conventional logistic regression models and penalized maximum likelihood estimation methods were used to minimize overfitting.

Statistical Modeling

We used the minor absolute shrinkage and selection operator (LASSO) along with the 10-fold cross-validation penalty parameter to avoid the risk of overfitting. Numeric variables such as age, KILLIP classification, SBP, pulse rate, LVEF, hemoglobin, serum CRP, creatinine and potassium level were included in our clinical model as flexible smooth parameters using restricted cubic spline. LASSO is a proposed shrinkage regression technique for regression analysis of models with a low incidence of candidate predictors. LASSO coefficients were feasible for prediction but not easily understandable and were presented with multivariable logistic regression models with reported results as odds ratio (OR) and 95% confidence interval (CI).

The Propensity Score (PS) was calculated using the multivariable logistic regression model with the dependent result (with VT/VF versus without). We used the spline function of the logit propensity score to evaluate the relationship between the groups (VT / VF with / without) and the primary outcome. Furthermore, the inverse probability weighting (IPW) method was used to adjust the differences between the two groups. All statistical analyses were performed by R-software v. 3.5.1 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria).

Results

One thousand one hundred thirty-seven patients admitted to the emergency department with chest pain accompanied by ST-segment elevation on surface ECG were included in the study. The mean age of the study population was 59.8±12.9 years, and male patients were 78.6% of the study population. Primary VT/VF was observed in 8.2% of the patients (n=93). During the hospital stay, the rate of new-onset AF was 7.3% (n=83), and at least second-degree AVB emerged at 3.1% (n=35). The baseline clinical characteristics of patients with and without VT/VF are summarized in Table 1.

The in-hospital mortality rate was 8.5% (n=96), and the rate of in-hospital MACE was 10.5% (n=119) in the whole study population. Additionally, the adverse clinical endpoints, cerebrovascular accident and stent thrombosis, were 1.1% (n=12) and 1.5% (n=17), respectively (Table 2).

KILLIP classification at the time of admission, prior MI, age, sex, DM and smoking history, SBP, pulse rate, VT/VF, in-hospital AF and non-AF SVT (atrial flutter, atrial tachycardia and other narrow QRS complex tachycardias), AVB, LVEF, serum CRP, hemoglobin and potassium level were associated with in-hospital mortality and aCPA in univariable analysis (Table 3). In univariate analysis, there might appear to be a positive relationship between female gender and MACE rates. Still, in multivariate analysis, a statistically significant relationship between gender and MACE couldn't have been established.

In multivariable regression analysis, the LASSO method was used to avoid the risk of overfitting. Accordingly, **MI history** (3.47 OR, 95% CI 1.41–8.55 p=0.007, LASSO regression coefficient: 0.388), **KILLIP classification** (1.52 OR, 95% CI 0.94–2.45 p=0.081, LASSO regression coefficient: 0.627), **primary VT/VF** (4.02 OR, 95% CI 1.44–11.2 p=0.008, LASSO regression coefficient: 0.440), **LVEF** (0.88 OR, 95% CI 0.78–0.99 p=0.0444, LASSO regression coefficient: -0, 032)

Table 1. *Baseline characteristics*

VARIABLE	OVERALL (n=1137)	VT/VF PRESENT (n=93)	VT/VF ABSENT (n=1044)
AGE (years)	59.8±12.9	60.1±14.1	59.7±12.7
MALE GENDER	%78.6	%76.1	%78.9
HYPERTENSION	%47.2	%40.9	%47.8
DIABETES MELLITUS			
INSULIN-DEPENDENT	11%, 7	9%, 7	11%, 8
OAD	15%, 7	14%	15%, 8
HISTORY of MI	%19.5	%23.7	%19.1
SMOKING HISTORY			
SMOKERS	53%, 1	65%, 1	52%
NON-SMOKERS	46%, 9	34%, 9	48%
KILLIP CLASSIFICATION			
1	89%	64%, 5	91%, 4
2	1%, 4	2%, 2	1%, 4
3	3%, 5	5%, 4	3%, 3
4	6%	28%	4%, 0
SYSTOLIC BLOOD PRESSURE (mmHg)	135.3±30.8	123.9±37.3	136.5±29.8
PULSE RATE (beat per minute)	83.1±23.1	90.1±26.1	82.5±20.6
IN-HOSPITAL AF	%7.3	%12.9	%6.8
IN-HOSPITAL non-AF SVT	%0.4	%2.2	%0.3
AVB	%3.1	%7.5	%2.7
INFARCT RELATED ARTERY			
LAD	39%, 9	58%, 4	38%, 3
NON-LAD	60%, 1	41%, 6	61%, 7
EJECTION FRACTION (%)	45.4±11.3	40.3±12.2	45.9±11.1
CRP (mg/dL)	2.7±4.2	3.4±5.1	2.7±4.1
HEMOGLOBIN (g/dL)	13.6±2.0	13.7±2.3	13.6±1.9
SERUM CREATININE (mg/dl)	1.08±2.5	1.25±1.15	1.06±2.6
SERUM POTASSIUM (mEq/L)	4.15±0.56	4.16±0.65	4.15±0.55

AF: atrial fibrillation, AVB: atrioventricular block, CPA: cardiopulmonary arrest, CRP: C-reactive protein, g/dL: grams per deciliter, LAD: left anterior descending, mEq/L: milliequivalents per liter, mg/dL: milligrams per deciliter, MI: myocardial infarction, mmHg: millimeter of mercury, OAD: oral antidiabetic, SVT: supraventricular tachycardia, VF: ventricular fibrillation, VT: ventricular tachycardia.

Table 2. *In-hospital adverse clinic endpoint rates in the overall group, patients with and without VT/VF*

VARIABLE	OVERALL (n=1137)	VT/VF PRESENT (n=93)	VT/VF ABSENT (n=1044)
IN-HOSPITAL MORTALITY	%8.5	%32.3	%6.3
IN-HOSPITAL CVA	%1.1	%1.1	%1.1
IN-HOSPITAL STENT THROMBOSIS	%1.5	%6.5	%1.1
IN-HOSPITAL MACE	%10.5	%38.7	%7.9

CPA: cardiopulmonary arrest, CVA: cerebrovascular accident, MACE: major adverse cardiovascular event, VF: ventricular fibrillation, VT: ventricular tachycardia.

and **serum CRP level** (1.81 OR, 95% CI 0.22–14.53 p=0.57, LASSO regression coefficient: 0, 036) were determined as independent predictors of in-hospital mortality and/or aCPA (Table-3). The relationship between independent predictors and in-hospital mortality/aCPA log odds is indicated in Fig. 1.

As depicted in Fig. 1a and Fig. 1b, having a history of MI and developing VT/VF within the first 48 hours are significantly associated with the primary outcome of in-hospital aCPA and in-hospital mortality. As graphically illustrated in Fig. 1c, an increase in KILLIP class at admission significantly affects the primary outcome. Fig. 1d shows the relationship between LVEF and in-hospital mortality/aCPA. Left ventricular ejection fraction is a parameter that considerably affects the primary outcome statistically, indicating that a decrease below 40% in LVEF could lead to poor outcomes. Finally, Fig. 1e demonstrates a significant relationship between CRP and MACE rates.

Besides, the relation between VT/VF and in-hospital mortality/aCPA remained statistically significant when the propensity score-adjusted multivariable model (**2.76 OR, 95% CI 1.17–6.35 p=0, 0168**) and inverse probability weighting model (IPW) (**6.87 OR, 95% CI 4.39–10.77 p<0, 001**) were performed.

