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Bilimsel araştırma alanındaki gelişmelere hızla katkıda bulunmak ve artan ilgiye layık bir biçimde karşılık vermek amacıyla, makale değerlendirme süreçlerini titizlikle ve hızla yürütmekteyiz. Amacımız, kabul edilen çalışmaları en kısa sürede siz değerli araştırmacıların ve bilim dünyasının dikkatine sunmaktır. Bilimsel üretkenliği ve akademik paylaşıma verdiğimiz önemin bir göstergesi olarak, dergimize değerli çalışmalarını göndererek bu sürece katkı sağlayan tüm yazarlarımıza ve bu çalışmaları ilgiyle takip eden siz okuyucularımıza en içten teşekkürlerimizi sunarız.

Bu sayımızda, tıp alanında farklı uzmanlıkları ve disiplinleri kapsayan toplam 19 makaleyi sizlerle buluşturuyoruz. Bu çalışmaların 13'ü orijinal araştırma makaleleri olup, literatüre önemli katkılar sunacak niteliktedir. Her bir makalenin, bilimsel gelişim ve toplumsal fayda sağlamada önemli bir rol oynayacağına inanıyoruz.

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Saygılarımla,

Doç. Dr. Abdulkerim YILDIZ
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From the Editor

Dear Scientists and Esteemed Readers,

We are thrilled to present the latest issue of Hitit Medical Journal to you. Our journal, having earned trust and recognition on a national scale, has now begun to establish its rightful place in the international scientific community. By being indexed in prestigious databases, it has achieved global accessibility. This development has brought immense joy to our editorial team and provided great motivation for our future publishing endeavors.

In order to promptly contribute to advancements in scientific research and respond to the growing interest in our journal, we are meticulously and swiftly conducting the manuscript review processes. Our goal is to present the accepted papers to you, esteemed researchers, and the scientific community as quickly as possible. As a testament to our commitment to scientific productivity and academic sharing, we extend our sincere thanks to all the authors who have chosen to submit their valuable works to our journal, and to all the readers who follow these contributions with great interest.

In this issue, we present to you a total of 19 articles covering various specialties and disciplines in the field of medicine. Thirteen of these are original research articles, each of which holds the potential to make significant contributions to the literature. We believe that each of these papers will play a key role in advancing scientific knowledge and promoting societal benefit.

We are delighted to accompany you on your academic journey with our journal. We wish you an enjoyable, productive, and inspiring reading experience.

Respectfully,

Doç. Dr. Abdulkerim YILDIZ
On behalf of the HMJ Editorial Board

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Decreased Autophagic Activity in Triple Negative Breast Cancer Cells upon Hydroxychloroquine and Thymoquinone Combination Treatment

Triple Negatif Meme Kanseri Hücrelerinde Hidroksiklorokin ve Timokinon Kombinasyon Uygulaması Sonrası Otofajik Aktivitenin Azalması

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Decreased Autophagic Activity in Triple Negative Breast Cancer Cells upon Hydroxychloroquine and Thymoquinone Combination Treatment

ABSTRACT

Objective: Autophagy plays a significant role in breast cancer tumorigenesis, including triple-negative breast cancer. Research indicates that hydroxychloroquine and thymoquinone modulate autophagy, potentially suppressing its activity. However, their combined effects on autophagy in triple-negative breast cancer remain unexplored. In this study, we investigated the potential anti-cancer and autophagy-modulating effects of hydroxychloroquine-thymoquinone combination on triple-negative breast cancer cells in vitro.

Material and Method: The viability of MDA-MB-231 cells was evaluated after treatment with hydroxychloroquine (10-210 µM) and thymoquinone (5-45 µM) for 24 and 48 hours using the WST-1 assay. Combination effects were analyzed using the Chou-Talalay method with CompuSyn (v.10). Autophagic vesicles were visualized using an Autophagy Detection Kit and fluorescence microscopy to investigate their role in the decrease in cell viability. Statistical analysis was performed with GraphPad Prism (v.8.3.0).

Results: At both 24- and 48-hour intervals post-treatment, a significant decrease in viability was observed for both hydroxychloroquine and thymoquinone treatments individually *($p<0.0001$)*. The combination of these drugs revealed pronounced synergistic effects at 24 hours, whereas antagonistic effects were noted at 48 hours (combination index>1). At 24 hours, favorable dose reduction effects were evident (dose reduction index >1), while the 48-hour results showed an unfavorable reduction (dose reduction index<1). Consequently, the 24-hour synergistic effects resulted in a reduction in autophagic vesicles *($p<0.0001$)*.

Conclusion: This study revealed, for the first time, a time-dependent decrease in triple-negative breast cancer cell viability via the autophagy mechanism induced by hydroxychloroquine and thymoquinone, highlighting their novel implications for triple-negative breast cancer treatment and autophagy modulation.

Keywords: Autophagy, breast cancer, drug-combination, hydroxychloroquine, thymoquinone.

ÖZET

Amaç: Otofaji, triple negatif meme kanseri alt tipi dahil olmak üzere meme kanserinde tümör oluşumunda etkili bir mekanizmadır. Araştırmalar, hidroksiklorokin ve timokinon'un otofajiyi düzenleyerek aktivitesini potansiyel olarak baskıladığını göstermektedir. Ancak, bu maddelerin kombine uygulanmasının triple negatif meme kanserinde otofaji üzerindeki etkileri henüz aydınlatılmamıştır. Bu çalışma, hidroksiklorokin ve timokinon kombinasyonunun triple negatif meme kanseri hücrelerinde hücrelerinde antikanser ve otofajik etkilerini in vitro olarak incelemeyi hedeflemektedir.

Gereç ve Yöntem: Hidroksiklorokin (10-210 µM) ve timokinon (5-45 µM)'nun 24 ve 48 saat boyunca MDA-MB-231 hücrelerine uygulanması sonucu hücrelerin canlılığı WST-1 testi ile değerlendirildi. Kombinasyonlarının etkileri, CompuSyn (v.10) ile kombinasyon indeksi ve doz azaltma indeksi hesaplanarak Chou-Talalay yöntemiyle analiz edildi. Hücre canlılığının azalmasındaki otofaji etkisini gözlemlemek adına, otofajik veziküllerin tanımlanması ve görüntülenmesi için "Autophagy Detection Kit" ve floresan mikroskobu kullanıldı. İstatistiksel analizler, GraphPad Prism (v.8.3.0) kullanılarak gerçekleştirildi.

Bulgular: Hidroksiklorokin ve timokinon'un 24 ve 48 saatlik uygulamaları sonucu hücre canlılığında anlamlı bir azalma gözlemlendi *($p<0.0001$)*. Kombinasyon uygulamaları sonucu sinerjistik etkileri 24 saatte belirgin olarak görülürken, 48 saat uygulanmaları sonucu ise antagonistik etkiler elde edildi (kombinasyon indeksi>1). Doz azaltmada olumlu etkiler 24 saatte belirgin iken (doz azaltma indeksi >1), 48 saatte tam tersi etkiler elde edildi (doz azaltma indeksi<1). Sonuç olarak, kombinasyonun 24 saatlik uygulamasıyla karşılaşılan sinerjistik etkilerin otofajik veziküllerı azalttığı gösterildi *($p<0.0001$)*.

Sonuç: Bu çalışma, hidroksiklorokin ve timokinon tarafından indüklenen otofaji mekanizması aracılığıyla triple negatif meme kanseri hücrelerinde zamanla bağımlı canlılık azalmasını ilk kez ortaya koymuştur. Bu kombinasyon ileriki çalışmalarla birlikte triple negatif meme kanseri tedavisi ve otofaji modülasyonunda etkin rol oynama potansiyeli taşımaktadır.

Anahtar Sözcükler: Hidroksiklorokin, ilaç kombinasyonu, meme kanseri, otofaji, timokinon.

Introduction

Triple-negative breast cancer (TNBC), accounting for 15–20% of newly diagnosed breast cancers (BCs), uniquely lacks targeted treatment compared to other BC subtypes. It is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2 (HER2) expression, and represents a particularly aggressive form of BC. This highly metastatic and heterogeneous disease demonstrates a notably poorer prognosis and relapse rates. Despite considerable research efforts to address TNBC, therapeutic interventions remain insufficient. Thus, there is a critical necessity for the development of innovative approaches. Advancements in comprehending its biological mechanisms, and drug development have facilitated the integration of targeted therapeutic approaches which potentially revolutionize the therapeutic strategies of TNBC (1,2).

Autophagy is a cellular degradation process that involves the breakdown and recycling of long-lived proteins and organelles through lysosomal activity. Autophagy plays a crucial role in both normal physiology and tumor biology. It serves as a tumor suppressor by preventing the accumulation of genetic defects that could lead to tumor formation. However, autophagy can also promote tumor progression, particularly in aggressive cancers with high metabolic demands. In such cases, autophagy provides energy to cancer cells by recycling cellular components as an alternative metabolic pathway in nutrient-deprived and hypoxic environments. Like in other cancer types, autophagy displays a wide-ranging influence in BC, potentially acting as both a promoter and inhibitor of tumor growth at different stages of tumorigenesis (3,4). It functions as both a promoter and inhibitor of metastasis in the BC progression. The role of autophagy in BC presents a challenge for effective therapy, as it can lead to drug and radiotherapy resistance. It promotes tumor stemness, and inhibits apoptosis, contributing to carcinogenesis (5). Autophagy plays a role in maintaining BC stem cells in TNBC through the Epidermal growth factor receptor (EGFR)/ Signal transducer and activator of transcription 3 (STAT3), Transforming growth factor beta (TGFβ)/Sma and Mad related protein (SMAD) and Interleukin-6 (IL6)/ Signal Transducer and Activator of Transcription 3 (STAT3) signaling pathways (3). Autophagy also interacts with tumor microenvironment components like macrophages and can be modulated by anti-tumor compounds like parthenolide and honokiol. Its consideration in BC therapy is essential due to its multifaceted nature, dual pro-survival and pro-death functions, and its crosstalk with critical molecular pathways such as apoptosis (5,6).

Hydroxychloroquine (HCQ) is a compound that is used in the treatment of malaria, lupus erythematosus and rheumatoid arthritis. Recent research supports using HCQ as an adjuvant therapy to enhance cancer treatment effectiveness and mitigate drug resistance. This is attributed to HCQ's ability to inhibit lysosomal acidification and impede autophagy (7). HCQ functions in the later stages of autophagy by elevating the pH in lysosomes. This elevation prevents the fusion between autophagosomes and lysosomes, consequently hindering the degradation of proteins within lysosomes (8). There are numerous phase I and phase II clinical trials investigating the use of HCQ in treating patients with diverse cancer types, including BC. Aggressive tumors such as TNBC exhibit elevated levels of autophagy, which aids in tolerating cellular stress encountered during the metastatic process (9). Elucidating HCQ's effects as an autophagy inhibitor is crucial for addressing treatment challenges in these cancers.

