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Prevalence of Intestinal Parasites Among Patients Attending A Tertiary Referral Hospital in Mogadishu, Somalia: A 6-year Retrospective Study

Somali, Mogadişu'daki Üçüncü Basamak Bir Hastaneye Başvuran Hastalarda İntestinal Parazitlerinin Prevalansı: 6 Yıllık Retrospektif Bir Çalışma

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ABSTRACT

Background: Parasitic intestinal infection is a neglected public health problem in developing countries, including Somalia. This study examined the prevalence of parasitic intestinal infections among patients who requested stool examination at University of Health Sciences Türkiye, Mogadishu Somalia Türkiye Recep Tayyip Erdoğan Training and Research Hospital.

Materials and Methods: We retrospectively reviewed the electronic medical records of patients who requested stool examination between January 2015 and December 2020. Stool samples were examined for the presence of parasites by direct wet smear using light microscopy.

Results: Seven percent (2738 of 37398) of patients tested for parasitic intestinal infections were positive for at least one species of intestinal parasite. *Giardia duodenalis* was the most prevalent parasite (3.85%), followed by *Entamoeba histolytica/dispar* (2.77%). Female patients had more episodes of parasitic intestinal infections than their male counterparts; however, no differences were found (p=0.31) between sex and parasitic infections. Compared with adults, children had significantly higher infection rates (p<0.001). Parasitic intestinal infections were significantly higher during the dry season than during the rainy season (p<0.001). Of the stool samples, double parasitic infections were detected in 2.26%.

Conclusions: A low prevalence of parasitic intestinal infections was observed among patients who attended a tertiary referral hospital in Mogadishu, Somalia. *Giardia duodenalis* was the most common intestinal parasite, followed by *Entamoeba histolytica/dispar*, while double parasite infections were also present. The introduction of effective community-based parasite control programs may help combat parasitic intestinal infections in the country.

Keywords: Parasitic intestinal infections, *Entamoeba histolytica/dispar*, *Giardia duodenalis*, seasonal variation, Somalia

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ÖZ

Amaç: Paraziter intestinal enfeksiyonları, Somali'nin de içinde bulunduğu gelişmekte olan ülkelerde ihmal edilen halk sağlığı sorunlarından biridir. Bu çalışma, Sağlık Bilimleri Üniversitesi, Mogadişu Somali Türkiye Recep Tayyip Erdoğan Eğitim ve Araştırma Hastanesi'nde dışkı muayenesi istenen hastalarda parazitik bağırsak enfeksiyonlarının prevalansını değerlendirmeyi amaçladı.

Gereç ve Yöntemler: Ocak 2015 ile Aralık 2020 arasında dışkı muayenesi talep edilen hastaların elektronik tıbbi kayıtları retrospektif olarak incelenmiştir. Dışkı örnekleri ışık mikroskobu kullanılarak doğrudan ıslak yayma ile parazit varlığı açısından incelendi.

Bulgular: Paraziter intestinal enfeksiyonları için test edilen hastaların %7'si (37398'in 2738'i) bağırsak parazitinin en az bir türü için pozitifti. *Giardia duodenalis* en yaygın parazitti (%3,85), ardından *Entamoeba histolytica/dispar* (%2,77) idi. Kadın hastalarda erkeklere göre daha fazla parazit intestinal enfeksiyon epizodu vardı, ancak cinsiyet ve paraziter enfeksiyonlar arasında fark bulunmamıştır (p=0,31). Yetişkinlerle karşılaştırıldığında, çocuklarda enfeksiyon oranları anlamlı olarak daha yüksekti (p<0,001). Paraziter bağırsak enfeksiyonları kurak mevsimde yağışlı mevsime göre önemli ölçüde daha yüksekti (p<0,001). Dışkı örneklerinin %2,26'sında çift parazit enfeksiyonu tespit edildi.

Sonuç: Somali, Mogadişu'daki bir üçüncü basamak hastaneye başvuran hastalar arasında düşük paraziter intestinal enfeksiyon prevalansı gözlenmiştir. *Giardia duodenalis* en sık görülen bağırsak parazitiydi, bunu *Entamoeba histolytica/dispar* izlemektedir ve ikili parazit enfeksiyonları da mevcuttu. Etkili toplum temelli parazit kontrol programlarının tanıtılması, ülkedeki parazitik intestinal enfeksiyonları ile mücadeleye yardımcı olabilir.

Anahtar Kelimeler: Parazitik barsak enfeksiyonları, *Entamoeba histolytica/dispar*, *Giardia duodenalis*, mevsimsel değişim, Somali

Introduction

Intestinal parasites are organisms that live in or feed on other organisms and reside in the human and animal gastrointestinal tract. Protozoa and/or helminths are the most prevalent parasites that cause intestinal illness (1). Intestinal parasites are common human parasitic infections, posing a global health threat that results in clinical morbidity and mortality (2). Enteric parasites infect 60% of the world's population, according to estimates, and this remains a major public health concern in both industrialized and developing nations (3).

According to the World Health Organization, over 3.5 billion individuals are infected with parasitic infections, and approximately 450 million individuals develop clinical illnesses (4). According to estimates, 895 million individuals are infected with soil-transmitted helminths, with *Ascaris lumbricoides*, *Trichuris trichiura* and hookworms infecting 447 million, 290 million, and 229 million people, respectively (5). Furthermore, 200-500 million people in sub-Saharan African countries were infected with one or more of these intestinal parasite (6).

Parasitic infections mostly affect developing countries, including Somalia, because of their spreading through ingestion or skin penetration by infective forms. Previous studies have reported that it is linked to low socioeconomic status, low education level, lack of awareness of simple health promotion practices, poor hygiene, insufficient toilet facilities, contaminated food and water, hot and humid climate, and environmental and sociocultural factors (5,6,7).Intestinal parasites are one of the major causes of gastrointestinal disorders such as diarrhea, dysentery, and symptoms of vomiting, loss of appetite, hematuria, and abdominal distension, as well as other critical public health issues such as malnutrition, anemia, growth retardation, and physical and mental health issues (7).

In Somalia, epidemiological data on the spread and frequency of intestinal parasites with cutting-edge public health solutions among cases attended in tertiary hospitals, population groups, and the general community are lacking. Only a few studies were carried out in the country, especially before the civil war, which reported that the most common intestinal parasite was *Trichuris trichiura* (8,9,10,11). The country has gone through a devastated civil war, in which nearly the entire healthcare facilities as well as the basic water, sanitation, and hygiene facilities have been non-functioning. Under these conditions, intestinal parasite transmission is likely to thrive. However, limited data on the current status of parasitic infections are available among Somali people. Therefore, we evaluated the prevalence of parasitic intestinal infections among patients attending a tertiary referral hospital in Mogadishu, Somalia.

Materials and Methods

The research was conducted at the University of Health Sciences Türkiye, Mogadishu Somalia Türkiye Recep Tayyip Erdoğan Training and Research Hospital located in Mogadishu, Somalia, which encompasses an altitudinal range of 900 to 2100 meters and has coordinates of 10° 00' N, 49°00' E. Mogadishu is the most populous city in Somalia, with a population of 2,587,183 individuals, 46.8% of whom are urban residents. The city is characterized by an arid to semi-arid climate, with an average annual

minimum temperature of 27 °C (81 °F) and a maximum of 30 °C (86 °F) and an average precipitation of 430 mm per year. Located just north of the Equator on the Indian Ocean, a hot and dry climate prevails throughout the year, along with periodic monsoon winds, erratic rainfalls, droughts, and floods caused by the Shebelle River crossing the region. The population suffers from poor access to safe drinking water, basic sanitation, and hygiene and lives in poverty.

The current study was conducted at the University of Health Sciences Türkiye, Mogadishu Somalia Türkiye Recep Tayyip Erdoğan Training and Research Hospital, which is a tertiary referral center with a 200-bed capacity that caters to approximately 327,000 patients annually and covers all areas of medicine and surgery. The research was conducted in accordance with the ethical principles of the Declaration of Helsinki. The Research Ethics Committee of the University of Health Sciences Türkiye, Mogadishu Somalia Türkiye Recep Tayyip Erdoğan Training and Research Hospital approved the study on April 19, 2021, under the reference number MSTH/6089. Because of the retrospective study design, informed consent was waived, as per the ethics committee that authorized the study.

Demographic and laboratory data were obtained from the electronic medical records of the hospital. Data were subsequently double extracted using Microsoft Excel 365 to ensure consistency and minimize errors in the extracted information. Records completeness and adequacy were checked, and insufficient records were excluded. All patients who were examined for the presence of parasitic infections during a 6-year period from January 2015 to December 2020 were included in this study. All stool samples were collected in labeled, disposable, clean, dry, leak-proof, plastic containers. Each stool sample was processed by direct wet smear and examined under light microscopy (Olympus CX23, Olympus Corporation, Japan) in the parasitology department for the presence or absence of intestinal parasites. Examination of single stool specimen per person was requested by physicians. *G. duodenalis*, *G. intestinalis,* and *G. lamblia* are used interchangeably in referring to the *Giardia species*; therefore, for the purpose of consistency, *G. duodenalis* is used in this study.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and compared using Student's t-test or Mann-Whitney U test after normality test using a one-sample Kolmogorov-Smirnov test. Categorical variables were expressed as frequencies and percentages and compared using the chi-square (χ^2) test to verify the possible association between the prevalence of parasitic intestinal infections and variables such as age, sex, and season. Odds ratio, 95% confidence intervals (95% CI), and p-values were calculated, and the results were considered significant when $p<0.05$. The age of patients was stratified into groups of under-five (<5), 5-14, 15-40, 41-65, and >65 years for statistical analysis. The age range was also categorized into children (≤14 years old) and adults (>14 years). Somalia recognizes two rainy (Gu' and Deyr) and two dry (Jiilaal and Hagaa) seasons. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA).

Results

From 2015 to 2020, 46994 stool samples were requested for the diagnosis of intestinal parasites at the involved hospital. After removing 3764 duplicates and 5832 records with incomplete information, the remaining 37398 records were used for the subsequent results. The mean age of the patients was 23.42±21.17 with a statistical difference (U=46134073, Z=-2.42, p=0.02) between the mean age of patients with parasitic intestinal infections (21.98) and patients without parasitic intestinal infections (23.53).

Overall, 2738/37398 (7.32%, 95% CI=7.06-7.59%) patients were infected with at least one intestinal parasite. Among them, 1407/19569 (7.19%, 95% CI=6.83-7.56%) were males and 1331/17829 (7.47%, 95% CI=7.08-7.86%) were females, but the difference was not statistically significant (p=0.31). A total of 604/8755 (6.89%, 95% CI=6.38-7.45%) children under five years of age were positive for parasitic intestinal infections. Table 1 shows that the highest prevalence was among those aged 5-14 years (9.22%, 95% CI=8.6-9.88) while those age over 65 years had the lowest prevalence (5.54% 95% CI=4.53-6.71), the difference was statistically significant (χ^2=25.32, p<0.001).The prevalence of parasitic intestinal infections was significantly higher during the dry (1893/22976, 8.24%, 95% CI=7.89-8.6%) than during the rainy (845/14422, 5.86%, 95% CI=5.48-6.26%) season (χ^2=73.96, p<0.001) (Table 1).

A total of 2676/37398 (7.16%, 95% CI=6.89-7.42%) patients had a single infection (Table 1). In other words, 97.74% (2676/2738) of the parasitic intestinal infections were single infections, whereas 2.26% (64/2738) were co-infections. Infections with *G. duodenalis* and *E. histolytica/dispar* comprised 92.29% of all positive cases.

Fourteen intestinal parasites were identified in this study. Among these parasites, *G. duodenalis* (1438/37398, 3.85%, 95% CI=3.65-4.05) and *E. histolytica/dispar* (1036/37398, 2.77%, 95% CI=2.61-2.94) were the most prevalent, whereas a low prevalence was recorded for hookworms (1/37398, 0.003%, 95% CI=0.0003-0.02) (Table 2).

Table 1. Prevalence of parasitic intestinal infections for each variable studied

Variable		+/n	Prevalence (%) (95% CI)	p-value
Sex	Female	1331/17829	7.47 (7.08-7.86)	0.31 (χ^2=1.04)
	Male*	1407/19569	7.19 (6.83-7.56)	
Age group-A	<5 years	604/8755	6.89 (6.38-7.45)	0.04 (χ^2=4.38)
	5-14 years	743/8055	9.22 (8.6-9.88)	<0.001 (χ^2=25.32)
	15-40 years	880/12849	6.85 (6.42-7.29)	0.04 (χ^2=4.28)
	41-65 years	412/5953	6.92 (6.29-7.59)	0.04 (χ^2=4.23)
	>65 years*	99/1786	5.54 (4.53-6.71)	
Age group-B	Children (≤14 years)	1347/16810	8.01 (7.61-8.43)	<0.001 (χ^2=21.54)
	Adult* (>14 years)	1391/20588	6.76 (6.42-7.11)	
Season	Rainy	845/14422	5.86 (5.48-6.26)	<0.001 (χ^2=73.96)
	Dry*	1893/22976	8.24 (7.89-8.6)	

*: Reference, +: Number of positive patients, n: Number of samples, CI: Confidence interval, χ^2: Chi-square

Table 2. Prevalence and distribution of intestinal parasites among patients who requested stool examination at a tertiary referral hospital in Mogadishu, Somalia, 2015-2020 (n=37398)

Parasites identified	Number of infected	Prevalence (%) (95% CI)
Overall prevalence	2738	7.32 (7.06-7.59)
Single infection	**2676**	**7.16 (6.89-7.42)**
Giardia duodenalis	1438	3.85 (3.65-4.05)
Entamoeba histolytica/dispar	1036	2.77 (2.61-2.94)
Ascaris lumbricoides	49	0.13 (0.09-0.18)
Enteromonas hominis	33	0.09 (0.06-0.12)
Trichomonas hominis	33	0.09 (0.06-0.12)
Hymenolepis nana	30	0.08 (0.05-0.11)
Trichuris trichiura	28	0.07 (0.05-0.11)
Enterobius vermicularis	10	0.03 (0.01-0.05)
Blastocystis hominis	6	0.02 (0.01-0.03)
Chilomastix mesnili	4	0.01 (0.003-0.03)
Entamoeba coli	3	0.01 (0.002-0.02)
Strongyloides stercoralis	3	0.01 (0.002-0.02)
Retortamonas intestinalis	2	0.005 (0.0003-0.02)
Hookworm	1	0.003 (0.0003-0.02)
Co-infection	**62**	**0.17 (0.13-0.21)**
G. duodenalis + E. histolytica/dispar	31	0.08 (0.06-0.12)
A. lumbricides + G. duodenalis	9	0.02 (0.01-0.05)
A. lumbricides + T. trichuria	5	0.01 (0.004-0.03)
A. lumbricoides + E. histolytica/dispar	4	0.01 (0.003-0.03)
G. duodenalis + H. nanoa	3	0.01 (0.002-0.02)
A. lumbricoides + E. coli	2	0.005 (0.0003-0.02)
G. duodenalis + E. coli	2	0.005 (0.0003-0.02)
G. duodenalis + T. hominis	2	0.005 (0.0003-0.02)
E. histolytica/dispar + E. vermicularis	1	0.003 (0.0003-0.02)
E. histolytica/dispar + T. trichuris	1	0.003 (0.0003-0.02)
E. hominis + H. nana	1	0.003 (0.0003-0.02)
A. lumbricides + H. nana	1	0.003 (0.0003-0.02)

CI: Confidence interval

Discussion

Intestinal parasitic infections are highly prevalent in developing countries, 40% of which are in the African continent, leading to a high burden of morbidity and mortality (12). Few studies have been reported on neglected parasitic intestinal infections in Somalia (8,9,10,11,13). To the best of our knowledge, this is the first comprehensive assessment of the prevalence of intestinal parasite infections in Somalia.

The overall prevalence of parasitic infections in the present study was lower (7.32%) than that in previous studies performed in Somalia (85%) (10), Ethiopia (52.9%) (14), Northeast Nigeria (17.5%) (15), North-Western Nigeria (11.8%) (16), Northwestern Saudi Arabia (45.38%) (17), Iran (31.2%) (18), Nepal (30.1%) (19), and India (6.63%) (20). Differences in the prevalence of parasitic intestinal infections may be explained by the diagnostic test used, different population densities, health status and habits of the people, seasonal fluctuations, the status of open space defecation, and the presence of control and prevention programs.

Fourteen different intestinal parasites were identified in the present study, and the most common parasitic infection was *G. duodenalis* (3.85%). This finding is higher than that of a previous study conducted in Somalia (11), but lower than that reported in a previous study in Ethiopia (14) and Kenya (7). This might be attributed to the differences in geographical regions, the characteristics of soil, altitude, climatic conditions, including temperature, rainfall, humidity, proper sanitary infrastructure, and socioeconomic factors. Provision of community-based low-cost interventions and introduction of control and elimination programs to combat preventable and treatable parasitic intestinal infections can be achieved by regular surveillance of the trending distribution of intestinal parasite species.

This study also revealed that parasitic intestinal infections were significantly higher in the dry season than in the rainy season, and this difference might be attributed to differences in water quality, access to clean water, and sample size between the two seasons.

Although the prevalence of parasitic intestinal infections was slightly higher in females than in male counterparts, the difference was not significant between genders. This finding is in agreement with studies in Ethiopia (7) and Kenya (15). This might be due to the differences in occupational exposure, such as females taking care of children and sick patients and performing chores in the house.

Intestinal parasitic infections can occur during the early stages of life and may lead to undernutrition and growth retardation. This study indicated that the prevalence of parasitic intestinal infections was significantly higher in children than in adults, and this finding is consistent with other studies in Ethiopia (7). This might be due to factors such as playing with soil and water, poor personal and environmental hygiene conditions, being in overcrowded classrooms, and being in close contact with each other, which makes the spread of parasitic intestinal infections easier.

Study Limitations

We are aware that our research may have several limitations. The first is a single direct wet smear method used for the detection of intestinal parasites at the hospital, which underestimates the true prevalence and intensity of parasitic intestinal infections in the country because of the low sensitivity of this method and inability to determine the infection intensity (21). Further studies should use more sensitive laboratory diagnostic methods to confirm and distinguish morphologically identical parasites. Moreover, the parasites were determined by examination of a single stool specimen from each patient, which may impede the diagnostic performance of the method used in this study. Furthermore, the findings presented here were collected from a single-centre health facility database, and thus cannot be generalized for the entire Somalia population. The strengths of the study were that it constitutes the six-year experience of the largest tertiary referral hospital in the region and represents the first comprehensive examination of the prevalence of parasitic intestinal infections in Somalia. However, we are confident that our research provides considerable insight into the burden of parasitic intestinal infections in Somalia and will serve as a basis for future studies. In addition, the descriptive epidemiological data generated in this study may assist health authorities in producing effective national intervention programs.

Conclusion

A low prevalence of parasitic intestinal infections was observed among patients who attended a tertiary referral hospital in Mogadishu, Somalia. Significantly higher parasitic intestinal infections were found in children than in adults. Further epidemiological studies should be conducted to halt the spread of parasitic intestinal infections in Somalia. The introduction of effective community-based parasite control programs may help combat parasitic intestinal infections in the country.

Ethics

Ethics Committee Approval: The Research Ethics Committee of the University of Health Sciences Türkiye, Mogadishu Somalia Türkiye Recep Tayyip Erdoğan Training

and Research Hospital approved the study on April 19, 2021, under the reference number MSTH/6089.

Informed Consent: Retrospective study.

Authorship Contributions

Concept: H.H.E., E.K., M.A.H.K., Design: H.H.E., E.K., M.A.H.K., Data Collection or Processing: H.H.E., M.M.O., Ş.K., A.M.O., A.A.H.K., Analysis or Interpretation: Ş.K., A.M.O., A.A.H.K., Literature Search: H.H.E., E.K., M.M.O., M.A.H.K., Ş.K., A.M.O., A.A.H.K., Writing: H.H.E., E.K., M.M.O., M.A.H.K., Ş.K., A.M.O., A.A.H.K.

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

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Evaluation of Optical Coherence Tomography Angiography Changes in Non-arteritic Anterior Ischemic Optic Neuropathy

Non-arteritik Anterior İskemik Optik Nöropatide Optik Koherens Tomografi Anjiyografi Değişikliklerinin Değerlendirilmesi

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ABSTRACT

Background: To explore microvascular changes in the optic disc (OD) of eyes with non-acute non-arteritic anterior ischemic optic neuropathy (NAION) using optical coherence tomography angiography (OCTA).

Materials and Methods: This cross-sectional study enrolled patients with NAION for a duration exceeding 3 months along with healthy volunteers. Vascular density (VD) measurements for OD were obtained across the entire area, inside the disc peripapillary, and in the superior and inferior hemi-regions using OCTA on a 4.5 mm scan.

Results: The mean age of the 41 NAION patients and 47 volunteers in the healthy group was 64.8±7.9 years and 62.9±7.5 years, respectively. No significant differences were observed in the sex and age distribution between the NAION patients and the healthy group. The mean VD of the optic nerve in the whole image for NAION patient eyes, fellow eyes, and the healthy group were 47.4±2.1, 50.0±2.3, and 49.6±2.0, respectively. Notably, the entire image VD in the NAION group was significantly lower than that in the other groups (p=0.001). Peripapillary and inferior VD in eyes with NAION were significantly lower than those in the other groups. However, no significant differences were observed in the inside disc and superior hemi VD between the patient and fellow eyes of NAION patients and the healthy group (p>0.179, p>0.829, respectively).

Conclusion: This study demonstrated a significant reduction in entire image, peripapillary, and superior hemi VD of the OD in NAION patients during the chronic period.

Keywords: Non-arteritic anterior ischemic optic neuropathy, optic disc, optical coherence tomography angiography, vascular density

ÖZ

Amaç: Non-arteritik anterior iskemik optik nöropatili (NAION) gözlerde optik diskteki (OD) mikrovasküler değişiklikleri optik koherens tomografi anjiyografi (OKTA) ile incelemektir.

Gereç ve Yöntemler: Bu kesitsel çalışmaya 3 aydan uzun süreli NAION hastaları ve sağlıklı kontrol grubu gönüllüleri dahil edilmiştir. OD'nin (4,5x4,5 mm) tüm alan, disk içi, peripapiller, süperior yarı ve inferior yarı vasküler dansitesi (VD) OKTA kullanılarak elde edilmiştir.

Bulgular: Çalışmaya dahil edilen 41 NAION hastasının ve 47 kontrol grubu gönüllülerinin sırasıyla yaş ortalaması 64,8±7,9 yıl ve 62,9±7,5 yıldı. NAION hastaları ve kontrol grubunun cinsiyet ve yaş dağılımları arasında anlamlı farklılık izlenmemiştir. NAION hastalarının hasta gözlerinde optik sinirin ortalama tüm alan VD'si, diğer gözlerinin ve kontrol grubunun VD'si sırasıyla 47,4±2,1, 50,0±2,3 ve 49,6±2,0 idi ve NAION grubunda tüm alan VD diğer gruplardan istatistiksel olarak anlamlı derecede düşüktü (p=0,001). NAION izlenen gözlerde peripapiller ve inferior VD diğer gruplardan anlamlı olarak düşüktü. NAION hastalarının hasta ve diğer gözü ile kontrol grubu arasında diskiçi ve süperior yarı VD arasında anlamlı farklılık izlenmemiştir (sırasıyla p>0,179, p>0,829).

Sonuç: Bu çalışma, kronik dönemde NAION hastalarında OD'nin tüm alan, peripapiller ve süperior yarı VD'nin önemli ölçüde azaldığını göstermektedir.

Anahtar Kelimeler: Non-arteritik anterior iskemik optik nöropati, optik disk, optik koherens tomografi anjiyografi, vasküler dansite

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Introduction

The most prevalent acute optics neuropathy in individuals aged 50 years and above is non-arteritic anterior ischemic optics neuropathy (NAION) (1). The primary pathology underlying NAION is vascular insufficiency in the optic nerve, which stems from decreased hydrostatic pressure in the posterior ciliary arteries (2). It is presumed to be associated with vascular insufficiency due to the loss of autoregulation. Despite the involvement of an interconnected series of factors, the pathophysiology of NAION remains not fully understood. The optic disc (OD) in these patients is typically small and crowded, potentially exacerbating blood flow jeopardy and leading to compartment syndrome.

Clinically, NAION typically manifests as a painless, sudden loss of monocular vision accompanied by a relative afferent pupillary defect, visual field loss, and OD edema, with or without nerve fiber thickening around the OD (3). Optic nerve damage can result in severe visual impairment or blindness. Early diagnosis is crucial for prompt and effective management of the disease. However, there is still no gold standard method for NAION diagnosis, necessitating a comprehensive diagnosis based on typical clinical symptoms, fundus findings, visual fields, and fundus fluorescein angiography (FFA) changes in the clinical setting.

Optical coherence tomography angiography (OCTA) is a novel vascular imaging technology that can rapidly and non-invasively visualize the vascular morphology and vessel density (VD) around the OD and macular area without the need for injectable dye or enhanced capillary imaging features (4,5). It can also perform qualitative analysis of retinal and choroidal vasculature disorders along with optic neuropathy. Several studies have previously used OCTA to identify microvascular changes in NAION (6,7). These studies have shown that acute and chronic NAION patients with OD edema have decreased peripapillary VD and a relationship between the superotemporal region and NAION. However, it is important to note that there is limited information about the ability of OCTA to diagnose eyes with NAION.

This study aimed to retrospectively evaluate the clinical data of patients in the chronic phase of NAION, focusing on OCTA features.

Materials and Methods

Between May 2018 and November 2021, 41 eyes diagnosed with chronic phase NAION and 41 fellow eyes of 41 patients in the outpatient clinic of our hospital were included in the study. In addition, 47 randomly selected eyes of 47 healthy individuals without any ocular or systemic disease were included. The diagnostic criteria for NAION were established based on previously defined criteria (8): 1) absence of ocular and systemic diseases that may affect or explain the patient's visual problems and sudden decrease in visual acuity; 2) visual field defects associated with OD pathologies; 3) regional or diffuse OD edema and peripapillary hemorrhage; 4) presence of relative afferent pupillary defects and/or impaired visual evoked potentials; 5) exclusion of other OD diseases. In the NAION group, all patients were consulted by the neurology department. Best corrected visual acuity assessment, anterior and posterior segment examinations with slit lamp microscopy, intraocular pressure measurement with applanation method, color fundus photography, visual field tests, and visual evoked potential examinations were performed in all patients. Only patients without contraindications underwent FFA. The study adhered to the principles of the Helsinki Declaration, and ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (no: 3255, date: 27/04/2021).

The inclusion criteria encompassed patients with NAION who had passed a 3-month period since the disease onset and were not in the acute phase. The exclusion criteria were as follows: 1) patients with non-NAION or acute-phase NAION; 2) non-acute phase NAION patients with concurrent eye pathologies; 3) inadequate cooperation or weak fixation for OCTA assessment; 4) ODs with abnormal anatomy hindering OCTA evaluation; and 5) individuals with a spherical equivalent refractive error exceeding ±5.0 diopters (D) or astigmatism greater than ±3.0 D. The control group comprised healthy individuals with normal ODs and no systemic or ocular diseases.

Optical Coherence Tomography Angiography Imaging

OD images, measuring 4.5 mm, were captured using OCTA with AngioVue Avanti RTVue-XR software, version 2017 (OptoVue, Fremont, CA, USA). VD in the whole area, within the disc and in the peripapillary regions of OD were meticulously examined. Image segmentation was performed using the RTVue software without manual adjustments. The device's algorithm autonomously analyzed the OD and peripapillary region, dividing it into several vascular layers. The software then automatically calculated the average VD for entire OD image, inside the disc peripapillary, superior hemi, and inferior hemi. Following the definition of the OD boundaries, the VD measurement is executed by analyzing the layer extending from the internal limiting membrane to 150 µm within this membrane for the OD. Radial peripapillary VD analysis was then conducted from the

internal limiting membrane on the retinal nerve fiber layer for measuring superficial peripapillary VD. To ensure data quality, ten images with a low signal strength index (<70) from 51 symptomatic eyes of patients with NAION were excluded. This exclusion criteria considered factors such as motion artifacts, blinking, and low image qualit.

Statistical Analysis

Descriptive statistics, including mean, standard deviation, median, minimum, maximum, frequency, and ratio values, were employed to characterize the data. The distribution of variables was assessed using the Kolmogorov-Smirnov test. For the analysis of quantitative independent data, Mann-Whitney U and Kruskal-Wallis tests were used. The Wilcoxon test was applied to analyze dependent quantitative data, whereas the chi-square test was employed for the analysis of qualitative independent data. All statistical analyses were performed using SPSS version 28.0.