Table 3. *Regression table*

VARIABLE	UNIVARIABLE ODDS RATIO (OR), 95% CONFIDENCE INTERVAL (CI)	p VALUE	MULTIVARIABLE ODDS RATIO (OR), 95% CONFIDENCE INTERVAL (CI)	LASSO	MULTIVARIABLE P VALUE
AGE (for an increase of each one year)	1.05 (1.03–1.06)	<0.001	0.92 (0.81–1.05)	-	0.26
GENDER (female vs. male)	0.46 (0.31–0.70)	0.02	0.51 (0.17–1.49)	-	0.22
HTN (presence vs. absence)	1.26 (0.86–1.85)	0.22	0.45 (0.17–1.18)	-	0.1
DM (presence vs. absence)	1.27 (1.01–1.61)	0.04	1.04 (0.59–1.80)	-	0.88
HISTORY of MI (presence vs. absence)	2.46 (1.63–3.72)	<0.001	3.47 (1.41–8.55)	0.388	0.0068
SMOKING (presence vs. absence)	0.53 (0.39–0.73)	<0.001	0.70 (0.37–1.33)	-	0.28
KILLIP CLASS (for increase of each 1 class)	3.64 (3.02–4.38)	<0.001	1.52 (0.94–2.45)	0.627	0.0813
SBP (for an increase of each one mmHg)	0.97 (0.96–0.98)	<0.001	0.94 (0.89–1.00)	-	0.0525
PULSE RATE (for increase of each one b. p. m.)	1.02 (1.01–1.03)	<0.001	0.98 (0.89–1.07)	-	0.7
VT/VF (presence vs. absence)	7.37 (4.58–11.84)	<0.001	4.02 (1.44–11.21)	0.44	0.0077
IN-HOSPITAL AF (presence vs. absence)	2.25 (1.25–4.03)	0.006	1.23 (0.32–4.64)	-	0.75
IN-HOSPITAL non-AF SVT (presence vs. absence)	6.09 (1.00–36.84)	0.04	2.57 (0.10–61.67)	-	0.55
AVB (presence vs. absence)	3.64 (1.70–7.78)	0.001	0.44 (0.03–6.22)	-	0.55
INFARCT RELATED ARTERY (LAD vs. NON-LAD)	1.48 (0.94–2.33)	0.08	0.52 (0.20–1.38)	-	0.19
EF (for increase of each 1%)	0.91 (0.89–0.93)	<0.001	0.88 (0.78–0.99)	-0.032	0.0444
CRP (for increase of each 1 mg/dl)	1.12 (1.08–1.16)	<0.001	1.81 (0.22–14.53)	0.036	0.57
ADMISSION HGB (for an increase of each one g/dl)	0.75 (0.68–0.82)	<0.001	0.47 (0.28–0.79)	-	0.0042
SERUM CREATININE (for an increase of each 1 mg/dl)	1.05 (0.98–1.12)	0.13	5.07 (0.0003–82909.2)	-	0.74
ADMISSION POTASSIUM (for an increase of each one mEq/L)	1.90 (1.37–2.61)	<0.001	5.76 (0.25–130.95)	-	0.27

AF: atrial fibrillation, AVB: atrioventricular block, b. p. m.: beat per minute, CI: confidence interval, CPA: cardiopulmonary arrest, CRP: C-reactive protein, DM: diabetes mellitus, EF: ejection fraction, g/dl: grams per deciliter, HTN: hypertension, LAD: left anterior descending, LASSO: least absolute shrinkage and selection operator, mEq/L: milliequivalents per liter, mg/dl: milligrams per deciliter, MI: myocardial infarction, mmHg: millimeter of mercury, OR: Odds Ratio, SVT: supraventricular tachycardia, VF: ventricular fibrillation, vs.: versus, VT: ventricular tachycardia.

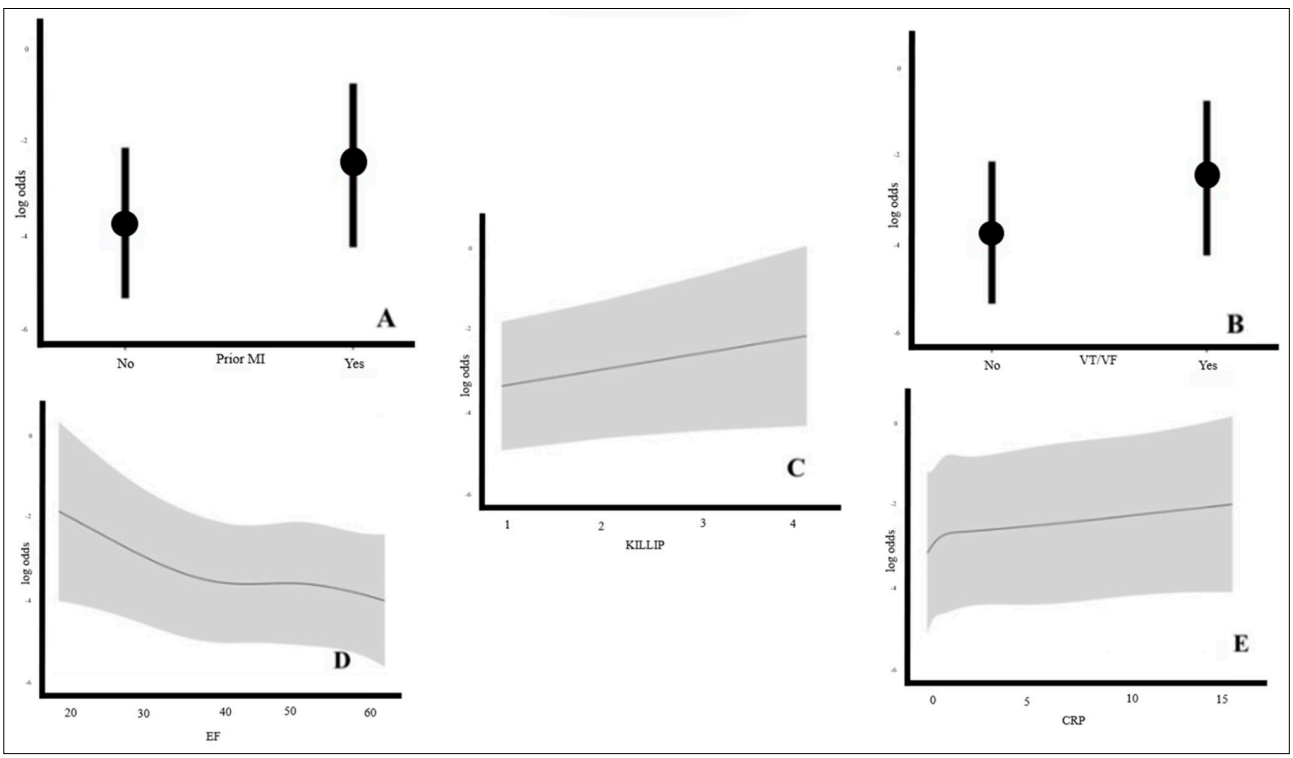

Figure 1. *The relationship between independent predictors and in-hospital mortality/aCPA log odds.*

Discussion

In our study, it was observed that primary VT/VF occurred in 8.2% (n=93) of patients with acute STEMI, and the results demonstrated that primary VT/VF, previous MI, admission KILLIP classification, LVEF and serum CRP level were independent predictors of in-hospital mortality and aCPA in STEMI patients. Among these parameters, primary VT/VF was the predictor with the highest odds ratio in multivariable regression analysis (4.02 OR). We conducted propensity score matching since our study was not a randomized controlled trial. Primary VT/VF occurrence was found to increase the risk of in-hospital mortality and aCPA 2.7 fold after PS adjustment, which was consistent with multivariable regression analysis (2.76 OR, 95% CI 1.17–6.35 p=0.0168 and 4.02 OR, 95% CI 1.44–11.2 p=0.008, respectively).

Previous reports on the prognostic importance of VAs in the setting of MI demonstrated different results[2,3,5,7,8,10,11]. According to the pooled data analysis results in The Primary Angioplasty in Myocardial Infarction (PAMI), VT/VF occurrence during pPCI in catheterization laboratory in STEMI patients didn't hurt in-hospital and one-year mortality and MACE. This favorable result might have been driven by excluding some high-risk patients, such as patients with cardiogenic shock or renal failure, from the study population[10].

Global Use of Streptokinase t-PA for Occluded Coronary Arteries (GUSTO-I) and Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) trials were conducted in thrombolytic era. Both the GUSTO-I and GISSI-2 trials suggested that patients with ventricular arrhythmias had higher in-hospital mortality rates than patients without16.17. Although pPCI is the contemporary treatment of choice in patients with STEMI and performed widely, our results revealed that the impact of VAs on the in-hospital course of MI can be considered similar to that in GUSTO-I and GISSI-2.

Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial revealed that early VAs didn't show statistical significance on 30-day MACE and mortality rates but had a significant adverse impact on 3-year MACE events[7]. Although in-hospital mortality rates were lacking in this study, short-term mortality rates contradict our results. A larger sample size in the HORIZONS-AMI study might drive this contradiction. Another cohort study, including 9015 patients with acute MI who underwent percutaneous coronary intervention, suggested that early VAs were associated with a 4-fold increase in in-hospital mortality rates. Interestingly, although successful mechanical revascularization decreased mortality rates, the association between in-hospital mortality and early VAs was similar to the study population in patients with successful coronary intervention[3]. Although the relation between early VAs and in-hospital mortality in this study was consistent with our results, it should be emphasized that this study was conducted with all MI patients, not only with STEMI.

Ectopic excitation and reentry circuits should be addressed as the underlying mechanisms of VAs in myocardial ischemia. Firstly, acute ischemia causes metabolic alterations such as adenosine triphosphate depletion and intracellular acidosis in myocytes. Due to metabolic alterations, intracellular calcium mishandling and action potential duration changes cause early and late after-depolarization-induced ventricular ectopics[19,20]. Unidirectional conduction disturbance, such as block or slow conduction in the ischaemic area, might create a re-entry circuit. In addition, myocardial sympathetic innervation abnormalities, innervation/perfusion mismatch and epinephrine retention might create VA substrate in ischemic myocardium[19–22].

Conclusion

Despite the conflicting results of different studies in the literature, our study demonstrated that primary VT/VF in patients with STEMI is significantly associated with in-hospital mortality and aCPA. It can be concluded that VT/VF occurrence within the first 48 hours of hospital admission in patients with STEMI might cause lower in-hospital survival rates than patients without VT/VF. As a matter of course, a high volume of prospective studies is needed on this issue.