Thymoquinone (TQ) is the most abundant natural bioactive compound found in Nigella sativa, known for its anti-cancer, anti-inflammatory and antioxidant effects (10,11). It has also gained attention for its potential in regulating autophagy. TQ-induced autophagic cell death can either inhibit or induce autophagy, depending on the specific cellular context. Studies have demonstrated that TQ induces autophagic cell death in renal carcinoma, BC and colon cancer (12). In TNBC cell line MDA-MB-231, TQ treatment significantly inhibited cell proliferation, migration, and autophagic activity by suppressing the expression of microtubule associated protein 1 light chain 3 α (LC3, also referred to as MAP1LC3A) and Beclin-1, suggesting its potential as a candidate for controlling autophagic activity in TNBC (13). Conversely, in cells like glioblastoma multiforme, which utilize autophagy as a survival mechanism,

TQ promotes cell death by inhibiting autophagy. It has been shown to inhibit autophagy in glioblastoma cells by disrupting the lysosomal membrane, and inducing cathepsin translocation, leading to caspase-independent apoptosis (11). While the understanding of the relationship between TQ and autophagy mechanism is still limited, studies suggest its ability to modulate autophagy pathways in cancer.

The effects of HCQ and TQ have been studied individually in various cancers both in vitro and in vivo. However, the combined effects of these two compounds on autophagy in cancer have not been previously reported. Therefore, the current study aims to investigate the combined anticancer and autophagy effects of TQ and HCQ on the aggressive BC subtype, TNBC, in vitro.

Material and Methods

Cell Culture

The MDA-MB-231 TNBC cell line was obtained from the American Type Culture Collection (ATCC) and provided by the Proteomics Laboratory of Kocaeli University. Dulbecco's modified Eagle's medium (DMEM; Sigma-Aldrich, USA) supplemented with high glucose and 10% fetal bovine serum (FBS, Gibco, Thermo Fisher Scientific, USA), as well as penicillin (100 U/mL) and streptomycin (100 µg/mL) (Gibco, Thermo Fisher Scientific, USA), were used to culture MDA-MB-231 cells. The cells were maintained in a humidified incubator at 37°C with 5% CO_2 (Thermo Fisher Scientific, USA). Since a commercially available cell line was used, ethical approval was not required.

Preparation of HCQ and TQ

The stock solutions of HCQ (TRC, Canada) and TQ (Glentham Life Science, United Kingdom) were prepared in water and dimethyl sulfoxide (DMSO) (Sigma-Aldrich, USA) at concentrations of 5000 µM and 600 µM, respectively. Next, dilutions were prepared to achieve the desired concentrations of HCQ (10, 30, 60, 90, 120, 150, 180, 210 µM) and TQ (5, 15, 25, 35, 45 µM).

WST-1 Assay

To assess the effects of HCQ and TQ on the viability of MDA-MB-231 cells, WST-1 assay (Roche Applied Science, Indianapolis, IN, USA) was employed. Initially, $1x10^4$ cells in 100 µl were seeded into the wells of a 96-well plate. After 24 hours of incubation at 37°C, the adherent cells were treated with drugs prepared at the designated concentrations for 24 and 48 hours. Subsequently, 10 µL of WST-1 reagent (Roche Applied Science, Indianapolis, IN, USA) was added to each well, and incubated for 2 hours at 37°C in darkness. Cell viability was then determined at a wavelength of 450 nm using a microplate reader, and viability percentages were calculated. The experiment was carried out with three replicates.

Combination of HCQ and TQ

In drug combination trials, the combination effect was examined for doses demonstrating viability percentages within the range of 60-70%, wherein the doses were found not to exert a significant impact on viability, as assessed by the WST assay. For the 24-hour period, we selected doses of 150, 180, and 210 µM HCQ combined with 15 and 25 µM TQ at 37°C. For the 48-hour period, doses of 10 and 30 µM HCQ combined with 15 and 25 µM TQ were applied to the cells at 37°C. Subsequently, the impact of these combinations on cell viability was determined using the WST-1 assay protocol, as provided above. Then, we employed the Chou-Talalay method to analyze the synergistic effects of HCQ and TQ and calculated the combination index (CI) using CompuSyn v.10 (14). Based on this assessment, a CI value below 1 signified synergism, a CI value of 1 suggested additivity, and a CI value exceeding 1 indicated antagonism. We also calculated dose reduction index (DRI) using the CompuSyn software. DRI values were divided into three categories: DRI<1 indicated an unfavorable reduction in dose, DRI=1 indicated no reduction in dose, and DRI>1 indicated a favorable reduction in dose.

Detection and Monitoring of Autophagy

Autophagy Detection Kit (ab139484, Abcam) was used to detect in vitro development of autophagic vesicle upon HCQ and TQ administration. According to the kit protocol, trypsinized cells were washed with 1x Assay Buffer. A staining solution was then prepared using 1:1000 Green Detection Reagent, 1:1000 Hoechst nuclear stain, and 5% FBS in this buffer, and cells were incubated with this solution for 30 minutes for staining at 37°C. Following fixation with 4% formaldehyde for 20 minutes at room temperature, autophagic vesicles were visualized

using a fluorescence microscope (Olympus, Tokyo, Japan). Finally, vesicles in three randomly selected fields were counted and statistically compared between groups.

Statistical Analysis

Statistical analysis was conducted using GraphPad Prism software (version 8.3.0), with data presented as mean ± standard deviation from three independently replicated experiments. Multiple comparisons were assessed through two-way analysis of variance (ANOVA) followed by Tukey's test. Moreover, CompuSyn (version 1.0) software was utilized to investigate the confidence intervals of the CI of HCQ combined with TQ. One-way ANOVA was employed to compare the percentages of autophagic vesicles among groups.

Results

Effect of HCQ and TQ on MDA-MB-231 Cell Viability

The cytotoxic effects of HCQ and TQ on MDA-MB-231 cells were assessed to determine the appropriate concentrations and durations for subsequent combination studies. The findings demonstrated that both HCQ and TQ reduced cell viability in a dose- and time-dependent manner. At 24- and 48-hours following drug application, a statistically significant decrease in viability compared to the negative control was observed from the first dose onwards *($p<0.0001$)*. Following the 24-hour application period, the viability of MDA-MB-231 cells treated with HCQ was 68.2%, 67.4% and 58.4% at doses of 150 µM, 180 µM and 210 µM, respectively. On the other hand, the viability of cells treated with TQ was 69.6%, 57% and 55.3% at doses of 15 µM, 25 µM and 35 µM, respectively. After 48 hours of treatment, MDA-MB-231 cell viability was 69.2% and 63.4% with HCQ doses of 10 µM and 30 µM, respectively. Additionally, TQ-treated cells exhibited viabilities of 65.3% and 56.2% at 15 µM and 25 µM, respectively (Figure I).

Time-dependent Effects of HCQ and TQ Combination on Cell Viability

The findings obtained from individual drug treatments led to the determination of combination doses for the subsequent combination studies. Specifically, doses of 15 and 25 µM for TQ and 150 µM, 180 µM, and 210 µM for HCQ were selected for the 24-hour treatment period, while doses of 15 and 25 µM for TQ and 10 µM and 30 µM for HCQ were identified for the 48-hour treatment period. After analysis of the combination results for 24 hours, a significant reduction in the viability of MDA-MB-231 cells was observed ($p<0.0001$), with viability decreasing to as low as 30%. Conversely, data obtained for the 48-hour period indicated an increase in viability with combination doses ($p<0.0001$) (Figure II). Typically, viability increase is observed within the range of 80%; however, the combination of 30 µM HCQ + 25 µM TQ reached 94.6%.

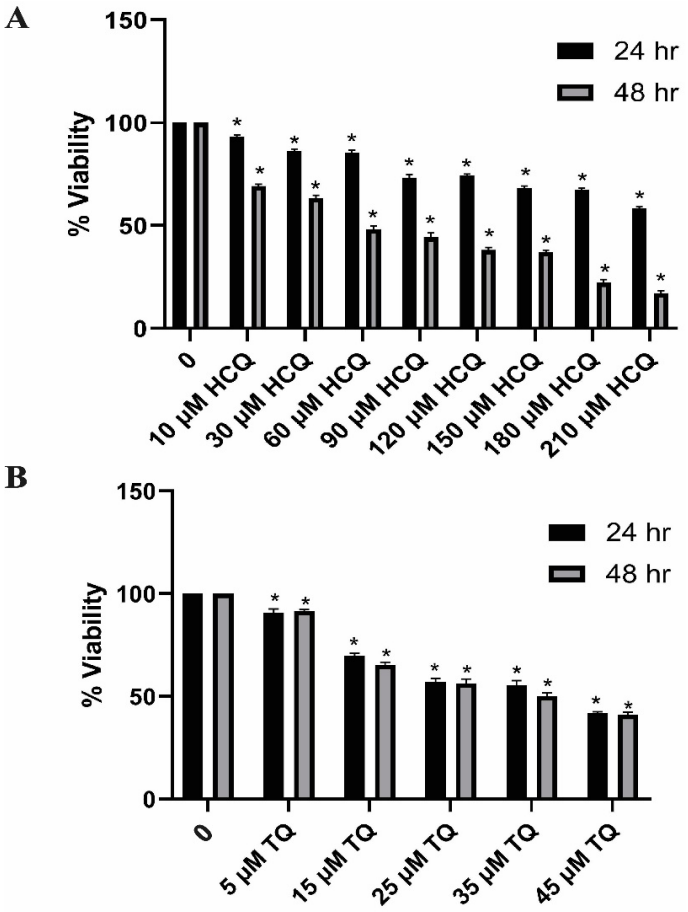

Figure I: Viability of MDA-MB-231 cells following administration of varying doses of HCQ (A) and TQ (B) at 24 and 48 hours. Each data point represents the mean of three independent experiments, and error bars indicate the standard deviation (*: $p<0.0001$).

Analysis of Synergistic Effects of HCQ and TQ

The Chou-Talalay combination index (CI) method, facilitated by Compusyn software, was employed to explore potential synergistic effects of HCQ and TQ. The results obtained for 24 hours indicated that the combination application of HCQ (150, 180, and 210

μM) with 15 μM and 25 μM TQ exhibited a synergistic effect (CI<1), except for the combination dose of 25 μM TQ + 150 μM HCQ (CI=1), which showed an additive effect. However, the results obtained for 48 hours of application showed that all combinations of TQ and HCQ exhibited an antagonistic effect (CI>1). CI data were summarized in Table I.

Table I: CI values of TQ and HCQ combinations applied to MDA-MB-231 cells at 24 and 48 hours

Combinations	Time (hr)			
	24 hr		48 hr	
	15 μM TQ	25 μM TQ	15 μM TQ	25 μM TQ
10 μM HCQ			7.101	7.675
30 μM HCQ			8.879	2.053
150 μM HCQ	0.754	1.047		
180 μM HCQ	0.589	0.822		
210 μM HCQ	0.764	0.826		

HCQ: Hydroxychloroquine, TQ: Thymoquinone

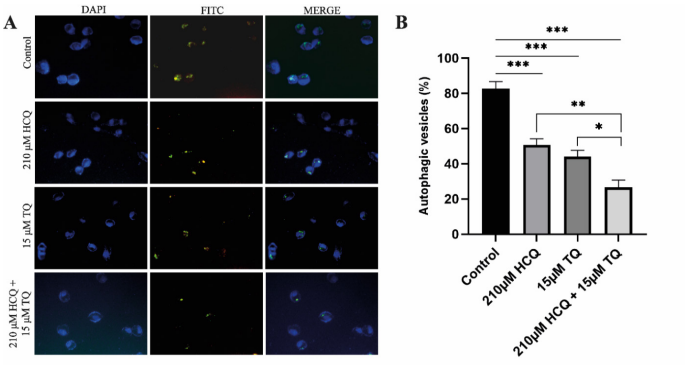

Figure II: The effects of HCQ and TQ combination on MDA-MB-231 cell viability. Each data point represents the mean of three independent experiments, and error bars indicate the standard deviation (*: *p<0.0001*).