Results

Among the NAION patients,there were 17 females (41.4%) and 24 males (58.6%), whereas the healthy group comprised 19 females (40.4%) and 28 males (59.6%). The mean ages of NAION patients and the healthy group were 64.8±7.9 years and 62.9±7.5 years, respectively. Demographic and clinical data for both the NAION patients and the healthy group are summarized in Table 1. Notably, there were no significant differences in gender and age distributions between the NAION patients and the healthy group (p>0.05). In the eyes of patients with NAION disease, fellow eyes, and eyes in the healthy group,the logMAR values were 1.05±0.21,-1.06±0.35, and -1.03±1.58, respectively (p<0.001). In addition, there were no significant differences in axial length and cup/disc ratio between the NAION patients and the healthy group (p>0.05). Smokers were observed as follows: in the NAION group, 11 out of 41 patients (26.8%); and in the healthy control group, 13 out of 47 volunteers (27.6%). Statistical analysis revealed no significant differences in smoking between these groups (p>0.05). In the NAION group, nine patients were on antihypertensive medication for systemic hypertension and three patients were on statin therapy. No history of systemic medication was reported in the healthy control group.

OCTA scans were meticulously analyzed to discern numerical variations in VDs of the OD between NAION patients and the healthy group (Table 2). VD measurements encompassed the whole image, inside the disc peripapillary, superior hemi, and inferior hemi for all eyes in the study. The average VD of the whole image in the affected eyes of NAION patients was significantly lower than that in their fellow eyes and the healthy group (p=0.01). Interestingly, no significant difference was observed in disc VD when comparing the affected eyes of NAION patients, their fellow eyes, and the healthy group. Notably, the peripapillary average VD values for the affected eyes, fellow eyes, and healthy group of NAION patients were 49.8±2.5%, 52.0±2.4%, and 52.7±2.6%, respectively (p=0.000).

Moreover, the average VD in the inferior hemi of affected eyes in NAION patients was significantly lower than that in their fellow eyes and the healthy group (p=0.00). In contrast, the average VD in the superior hemi for affected eyes, fellow eyes, and the healthy group of patients with NAION were 51.1±2.7%, 51.8±5.2%, and 52.9±2.6%, respectively (p>0.05). Importantly, no significant differences were observed between the healthy group and the fellow eyes of patients with NAION concerning the mean VD across the whole image, inside the disc, peripapillary, superior hemi, and inferior hemi.

Discussion

NAION, a leading cause of sudden vision decline in the elderly, is one of the most prevalent contributors to acute OD ischemia (9). Its etiology is attributed to circulatory

Table 1. Demographic and clinical characteristics of the participants

		NAION eye	Fellow eye	Control group	
Age		64.8±7.9/66 (48-74)	64.8±7.9/66 (48-74)	62.9±7.5/65.5 (51-79)	0.448[a]
Sex	Female	17 (41.4)	17 (41.4)	19 (40.4)	0.317[b]
	Male	24 (58.6)	24 (58.6)	28 (59.6)	
Lens status	Phakic	23 (56.0)	23 (56.0)	25 (53.1)	0.658[c]
	Pseudophakic	17 (44.0)	17 (44.0)	22 (46.9)	
Axial length (mm)		23.3±1.5/23.5 (22.4-26.8)	23.2±1.4/23.5 (21.9-27.4)	23±1.5/23.4 (20.1-25.4)	0.411[a]
Vertical cup/disc ratio		0.41±0.2/1 (0.3-0.7)	0.43±0.2/1 (0.2-0.8)	0.39±0.1/1 (0.2-0.8)	0.945[a]
Visual acuity (LogMAR)		1.05±0.21/1.2 (0.5-2.0)	-1.06±0.35/0.35/1.3 (1.33)	-1.03±1.58/1.58/1 (1.30.2)	**<0.001**[*,a]

[a]: Mann-Whitney U, [b]: Chi-square test, [c]: Fisher's Exact test, *: p<0.05, continuous variables are presented as mean ± standard deviation/median (min-max). Categorical variables are presented as number (%), NAION: Non-arteritic anterior ischemic optic neuropathy

Table 2. Mean vascular densities of the optic disc of patients with NAION and control group

	Control group		NAION eye		pm	Fellow eye		pm	p*
	Avg. ± SD	Median	Avg. ± SD	Median		Avg. ± SD	Median		
Optic disc (% VD)									
Whole image	50.0±2.3	50.1	47.4±2.1	47.8	**0.001**^{m}	49.6±2.0	49.9	0.233^{m}	**0.001**^{w}
Inside disc	50.2±5.4	49.7	49.2±4.2	48.7	0.177^{m}	49.8±4.6	49.9	0.352^{m}	0.179^{w}
Peripapillary	52.7±2.6	52.6	49.8±2.5	50.4	**0.000**^{m}	52.0±2.4	52.2	0.169^{m}	**0.000**^{w}
Superior hemi	52.9±2.6	52.9	51.1±2.7	51.8	0.227^{m}	51.8±5.2	52.6	0.229^{m}	0.829^{w}
Inferior hemi	52.4±3.0	52.7	48.4±2.5	49.5	**0.000**^{m}	51.7±2.6	51.2	0.124^{m}	**0.000**^{w}

^{m}: Mann-Whitney U test, ^{w}: Wilcoxon test, p: Difference with control group/p, *: Difference between patient and fellow eye of NAION patients, Avg.: Average, SD: Standard deviation, VD: Vascular density, NAION: Non-arteritic anterior ischemic optic neuropathy

insufficiency in the OD, with anatomical and mechanical factors influencing the risk of NAION development (10). Specifically, a smaller OD with a short radius and a reduced scleral canal are associated with this condition. The increased concentration of nerve fibers within this narrow channel, coupled with the slowing of axoplasmic flow related to OD edema, are considered to be key factors contributing to anterior OD ischemia (11,12). Factors such as vascular insufficiency and hemodynamic alterations are believed to contribute to the development of NAION. The occlusion of short posterior ciliary arteries is specifically associated with NAION development (13). FFA plays a pivotal role in the examination of NAION, revealing early-stage OD hypoperfusion and late-stage dye leakage. However, fluorescein-induced dye leakage can hinder the selection of the vascular network on the OD surface (14). Although FFA provides valuable data on the superficial capillary network of the OD, its capability to visualize deeper vascular structures is limited.

OCTA facilitates the visualization of retinal and peripapillary vessels, allowing the assessment of the superficial vascular plexus within the retinal nerve fiber layer. This is achieved through the detection of motion contrast originating from blood flow, coupled with automatic segmentation provided by its algorithm. Notably, OCTA distinguishes itself from FFA by enabling imaging and evaluation of radial peripapillary capillaries. These capillary connections exhibit a radial distribution around the OD, extending along the nerve fibers and serving as the primary capillary source for radial peripapillary nerve fibers (15). OCTA proves invaluable in the clinical assessment of patients with NAION, offering both structural and vascular measurements of the OD and macula. This capability positions OCTA as a promising biomarker for predicting visual outcomes (16,17). Moreover, the expanding use of OCTA as a non-invasive technology is notable in the evaluation of various optic neuropathies, including conditions such as glaucoma, and in the identification of underlying causes.

In this study employing OCTA on patients with NAION, we observed statistically significant reductions in VD across the whole area, peripapillary region, and inferior segments when compared to both the fellow eye and healthy group in the microvascular examination of the OD. This cross-sectional analysis assessed the efficacy of OCTA in delineating peripapillary vascularity in non-acute, unilateral NAION cases. Notably, we restricted our study to NAION cases lasting more than 3 months because the acute phase is marked by disc edema and hemorrhage, potentially impeding imaging accuracy. Although OCTA enables excellent visualization of the microvascular structure of the OD and peripapillary region, its utility in these patients has not been clearly defined. OCTA imaging reflects changes in VD that can indicate functional impairment before irreversible structural changes. In a study by Spaide et al. (18), a comparison between OCTA images of healthy eyes' ODs and FFA revealed that the radial peripapillary capillary network was more effectively visualized in OCTA images, contrasting with its less clear visualization in FFA.

Higashiyama et al. (19) pioneered the observation of reduced retinal perfusion in an acute case of NAION using OCTA. OCTA clinical applications in patients with NAION have been further elucidated in several other studies evaluating retinal VD, choroid, and OD perfusion (20,12). Another study reported a significant decrease in OD perfusion in a prospective case series of patients with NAION (21). In a parallel investigation by Sharma et al. (22) encompassing six cases of acute NAION, the study revealed a reduction in both retinal and choroidal peripapillary VD. Notably, these findings may reflect distinct vascular changes influenced by the presence of disc edema and hemorrhages in NAION cases, potentially introducing variations in masking effects during imaging. In alignment with these observations, our study, using automated indices generated by the device software, also identified a reduction in peripapillary retinal VD. Peripapillary retinal VD and perfusion decrease in the peripapillary choriocapillaris have been reported in nine

cases of both acute and chronic NAION with an average duration of 23 months since the onset of the disease (23). Overall, OCTA VD patterns suggest a secondary watershed infarct hypothesis in NAION, possibly related to transient hypoperfusion or venous infarction (24). The decrease in microvascular connections associated with peripapillary tortuous capillaries detected in some cases may be consistent with the venous insufficiency hypothesis in NAION (22).

The analysis of the OCTA VD offers valuable quantitative insights. In patients with NAION, reductions in both the VD of the whole optic nerve area and the peripapillary region are observed compared to control subjects. These parameters hold promise as discerning indicators for distinguishing ischemic forms of OD edema from alternative etiologies. Future investigations should delve into distinct OCTA features and assess potential VD modifications in cases of inflammatory, infectious, and hypertensive acute OD edema. Such studies may pave the way for a more nuanced understanding of these conditions and contribute to the refinement of diagnostic approaches.

Study Limitations

Although this study presents valuable insights, it is essential to acknowledge certain limitations. These include a restricted patient sample and confinement of the study to a single center. Nevertheless, it is crucial to note that OCTA stands out as a pioneering diagnostic tool, and NAION is an uncommon ocular disease. Despite these limitations, we contend that our documented cases offer valuable contributions to ophthalmologists in their clinical practice. Looking ahead, the expansion of case collection holds promise for a more comprehensive understanding of the diseases and may unveil diverse pathophysiologies associated with NAION. The prospect of larger screenings, coupled with improved visualization of the choriocapillaris through OCTA, can augment future investigations into choroidal microvasculature. It is worth mentioning that some OCTA images from certain patients were excluded because of motion artifacts. Anticipating advancements in software, particularly with the incorporation of real-time eye tracking, we are optimistic that this issue will be mitigated in future studies.

Conclusion

In conclusion, OCTA is a repeatable, highly rapid, and non-invasive imaging method that can be used to detect VD defects in patients with NAION. In addition, it provides information about the vascular structures of the retina, choroid, and OD head using a short scan. If OCTA fails to yield a definitive diagnosis, more invasive and time-consuming examination methods, such as FFA and indocyanine green angiography, can be subsequently employed.

Ethics

Ethics Committee Approval: The study adhered to the principles of the Helsinki Declaration, and ethical approval was obtained from the Clinical Research Ethics Committee of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital (no: 3255, date: 27/04/2021).

Informed Consent: Retrospectively study.

Authorship Contributions

Surgical and Medical Practices: D.Ö., M.K., D.Ç.Y., Concept: D.Ö., M.K., D.Ç.Y., Design: D.Ö., M.K., D.Ç.Y., Data Collection or Processing: D.Ö., M.K., D.Ç.Y., Analysis or Interpretation: D.Ö., M.K., D.Ç.Y., Literature Search: D.Ö., M.K., D.Ç.Y., Writing: D.Ö., M.K, D.Ç.Y.

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

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The Effects of the COVID-19 Pandemic Process on the Treatment and Follow-up of Diabetes Mellitus in Type 2 Diabetic Patients

Tip 2 Diyabetik Hastalarda COVID-19 Pandemi Sürecinin Diabetes Mellitus Tedavi ve İzlemine Etkileri

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ABSTRACT

Background: During the Coronavirus disease-2019 (COVID-19) pandemic, the frequency of doctor visits may decrease in patients with type 2 diabetes, physical activity may decrease due to restrictions, and eating habits may change. This study aimed to examine the impact of the COVID-19 on glycemic control, lipid profile, body mass index (BMI), blood pressure, and liver and kidney functions in patients with type 2 diabetes.

Materials and Methods: In this study, the biochemical values of type 2 diabetic patients admitted to the internal medicine and endocrinology outpatient clinics of our hospital between 01/04/2022 and 01/04/2023 were compared with their initial values before and during the pandemic. In addition, anti-diabetic drugs, BMI, blood pressure, and frequency of doctor visits were compared before and after the pandemic.

Results: The patients' glycated hemoglobin (HbA1c) levels demonstrated a significant increase from both their initial and current readings during the pandemic, surpassing the values before the pandemic ($p<0.05$). Additionally, the initial glucose levels of the patients during the pandemic also exhibited a notable rise in contrast to the pre-pandemic measurements ($p<0.05$). On the other hand, the current levels of total cholesterol, low-density lipoprotein cholesterol, and BMI for the patients saw a significant decrease in relation to their pre-pandemic values ($p<0.05$).

Conclusion: This study noted a decline in the frequency of doctor visits and a subsequent deterioration in glycemic control among patients with type 2 diabetes during the COVID-19 pandemic. In case of a natural disaster that may occur, deterioration in glycemic control can be prevented by increasing physical activities, paying attention to diet, and providing intensified diabetes treatment with tele-medicine when necessary.

Keywords: COVID-19 pandemic, glucose, HbA1c, type2 diabetes mellitus

ÖZ

Amaç: Koronavirüs hastalığı-2019 (COVID-19) pandemi sürecinde tip 2 diyabetli hastalarda hekim başvuru sıklığı azalabilmekte, kısıtlamalara bağlı fiziksel aktivitelerde azalma ve yemek yeme alışkanlıkları değişebilmektedir. Bu çalışmamızda COVID-19 pandemi sürecinin tip 2 diyabetli hastalarda glisemik kontrol, lipid profili, beden kitle indeksi (BKİ), kan basıncı, karaciğer ve böbrek fonksiyonları üzerine etkisini incelemeyi amaçladık.

Gereç ve Yöntemler: Bu çalışmada 01/04/2022 ile 01/04/2023 tarihleri arasında hastanemiz iç hastalıkları ve endokrinoloji polikliniğine başvurmuş tip 2 diyabetik hastaların rutin tetkikleri sırasında bakılmış olan biyokimyasal değerleri, pandemi öncesi ve pandemi sürecindeki ilk değerleri ile karşılaştırıldı. Ayrıca kullandığı anti-diyabetik ilaçlar, BKİ, kan basıncı, hekim başvuru sıklığı pandemi öncesi ve sonrası karşılaştırıldı.

Bulgular: Hastaların pandemi sürecindeki ilk glikozlanmış hemoglobin (HbA1c) değeri ve güncel HbA1c değeri, pandemi öncesi değerine göre anlamlı düzeyde artmıştır ($p<0,05$). Hastaların pandemi sürecindeki ilk glukoz değeri de pandemi öncesine göre anlamlı düzeyde artmıştır ($p<0,05$). Hastaların güncel toplam kolesterolü, düşük yoğunluklu lipoprotein (LDL) kolesterol ve BKİ değerleri, pandemi öncesine göre anlamlı düzeyde azalmıştır ($p<0,05$).

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ÖZ

Sonuç: Bu çalışmada COVID-19 pandemi sürecinde tip 2 diyabetli hastalarda hekim başvuru sıklığının azaldığını ve glisemik kontrolün bozulduğunu gözlemledik. İleride meydana gelebilecek doğal afet durumunda fiziksel aktiviteler artırılıp, beslenme tarzına dikkat edilip, tele-tıp ile gerektiğinde yoğunlaştırılmış diyabet tedavisi verilerek glisemik kontrolde bozulmanın önüne geçilebilir.

Anahtar Kelimeler: COVID-19 pandemisi, glukoz, HbA1c, tip 2 diabetes mellitus

Introduction

Coronavirus disease-2019 (COVID-19), which emerged in December 2019 in Wuhan, Hubei province of China, and was declared a pandemic on March 11, 2020, is an infectious disease caused by severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) (1). According to World Health Organization (WHO) data, as of January 29, 2023, it has caused more than 753 million cases and more than 6.8 million deaths worldwide (2). Bats are natural hosts of alpha and beta coronaviruses. The Hunan seafood market in Wuhan, China, is the starting point of the COVID-19 outbreak, and bats are considered possible SARS-CoV-2 reservoirs (3,4). According to WHO data, the number of patients with diabetes increased from 108 million in 1980 to 422 million in 2014. In 2014, 8.5% of adults over the age of 18 years had diabetes. In 2019, 1.5 million diabetes-related deaths occurred (5). According to the TURDEP-II study conducted in our country in 2010, the prevalence of diabetes was found to be 16.5%. It was 7.2% in the TURDEP-I study conducted 12 years before this study (6). Individuals with diabetes are more likely to develop acute and chronic infections than those without diabetes. Among the 72,314 reported cases of COVID-19 by the Chinese Center for Disease Control and Prevention, diabetic patients experienced a mortality rate of 7.3%, whereas non-diabetic patients had a lower mortality rate of 2.3%. Viral infections may cause dysregulation in glucose levels in diabetic patients or new-onset diabetes in those without a history of diabetes (7).

The curfew, change in eating habits, decrease in physical activity, and difficulties in accessing medications used for diabetes during the COVID-19 pandemic had a negative impact on blood glucose levels (8). The COVID-19 pandemic presented challenges in effectively managing patients with diabetes mellitus. Even if patients with diabetes were not infected with COVID-19, they were at risk of irregular glycemic control because of restrictive measures that jeopardized healthcare delivery (9). Doctors should be aware of the impact of social distancing and quarantine measures on glycemic control when treating patients with diabetes. Urging people to stay home during the pandemic reduced the amount of physical exercise compared with the normal daily routine. Although there is no reliable data on this, it can be expected that calorie balance may have increased in some patients with diabetes during the COVID-19 process. Both situations may lead to deterioration in glycemic control (10). During the COVID-19 pandemic, the frequency of routine doctor visits of patients with type 2 diabetes may change, physical activity may decrease due to restrictions, and eating habits may change. The purpose of this study was to investigate the impact of COVID-19 on various aspects including glycemic control, liver and kidney functions, lipid profile, body mass index (BMI), systolic and diastolic blood pressure (DBP), and diabetes treatment in patients diagnosed with type 2 diabetes.

Materials and Methods

This is a retrospective quasi-experimental study conducted among patients who applied to the internal diseases and endocrinology outpatient clinic between 01/04/2022 and 01/04/2023 at the University of Health Sciences Türkiye, İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital with the approval number 132781 at the University of Health Sciences Türkiye, Hamidiye Clinical Research Ethics Committee meeting dated 12.05.2022. The power analysis of our study was calculated using the R-Studio program, and the number of patients required at 0.80 power and 0.95 confidence interval was 93, and 120 patients were included in the study, considering 0.2 missing data. Total cholesterol (mg/dL), triglycerides (mg/dL), serum glycated hemoglobin (HbA1c) (%), glucose (mg/dL), aspartate aminotransferase (AST) (U/L), high-density lipoprotein (HDL) cholesterol (mg/dL), low-density lipoprotein (LDL) cholesterol (mg/dL), urea (mg/dL), and creatinine (mg/dL) were measured during routine examinations. Alanine aminotransferase (ALT) (U/L) values were screened retrospectively, and the latest values before the COVID-19 pandemic in our country (before March 1, 2020) and the first values during the pandemic (after June 1, 2020) and the current values in outpatient clinic applications were compared. In addition, the frequency of doctor visits for annual routine control before the COVID period, the frequency of doctor visits for annual routine control during the COVID period, the antidiabetic drugs used before the COVID period, and

the drugs currently used were questioned. The BMI (kg/m^2) and arterial blood pressure (mm/Hg) values before the COVID period were compared with the current values during the last outpatient clinic visit. The inclusion criteria were as follows: adult patients over 18 years of age and under 75 years of age, patients with type 2 diabetes mellitus diagnosed at least one year before the start of the COVID-19 pandemic (before March 1, 2019), patients without any known history of malignancy, and people without psychiatric disability who can personally give consent for the examination of file records in the study. Patients under 18 years of age and over 75 years of age, patients with type 1 diabetes mellitus, patients with gestational diabetes mellitus, pregnancy status, and breastfeeding, patients with any known history of malignancy, and patients with psychiatric disability who could not give personal consent for the examination of file records in the study were excluded.

Statistical Analysis

Parametric tests were used without normality tests because of conformity with the central limit theorem (11). In the data analysis, the mean and standard deviation, median, minimum, and maximum values were given for the statistics of continuous data. Descriptive statistics are given as number (n) and percentage (%) for categorical variables. A paired t-test was used to evaluate the difference between two dependent measurements. Repeated ANOVA test statistic was used to compare the mean of more than two (3) measurements, and in case of a difference, pairwise comparisons were evaluated using Tukey statistics. The statistical significance level of the data was taken as $p<0.05$. IBM SPSS 21 and the MedCalc statistical package program was used for data evaluation.

Results

The study included 120 patients with type 2 diabetes admitted to the internal medicine and endocrinology outpatient clinic of İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital between 01/04/2022 and 01/04/2023. Table 1 presents the descriptive characteristics of the patients. The minimum age of the patients was 35 years, and the maximum age was 74 years, with a mean age and standard deviation of 58.1±8.22 and a median value of 58 years. The minimum duration of diabetes was 4 years and the maximum was 35 years. The mean duration and standard deviation were 11.8±6.5 years, and the median was 10. 45.8% of the patients had a history of COVID. While the mean number of annual doctor visits was 2.6±1.1 times before the pandemic, it was 1.8±0.99 times during the pandemic period, which was lower. While 30% of the patients were using insulin before the pandemic, the number of patients using insulin increased during the pandemic, and 41.7% of the patients are currently using insulin.

Table 2 shows the change in the patients' biochemical values depending on the pandemic time. The change in the mean HbA1c value of the patients according to time was significant ($p<0.05$). The mean pre-pandemic HbA1c value (%) was 7.79±1.75, the first HbA1c value (%) during the pandemic was 8.51±2.13, and the current HbA1c value (%) was 8.17±2.01. The initial HbA1c value of the patients during the pandemic increased significantly compared with the pre-pandemic HbA1c value ($p<0.05$). The current HbA1c value also increased significantly compared with the pre-pandemic HbA1c value ($p<0.05$). The initial glucose value of the patients during the pandemic process increased

Table 1. Distribution of patients diagnosed with type 2 diabetes based on descriptive characteristics (n=120)

Descriptive characteristics	**Mean ± SD**	**Median (min-max)**
Age	58.1±8.22	58 (35-74)
Gender	**Number (n)**	**Percentage (%)**
Female	77	64.2
Male	43	35.8
Hypertension	77	64.2
Cardiovascular disease	21	17.5
COVID	55	45.8
Current cigarette use	30	25
Smoking before the pandemic	35	29.2
Insulin use before the pandemic	36	30
Current use of insulin	50	41.7
Anti-diabetic drug use before the pandemic		
Single oral antidiabetic	34	28.3
Dual oral antidiabetic	23	19.2
Triple oral antidiabetic	27	22.5
Insulin	36	30
Current use of anti-diabetic drugs		
Single oral antidiabetic	21	17.5
Dual oral antidiabetic	18	15
Triple oral antidiabetic	31	25.8
Insulin	50	41.7
	Mean ± SD	**Median (min-max)**
DM duration	11.8±6.5	10 (4-35)
Annual number of pre-COVID doctor referrals	2.6±1.1	2 (1-4)
Annual number of doctor referrals during the COVID period	1.8±0.99	2 (1-4)

SD: Standard deviation, COVID: Coronavirus, DM: Diabetes mellitus

significantly compared with the pre-pandemic glucose value (p<0.05). The current glucose value decreased significantly compared with the first glucose value during the pandemic (p<0.05). Current total cholesterol and LDL cholesterol values of the patients decreased significantly compared with pre-pandemic total cholesterol and LDL cholesterol values (p<0.05). Current AST and ALT values of the patients decreased significantly compared with pre-pandemic AST and ALT values (p<0.05). The current AST and ALT values of the patients decreased significantly compared with those at the beginning of the pandemic (p<0.05). The current urea value of the patients increased significantly compared with the pre-pandemic urea value (p<0.05). There was no significant difference between the patients' HDL cholesterol, triglyceride, and creatinine values during the pandemic and pre-pandemic (p>0.05).

Table 3 illustrates the changes in the patients' systolic blood pressure (SBP), BMI, and DBP values according to the time of the pandemic. The patients' mean BMI before the pandemic was 30.92±5.74 (kg/m^2), whereas the current value was 30.4±5.64 (kg/m^2). The patients' current mean BMI values showed a significant decrease from the pre-pandemic BMI value (p<0.05). Likewise, the patients' current mean DBP values exhibited a significant decrease from the pre-pandemic DBP value (p<0.05). No significant difference was found between the pre-pandemic and current SBP values (p>0.05).

Discussion

The course of the global COVID-19 has revealed that COVID-19 and diabetes share a mutual link. Diabetes increases the risk of having a serious COVID-19 infection, and COVID-19 infection is also associated with the development of diabetes and deterioration of diabetes control (12). The COVID-19 pandemic has caused healthcare access and medication difficulties for patients with chronic conditions. Patients avoided face-to-face care because of fear of exposure to COVID-19. In the study conducted by Yoon et al. (13) in the early pandemic period, there were decreases in the rates of primary care visits, emergency room visits, and hospitalizations. Similar to this study, it was determined that the frequency of doctor visits decreased during the pandemic. During the COVID-19 pandemic, the number of applications to primary healthcare services and

Table 2. Change in biochemistry values depending on the pandemic period (n=120)

	Before the pandemic	Pandemic period first value	Current	Repeated ANOVA test	Post-hoc Tukey test
	Mean ± SD	Mean ± SD	Mean ± SD	p-value	p-value 1 vs. 2,1 vs. 3,2 vs 3
HbA1c (%)	7.79±1.75	8.51±2.13	8.17±2.01	**<0.001**	**<0.001/0.04**/0.07
Glucose (mg/dL)	159.01±69.48	187.31±81.94	167.84±74.84	**<0.001**	**<0.001**/0.49/**0.03**
Total cholesterol (mg/dL)	206.49±45.64	202.08±48.45	196.81±44.63	**0.04**	0.6/**0.03**/0.51
HDL (mg/dL)	47.71±11.95	47.24±14.16	47.42±13.32	0.8	-
LDL (mg/dL)	122.74±38.71	116.25±37.53	112.34±37.36	**0.004**	0.11/**0.003**/0.65
Triglycerid (mg/dL)	179.98±90.62	201.94±150.42	205.49±140.41	0.08	-
Urea (mg/dL)	30.31±14.56	31.86±14.36	32.97±15.01	**0.02**	0.32/**0.02**/0.58
Creatinine (mg/dL)	0.85±0.21	0.87±0.24	0.84±0.34	0.06	-
AST (U/L)	20.88±11.98	20.66±10.13	17.95±10.16	**<0.001**	0.99/**<0.001/0.004**
ALT (U/L)	26.06±14.59	24.82±15.42	20.46±14.56	**<0.001**	0.99/**<0.001/0.001**

HDL: High-density lipoprotein, LDL: Low-density lipoprotein, HbA1c: Glycated hemoglobin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, SD: Standard deviation, ANOVA: Analysis of variance

Table 3. Changes in BMI, SBP, and DBP depending on pandemic time (n=120)

	Before the pandemic	Current	Paired t-test
	Mean ± SD	Mean ± SD	p-value
BMI (kg/m^2)	30.92±5.74	30.4±5.64	**0.03**
SBP (mm/Hg)	123.8±13.2	122.3±10.6	0.23
DBP (mm/Hg)	78.9±8.4	76.1±7.3	**0.003**

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SD: Standard deviation

consultations decreased. In addition, low-income countries experienced problems accessing drugs and difficulty reaching hospitals during lockdown (14). In our study, we noticed a deterioration in diabetes control among patients with type 2 diabetes among the pandemic. This may be attributed to the decreased frequency of doctor visits for routine control purposes due to patients' compliance with stay-at-home calls during the pandemic, curfews, and fear of being infected with COVID-19.

Fonseca et al. (15) examined the impact of Hurricane Katrina on diabetes in the United States in 2005. A total of 1795 patients participated in the study, with HbA1c values measured 6 months before and 6-16 months after the hurricane. The HbA1c level assessed post-hurricane exhibited a significant increase compared with the pre-hurricane measurement ($p<0.01$) (15). In a study by Inui et al. (16), the effect of the Kobe earthquake in Japan in 1995 on glycemic control in diabetic patients was examined. HbA1c levels in the two years before the earthquake were compared with HbA1c levels 1 year after the earthquake. HbA1c levels increased 3-4 months after the Kobe earthquake and then returned to their previous levels (16). These studies show that natural disasters such as earthquakes and hurricanes have a negative effect on glycemic control in patients with diabetes.