Our study's main limitation is its retrospective and single-center nature. The second limitation is that our study results consist of only in-hospital endpoints; long-term follow-up results are still missing. Also, the primary endpoint of our study is in-hospital mortality and aCPA, which prevents the interpretation of whether VT/VF occurrence affects in-hospital mortality rates independently.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Clinical and Demographic Characteristics of Uveitis Patients: Eastern Black Sea Region Sample

Üveit Hastalarının Klinik ve Demografik Özellikleri: Doğu Karadeniz Bölgesi Örneği

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ABSTRACT

Aim: *Uveitis is one of the leading causes of visual impairment worldwide. This study aims to delineate the demographic and clinical characteristics of uveitis patients who underwent treatment and monitoring at our facility.*

Material and Methods: *A retrospective examination was conducted on the medical records of uveitis patients monitored at the Uvea-Behçet Unit of Karadeniz Technical University Faculty of Medicine Farabi Hospital between 1997 and 2020. Four hundred and fifty uveitis patients, whose records comprehensively met the study criteria, were evaluated for analysis.*

Results: *Females constituted 56.2% (n=253) while males represented 43.8% (n=197) of the study group. Patients exhibited a mean age of 35.85±16.79 years. The predominant clinical presentation was a decline in visual acuity reported by 84.9% (n=382) of the patients. Idiopathic uveitis emerged as the most prevalent subtype accounting for 23.5% (n=106) of cases. Topical steroids were the primary treatment administered to 78.4% (n=353) of the study group. Six hundred eleven of a total of 900 eyes were involved. Anatomically, anterior uveitis was the most common form in all eyes, with 38.7% (n=349). Of the eyes with involvement, 59.1% (n=367) fully recovered, while 38.5% (n=239) experienced symptom management with ongoing treatment, and 2.4% (n=15) of patients were non-responsive to treatment.*

Conclusion: *The prevalence, subtype distribution, and clinical manifestations of uveitis can exhibit regional variations. This study demonstrates the demographic and clinical characteristics of uveitis patients in the Eastern Black Sea Region.*

Key words: *uveitis; uveal diseases; uveitis therapy; uveitis complications*

ÖZET

Amaç: *Üveit, küresel ölçekte görme bozukluklarının başlıca etkenlerinden biridir. Bu çalışmada, kurumumuzda tedavi ve izlem süreçlerine tabi tutulan üveit hastalarının demografik ve klinik özelliklerinin ayrıntılı bir şekilde çıkarımını yapmayı amaçladık.*

Materyal ve Metot: *Karadeniz Teknik Üniversitesi Tıp Fakültesi Farabi Hastanesi Üvea-Behçet Ünitesi'nde izlenen üveit hastalarının tıbbi kayıtları üzerinden retrospektif bir değerlendirme gerçekleştirildi. 1997 ile 2020 yılları arasında, çalışma kriterlerini eksiksiz olarak sağlayan 450 üveit hastası analiz için ele alındı.*

Bulgular: *Çalışma grubunda kadınlar %56,2 (n=253) oranında iken, erkekler %43,8 (n=197) oranında temsil edilmekteydi. Hastaların ortalama yaşı 35,85±16,79 yıl olarak belirlendi. En yaygın klinik sunum, hastaların %84,9'u (n=382) tarafından bildirilen görme keskinliğindeki azalmaydı. İdiyopatik uveit, vakaların %23,5'ini (n=106) oluşturarak en yaygın alt tip olarak ortaya çıktı. Çalışma grubunun %78,4'üne (n=353) başlıca tedavi olarak topikal steroidler uygulandı. Tüm gözlerin (n=900) 611'inde tutulum mevcut idi. Tüm gözler incelendiğinde, %38,7 oranla (n=349) anatomik olarak en yaygın form anterior üveit idi. Tutulum izlenen gözlerin %59,1'i (n=367) tamamen iyileşirken, %38,5'i (n=239) devam eden tedavi ile semptom yönetimi yaşadı ve gözlerin %2,4'ü (n=15) tedaviye yanıt vermedi.*

Sonuç: *Üveitin prevalansı, alt tip dağılımı ve klinik gösterimleri coğrafi bölgelere göre değişiklik gösterebilir. Bu çalışma, Doğu Karadeniz Bölgesi'ndeki üveit hastalarının demografik ve klinik özelliklerini sunmaktadır.*

Anahtar kelimeler: *üveit; uveal hastalıklar; üveit tedavisi; üveit komplikasyonları*

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Introduction

Uveitis denotes an inflammatory condition that predominantly affects the uveal layer of the eye, encompassing the iris, ciliary body, and choroid. This inflammation can also extend to adjacent ocular structures such as the vitreous, retina, vessels, and optic nerve[1]. Recognized as a significant contributor to ocular morbidity, the diverse manifestations of uveitis often pose challenges in accurate diagnosis. A comprehensive diagnosis is typically achieved through a synthesis of detailed anamnesis and meticulous clinical examination, emphasizing ocular symptoms, onset patterns, historical data on previous episodes, familial and social backgrounds, and an exhaustive systemic investigation. Nevertheless, a subset of patients experience delayed diagnosis or suboptimal therapeutic interventions. Consequently, it is estimated that nearly one-third of uveitis-afflicted individuals might have vision impairment, escalating to potential blindness[2,3]. Globally, uveitis accounts for an estimated 5% to 10% of vision loss cases[4].

From a public health perspective, uveitis predominantly impacts the economically active demographic, underscoring its societal implications. Effective management of uveitis not only facilitates the continuation of professional endeavours but also ensures an individual's holistic integration into societal and social frameworks.

Uveitis can be dichotomized into infectious and non-infectious categories, with the latter being predominantly autoimmune or immune-mediated. Notably, non-infectious variants constitute the majority of uveitis presentations[5]. A myriad of factors, including age, gender, ethnicity, geographical distribution, environmental exposures, genetic predispositions, and sociocultural practices, influence the prevalence and clinical presentation of uveitis.

The primary objective of our research is to undertake a holistic evaluation of uveitis patients presenting to our clinic in Trabzon, which caters to a vast demographic, predominantly from the Black Sea Region and its adjoining provinces. By delineating the sociodemographic profiles of these patients, systematically analyzing their therapeutic regimens, comparing treatment outcomes, and assessing long-term prognostic indicators, we aim to derive insights that could potentially guide clinical practice. The exigency of such a study is palpable in the current clinical landscape.

Materials and methods

Study Design and Population

This study employed a cross-sectional descriptive design. The target population comprised uveitis patients who received care at the Ophthalmology Uvea and Behçet Unit of the Karadeniz Technical University Faculty of Medicine Farabi Hospital, spanning the period from 1997 to 2020.

Inclusion and Exclusion Criteria

Eligibility for inclusion in the study was determined based on the comprehensiveness and availability of patient medical records. Specifically, uveitis patients with well-maintained medical files that sufficiently addressed the data parameters of this study were considered. Conversely, patients with incomplete or inconsistent data and those whose records were inaccessible from the hospital archives for any reason were excluded. Based on these criteria, a total of 450 patients with comprehensive medical records were incorporated into the study.

Ethical Considerations

Before the commencement of the study, Ethical approval was obtained from the Ethics Committee of the Karadeniz Technical University Faculty of Medicine, with the approval dated 31.12.2018 and bearing reference number 2018/310.

Data Analysis

The collected data, encompassing nominal, ordinal, and numerical types, were inputted and analyzed using the Statistical Package for Social Sciences (SPSS) program version 18 software (IBM Inc., Chicago, IL, USA). Descriptive statistics were employed for data interpretation. Quantitative data were expressed as mean ± standard deviation. The one-sample Kolmogorov-Smirnov test was utilized to assess the normality of the distribution of these data.

A p-value of less than 0.05 was considered indicative of statistical significance.