On the other hand, our DRI results indicated that for all combinations applied for 24 hours, the DRI values of HCQ and TQ were greater than 1. Remarkably, in the combination of 15 μM TQ + 180 μM HCQ, the DRI values for TQ and HCQ were 4.625 and 2.685, respectively. Additionally, in the administration of the 15 μM TQ + 150 μM HCQ combination, DRI values of 3.025 and 2.359 were obtained for TQ and HCQ, respectively (Table II). This suggests that these combinations allow for a favorable reduction in dose compared to when each drug is administered individually. Contrary to these findings, DRI values less than 1 were obtained for nearly all doses applied for 48 hours (except for 25 μM TQ + 30 μM HCQ combination), indicating an unfavorable reduction in dose (Table III). Thus, the efficacy of HCQ and TQ combination decreased with prolonged duration.

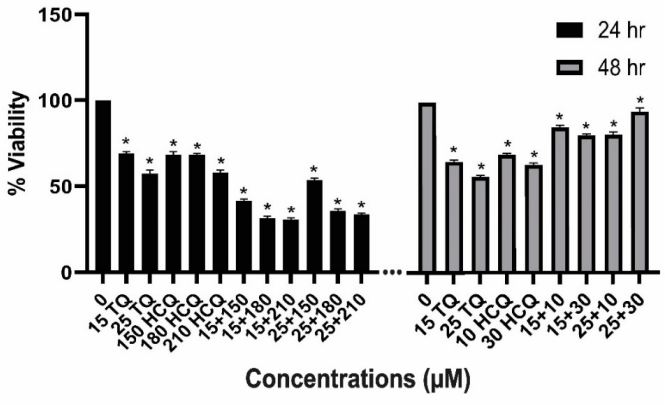

Figure III: Autophagy patterns of MDA-MB-231 cells under fluorescence microscopy (40X) following treatment with HCQ, TQ, and their combination for 24 hours. A. Nuclear morphology was assessed using DAPI staining (blue), while autophagic vacuoles were assessed using Green Detection Reagent (green). B. Comparison of autophagic vesicle percentages among groups (***p<0,0001*, **p<0,0005*, **p<0,005*).

Decrease in Cell Viability Attributed to Autophagy under Synergistic Effect

Autophagy patterns were observed to elucidate whether autophagy underlies the decrease in cell viability observed with the synergistic effect of HCQ and TQ combination treatment in MDA-MB-231 cells after 24 hours of application. Nuclear morphology was examined through DAPI staining, and it was obtained that the nuclei of BC cells remained intact following the application of TQ, HCQ, and their combination. The autophagy assay conducted with the combination of doses that most significantly reduced cell viability (210 μM HCQ + 15 μM TQ) showed a prominent presence of green autophagic vesicles in nearly every cell in the control group. While a decrease in vesicle numbers compared to the control was observed with the individual applications of HCQ and TQ, a notably lower abundance of autophagic vesicles was observed with their combined application (Figure IIIA). For each treated group, a statistically significant reduction in autophagic vesicle percentage was observed compared to the untreated control group (*p<0.0001*). Additionally, a statistically significant decrease was obtained in the HCQ-TQ combination group compared to individual treatment of HCQ (*p<0.05*), and TQ (*p<0.05*) (Figure IIIB). The mean

percentages of autophagic vesicles for the control, 210 µM HCQ, 15 µM TQ, and combination groups were 82.7, 50.7, 44, and 26.7, respectively.

Table II: DRI values of TQ and HCQ combinations applied to MDA-MB-231 cells at 24 hours

	24 hr		
	Combinations	**15 µM TQ**	**25 µM TQ**
150 µM HCQ	DRI TQ	3.025	1.674
	DRI HCQ	2.359	2.224
180 µM HCQ	DRI TQ	4.625	2.430
	DRI HCQ	2.685	2.436
210 µM HCQ	DRI TQ	2.905	2.653
	DRI HCQ	2.380	2.227

HCQ: Hydroxychloroquine, TQ: Thymoquinone

Discussion

Recent research has underscored the roles of TQ and HCQ in oncology, attributed to their capacity to modulate carcinogenesis and autophagy (12,15). While HCQ is an FDA-approved autophagy inhibitor (15), studies investigating the effects of TQ on autophagy are still ongoing. In the clinical implementation, the dosage and timing of administration are essential factors that influence the emergence of side effects (15). Prolonged exposure to cumulative doses of HCQ has been linked with adverse effects such as retinal toxicity, cardiomyopathy and hypoglycemia (16). Identifying the combined effects of herbal products and conventional drugs is crucial, as any enhancements resulting from this synergy can be harnessed for the disease treatment. In complex conditions like cancer, exploring positive synergies between natural compounds and drugs is essential for optimizing outcomes such as enhancement in therapeutic benefits for patients, or minimizing adverse effects (17). Based on this information, in the current study, we investigated the impact of the HCQ and TQ combination on the viability and autophagy patterns of TNBC cells in vitro.

Firstly, we investigated the effects of HCQ and TQ individually on cell viability following 24- and 48-hour treatments, which informed the selection of durations and doses for subsequent combination studies. Our results demonstrated a decrease in cell viability at both time points, which prompts to examine combination effects within these times. Consistent with existing literature, studies have shown that HCQ reduces viability in various cancer cell lines, including MDA-MB-231 cells (18), as well as in leukemia (19), ovarian cancer, gastric cancer, and other BC subtypes (15,20). Similarly, viability studies on TQ align with our findings, indicating a reduction in cell viability for several cancer types (10).

Table III: DRI values of TQ and HCQ combinations applied to MDA-MB-231 cells at 48 hours

	48 hr		
	Combinations	**15 µM TQ**	**25 µM TQ**
10 µM HCQ	DRI TQ	0.221	0.178
	DRI HCQ	0.387	0.483
30 µM HCQ	DRI TQ	0.325	1.385
	DRI HCQ	0.172	0.751

HCQ: Hydroxychloroquine, TQ: Thymoquinone

During the determination of combination doses, we selected concentrations potent enough to significantly affect cell viability while still allowing some cells to survive. Significant decreases in viability were observed compared to the control in 24 hours co-administration of these doses, with a subsequent significant increase in viability observed after 48 hours. The time-dependent effects of the combination imply potential synergistic and antagonistic actions of HCQ and TQ. These effects were verified using Chou-Talalay CI analysis. Overall, when HCQ and TQ were co-administered, they decreased viability with a synergistic effect in 24 hours (except only for 25 µM TQ + 150 µM HCQ), while they increased viability by working antagonistically in 48 hours. Changes in drug toxicity over time are a well-documented phenomenon in the literature, demonstrated in various subtypes of BC, including TNBC, as well as in other cancers (21–24). For instance, the significance of the time factor has been highlighted in the synergistic effects observed when tyrosine kinase inhibitors targeting the human epidermal growth factor receptors were combined with Doxorubicin in MCF-7 and MDA-MB-231 cells (24). The time-dependent differential effects of the combined drugs, HCQ and TQ, on cell viability observed in our study may be attributed to pharmacological mechanisms. One possible explanation is the dynamic interplay between the pharmacokinetics and pharmacodynamics of HCQ and TQ over time (25,26). At 24 hours post-administration,

the drugs may reach peak concentrations in the cellular microenvironment, leading to a maximal inhibitory effect on key cellular processes such as autophagy and proliferation. This synergistic action may result from the combined targeting of multiple pathways involved in cell survival and proliferation, thereby exerting a greater inhibitory effect on cell viability. However, as the duration of exposure increases to 48 hours, the pharmacokinetic profiles of HCQ and TQ may change, leading to altered drug concentrations and distribution within the cells. This temporal shift in drug exposure may result in the activation of compensatory cellular mechanisms, or the development of drug resistance, ultimately attenuating the inhibitory effects of the combination therapy (26,27). Individually, previous studies have supported the duration-dependent effects of both drugs, demonstrating the time-dependent cytotoxic effects of TQ on BC cells including MDA-MB-231 cell line, (28) and the time-varying inhibition of cholangiocarcinoma cells by HCQ (29). Overall, the time-dependent effects of combined HCQ and TQ therapy likely stem from a complex interplay of pharmacokinetic and pharmacodynamic factors, emphasizing the importance of considering temporal dynamics in drug response for the development of effective cancer treatment strategies.

Following the analysis of HCQ-TQ interaction effects, DRI values were calculated. The DRI analysis quantifies how much the combined dose of drugs in a synergistic combination can be reduced compared to the individual doses of each drug alone, while still achieving the same therapeutic effect. It helps optimize combination therapies by minimizing individual drug doses while maintaining efficacy (30). Specifically, the DRI values greater than 1 for all combinations applied for 24 hours indicate a favorable reduction in dose, suggesting a synergistic effect of the drugs in inhibiting cell viability within this time interval. This observation aligns with the notion of maximal inhibitory effects occurring at 24 hours, as discussed earlier. In the literature focusing on cancer research, DRI values have not been reported for HCQ, whereas some data exist for TQ. For instance, DRI values obtained with the combination of paclitaxel and TQ are similar to those in our study, primarily concentrating around 2. They have shown that TQ and paclitaxel which is an FDA-approved chemotherapy drug, significantly reduce each other's effective doses in MDA-MB-231 cells. The underlying mechanism for this phenomenon is attributed to the increased expression levels of Beclin-1, ATG-5, and ATG-7, which trigger autophagy (31). In other studies, these combinations have been shown to suppress BC cells by upregulating apoptosis through Caspases 12, 7, and 3, and also tumor suppressors such as BRCA1, p53 and p21 (32,33). In a study on colorectal cancer, different DRI values were observed as compared to our investigation regarding the synergistic co-administration of TQ and Imatinib. It has been demonstrated that TQ enhances the effectiveness of Imatinib through the regulation of uptake/efflux genes (34). Conversely, the DRI values which was obtained as less than 1 for nearly all doses applied for 48 hours. This indicates an unfavorable reduction in dose, reflecting a diminished efficacy of the combination therapy with prolonged duration, which aligns with the previously observed antagonistic effect. These findings confirm once more the significance of duration factor in the combination HCQ and TQ.