Sasidharan et al. (17) investigated the occurrence of young-onset type 2 diabetes mellitus in individuals aged 21 years and younger before the pandemic, during the initial year of the pandemic, and in the subsequent year of the pandemic. According to their findings, there was an approximately threefold increase in the annual incidence of type 2 diabetes cases during the first year of the pandemic compared with the period before the pandemic. During the second year of the pandemic, the occurrence of type 2 diabetes increased by 61% in contrast to the initial year of the pandemic, and this upward trend persisted (17). In the meta-analysis led by Ojo et al. (18), which encompassed eleven studies, a comprehensive assessment of 16,895 patients with type 2 diabetes was conducted. The study compared HbA1c values before and after the COVID-19 pandemic. Following the pandemic, the average HbA1c level was found to be 0.34% higher than that prior to the pandemic, and this increase was statistically significant ($p<0.01$) (18). Our research outcomes aligned with the findings of this study, indicating a deterioration in diabetes management among patients with type 2 diabetes due to the pandemic. In an investigation carried out by Tanji et al. (19) in Japan, they assessed the impact of the COVID-19 pandemic on glycemic control in individuals with type 2 diabetes. The study encompassed 1009 patients with type 2 diabetes, and HbA1c values were compared before and after the COVID-19 outbreak. Following the COVID-19 outbreak, there was a notable increase in HbA1c values, particularly among women, patients aged 65 years, individuals with a BMI of 25 kg/m^2), and those not using insulin ($p<0.05$) (19). The research conducted by Sawada et al. (20) and associates at Tokyo University Hospital delved into the impact of the COVID-19 pandemic on diabetes control. The study encompassed 408 patients with diabetes, comprising 13 individuals with type 1 diabetes and 395 with type 2 diabetes. It was observed that the mean HbA1c value experienced a significant increase during the COVID-19 pandemic period as opposed to the pre-pandemic period ($p=0.010$) (20).

In a meta-analysis led by Bouchi et al. (21) and his team in Japan, the study delved into the impact of the COVID-19 pandemic on glycemic control. A total of 2348 patients were included in this retrospective analysis, representing 15 different centers. Among these patients, 423 were diagnosed with type 1 diabetes, 1839 with type 2 diabetes, and 86 had other forms of diabetes. The study compared parameters such as HbA1c, lipids, AST, ALT, BMI, and blood pressure (both systolic and diastolic) before the pandemic, in the first year, and in the second year. Despite an initial increase in HbA1c levels during the first year of the pandemic followed by a decrease in the second year, no significant difference was observed ($p>0.05$). This suggests that glycemic control in the patients in this study did not worsen during the pandemic. It is worth noting that the participants in this study were chosen from specialized diabetes care facilities and maintained regular visits to their clinics or hospitals both before and throughout the pandemic. The pandemic led to an intensification of diabetes treatments, effectively averting any deterioration in glycemic control (21). In our study, patients disrupted their routine controls during the pandemic; thus, diabetes treatments could not be intensified, leading to deterioration of glycemic regulation. This meta-analysis found no significant difference in triglyceride and HDL cholesterol levels before and during the pandemic. There was a significant decrease in both LDL and total cholesterol values during the pandemic ($p<0.01$). In our study, similar to this, we found no significant difference in triglyceride and HDL cholesterol values during the pandemic, whereas total cholesterol and LDL cholesterol values decreased significantly ($p<0.05$). In this study, the mean BMI was 25.2 (kg/m^2) before the pandemic and 25.1 (kg/m^2) during the pandemic and decreased significantly ($p<0.01$). Both in this study and our study, the significant decrease in BMI during the pandemic may have caused a decrease in total and LDL cholesterol levels. In this study, no notable disparity was detected in SBP. However, a significant reduction in DBP

was observed in the second year of the pandemic compared with the pre-pandemic period (p<0.01). This aligns with findings similar to those of this study whereby SBP showed no significant variance, whereas DBP exhibited a significant decrease during the pandemic period in contrast to the pre-pandemic period (p<0.05).

In a study by Khare and Jindal (22) in India, 143 patients' pre-pandemic fasting and postprandial blood glucose values at the second hour after breakfast were compared with those in the third week of quarantine. Before the pandemic, the mean fasting blood glucose level was 115.9 mg/dL and increased to 119.4 mg/dL in the third week of quarantine. However, this increase was not significant (p>0.05). The patients' mean 2nd-hour post-prandemic post-prandial blood glucose value was 124.9 mg/dL before the pandemic and increased to 159 mg/dL in the third week of quarantine. This increase was significant (p=0.02). This study showed that general glycemic control deteriorated during the 3-week quarantine period (22). In our study, the difference between the mean fasting glucose values last checked before the pandemic and those checked during the pandemic was significant (p<0.05). In our research, we scrutinized data collected at a minimum of three months following the onset of the pandemic. This timeframe is crucial for observing the pandemic's impact more clearly. Nonetheless, our findings corroborate that glycemic control was compromised during the pandemic, aligning with the results of this study.

Wu et al. (23) conducted a study investigating the impact of COVID-19 on renal function. The study included 758 stage 5 chronic kidney patients not receiving dialysis. This study found no significant difference between blood creatinine levels before and during the pandemic (23). Our study found no significant difference in the creatinine levels measured before and during the pandemic (p>0.05). In López-González et al. (24) in Spain, the effect of the COVID-19 pandemic process on non-alcoholic fatty liver disease and insulin resistance was examined. In this study, 6236 patients participated, and AST, ALT, BMI, and waist-hip circumference were analyzed in 2018, 2019, and 2020, the pandemic years. Patients exhibited a significant increase in AST and ALT values during the pandemic in contrast to the years preceding it (p<0.001). Furthermore, there was a significant rise in BMI, waist circumference, and hip circumference in these patients during the pandemic compared with the years before it (p<0.001) (24). In this study, the increase in AST and ALT values during the pandemic may be related to non-alcoholic fatty liver disease with increased BMI and waist-hip circumference. In our research, it was observed that the mean AST and ALT values registered a significant decrease during the pandemic compared with the pre-pandemic measurements (p<0.05). Additionally, there was a reduction in BMI values in the pandemic period as opposed to the pre-pandemic period. In both our study and the referenced one, AST and ALT values demonstrated a correlation with BMI.

Several meta-analyses have shown that obesity increases the severity of COVID-19 infection but does not increase mortality (25,26,27). A decrease in physical activity was observed during the COVID-19 pandemic. Based on step count estimates, in more than 30 million people in Europe, there was a decrease in physical activity between 7% and 38% during the pandemic (28). Our study found that the current average BMI values during the pandemic were lower than the pre-pandemic values. Our study examined current BMI values between 01/04/2022 and 01/04/2023. This period is two years after the pandemic began and is when the curfew and some restrictions were lifted. The BMI may have increased because of the decrease in physical activities at the beginning of the pandemic process, and with the lifting of the bans and restrictions, patients may have paid more attention to their physical activities and diet, and their BMI may have decreased.

Study Limitations

This study has some limitations. This is a retrospective study comparing pre-pandemic biochemical values such as HbA1c, lipid panel, and liver and kidney functions with their current values at the beginning of the pandemic. Because these biochemical values are not routinely checked in healthy people before and during the pandemic, no healthy control group exists. This study is a quasi-experimental research in which the control group is the patient himself/herself. Our study compared current systolic and DBP and BMI values with pre-pandemic values. Because these values could not be measured before the pandemic because it was a retrospective study, they were given based on the patient's declaration in the patient questioning.

The strength of our study is to examine the effect of the COVID-19 pandemic process on glycemic control in type 2 diabetic patients by comparing the three-month average HbA1c values, which are effective in showing glycemic regulation, with the pre-pandemic, pandemic onset, and current values. The absence of patients with newly diagnosed type 2 diabetes in our study was a factor in the significant increase in the mean HbA1c values during the pandemic compared with the pre-pandemic period.

Conclusion

As a result of this study, the mean HbA1c and glucose values increased significantly in patients with type 2

diabetes during the COVID-19 pandemic compared with the pre-pandemic period ($p<0.05$). During the COVID-19 pandemic, diabetes regulation deteriorated due to reasons such as the decrease in the number of annual doctor visits for diabetes control, a decrease in physical activity due to restrictions, and changes in diet. Our study found that the glycemic control of patients with type 2 diabetes was impaired during the pandemic. In future natural disasters, deterioration in glycemic control can be prevented by increasing physical activity, paying attention to diet, and using telemedicine.

Ethics

Ethics Committee Approval: This is a retrospective quasi-experimental study conducted among patients who applied to the internal diseases and endocrinology outpatient clinic between 01/04/2022 and 01/04/2023 at the University of Health Sciences Türkiye, İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital with the approval number 132781 at the University of Health Sciences Türkiye, Hamidiye Clinical Research Ethics Committee meeting dated 12.05.2022.

Informed Consent: Retrospectively study

Authorship Contributions

Surgical and Medical Practices: E.K., İ.E., A.Y., Concept: E.K., İ.E., A.Y., Design: E.K., İ.E., A.Y., Data Collection or Processing: E.K., Analysis or Interpretation: E.K., İ.E., A.Y., Literature Search: E.K., İ.E., A.Y., Writing: E.K.

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The Relationship Between Medication Burden and 30-day Mortality in Patients Undergoing Transcatheter Aortic Valve Implantation

Transkateter Aort Kapak İmplantasyonu Uygulanan Hastalarda İlaç Yükü ile 30 Günlük Mortalite Arasındaki İlişki

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ABSTRACT

Background: Transcatheter aortic valve implantation (TAVI) is a treatment method that is particularly relevant to the geriatric population and is applicable to fragile patients. However, data on the predictive value of medication burden, which is a component of fragility, for post-TAVI clinical outcomes are very limited. The aim of this study was to evaluate the effect of polypharmacy on 30-day clinical outcomes, especially mortality, in patients undergoing TAVI.

Materials and Methods: In this retrospectively designed study, 225 patients who underwent TAVI between December 2017 and December 2021 were examined. The patients' medications were divided into three groups according to the Multum Lexicon Drug Database: heart failure drugs, cardiovascular drugs, and non-cardiovascular drugs. Hyperpolypharmacy (HPP) was defined as the use of ten or more medications. Clinical outcomes were compared between the groups with and without HPP.

Results: According to the analysis, HPP was present in 39.1% of patients. The HPP group had a significantly higher 30-day mortality rate than the non-HPP group. Additionally, major bleeding was more common in the HPP group. Multivariate logistic regression analysis revealed that HPP was independently associated with 30-day mortality.

Conclusion: Our study highlights the high prevalence of medication burden in patients undergoing TAVI and the association between HPP and adverse clinical outcomes. HPP should be considered as a potential risk factor for 30-day mortality and major bleeding in patients with TAVI. Strategies such as avoiding unnecessary drug use and reducing the number of medications should be implemented in the geriatric assessment of patients with TAVI to optimize outcomes. Further studies are needed to confirm these findings and explore potential interventions to improve medication management in patients with TAVI.

Keywords: Hyperpolypharmacy, aortic stenosis, transcatheter aortic valve implantation, 30-day mortality, aging

ÖZ

Amaç: Transkateter aort kapak implantasyonu (TAVI), özellikle geriatrik popülasyonu ilgilendiren ve frajil hastalara uygulanan bir tedavi yöntemidir. Ancak TAVI sonrası klinik sonuçlar için frajilitenin bir komponenti olan ilaç yükünün prediktif değerine dair veriler çok sınırlıdır. Bu çalışmanın amacı, TAVI uygulanan hastalarda 30 günlük mortalite ve majör kanamayı öngörmede hiperpolifarmasinin (HPP) prognostik değerini araştırmaktır.

Gereç ve Yöntemler: Retrospektif olarak tasarlanan bu çalışmaya Aralık 2017 ile Aralık 2021 arasında TAVI uygulanan toplam 225 hasta dahil edildi. Hastaların kullanmış olduğu ilaçlar Multum Lexicon İlaç Veri Tabanı'na göre üç gruba ayrıldı: kalp yetmezliği (KY) ilaçları, KY olmayan kardiyovasküler ilaçlar ve kardiyovasküler olmayan ilaçlar. HPP, on veya daha fazla ilaç kullanımı olarak tanımlandı. HPP ve klinik sonuçlar arasındaki ilişki, çok değişkenli lojistik regresyon modelleri kullanılarak analiz edildi.

Bulgular: Ortalama toplam ilaç sayısı 9'du ve hastaların %39,1'inde HPP mevcuttu. HPP grubu, non-HPP grubuyla karşılaştırıldığında önemli ölçüde daha yüksek 30 günlük ölüm oranına sahipti. Ayrıca, HPP grubunda majör kanama daha sık olarak saptandı. Çok değişkenli lojistik regresyon analizi, HPP 30 günlük mortalite ile bağımsız olarak ilişkili olduğunu ortaya koydu.

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ÖZ

Sonuç: Çalışmamız, TAVI uygulanan hastalarda ilaç yükünün yüksek prevalansını ve HPP ile olumsuz klinik sonuçlar arasındaki ilişkiyi vurgulamaktadır. HPP, TAVI hastalarında 30 günlük mortalite ve majör kanama için potansiyel bir risk faktörü olarak düşünülmelidir. Sonuçları optimize etmek için TAVI hastalarının geriatrik değerlendirmesinde gereksiz ilaç kullanımından kaçınmak ve ilaç sayısını azaltmak gibi stratejiler uygulanmalıdır. Bu bulguları doğrulamak ve TAVI hastalarında ilaç yönetimini iyileştirmeye yönelik potansiyel müdahaleleri araştırmak için daha ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Hiperpolifarmasi, aort stenozu, transkateter aort kapak implantasyonu, 30-günlük mortalite, yaşlanma

Introduction

Aortic stenosis (AS) is a prevalent disease among the elderly population. The global demographic shift toward an aging population has increased the number of elderly patients requiring invasive cardiological treatments or cardiac surgery. From 1992 to 2008, there was an increase in the percentage of elderly patients receiving heart surgery in Germany, with the proportion rising from 2.3% to 10.8% (1). In recent years, this trend has continued to accelerate, with the need for surgical or interventional treatment primarily driven by severe AS. Although aortic valve surgery is considered the standard of care, transcatheter aortic valve implantation (TAVI) has become a common treatment method for patients with underlying conditions and risk factors. TAVI is a minimally invasive, safe, and effective procedure that presents a valuable therapeutic option for patients with severe AS and a high risk of complications during traditional surgery (2). However, despite its many benefits, adverse events after the procedure cannot be underestimated (3).

Various parameters have been studied for their association with poor clinical outcomes in patients undergoing TAVI, with comorbid burden and frailty emerging as noteworthy issues (4,5). Elderly and high-risk patients often have multiple comorbidities that impact their prognosis after the procedure. Furthermore, the use of multiple drugs is a significant risk factor associated with the course of multiple diseases. Polypharmacy, defined as the use of five or more drugs, has been categorized as a geriatric syndrome and is frequently observed in elderly patients (6). Approximately 40% of individuals over 65 use five or more drugs. In addition to comorbidities, polypharmacy leads to negative outcomes due to drug-drug interactions and increased drug side effects (7). Prior research indicates that polypharmacy is associated with several adverse events, including declines in functional capacity, increased drug interactions, length of hospital stay, recurrent hospital admissions, and mortality (8). The use of drugs in cardiovascular diseases is particularly high, with hyperpolypharmacy (HPP) defined as the use of ten or more drugs. HPP is detected in one out of every four patients with heart failure (HF) and predicts poor outcomes (9). Furthermore, HPP predicts worse outcomes, exacerbating frailty in elderly patients.

Despite numerous studies on the effects of polypharmacy on clinical outcomes in geriatric patients, there is a significant gap in the literature regarding the association between polypharmacy and clinical outcomes in patients who have undergone TAVI. The focus of this research is to assess how HPP affects 30-day mortality and Valve Academic Research Consortium-3 (VARC-3) endpoints among patients who have undergone TAVI.

Materials and Methods

Study Population

In this retrospective study, the records of 257 consecutive patients with symptomatic severe AS who underwent TAVI in a tertiary center between December 2017 and December 2021 were reviewed. The heart team, comprising cardiovascular surgeons, cardiologists, anesthesiologists, and pulmonologists, decided on TAVI after assessing preoperative risk using the Society of Thoracic Surgeons (STS) risk calculator system. Severe AS was defined according to the European Society of Cardiology valvular heart disease guidelines (10). Exclusion criteria were absence of medical records. Demographic, clinical, biochemical, and echocardiographic evaluations were recorded for all patients. The study protocol was approved by the University of Health Sciences Türkiye, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee in April 2021 (decision no: 2021/38, date: 27.04.2021), and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Definition of Hyperpolypharmacy

In this study, we used the classification of medications according to the Multum Lexicon Drug Database, as used by Unlu et al. (11) on patients with HF. The categorization comprises three primary clusters of medicines: HF medications, cardiovascular system drugs other than HF, and drugs used to treat non-cardiovascular diseases (12).

At admission, patients were questioned regarding their drug usage, and their drug containers were checked and recorded in their medical records. These records were scanned retrospectively, and the number and types of drugs used by the patients were determined. While studies generally accept the presence of polypharmacy (≥5 drugs) as a predictor, the high rate of polypharmacy in the TAVI patient group encouraged us to evaluate HPP (≥10 drugs).

Endpoints

The focus of this study was to assess the impact of HPP on 30-day mortality rates. To complement this primary endpoint, several secondary endpoints were also investigated, including major bleeding, stroke, myocardial infarction, acute kidney injury (AKI), major vascular complications, and the need for a new permanent pacemaker (PACE), as outlined by the VARC-3 (13). The definition of major bleeding is outlined by the VARC-3 consortium as type 2 (major), type 3 (life-threatening), and type 4 (leading to death) bleeding. Accordingly, the spectrum ranging from the need for at least 2-4 units of whole blood/red blood cells transfusion to life-threatening or fatal bleeding has been considered to be within the scope of major bleeding (13).

Statistical Analysis

The Statistical Package for the Social Sciences, version 24.0 (SPSS Inc., Chicago, Illinois, USA), was used to analyze the data. The normal distribution of variables was assessed through visual methods such as histograms and probability curves, and analytical methods including the Kolmogorov-Smirnov and Shapiro-Wilk tests. Numerical variables showing normal distribution were presented as mean ± standard deviation, whereas those not showing normal distribution were expressed as median (interquartile range) and categorical variables as percentage (%). For statistical analysis of numerical variables between groups, either Student's t-test or Mann-Whitney U test was used, whereas chi-square or Fisher's Exact test was employed for categorical variables. To identify the independent predictors of 30-day mortality, univariate logistic regression analysis was performed first, and subsequently, multivariate logistic regression analysis was conducted using the parameters that were significant (p-value <0.1) in the initial analysis. A p-value of <0.05 was considered significant throughout the study.

Results

Upon screening for inclusion and exclusion criteria, we enrolled 225 patients who underwent TAVI. The patient population had a mean age of 78.4 years, with females accounting for 62.2% of the cohort. Based on HPP status, patients were stratified into two groups, with 88 patients in the HPP group and a HPP rate of 39.1%. Table 1 outlines the demographic and clinical characteristics of the study population. In the HPP group, hyperlipidemia [50 (36.2) vs. 59 (67.0), p<0.001] and atrial fibrillation [22 (16.1) vs. 30 (34.1), p=0.002] were observed more frequently, and the aortic valve area (AVA) was lower in the HPP group (0.77±0.14 vs. 0.72±0.13, p=0.024). No significant difference was detected between the groups for other clinical and demographic characteristics, except for a higher STS score in the non-HPP group.

Table 2 presents the medication profile according to the HPP status. The mean medication count was 9 for the entire cohort, with HPP and non-HPP groups having 12 and 7 mean medication counts, respectively. Beta-blockers were the most commonly used drug group, with all drug groups, except antiplatelet agents and bronchodilators, being used at a higher rate in the HPP group.

Table 3 outlines the clinical endpoints of the patients based on HPP status. HPP was associated with higher 30-day mortality [2 (1.5) vs. 8 (8.9), p=0.016] and major bleeding [11 (8.1) vs. 21 (23.3), p<0.001]. Although stroke, AKI, myocardial infarction, and the need for a new permanent PACE were proportionally higher in the HPP group, no statistically significant difference was detected between the two groups. Major vascular complications were also higher in the HPP group. A comparison of 30-day mortality and VARC-3 outcomes based on HPP status is shown in Figure 1.

To identify independent predictors of 30-day mortality in patients undergoing TAVI, we performed univariate logistic regression analysis (Table 4). The analysis revealed

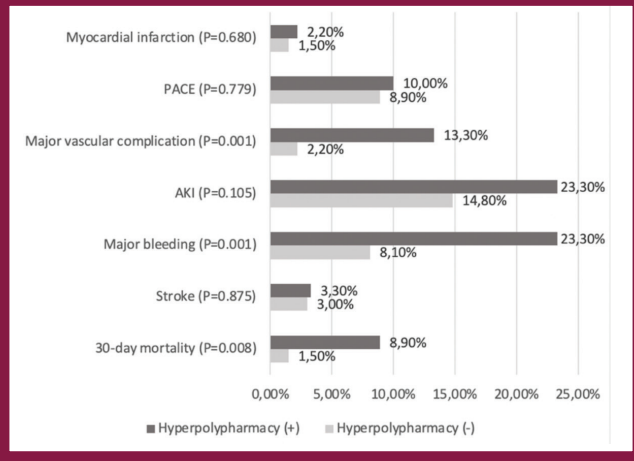

Figure 1. Comparison of 30-day mortality and VARC-3 outcomes in the presence of hyperpolypharmacy

PACE: Pacemaker, AKI: Acute kidney injury, VARC-3: Valve Academic Research Consortium-3

Table 1. Baseline clinical and echocardiographic characteristics according to the presence of hyperpolypharmacy

Variables	Total (n=225)	Hyperpolypharmacy (-) (n=137)	Hyperpolypharmacy (+) (n=88)	p-value
Age, years	78.4±7.9	78.2±8.1	78.7±7.7	0.614
Gender (male), n (%)	85 (37.8)	55 (40.1)	30 (34.1)	0.361
Hypertension, n (%)	155 (68.9)	91 (66.4)	64 (72.7)	0.319
Previous cardiac surgery, n (%)	51 (22.7)	27 (19.7)	24 (27.3)	0.186
Coronary artery disease, n (%)	137 (60.9)	82 (59.9)	55 (62.5)	0.691
COPD, n (%)	133 (59.1)	82 (59.1)	51 (58)	0.777
Diabetes mellitus, n (%)	92 (40.9)	53 (38.7)	39 (44.3)	0.402
Hyperlipidemia, n (%)	109 (48.4)	50 (36.5)	59 (67)	<0.001
CKD, n (%)	72 (32)	44 (32.1)	28 (31.8)	0.963
PAD, n (%)	73 (32.4)	47 (34.3)	26 (29.5)	0.457
CVD, n (%)	8 (3.6)	4 (2.9)	4 (4.5)	0.520
Atrial fibrillation, n (%)	52 (23.1)	22 (16.1)	30 (34.1)	**0.002**
STS score	9.5±3.2	10±3.2	8.8±3.2	0.006
Hemoglobine (g/dL)	11.4±1.7	11.3±1.7	11.3±1.6	0.831
Albumin (g/dL)	3.66±0.46	3.62±0.45	3.71±0.49	0.188
Creatinine (mg/dL)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	1.0 (0.8-1.3)	0.147
e-GFR (mL/min)	64.3±24	63.8±25.6	65.1±21.5	0.689
LVEF (%)	53.8±11.3	54.1±10.9	53.7±12.1	0.784
AVA, cm^2	0.75±0.14	0.77±0.14	0.72±0.13	**0.024**
Mean aortic gradient (mm/Hg)	49.4±12.7	49.9±12.8	48.5±12.5	0.415
Valve type (self-expandable), n (%)	65 (28.9)	41 (29.9)	24 (27.3)	0.668
Valve size (mm)	26 (25-29)	26 (25-29)	26 (23-29)	0.105

AVA: Aortic valve area, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, GFR: Glomerular filtration rate, HP: Hyperpolypharmacy, LVEF: Left ventricular ejection fraction, PAD: Peripheral artery disease, STS: Society of thoracic surgeons

that advanced age, hyperlipidemia, low left ventricular ejection fraction (LVEF), low hemoglobin levels, low AVA, and HPP were associated with 30-day mortality. Using the parameters that were significant in the univariate analysis, we conducted multivariate logistic regression analysis, which identified hemoglobin <10.1, LVEF <60%, low AVA, and HPP as independent predictors of 30-day mortality in TAVI patients (Table 4).

A comparison of medication burden based on the presence of 30-day mortality in patients with TAVI is depicted in Figure 2. Patients with 30-day mortality had a mean of 14 drugs, whereas those without had a mean of 9 drugs (p<0.001).

Discussion

The main finding of the present study was that HPP, defined as the use of at least 10 drugs, emerged as a significant independent predictor of 30-day mortality in patients undergoing TAVI. In addition, low hemoglobin levels, low LVEF, and lower AVA were independent predictors of 30-day mortality following TAVI. The prevalence of polypharmacy and HPP in the study population was 91% and 39.1%, respectively.

Our study revealed a high prevalence of polypharmacy and HPP, with rates of 91% and 39.1%, respectively. HPP, which is characterized by the use of at least 10 drugs according to geriatric literature (14), is a severe form of polypharmacy that has been linked to adverse outcomes such as disability, hospitalizations, and mortality (9). In defining polypharmacy, various criteria for drug classification exist, with the Anatomical Therapeutic Chemical and Multum classifications being commonly used. For instance, Unlu et al. (11) used the Multum classification in a study that examined the impact of polypharmacy in patients with HF. Given the high prevalence of cardiovascular comorbidities (such as coronary artery disease and HF) among patients with TAVI, the Multum classification used by Unlu et al. (11) may hold greater relevance.

Table 2. Medication profile based on hyperpolypharmacy

Variables	Total (n=225)	Non-HPP (-) (n=137)	HPP (+) (n=88)	p-value
Total medication count, mean (SD)	9 (7-12)	7 (5.5-9)	12 (11-14)	<0.001
Heart failure medications				
Beta blockers, n (%)	193 (85.8)	111 (82.2)	82 (91.1)	0.061
ACEI/ARB, n (%)	141 (62.7)	66 (48.9)	75 (83.3)	<0.001
MRA, n (%)	18 (8.0)	8 (5.9)	10 (11.1)	0.160
Vasodilators, n (%)	24 (10.7)	4 (3.0)	20 (22.2)	<0.001
Diuretics, n (%)	132 (58.7)	59 (43.7)	73 (81.1)	<0.001
Digoxin, n (%)	22 (9.8)	4 (3.0)	18 (20.0)	<0.001
Other cardiovascular agents				
Lipid lowering, n (%)	109 (48.4)	48 (35.6)	61 (67.8)	<0.001
Antiplatelets, n (%)	171 (76.0)	107 (79.3)	64 (71.1)	0.161
Anticoagulants, n (%)	48 (21.3)	20 (14.8)	28 (31.1)	0.003
Antiarrhythmics, n (%)	14 (6.2)	5 (3.7)	9 (10.0)	0.055
Calcium channel blockers n (%)	111 (49.3)	46 (34.1)	65 (72.2)	<0.001
Anti-anginal agents, n (%)	37 (16.4)	7 (5.2)	30 (33.3)	<0.001
Other antihypertensives, n (%)	50 (22.2)	15 (11.1)	35 (38.9)	<0.001
Non-cardiovascular medications				
Opioids, n (%)	40 (17.9)	13 (9.6)	27 (30.3)	<0.001
Non-opioid analgesics, n (%)	95 (42.2)	40 (29.6)	55 (61.1)	<0.001
Benzodiazepine, n (%)	22 (9.8)	6 (4.4)	16 (17.8)	<0.001
Antidepressants, n (%)	86 (38.2)	33 (24.4)	53 (58.9)	<0.001
Antipsychotics, n (%)	13 (5.8)	3 (2.2)	10 (11.1)	0.007
Anti-diabetics, n (%)	93 (41.3)	53 (39.3)	40 (44.4)	0.439
Antacids, n (%)	132 (58.9)	63 (46.7)	69 (77.5)	<0.001
Thyroid agents, n (%)	80 (35.6)	30 (22.2)	50 (55.6)	<0.001
Bronchodilators, n (%)	130 (57.8)	79 (58.5)	51 (56.7)	0.783
GU tract agents, n (%)	52 (23.1)	16 (11.9)	36 (40.0)	<0.001
Minerals/vitamins, n (%)	90 (40.0)	35 (25.9)	55 (61.1)	<0.001
Anti-infective agents, n (%)	66 (29.3)	24 (17.8)	42 (46.7)	<0.001
Anti-neoplastic agents, n (%)	14 (6.2)	4 (3.0)	10 (11.1)	<0.001
Topical agents, n (%)	90 (40.0)	35 (25.9)	55 (66.1)	<0.001

ACEI: Angiotensin-converting enzyme inhibitors, ARB: Angiotensin II receptor antagonists, GU: Genitourinary, MRA: Mineralocorticoid receptor antagonists, HPP: Hyperpolypharmacy, SD: Standard deviation

Risk assessment before surgical or transcatheter treatment is recommended in geriatric patients with severe AS (15). Frailty measurement is of great importance in this assessment and is effective in determining the prognosis of patients after the procedure. The multidimensional prognostic index (MPI) is recommended as a parameter to be used before the procedure and in long-term follow-up (16). MPI includes the number of drugs used, and the use of ⩾7 drugs is defined as a serious drug burden (17). Previous studies have reported a negative correlation between increased medication burden and functional capacity, which directly affects the prognosis of patients with TAVI (18,19,20). The Charlson Comorbidity Index (CCI) is a widely used measure of frailty that is associated with polypharmacy (21). George et al. (22) conducted a study that found CCI to be correlated with 30-day mortality and VARC-2 outcomes in patients undergoing TAVI. Additionally, the literature has reported a negative correlation between increased medication burden and functional capacity, which directly impacts the prognosis of TAVI patients (23).