Results

Demographics and Clinical Presentation

From 1997 to 2020, 450 uveitis patients presented to our Uvea-Behçet unit and were subsequently included in this study. Notably, 71.1% (n=320) of these patients sought consultation at our clinic without prior treatment. The cohort comprised 253 females (56.2%) and

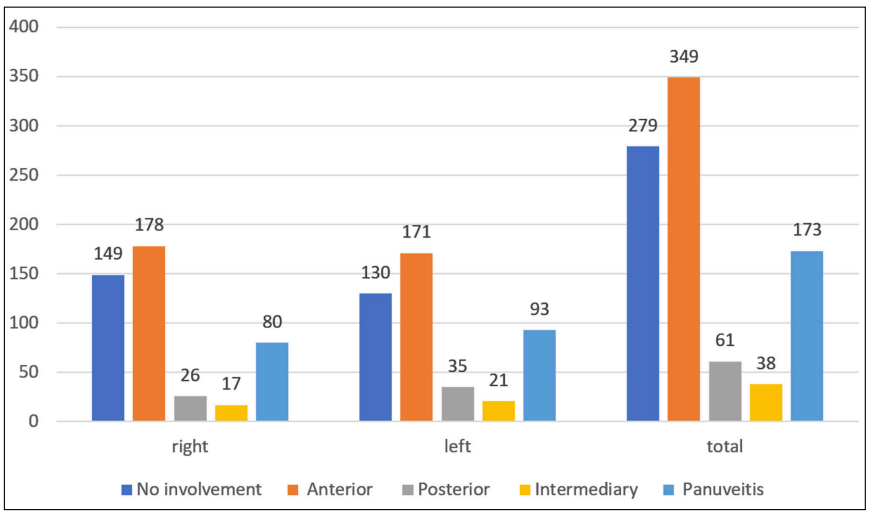

Figure 1. *Anatomical classification of uveitis in right, left, and total eyes.*

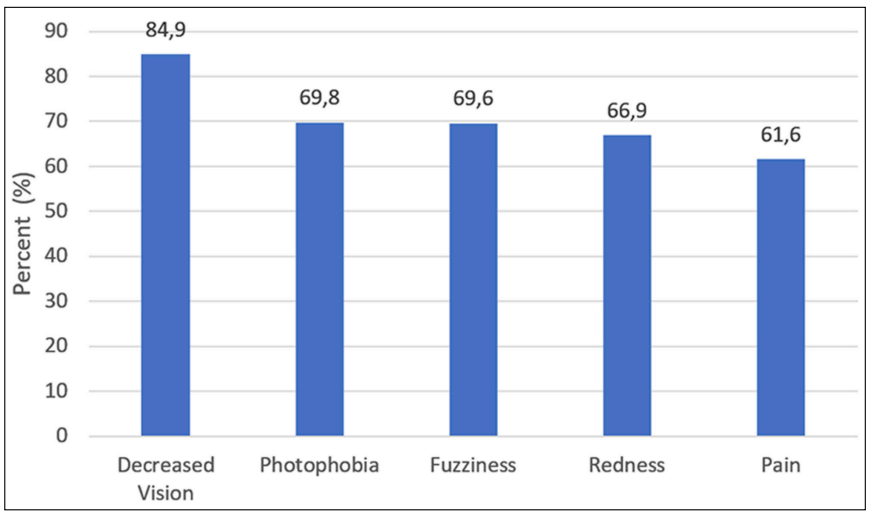

Figure 2. *Distribution of admission complaints in patients with uveitis.*

197 males (43.8%). The patients had a mean age of 35.85±16.79 years, with a range from 3 to 91 years. A total of 70 patients were under 18 years of age. The average duration of follow-up was 4.6±4.0 years (range: 0.4 – 21 years), while the mean disease duration at the time of presentation was 2.19±4.13 years (range: 0 – 40 years).

Ocular Involvement

During the observation period, bilateral eye involvement was documented in 36.2% (n=163) of the patients. Unilateral involvement was observed in 30% (n=133) for the right eye and 34% (n=154) for the left eye. Anatomical localization of inflammation showed that anterior uveitis was the most common form with 38.7%. This was followed by panuveitis at 19.2%, posterior uveitis at 6.7% and intermediate uveitis at 4.2%. This distribution was 37.8%, 22.1%, 6.4% and 7.8% in children, respectively (Fig. 1).

Etiological Distribution

The etiological breakdown of uveitis in our cohort is detailed in Table 1. Predominantly, the etiology remained idiopathic. However, among the identifiable causes, Behçet's disease and Ankylosing spondylitis emerged as the predominant contributors.

Clinical Symptoms and Examination Findings

The predominant clinical symptom reported by the patients was a decline in visual acuity, with 84.9% (n=382) of the patients citing this complaint (as illustrated in Fig. 2). Upon clinical examination during uveitis episodes, cells in the anterior chamber were the most frequently observed finding, noted in 60.3%

Table 1. *Distribution of diagnoses of patients with uveitis*

DIAGNOSIS	n	%
Idiopathic	106	23.5
Behcet's disease	92	20.4
Ankylosing spondylitis	50	11.1
Fuchs heterochromic iridocyclitis	42	9.3
Infectious parasitic (toxoplasma)	36	8
Spondyloarthropathy	23	5.1
Sarcoidosis	21	4.7
Juvenile idiopathic arthritis	20	4.4
Infectious viral, HSV	14	3.1
Infectious bacterial (Lyme)	9	2
Multiple sclerosis	7	1.6
Infectious bacterial (tuberculosis)	4	0.9
Infectious viral (CMV)	3	0.7
Inflammatory bowel disease	3	0.7
Incomplete Behcet	3	0.7
Infectious viral (VZV)	2	0.4
Vogt Koyagani Harada	2	0.4
Rheumatoid arthritis	2	0.4
Acute lymphoblastic leukemia	2	0.4
White spot syndromes (multifocal choroiditis)	2	0.4
Infectious bacterial (syphilis)	1	0.2
Psoriasis	1	0.2
Systemic lupus erythematosus	1	0.2
Sympathetic ophthalmia	1	0.2
Secondary to systemic infection	1	0.2
Gittelman syndrome	1	0.2
Paraneoplastic syndrome	1	0.2

Table 2. *Eye examination findings observed during attacks in patients with uveitis*

Findings			n*	%
Anterior chamber cell	Right	Yes	268	59.6
		No	182	40.4
	Left	Yes	275	61.1
		No	175	38.9
	Total	Yes	543	60.3
		No	357	39.7
Keratic precipitate	Right	None	206	45.8
		Non-granulomatous	239	53.1
		Granulomatous	5	1.1
	Left	None	202	44.9
		Non-granulomatous	242	53.7
		Granulomatous	6	1.3
	Total	None	408	45.3
		Non-granulomatous	481	53.4
		Granulomatous	11	1.3
Conjunctival hyperemia	Right	Yes	194	43.1
		No	256	56.9
	Left	Yes	191	42.4
		No	259	57.6
	Total	Yes	385	42.7
		No	515	57.3
Posterior synechia	Right	Yes	103	22.9
		No	347	77.1
	Left	Yes	101	22.4
		No	349	77.6
	Total	Yes	204	22.6
		No	696	81.4
Hypopyon	Total	Yes	29	6.4
		No	421	93.6
Anterior synechia	Right	Yes	8	1.8
		No	442	98.2
	Left	Yes	9	2.0
		No	441	98.0
	Total	Yes	17	1.9
		No	883	98.1

* Total eyes.

Table 3. *Treatment approaches applied during the follow-up of patients with uveitis*

Treatment	n	%
Topical steroid	353	78.4
Systemic steroid	202	44.9
Azathioprine	90	20
Periocular-intravitreal steroid	66	14.7
Colchicine	61	13.6
Adalimumab	51	11.3
Systemic antibiotic	49	10.9
Sulfasalazine	41	9.1
Cyclosporine	34	7.6
Methotrexate	34	7.6
Systemic antiviral	18	4
Infliximab	15	3.3
Interferon alpha	7	1.6
Etanercept	3	0.7
Golimumab	2	0.4

of the cases. A comprehensive breakdown of other ocular examination findings can be found in Table 2.

Therapeutic Interventions

The therapeutic modalities employed for managing uveitis throughout the observation period are delineated in Table 3.

Complications

Complications arising from uveitis were also documented. Glaucoma was observed as a sequela in 6.8% (n=62) of the patients. In terms of ocular complications across all eyes, cataract formation was noted in 3.8% (n=35), band keratopathy in 1.8% (n=17), and corneal opacity in 1.5% (n=14).

Table 4. *The relationship between the site of involvement and treatment outcome in patients with uveitis**

Involvement	Result	n	%
Anterior	Healing	247	70.7
	Treatment continues	102	29.3
	No response received	0	0
Posterior	Healing	41	67.2
	Treatment continues	20	32.8
	No response received	0	0
Intermediate	Healing	30	78.9
	Treatment continues	8	21.1
	No response received	0	0
Panuveitis	Healing	49	28.3
	Treatment continues	109	63.0
	No response received	15	8.7
Total	Healing	367	59.1
	Treatment continues	239	38.5
	No response received	15	2.4

* Eyes with different involvement sites between right and left were recorded separately.

Treatment Outcomes

The correlation between the anatomical site of uveitis and the therapeutic outcomes is elucidated in Table 4.

Discussion

Our study provides valuable insights into the epidemiology and clinical presentation of uveitis in our patient cohort, contributing to the broader understanding of this complex ocular condition. We observed notable similarities and differences while comparing our findings with global trends, particularly in demographic distributions and clinical manifestations. In our cohort, the prevalence of uveitis in females was higher than in males, contrasting with some global epidemiological data where gender distribution in uveitis is often more balanced[3,6]. However, our findings align with several domestic studies that reported a female predominance[7,8].

Uveitis often remains asymptomatic, particularly among younger individuals, with diagnoses frequently made post-complication[9]. Symptomatology can vary across age groups. For instance, while children predominantly present with blurred vision, adults often report symptoms like redness, photophobia, pain, and floaters[10]. Our study's primary presenting complaint was decreased vision, followed by photophobia, floaters, redness, and pain. These findings are consistent with Sizmaz et al., who reported blurred vision as the primary symptom in 68% of their cohort[7]. The variations in symptom percentages might be attributed to the retrospective nature of our study and potential inconsistencies arising from multiple clinicians conducting examinations.