Based on the individual significant roles of HCQ and TQ in autophagy (7–9,11–13), one of the most plausible mechanisms by which co-administration of these exert their effects on cell viability is through autophagy. In line with this rationale, we evaluated whether the synergistic decline in cell viability observed within a 24 hours administration is mediated through the autophagy mechanism. As a result, we demonstrated that the combinative effect led to an increase in autophagy in TNBC cells. When given simultaneously, HCQ and TQ induced the autophagy mechanism to a greater extent compared to when administered separately. Beyond the cancer perspective, autophagy operates at basal levels in all cells and plays a vital role in maintaining cellular health by eliminating misfolded proteins, clearing damaged organelles like endoplasmic reticulum, peroxisomes and mitochondria, and eliminating intracellular pathogens. Additionally, under stress conditions, such as nutrient deprivation, autophagy facilitates the recycling of cellular resources to sustain cell survival. Moreover, autophagy is intricately involved in cellular differentiation and development

processes. Given its pivotal role in organismal homeostasis, dysregulation of autophagy contributes to the pathogenesis of various human diseases (35). Therefore, illustration of the combinative modulatory effects of HCQ and TQ on autophagy not only holds promise for TNBC treatment strategies but also warrants exploration in other diseases, underscoring its broader therapeutic potential.

This study provides valuable insights into the synergistic effects of HCQ and TQ on TNBC cells, but there are several limitations. The in vitro nature of the study restricts the findings to cellular models, and further validation in animal models or clinical trials is needed to confirm the therapeutic potential. Additionally, the long-term effects and safety of HCQ and TQ combinations have not been fully explored, particularly regarding potential adverse effects and optimal dosing strategies. The observed time-dependent effects underscore the need for further investigation into the pharmacokinetics and pharmacodynamics of these compounds. Future studies should focus on evaluating the combination therapy in vivo, exploring its effects in different cancer models, and investigating the detailed mechanisms underlying autophagy modulation by HCQ and TQ. Additionally, assessing the impact of this combination on other cancer cancers and patient populations could provide broader insights into its potential clinical applications.

Conclusion

Our study is the first to reveal the time-dependent synergistic and antagonistic effects of the HCQ and TQ combination on TNBC cells. This study also demonstrated, for the first time, the time-dependent reduction in cell viability in TNBC through the autophagy mechanism induced by these two drugs, highlighting their novel potential for modulating autophagy and providing new insights into TNBC treatment strategies. Our findings emphasize the critical importance of timing in the co-administration of HCQ and TQ, suggesting that careful consideration of treatment schedules is essential for maximizing therapeutic efficacy. Future research should focus on elucidating the specific mechanisms by which HCQ and TQ influence autophagy, both in vitro and in vivo. Additionally, understanding the transition point from synergistic to antagonistic effects and the underlying pharmacodynamic mechanisms will enhance our perspective of the time-dependent dynamics of this combination therapy. Given the aggressive nature and poor prognosis of TNBC, identifying the key targets and interactions of HCQ and TQ could significantly advance therapeutic strategies for this challenging cancer subtype.

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Deep Convolutional Neural Network Model for Automated Diagnosis of Schizophrenia Using EEG Signals

EEG Sinyallerini Kullanarak Şizofreninin Ayırıcı Tanısı için Derin Konvolüsyonel Sinir Ağı Modeli

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Deep Convolutional Neural Network Model for Automated Diagnosis of Schizophrenia Using EEG Signals

ABSTRACT

Objective: One of the serious mental disorders in which people interpret reality in an abnormal situation is schizophrenia. A combination of extremely disordered thoughts, delusions, and hallucinations occurs due to schizophrenia, and the person's daily functions are seriously impaired due to this disease. For general cognitive activity analysis, electroencephalography signals are widely used as a low-resolution diagnostic tool. This study aimed to diagnose schizophrenia using the transfer learning method by including the EEGs of 73 patients diagnosed with schizophrenia, and 67 patients from the healthy group.

Material and Method: In the first step of the study, digital electroencephalography signal data was converted into spectrograms to make them usable. In the classification phase, ResNet18, ResNet50 and EfficientNet models, which are FastAI, and Convolutional Neural Network (CNN) based deep learning models, were used.

Results: Despite the complexity of electroencephalography data, CNN-based models in the study were successful in capturing different aspects of neurophysiological activity. The best performance was obtained from the ResNet-50 model with an accuracy rate of 97%. Afterwards, the classification process was finalized with 95% ResNet-18, and 83% EfficientNet models, respectively.

Conclusion: It is thought that the classification performance of the result obtained in the application is promising and may be a guide for future studies.

Keywords: Artificial Intelligence, EEG, FastAI, Schizophrenia, transfer learning.

ÖZET

Amaç: İnsanların gerçekliği anormal bir durumda yorumladığı ciddi zihinsel bozukluklardan biri de şizofrenidir. Şizofreni nedeniyle aşırı derecede düzensiz düşünce, sanrı ve halüsinasyonların birleşimi ortaya çıkmakta ve bu hastalık nedeniyle kişinin günlük işlevleri ciddi şekilde bozulmaktadır. Genel bilişsel aktivite analizi için elektroensefalografi sinyalleri, düşük çözünürlüklü bir teşhis aracı olarak yaygın olarak kullanılmaktadır. Bu çalışmaya şizofreni tanısı almış 73 hasta ile sağlıklı grubuna ait 67 hastanın EEG'si dahil edilerek transfer öğrenme metodu ile şizofreni teşhisi gerçekleştirmek amaçlanmıştır.

Gereç ve Yöntem: Çalışmanın ilk adımında sayısal elektroensefalografi sinyal verilerini kullanılabilir hale getirmek amacıyla spektogramlara dönüştürme işlemi gerçekleştirilmiştir. Sınıflandırma aşamasında FastAI ile Convolutional Neural Network (CNN) tabanlı derin öğrenme modelleri olan ResNet18, ResNet50 ve EfficientNet modelleri kullanılmıştır.

Bulgular: Elektroensefalografi verilerinin karmaşıklığına rağmen çalışmada CNN tabanlı modeller, nörofizyolojik aktivitenin farklı yönlerini yakalamada başarılı olmuştur. En iyi performans %97 doğruluk oranı ile ResNet-50 modelinden elde edilmiştir. Sonrasında sırasıyla %95 ResNet-18 ve %83 EfficientNet modelleri ile sınıflandırma işlemi sonuçlandırılmıştır.

Sonuç: Uygulamada ulaşılan sonucun sınıflandırma performansının umut verici olduğu ve bundan sonraki yapılacak çalışmalar için yol gösterici nitelikte olabileceği düşünülmektedir.

Anahtar Sözcükler: EEG, FastAI, şizofreni, transfer öğrenme, yapay zekâ.

Introduction

Schizophrenia is a mental illness accompanied by disorders of perception, cognition, thought, behavior, and mood that affects approximately 1% of the world's population (1,2). Today, the diagnosis of schizophrenia is based solely on interviews, and observations of patient behavior by a trained psychiatrist. The diagnosis is made by subjective evaluations between different doctors, and/or centers (3). For this reason, the underlying organic causes (such as drug use that causes psychotic symptoms, brain tumours, susac syndrome, demyelinating diseases) may be missed. Omission of organic causes may lead to failure of the treatments given and progression of the underlying disease.

Since schizophrenia shares many clinical features with other psychiatric disorders, difficulties are encountered in the diagnosis phase. For this reason, biomarkers are sought to help diagnose and monitor schizophrenia. Biomarker evaluation is performed not only in the fields of genetics, morphology/anatomy, but also in the fields of functional imaging, perceptual physiology, and electrophysiology (4-9). In the diagnostic process, performing magnetic resonance imaging or biomaker studies in every patient presenting with schizophrenia symptoms increases the cost considerably. For all these reasons, it would be an appropriate approach to develop methods that are not used routinely but are easy to obtain in case of necessity, economically feasible but can also prevent subjective evaluation. EEG is the most appropriate study for this definition. EEG is an accessible, cheap, and easy-to-use technology. For this reason, EEG is frequently preferred and used in the differential diagnosis of psychiatric diseases (10).

In the literature, EEG studies have been conducted comparing patients diagnosed with schizophrenia based on anamnesis, and mental status examination with other patient groups, and controls. In general, an increase in non-specific abnormalities has been reported in patients with schizophrenia (11). Some studies have stated that EEG abnormalities, and paroxysmal arrhythmias may have a positive effect on prognosis in schizophrenia (12). Using a classification system similar to DSM-IV, Abrams, and Taylor showed that patients with schizophrenia had twice as many left-sided temporal EEG abnormalities as patients with affective disorders (13).

EEG waves may show waveform changes due to physiological artefacts such as blink artefacts, muscle artefacts, movement artefacts, pulse and respiration artefacts, which may adversely affect interpretation or cause misinterpretation. Although it is possible to eliminate environmental artefacts, it is often not possible to eliminate physiological artefacts. This limitations in traditional methods, and special results in EEG data lead to the need to use artificial intelligence, and deep learning methods. With the increasing emphasis on the role of artificial intelligence in medical diagnoses, analysis of EEG data offers significant hope for better understanding and treating psychiatric diseases. This study aims to identify EEG features that may be helpful in diagnosing schizophrenia. By examining the EEG records of schizophrenia patients, the data of the healthy, and control groups were tried to be distinguished using artificial intelligence methods. In the first step, EEG data was converted into spectrograms to make them usable. In the classification phase, Pytorch-based FastAI, and CNN-based ResNet18, ResNet50, and EfficientNet models were used. Despite the complexity of EEG data, CNN-based models have been successful in capturing different aspects of neurophysiological activity.

Material and Method

In the study, EGG data of patients who applied to Binali Yıldırım University Mengücek Gazi Education and Research Hospital Psychiatry Clinic were used. These EEG data, which were taken while the patients were under the follow-up of the psychiatrist for consultations requested from the Neurology Department to rule out organic pathologies, were collected retrospectively between January 1, 2022 and November 1, 2022. EEG data obtained from 73 patients diagnosed with schizophrenia, and 67 individuals from the healthy group constitute the main data source of the study. Local ethics committee approval was obtained on 13.10.2022, number 03/9, and the study was conducted in accordance with the ethical standards specified in the 1983 revision of the Declaration of Helsinki. EEG recordings were made with longitudinal montage on a Micromed branded SD plus 38-channel device

with a high transmittance of 70 hertz, and a low transmittance of 0.53 hertz. EEG recordings were taken from FP1, FP2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, A1, A2 channels. The naming, and locations of these channels are determined according to the international 10-20 system. Figure I shows the placement of electrodes according to the 10-20 system (14).

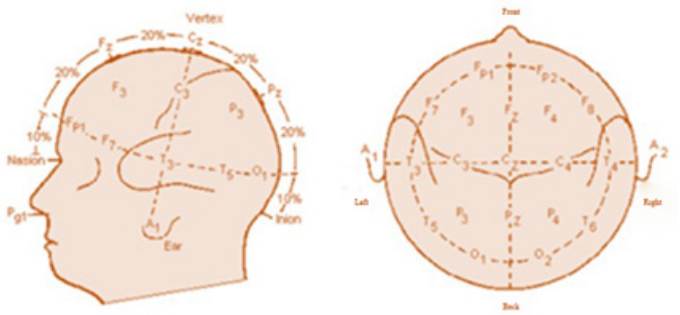

Figure I International 10-20 electrode placement system

Method

The study aimed to detect schizophrenia, and healthy individuals with deep learning methods using EEG data of schizophrenia patients. EEG is a method used to measure brain activity and was used in this study to identify potential differences between healthy, and schizophrenic individuals. The study process flow consists of data collection, data pre-processing, model selection, and model training stages. The process flow of the study is given in Figure II.