These findings are supported by our study, which suggests that polypharmacy is a significant indicator of frailty and is associated with adverse clinical outcomes and 30-day mortality in patients with TAVI. Our study underscores the importance of conducting a thorough geriatric and frailty assessment in patients with TAVI to optimize their care.

The relationship between polypharmacy and adverse events in patients undergoing TAVI cannot be elucidated through a unifying mechanism. Utilization of multiple medications primarily arises from comorbidities associated with multiple diseases, representing a pivotal determinant influencing unfavorable outcomes (24). Polypharmacy is intricately linked to various mechanisms. Notably, drug-drug interactions constitute a significant facet of this relationship. The interplay among diverse pharmacological agents can induce alterations in their plasma concentrations, accentuating harmful aspects of their effects or side effects, thereby precipitating instances of bleeding and cognitive impairment among patients (24). Concurrently, heightened instances of medication non-adherence and administration errors engender therapeutic dissociation, impeding optimal treatment outcomes. Furthermore, the decline in cognitive functions, which frequently results in fall incidents, has emerged as a substantial contributor to mortality, particularly in the elderly population (25). The combination of these complexities, along with other factors related to taking multiple medications after TAVI, increases the possibility of negative events. We believe that the combination of more bleeding, higher chances of falls, increased vulnerability to infections, and cognitive problems, along with longer stays in intensive care and the hospital, contribute to the higher mortality rates in this group. Indeed, the high rate of 30-day mortality in the polypharmacy group, as well as the elevated incidence of major bleeding, can be explained through these mechanisms in our study. Furthermore, a study examining the relationship between the frailty index, which includes polypharmacy, and major bleeding in patients with TAVI also supports this finding (26). Therefore, optimizing the number of drugs and preventing unnecessary prescribing are of critical importance in patients with TAVI.

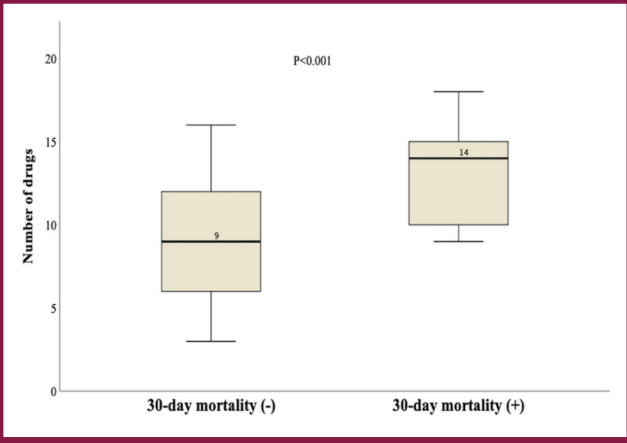

Figure 2. Comparison of medication burden according to the presence of 30-day mortality in TAVI patients
TAVI: Transcatheter aortic valve implantation

Study Limitations

This study has some limitations, such as its retrospective and single-center nature, which may limit the generalizability of the findings. Furthermore, various parameters for frailty assessment, including albumin levels, sarcopenia, and the CCI, were not incorporated into the study design. The study did not consider post-procedure management, which could have had an impact on both 30-day mortality and clinical outcomes. In addition, the medication count did not consider combination pills containing multiple pharmacologically active ingredients, and drug dosages were not fully determined. These limitations should be considered in future research. Finally, angiotensin receptor-neprilysin inhibitors were not included in the study, and sodium-glucose cotransporter 2 inhibitors, which are now considered HF drugs, were evaluated in the antidiabetic medication group.

Table 3. Clinical outcomes of patients based on hyperpolypharmacy

Variables	Total (n=225)	Non-HPP (-) (n=137)	HPP (+) (n=88)	p-value
30-day mortality	10 (4.4)	2 (1.5)	8 (8.9)	**0.016**
Stroke	7 (3.1)	4 (3)	3 (3.3)	0.875
Major bleeding	32 (14.2)	11 (8.1)	21 (23.3)	**<0.001**
AKI	41 (18.2)	20 (14.8)	21 (23.3)	0.105
Major vascular complications	15 (6.7)	3 (2.2)	12 (13.3)	**<0.001**
Pacemaker	21 (9.3)	12 (8.9)	9 (10)	0.779
MI	5 (2.2)	2 (1.5)	3 (3.3)	0.391

AKI: Acute kidney injury, MI: Myocardial infarction, HPP: Hyperpolypharmacy

Table 4. Logistic regression analysis of 30-day mortality

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age, years	1.092 (0.985-1.210)	**0.094**	1.174 (0.955-1.510)	0.173
Gender (male)	1.439 (0.362-5.720)	0.606		
Hypertension	1.056 (0.265-4.211)	0.938		
Previous cardiac surgery	1.491 (0.371-5.987)	0.573		
Coronary artery disease	0.962 (0.264-3.510)	0.953		
COPD	1.648 (0.415-6.548)	0.478		
Diabetes mellitus	0.607 (0.153-2.410)	0.478		
Hyperlipidemia	1.899 (0.901-4.002)	**0.092**	1.978 (0.805-4.561)	0.211
CKD	1.441 (0.394-5.274)	0.581		
PAD	0.888 (0.223-3.537)	0.866		
CVD	3.048 (0.912-9.124)	0.167		
Atrial fibrillation	2.319 (0.629-8.555)	0.206		
STS score	1.018 (0.845-1.226)	0.855		
Hemoglobine	0.549 (0.343-0.879)	**0.013**	0.478 (0.268-0.899)	**0.017**
Albumin	0.882 (0.228-3.413)	0.856		
Creatinine	0.990 (0.318-3.082)	0.986		
e-GFR	0.988 (0.961-1.017)	0.418		
LVEF	0.937 (0.892-0.983)	**0.008**	0.934 (0.864-0.988)	**0.018**
AVA	0.004 (0.000-0.399)	**0.019**	0.020 (0.000-4.010)	0.165
Mean aortic gradient	1.001 (0.952-1.052)	0.970		
Valve type (self-expandable)	2.583 (0.722-9.244)	0.145		
Valve size	0.984 (0.800-1.211)	0.811		
Hyperpolypharmacy	6.488 (1.345-31.301)	**0.020**	5.42 (1.187-28.549)	**0.041**

AVA: Aortic valve area, CKD: Chronic kidney disease, COPD: Chronic obstructive pulmonary disease, CVD: Cerebrovascular disease, GFR: Glomerular filtration rate, HPP: Hyperpolypharmacy, LVEF: Left ventricular ejection fraction, PAD: Peripheral artery disease, STS: Society of thoracic surgeons, OR: Odds ratio, CI: Confidence interval

Conclusion

In summary, the present study provides evidence that HPP, defined as the use of at least 10 drugs, is prevalent among patients undergoing TAVI and is associated with unfavorable clinical outcomes. The coexistence of polypharmacy, frailty, and multiple comorbidities in the elderly necessitates appropriate prescribing practices and medication management strategies to prevent adverse events. Therefore, clinicians should increase their awareness of this issue and strive to reduce unnecessary drug use to mitigate the negative impact of polypharmacy. The results of our study highlight the importance of geriatric assessment in patients with TAVI, particularly for identifying HPP, as it plays a crucial role in predicting adverse outcomes.

Ethics

Ethics Committee Approval: The study protocol was approved by the University of Health Sciences Türkiye, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital Ethics Committee in April 2021 (decision no: 2021/38, date: 27.04.2021), and the study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: Retrospectively study.

Authorship Contributions

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

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

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Morphometric and Clinical Importance of Anatomical Structures Related to Fossa Cerebellaris in Surgical Approaches

Fossa Cerebellaris'te Bulunan Anatomik Yapıların Cerrahi Yaklaşımlardaki Morfometrik ve Klinik Önemi

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ABSTRACT

Background: Surgical approaches to the posterior fossa are always challenging and complex anatomical structures pose risks for the removal of cerebellar lesions. In this study, we aimed to define a safe corridor for tumor surgery for neurosurgeons by examining the anatomy of the fossa cerebellaris in detail and measuring some osseous landmarks.

Materials and Methods: In this study, 15 dry bone craniums and 8 cadavers were morphometrically examined and the distances between some important bony landmarks were measured with a digital caliper with millimeter precision. The measurements were compared using statistical methods.

Results: The distance between anterior margin of foramen magnum (FM) and spheno-occipital synchondrosis (SOS) was found to be longer in dry skull than in cadaver measurements, and a statistically significant difference was found. There was no significant difference between right and left side comparisons for for. jugulare, for. magnum, porus acousticus internus and canalis nervi hypolossi in both dry skull and cadaver samples.

Conclusion: Longer distance between the anterior border of FM and SOS make difficult the surgical approach to the clivus lesions, but facilitate to the reach the anterior FM tumors. Careful preoperative evaluation of this distance provides good anatomical knowledge for neurosurgeons dealing with such lesions.

Keywords: Posterior fossa, tumor, spheno-occipital synchondrosis, anatomy

ÖZ

Amaç: Posterior fossaya cerrahi yaklaşımlar her zaman zorlayıcı olmuştur ve karmaşık anatomik yapılar, serebellar lezyonların eksizyonu ameliyatlarında risk oluşturmaktadır. Bu calışmada, fossa cerebellarisin anatomisi ayrıntılı olarak incelenerek ve bazı osseoz işaretler ölçülerek beyin cerrahlarına tümor cerrahisi için güvenli bir koridor tanımlamak amaçlandı.

Gereç ve Yöntemler: Bu çalışmada 15 kuru kemik kranyum ve 8 kadavra morfometrik olarak incelendi ve bazı önemli kemiksel işaretler arasındaki mesafeler milimetre hassasiyetinde bir dijital kumpasla ölçüldü. Ölçümler istatistiksel yöntemler kullanılarak karşılaştırıldı.

Bulgular: Foramen magnum'un (FM) ön kenarı ile sfeno-oksipital sinkondroz (SOS) arasındaki mesafe kuru kafatası ölçümlerinde kadavra ölçümlerine göre daha uzun bulunmuş ve istatistiksel olarak anlamlı bir fark tespit edilmiştir. Hem kuru kafatası hem de kadavra örneklerinde for. jugulare, for. magnum, porus acousticus internus ve canalis nervi hypolossi için sağ ve sol taraf karşılaştırmaları arasında anlamlı bir fark bulunmamıştır.

Sonuç: FM'nin ön sınırı ile SOS arasındaki mesafenin uzun olması klivus lezyonlarına cerrahi yaklaşımı zorlaştırırken, anterior FM tümörlerine ulaşmayı kolaylaştırır. Bu mesafenin ameliyat öncesi dikkatli bir şekilde değerlendirilmesi, bu tür lezyonlarla uğraşan beyin cerrahları için iyi bir anatomik bilgi sağlamaktadır.

Anahtar Kelimeler: Posterior fossa, tümör, sfeno-oksipital sinkondroz, anatomi

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Introduction

The fossa cerebellaris is located in the fossa crane posterior. Fossa cranii posterior is surrounded by the clivus and dorsum sellae anteriorly, the pars petrosa and pars mastoidea of the temporal bone laterally, and the occipital bone and angulus mastoideus of the parietal bone posteriorly. It contains the occipital lobe, cerebellum, and related anatomical structures (1). The fossa crane posterior is the deepest and largest fossa of the cranium. Important osseous structures in this region are the foramen magnum (FM), meatus acousticus internus, foramen jugulare (FJ), canalis nervi hypoglossi, canalis condylaris, sulcus sinus petrosi inferioris, sulcus sinus transversi, sulcus sinus sigmoidei, protuberantia occipitalis interna, and dorsum sellae. During surgical approaches to posterior fossa lesions, these structures pose some risks for neurosurgeons and require special attention. Injuries to these delicate anatomical structures may result in catastrophic outcomes (2).

In this study, we plan to examine the osseous anatomy and neighborhood and distance relations of the region, which are important for surgical interventions to the fossa cerebellaris [pathologies of the cerebellum, for. magnum and upper cervical region pathologies and congenital malformations of this region, schwannoma-like pathologies localized to the meatus acusticus, pathologies such as glomus jugulare involving the jugular foramen (JF), etc.]. Some morphometric measurements were performed, and the results were compared with those reported in the relevant literature.

Materials and Methods

In this study, following the approval of the Dokuz Eylül University Non-Invasive Research Ethics Committee (no: 2012/22-8, date: 21/06/2012) we morphometrically examined the osseous structures in 15 dry bone cranium and 8 cadavers, which can be measured with a maximum of 3 mm deficiencies, in the Dokuz Eylül University Faculty of Medicine Anatomy Department Laboratory.

All measurements were recorded with a digital caliper, accurate to millimeters. Measurements made on dry bones and cadavers are listed separately in the table. The results of the right and left comparisons and reciprocal comparisons of the measurements made separately (cadaver-dry bone) within their group were statistically analyzed. None of the skulls and cadavers examined showed signs of previous cranial surgery, malformation, or trauma. All samples were photographed using a Canon EOS 700D (55 mm lens) camera.

Important anatomical foramens, passages, and clinically related structures in this fossa and its neighbors; the measurable distances in dry bone and cadaver, and the distances that may be of clinical (application area) importance were measured (Figures 1, 2, 3).

Parameters that can be measured on dry bone (right/left); FM anterior-posterior length, FM transverse length, porus acusticus internus (PAI) superior-inferior diameter, PAI anterior-posterior diameter, FJ superior-inferior diameter, FJ mediolateral diameter, PAI lower edge, the distance between the upper edge of the FJ, the distance between the lower edge of the FJ and the canalis nervi hypolossi (CNH), the distance between the anterior border of the CNH-FM, the distance from the PAI-sinus transversus (ST)-sinus sigmoideus (SS) junction, the posterior edge of the FJ-ST and SS junction, and ST and SS junction-protuberentia occipitalis interna (POI) were measured.

Parameters measured on dry bone and cadaver are, respectively, as right/left distance; distance between PAIs and midline, distance between FJs and midline, distance between CNHs and midline, distance between FM posterior border and POI, and between FM anterior border-spheno-occipital synchondrosis (SOS) joint distance was measured.

The distance of the ST-SS junction to the midline was measured as the right/left distance of the parameters measured on the cadaver.

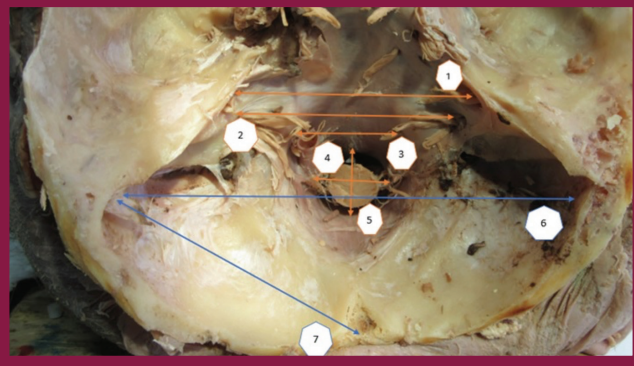

Figure 1. Measurement distances
1. Distances between the porus acousticus internus and distances to the midline
2. Distances between the foramen jugulares and distances to the midline
3. Distances between the canalis nerve hypoglossies and distances to the midline
4. Foramen magnum (FM) transverse length
5. FM anteroposterior length
6. Distance between the midline and the junction of the transversus-sigmoid sinus
7. Distance between the protuberantia occipital interna and the junction of the transversus-sigmoid sinus

Statistical Analysis

SPSS version 15.0 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA) was used to evaluate the data. The obtained values are shown as mean ± standard deviation or median (minimum-maximum) where appropriate. Examination of normal distribution assumptions for continuous data was evaluated using QQ plots, histograms, and the Shapiro-Wilk test. Normally distributed variables were analyzed using Student's t-test, and non-normally distributed variables were analyzed using the Mann-Whitney U test. Paired t-test or Wilcoxon signed-rank test was used to compare the differences between the measurements made separately in the same dry bone and cadaver for the right and left sides depending on the data distribution. The level of significance was set as $p<0.05$ in all statistical analyses. Because our research was a cadaveric study, patient consent could not be obtained.

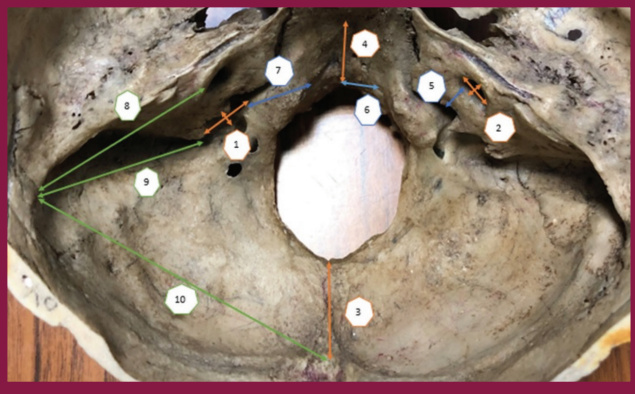

Figure 2. Some posterior fossa measurement distances in the dry skull
1. Superior-inferior and mediolateral diameters of the foramen jugulare (FJ)
2. Superior-inferior and anteroposterior diameters of the porus acousticus internus
3. Distance between the posterior margin of the foramen magnum (FM) and the protuberantia occipital interna
4. Distance between the anterior margin of the FM and spheno-occipital synchondrosis
5. Distance between the inferior margin of the porus acousticus internus and the superior margin of the FJ
6. Distance between the superior margin of the FM and canalis nervi hypoglossi
7. Distance between the inferior margin of the FJ and canalis nervi hypoglossi
8. Distance between the porus acousticus internus and the junction of the transversus-sigmoid sinus
9. Distance between the posterior margin of the FJ and the junction of the transversus-sigmoid sinus
10. Distance between the protuberantia occipital interna and the junction of the transversus-sigmoid sinus

Results

According to the analysis results of the data obtained from 15 dry bones;

The mean magnum anterior-posterior length was measured as 34.3±2.55 mm; the mean magnum transverse length was measured as 27.9±3.27 mm. Anteroposterior (AP) diameter/transverse diameter was defined as FM index 8, and 9 dry bones (60%) were observed as FMI >1.2 and were defined as ovoid-shaped.

PAI superior-inferior diameter, right/left mean=2.59±1.12 mm/2.85±1.35 mm; the anterior-posterior diameter of the PAI was measured as right/left mean=3.78±1.35 mm/4.43±1.49 mm. For. jugulare superior-inferior diameter, right/left mean=5.47±1.15 mm/5.88±1.50 mm; for. jugulare mediolateral diameter was measured as right/left mean: 10.9±2.37 mm/11.1±2.29 mm. The distance between the

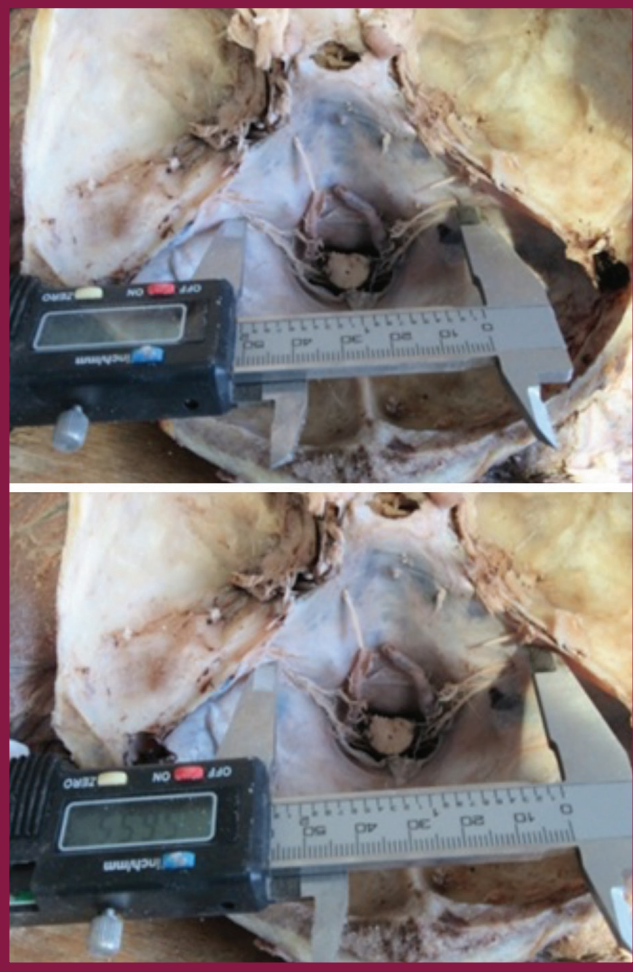

Figure 3. Measurement of distances between the porus acousticus internus and foramen jugulares using a digital caliper

upper edge of the for. jugulate was measured as the right/left mean=6.0±0.76 mm/6.02±0.71 mm. The distance between the lower edge of the for. jugulare and the hypoglossi of the canalis nerve was measured as the right/left mean=9.47±1.39 mm/9.5±1.40 mm. The distance between the anterior border of the for. magnum was measured as the right/left mean=9.86±1.65 mm/9.8±1.60 mm.

The distance from the PAI to the ST and SS junction right/left mean=30.9±4.30 mm/31.04±4.42 mm, the distance from the posterior edge of the jugulare to the ST and SS junction right/left mean=31.7±4.27 mm/31.8±4.18 mm, and the distance from the sinus trasversus and SS junction to the POI right/left mean=31.9±1.60 mm/32±1.79 mm.

The distance between the right and left PAI dry bone cadaver (mean=48.8±4.70 mm/53.2±6.85 mm), the distance between the right and left FJ dry bone cadaver (mean=51.1±2.54 mm/48.7±6.84 mm), and the distance between the right and left canalis nervi hypoglossis were measured as dry bone cadaver (mean=26.7±2.02 mm/23.2±3.53 mm).

The distance between posterior border of for. magnum and protuberantia occipitalis interna dry bone cadaver (mean=40.5±5.76 mm/46.4±9.90 mm), and the distance between anterior border of for. magnum and SOS was measured as dry bone cadaver (mean=19.2±4.42 mm/11.9±2.47 mm).

PAI distance from the midline to the right (dry bone 24.4±2.37 mm; cadaver 26.2±3.34 mm), PAI distance from the midline to the left (dry bone 24.4±2.37 mm; cadaver 26.8±3.50 mm), distance of for. jugulares from the midline to the right (dry bone 25.5±1.26 mm; cadaver 24.2±3.47 mm), for. jugulares distance from the midline to the left (dry bone 25.5±1.27 mm; cadaver 24.5±3.43 mm), canalis nervi hypoglossi distance from the midline to the right (dry bone 14.3±2.97 mm; cadaver 11.5±1.59 mm), and canalis nervi hypoglossi distance from the midline to the left (dry bone 14.4±2.88 mm; cadaver 11.7±2.01 mm).

For the right and left sides, when the paired t-test or Wilcoxon signed-row test, sample t-test results were analyzed to compare the differences between the measurements made separately in the same dry bone and cadaver, the results obtained are shown in Tables 1, 2, 3.

In comparative analyses, only the distance between the FM anterior border and SOS was found to be longer in dry

Table 1. Comparison of measurements between the dry skull and cadavers

Measurement/mm	Material	Mean	SD	Median	p-value
Distance between the right and left porus acusticus internus	Dry skull	48.8	4.70	50.3	0.080
	Cadaver	53.2	6.85	54.0	
Distance between the right and left foramen jugularis	Dry skull	51.1	2.54	51.3	0.226
	Cadaver	48.7	6.84	49.5	
Distance between the right and left canalis nervi hypoglossi	Dry skull	26.7	2.02	26.9	0.006
	Cadaver	23.2	3.53	22.1	
Distance between the posterior margin of for. magnum area snr and the protuberantia occipitalis interna	Dry skull	40.5	5.76	39.2	0.083
	Cadaver	46.4	9.90	47.5	
Distance between the anterior margin of the for. magnum and spheno-occipital synchondrosis	Dry skull	19.2	4.42	18.2	<0.001
	Cadaver	11.9	2.47	12.1	
Distance between porus acusticus internus and midline (Right)	Dry skull	24.4	2.37	25.1	0.149
	Cadaver	26.2	3.34	26.8	
Distance between porus acusticus internus and midline (Left)	Dry skull	24.4	2.37	25.1	0.064
	Cadaver	26.8	3.50	26.3	
Distance between the foramen jugulate and midline (Right)	Dry skull	25.5	1.26	25.8	0.202
	Cadaver	24.2	3.47	24.8	
Distance between the foramen jugulate and midline (Left)	Dry skull	25.5	1.27	25.9	0.308
	Cadaver	24.5	3.43	24.6	
Distance between the canalis nerve hypoglossi and midline (Right)	Dry skull	14.3	2.97	13.4	0.021
	Cadaver	11.5	1.59	11.4	
Distance between the canalis nervi hypoglossi and midline (Left)	Dry skull	14.4	2.88	13.8	0.030
	Cadaver	11.7	2.01	10.8	

SD: Standard deviation

Table 2. Comparison of right-left side measurements performed in the dry skull

Measurement	T-statistic	p-value
Superior-inferior diameter of the porus acousticus internus	-1.476	0.162
Anteroposterior diameter of the porus acousticus internus	-2.785	0.015
Superior-inferior diameter of the foramen jugulate	-1.678	0.116
Mediolateral diameter of the foramen jugulate	-0.799	0.438
Distance between inferior margin of porus acousticus internus and superior margin of foramen jugulare	0.923	0.372
Distance between the inferior margin of the foramen jugulare and canalis nerve hypoglossi	-0.541	0.597
Distance between canalis nerve hypoglossi and anterior margin of the foramen magnum	0.888	0.389
Distance between porus acousticus internus and junction of sinus transversus sinus sigmoideus	-0.961	0.353
Distance between the posterior margin of the Foramen jugulare and the junction of the sinus transversus sinus sigmoideus	-1.642	0.123
Distance between porus acousticus internus and midline	-0.700	0.635
Distance between foramen jugulare and midline	-0.947	0.756
Distance between canalis nervi hypoglossi and midline	-0.798	0.719
Distance between protuberentia occipitalis interna and junction of sinus transversus sinus sigmoideus	-1.002	0.333

Table 3. Comparison of right-left side measurements performed on the cadaver

Measurement	T-statistic	p-value
Distance between porus acousticus internus and midline	-1.248	0.252
Distance between foramen jugulare and midline	-1.042	0.332
Distance between canalis nervi hypoglossi and midline	-0.757	0.474
Distance between the junction of the sinus transversus sinus sigmoideus and the midline	-0.717	0.497

bone than in cadaver measurements, and a statistically significant difference was found (p<). The reason for this was evaluated as SOS is quite evident in some materials, but it is more difficult to detect in cadaver samples than in dry bone. There was no significant difference between the right and left side comparisons in both dry bone and cadaver samples.

Discussion

The area between the cerebellum, pons, and pyramid and filled by the pontocereballaris system is the region that should be evaluated clinically because of primary or metastatic tumor formations. Cerebellar metastases constitute only 10-15% of brain metastases, and approximately 31-32% of these metastases are single metastases. Cerebellar metastases are grouped as life-threatening lesions compared with metastases located in other parts of the brain. They can cause hydrocephalus, irreversible brainstem compression, and herniation of posterior fossa structures (such as tonsils) up and down (through the FM) (2). VII, IX, X, Xl, XII. cranial nerves, a. vertebralis, and v. petrosa are located in this region (3).