Anatomically, anterior uveitis emerged as the most prevalent form of involvement, consistent with several studies in the literature[11,12]. Etiologically, idiopathic uveitis was predominant, followed by Behçet's disease and Ankylosing spondylitis. This distribution mirrors findings from studies by Rathinam et al. and Khairallah et al., underscoring the global prevalence of idiopathic uveitis[13,14].

Therapeutically, corticosteroids remain the cornerstone of uveitis management[15,16]. In our cohort, topical steroids were the most frequently administered treatment, followed by systemic steroids. The choice of immunosuppressants varied, with azathioprine being the most commonly prescribed in our centre, especially for Behçet's disease and steroid-resistant autoimmune uveitis[17,18].

The observed incidences of secondary glaucoma and cataract formation align with existing literature[19,20]. This concordance reinforces the established understanding of these complications as common sequelae in uveitis patients. Our data contribute to the broader narrative on the ocular risks associated with uveitis.

In our study, treatment outcomes, particularly in cases of panuveitis, were notably poor. Panuveitis demonstrates a more aggressive clinical course than other uveitis types[2]. The literature indicates that a significant proportion of panuveitis cases encounter poor visual outcomes despite aggressive treatment[21,22]. The data obtained in our study reflect this aggressive progression and the challenges in management. These findings underscore the necessity for customized treatment strategies to manage panuveitis.

Limitations

Our study's limitations include potential inconsistencies arising from multiple clinicians conducting patient evaluations and the inherent challenges of retrospective research. Despite these limitations, our study offers a comprehensive overview of uveitis, filling a gap in the literature that often lacks more holistic data on uveitis patients.

In summary, our study provides a nuanced understanding of our region's demographic and clinical profiles of uveitis patients, highlighting the distinct gender

distribution, symptomatology, anatomical involvement, etiological factors, and therapeutic approaches. The predominance of idiopathic uveitis and the therapeutic reliance on corticosteroids underscore the universality of certain aspects of uveitis management. At the same time, regional variations emphasize the importance of context-specific clinical insights. As the global medical community grapples with the challenges of uveitis, studies like ours serve as crucial reference points, facilitating evidence-based clinical decisions and guiding future research endeavours. We hope subsequent investigations will build upon our findings, fostering a more integrated and holistic understanding of uveitis across diverse populations.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

The Impact of Physical Activity Level and Sexual Activity During Pregnancy on Labor

Gebelikte Fiziksel Aktivite Düzeyi ve Cinsel Aktivitenin Doğum Eylemi Üzerindeki Etkisi

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ABSTRACT

Aim: *We aimed to obtain epidemiologic data on the level of physical activity during pregnancy, physical activity barriers of pregnant women, and sexual activity during pregnancy in Türkiye. We investigated the relationships between physical and sexual activity in pregnant women and labor-related variables.*

Materials and Methods: *The study included volunteers who gave birth in the maternal ward of tertiary training and research hospital. To determine the physical activity levels in pregnancy, "International Physical Activity Questionnaire (IPAQ)" and "Physical Activity Readiness Medical Examination (PARMED-X)" scales were used. In addition, participants were questioned about their sexual activity during pregnancy. Participants' data on the duration of the first and second phases of labor, postpartum hemorrhage, oxytocin administration for labor induction, and unplanned Cesarean section (Cs) were obtained from patients' electronic medical records.*

Results: *The study included 173 pregnant women. Seventy-seven (44.50%) participants were nulliparous. With increasing age, participants were found to be less physically active (p=0.235). There was no correlation between physical activity levels and duration of the phases of labor, gestational age, oxytocin usage, postpartum hemorrhage, and type of delivery. Lower gestational weight gain was observed in the physically active group. There was a relationship between an increase in sexual activities during pregnancy and a shorter duration of the second phase of labor (p=0.018).*

Conclusion: *Our study showed that physical activity levels tended to decrease in pregnant women, and pregnancy-related side effects were mainly responsible for this situation. It was observed that physical activity levels and sexual activity had limited effects on labor.*

Key words: *exercise; pregnancy; sexual behavior; labor; oxytocin*

ÖZET

Amaç: *Türkiye'de gebelik sırasında fiziksel aktivite düzeyi, gebelerin fiziksel aktivite engelleri ve gebelik sırasında cinsel aktivite hakkında epidemiyolojik veri elde etmeyi amaçladık. Gebe kadınlarda fiziksel ve cinsel aktivite ile doğumla ilgili değişkenler arasındaki ilişkileri araştırdık.*

Materyal ve Metot: *Çalışmaya üçüncü basamak eğitim ve araştırma hastanesinin doğum servisinde doğum yapan gönüllüler dâhil edilmiştir. Gebelikteki fiziksel aktivite düzeylerini belirlemek için "International Physical Activity Questionnaire" (IPAQ) ve "Physical Activity Readiness Medical Examination (PARMED-X)" ölçekleri kullanılmıştır. Ayrıca, katılımcılara gebelik sırasında cinsel aktiviteleri hakkında sorular sorulmuştur. Katılımcıların doğumun birinci ve ikinci evresinin süresi, doğum sonrası kanama, doğum endüksiyonu için oksitosin uygulaması ve planlanmamış sezaryen (Cs) ile ilgili verileri hastaların elektronik tıbbi kayıtlarından elde edilmiştir.*

Bulgular: *Çalışmaya 173 gebe kadın dâhil edilmiştir. Katılımcıların 77'si (%44,50) nullipardı. Katılımcıların yaşları arttıkça fiziksel olarak daha az aktif oldukları bulunmuştur (p=0,235). Fiziksel aktivite düzeyleri ile doğumun evrelerinin süresi, gebelik yaşı, oksitosin kullanımı, doğum sonrası kanama ve doğum şekli arasında bir ilişki bulunmamıştır. Fiziksel olarak aktif grupta daha düşük gestasyonel kilo alımı gözlenmiştir. Gebelik sırasında cinsel aktivitelerin artması ile doğumun ikinci evresinin daha kısa sürmesi arasında bir ilişki saptanmıştır (p=0,018).*

Sonuç: *Çalışmamız, gebelerde fiziksel aktivite düzeylerinin azalma eğiliminde olduğunu ve bu durumdan esas olarak gebeliğe bağlı yan etkilerin sorumlu olduğunu göstermiştir. Fiziksel aktivite düzeylerinin ve cinsel aktivitenin doğum eylemi üzerinde sınırlı etkileri olduğu gözlenmiştir.*

Anahtar kelimeler: *egzersiz; gebelik; cinsel aktivite; doğum; oksitosin*

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Introduction

It is common knowledge that physical activity during and after pregnancy benefits both the health of the mother and the fetus. Pregnant women with a combination of diet and exercise are less likely to have fetal risks such as fetal death and macrosomia and maternal risks such as gestational diabetes and pre-eclampsia[1]. However, in this period, physical activity decreases due to factors such as motivation, knowledge, and family support[2].

In animal studies, there is evidence that exercise increases oxytocin production and oxytocin receptor production[3]. Similar to the impact of exercise, Cera et al. showed that oxytocin concentrations in plasma and various secretions increased during sexual activity in humans[4]. However, during pregnancy, women consider sexual activity to be unsafe, and sexual functions decrease[5]. Furthermore, oxytocin causes positive feedback on its secretion[6]. Oxytocin is known to have effects on pregnancy, childbirth, and breastfeeding. Following these effects, oxytocin receptor expression increases significantly in many tissues, especially in the brain, during pregnancy but returns to pre-pregnancy levels after delivery[7]. Besides these physiological roles, oxytocin has been used for labor induction and treatment of postpartum hemorrhage[8].

There is limited information on the relationship between physical activity levels and sexual activity in the labor event. A study conducted in Sweden investigated the effects of physical activity and sedentary time separately on factors such as gestational weight gain (GWG) and indication for emergency cesarean section[9]. In another recent study, the physical activity levels of pregnant women were evaluated with the Kaiser Physical Activity Questionnaire. Pregnant women with high and low physical activity levels were divided into two groups, and variables such as the duration of the active phase of labor, operative vaginal delivery, and maternal complications related to delivery were compared between these groups[10]. A meta-analysis shows that sexual activity during pregnancy did not affect spontaneous labor onset[11].

In this study, we aimed to obtain epidemiologic data on the level of physical activity during pregnancy, physical activity barriers of pregnant women, and sexual activity during pregnancy in Türkiye. In addition, we investigated the relationships between physical and sexual activity in pregnant women and labor-related variables.

Method

The study included volunteers who gave birth in the maternal ward of a tertiary training and research hospital. Data were obtained from a questionnaire and electronic medical records of patients. In the first part of the questionnaire, sociodemographic data of the participants; in the second part, the level of physical activity during pregnancy and the frequency of vaginal sexual intercourse in the first, second, and third trimesters and after 37 weeks of pregnancy were questioned.