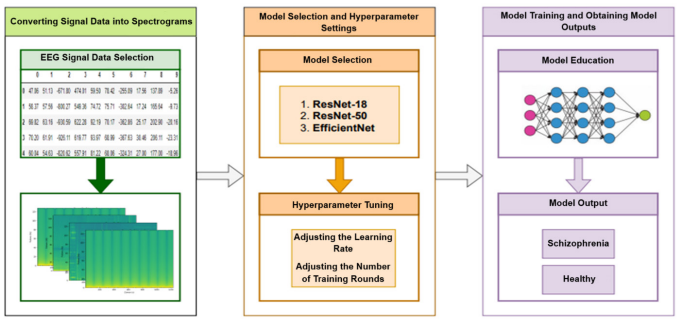

Figure II Working Flow Process

The first step of the study aims to make digital EEG signals more meaningful, and processable. At this stage, the signal data is converted into spectrograms. Spectrograms are matrices that visually express the frequency components of the EEG signal over time (15). These matrices are represented by colored graphs that represent time on the horizontal axis, and frequency on the vertical axis. This approach helps us better understand the complexity of EEG data, and track changes in activity at specific frequencies. Figure III shows an example of a spectrogram of the transformed healthy, and schizophrenia groups.

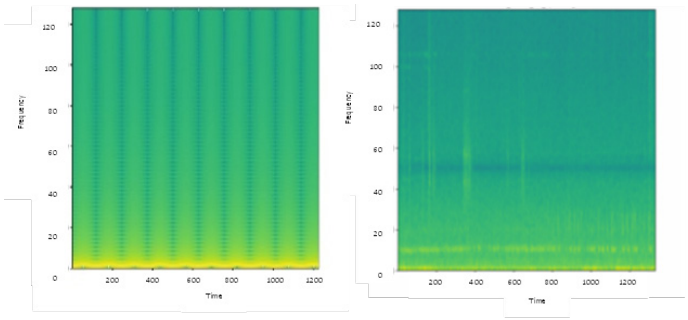

Figure III (a) Transformed spectrogram example for the schizophrenia group (b) Transformed spectrogram example for the healthy group

In the second step, model selection, and hyperparameter settings were carried out by adopting the transfer learning approach. The principle of transfer learning is based on the fact that the general properties, and patterns of the models have previously been examined in a large dataset (16). The convolutional neural network (CNN) is nowadays developing as a reliable method for image classification. Many models in CNN (such as ResNet, DenseNet, EfficientNet, Inception-v3 and others) are used for image classification. CNN can improve its performance by adding layers. However, adding layers can lead to increased layer complexity and loss of gradient. Since this phase greatly affects the success of the study, several different deep network models were evaluated. Depending on the complexity, and nature of the data, ResNet-18, ResNet-50, and EfficientNet neural networks were selected for model training, and classification. Learning rate, number of epochs, and batch-size hyperparameters were adjusted by trial, and error method. Setting these parameters correctly helps the model understand the information better and make better generalization. A summary containing model descriptions of selected deep networks is given in Table I.

Table I Descriptions of pre-trained models

Model	Layer Depth	Input Image Size	Feature Size	Parameters
0ResNet-18	18	224 × 224 × 3	512	11.7 M
ResNet-50	50	224 × 224 × 3	2048	25.6 M
EfficientNet0	0	224 × 224 × 3	1280	(variable)

ResNet

ResNet is a CNN model that has the ability to quickly classify various image types. ResNet is a good solution to eliminate the layer complexity and gradient loss problems caused by adding layers to CNN. ResNet-18, and ResNet-50, which are the most preferred models of the ResNet family, which includes different models according to the number of layers, were preferred within the scope of the study. In both models, batch size 32, and epoch number 100 were used. Using FastAI's lr_find function, the learning rate was determined as 1.3e-3 for ResNet-18, and 1.4e-3 for ResNet-50. While ResNet-18 consists of 18 layers, ResNet-50 has a 50-layer structure. The most important feature of ResNet is that as the network gets deeper, it can learn better by using skipped connections to prevent information loss. This provides the ability to create much deeper networks, and successfully complete more complex visual tasks (17).

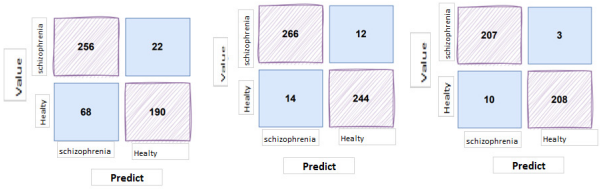

Figure IV (a) Complexity matrix for EfficientNet (b) Complexity matrix for ResNet-18 (c) Complexity matrix for ResNet-50

EfficientNet

EfficientNet is a lightweight, and efficient CNN model. It is optimized using a learning approach that automatically scales network depth, width, and resolution. However, since it is a customizable model, it can be easily adapted to various tasks or data sets. EfficientNet is used successfully in many visual processing tasks such as image classification, and object detection. At the same time, the high level of accuracy shows that EfficientNet also works well on large, and complex datasets (18,19). In the study, EfficientNetB0 was chosen because of its ability to scale CNNs as well as achieving better precision and efficiency. EfficientNetB0 was used with batch size 32, and epoch number 100. With the lr_find function, the learning rate was determined as 1.3e-4. The final step involves training B0 Efficient Networks on the augmented dataset. Transfer learning is used using pre-trained weights from the ImageNet dataset. This approach utilises the knowledge gained by the model on a large-scale dataset (ImageNet). After model selection, and hyperparameter adjustments were completed, the training process was started using FastAI, a PyTorch-based framework. This framework is simple to use, provides fast model training, comprehensive data cleaning, etc. It was preferred for the study due to its features (20). EEG spectrograms, which were part of the training data, were associated with the correct labels (healthy or schizophrenia). In other words, the model accomplished the task of distinguishing between schizophrenic patients, and healthy individuals. As a result of this step, success metrics measuring the performance of the model were evaluated mutually for each model. Table II gives the success metrics used in the study, and explanations of these metrics.

Table II Performance evaluation metrics

Metric	Explanation	Calculation
Truth	Percentage of samples classified correctly	(TP + TN) / (TP + TN + FP + FN)
Sensibility	Ratio of predicted positives to true positives	TP / (TP + FP)
Sensitivity	Ratio of true positives to predicted positives	TP / (TP + FN)
F1 Score	Harmonic mean of precision and sensitivity	2 * (Sensitivity * Sensitivity) / (Sensitivity + Sensitivity)

True Positives (TP): The number of true positives, examples that the model predicts as healthy, and those that are actually healthy,

True Negatives (TN): The number of true negatives, the number of examples that the model predicts as schizophrenia, and those that actually have schizophrenia,

False Positives (FP): The number of false positives, examples that the model predicts as healthy but actually have schizophrenia,

False Negatives (FN): The number of false negatives

represents samples that the model predicts as having schizophrenia but are actually healthy.

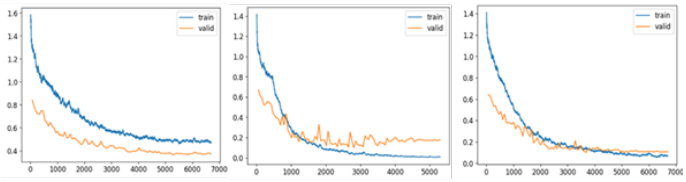

Figure V (a) Loss graph for EfficientNet (b) Loss graph for ResNet-50 (c) Loss graph for ResNet-18

Performance metrics are used to measure how well a model or system processes data, and how reliable the decisions are. These measurements determine the quality, and reliability of the results by evaluating a model's accuracy, precision, sensitivity, and other performance indicators. Application requirements provide a fundamental tool in the decision support phase by determining which metric to use. The results obtained at the end of the study process show how well which model Works, and its ability to diagnose schizophrenia.

Table III Operating performance results

Model	Class	Precision (%)	Sensitivity (%)	F1 Score (%)	Average Accuracy (%)
EfficientNet	Schizophrenia	79	92	85	83
	Healthy	90	74	81	
ResNet-50	Schizophrenia	95	99	97	97
	Healthy	99	95	97	
ResNet-18	Schizophrenia	95	96	95	95
	Healthy	95	95	95	

Power of delta, theta, alpha and beta bands (DP, TP, AP and BP)

Common EEG characteristics primarily include the time-domain features, frequency-domain features and entropy features. The frequency features of EEG are simple and intuitive, and some studies confirmed that frequency features could be effective for recognition of human emotion. Power spectral analysis is a conventional method in EEG analyses. It is based on decomposing the signal, using Fourier transform, into functionally distinct frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–30 Hz). Then an estimation of the power spectral density of the signal is performed, from which the average band power is computed for each frequency band (DP, TP, AP and BP).

Results

The study aimed to distinguish schizophrenia, and healthy patients with high accuracy using deep learning methods using EEG signal data from a total of 67 healthy and 73 schizophrenia patients. Digital EEG signal data converted into spectrograms were classified with pre-trained CNN models EfficientNet, ResNet-18, and ResNet-50. The performances of deep networks were evaluated using accuracy, sensitivity, precision, and F1-Score metrics. The metric performances obtained because of the study are given in Table III.

When Table III is examined, it can be seen that the targeted high-performance classification process has been successfully carried out. According to Table 3, according to the high sensitivity, sensitivity, and F1 score values in the three models, it is understood that the model has the ability to both accurately identify the disease, and correctly classify healthy individuals. When the average accuracy values are examined, it is seen that the most successful model is ResNet-50 with an accuracy rate of 97%. This success is followed by ResNet-18, and EfficientNet models with 95%, and 83% respectively. Complexity matrices, which express the number of correct, and incorrect predictions in the classification process of the models used, are given in Figure IV.

It can be seen that the complexity matrices given in Figure IV support the accuracy rates given in Table III. When the complexity matrix for the ResNet-50 model, which shows the most successful performance, is examined, it is understood that the prediction rate for the schizophrenia group is higher. In addition to performance metrics, and complexity matrices, loss graphs showing incorrect predictions, and error rates of validation data were also examined. The graphs in Figure V clearly show that the ResNet-50 model exhibits higher performance compared to other models.

The loss graphs given in Figure V are an important tool to closely monitor the training process of the model and evaluate its performance. The observed steady decrease indicates that the model is effectively

learning the data and improving the overall accuracy. Without overfitting, the model will adapt to new, and unseen data. This shows that the performance evaluation standards determined to achieve the objectives of the study are compatible with each other.

Discussion

Millions of people worldwide experience a complex psychiatric disorder known as schizophrenia. Correct diagnosis of this disorder, whose diagnosis, and treatment is a long, and difficult process, is of critical importance. In recent years, the use of EEG data has attracted great attention in both clinical, and neurological evaluations for the diagnosis of schizophrenia. The EEG method used to record brain activity helps diagnose neuropsychiatric disorders such as schizophrenia earlier. In this context, artificial intelligence methods play a supporting role by assisting the physician in the analysis of EEG data.

Aslan et al. presented an artificial intelligence-based method to automatically detect schizophrenia from EEG recordings. In the first step, they converted the EEG signals to 2D using Continuous Wavelet Transformation to obtain the time-frequency properties of the EEG signals. They used the VGG16 model of CNN architecture to classify the resulting scalogram images. As a result of the study, they achieved a correct prediction success rate of 99.5% for the healthy group, and 98% for the patient group (21).