Surgically, this area can be accessed via the occipital, temporal, pyramidal, and translabyrinthine routes. The accessorius system crosses the pontocerebellar and emerges from the pars nervosa of the FJ. N. hypoglossus leaves the medulla oblongata with a more internal course between the pyramid and oliva. Its exit from the canalis hypoglossi is more basal and somewhat sheltered. The exit points of the petrosa are lateral to the superior vesinus petrosus in the medulla oblongata.

During the operation, from the occipital to the upper n. vestibularies, n. facialis is seen to occur deeper. The facial nerve leads to the PAI. More basally, n. cochlearis and in between them, n. intermediateus is found in a more hidden position. All these nerve structures are covered by the arachnoid membrane. The vasa labyrinth accompanies these nerve structures. Following the pontocerebellar junction on both sides, n. trigeminus tends anteriorly in the sagittal direction and is observed as a structure that can be encountered in the pontocerebellar region.

The cisternal part of n. trigeminus protrudes bilaterally from the anterior aspect (anterior-lateral part) of the pons. When the exit site is carefully examined, a small motor root (radix motoria) and a large sensory root (radix sensoria) stand out. N. trigeminus leaves the fossa cranii posterior and moves forward (4,5,6). Around the for. magnum, there is the sulcus sinus marginalis, right next to the crista occipitalis

interna, i.e., the sulcus sinus occipitalis. For. magnum is surrounded by the sinus marginalis. There are anastomoses to the vertebral veins, v. cervicalis profunda, and sinus occipitalis. A. vertebralis enters the region over the atlas by passing the membrane atlanta-accipitalis. The flocculus and tonsils of the cerebellum are in a topographically close relationship with the for. magnum. Because of sudden changes in cerebrospinal fluid compression or pressure caused by tumors, the posterior tracts of the medulla oblongata, tonsils, and n. The ascending spinal cord of the accessorius is significantly affected (3,6).

It is important to evaluate the anatomical structure of the patient to determine the surgical access and technique for surgical interventions for the fossa cerebellaris and its neighbors. For surgical approaches of this region, the magnum has special importance and value. For. magnum's anterior-posterior and transverse diameters can change the shape of the surgical approach. Also flat or ovoid for. magnum may cause early symptomatization of pathologies of this region such as Chiari malformations and basilar invagination. Anatomical morphological studies and three-dimensional radiology studies of this region make surgical interventions for regional pathologies safer.

Cerebellopontine angle tumors are the most common tumors in the posterior fossa cranii. Most of them are benign and approximately 80% of them are vestibular schwannomas, although they can be observed in meningiomas, subgroup cranial nerve schwannomas, and epidermoid tumors (7,8). Three pairs of cerebellar arteries are associated with certain neural structures during their course. Each artery is associated with a cerebellar surface, cranial nerve, and fissure. This rule was proposed by Rhoton (9) to simplify the surgical corridor, craniotomy, and cerebellar retraction.

Natsis et al. (10) evaluated the diameters of the occipital condyle and FM in 143 dry bones in a Greek population in 2013 and found the FM AP length as 35.53±3.06 mm and the FM transverse length as 30.31±2.79 mm. In our measurements, the mean FM AP length was measured as 34.3±2.55 mm; the mean FM transverse length was evaluated as 27.9±3.27 mm and was considered consistent with many morphometric studies in the literature. In the same study, they divided the for. magnum structure into 7 shapes and especially emphasized that the shape of the FM is important in terms of approaching the lesions in the ventral for. magnum (10).

Wanebo and Chicoine (11), in 32 cranial and 6 cadavers in whom they evaluated transcondylar approaches to FM, stated that longer FM AP diameters resulted in a wider contralateral visual angle after condylar bone resection. Manoel et al. (12) examined FM morphometry in 215 dry bones and stated that there were morphometric differences in terms of ethnicity and gender, but there was no morphological difference, as in some other studies. There are many studies in the literature on FM morphometry in line with gender and ethnic characteristics.

Avci et al. (13) evaluated FM diameters and shapes in 30 skulls and 10 cadavers; they measured the mean AP diameters as 34.5 mm and the transverse diameters as 29 mm. They also defined the AP diameter/transverse diameter as the FM index and defined FMI >1.2 as FM with an ovoid shape. They also stated that surgical exposure of the anterior part of ovoid-shaped FM may be more difficult (13). Our dry bone measurements were also evaluated in accordance with the literature on the lengths of FM diameters. It was defined as 1.2< and ovoid shaped in 9 (60%) of the FMI materials.

Gupta et al. (14), in a morphometric study of the JF in 50 dry bones, measured the mean mediolateral length as 13.25±1.56 and 12.26±1.33 mm on the right and left, respectively, which is similar to our measurements. Das et al. (15), in their extensive morphometric studies for JF, determined the AMW diameters as 4.34-5 mm, right/left respectively, and PLW 7.07-5.51 mm, respectively. Our measurements were determined as 5.47-5.88 mm, right/left, respectively, and they are similar.

Matsushima et al. (16), in laboratory studies where they evaluated the surgical anatomical limitations of the retrosigmoid approach for suprajugular localized pathologies, suggested that retrosigmoid or condylar approaches can be preferred in the approach to intracranially located jugular pathologies (9,17); however, they reported that residual lesions may remain in lesions located or extending in the upper part of the JF (18). Our study is limited as it only evaluates the intracranial section for JF, and there are many surgical approaches (infratemporal, transcondylar, suboccipital, retrosigmoid, etc.) that will be able to recommend the use of a standard technique or combined techniques to evaluate the width of the surgical field with morphometric studies for the structure.

Sekerci et al. (19) evaluated the PAI and examined 120 dry temporal bones, evaluated PAI in terms of ethnicity, diameters, and shapes, and measured superior-inferior diameter of 4.31±0.88 mm and anterior-posterior diameter of 6.64±0.94 mm, respectively. Özandaç et al. (20) evaluated meatus acusticus internus (MAI) as 2.3-5.7 mm and 3.1-7.7 mm, respectively, in their radiological studies. In our study, the superior-inferior diameter of the PAI was measured as right/left mean=2.59±1.12 mm/2.85±1.35 mm. The anterior-posterior diameter of the PAI was measured as right/left mean=3.78±1.35 mm/4.43±1.49 mm.

Akın-Saygin et al. (21), in their study where they evaluated the MAI morphometry on 166 temporal dry bone, found the mean distance of MAI to JF as 6.15±1.37 mm /6.19±1.55

mm on the right and left, respectively, and their findings are consistent with our measurements. Kolagi et al. (22), in their anatomical morphometric studies, in which they evaluated the suboccipital retrosigmoid approach in 224 dry bones, the mean right/left distance between the uppermost part of the SS and the outermost part of the PAI, respectively; they evaluated it as 38.94 mm /38.09 mm (in the range of 32-44 mm). This is longer than our measurements (22).

The shortest distance between PAI and SS was reported by Bozbuğa et al. (23) and Day et al. (24) as an average of 31.1 mm and 34.5 mm, respectively. In our study, the distance between the PAI and the SS-ST junction was 30.9 mm on the right; it was measured as 31.04 mm on the left and was evaluated as similar to the results in the literature. These distances, especially in retrosigmoid approaches, are in the pre-surgical preparation phase; we believe that it will gain more importance with morphometric studies to reduce cerebellar retraction; however, it should be supported by radiological studies including three-dimensional angle measurements for this region.

Study Limitations

Our study was limited by the number of samples and evaluated only the foramen and intracranial region in relation to the measured parameters. There is a need for more anatomical studies in which the structure of this region is evaluated in three dimensions and each surgical approach technique is examined separately.

Conclusion

In surgical interventions for the fossa cerebellaris and adjacent structures at the posterior skull base, especially considering brain stem and pontocerebellar angle tumor surgical approaches, the evaluation of fossa cerebralis and fossa cerebellaris related structures, the locations of the neural foramen, and the pre-surgical evaluation of the three-dimensional structure of the FM, fossa cerebellaris, and posterior fossa are critical in terms of determining the surgical technique and planning a safe approach.

Ethics

Ethics Committee Approval: In this study, following the approval of the Dokuz Eylül University Non-Invasive Research Ethics Committee (no: 2012/22-8, date: 21/06/2012) we morphometrically examined the osseous structures in 15 dry bone cranium and 8 cadavers, which can be measured with a maximum of 3 mm deficiencies, in the Dokuz Eylül University Faculty of Medicine Anatomy Department Laboratory.

Informed Consent: Our research was a cadaveric study, patient consent could not be obtained.

Authorship Contributions

Surgical and Medical Practices: M.O.D, N.G.K., Concept: M.O.D, M.C.E., N.G.K., Design: M.O.D, M.C.E., N.G.K., Data Collection or Processing: M.O.D, M.C.E., N.G.K., Analysis or Interpretation: M.O.D, M.C.E., N.G.K., Literature Search: M.O.D, M.C.E., N.G.K., Writing: M.O.D, M.C.E., N.G.K.

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Early Radiological Evaluation of Distal Radius Fractures Treated by Closed Reduction and Percutaneous Pinning in Adults Patients

Yetişkin Hastalarda Kapalı Redüksiyon ve Perkütan Pinleme ile Tedavi Edilen Distal Radius Kırıklarının Erken Radyolojik Değerlendirilmesi

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ABSTRACT

Background: The use of closed reduction and percutaneous pinning in the treatment of distal radius fractures, both extra-articular and partial intra-articular, is a minimally invasive and cost-effective option that yields effective results. This study aimed to assess the radiological outcomes in adult patients, as well as to determine if the initial reduction is maintained over time and identify any demographic risk factors that may impact reduction loss.

Materials and Methods: Retrospective screening of patients with distal radius fracture treated by closed reduction and internal fixation in years between 2011 and 2020 yielded 47 adult patients with regular follow-up and accessible medical records. The included patients were divided into two groups according to their ages, 32 patients were under 60 years (group 1), and 14 were 60 years or older (group 2). Radiological assessment of radial height (Rh), radial inclination, ulnar variance, articular step, anterioposterior distance, palmar tilt, and teardrop angle in the posteroanterior and lateral radiographs obtained preoperatively, in the first follow-up (2 weeks) and when Kirschner (k) wires were removed (6-8 weeks) postoperatively. The measurements of both groups were statistically analyzed and compared.

Results: The mean age of patients was 52 (26-86) years and the mean period elapsed for K-wire removal was 6.5 (4-9) weeks. All radiological measurements showed improvement postoperatively in both groups. While the improved parameters were maintained in the third measurement of group 2 ($p>0.05$), the Rh of the third measurement in group 1 displayed a significant difference (0.78 mm) ($p=0.004$).

Conclusion: Percutaneous pinning can be an effective method for restoring radiographic parameters with minimal risk in appropriately selected fracture patterns. The good reproducible outcomes are not confined to young patients only but also can be utilized in elderly patients.

Keywords: Distal radius fracture, closed reduction, percutaneous pinning

ÖZ

Amaç: Hem eklem dışı hem de kısmi eklem içi distal radius kırıklarının tedavisinde kapalı redüksiyon ve perkütan çivilemenin kullanılması, etkili sonuçlar veren, minimal invaziv ve uygun maliyetli bir seçenektir. Bu çalışma yetişkin hastalarda radyolojik sonuçları değerlendirmeyi, başlangıçtaki redüksiyonun zaman içinde korunup korunmadığını belirlemeyi ve redüksiyon kaybını etkileyebilecek demografik risk faktörlerini tanımlamayı amaçladı.

Gereç ve Yöntemler: 2011-2020 yılları arasında kapalı redüksiyon ve internal tespit ile tedavi edilen distal radius kırığı olan hastaların retrospektif taranması sonucunda düzenli takipleri ve erişilebilir tıbbi kayıtları olan 47 yetişkin hasta çalışmaya dahil edildi. Hastalar yaşlarına göre iki gruba ayrıldı; 32 hasta 60 yaş altı (grup 1), 14 hasta ise 60 yaş ve üzerindeydi (grup 2). Ameliyat öncesi, ilk takipte (2 hafta) ve ameliyat sonrası (6-8 hafta) Kirschner (k) telleri çıkarıldığında çekilen posteroanterior ve yan radyografilerde radial yükseklik, radial inklinasyon, ulnar varyans, eklemde basamaklanma, ön-arka mesafe, palmar eğim ve tear drop açısının radyolojik değerlendirilmesi yapıldı. Her iki grubun ölçümleri istatistiksel olarak analiz edildi ve karşılaştırıldı.

Bulgular: Hastaların ortalama yaşı 52 (26-86) yıl ve K telin çıkarılması için geçen süre ortalama 6,5 (4-9) haftaydı. Ameliyat sonrası tüm radyolojik ölçümlerde her iki grupta da iyileşme görüldü. Grup 2'de üçüncü ölçümde iyileşen parametreler korunurken ($p<0,05$), grup 1'de üçüncü ölçümde radial yükseklik anlamlı farklılık gösterdi (0,78 mm) ($p=0,004$).

Sonuç: Perkütan çivileme, uygun şekilde seçilmiş kırık modellerinde radyografik parametrelerin minimum riskle düzeltilmesinde etkili bir yöntem olabilir. Tekrarlanabilir iyi sonuçlar yalnızca genç hastalarla sınırlı değildir, aynı zamanda yaşlı hastalarda da kullanılabilir.

Anahtar Kelimeler: Distal radius kırığı, kapalı redüksiyon, perkütan çivileme

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Introduction

One of the most frequent injuries to the upper extremities is a distal radius fracture. They exhibit a bimodal distribution with different characteristics. The first peak is seen in young patients with male predominance who most commonly sustained high-energy trauma, whereas elderly osteoporotic women who experienced low-energy trauma are the most common second peak representation (1). In this wide range of population, a large variety of fracture patterns can be distinguished, ranging from displaced comminuted intra-articular fractures to undisplaced simple extra-articular fractures. The diversity of fracture patterns merits different treatment options that also vary from non-operative treatment with closed reduction and cast immobilization to surgical intervention with the implementation of different devices such as Kirschner (k) wires, external fixators, different types of plates, and intramedullary nails (1,2).

Despite the recent tendency of trauma surgeons to internal fixation of radius fracture following the development of volar locking plates (3), complaints from tendon irritation and possible wound and fracture healing complications that may arise from extensive dissection of already injured soft tissue (3,4,5) disrupt the consensus on the ideal treatment of partial articular and extra-articular distal radius fracture (6), providing that there is no long-term outcome superiority of any fixation method to any other (7).

Closed reduction and percutaneous pinning (CRPP) of the distal radius are considered effective, minimally invasive, not technically demanding, and cost-effective treatment options for extra- and intra-articular fractures (8). The less invasive technique that prevents soft tissue damage and leaves no retained hardware tends to be more appealing because it avoids the complications that may arise from distal radius plating and achieves more biological osteosynthesis (8). The current study aimed to assess the radiological outcomes of extra-articular and partially intra-articular distal radius fractures in adult patients treated by CRPP, determine whether the initial reduction is maintained sufficiently, and identify the demographic risk factors that may affect the reduction loss.

Materials and Methods

Between 2011 and 2020, following the Medicana International İstanbul Hospital Ethics Committee's approval of the study, the medical records of surgically operated distal radius fractures that were presented to our emergency department were identified and analyzed. The inclusion criteria were skeletally mature patients with an extra-articular or partial intra-articular fracture of the distal radius (AO type 23-A2, A3 and 23-C1, C2) who were treated with CRPP. Regular postoperative follow-up for a minimum of 6-8 weeks and accessibility to medical records are required for patient inclusion. Cases with open epiphysis, concomitant fracture of the affected limb, and pathologic fractures were excluded.

The medical records of 624 adult patients with distal radius fractures admitted to our hospital were reviewed; 52 of them had extra-articular or partial intra-articular fractures that were treated with CRPP. However, 6 patients were excluded because of the inaccessibility of medical records and loss of follow-up. To evaluate the effect of age and osteoporosis on reduction loss based on age 60 years. The 47 patients with 47 wrist fractures (Table 1) were grouped according to their age into two groups: 32 patients were under 60 years of age (group 1) and 14 were 60 years or older (group 2). Radiological imaging was used to confirm the union and to compare both groups concerning any loss of reduction.

Conventional radiographs with posterior-anterior and lateral views were used for diagnosing and regularly following up with the patients. Radiologic measurement of radial height (Rh), palmar tilt (Pt), radial inclination (Ri), ulnar variance (Uv), articular step (As), anterioposterior distance (Apd), and teardrop angle (Tda) of the images taken in the preoperative, first follow-up, and last follow-up settings. The first follow-up visits were within 2 weeks of the operation, whereas the last follow-up visits were 6 to 8 weeks after the surgery when the K-wires were removed. All parameters were measured separately by two board-certified orthopedic surgeons, and any discrepancy was resolved by accepting the mean value. The measurements were then statistically analyzed and compared.

Surgical Technique

Under general anesthesia or axillary block following surgical preparation and draping, closed reduction was performed by applying longitudinal traction to disimpact the fracture fragments and direct manipulation by flexing or extending the distal fragment with ulnar deviation according to the displacement pattern. The reduction was assessed by fluoroscopic examination, and in cases where the anatomic reduction could not be achieved, CRPP was performed. Following fluoroscopic verification of anatomical reduction, a small stab incision with blunt dissection through the subcutaneous tissue to the tip of the radial styloid was performed before K-wire placement to minimize tendon and nerve injury. The first K-wire was introduced retrogradely using a soft tissue protector from the tip of the styloid process crossing the fracture site to engage the medial cortex of the proximal fragment. A second K-wire was placed in the

same manner but in a divergent projection. In intra-articular distal radius fractures, a third K-wire was placed. Before its insertion another stab incision and blunt dissection were made to expose the dorsoulnar corner of the radius. The wire was placed under fluoroscopic guidance, crossing the fracture and penetrating the proximal fragment cortex volarly, creating a cross-shaped configuration with the other K-wires. According to the morphology of the fracture, extra wires could be placed to secure the fracture fragments and augment the stability. After confirming the position of the wires, they were cut and the ends bent, and dressing and a well-padded short arm cast were applied. For pin site care, windows in the cast directly over the pin site were created.

Postoperative Care

The patients were discharged on the same or the next day of the operation. The physical examination was routinely performed in the 2nd, 4th, and 6th to 8th week. Radiological assessment was performed during the first and last follow-up visits (Figures 1, 2). K-wires were removed in outpatient settings during the sixth to eighth week when clinical and radiological fracture union was achieved. Fracture union was defined by the absence of tenderness over the fracture

Table 1. Demographic data of the patients

	n	%				
Age						
<60	33	70.2%				
>60	14	29.8%				
Gender						
Female	34	72.3%				
Male	13	27.7%				
Side						
Right	23	48.9%				
Left	24	51.1%				
AO muller						
A2	7	14.9%				
A3	17	36.2%				
C1	16	34.0%				
C2	7	14.9%				
Additonal fracture						
No	44	93.6%				
Yes	3	6.4%				
Complication						
No	37	78.7%				
Yes	10	21.3%				
Trauma						
Simple fall	43	91.5%				
Traffic accident	2	4.3%				
Fall*	1	2.1%				
Falling from the ladder	1	2.1%				
	Mean ± SD	Min	Q1	Q2	Q3	Max
Age/years	52.11±13.58	26	42	54	61	86
Number of K-wires	2.77±1.11	2	2	2	3	7
Remove of K-wires/week	6.34±1.05	4	6	6	7	9
Days from trauma to surgery/day	1.55±2.51	0	0	1	2	14

*Operated 2 weeks later because of open fracture
SD: Standard deviation, Min: Minimum, Max: Maximum, Q1: Percentile 25, Q2: Percentile 50 (Median), Q3: Percentile 75, K-wires: Kirschner wires

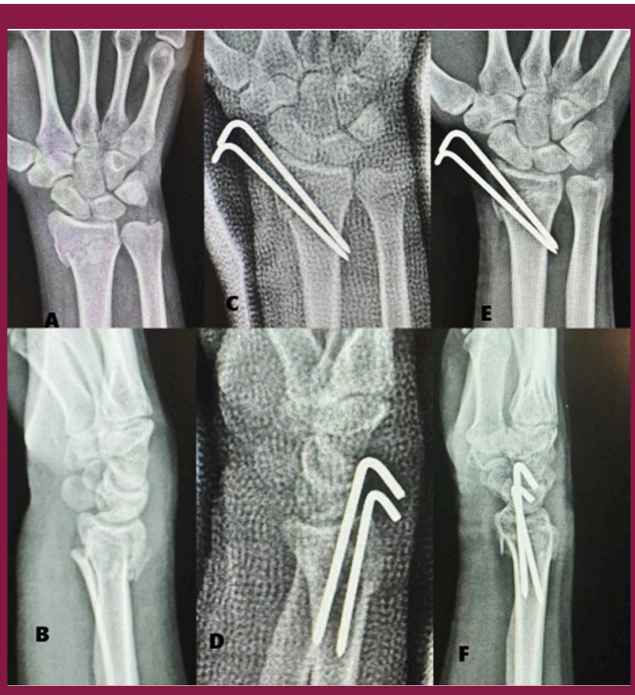

Figure 1. A 27-year-old female patient. A/B: Preoperative, C/D: After 2 weeks of operation, E/F: After 6 weeks of operation Pa and Lateral wrist X-ray

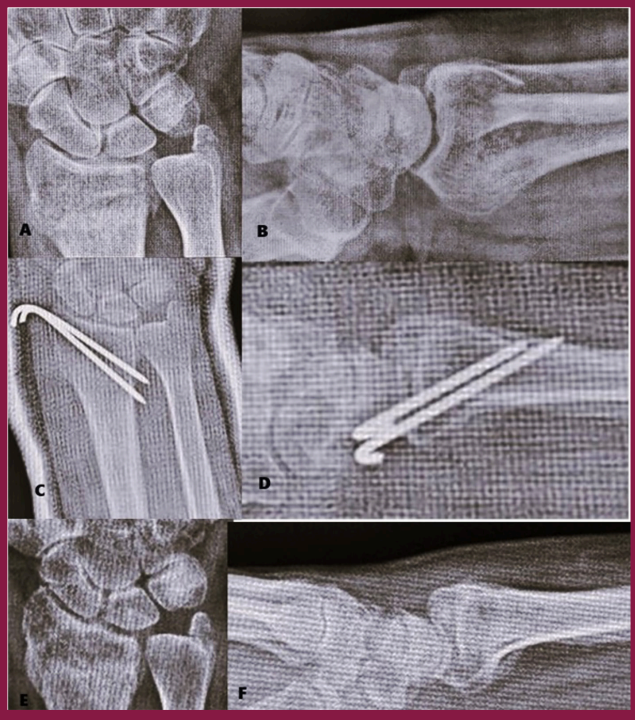

Figure 2. A 62-year-old female patient. A/B: Preoperative, C/D: After 2 weeks of operation, E/F: After 8 weeks of operation Pa and Lateral wrist X-ray

site and the presence of a bridging callus on X-ray. After K-wire removal, patients with limited range of motions were referred to the physical therapy department.

Statistical Analysis

The SPSS 26.0 program and PAST 3 software were used to analyze the study variables. To evaluate the conformity of univariate data to a normal distribution, we employed the Kolmogorov-Smirnov and Shapiro-Wilk tests. In addition, we used the to assess the homogeneity of variance. For multivariate data, we conducted the Mardia test for normal distribution, the Dornik and Hansen omnibus test, and the Box-M test for homogeneity of variance. When comparing two independent groups based on quantitative data, we used the independent samples t-test with bootstrap results and the Mann-Whitney U test with Monte Carlo results. When comparing more than two groups, we used One-Way analysis of variance (ANOVA), a parametric method, and Fisher's least significant difference (LSD) tests for post hoc analyses. Alternatively, we employed the Kruskal-Wallis H test, a non-parametric test, along with the results from the Monte Carlo simulation technique and Dunn's test for post hoc analyses. When conducting post hoc analysis to compare multiple repeated measurements of dependent quantitative variables and examine their interaction according to groups, the General Linear Model-Repeated ANOVA test and Fisher's LSD tests were used. For non-parametric methods, Friedman's two-way test and stepwise post hoc test, which involved step-down comparisons, were used. In evaluating categorical variables, Pearson's chi-square and Fisher's Exact tests were employed, with exact results used for the Fisher's Exact test. The Fisher-Freeman-Holton test was performed using the Monte Carlo simulation technique, and column ratios were compared and expressed in terms of the Benjamini-Hochberg-corrected p-value results. The presentation of quantitative variables included the mean ± standard deviation in the tables, and the median (percentile 25/percentile 73). Categorical variables are displayed as n (%). The analysis was conducted at a 95% confidence level, and a p-value <0.05 was considered significant.

Results

The mean age of the patients was 52 (26-86) years, and the mean period elapsed for K-wire removal was 6.5 (4-9) weeks. Radiological evaluation showed improvement in Rh, Ri, Uv, As, Pt, Apd, and Tda parameters in all patients postoperatively, and this improvement was maintained at the time of K-wire removal in group 2. The mean values of these parameters are shown in Table 2.

In group 1 patients, no significant difference was detected in Ri, Uv, As, Pt, Apd, and Tda values between the

Table 2. Average values of radiological measurements made 1) before surgery, 2) 2 weeks after surgery, and 3) 6-8 weeks after surgery			
	1 (preoperative)	2 (2nd week)	3 (6-8th week)
Radial height (mm)	8.85±2.24	10.84±1.31	10.12±1.40
Radial inclination degrees	15.87±6.34	20.00±2.82	19.85±3.88
Ulnar variance (mm)	2.09±3.24	0.49±1.90	1.06±1.94
Articular step (mm)	0.17±0.76	0.04±0.53	0.09±0.39
Anteroposterior distance (mm)	17.77±7.6	18.66±2.98	18.08±2.72
Palmar tilt, degrees	-17.84±16.12	9.84±7.36	9.45±9.59
Teardrop angle, degrees	19.58±23.46	43.8±9.15	41.13±8.20

3rd and 2nd measurements, yet a significant difference was detected in Rh values between these measurements (0.004) ($p<0.05$). All values are shown in Table 3.

Discussion

In the current study, we evaluated the role of K-wires in sustaining the reduction of extra-articular or partial articular distal radius fracture in adults treated with CRPP. Our results showed that CRPP is an effective technique for restoring and sustaining radiologic parameters during the healing process regardless of patient demographic criteria and fracture pattern (AO type 23-A2, A3 and 23-C1, C2).

Several clinical and biomechanical studies have highlighted the significance of ensuring an articular gap of 2 mm and maintaining optimal Pt, Uv, and Rh in achieving favorable patient outcomes (9). Failure to meet and maintain these objectives during fracture reduction and the osseous union process suggests that non-surgical management could not obtain the intended outcomes. Lafontaine et al. (10) defined unstable fractures and identified risk factors for loss of initial reduction with non-operative treatment, which was verified by other studies (11). The predictors for loss of reduction were intra-articular fracture, dorsal comminution dorsal angulation more than 20 degrees, concomitant ulnar fractures, and age older than 60 years. The indication for surgical intervention in our study was largely based on these predictors, which estimate a low possibility of successful non-surgical management.

Although there is a substantial amount of research on the surgical management of distal radius fractures, only limited evidence-based recommendations are available for surgeons in selecting a fixation method (12). Many surgeons prefer CRPP because of its practicality, minimal morbidity, and low complication rate in treating extra-articular and partial intra-articular fractures with minimal reducible As (13). However, advances in biomedical hardware manufacturing have shifted the tendency to treat distal radius fractures from CRPP to open reduction and internal fixation (ORIF) (12). However, the long-term results of many studies showed no superiority of ORIF over CRPP (14,15). Thus, CRPP was the mainstay of treatment for these specific distal radius fractures in our institution.

Successful management of distal radius fracture is not based only on the achievement of anatomical reduction but also on its maintenance until bone healing is ensured. Unstable non-displaced fractures, especially those that require initial reduction, are at great risk of redisplacement (16). Loss of reduction develops most frequently in the second week of non-operative management (17). Percutaneous pinning has been criticized for its inability to maintain the initial postoperative reduction and for allowing the fracture to subside during the healing process (18). Conversely, we demonstrated that all patients treated with CRPP had preserved initial reduction in the second week of follow-up and until osseous union had been achieved.

The most important finding in our study demonstrates that percutaneous pinning provides good radiological outcomes in elderly patients over 60 years of age who have extra-articular or partially intra-articular distal radius fractures. Previous studies have shown that this technique has less favorable results in elderly patients (19); even some authors considered these fractures a contraindication to CRPP (20) provided that previous studies in elderly patients had a considerable rate of secondary instability after pinning fixation (21,22). Furthermore, Azzopardi et al. (19) showed only a marginal improvement in the radiological parameters in patients aged over 60 years with extra-articular distal radius fractures compared with non-operative treatment. In contrast, our results reported good radiological outcomes in patients older than 60 years, comparable to the outcomes of younger patients. These results were consistent with those of some other prior studies despite their age heterogeneity (12) and application of different pinning techniques (23).