Since physical activity during pregnancy is more limited than in other periods of life, special scales are used to classify the level of physical activity. For this purpose, the "International Physical Activity Questionnaire" (IPAQ) was used to question pregnant women's sitting, walking, moderate activity, and vigorous physical activity[12]. According to the questionnaire responses, pregnant women were categorized into three groups: inactive, minimally active and very active. In addition, pregnant women were divided into three groups: unfit, active, and fit, using the Physical Activity Readiness Medical Examination (PARMED-X) prepared by the Canadian Society of Exercise Physiology, which specifically questions exercise levels during pregnancy[13,14]. This template questioned how many days per week pregnant women exercised in the last trimester and whether these exercises lasted more than 20 minutes.

Participants' data on the duration of the first and second phases of labor, postpartum hemorrhage, oxytocin administration for labor induction, and unplanned Cesarean section (Cs) were obtained from patient files.

Pregnant women were also divided into two categories, nulliparous and multiparous, and the analyses were performed separately for both categories.

Ethical approval of the study was obtained from the XXX Training and Research Hospital Ethics Committee for Scientific Research with the date 14.12.2022 and number 2022/147. All participants provided informed consent, and voluntary participants were included in the study. The study was conducted in accordance with the principles of the Helsinki Declaration.

Frequency, mean, standard deviation, minimum, and maximum values were used in descriptive epidemiologic data statistics related to physical activity levels, sexual activity, and labor. Shapiro Wilk test was applied to determine the normal distribution of the groups. One-way ANOVA, Independent T test, and Kruskal Wallis tests were then applied. Simple and multiple linear regression

tests were used to investigate the relationship between numerical variables. All analyses were performed using R Statistical Software (v4.2.2; R Core Team 2022). $p < 0.05$ was considered statistically significant.

Results

The study included 173 pregnant women. Seventy-seven (44.50%) participants were nulliparous, and the others were multiparous. The mean age of the study group was 26.89±5.09 years.

Physical Activity in Pregnancy

Physical activity levels increased in 26 (33.7%) and decreased in 23 (29.8%) with pregnancy in nulliparas. In multiparous women, it increased in 20 (20.61%), decreased in 42 (43.29%), and remained unchanged in 34 (35.41%) participants. The most common reason stated by those whose physical activity level decreased was the side effects of pregnancy in 40 (61.53%) of the participants. Eight participants indicated that they did less physical activity due to lack of motivation, eight due to fear of harm to pregnancy, four due to lack of time, one due to medical reasons, and three due to other causes.

The Relationship Between Physical Activity Levels and Labor

There was no effect of the change in physical activity level on the duration of the phases of labor, postpartum hemorrhage, OT usage and gestational age.

Participants were divided into three groups according to their physical activity levels using PARMED-X scoring as fit 74 (42.8%), active 60 (34.7%) and unfit 39 (22.5%). Unfit women were older than active and fit pregnant women (p=0.235). There was no correlation between physical activity level, the duration of labor phases and gestational age. Chi-square tests showed no association between physical exercise levels and postpartum hemorrhage, oxytocin usage and unplanned Cs. Less gestational weight gain was observed in the fit group (p=0.06). The relationship between physical activity levels and labor is summarized in Table 1.

Pregnants were divided into three groups: very active 15 (8.7%), minimally active 68 (39.3%), and inactive 90 (52%) based on their physical activity levels using the IPAQ scale. It was observed that physical activity levels did not affect the duration of labor phases, gestational age, postpartum hemorrhage, oxytocin use, and unplanned Cs (Table 2).

Relationship between Sexual Activity Levels and Labor

Sexual activity in any trimester during pregnancy did not affect the duration of the phases of labor and gestational age. Similarly, chi-square tests showed that sexual activity did not pose a risk for postpartum hemorrhage and unplanned Cs. However, the linear regression test showed that an increased frequency of sexual intercourse was associated with a shorter duration of the second phase of labor in nulliparous (R^2=0.089, p=0.023) as represented in Table 3.

Table 1. *The relationship between physical activity levels and labor*

		Unfit (Mean ± SD or Number)	Active (Mean ± SD or Number)	Fit (Mean ± SD or Number)	*p Value*
First phase of labor in nulliparous		758.46±544.08	852.94±621.20	936.25±741.52	0.726
Second phase of labor in nulliparous		53.25±51.67	50.29±35.44	52.629±42.11	0.972
First phase of labor in multiparous		411.73±326.69	540.38±463.90	421.52±413.38	0.409
Second phase of labor in multiparous		25.18±23.02	31.14±49.05	23.05±24.63	0.646
Oxytocin usage in nulliparous	Yes	6	15	21	0.475
	No	8	13	13	
Oxytocin usage in multiparous	Yes	8	11	11	0.852
	No	17	21	28	
Unplanned Cs in nulliparous	Yes	2	1	7	0.154
	No	12	27	28	
Unplanned Cs in multiparous	Yes	2	3	2	0.781
	No	23	29	37	
Postpartum hemorrhage in nulliparous	Yes	1	1	1	0.777
	No	13	27	34	
Postpartum hemorrhage in multiparous	Yes	2	2	3	0.961
	No	23	30	36	

Cs: cesarean section, SD: standard deviation. One-way ANOVA and Tukey post-hoc test were used to compare the means of the groups. Chi-square test was used to analyze categorical data.

Table 2. *The relationship between physical activity levels and labor*

		Inactive (Mean ± SD or number)	Minimally active (Mean ± SD or Number)	Very Active (Mean ± SD or Number)	*p Value*
First phase of labor in nulliparous		805±635.2	912.2±661	1008±622.7	0.72
Second phase of labor in nulliparous		54.70±44.58	47.97±40.12	66±32.86	0.60
First phase of labor in multiparous		557.3±472.6	348.2±314.7	420.6±337.3	0.071
Second phase of labor in multiparous		26.39±22.43	27.88±47.26	20±19.03	0.831
Oxytocin usage in nulliparous	Yes	22	16	4	0.835
	No	19	13	2	
Oxytocin usage in multiparous	Yes	19	9	2	0.266
	No	30	29	7	
Unplanned Cs in nulliparous	Yes	4	5	1	0.666
	No	37	25	5	
Unplanned Cs in multiparous	Yes	4	3	0	0.675
	No	45	35	9	
Postpartum hemorrhage in nulliparous	Yes	1	2	0	0.579
	No	40	28	6	
Postpartum hemorrhage in multiparous	Yes	5	2	0	0.459
	No	44	36	9	

Cs: cesarean section, SD: standard deviation. One-way ANOVA and Tukey post-hoc test were used to compare the means of the groups. Chi-square test was used to analyze categorical data.

Table 3. *Relationship between sexual activity levels and labor*

	R^2	Estimate	Std error	t value	*p Value*
Nulliparous	(Intercept)	5.688	40.169	0.142	0.135
	First phase	-0.0007	0.002	-0.270	0.788
	Second phase	0.0968	0.041	2.330	0.023
	Gestational age	0.0064	0.144	0.044	0.964
Multiparous	(Intercept)	49.618	43.528	1.14	0.258
	First phase	-0.004	0.003	-1.29	0.199
	Second phase	0.037	0.040	0.92	0.360
	Gestational age	-0.14	0.157	-0.91	0.365

Table 4. *The effect of gestational history on labor*

		Nulliparous (mean ± SD or number)	Multiparous (mean ± SD or number)	*p-value*
First phase of labor		863.8±645	459.9±411	<0.001
Second phase of labor		51.08±41.2	26.02±34.11	<0.001
Oxytocin usage	Yes	42	30	0.0015
	No	34	66	
Unplanned Cs	Yes	10	7	0.211
	No	67	89	
Postpartum hemorrhage	Yes	3	7	0.3416
	No	74	89	

Cs: cesarean section, SD: standard deviation. The Independent Samples t Test used to compare the means of groups. Chi-square test was used to analyze categorical data.

The Effect of Gestational History on Labor

The mean duration of the first phase of labor was 863.8±645 min in nulliparous women and 459.9±411 min in multiparous women. This difference was statistically significant (p<0.001). Similarly, the duration of the second phase of labor was significantly higher in nulliparous women (p<0.001). A similar finding was observed with an increase in the number of deliveries with shorter duration of the first and second phases of labor (p<0.001).

No association was found between pregnancy history and gestational age (p=0.84) and number of births and gestational age (p=0.88).

Oxytocin administration for labor induction occurred in 55% of nulliparous women and was significantly lower (31.25%) in multiparous women (p=0.0015). However, no significant difference was observed in unplanned Cs and postpartum hemorrhage in nulliparous and multiparous women. The relationship between pregnancy history and delivery is shown in Table 4.

Discussion

In this study, it was observed that pregnancy caused a change in physical activity levels, and the most important obstacle to being less physically active was pregnancy-related side effects. It was determined that physical activity levels decreased with increasing age during pregnancy. Physical activity level and sexual activity during pregnancy were found to be neither protective nor risky for the duration of labor, postpartum hemorrhage, oxytocin use and operative vaginal delivery. However, physical activity was found to be helpful in controlling weight gain during pregnancy.