Shalbaf et al. proposed a transfer learning-based method using EEG signals to distinguish schizophrenia patients from healthy people. In this study, they converted EEG signals into images with time-frequency analysis, and then applied pre-trained CNN models (AlexNet, ResNet-18, VGG-19 and Inception-v3). They classified the deep features obtained from the convolution, and pooling layers of these models using the SVM classifier. As a result of the study, by combining the frontal, central, parietal, and occipital regions on the ResNet-18-SVM model, the highest performance metrics were accuracy (98.60 ± 2.29%), sensitivity (99.65 ± 2.35), and specificity (99.65 ± 2.35), respectively. It was obtained as 96.92% ± 2.25) (22).

Khare et al. aimed to develop an automatic model that automates the diagnosis of schizophrenia using EEG signals, instead of manual, time-consuming, subjective, and error-prone traditional diagnostic methods. They created an automatic model combining Robust Variational Mode Decomposition (RVMD) and Optimized Extreme Learning Machine (OELM) classifier. Whale Optimization Algorithm was used to optimize the α, and L values of RVMD, and the hyperparameters of the OELM classifier. They stated that this method increased the classification accuracy of the OELM classifier for each mode, while also reducing the root mean square error for RVMD. They were evaluated with the ten-fold cross-validation technique of the OELM classifier, in which the features selected by the Kruskal Wallis test were used. As a result of this evaluation, sensitivity (93.94%), specificity (91.06%), F-1 measure (94.07%), sensitivity (97.15%), and Cohen's Kappa (85.32%) performance measurements were obtained (23).

Padayatty et al. presented a method to distinguish EEG signals in patients with schizophrenia using wavelet transform, and machine learning. They included data from a total of 81 patients, 32 healthy, and 40 schizophrenics, in the study. They obtained frequency, and time data by decomposing non-linear, and non-stationary EEG signals into wavelet coefficients. They performed the classification process by applying KNN, LDA, QDA, and SVM classifiers on the feature set. At the end of the study, they achieved the highest success rate of 90.14% with the SVM classifier. They stated that EEG is an effective biomarker in the diagnosis of schizophrenia, depending on the success rate they achieved (24).

Zulfikar et al. aimed to develop a Computer Aided Diagnosis (CAD) system to support experts for the automatic diagnosis of schizophrenia. They included two different data sets in the study. The first data set used in the study consists of 19-channel EEG signals obtained from 28 participants (14 SZ patients, and 14 healthy controls), and the second data set consists of 16-channel EEG signals obtained from 84 participants (45 SZ patients, and 39 healthy controls). First, they created Hilbert Spectrum (HS) images of the first four Intrinsic Mode Function (IMF) components by applying Empirical Mode Decomposition (EMD) to EEG signals. They then classified these images with VGG16, a pre-trained CNN model. As a result of the

study, they reached an accuracy rate of 98.2% for the first data set, and 96.02% for the second data set (25).

Weikoh et al. aimed to automatically diagnose schizophrenia using EEG signals. A total of 1142 EEG recordings, 626 schizophrenic, and 516 normal, were included in the study, collected with a 19-channel electrode array. They used decision tree, support vector machine, and k-nearest neighbor algorithms to classify normal, and schizophrenia groups. They achieved the highest performance with 97.20% with the KNN algorithm (26).

Das et al. proposed a method that examines multivariate EEG signals and extends the univariate iterative filtering (IF) technique to detect schizophrenia. The proposed approach to separate EEG signals into different spectral bands Frequency is a new technique known as multivariate iterative filtering (MIF). They evaluated schizophrenia, and healthy EEG groups with KNN, linear discriminant analysis (LDA), and support vector machine (SVM) classifiers. As a result of the study, they achieved 98.9% accuracy with the SVM (Cubic) classifier (27).

In a study conducted by Bagherzadeh et al. they identified 2 databases including 14 adult schizophrenia and 45 pediatric schizophrenia patient groups. In this study, they used EfficientNetB0, ResNet-50 and NasNet-Mobile models in combination and increased the accuracy rate by 3% compared to other methods and reached 96.67% (28).

The designed system aims to provide support to experts in the decision-making phase with its calculation, and prediction capabilities. The findings show that the system can be used as a reliable tool and can provide significant assistance to healthcare professionals in clinical practice.

Limitations

Small number of patients and healthy control groups, neurological examination, medical history, medical history and medication information were not included in the study, the fact that it has not been evaluated whether the accuracy rate can be increased by combining the available data with several different machine learning methods (such as EfficientNetB0ResNet-50, ResNet-50/NasNet-Mobile).

All these limiting parameters can be overcome by recording patient data in more detail, using several machine learning methods in combination in the same study and performing meta-analyses.

Conclusion

This study investigates the effect of deep learning methods to distinguish between schizophrenia patients, and healthy individuals using EEG data. As a result of the classification process performed using the transfer learning method within the scope of the study, it is seen that ResNet-based models are superior to the EfficientNet model. The results obtained in all three models show that artificial intelligence, and EEG data have a high potential to be used in schizophrenia diagnosis, but the study performance can be improved considering the information available in the literatüre, and the complexity of schizophrenia diagnosis. It is thought that this potential can be further increased in future research by using larger data sets, creating more sensitive algorithms, and integrating neurological examinations. The use of machine learning methods, which are determined to have a high accuracy rate in the diagnostic process, reduces the rate of change in diagnoses according to the evaluating physician. In addition, it enables early detection of underlying organic pathologies and early initiation of the treatment process. The results show that this method can speed up the diagnosis process of schizophrenia, and help obtain more accurate results, and will shed light on future studies in this field.

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Comparison of Anthropometric Measurements to Evaluate Abdominal Obesity in Older Adults

Yaşlı Erişkinlerde Abdominal Obeziteyi Değerlendirmek İçin Antropometrik Ölçümlerin Karşılaştırılması

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Comparison of Anthropometric Measurements to Evaluate Abdominal Obesity in Older Adults

ABSTRACT

Objective: Central/Abdominal obesity is an important health problem that is growing all over the world. Abdominal obesity has been recognized as a main risk factor for cardiovascular and metabolic events. There are various measurements ranging from anthropometric indices to imaging methods for the determination of abdominal obesity. However, anthropometric studies involving older adults are scarce in the literature. The purpose of this study is to compare the current anthropometric measures used to evaluate abdominal obesity in older adults.

Material and Method: In total, 104 outpatients aged 65 years or older were enrolled in this cross-sectional study. For any reason, patients with an indication for Dual-energy-X-ray Absorptiometry (DXA) were included. Anthropometric and hemodynamic measurements were taken. DXA was used to measure body composition, especially fat ratio.

Results: The mean age of patients was 74.6-6.9. The ratio of adiposity determined by DXA, which was used as reference/gold standard method, was in the range of 3.8-52.5%. Mean value of adiposity was 31.5-10.9%. When gender and anthropometric indicators were compared, body mass index (BMI), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), and body adiposity index (BAI) were significant *(p<0.05)*; conicity index (CI), a new body shape index (ABSI) and abdominal volume index (AVI) were not significant *(p>0.05)*. The best three anthropometric indicators that estimating the fat ratio in participants were; BMI *(r=0.718, p<0.05)*, WHtR *(r=0.503, p<0.05)*, and AVI *(r=0.480, p<0.05)*, respectively.

Conclusion: Many advanced diagnostic methods and medical devices, can not be used in primary healthcare clinics. Therefore, practical approaches that are most compatible with advanced research are coming to the fore. In this study, we have shown that BMI is the most appropriate anthropometric measurement to detect abdominal obesity in geriatric patients.

Keywords: Abdominal obesity, adiposity, anthropometry, dual-energy x-ray absorptiometry, obesity, older adults.

ÖZET

Amaç: Santral/Abdominal obezite tüm dünyada büyümekte olan önemli bir sağlık sorunudur. Abdominal obezite, kardiyovasküler ve metabolik olaylar için ana risk faktörü olarak kabul edilmiştir. Abdominal obezitenin belirlenmesi için antropometrik indekslerden görüntüleme yöntemlerine kadar çeşitli ölçümler mevcuttur. Bununla birlikte, literatürde yaşlı erişkinleri içeren antropometrik araştırmalar azdır. Bu çalışmanın amacı ise, yaşlı erişkinlerde abdominal obeziteyi değerlendirmek için güncel antropometrik ölçümleri karşılaştırmaktır.

Gereç ve Yöntem: Toplamda, 65 yaş ve üstü 104 ayaktan poliklinik hastası bu kesitsel çalışmaya dahil edildi. Herhangi bir sebepten ötürü, Dual-Energy X-ray Absorbsiyometri (DXA) endikasyonu olan hastalar çalışmaya alındı. Görüntülemeye ek olarak antropometrik ve hemodinamik ölçümleri alındı. DXA, vücut kompozisyonunu, özellikle yağ oranını ölçmek için kullanıldı.

Bulgular: Yaş ortalaması 74,6 - 6,9 olan toplam 104 hasta çalışmaya alındı. Referans/altın standart yöntem olarak kullanılan DXA ile belirlenen adipozite oranı %3,8-52,5 aralığındaydı. Yağlanmanın ortalama değeri %31,5 -10,9 idi. Cinsiyet ve antropometrik göstergeler karşılaştırıldığında, body mass index (BMI), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR) ve body adiposity index (BAI) anlamlıydı *(p<0,05)*; conisity index (CI), a new body shape index (ABSI) ve abdominal volume index (AVI) anlamlı değildi *(p>0,05)*. Katılımcılarda yağ oranını tahmin eden en iyi üç antropometrik gösterge ise sırasıyla; BMI *(r=0,718, p<0,05)*, WHtR *(r=0,503, p<0,05)* ve AVİ *(r=0,480, p<0,05)* olarak tespit edildi.

Sonuç: Birçok ileri tetkik yöntemleri ve tıbbi cihazlar, birinci basamak sağlık kliniklerinde kullanılamamaktadır. Bu nedenle, ileri düzeydeki araştırmalarla en uyumlu pratik yaklaşımlar ön plana çıkmaktadır. Bu çalışmada geriatrik hastalarda, BMI'nin abdominal obeziteyi tespit etmede en uygun antropometrik ölçüm olduğunu gösterdik.

Anahtar Sözcükler: Abdominal obezite, adipozite, antropometri, Dual-Energy X-ray Absorbsiyometri, obezite, yaşlılar.

Introduction

The increase in the older adults population is a global reality and is gaining momentum (1). The prevalence of overweight and obesity is increasing in oldeionizingr adults. Accordingly, morphophysiological changes and chronic noncommunicable diseases are increasing in this elderly population (2).

Excessive fat concentration in the abdominal region, especially the increase of visceral adipose tissue, is independently associated with higher incidence of metabolic alterations, particularly cardiovascular diseases, diabetes, stroke, which are the main causes of morbidity and mortality (3, 4). For these reasons, body composition and fat distribution assessments have become more important in clinical practice and epidemiological studies. These high fat concentrates in the abdomen have been associated with metabolic and cardiovascular changes (5). Despite the important role of abdominal obesity, practical measurements of abdominal fat are not readily available. For obesity-related chronic diseases, it is important to target the efforts to reduce adiposity in the risk group.