The relationship between radiological and functional outcomes is a topic of debate. Despite many studies demonstrating a significant functional deficiency in the elderly who presented with malunited distal radius fractures (23,24,25), other studies could not find any relationship between radiological and functional outcomes (19,26).

Table 3. Comparison of mean radiological parameter values in patients under and over 60 years of age

Age			
	<60 (A)	**>60 (B)**	**p-value**
	(n=33)	**(n=14)**	**(A-B)**
	Median	**Median**	
Ri			
1	16.0	17.5	0.358
2	20.0	21.0	0.166
3	20.0	19.5	0.802
Diference 3-2	0.0	-2.0	0.285
P-value 3-2	0.999	0.999	-
Uv			
1	1.8	2.9	0.537
2	0.0	1.0	0.261
3	0.0	1.6	0.215
Diference 3-2	0.0	0.4	0.354
P-value 3-2	0.196	0.073	-
As			
1	0.0	0.3	0.034
2	0.0	0.0	0.788
3	0.0	0.0	0.147
Diference 3-2	0.0.	0.0	0.999
P-value 3-2	Ns.	Ns.	-
Apd			
1	17.8	19.6	0.024
2	17.8	18.5	0.093
3	17.6	18.0	0.085
Diference 3-2	-0.2	-0.4	0.646
P-value 3-2	Ns.	Ns.	-
Pt			
1	-24.0	-8.5	0.084
2	11.0	11.0	0.899
3	10.5	11.8	0.458
Diference 3-2	-0.1	0.0	0.899
P-value 3-2	0.622	0.705	-
Rh			
1	8.56	9.54	0.204
2	10.72	11.14	0.351
3	9.93	10.59	0.128
Diference 3-2	-0.78	-0.55	0.654
P-value 3-2	0.004	Ns.	-
Tda			
1	18.11	23.07	0.501
2	43.18	45.29	0.482
3	40.75	41.94	0.746
Diference 3-2	-2.43	-3.35	0.701
P-value 3-2	0.057	0.126	-

Patients under the age of 60 years were shown as group A, and patients aged 60 and over were shown as group B. Statistical significance values of columns A-B are written in the p-value (A-B) column. In the p-value 3-2 line, statistical significance values between the 3rd and 2nd measurements are given.
Ns.: Not significant, Ri: Radial inclination, Uv: Ulnar variance, As: Articular step, Apd: Anterioposterior distance, Pt: Palmar tilt, Rh: Radial height, Tda: Teardrop angle

In our opinion, anatomical reduction and acceptable radiological parameters are strongly associated with better functional outcomes not only in young patients but also in elderly patients. This was the reason for performing surgical intervention with percutaneous pinning instead of non-operative treatment in elderly patients.

K-wire placement may accompany the different types of nerve and tendon injuries. Dorsally positioned K-wires are generally favored over volar-placed wires because of the potential danger of injury to the neurovascular structures and flexor tendons of the digits. However, several structures are at risk of being injured by dorsally placed K-wires. Cadaveric dissection showed that the extensor tendons of the digit and the superficial branch of the radial nerve were at the highest risk of injury (27). A tiny incision extending through subcutaneous tissue to the bone and the use of soft tissue protectors were adopted to avoid inadvertent injury during pinning. We believe that these measures were the reason for not encountering such complications in our cohort. The only complication that we encountered was a pin tract infection that was treated by systemic antibiotics and pin site care. All of these infections were resolved following pin removal.

Study Limitations

The retrospective nature of the study, short-term follow-up, and small number of patients may represent the main limitations of the current study. A prospective, randomized trial with a longer follow-up period and a larger patient population is needed for the evaluation of K-wire long-term radiological outcomes and its association with clinical and functional outcomes. The current study is designed to highlight the effectiveness of CRPP for treating elderly patients with specific types of distal radius fractures and to form a base for further studies directed toward standardization of treatment.

Conclusion

Percutaneous pinning can be an effective method for restoring radiographic parameters with minimal risk in properly selected fracture patterns. The good reproducible outcomes are not confined to young patients only; elderly patients can also be treated successfully by CRPP. This method can offer sufficient fracture stability, the lowest complication rate, and low patient morbidity, which, in contrast to more invasive treatments, may provide a faster functional recovery.

Ethics

Ethics Committee Approval: Between 2011 and 2020, following the Medicana International İstanbul Hospital Ethics Committee's approval of the study, the medical records of surgically operated distal radius fractures that were presented to our emergency department were identified and analyzed.

Informed Consent: Retrospectively study.

Authorship Contributions

Surgical and Medical Practices: M.B.Y., Concept: M.B.Y., A.H., Design: M.B.Y., A.H., Data Collection or Processing: M.B.Y., A.H., Analysis or Interpretation: M.B.Y., A.H., Literature Search: M.B.Y., A.H., Writing: M.B.Y., A.H.

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

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ORIGINAL ARTICLE

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Epidemiological, Clinical and Evolutionary Analyses of Cardiovascular Damage During Pulmonary Tuberculosis

Akciğer Tüberkülozu Sırasındaki Kardiyovasküler Hasarın Epidemiyolojik, Klinik ve Evrimsel Analizleri

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ABSTRACT

Background: Tuberculosis (TB) remains a major public health problem with nearly 8 million new cases each year and more than 1 million deaths per year. TB is a risk factor for cardiovascular damage and thromboembolic disease and a state of hypercoagulability by genetic predisposition could be incriminated. Our study aimed to study the epidemiological, clinical and evolutionary aspects of cardiovascular damage during pulmonary TB in Bujumbura hospitals.

Materials and Methods: This was a retrospective study conducted from September 1, 2017 to September 30, 2022 in the Internal Medicine Department of the University Teaching Hospital of Kamenge (CHUK) in Bujumbura. The study population consisted of active or sequellar TB patients with cardiovascular involvement.

Results: During the study period, 374 patients were admitted with TB to the internal medicine department of the CHUK, 49 of whom had at least one cardiovascular disease, representing a prevalence of 13.10%. Cardiovascular disease affected 25 women and 24 men, with a sex ratio of 0.96 in favor of women. The mean age was 50.73 years, with extremes of 22 and 90 years. Cardiovascular disorders were dominated by chronic pulmonary heart disease (53.06%); tuberculous pericarditis (34.70%); and venous thromboembolic disease (12.24%). Comorbidities including human immunodeficiency virus infection, diabetes and chronic respiratory insufficiency were respectively associated with 26.53%, 8.20% and 4.08% of cases. The clinical picture was dominated by dyspnea, cough and chest pain in 75.5%, 59.7% and 38.77% of cases respectively. Progression under treatment was considered favorable in 69.4% of patients, compared with 30.6% who died in respiratory distress.

Conclusion: Cardiovascular damage in TB is a frequent and serious pathology in Bujumbura Hospitals. Diagnosis and management are often delayed or even unavailable, resulting in many deaths. Their prognosis depends on the type of disease and its immediate management, and they are chronic, disabling diseases.

Keywords: Tuberculosis, cardiovascular damage, analyse

ÖZ

Amaç: Tüberküloz (TB), her yıl yaklaşık 8 milyon yeni olgu ve 1 milyondan fazla ölümle birlikte önemli bir halk sağlığı sorunu olmaya devam etmektedir. TB, kardiyovasküler hasar ve tromboembolik hastalık için bir risk faktörüdür ve genetik yatkınlık nedeniyle aşırı pıhtılaşma durumu suçlanabilir. Çalışmamız Bujumbura'daki hastanelerinde akciğer TB'yi sırasında ortaya çıkan kardiyovasküler hasarın epidemiyolojik, klinik ve evrimsel yönlerini incelemeyi amaçladı.

Gereç ve Yöntemler:. Bu çalışma, 1 Eylül 2017 ile 30 Eylül 2022 tarihleri arasında Bujumbura'daki Kamenge Üniversitesi Eğitim Hastanesi'nin (CHUK) iç hastalıkları bölümünde yürütülmüş retrospektif bir çalışmadır. Çalışma popülasyonu, kardiyovasküler tutulumu olan aktif veya sekel TB hastalarından oluşuyordu.

Bulgular: Çalışma döneminde CHUK dahiliye bölümüne 374 TB hastası başvurdu, bunların 49'unda en az bir kardiyovasküler hastalık vardı ve prevalans %13,10 idi. Kardiyovasküler hastalık 25 kadın ve 24 erkeği etkiledi; cinsiyet oranı kadınlar lehine 0,96 oldu. Ortalama yaş 50,73 idi, uç noktalar ise 22 ve 90 idi. Kardiyovasküler bozukluklarda kronik pulmoner kalp hastalığı (%53,06)

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ÖZ

hakimdi; TB perikarditi (%34,70); ve venöz tromboembolik hastalık (%12,24). İnsan bağışıklık eksikliği virüsü enfeksiyonu, diyabet ve kronik solunum yetmezliği gibi komorbiditeler sırasıyla olguların %26,53'ü, %8,20'si ve %4,08'i ile ilişkiliydi. Klinik tabloya olguların sırasıyla %75,5, %59,7 ve %38,77'sinde dispne, öksürük ve göğüs ağrısı hakimdi. Solunum sıkıntısından ölen hastaların %30,6'sına kıyasla tedavi altında ilerlemenin hastaların %69,4'ünde olumlu olduğu değerlendirildi.

Sonuç: TB'de kardiyovasküler hasar Bujumbura Hastaneleri'nde sık görülen ve ciddi bir patolojidir. Teşhis ve tedavi sıklıkla gecikiyor, hatta kullanılamıyor, bu da birçok ölümle sonuçlanıyor. Prognozları hastalığın türüne ve acil tedavisine bağlıdır ve bunlar kronik, sakatlığa yol açan hastalıklardır.

Anahtar Kelimeler: Tüberküloz, kardiyovasküler hasar, analiz

Introduction

Tuberculosis (TB) remains a major public health problem with nearly 8 million new cases each year and more than 1 million deaths per year.

The distribution of TB cases appears to be uneven worldwide, with more than 95% of cases and more than 98% of TB deaths reported in Africa, Asia, and Latin America (1).

Despite the existence of effective measures such as chemotherapy and vaccination, TB continues to progress worldwide, which can be explained in part by a high frequency of co-infection with the human immunodeficiency virus (HIV) and by the emergence of resistant strains (1,2).

In Burundi, in 2021, 6,874 new cases of TB of all forms were recorded, i.e., an incidence rate of 100 per 100,000 people. The mortality rate was 20 per 100,000 people. TB/HIV co-infection remains a concern (prevalence of HIV among TB patients: 12%, as does multi-resistant TB: 200 cases of multidrug-resistant TB are estimated (3,4). Cardiovascular damage during TB has been described for a long time, and tuberculous pericarditis is the most common. Chronic pulmonary heart disease, also known as cor pulmonale, is the enlargement and failure of the right ventricle of the heart as a response to increased vascular resistance. It is a possible progressive complication of the disease, followed by mutilating scleral-retractile, bronchopleural, and pulmonary vascular bed lesions. TB is a risk factor for thromboembolic disease (deep vein thrombosis, pulmonary embolism), and a state of hypercoagulability due to genetic predisposition could be incriminated (5).

Our study aimed to investigate the epidemiological, clinical, and evolutionary aspects of cardiovascular damage during pulmonary TB in Bujumbura.

Materials and Methods

This was a retrospective descriptive study conducted at CHUK in the Internal Medicine Department of University Teaching Hospital of Kamenge over 5 years from September 1, 2017, to September 30, 2022. Ethics Committee permission was previously requested from the administrative authorities of the hospital before conducting our study and was granted on 15.01.2023. Informed consent was obtained from all participants included in the study. Patients hospitalized in this department with progressive or sequelae TB with cardiovascular involvement were included.

The information collected covered sociodemographic, clinical, and evolutionary aspects.

Statistical Analysis

Text processing was performed using Microsoft Word version 2016. Data entry and analysis were performed using KoboCollect v2022.2.3 softwar.

Results

During the study period, 374 patients were admitted for TB, 49 of whom had at least one cardiovascular disease, representing a prevalence of 13.10%. Cardiovascular disease affected 25 women and 24 men, with a sex ratio of 0.96 in favor of women. The mean age was 50.73 years, with extremes of 22 and 90 years (Figure 1). Low-income rural areas were most affected. Cardiovascular disorders were dominated by chronic pulmonary heart disease (53.06%), tuberculous pericarditis (34.70%), and thromboembolic disease (12.24%) and were diagnosed by electrocardiogram, echocardiography, Doppler

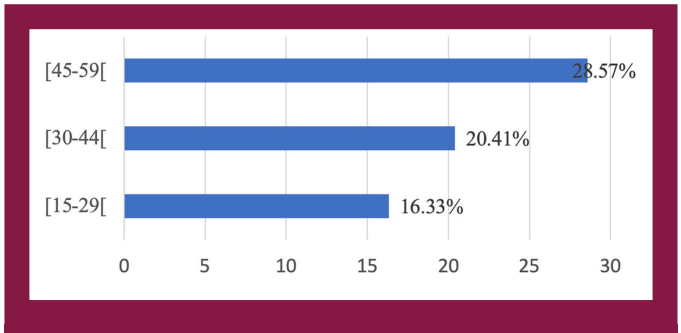

Figure 1. Distribution of patients by age group

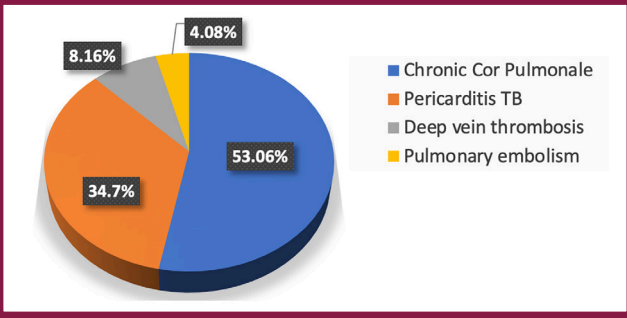

Figure 2. Distribution of patients according to cardiovascular conditions
TB: Tuberculosis

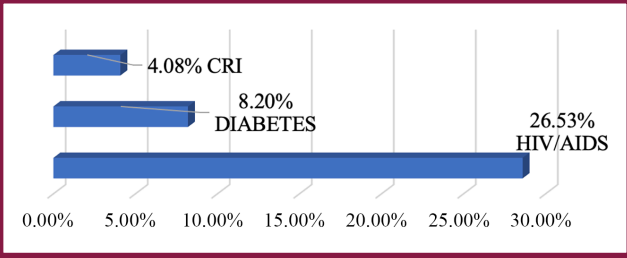

Figure 3. Distribution of patients by comorbidities
CRI: Chronic respiratory insufficiency, HIV: Human immunodeficiency virus, AIDS: Acquired immune deficiency syndrome

ultrasound, and chest computerized tomography (Figure 2). Comorbidities including HIV/acquired immune deficiency syndrome infection, diabetes, and chronic respiratory insufficiency were associated with 26.53%, 8.20%, and 4.08% of cases, respectively (Figure 3). Respectively; dyspnea, cough and chest pain in 75.5%, 59.7% and 38.77% of patients dominate the clinical picture. Progression on treatment was considered favorable in 69.4% of patients, compared with 30.6% who died in respiratory distress.

Discussion

We conducted a retrospective descriptive study on the epidemiological, clinical, and evolutionary analysis of cardiovascular disease during pulmonary TB in Bujumbura Hospitals. Our study showed that this pathology represents a public health problem, as out of 374 patients admitted for TB in the targeted Internal Medicine Department of the CHUK, we reported 49 cases with at least one cardiovascular involvement, i.e., a prevalence of 13.10%. Coulibaly (6) in 2015 in Mali found a prevalence of 6.8%.

In Bujumbura, this high frequency can be explained by the fact that most of our patients were co-infected with HIV/TB, and sometimes non-adherence to antiretroviral treatment led to severe forms such as tuberculous pericarditis (7). However, the delay in diagnosis and management, as well as smoking in some of our patients, led to sclero-retractile lung lesions, the cause of chronic pulmonary heart disease, which increased over time (8).

Analysis of the results showed a slight female predominance, with 25 women (51%) and 24 men (49%). The male/female sex ratio was 0.96. Our results concurred with those of Hadjer et al. (9) in 2017 in a study of venous thromboembolism (VTE) during TB, where he found a sex ratio of 0.71. However, numerous other studies have found male predominance. The fact that the Burundian population is predominantly female explains this (10).

In our series, the mean age of the sample was 50.73 years, with extremes of 22 and 90 years. Our results were close to those of Coulibaly (6) in 2015 in Mali, who found a mean age of 51.2±17.4 years. The 60+ age group was the most represented with 34.69% of the workforce. This is because the weakening of the immune defenses of elderly subjects and the reawakening of old TB lesions would explain this recruitment with age (11).

Many authors have found that the dominant functional signs were dyspnea, altered general condition, cough, and chest pain.

These results were in agreement with our own: dyspnea (77.34%), altered general condition (71.42%), cough (59.17%), and chest pain (38.77%).

This predominance of respiratory signs could be linked to the pulmonary localization of the tubercle bacillus and the extent of irreversible damage caused by TB.

Cardiovascular disorders in TB in our series defined the cardiovascular conditions responsible for the clinical pictures, with chronic pulmonary heart disease and tuberculous pericarditis predominating in 53.06% and 34.70% of patients, respectively. Thromboembolic venous disease alone accounted for a frequency of 12.24%. Our results on the frequency of chronic pulmonary heart disease agree with those of the literature, which ranged from 20% to 91% (12). Those of pericarditis and VTE were 36.6% in Coulibaly (6) and 9.8% in Amar et al. (13).

Acute and subacute complications of TB are attributable to structural damage or vascular compromise caused by *Mycobacterium* TB, as well as metabolic abnormalities and inflammatory responses of the host. Despite the successful cure of TB, chronic complications may result from anatomical alterations at disease sites, notably impaired pulmonary function, which will impact the heart (14).

The high incidence of chronic pulmonary heart disease is linked to the classically mutilating bronchopulmonary sequelae of TB in black people and to the high association of tobacco use as a bronchopulmonary cofactor (6).

Pericardial involvement is relatively frequent in TB. Myocarditis and aortitis due to TB are rare (15).

Although no cases of myocarditis were recorded in our series, myocardial involvement may be associated with pericarditis in the form of myopericarditis, which may cover other clinical scenarios. Tuberculous myocarditis is particularly rare (16).

In addition, patients with TB are predisposed to the development of thromboembolism. Inflammation activates the coagulation cascade while reducing the activity of the anticoagulant mechanism. Moreover, the hypercoagulable state persists for 2 weeks even after the initiation of anti-TB medication and improves with continued treatment (17).

During the stay, we recorded 15 deaths (30.6%), i.e., 10.20% patients from tuberculous pericarditis, 16.32% from chronic cor pulmonale, and 4.08% from pulmonary embolism. On discharge, 34 patients had favorable outcomes. Coulibaly (6) in 2015 in Mali found a favorable outcome rate in 75.6% of cases, with three cases of death (7.3%).

Conclusion

Cardiovascular damage in TB is a serious pathology, both in terms of clinical severity and lethality. Strengthening prevention and raising public awareness of the morbidity and mortality associated with TB, as well as encouraging early consultation and compliance with treatment, will certainly help to reduce the prevalence of TB and limit its complications.

Ethics

Ethics Committee Approval: This was a retrospective descriptive study conducted at CHUK in the Internal Medicine Department of University Teaching Hospital of Kamenge over 5 years from September 1, 2017, to September 30, 2022. Ethics Committee permission was previously requested from the administrative authorities of the hospital before conducting our study and was granted on 15.01.2023.

Informed Consent: Informed consent was obtained from all participants included in the study

Authorship Contributions

Surgical and Medical Practices: T.S., T.I., J.C.N., D.N., Concept: T.S., T.I., J.C.N., D.N., Design: T.S., T.I., J.C.N., D.N., Data Collection or Processing: T.S., T.I., J.C.N., D.N., Analysis or Interpretation: T.S., T.I., J.C.N., D.N., Literature Search: T.S., T.I., J.C.N., D.N., Writing: T.S., T.I., J.C.N., D.N.

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The Relationship Between the Intolerance of Uncertainty and Time Management in Individuals with Generalized Anxiety Disorders

Yaygın Anksiyete Bozukluğu Olan Bireylerde Belirsizliğe Tahammülsüzlük ve Zaman Yönetimi Arasındaki İlişki

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ABSTRACT

Background: There are limited data on the relationship between intolerance of uncertainty (IU) and time management (TM) in patients with generalized anxiety disorder (GAD). In this study, we aimed to investigate the relationship between IU and TM in GAD patients and the effect of sociodemographic variables on this relationship.

Materials and Methods: One hundered thirty one GAD patients (68 women, 63 men) and 120 healthy individuals (62 women, 58 men) as a control group (CG) were included in the study. The data form regarding sociodemographic characteristics was administered by the clinician. After the interview, all participants filled out the IU scale and TM inventory.

Results: The average age of those with GAD was 32.76±11.82, and the average age of those with CG was 33.41±11.89. The proportion of women with GAD was 51.9%. IU and TM levels were higher in GAD patients than in CG ($p<0.05$), and a significant difference was observed in IU and TM levels in terms of age, gender, marital status, occupational status ($p<0.05$). There was no difference between the groups in terms of educational status and family history of psychiatric disease ($p>0.05$). A positive relationship was found between IU and TM levels in patients with GAD ($r=0.248$, $p=0.004$). There was a negative relationship between the average age and IU ($r=-0.173$, $p<0.05$) and TM ($r=-0.313$, $p<0.05$) levels.

Conclusion: IU, which plays an important role in the development, maintenance and symptomatology of GAD, is effective in the development of TM skills. Age, gender and various sociodemographic characteristics play a role in this interaction. Evidence from this study will be valuable in further research into how the relationship between IU and TM plays a role in the development of other anxiety disorders and how sociodemographic variables may influence these processes.

Keywords: Generalized anxiety disorder, intolerance of uncertainty, time management.

ÖZ

Amaç: Yaygın anksiyete bozukluğu (YAB) hastalarında belirsizliğe tahammülsüzlük (BT) ve zaman yönetimi (ZY) ilişkisine ilişkin veriler sınırlıdır. Bu çalışmada YAB hastalarında BT ile ZY arasındaki ilişkiyi ve bu ilişkide sosyodemografik değişkenlerin etkisini araştırmayı amaçladık.

Gereç ve Yöntemler: Çalışmaya 131 YAB hastası (68 kadın, 63 erkek) ve kontrol grubu (KG) olarak 120 sağlıklı birey (62 kadın, 58 erkek) dahil edildi. Sosyodemografik özelliklere ilişkin veri formu klinisyen tarafından uygulandı. Görüşmenin ardından tüm katılımcılar BT ölçeği ve ZY envanterini doldurdu.

Bulgular: YAB olanların yaş ortalaması 32,76±11,82, KG olanların yaş ortalaması 33,41±11,89 idi. YAB'lı kadınların oranı %51,9 idi. YAB hastalarında KT ve ZY düzeyleri KG'ye göre daha yüksekti ($p<0,05$), yaş, cinsiyet, medeni durum, mesleki durum açısından BT ve ZY düzeylerinde anlamlı farklılık gözlendi ($p<0,05$). Gruplar arasında eğitim durumu ve ailede psikiyatrik hastalık öyküsü açısından fark yoktu ($p>0,05$). YAB hastalarında BT ve ZY düzeyleri arasında pozitif ilişki bulundu ($r=0,248$, $p=0,004$). Yaş ortalaması ile BT ($r=-0,173$, $p<0,05$) ve ZY ($r=-0,313$, $p<0,05$) düzeyleri arasında negatif ilişki vardı.

Sonuç: YAB'nin gelişiminde, sürdürülmesinde ve semptomatolojisinde önemli rol oynayan BT, TM becerilerinin geliştirilmesinde etkilidir. Bu etkileşimde yaş, cinsiyet ve çeşitli sosyodemografik özellikler rol oynamaktadır. Bu çalışmadan elde edilen kanıtlar, BT ve ZY arasındaki ilişkinin diğer anksiyete bozukluklarının gelişiminde nasıl bir rol oynadığı ve sosyodemografik değişkenlerin bu süreçleri nasıl etkileyebileceği konusunda yapılacak ileri araştırmalarda değerli olacaktır.

Anahtar Kelimeler: Yaygın anksiyete bozukluğu, belirsizliğe tahammülsüzlük, zaman yönetimi

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Introduction

Generalized anxiety disorder (GAD) is characterized by excessive and persistent worry and anxiety about daily internal and external events and impairments in autonomic arousal, restlessness, fatigue, concentration difficulties, irritability, sleep problems, and psychosocial functions (1). The 12-month prevalence of GAD worldwide is estimated to range from 0.2% to 4.3% (1). A recent study in Türkiye reported that the lifetime prevalence of GAD was 14.7% (2). GAD is accompanied by many mental disorders. Approximately 50-80% of GAD patients have major depressive disorder and 25% have panic disorder (3).

Intolerance of uncertainty (IU) is a common phenomenon used to explain anxiety and is expressed as the tendency to think that a negative event will occur as threatening and unacceptable, regardless of its potential occurrence (4). Carleton (5) found that a range of anxiety-related disorders were associated with significantly higher levels of IU than those in community samples. A recent meta-analysis revealed a strong and significant association between IU and the clinical symptoms of GAD (6).

Since rapid changes in modern life lead individuals to act according to various demands for their time, time management (TM) has increasingly become the focus of attention recently. Attempts to manage time help individuals achieve the results of their activities more effectively and efficiently (7). Those who can use their time effectively and efficiently are those who can distribute their time among various activities such as work, private life, and personal interests (8). In contrast, inadequate time planning (TP) causes insufficient time to be allocated for personal and social activities, reducing individual satisfaction and increasing stress levels (9). This situation also affects the development of positive personality traits such as decision-making, leadership, and critical thinking (9).

The main reason for the problems faced by people who cannot manage their time well, experience intense stress, and think that they do not have enough time to do many things during the day is that they do not know how to use and manage their time (10). In a study conducted on university students, it was reported that students with low TM skills had high trait anxiety levels, female students were more successful than male students in TM and TP, and the anxiety levels of male students were higher than female students (10). In a recent study, it was found that there is a negative relationship between students' TM skills and their depression-anxiety and stress levels, that the high level of anxiety, especially in senior year students, may be related to the end of the university period and starting to live, and that women's ability to use time effectively has a social basis (9). students with high levels of depression, anxiety, or stress have low TM skills (9).

It is predicted that individuals who cannot tolerate uncertainty may experience an increase in their anxiety levels and poor TM because they are too busy with processes whose outcome is uncertain. Poorly organized TM can also increase anxiety levels. In light of this information, we hypothesized that there may be a relationship between anxiety and depression levels, IU, and TM, and that sociodemographic data may be effective in determining this relationship. We did not find any studies on the relationship between IU and TM in the clinical setting. In this study, we aimed to fill this gap in the literature, investigate the relationship between IU and TM in patients with GAD, and examine the effect of sociodemographic data on these components.

Materials and Methods

In this study, 284 adults aged 18 and over who applied to the Mental Health and Diseases Polyclinic of University of Health Sciences Türkiye, İstanbul Sultan 2. Abdülhamid Han Training and Research Hospital of the University of Health Sciences Türkiye participated in the study.

Participants who were volunteers, who were diagnosed with GAD according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria (patient group, PG) and who were not (control group, CG), and who had no problem reading and understanding the semi-structured sociodemographic data form, the Beck anxiety inventory (BAI), the Beck depression inventory (BDI), the IU scale (IUS), and the TM inventory (TMI). Individuals were included in the study.

Those who are younger than 18 years of age, who did not agree to participate in the study, who have comorbid psychiatric diseases (depression, psychotic disorder, personality disorder etc.) other than GAD according to DSM-5 diagnostic criteria, who have a chronic disease or systemic disease (neurological, cardiac, orthopedic, etc.) and semi-structured sociodemographic data, and those with psychiatric disorders who could not read and fill out the data form, IUS, and TMI were not included in the study. People who were similar to the PG in terms of age, gender, education level, etc., and who had no previous psychiatric disease, psychotropic drug use, or medical illness constituted the CG.

The sample size of this study was calculated using the G*Power statistical program (ver.3.1.9.7). Accordingly, it was determined as "90 patients in total, with a minimum of 45 patients in each group" (for Study and CGs) by taking power (power of the test) 0.80, effect size 0.6 (t-test effect size

value range), and Type-1 error (a) 0.05. However, to secure the number of samples and to keep the power value high, the number of samples was increased and 200 samples (100 samples in each group) were used. The power (power of the test) recalculated according to this sample number increased to 98%.