Previous studies have shown that pregnant women do not have sufficient awareness of physical activity during pregnancy. Therefore, most pregnant women tend to lead a sedentary life. In our study, a relatively balanced distribution was observed in nulliparous women regarding physical activity change, whereas multiparous women's physical activity levels mainly decreased with pregnancy. In a study conducted in Türkiye, pregnant women stated that the most critical barriers to physical activity were lack of motivation and lack of time[2]. However, our study showed participants stated that they had difficulty in doing physical activity, especially due to the side effects of pregnancy and motivation problems

Several studies have shown that physical activity during pregnancy is safe. Scientific evidence suggests that aerobic exercise has additional benefits for almost all pregnant women[15]. Leet and Flick reported that maternal exercise may have minimal or no effect on the baby's birth weight[16]. Watson et al. showed that physical activity during pregnancy does not have risks for fetal development and provides benefits in controlling gestational weight gain[17]. All these data support our study.

In a randomized controlled trial, the total delivery time of women who exercised in water was 3 hours shorter than the control group[18]. Watkins et al. showed that a higher physical activity level was associated with a shorter duration of labor stages but not with postpartum hemorrhage, perineal laceration, or operative vaginal delivery[10]. The main difference of this study, which is similar to the results of our research in most aspects, is the relationship between the duration of labor and physical activity levels. We used two different physical activity scales in our study to clarify this relationship. In addition, in the IPAQ scale, we assessed the data on both categorical and total MET scores, and these analyses were performed separately in nulliparous and multiparous women, but no correlation was found. Therefore, there may be factors that were not considered in the two studies.

In a study conducted in Cameroon, pregnant women who were sexually active after 37 weeks of gestation had shorter labor times, less oxytocin requirement and higher rates of spontaneous vaginal delivery[19]. Schaffir showed in a study that women who were sexually active in the week before delivery had a higher gestational age, but there was no significant difference in Bishop scores between the physically active group and the control group[20]. In contrast, another study revealed that sexual activity was associated with lower gestational age[21]. The same study found that sexual activity during pregnancy did not affect the type of labor. In a meta-analysis, it was stated that it does not cause a risk for the onset of spontaneous labor and that it is not necessary to restrict sexual activity in low-risk pregnancies[11]. These studies suggest no clarity about the effects of sexual activity during pregnancy on delivery. However, although the possible benefits of sexual activity are controversial, there is consistent evidence that it is not a restriction for low-risk pregnancies. Similarly, in our study, sexual activity did not pose an additional risk. Still, only a weak association was found between the frequency of sexual activity and the second phase of labor. Apart from this, no effect on delivery was observed. Therefore, it is understood that this issue has not yet been fully clarified.

The most obvious limitation of the study was the low participant numbers. This limitation was particularly noticeable in the analysis of categorical data. However, analyzing our data with multiple scales and statistical analysis methods reduces this restriction.

Conclusion

In conclusion, this study provides essential epidemiologic data on the attitudes of pregnant women toward exercise and sexual activity in Türkiye. It was observed that physical activity levels decrease during pregnancy, and the biggest obstacle to physical activity is the side effects of pregnancy. Pregnant women exercised less as their age increased. It was observed that exercise levels during pregnancy have limited impacts on labor and may be helpful in controlling weight gain during pregnancy. Similarly, it was confirmed that the effects of sexual activity during pregnancy on labor were minimal, and sexual activity did not need to be restricted in low-risk pregnancies. It was also reconfirmed that pregnancy history accelerates and facilitates labor in parallel with the literature.

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OLGU SUNUMU / *CASE REPORT*

Taenia saginata Removed Via Nasogastric Route: Case Report*

*Nazogastrik Yolla Çıkarılan Taenia saginata: Olgu Sunumu**

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ABSTRACT

Inguinal hernia repair is one of the most frequently performed elective surgeries in general surgery. However, this surgery may sometimes encounter complications such as incarceration and especially strangulation, which require urgent surgical intervention. In such emergency cases, severe conditions may occur, ranging from simple hernia repair to bowel resection, which may lead to high morbidity and even mortality. Parasitic infections occurring during or after surgery have rarely been reported in the literature. In this case report, we wanted to emphasize the importance of the Taenia saginata (T. saginata) helminth parasite removed by the nasogastric route. A 66-year-old female patient who came to the emergency room with complaints of nausea and vomiting was diagnosed with ileus due to an incarcerated hernia and, therefore, underwent small bowel resection. During aspiration of stomach content, a gastrointestinal parasite wrapped around a nasogastric tube was found. Macroscopic and microscopic examinations revealed that this parasite was T. saginata. After oral intake was deemed appropriate, anthelmintic treatment was administered, and the patient's general condition improved, and she was discharged. It should be kept in mind that T. saginata parasitic infection, which cannot be detected in clinical and laboratory tests and occurs coincidentally, may contribute to the development of incarceration in inguinal hernia patients living in areas with low socio-economic status, especially where sanitation is inadequate, consumption of raw or undercooked meat is common.

Key words: *inguinal hernia, incarceration, strangulation, nasogastric, Taenia saginata*

ÖZET

İnguinal herni onarımı, genel cerrahide elektif şartlarda en sık gerçekleştirilen ameliyatlardan biridir. Ancak, bu ameliyat bazen inkarserasyon ve özellikle strangülasyon gibi acil cerrahi müdahale gerektiren komplikasyonlarla karşı karşıya kalabilir. Bu tür acil vakalarda, basit bir fıtık onarımından bağırsak rezeksiyonuna kadar varabilen ve yüksek morbidite ile hatta mortaliteye yol açabilen ciddi durumlar ortaya çıkabilir. Cerrahi sırasında veya sonrasında ortaya çıkan paraziter enfeksiyonlar literatürde nadir olarak bildirilmiştir. Bu vaka sunumunda, nazogastrik yolla çıkan Taenia saginata (T. saginata) helmint parazitinin önemini vurgulamak istedik. Bulantı ve kusma şikâyetleriyle acil servise gelen 66 yaşındaki kadın bir hastada, inkarsere herniden kaynaklı ileus tanısı konulmuş ve bu nedenle ince bağırsak rezeksiyonu gerçekleştirilmiştir. Mide içeriği aspirasyonu sırasında nazogastrik sondaya sarılı gastrointestinal bir parazit bulunmuştur. Makroskobik ve mikroskobik incelemeler sonucunda bu parazitin T. saginata olduğu tespit edilmiştir. Hastaya oral alım uygun görüldükten sonra antihelmintik tedavi uygulandıktan sonra genel durumu iyileşen hasta taburcu edilmiştir. Klinik ve laboratuvar testlerinde tespit edilemeyen ve rastlantısal olarak ortaya çıkan T. saginata paraziter enfeksiyonunun, özellikle sanitasyonun yetersiz olduğu, çiğ veya iyi pişmemiş et tüketiminin yaygın olduğu, sosyo-ekonomik düzeyi düşük bölgelerde yaşayan inguinal herni hastalarında inkarserasyon gelişimine katkıda bulunabileceği göz önünde bulundurulmalıdır.

Anahtar kelimeler: *inguinal herni, inkarserasyon, strangülasyon, nazogastrik, Taenia saginata*

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Introduction

Taenia saginata, known as bovine tapeworm, is the most common tapeworm transmitted to humans. It is known that they widely infect many people in the world and our country. However, they are more frequently found in European and Asian regions where raw meat consumption is common. The most important reasons for this are societies' lack of socioeconomic, hygiene and education levels. In *T. saginata* infection, cattle are the intermediate host, and humans are the final host of the adult form[1]. Tapeworms can be found parasitically in the human digestive tract. Due to the tight adhesion to the intestinal wall or the inhibitory effect of gastric acidity, the parasite is unlikely to be transported to other sites. However, it has an irritative and traumatic impact on the adult; it may obstruct the respiratory tract during vomiting and enter the middle ear, uterine cavity and biliary tract through the Eustachian tube. Sometimes, proglottids in taeniasis can cause acute appendicitis by blocking the lumen of the appendix[2,3] and asphyxia by aspirating proglottids during vomiting, which can lead to life-threatening situations[4]. In summary, although rare, the literature suggests that these cases may require surgical intervention due to obstructions in the appendix, bile ducts or pancreatic ducts[3,5–7].

Inguinal hernia (inguinal hernia) is a surgical condition that occurs when a weak point in the abdominal wall pushes a part of the abdominal organs or intestine through the peritoneum. Inguinal hernia surgery is one of the most common operations performed in elective conditions in general surgery. Although it is not a dangerous condition on its own, sometimes the peritoneum or intestine that enters through the hole in the abdominal wall can get stuck there. If the swelling does not go in spontaneously and causes persistent and severe pain, an incarcerated hernia is mentioned, and a doctor should be consulted urgently. The continuation of this compression prevents the blood flow in the vessels, disrupts the nutrition of the compressed tissue and causes gangrene. This condition is called strangulated inguinal hernia. If not intervened urgently, it causes serious complications that can be life-threatening[8].

Although parasitic infections occurring after or during surgery are available in the literature, their numbers are very few. This study included T. saginata endo-parasite, which was removed via nasogastric route in a patient diagnosed with ileus due to incarcerated hernia.