Various methods have been developed to evaluate adiposity, ranging from waist circumference (WC) to computed tomography (CT). Currently, we can evaluate abdominal fat sections in detail with CT and magnetic resonance imaging (MRI) for the evaluation of body composition (6, 7). However, application of CT/MRI for body composition assessment in routine clinical practice is limited and impractical because of cost, scanner access, and exposure to significant ionising radiation. Another imaging method, Dual energy X-ray absorptiometry (DXA) is a technique that provides a reliable estimate of whole body composition and regional distribution of fat and lean mass (8). Unlike CT/MRI, this technique is quick, accurate, widely available, relatively inexpensive, and exposes subjects to minimal amounts of ionizing radiation (9). Furthermore, such technologically complex imaging methods are very difficult to implement routinely.

Expect these imaging methods, various anthropometric indices are used to measure central obesity. Body mass index (BMI) is by far the most commonly applied approach that is used to categorise obesity in individual subjects. Despite its widespread use; it is also routinely applied to estimate body fat in both epidemiological studies and clinical applications. But, BMI does not offer a true indication of body composition and is affected by age, gender, and ethnic differences (10, 11). Therefore, many anthropometric indicators have been developed.

Several indices have been proposed to measure central obesity, including waist circumference (WC), waist-to-hip ratio (WHR), and waist-to-height ratio (WHtR). More recent indices; body adiposity index (BAI), abdominal volume index (AVI), conisity index (CI), and a new body shape index (ABSI), which can be calculated from simple data such as weight, height, WC, and hip circumference (HC) are also in place (12-15).

Therefore, the present study aims to determine which anthropometric indicators are more compatible by using DXA as the "gold standard" for the detection of adiposity and central obesity in the older adults.

Material and Methods

A total of 104 outpatients, who applied an Internal Medicine Clinic between May 2020 – April 2021, were included in this cross-sectional study. The criteria for inclusion were age 65 years or over, who applied to clinic for any reason, and the ability to understand and answer questions. The investigation conformed to the Declaration of Helsinki and approved by the local ethics committee (Ermenek Devlet Hastanesi-23.08.2019-E.195/99795470), and verbal and written informed consent was obtained from all participants. Exclusion criteria included refusal to participate in the study, patients under 65 years of age, those receiving parenteral/enteral nutritional support, bedridden patients whose height and weight could not be measured, and those with serious diseases that could cause deterioration in general condition. A designed questionnaire was administered to consented study participant. Trained healthcare providers measured blood pressure and anthropometric data, including weight (kg), height (m), WC (cm), and HC (cm). Moreover, excessive clothing, accessories, and shoes were removed to ensure accurate measurements. Weight was measured with on a digital electronic scale (Genius 220 PLUS, Korea) with a capacity of 250 kg and a sensitivity of 100g. Height was measured while participants stood against a wall with their heels and buttocks in contact with the

wall. WC was recorded while standing at the time of normal expiration. The measurement was obtained at the midpoint between the inferior angle of the ribs and the suprailiac crest. HC was measured at the maximal circumference over the buttocks. Both WC and HC were done with a non-stretchable and accurately calibrated scale with 0.5-cm precision and the mean value of the three trials was used as the criterion value. The other indicators used to evaluate obesity and adiposity were calculated using the following formulas:

$$WHR = waist\ (cm)/hip\ (cm)$$

$$WHtR = waist\ (cm)/height\ (cm)$$

$$BMI = \frac{weight\ (kg)}{height\ (m)^2}$$

$$CI = \frac{waist\ (m)}{[0.109\ x\ \sqrt{weight\ (kg)/height\ (m)}]}$$

$$BAI = \frac{hip\ (cm)}{height\ (m)^{1.5}} - 18$$

$$AVI = \frac{[2\ x\ (waist\ (cm)^2) + 0.7\ x\ [(waist\ (cm) - hip\ (cm))^2]]}{1000}$$

$$ABSI = \frac{waist\ (m)}{BMI^{2/3} x\ height\ (m)^{1/2}}$$

Systolic and diastolic blood pressures were measured on the nondominant arm, using a properly fitted cuff with participants in sitting position, with back supported and legs uncrossed.

A venous blood sample was collected from participants following 12-hours of fasting to evaluate serum concentrations of glucose, total cholesterol, triglycerides, Low Density Lipoprotein (LDL), and High Density Lipoprotein (HDL).

Histogram, QQ graphs, and Shapiro-Wilk test were used to analyze the data distribution. Levene test was used for homogeneity of variance. Pearson chi-square analysis and Fisher exact tests are conducted for evaluating qualitative data. The correlations coefficients and their significance were calculated using Pearson test. The correlations were also tested separately for the eight work status groups (WC, WHR, WHtR, BAI, AVI, CI, ABSI, BMI). *p<0.05* was considered significant.

Results

The overall characteristics of the 104 patients, of whom the mean age 74.6±6.9 years, are shown in Table I. The majority of the participants were women (63.5% vs 36.5%). The ratio of adiposity determined by DXA, was in the range of 3.8-52.5% and the mean value of adiposity was 31.5±10.9%. Also, there was a significant difference between gender and fat percentage (women vs men; 34.1±9.1 vs 26.9±8.7, *p<0.05*).

Table I Anthropometric, clinical and biochemical characteristics of the participants according to gender

Variables	Total (n=104)	Women (n=66)	Men (n=38)	*p value*
Age (years)	74.6±6.9	73.8±5.7	76.1±5.1	*0.105*
Weight (kg)	63.5±11.5	62.5±10.4	65.2±10.6	*0.277*
Height (cm)	154.2±8.99	149.6±6.8	162.1±6.4	*<0.001*
Waist (cm)	94.6±10.9	94.8±9.4	94.3±9.4	*0.832*
Hip (cm)	103.5±11.5	105.9±9.3	99.2±8.5	*0.004*
Fat (%)	31.5±10.9	34.1±9.1	26.9±8.7	*<0.001*
BMI	26.7±4.9	27.8±5.2	24.8±3.8	*0.003*
CI	1.36±0.11	1.35±0.12	1.36±0.10	*0.609*
WHR	0.91±0.08	0.89±0.07	0.95±0.08	*<0.001*
WHtR	0.61±0.07	0.63±0.06	0.58±0.05	*<0.001*
BAI	35.8 (30.6-41.3)	39.1 (35.4-43.7)	30.0 (26.3-32.3)	*<0.001*
AVI	17.7 (15.0-20.1)	17.6 (14.9-20.8)	17.7 (15.4-19.7)	*0.960*
ABSI	0.86±0.86	0.85±0.08	0.87±0.07	*0.184*
SBP (mm/Hg)	134.06±17.1	136.5±16.7	129.8±17.3	*0.055*
DBP (mm/Hg)	76.3±1.01	77.3±9.78	74.6±11.11	*0.209*
Glucose (mg/dL)	105 (96-119)	106 (96-119)	104 (96-104)	*0.700*
Cholesterol (mg/dL)	189±51.7	199.3±53.2	171.1±44.2	*0.007*
Triglycerides (mg/dL)	132.2 (78-156)	123.5 (86.7-192.5)	98 (74.5-117.7)	*0.008*
HDL (mg/dL)	47.7±12.7	50.5±12.9	42.9±10.8	*0.003*
LDL (mg/dL)	114.2±37.1	118.6±38.4	106.5±33.9	*0.110*

ABSI: A Body Shape Index, AVI: abdominalvolume index, BAI: body adiposity index, BMI: Body mass index, CI: Conicity index, DBP: diastolic blood pressure, HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, SBP: Systolic blood pressure, WHR: waist-to-hip ratio, WHtR: waist-to-height ratio. The data is expressed mean±standard deviation or median at first and third quarter.

When gender and anthropometric indicators were compared, BMI, WHR, WHtR, and BAI were

significant (*p<0.05*), while CI, ABSI, and AVI were not significant (*p>0.05*). There was no statistical difference between men and women for the variables: systolic blood pressure (SBP), diastolic blood pressure (DBP), glucose, and LDL (Table I).

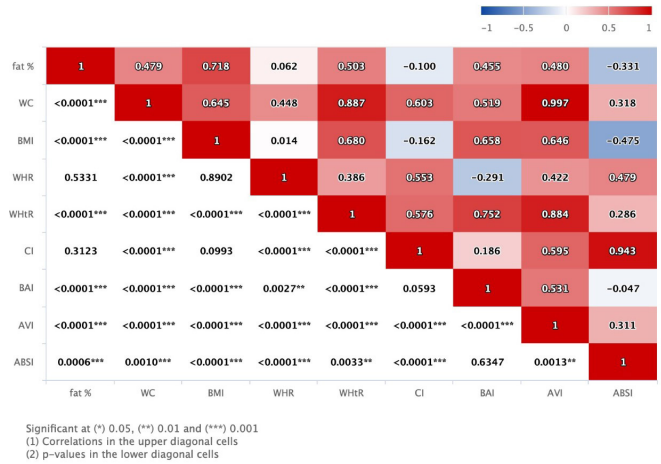

Figure I Correlation of anthropometric indicators in predicting the abdominal fat ratio in all participants

The performance of anthropometric indicators in predicting the abdominal fat ratio in older adults is presented in Figure I. The best three anthropometric indicators that estimating the fat ratio in the total sample were; BMI (*r=0.718, p<0.05*), WHtR (*r=0.503, p<0.05*), and AVI (*r=0.480, p<0.05*), respectively (Figure I).

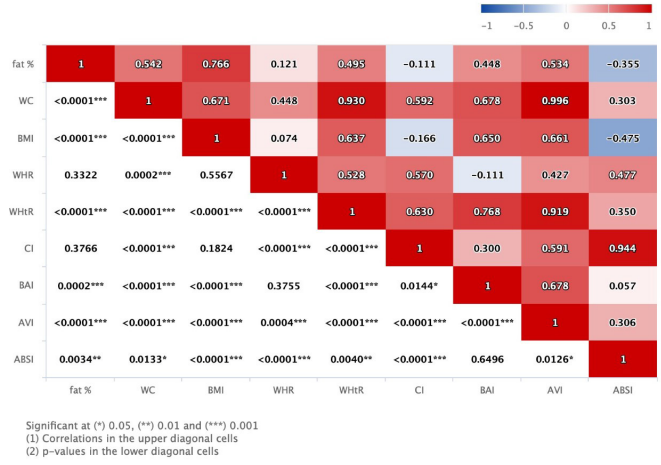

Figure II Correlation of anthropometric indicators in predicting the abdominal fat ratio in female participants

If we evaluate according to gender, the anthropometric indicators that performed well in predicting the fat ratio were; BMI (*r=0.766, p <0.05*), WC (*r=0.542, p<0.05*), and AVI (*r=0.534, p<0.05*) for women (Figure II-III). The most consistent anthropometric measurements for men were BMI (*r=0.548, p<0.05*), AVI (*r=0.422, p<0.05*), and WC (*r=0.420, p<0.05*) (Figure II-III). When the correlation of anthropometric indicators, which is statistically significant with the percentage of fat, is carefully analyzed, it is realized that the indicators that perform best in all three groups (total, women, and men) are almost the same. Furthermore, adiposity was negatively correlated with ABSI in all groups (*r=-0.331* in total, *r=-0.355* in women, and *r=-0.216* in men).