Thirteen people in the PG, nine people in the CG, who completed the questionnaires incompletely, and six people diagnosed with depressive disorder, three people diagnosed with psychotic disorder, and two people diagnosed with personality disorder were excluded from the analysis. Thus, 131 people diagnosed with GAD (63 men, 68 women) and 120 people in the CG (58 men, 62 women) participated in the study.

Data Collection Tools

Sociodemographic Data Form: This form was developed by the researcher to determine the sociodemographic characteristics of the participants (age, gender, education level, marital status, professional status, place of residence, history of psychiatric disease, family history of psychiatric disease, smoking and alcohol use) in accordance with the purpose of the research.

Beck Anxiety Disorder (BAI): BAI is a 21-item Likert-type scale developed by Beck et al. (11) and can be scored between 0 and 3. The higher total scores obtained from the scale indicate the severity of anxiety experienced by the person. The adaptation of the scale to Turkish was made by Ulusoy et al. (12). The Cronbach's alpha internal consistency coefficient of the scale was found to be 0.93 in a psychiatric patient sample.

Beck Depression Inventory (BDI): The BDI is a 21-item Likert-type scale developed by Beck et al. (13) and can be scored from 0 to 3. A higher total score obtained from the scale indicates the severity of depression experienced by the person. The scale was adapted into Turkish by Hisli (14). Cronbach's alpha internal consistency coefficient of the Turkish form of the scale was found to be 0.74.

Intolerance of Uncertainty Scale (IUS): IUS is a four-dimensional scale consisting of 27 items developed by Freeston et al. (15) and adapted into Turkish by Sarı and Dağ (16). These dimensions are "Uncertainty is distressing and upsetting" (Factor 1, IU-F1), "Uncertain events are negative and should be avoided" (Factor 2, IU-F2), "Being uncertain is unfair" (Factor 3, IU-F3) and "Uncertainty leads to the inability to act" (Factor 4, IU-F4). High scores on the scale and subscales indicate high IU. The Cronbach alpha internal consistency coefficient of the scale is 0.95, and the internal consistency coefficients of the subdimensions are between 0.70 and 0.89 (16). In our research, the Cronbach alpha internal consistency coefficient of the scale value was between 0.79 and 0.95.

Time Management Inventory (TMI): TMI is a three-dimensional scale with 27 items developed by Britton and Tesser (17) and adapted into Turkish by Alay and Koçak (18). These dimensions are TP, time attitudes (TA), and time wasters (TW). The TP sub-dimension measures the planning that the respondents do during the day and week, and high scores indicate that people plan the current week and day correctly. TA questions are asked about how people use their time, and high scores identify people as people who use their time well. In TW questions, questions about long-term planning and future planning are asked, and high scores indicate that people are successful in determining their future goals and objectives. In Alay and Koçak's (18) adaptation study of the scale into Turkish, the internal consistency coefficient of the scale was found to be 0.88 for the TP dimension, 0.66 for the TA dimension, 0.47 for the TW dimension, and 0.80 for the overall scale (18). In our research, the Cronbach alpha internal consistency coefficient of the scale value was between 0.60 and 0.91.

Before starting the research, ethics committee approval (HNEAH-KAEK 2023/71/4368) was obtained from the University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki. An expert psychiatrist provided information to the volunteers about the study, and written informed consent was obtained from the participants.

Statistical Analysis

Analyses were performed using SPSS (Version 22.0; SPSS Inc., Chicago, Illinois, USA). Number, percentage, mean value, and standard deviation were used to describe the data. The Kolmogorov-Smirnov test was used to examine whether the data conformed to a normal distribution. In pairwise and multiple comparisons, independent sample t-test and One-Way analysis of variance were used for data with normal distribution, Mann-Whitney U test and Kruskal-Wallis test for data that did not comply with normal distribution, and chi-square test for categorical variables. In this study, the relationships among anxiety, depression, IU, and TM were analyzed using the Pearson correlation coefficient. In statistical interpretations, p-values <0.05 were considered significant within the 95% confidence interval.

Results

The average age of the participants was 32.76±11.82 in those with GAD and 33.41±11.89 in the CG. The rate of

Table 1. Sociodemographic data of participants

	Group						Statistical analyse		
	GAD		Control		Total				
	Number (n=131)	Percent (%)	Number (n=120)	Percent (%)	Number (n=251)	Percent (%)	χ^2	df	p*
Age									
18-24 age	43	32.8	35	29.2	78	31.1	4.719	3	0.194
25-34 age	41	31.3	38	31.7	79	31.5			
35-44 age	18	13.7	28	23.3	46	18.3			
45 age and upper	29	22.1	19	15.8	48	19.1			
Sex									
Male	63	48.1	58	48.3	121	48.2	0.001	1	0.969
Female	68	51.9	62	51.7	130	51.8			
Educational status									
Illiterate	1	0.8	2	1.7	3	1.2	0.912	3	0.823
Primary education	25	19.1	21	17.5	46	18.3			
High school	49	37.4	41	34.2	90	35.9			
University	56	42.7	56	46.7	112	44.6			
Marital status									
Single	83	63.4	77	64.2	160	63.7	0.180	1	0.894
Married	48	36.6	43	35.8	91	36.3			
Professional status									
Employee	55	42.0	50	41.7	105	41.8	3.469	4	0.483
Officer	14	10.7	22	18.3	36	14.3			
Retired	8	6.1	7	5.8	15	6.1			
Student	30	22.9	24	20.0	54	21.5			
Housewife	24	18.3	17	14.2	41	16.3			
Place of residence									
Villiage	3	2.3	7	5.8	10	4.0	2.201	2	0.333
Town	18	13.7	14	11.7	32	12.7			
Town center	110	84.0	99	82.5	209	83.3			
Cigarette									
Yes	61	46.6	50	41.7	111	44.2	0.609	1	0.435
No	70	53.4	70	58.3	140	55.8			
Alcohol									
Yes	50	38.2	32	26.7	82	32.7	3.766	1	0.052
No	81	61.8	88	73.3	169	67.3			
Psychiatric treatment history									
Yes	84	64.1	41	34.2	125	49.8	22.480	1	**<0.001**
No	47	35.9	79	65.8	126	50.2			
Family history of psychiatric illness									
Yes	59	45.0	32	26.7	91	36.3	9.146	1	**0.002**
No	72	55.0	88	73.3	160	63.7			

*p<0.05, χ^2: Chi-square value, df: Degree of freedom, GAD: Generalized anxiety disorder

women with GAD was 51.9%, and 42.7% were university graduates, 63.4% were single, 42.0% were workers, 84% lived in the city center, 53.4% were smokers, 61.8% used alcohol, 64.1% had a history of a psychiatric disorder, and 45.0% had a family history of psychiatric illness (Table 1).

The participants' BAI, BDI, IUS, and TMI total and subscale mean scores are given in Table 2. BAI, BDI, IU, and TM mean scores of PG were significantly higher than those of CG (p<0.05, Table 2).

In the PG, while anxiety levels were significantly higher in women, those with a history of psychiatric treatment, and smokers (p<0.05), depression levels were higher in the 18-24 age group and smokers (p<0.05, Table 3). The mean scores of people with GAD regarding their TA and "uncertainty is distressing and upsetting (IU-F1)" levels vary according to age (p<0.05).

There was a significant difference between the mean scores of TA between men and women (p<0.05). TA, TW, IU-F1, "uncertain events are negative and should be avoided (IU-F2)" and "uncertainty leads to the inability to act (IU-F4)" mean scores were significantly higher in single individuals than in married individuals (p<0.05, Table 3).

According to their professional status, TP, TA, TM-total, and IU-F1 levels differed significantly in patients with GAD than in those with CG. TP levels in housewives and TA, TM-total, and IU-F1 levels in students were higher than those in other professional groups in the PG (p<0.05, Table 3).

TA, TM-total, IU-F1, and IU-F2 subscale levels were significantly higher in patients with a history of psychiatric treatment than in those without psychiatric treatment (p<0.05, Table 3).

In non-smokers, TP, TW, TM-total, IU-F1 and "being uncertain is unfair (IU-F3)" subscale scores were significantly higher than smoker (p<0.05, Table 3). TM-total and IU-F4 subdimensions were significantly higher in alcohol users (p<0.05, Table 3).

There was no significant difference between education level, place of residence, family history of psychiatric disease, and IU and TM levels (p>0.05).

It was determined that there was a positive significant relationship between IU and TM levels (r=0.248, p<0.05, Table 4). A positive significant relationship was found between anxiety and depression levels (r=0.660, p<0.001, Table 4), IU (r=0.499, p<0.001) and TM total scores (r=0.287, p=0.001, Table 4). A positive significant relationship was found between depression levels and IU (r=0.480, p<0.001, Table 4) and TM total scores (r=0.480, p<0.001, Table 4).

There was a negative significant relationship between the average age and BAI (r=-0.252, p=0.004), BDI (r=-343, p<0.001), and the total and subscale scores of IU (r=-0.173, p=0.004) and TM (r=-0.313, p>0.05) patients with GAD (Table 4).

Discussion

This study examined the relationship between uncertainty intolerance and TM skills in people with GAD and whether this relationship differs according to sociodemographic data. To the best of our knowledge, this is the first study to

Table 2. Comparison of scale scores of cases

	Group		Statistical analyze			
	GAD (Mean ± SD)	Control (Mean ± SD)	t	df	95% CI of the difference	
					Lower	Upper
BAI	28.81±12.32	8.10±9.72	14.843	243.768	**17.961**	**23.457**
BDI	22.54±12.52	7.92±9.35	10.542	239.549	**11.892**	**17.358**
Intolerance of incertainty scale (IUS)						
IU-total	90.16±21.13	65.55±22.97	8.809	241.902	**19.107**	**30.114**
IU-F1	33.56±8.45	23.84±9.15	8.720	242.221	**7.527**	**11.920**
IU-F2	25.12±6.91	17.78±7.25	8.204	244.476	**5.583**	**9.111**
IU-F3	13.63±4.30	10.68±4.24	5.473	247.595	**1.889**	**4.013**
IU-F4	17.85±4.39	13.26±4.78	7.906	241.846	**3.446**	**5.732**
Time management inventory (TMI)						
TM-total	86.98±15.99	75.46±16.36	5.637	246.001	**7.499**	**15.554**
TP	54.92±12.29	47.53±13.92	4.442	238.331	**4.113**	**10.669**
TA	20.88±5.84	17.40±3.59	5.736	218.576	**2.283**	**4.673**
TW	11.19±3.98	10.53±3.75	1.344	249.000	-0.306	1.621

*p<0.05, t: Independent sample test value, CI: Confidence interval, BAI: Beck anxiety inventory, BDI: Beck depression inventory, IU-F1: Uncertainty is stressful and upsetting, IU-F2: Unexpected events are neative and should be avoided, IU-F3: Being uncertain is unfair, IU-F4: Uncertainty leads to the inability to act, TP: Time planning, TA: Time attitudes, TW: Time wasters, df: Degree of freedom, GAD: Generalized anxiety disorder, SD: Standard deviation

Table 3. Time management inventory and intolerance of uncertainty scale mean score distribution according to sociodemographic characteristics of those with GAD

	n=131	BAI	BDI	IU-F1	IU-F2	IU-F3	IU-F4	IU-Total	TP	TA	TW	TM-total
Age group (mean rank)												
18-24 year	43	75.84	79.15	75.41	72.10	71.47	73.85	74.37	64.83	82.99	71.35	73.79
25-34 year	41	65.27	66.41	70.68	68.70	68.59	68.40	70.12	72.84	66.77	64.56	70.39
35-44 year	18	66.81	65.22	67.64	65.36	62.83	67.92	66.50	58.39	49.61	59.83	51.61
45 year and upper	29	51.95	46.40	44.41	53.53	56.21	49.78	47.50	62.79	49.90	63.93	57.17
Chi-square		6.89	12.92	12.70	4.46	3.16	7.39	9.51	2.31	17.26	1.48	6.52
df		3	3	3	3	3	3	3	3	3	3	3
p*		0.075	**0.005**	**0.005**	0.216	0.368	0.060	**0.023**	0.511	**0.001**	0.686	0.089
Sex (mean ± SD)												
Male	63	24.79±11.89	20.92±13.37	32.75±8.22	24.78±6.60	13.27±3.88	17.56±4.26	88.35±20.12	54.59±12.01	19.51±5.26	11.05±3.61	85.14±88.69
Female	68	32.53±11.60	24.04±11.57	34.32±8.65	25.44±7.22	13.96±4.65	18.12±4.52	91.84±21.96	55.22±12.62	22.15±6.10	11.32±4.32	15.22±16.61
t		-3.765	-1.425	-1.070	-0.550	-0.919	-0.733	-0.947	-0.294	-2.657	-0.398	-1.276
df		127.673	123.080	128.911	128.977	127.653	128.956	128.996	128.906	128.342	127.635	128.985
p*		<0.001	0.157	0.287	0.583	0.360	0.465	0.345	0.769	0.009	0.692	0.204
Marital status (mean ± SD)												
Single	83	29.40±11.60	24.08±12.88	35.24±7.92	26.16±7.05	14.10±4.54	18.46±4.22	94.13±20.49	54.48±13.10	21.87±5.61	11.90±3.72	88.25±17.37
Married	48	27.79±13.55	19.88±11.51	30.67±8.65	23.33±6.34	12.81±3.75	16.79±4.52	83.60±20.13	55.67±10.84	19.17±5.90	9.96±4.15	84.79±13.17
t		0.688	1.930	3.008	2.357	1.745	2.122	2.824	-0.558	2.570	2.682	1.286
df		86.405	107.435	91.314	106.944	113.559	129.000	101.230	113.514	94.170	89.784	119.701
p*		0.493	0.056	**0.003**	**0.020**	0.084	**0.036**	**0.006**	0.578	**0.012**	**0.009**	0.201
Professional status (mean rank)												
Employee	55	66.59	68.44	65.36	70.17	65.80	67.89	67.85	70.68	62.97	62.42	67.29
Officer	14	66.50	68.32	79.29	67.14	78.57	71.46	74.89	71.11	65.82	64.50	68.86
Retired	8	54.38	48.00	41.06	47.19	57.50	43.50	42.13	27.06	34.44	64.75	25.75
Student	30	73.00	70.47	80.15	68.28	75.48	71.27	74.98	59.03	84.03	80.58	72.22
Housewife	24	59.48	59.48	50.33	59.19	50.10	59.40	53.31	73.98	61.02	57.27	67.02
Chi-square		2.497	3.205	13.467	3.533	8.073	4.57	8,428	11.591	13.109	6.258	9.968
df		4	4	4	4	4	4	4	4	4	4	4
p*		0.645	0.524	**0.009**	0.473	0.089	0.334	0.077	**0.021**	**0.011**	0.181	**0.041**
Psychiatric treatment history (mean ± SD)												
Yes	84	31.29±11.82	23.62±12.06	34.55±8.29	26.04±6.78	14.48±4.17	18.05±4.44	93.11±20.58	55.64±12.67	22.10±5.27	11.83±4.02	89.57±16.16
No	47	24.38±12.06	20.62±13.20	31.81±8.54	23.49±6.90	12.11±4.13	17.49±4.32	84,89±21,279	53.62±11.61	18.70±6.22	10.04±3.68	82.36±14.75
t		3.164	1.287	1.780	2.039	3.139	0.702	2.144	0.927	3.157	2.584	2.592

Table 3. continued

	n=131	BAI	BDI	IU-F1	IU-F2	IU-F3	IU-F4	IU-Total	TP	TA	TW	TM-total
df		93.726	88.334	93.045	93.954	96.168	97.436	92.695	102.508	82.946	102.730	102.878
p*		0.002	0.201	0.078	0.044	0.002	0.484	0.035	0.356	0.002	0.011	0.011
Cigarette (mean ± SD)												
Yes	61	31.46±12.90	24.87±14.34	34.03±9.08	26.57±7.17	13.85±4.44	17.74±4.12	92.20±22.43	57.33±11.69	21.75±6.14	12.75±3.65	91.84±15.99
No	70	26.50±11.39	20.51±10.37	33.16±7.91	23.86±6.46	13.43±4.19	17.94±4.64	88.39±19.92	52.81±12.49	20.11±5.50	9.83±3.77	82.76±14.86
t		2.317	2.009	0.584	2.265	0.560	-0.268	1.022	2.135	1.600	4.502	3.350
df		120.739	129.000	119.914	121.847	124.230	128.948	121.092	128.332	121.516	127.538	123.468
p*		**0.022**	**0.047**	0.560	**0.025**	0.577	0.789	0.309	**0.035**	0.112	**<0.001**	**0.001**
Alcohol (mean ± SD)												
Yes	50	30.12±12.91	23.66±14.61	34.92±8.55	26.26±7.98	14.02±4.41	18.86±4.04	94.06±22.52	57.00±11.43	22.06±5.78	12.00±3.82	91.06±16.16
No	81	28.00±11.95	21.85±11.07	32.73±8.33	24.42±6.10	13.38±4.24	17.22±4.50	87.75±19.98	53.63±12.69	20.15±5.79	10.69±4.02	84.47±15.46
t		0.939	0.802	1.439	1.488	0.816	2.158	1.624	1.572	1.837	1.866	2.306
df		97.828	129.000	101.796	129.000	100.774	112.540	94.53	112.201	104.041	107.944	100.382
p*		0.350	0.424	0.153	0.139	0.416	**0.033**	0.108	0.119	0.069	0.065	**0.023**

*p<0.0, t: Independent sample t-test value, df: Degree of freedom, N: Number, BAI: Beck anxiety inventory, BDI: Beck depression inventory, IU-F1: Uncertainty is stressful and upsetting, IU-F2: Unexpected events are neative and should be avoided, IU-F3: Being uncertain is unfair, IU-F4: Uncertainty leads to the inability to act, TP: Time planning, TA: Time attitudes, TW: Time wasters, SD: Standard deviation, GAD: Generalized anxiety disorder

evaluate the relationship between IU and TM in patients with GAD. In our study, it was found that BAI, BDI, IU, and TM levels were higher in people with GAD than in those without GAD, and that this difference may vary according to age, gender, and various sociodemographic data, and that there was a positive relationship between IU and TM.

Anxiety and depression levels were found to be higher in the PG group than in the CG. In GAD, anxiety and depression symptoms frequently occur together. The high level of these symptoms in the participants is an expected finding.

Scale scores of those with GAD, except for IU and TW, were higher than those of the CG. In GAD, IU can cause anxiety symptoms. In a study conducted by Watts et al. (19), it was found that IU and negative problem orientation predicted GAD symptoms, whereas positive beliefs about worry and cognitive avoidance were less important in predicting GAD symptoms. Ren et al. (20) stated that the relationship between the divergent dimension of IU and various symptoms of GAD may provide some references for prevention and interventions related to GAD, and that targeting the component "I am frustrated by not having all the information I need" may be more effective in reducing symptoms. On the other hand, inadequate TP reduces individual satisfaction due to insufficient time allocated to personal and social activities, increases stress, and affects the acquisition of positive personality traits such as decision-making, leadership, and critical thinking (21). In fact, studies conducted on nursing and midwifery students stated that as students' anxiety levels increase, their TM skill decreases (22). The findings of our study support the findings in the literature.

When those with GAD were examined in terms of sociodemographic characteristics, TA was higher in women than in men, but no difference was detected in terms of IU levels and other TM subscale scores. It was thought that this situation had a sociocultural background and might have been related to the level of upbringing. Studies have found that women can manage their time better than men (9,10,22). The findings of our study are compatible with these findings.

The levels of TA, TW, IU-F1, IU-F2, and IU-F4 were significantly higher in single people than in married people. Marriage is an institution that ensures order in human life. It can motivate individuals and relieve their anxiety despite uncertainty and TP. The findings of our study support this view.

In terms of their occupational status, significant differences were observed in TP, TA, and TM-total levels and IU-F1 levels in those with GAD. TP levels in housewives and TA, TM-total, and IU-F1 levels in students were higher than those in other professional

Table 4. Relationships between age and scale scores in GAD group

		Mean ± SD	1	2	3	4	5	6	7	8	9	10	11	12
1. Age	r	32.76±11.82	-											
	p													
2. BAI	r	28.81±12.32	-0.252**	-										
	p		**0.004**											
3. BDI	r	22.54±12.52	-0.343**	0.660**	-									
	p		**<0.001**	**<0.001**										
Intolerance of uncertainty scale														
4. IU-Total	r	90.16±21.13	-0.313**	0.499**	0.480**	-								
	p		**<0.001**	**<0.001**	**<0.001**									
5. IU-F1	r	33.56±8.45	-0.369**	0.479**	0.447**	0.940**	-							
	p		**<0.001**	**<0.001**	**<0.001**	**<0.001**								
6. IU-F2	r	25.12±6.91	-0.224*	0.452**	0.510**	0.881**	0.728**	-						
	p		**0.010**	**<0.001**	**<0.001**	**<0.001**	**<0.001**							
7. IU-F3	r	13.63±4.30	-0.177*	0.442**	0.323**	0.804**	0.710**	0.630**	-					
	p		**0.043**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**						
8. IU-F4	r	17.85±4.39	-0.270**	0.333**	0.330**	0.831**	0.758**	0.647**	0.534**	-				
	p		**0.002**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**					
Time management inventory														
9. TM-Total	r	86.98±15.99	-0.173*	0.287**	0.480**	0.248**	0.239**	0.322**	0.054	0.173*	-			
	p		**0.048**	**0.001**	**<0.001**	**0.004**	**0.006**	**<0.001**	0.543	**0.049**				
10. TP	r	54.92±12.29	-0.043	0.149	0.370**	0.059	0.048	0.168	-0.099	0.024	0.870**	-		
	p		0.623	0.089	**<0.001**	0.504	0.590	0.055	0.263	0.789	**<0.001**			
11. TA	r	20.88±5.84	-0.332**	0.379**	0.490**	0.396**	0.393**	0.386**	0.246**	0.301**	0.631**	0.243**	-	
	p		**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.005**	**<0.001**	**<0.001**	**0.005**		
12. TW	r	11.19±3.98	-0.074	0.138	0.067	0.232**	0.236**	0.207*	0.159	0.180*	405**	0.052	317**	-
	p		0.400	0.117	0.446	**0.008**	**0.007**	**0.018**	0.070	**0.040**	**<0.001**	0.555	**<0.001**	

*p<0.05, BAI: Beck anxiety inventory, BDI: Beck depression inventory, IU-F1: Uncertainty is stressful and upsetting, IU-F2: Unexpected events are neative and should be avoided, IU-F3: Being uncertain is unfair, IU-F4: Uncertainty leads to the inability to act, TP: Time planning, TA: Time attitudes, TW: Time wasters, SD: Standard deviation

groups. In a study conducted in Pakistan, it was suggested that being a housewife was among the factors positively associated with anxiety and depressive disorders (23), and arguments with spouses and relationship problems with the mother-in-law were positively associated with GAD. In a study conducted by Çulha (24) on healthcare workers, it was stated that the GAD of married people was lower than that of single people, and there was no difference in their IU levels.

A study conducted on university students showed that there was a significant negative relationship between students' TM skills and anxiety levels (10). Kırıcı (25) found that the trait anxiety levels of unemployed women were higher than those of working women. TM skills of those with high anxiety levels also decrease. These findings are consistent with the findings of our study.

It was observed that the TA, TM-total, IU-F1, and IU-F2 levels of patients with a history of psychiatric treatment were higher than those without a history of psychiatric disease in the PG. People with GAD who are distressed by uncertainty and avoid uncertain events may experience anxiety and worry due to psychiatric disorders in their past experiences. In this regard, it can be predicted that these people's uncertainty levels will be high. In addition, these people may have different perspectives on the concept of time during the disease process. TM skills can improve with experiences during the previous disease process.

It was found that the levels of TP, TW, and TM-total, and IU-F1 and IU-F3, were higher in non-smokers than in smokers. In a study by Özdemir et al. (26), the perceived stress levels of nurses who smoke were high. In a study by Şimşek (27) on university students, it was found that IU levels were higher in non-smokers. Despite these findings, Coşkun (28) reported that smoking does not affect IU levels.

While periods of stress increase the prevalence of smoking (29), smoking also increases stress and anxiety (30).

A study conducted by Xu et al. (31) showed that regardless of smoking level, improving health-related knowledge, TM awareness, and self-control ability can contribute to reducing the prevalence of smoking behavior. Smoking behavior can increase anxiety levels and negatively affect IU and TM levels. Although there are different results in the literature, according to the findings of our study, the high levels of IU and TM in non-smokers may be because these people have GAD.

Another finding of our study was that TM-total and the IU-F4 sub-dimension were higher in alcohol users than in non-alcohol users. Alcohol use, which is used to eliminate daily problems and create temporary comfort, becomes a habit over time. Kraemer et al. (32) examined the role of IU in terms of drinking reasons among university students, revealed that individuals who cannot tolerate uncertainty consume more cigarettes alcohol and marijuana. This suggests that IU is associated with drinking to manage or avoid negative emotions and that interventions aimed at reducing IU may be helpful in reducing problematic alcohol consumption in patients with GAD. Alcohol use may reduce anxiety levels in people with GAD, who are prevented from taking action in uncertain situations, and may play a role in relieving stress that negatively affects TM. The reason why people with GAD use alcohol is that it may be effective in improving uncertainty and TM in relation to reducing anxiety.

It has been determined that there is a significant positive relationship between IU and TM in patients with GAD. A study conducted in Tehran found a negative relationship between TM levels and state and trait anxiety levels (33). In a study conducted in our country, it was stated that TM skills decrease as the level of anxiety increases (21). In light of these findings, it can be stated that as the IU levels of those with GAD increase, their TA and TW behaviors increase.

A positive significant relationship was found between anxiety and depression levels, IU, and TM scores. A positive significant relationship was found between depression levels and IU and TM scores. In a study by Belge (3), a significant positive relationship was found between IU, anxiety, and depression symptoms. In a study conducted on university students, a negative relationship was found between students' TM skills and their depression-anxiety and stress levels (9). Interestingly, in our study, high levels of anxiety and depressive symptoms in the PG positively affect TM skills. This may be because of partial recovery due to the effect of antidepressant medications used by people with GAD.

It has been found that there is a negative relationship between the average age of patients with GAD and their IU and TM levels. In a study conducted on individuals with chronic diseases, IU levels decreased with age (34). On the other hand, in a study conducted on university students, it was stated that the age variable was not related to the IU (35). In a study conducted by Kaya et al. (22), it was shown that students' TM skill levels did not change according to age. It can be stated that the levels of IU and TM in people with GAD decrease with age, and this may be related to the change in the way they approach events with advancing age.

The results of this research are important in terms of investigating whether there is a relationship between IU and TM in people with GAD, guiding future studies, and adding to the literature the effect of sociodemographic characteristics on the relationship between IU and TM skills in people with GAD. The findings obtained because of the research were interpreted and evaluated, and these findings were discussed by comparing them with other research findings in the literature.

Study Limitations

Our study has several limitations. One limitation of this study is related to the scales used. The focus of this study and the questions sought to be answered under its other subheadings are limited to the measurement capabilities of the IU and TM inventories. Therefore, the findings can be strengthened if the relationship between IU and TM levels is evaluated using different inventories. Another limitation may be specific to the demographic information form. Further studies can be designed with more detailed demographic questions. Because this was a cross-sectional study, causal inferences are limited. Although the above limitations and assumptions constitute a limitation, the relationship between IU and TM in patients with GAD has not been directly examined. In this respect, it was thought that our study could contribute to the literature.

Conclusion

IU, which contributes to the development and maintenance of GAD and plays an important role in its symptomatology, is effective in the development of TM skills in these individuals. This interaction may differ depending on sociodemographic characteristics such as age and gender. Broader sociodemographic characteristics may generate new findings on how IU in GAD affects TM. The evidence from this study warrants further research to determine whether specific aspects of IU and TM may aid in the treatment of GAD. It would also be valuable to conduct further research into how the relationship between IU and TM plays a role in the development of other anxiety disorders and how it contributes to the comorbidity of these disorders.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Institutional Ethics Committee of University of Health Sciences Türkiye, Haydarpaşa Numune Training and Research Hospital (approval no: 2023/71/4368) and conducted in accordance with the Declaration of Helsinki.

Informed Consent: Written informed consent was obtained from all participants before registration.