Case report

History

A 66-year-old woman residing alone in a rural area came to the emergency department with symptoms of nausea and vomiting that had persisted for three days. It was learnt that the patient had no fever, diarrhoea-constipation, no known chronic disease and no history of drug use. Socioeconomic status was low.

Assessment

As a result of blood tests performed in the emergency department, WBC: 14700 µl, HGB: 14,2 g/dl, CRP: 115, Urea: 171.2, CREATININE: 2,54 mg/dl, GFR: 19,07 were determined. On standing direct abdominal radiograph, diffuse air-fluid levels in the tiny bowel anus and whole abdomen non-contrast computed tomography (CT) scan were reported as suspicion of ileus. The patient was consulted with general surgery with a prediagnosis of ileus. On physical examination, the general condition of the patient was moderate, consciousness was clear, orientation and cooperation were poor, and he was highly cachectic and hypotensive. Abdominal distension is a metallic ringing sound in the intestines on auscultation, which is pathognomic for ileus. There was widespread tenderness in all quadrants of the abdomen and an incarcerated hernia in the right inguinal region. However, the diagnosis of incarcerated inguinal hernia detected in the physical examination was not included in the official tomography report (Fig. 1).

Operation Summary

Ileus, due to the right incarcerated inguinal hernia, was diagnosed. Segmental small bowel resection was performed. After resection, gastric contents were tried

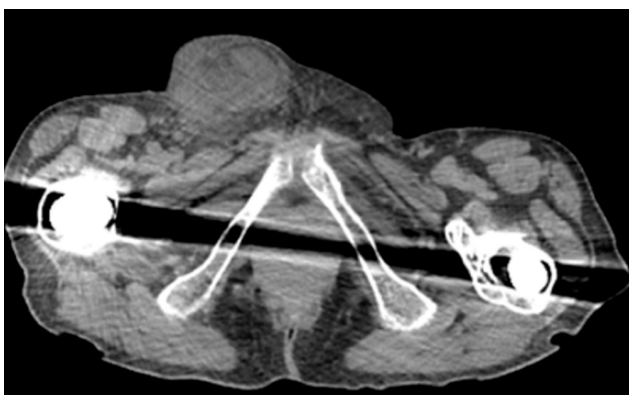

Figure 1. *Incarcerated inguinal hernia appearance on computed tomography (CT).*

Figure 2. *T. saginata is emerging from the nose of an adult.*

Figure 3. *T. saginata adult.*

to be aspirated with the help of a nasogastric probe. During the operation, palpation revealed that the stomach was complete, and the probe was in the appropriate position. Despite this, gastric contents could not be aspirated. Changing the nasogastric catheter was decided. When the nasogastric catheter was withdrawn, it was found that there was a gastrointestinal (GI) tract parasite wrapped around the catheter. After the nasogastric catheter was withdrawn, two more parasites approximately 106 cm in size were removed from the patient via the nasal route (Fig. 2). The stomach was still packed when palpated, and the removal of the remaining parasites by endoscopy was decided after surgery. Parasite samples were sent to the parasitology laboratory. Macroscopic and microscopic examination revealed *T. saginata* (Fig. 3). The patient was admitted to the postoperative 3rd step intensive care unit.

Outcome

On the 1st postoperative day, the patient's general condition was good, vitals were stable, and the patient was followed up with oral closure. Appropriate hydration

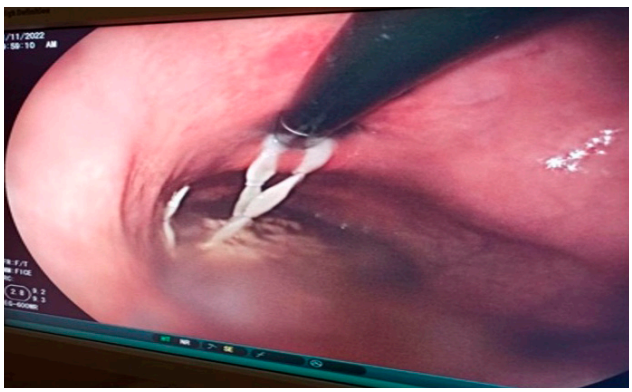

Figure 4. *T. saginata removed by endoscopy.*

and antibiotic treatment were planned. Parenteral nutrition was started for the very cachectic patient. Upper GI tract endoscopy was scheduled with a gastroenterologist. Upper GI tract endoscopy revealed a diffuse *T. saginata* cestode in the stomach. It was tried to be removed by endoscopy (Fig. 4). Since there was a risk of adhesion to the esophagus, especially the oropharynx, the anesthetist thought there might be a risk of airway obstruction. It was decided not to remove the remaining parasites endoscopically.

On the 4th postoperative day, since the patient no longer needed intensive care, she was taken to the general surgery service. To evaluate the anastomosis, oral contrast-enhanced CT was performed on the patient, which was suitable for renal function tests (RFT). Based on all these procedures, it was observed that the patient's anastomosis is intact, there is no leakage, and it is suitable for oral intake. The patient was started on oral nutrition and oral niclosamide (YOMESAN 500 mg tb 1x4 dose for one day) as an antihelminthic treatment. Approximately 48 hours later, in the anamnesis given by the patient's relatives, it was learned that the proglottids of the *T. saginata* parasite were defecated.

On the 8th postoperative day, it was learned that the patient, whose general condition was excellent and oral intake was average, was still defecating proglottids. The patient, who was planned to be discharged from general surgery, was consulted about infectious diseases. Infectious diseases outpatient clinic control was recommended, and the patient was discharged. It was learned from the patient's relatives that they would take the patient to a center in their city of residence for control purposes.

Consent was obtained from the patients participating in this study.

Discussion

Taenia saginata occurs where cattle are raised, human feces are not disposed of properly, meat inspection programs are weak, and meat is eaten without proper cooking. Of the 32 known *Taenia* species, only *Taenia solium* and *Taenia saginata* have significant medical relevance. About 50 million people globally are infected with *T. saginata* or *T. solium*[9]. Most people with taeniasis are either asymptomatic or have only mild to moderate symptoms. When symptoms do occur, they usually are mild and have abdominal pain, anorexia, weight loss or weakness. The most common complaint is the passing of proglottids (worm parts) in feces, which is associated with mild discomfort[1,10].

The most frequent severe complication of *T. saginata* infection in adults is appendicitis[3]. Additional reported complications encompass intestinal obstruction, bile or pancreatic duct blockage, abnormal vaginal bleeding, pneumatosis cystoid intestinalis (PKI), and, though rarely, anastomotic leakage or granulomatous gastritis[5,11,12]. Taeniasis invades the upper small intestine in humans. Unusually, this parasite is found in the stomach. A case in which the *Taenia* parasite found in the stomach of a young adult patient living in a rural area complained of nausea and vomiting excreted through the nasal route was reported in the literature [9]. Similarly, another study reported that *Taenia* proglottids were excreted from the nose and feces in a 4-year-old male child[13]. However, neither of the studies provided any comments on why the parasite is present in the stomach. In this case, it was observed that the patient developed intestinal obstruction due to an incarcerated hernia. Secondary to this, the parasites could not pass into the distal segments, thus reaching the stomach and esophagus. This brought to mind the idea that the parasite was not tightly attached to the intestinal wall; it created a very unusual living space in the stomach, and it might have moved to the nose because it was not sufficiently blocked by stomach acid.

Incarceration develops in approximately 5% of abdominal wall hernias and requires emergency surgery[14]. In the literature, only one case report has been found in which the *T. saginata* parasite was detected during minor intestine perforation repair after blunt abdominal trauma in a patient with inguinal hernia[12]. In this study, the patient had no history of trauma and resection was performed due to incarceration, and the GI tract parasite *T. saginata* was incidentally detected. Due to the rare cases and the limited number of studies, no definitive conclusion can be drawn regarding the role of GI tract parasites in developing inguinal hernia and its complications.

Parasitic infections are more common in regions with inadequate sanitation, consumption of raw or undercooked meat is typical, and in areas with low socio-economic levels. One of the pathogens that cause parasitic infections is *T. saginata*. In this case, diagnosed as an inguinal hernia, the *T. saginata* parasite was detected incidentally during surgery and endoscopy. Although such cases are rare, the presence of *Taenia* should be taken into consideration, and parasitological analysis should be requested during the evaluation of the etiology of patients presenting with abdominal pain and weight loss in areas with low socio-economic status. To prevent *Taenia* infection, it is emphasized that veterinary-controlled, hygienically preserved and well-cooked meat should be consumed. Educating the public about hygiene and cooking practices is of great importance in preventing such infections.

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Concept: N.M., B.B.S.; Design: N.M., B.B.S.; Data collection &/or proces- sing: N.M., B.B.S.; Analysis and/or interpretation: N.M., B.B.S.; Literature search; N.M.; Writing: N.M., B.B.S.; Critical re-view: N.M., B.B.S.

Ethical Approval

Consent was obtained from the patients participating in this study.

Conflict of Interest

None declared.

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