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CASE REPORT

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Multiple Spindle Cell Lipomas and Spindle Cell Lipoma as A Component of Multiple Lipomas: A Case Series of Seven Patients

Multiple İğsi Hücreli Lipomlar ve Multipl Lipomların Komponenti Olarak İğsi Hücreli Lipom: Yedi Olguluk Seri

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ABSTRACT

Spindle cell lipoma (SCL) is a benign lipomatous tumor consisting of mature adipose and spindle cells with a thick collagen component. Although SCLs are characteristically seen as solitary tumors in elderly male patients on the posterior neck, shoulder and back, they rarely can be presented as multiple tumors or synchronously with multiple ordinary lipomas in the same patient. It has been claimed that the natural progression of the disease might be sequential, and the later lesions were more cellular. We present 7 patients diagnosed as either multiple spindle cell lipomatosis or SCL as a component of multiple lipomas. In 4 tumors of two patients, we observed multifocal spindle cell proliferation areas within myxoid stroma containing ropy collagen bundles. The finding of SCL component as multiple small foci in otherwise ordinary lipoma-like mature adipocytic cells may support the claim that within a period, ordinary lipomas may be converted into SCLs.

Keywords: Spindle cell lipoma, lipoma, CD34

ÖZ

İğsi hücreli lipom (SCL) kalın kollagenöz komponent içeren matür adipöz ve iğsi hücrelerden oluşan benign lipomatöz bir tümördür. SCL'ler karakteristik olarak orta yaşlı erkek hastaların ense, omuz ve sırtında soliter olarak görülüyor olsa da nadiren multipl tümörler olarak ya da aynı hastada multipl olağan lipomlarla aynı anda bulunabilirler. Hastalığın doğal gidişinin sıralı olabileceği ve daha sonra gelişen lezyonların daha hücresel olabileceği iddia edilmiştir. Bu raporda multipl SCL veya multipl lipomların komponenti olarak SCL tanısı almış 7 hasta sunuldu. Hastalardan ikisinde toplam 4 lezyonda miksoid stroma içinde kalın, halatsı kollajen içeren multifokal iğsi hücre proliferasyonu gözlemlendi. İki hastada olağan lipom benzeri matür adipositik hücreler arasında multipl küçük SCL odaklarının varlığı bize göre belli bir zaman dilimi içinde olağan lipomların SCL'ye dönüşebileceği iddiasını destekliyor olabilir.

Anahtar Kelimeler: İğsi hücreli lipom, lipom, CD34

Introduction

Spindle cell lipoma (SCL) is a benign lipomatous tumor consisting of mature adipose and spindle cells with a thick collagen component, first described by Enzinger and Harvey (1) in 1975. Diagnosis can be difficult because of heterogeneous histopathological features (2,3,4). Although SCL is characteristically seen on the posterior neck, shoulder, and back as a solitary, well-circumscribed lesion in elderly men, multiple synchronous tumors can rarely be seen in a patient, and some of these are reported to be familial (5). SCL can rarely occur synchronously with multiple ordinary lipomas in the same patient (6,7,8). In this report, we presented seven patients with either multiple SCLs or SCL as a component of multiple lipomas.

Case Report

All patients were male. Clinicopathological features are summarized in Table 1.

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Table 1. Clinicopathological features

P	A	S	SCL (N)	L	Max diameter	Additional findings
1	47	M	5	Trunk	2.5 cm, 2.5 cm, 3 cm, 3 cm, 3 cm	-
2	64	M	4	Neck	3.5 cm, 4 cm, 4 cm, 4.5 cm	5 ordinary lipomas, 1 seborrheic keratosis
3	53	M	4	Neck	1.5 cm, 1.5 cm, 2 cm, 2.2 cm	-
4	47	M	1	Arm	2.5 cm	2 ordinary lipomas
5	60	M	1	Neck	1.2 cm	1 angiolipoma
6	38	M	2	Shoulder	4 cm, 3.5 cm	4 ordinary lipomas
7	64	M	2	Back	3 cm, 2 cm	2 angiolipomas, 1 FEP

A: Age, FEP: Fibroepithelial polyp, L: Location, M: Male, N: Number, P: Patient, S: Sex, SCL: Spindle cell lipoma

Clinical History

Patient 1: A 47-year-old male patient presented with 5 simultaneous painless soft tissue lesions in the right hemithorax. Five excisional biopsy materials, yellow and brownish in color and soft were sent to our laboratory. They had a maximum diameter of 2.5-3 cm.

Patient 2: A 64-year-old male patient presented with 9 simultaneous painless soft tissue lesions. Four of these lesions were at the neck and five were at the back. Four excisional biopsy materials from the neck were yellow and brownish in color, soft in consistency, the smallest measuring 3.5x3x1.5 cm and the largest measuring 4.5x3x1.5 cm. The other five soft tissue lesions from the back were homogenously yellow in color and soft in consistency, with diameters ranging between 2.5 and 5 cm. He also had a hyperpigmented skin lesion on the scalp.

Patient 3: A 53-year-old male patient presented with 4 painless soft tissue lesions in the neck. These four lesions were yellow and brownish in color, soft in consistency, and had a maximum diameter ranging between 1.5-2 cm. Clinical history revealed that his father and brother had similar soft tissue lesions.

Patient 4: A 47-year-old male patient presented with 3 soft tissue lesions in the arm. Three lesions, yellow and brownish in color, soft in consistency, with a maximum diameter ranging between 2.5-3.5 cm, were sent.

Patient 5: A 60-year-old male patient presented with 2 soft tissue lesions at the neck and lumbar region. The lesions were yellow in color and soft in consistency, with a maximum diameter of 1.5 cm each, and were sent to our laboratory.

Patient 6: A 38-year-old male patient presented with 6 soft tissue lesions at the right shoulder. The lesions, which were tan-yellow in color and soft in consistency, with a maximum diameter varying between 3 and 5 cm, were sent to our laboratory.

Patient 7: A 64-year-old male patient presented with 4 soft tissue lesions on the back. Lesions that were tan-yellow in color, soft in consistency, with a maximum diameter varying between 2 and 3 cm, were sent to our laboratory. He also had a polypoid skin lesion on his back.

An informed consent form has been received from all patients.

Pathological Findings

SCL: Five lesions from patient 1; 4 lesions from patient 2; 4 lesions from patient 3; 1 lesion from patient 4; 1 lesion from patient 5; 2 lesions from patient 6; and 2 lesions from patient 7 showed similar microscopic features, consistent with SCL. All these lesions comprised fibroblast-like bland spindle cells and mature adipocytes interspersed within a fibromyxoid stroma containing coarse collagen fibers (ropy collagen) (Figures 1 and 2). In patients 1, 2, and 5, the spindle cell component was dominant and the adipose component was minor (Figure 2). These tumors had prominent areas of myxoid degeneration. In patients 6 and 7, the tumors showed multiple myxoid degeneration areas with a maximum diameter of 2 mm (Figure 3), containing spindle cells. These tumors contained prominent adipose components. Immunohistochemically, in all tumors, the spindle cells were diffusely positive for CD34 (Figure 4). In all SCLs, except for patient 2, scattered mast cells were also observed (Figure 2). Histopathological examination revealed no atypical cells. No mitotic activity or necrosis were observed.

Additional pathological findings: In 5 patients, multiple ordinary lipomas consisting of mature fat cells displaying no atypical features were observed. Patient 2 also had seborrheic keratosis. Two patients had coexistent angiolipomas consisting of mature fat cells and narrow vascular structures. Patient 7 also had a fibroepithelial polyp.

After a maximum two years of follow-up, none of the SCL lesions showed recurrence.

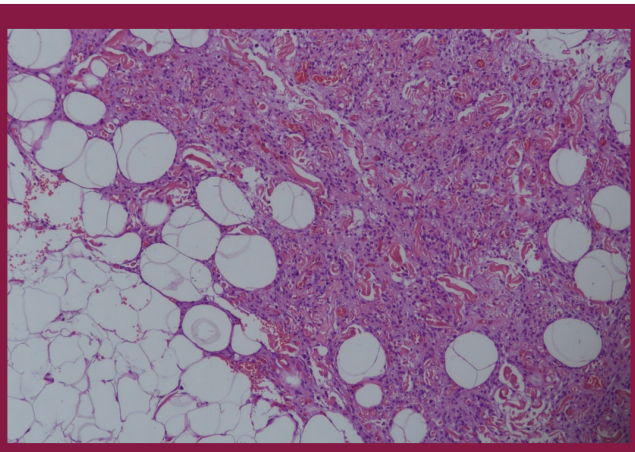

Figure 1. Spindle cells and mature adipocytes interspersed within a fibromyxoid stroma with coarse collagen fibers (x100; H-E)

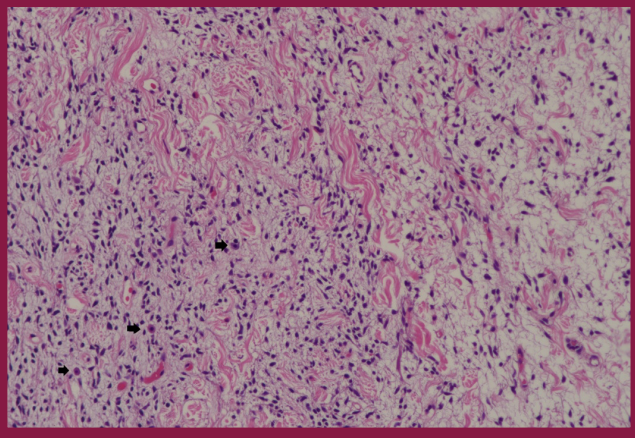

Figure 2. Prominent spindle cell component and scattered mast cells (arrows) within the fibromyxoid stroma and ropy collagen fibers (x200; H-E)

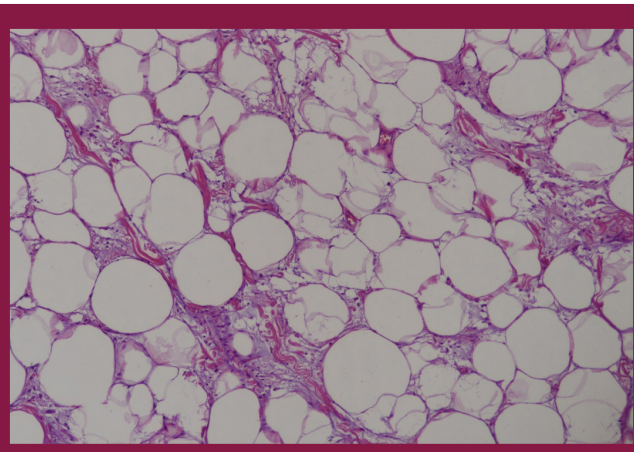

Figure 3. Small foci of spindle cell proliferation within a myxoid stroma containing coarse collagen bundles (x100; H-E)

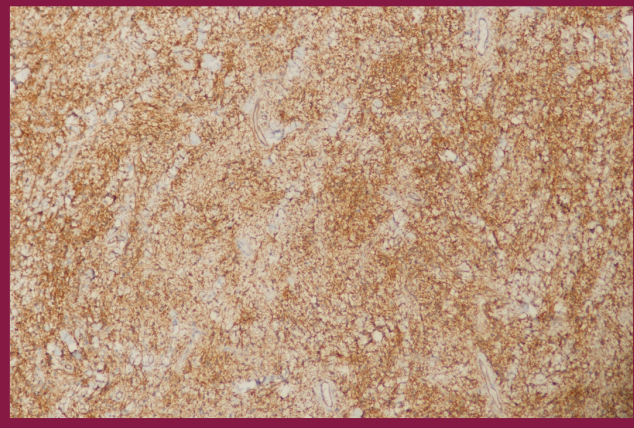

Figure 4. Diffuse CD34 immunopositivity in the SCL (100; CD34)

Discussion

SCL is a benign lipomatous tumor characteristically occurring as a solitary lesion in the posterior neck, back, and shoulders of elderly men (1). Its etiology and pathogenesis remain unclear. Multiple SCL cases are reported to be very rare. Fanburg-Smith et al. (5) reported that the ratio of patients with multiple SCLs in two different series was 0.5% and 3%, respectively. In our series, two male patients had multiple SCLs having synchronous tumors 4 and 5 in number. The distribution of lesions was limited to the trunk and posterior neck. In the English literature, multiple SCLs at the tongue and upper extremities have been reported (9,10,11). Histopathological findings were similar in both patients. It has been claimed that the natural progression of the disease may be sequential, and the later lesions may be more cellular (5). In 3 patients, concurrent lipomas and in 2 patients, coexistent angiolipomas were present. Interestingly, in two patients (patient 6 and 7), we observed multiple foci of spindle cell proliferation in a myxoid stroma. These foci had a maximum diameter of 2 mm. We believe that these areas support the suggestion that ordinary lipomas may convert into SCLs within time. Currently the mechanisms of this alteration cannot be explained. It has been reported that human mast cells activate fibroblast proliferation and collagen synthesis (12). Although SCLs in our series contained scattered mast cells except for one case, as Sakai et al. (6) reported, we also could not observe mast cells in ordinary lipomas.

Patients with synchronous multiple ordinary lipomas are reported to be approximately 5% (3). The coexistence of SCL

and ordinary lipomas (or angiolipomas) is very rare (6,7,8). To the best of our knowledge, the coexistence of SCLs and angiolipomas has not been reported before.

Histopathological differential diagnosis of SCL includes neurofibroma, dermatofibrosarcoma, angiomyofibroblastoma, superficial angiomyxoma, and myxoid liposarcoma (4,5). The diagnosis of classic SCL is usually not difficult. However, special variants and heterogeneous composition of SCLs make the diagnosis difficult (4). Diffuse CD34 immunopositivity in spindle cells is helpful in differential diagnosis (5). Fletcher et al. (13), in their report of cytogenetic analysis, found that SCLs showed chromosomal aberrations involving 16q.

Unfortunately, we could not perform any cytogenetic or molecular analysis in our cases.

In summary, we have reported multiple SCLs in 2 patients and SCL as a component of multiple lipomatosis in 5 patients. Both conditions are reported to be very rare. In 2 patients, we detected a diagnostic SCL component as multiple small foci in otherwise ordinary lipoma-like mature adipocytic cells. We believe that this finding may support the claim that ordinary lipomas may be converted into SCLs within a period of time.

Ethics

Informed Consent: An informed consent form has been received from all patients.

Authorship Contributions

Surgical and Medical Practices: C.Ç., H.B., R.T., Concept: C.Ç., H.B., R.T., Design: C.Ç., H.B., R.T., Data Collection or Processing: C.Ç., H.B., R.T., Analysis or Interpretation: C.Ç., H.B., R.T., Literature Search: C.Ç., H.B., R.T., Writing: C.Ç., H.B., R.T.

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

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CASE REPORT

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Absorption or Circulation of the Subdural Hematoma? How Should We Name It? A Case Report and Literature Review

Subdural Hematomun Emilimi mi, Dolaşımı mı? Adını Nasıl Koymalıyız? Bir Olgu Sunumu ve Literatür Taraması

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ABSTRACT

Traumatic acute subdural hematoma (TASH) is a life-threatening entity. 90% of cases undergo urgent surgery. Evacuation of the hematoma and decompression of the brain tissue are necessary. If the neurological status of the patient is good, conservative treatment for resolution of the hematoma is an option. In addition, spontaneous resolutions of TASHs have been reported, but their mechanism has not been investigated. An 85-year- old female was admitted to our emergency department with deterioration of mental status and vomiting after a traffic accident, diagnosed with bilateral frontoparietal TASH. Surprisingly, control computed tomography (CT) showed a remarkable reduction in the hematoma size and decrease in the midline shift preoperatively. There was an arachnoid injury at cranial CT and thoracolumbar magnetic resonance imaging (MRI) study was verified that blood in subarachnoid space at the lumbar region. Control CT revealed intraventricular hematoma 5 days after the initial cranial CT. The patient was discharged two weeks later without any neurological deficits. Rapid spontaneous evacuation of TASH into the intraventricular space via the thoracolumbar subarachnoid cerebrospinal fluid (CSF) circulation is presented and possible related mechanisms are discussed. TASH as an event of traumatic head injury or secondary to tearing of corticodural bridging vessels could occur incidentally. Arachnoid tears and the effect of CSF flow due to high pressure are responsible for redistribution and relocation of the TASH. Radiological investigation with thoracolumbar spine MRI and repeated cranial CT is necessary for rapid resolution.

Keywords: Subdural, hematoma, MRI, cerebrospinal fluid, trauma

ÖZ

Travmatik akut subdural hematom (TASH) yaşamı tehdit eden bir durumdur. Olguların %90'ı acil ameliyata alınıyor. Hematomun boşaltılması ve beyin dokusunun dekompresyonu gereklidir. Hastanın nörolojik durumu iyi ise hematomun çözülmesi için konservatif tedavi bir seçenektir. Ayrıca TASH'lerin kendiliğinden çözüldüğü de bildirilmiş ancak mekanizması araştırılmamıştır. Seksen beş yaşında kadın hasta trafik kazası sonrası bilinç durumunun bozulması ve kusma şikayetiyle acil servisimize başvurdu ve çift taraflı frontoparietal TASH tanısı aldı. Şaşırtıcı bir şekilde, ameliyat öncesi kontrol bilgisayarlı tomografi'si (BT) hematom boyutunda kayda değer bir azalma ve orta hat kaymasında azalma olduğunu gösterdi. Kraniyal BT'de araknoid yaralanma olduğu ve torakolomber manyetik rezonans görüntüleme (MRG) çalışmasıyla lomber bölgede subaraknoid boşlukta kan olduğu doğrulandı. Hastanın kontrol BT'sinde, ilk kraniyal BT'den 5 gün sonra intraventriküler hematom saptandı. Hasta iki hafta sonra herhangi bir nörolojik defisit olmaksızın taburcu edildi. TASH'ın torakolomber subaraknoid beyin omurilik sıvısı (BOS) dolaşımı yoluyla intraventriküler boşluğa hızlı spontan geçişi sunulmuş olup olası ilgili mekanizmalar tartışılmıştır. Travmatik kafa travması sonucu veya kortiko-dural köprü damarlarının yırtılmasına ikincil olarak TASH tesadüfen meydana gelebilir. Araknoid yırtıklar ve yüksek basınca bağlı BOS akışının etkisi, TASH'ın yeniden dağılımından ve yer değiştirmesinden sorumludur. Hızlı çözüm için torakolomber omurga MRG ve tekrarlanan kraniyal BT ile radyolojik inceleme gereklidir.

Anahtar Kelimeler: Sudural, hematom, MRG, beyin omurilik sıvısı, travma

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Introduction

Traumatic acute subdural hematoma (TASH) is a life-threatening entity. TASH is associated with a mortality rate of 40-60%. 90% of cases undergo urgent surgery, and evacuation of the hematoma and decompression of the brain are necessary (1,2). Neurological deterioration of the patient and a hematoma greater than 10 mm or midline shift greater than 5 mm on a computed tomography (CT) scan have been used for the proper indication and timing of surgical evacuation of hematoma (3). If neurological status of the patient is good, conservative treatment is an option (4). In addition, spontaneous resolutions of TASHs have been reported, but the mechanism has not been investigated (5).

We presented a case of rapid spontaneous evacuation of TASH into the subarachnoid space of the thoracolumbar spine and discussed possible related mechanisms.

Case Report

An 85-year-old female was admitted to our emergency department with deterioration of mental status and vomiting after a traffic accident. On admission, the patient was confused with a score of 13 on the Glasgow Coma score (GCS) in the emergency room. Cranial CT was performed initially and demonstrated bilateral frontoparietal TASH with a midline shift (Figure 1a). She had an acetyl salicylic acid use story. After preoperative preparation for decompressive surgery, control CT was planned to reveal considerable and accompanying pathologies with the hematoma. Surprisingly, control CT showed a remarkable reduction of the hematoma size and decrease of the midline shift (Figure 1b). Based on CT findings, we started medical treatment and decided to follow up the patient with CT scan. There was an arachnoid injury at cranial CT (Figure 1c), and thoracolumbar magnetic resonance imaging (MRI) study was planned to identify the hematoma location. Thoracolumbar MRI verified blood in the subarachnoid space at the lumbar region due to cerebrospinal fluid (CSF) circulation with microgravity (Figure 2a,b,c,d). After 5 days, the patient's control CT revealed an intraventricular hematoma. As mentioned in our hypothesis, the hematoma in the lumbar region was again in the ventricular space in the cranial region due to the effect of CSF circulation (Figure 3).

The patient's course was uneventful, and the last control CT scan revealed a reduction in the hematoma size (Figure 4a,b). The patient was discharged two weeks after admission with 15 GCS.

Discussion

TASH is a severe head injury with a high mortality rate. Surgery is usually the first treatment option in patients with poor neurological condition, severe midline shift, or great hematoma. Despite the surgical management guidelines of TASH, conservative treatment is a plausible option for patients in good condition. The true incidence of rapid resolution of TASH is underestimated because of urgent neurosurgical intervention with removal of subdural hematoma. Rapid and spontaneous resolution of TASH has been reported in the literature and expressed differently (5).

Two possible mechanisms have been proposed for rapid resolution of TASH: a) The dilution and redistribution of hematoma by the flow of CSF through the arachnoid tear, followed by retrograde flow into the subarachnoid space (3,6,7). b) The compression and redistribution of the hematoma can be induced by increased intracranial pressure (8). This hypothesis is supported by the finding of dispersal of blood in the cerebellar tentorium, interhemispheric subdural space, or spinal subdural space on follow-up MRI (3,8,9). Vital et al. (5) believed that the resolution of the hematomas is due to the effect of these two mechanisms. However, there is the rule of Lavoisier law "There is nothing to exist, and none can exist". According to Lavoisier fluid dynamics, relocation of the hematoma with CSF flow is the main reason for redistribution due to the adjacent arachnoid injury and the effect of arachnoid tear, as in our case. Legros et al. (10) emphasized fluid dynamics, microgravity, and body forces. There are driving forces for flow on fluids. We believe that there are forces on CSF flow due to microgravity. In the present case, the subdural hematoma relocalize through the thoracolumbar subarachnoid space due to microgravity and CSF flow.

The majority of reported cases of rapid spontaneous resolution of TASH occurred in elderly patients or infants. Vital et al. (5) reviewed the literature and listed the patients. The mean age was 36 years (range; 8 months-92 years). Our patient was an 85-year-old female with TASH. In our opinion, there is not any significant relation between the age and spontaneous resolution.

Patients with spontaneous resolution of TASH were admitted to the hospital with low back pain after three days or more. All patients underwent lumbar MRI due to low back pain. Spinal subdural hematoma identified incidentally (5,8,11,12). In spite of the literature, 2 h after initial CT, there was thoracolumbar subdural hematoma without low

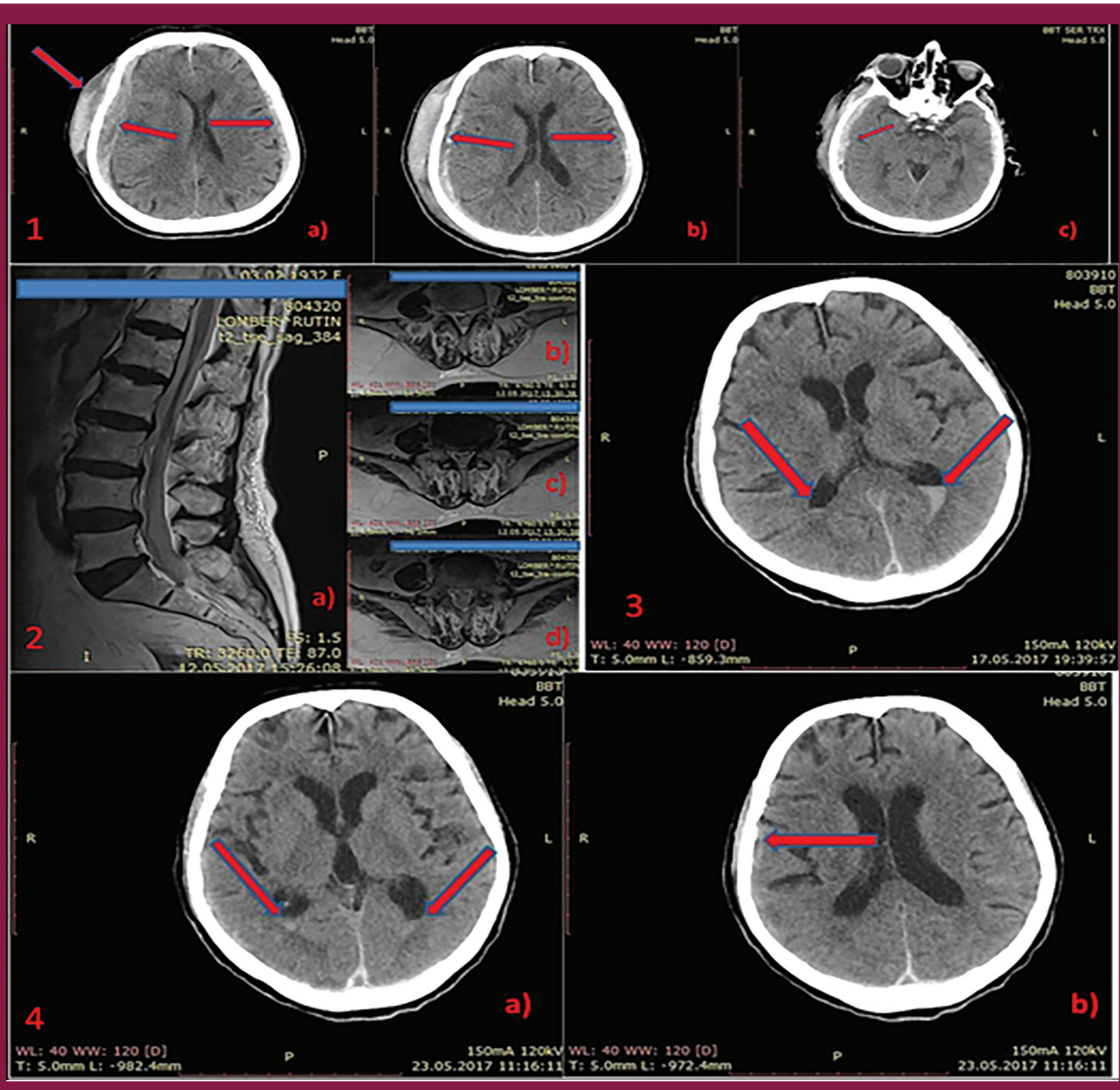

Figure 1a. Cranial CT was initially performed and demonstrated bilateral frontoparietal TASH with a midline shift and cephal hematoma. (red arrows)
CT: Computed tomography, TASH: Traumatic acute subdural hematoma
Figure 1b. Control CT showed a remarkable reduction in the hematoma size and decrease in the midline shift (red arrow)
CT: Computed tomography
Figure 1c. An arachnoid injury on cranial CT is shown with a red arrow
CT: Computed tomography
Figure 2. Thoracolumbar MRI verified blood in the subarachnoid space at the lumbar region (a) sagittal and (b-d) axial views
MRI: Magnetic resonance imaging
Figure 3. Bilateral intraventricular hemorrhage was seen in the control CT at the 5th days in the intensive care unit (red arrows)
CT: Computed tomography
Figure 4. The last control CT scan revealed a reduction in the hematoma size. a) Intraventricular b) subdural
CT: Computed tomography

back pain and neurological improvement with subdural hematoma resolution in the presented case. In our opinion, timing and back pain are not mandatory for showing the redistribution and relocation of subdural hematoma.

Radiological studies were limited to cranial CT or MRI. There was not any investigated anatomic localization after spontaneous resolution of the hematoma radiologically in the relevant literature. In the presented case, the subdural hematoma was shown as resolute on cranial CT; however, there was hematoma in the subarachnoid space of the thoracolumbar spine due to the CSF flow and microgravity. In the literature, all cases underwent thoracolumbar MRI due to low back pain and there was a time interval. In our opinion, all patients with rapid subdural hematoma resolution without neurological deterioration should undergo radiological evaluation for hematoma relocalization.

Surprisingly, we experienced an unusual case whose neurological condition improved because of rapid spontaneous resolution of TASH under conservative treatment. In this article, we wanted to emphasize for the first time that, unlike the cases published in the more recent literature, CSF circulation carries bleeding from the spinal region into the ventricles. In general, subdural hemorrhages are always evaluated using brain CT. Spinal MRI was not performed. Brain CT is not performed when bleeding in the spinal area is also absorbed or disappears.

However, it is very difficult to distinguish which patient should be treated surgically or conservatively. The neurosurgeon should make this critical decision according to the neurological examination and premorbid state of the patients.

Conclusion

TASH as an event of traumatic head injury or secondary to tearing of corticodural bridging vessels could have occurred incidentally. We wanted to remind the readers of the forgotten importance of post-traumatic arachnoid tears in this case. Arachnoid tears and the effect of CSF flow due to high pressure are responsible for redistribution and relocation of the TASH. Radiological investigation with thoracolumbar spine MRI and repeated cranial CT is necessary for rapid resolution.

Ethics

Informed Consent: Before treatment, consent was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: A.G., A.Ş., Design: A.Ş., Analysis or Interpretation: A.Ş., Literature Search: A.G., C.A., Writing: C.A.

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

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