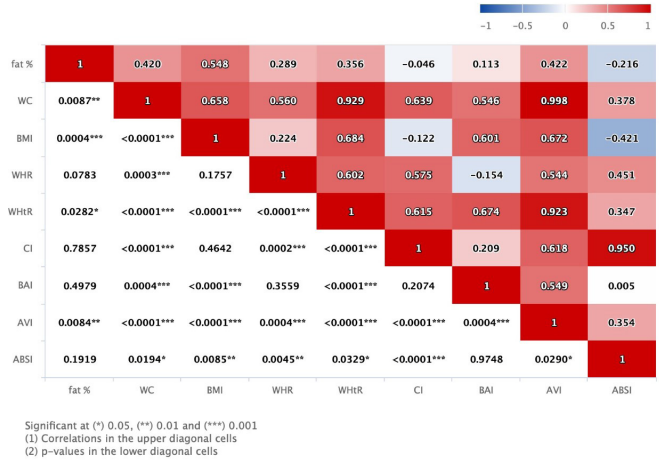

Figure III Correlation of anthropometric indicators in predicting the abdominal fat ratio in male participants

Discussion

Abdominal obesity is a major risk factor for chronic diseases such as cardiovascular disease, stroke and diabetes (16). Various anthropometric indicators have been developed to detect abdominal obesity quickly and effectively. This study evaluated multiple anthropometric indicators to detect abdominal obesity in older adults, using DXA as the reference method.

BMI, despite its widespread use in clinical practice, does not assess body fat distribution and is influenced by factors such as age, gender, and ethnicity. Our study found a strong association between abdominal obesity and BMI in elderly individuals. The lack of athletic individuals in our study population likely contributed to the success of BMI in predicting abdominal obesity. Studies conducted by Geliebter et al. and YA Sung et al. also demonstrated BMI's

superiority in estimating body fat compared to other anthropometric measurements . However, the limited number of studies focusing on older adults and our study's sample size restrict generalization. Previous research indicates that while BMI is a convenient and widely used measure, it fails to differentiate between muscle and fat mass. In older adults, where muscle mass tends to decrease with age, BMI may not accurately reflect adiposity. This limitation is particularly significant in populations with a high prevalence of sarcopenia. Therefore, while BMI provides a useful general indication of obesity, it should be used in conjunction with other measures for a more comprehensive assessment.

Geliebter et al. investigated the best method to determine abdominal fat ratio in 19 severely obese female patients and found BMI to be the most appropriate anthropometric measurement, similar to our findings (17). Another study showed a significant correlation between BMI and body fat in postmenopausal older women A cross-sectional study by YA Sung et al. with 2950 female patients demonstrated that BMI-based classification was superior to other anthropometric measurements (18, 19). While our study is consistent with literature data, the lack of sufficient studies in older adults and our study's sample size do not allow for generalization in this regard.

WHtR was also found to be strongly associated with adiposity in all participants (*r=0.503, p<0.05*). WHtR adjusts for height and provides a single cut-off point, regardless of gender and ethnicity, making it an effective measure. Roriz et al. reported high accuracy of WHtR in obesity discrimination, supporting our findings (5).

Lee et al.in their meta-analysis showed that WHtR was more successful than BMI, WC, and WHR in determining cardiovascular risk (20). WHtR's ability to adjust for height and provide a single cut-off point regardless of gender and ethnicity makes it a versatile tool. Ashwell and Hsieh highlighted the simplicity and effectiveness of WHtR, suggesting it could simplify the public health message on obesity (21).

AVI, a newer anthropometric tool, ranked third after BMI and WHtR in detecting abdominal obesity (*r=0.480, p<0.05*). It has shown strong obesity assessment capability in both male and female patients. Studies from Iran and China corroborate our results, highlighting AVI's utility in obesity assessment (22, 23).

AVI was developed to assess glucose metabolism impairment and measure general body volume, providing a comprehensive assessment of body fat distribution. Guerrero-Romero and Rodríguez-Morán found that AVI was strongly related to impaired glucose tolerance and type 2 diabetes mellitus, further supporting its use in clinical settings (13). WC is a well-known marker of visceral adiposity and is associated with a higher risk of metabolic abnormalities and cardiovascular diseases compared to BMI (24). Our study found WC to be strongly correlated with adiposity in all participants (r=0.479, p<0.05), particularly in female patients (*r=0.542, p<0.05*) and to a lesser extent in male patients (r=0.420, p<0.05). The correlation between WC and AVI may be due to their shared reliance on waist and hip circumference in their formulas.

ABSI, designed to minimize correlation with weight, height, and BMI, showed a negative correlation with adiposity in all groups. This distinct characteristic suggests that ABSI may offer unique insights into central obesity and its cardiometabolic risks . Despite its significant correlation with the female group and all participants, ABSI did not show a significant relationship in the male group.

ABSI was proposed by Krakauer and Krakauer as a novel index that better captures the contribution of WC to central obesity and its clinical outcomes (25). Bertoli et al. found ABSI to be associated with cardiometabolic risk factors in a large cohort of Caucasian adults, further supporting its potential utility (15).

Given the practical limitations in primary healthcare settings, DXA, though reliable and accurate, is not always feasible due to cost and complexity. Our study demonstrated that simple, economical, and convenient anthropometric measurements like BMI, WHtR, and AVI can effectively assess obesity in older adults. These measurements are easy to implement in primary healthcare, offering a pragmatic alternative when advanced imaging methods are unavailable. The increasing prevalence of obesity among older adults necessitates effective and accessible methods

for assessment and intervention. Practical approaches like BMI, WHtR, and AVI can aid in early detection and management of obesity-related complications, ultimately reducing the burden on healthcare systems. The results of this study provide an understanding of the efficacy of BMI, WHtR, and AVI as indicators of abdominal obesity in an elderly population, particularly within the operational limitations of primary healthcare settings. Our comparative analysis, juxtaposed with the DXA gold standard, not only corroborates BMI's significant correlation with abdominal adiposity but also highlights the diagnostic relevance of WHtR and AVI. This underlines their utility in geriatric obesity assessment, offering a pragmatic alternative in scenarios where DXA is not feasible.

Further research, particularly longitudinal studies, is needed to explore the long-term reliability of these measurements and their correlation with clinical outcomes in elderly patients. With the increasing prevalence of obesity in older populations and its associated health risks, these findings have significant implications for public health strategies. Practical approaches that are simple and cost-effective can help manage obesity-related complications and reduce the burden on the healthcare system.

Longitudinal studies would be invaluable in understanding the dynamic changes in body composition and fat distribution over time in older adults. Such investigations would help refine obesity management protocols and improve patient care in geriatric populations.

Conclusion

This study systematically evaluated the efficacy of various anthropometric measurements in detecting abdominal obesity in older adults using DXA as the gold standard. The findings revealed that BMI, WHtR, and AVI are reliable indicators, with BMI showing the highest correlation with DXA measurements. This suggests that BMI is a practical tool for assessing abdominal obesity in primary healthcare settings due to its simplicity and strong correlation. The study underscores the importance of easily implementable methods in managing health risks in older populations. Further research is needed to validate these findings and enhance obesity management protocols in geriatric populations.

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The Roles of Maternal Height and Body Mass Index in Preterm Birth Prediction

Erken Doğumu Öngörmede Anne Boyu ve Vücut Kitle İndeksinin Rolü

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The Roles of Maternal Height and Body Mass Index in Preterm Birth Prediction

ABSTRACT

Objective: To investigate the role of maternal height and body mass index in the prediction of preterm birth.

Material and Method: Patients who had either cesarean section and/or spontaneous vaginal delivery in Department of Obstetrics and Gynecology in the last 5 years were included in the study. Demographic data, weeks of gestation at the time of delivery, maternal height and body mass index of the patients with preterm delivery were recorded retrospectively for the study group. The control group consisted of retrospectively selected patients who had given birth after the expected date of delivery using the Naegele method.

Results: In the study, 295 of 541 pregnant women had a preterm birth (study group), while 246 women had given birth after the expected date of delivery (control group). Maternal height and body mass index had an influence on preterm birth. The sensitivity and specificity values for a height of 152.5 cm and a body mass index of 21.3 kg/m2 were (1.0 and 0.13) and (1.0 and 0.06), respectively. In the receiver characteristics analysis of these variables affecting preterm birth, the area under the curve for body mass index and maternal height were 0.763 and 0.708, respectively.

Conclusion: We conclude that height and body mass index were found to be good discriminators for the prediction of preterm birth.

Keywords: Body mass index, height, labour, pregnancy.

ÖZET

Amaç: Erken doğumun öngörülmesinde anne boyu ve vücut kitle indeksinin rolünü araştırmak.

Gereç ve Yöntem: Kadın Hastalıkları ve Doğum Kliniğinde son 5 yıl içinde sezaryen ve/veya spontan vajinal doğum yapan hastalar çalışmaya dahil edildi. Çalışma grubu için erken doğum yapan hastaların demografik verileri, doğum sırasındaki gebelik haftaları, anne boyu ve vücut kitle indeksi retrospektif olarak kaydedilmiştir. Kontrol grubu, Naegele yöntemi kullanılarak beklenen doğum tarihinden sonra doğum yapan ve retrospektif olarak seçilen hastalardan oluşmuştur.

Bulgular: Çalışmada 541 gebenin 295'i erken doğum yapmış (çalışma grubu), 246'sı ise beklenen doğum tarihinden sonra doğum yapmıştır (kontrol grubu). Anne boyunun ve vücut kitle indeksinin erken doğum üzerinde etkisi vardı. Boy uzunluğunun 152,5 cm ve vücut kitle indeksinin 21,3 kg/m2 olması için duyarlılık ve özgüllük değerleri sırasıyla (1,0 ve 0,13) ve (1,0 ve 0,06) idi. Erken doğumu etkileyen bu değişkenlerin alıcı özellikleri analizinde, vücut kitle indeksi ve anne boyu için eğri altında kalan alan sırasıyla 0,763 ve 0,708'dir.

Sonuç: Boy ve vücut kitle indeksinin erken doğumun öngörülmesinde iyi ayırt edici değişkenler olduğu sonucuna varılmıştır.

Anahtar Sözcükler: Boy, doğum, gebelik, vücut kitle indeksi.

Introduction

In recent times, medical and technological developments in neonatal units have significantly improved the prognosis for low birth weight babies. However, the number of premature births has not decreased. Preterm births, which occur in 11% of all pregnancies, are births before 37 weeks gestation (1). In the United States, the preterm birth rate is about 9.7% (2). The causes of preterm delivery are heterogenous, and numerous risk factors have been identified, including both young and advanced maternal age, intrauterine infections, smoking, previous preterm delivery, short maternal stature, and prepregnancy underweight [body mass index (BMI) < 18.5 kg/m^2]. In addition, some studies have shown that pre-pregnancy obesity (BMI ≥ 25 kg/m^2) is associated with an increased risk of very and moderately preterm births (3).

Preterm birth is the single most important factor in determining the future of a fetus without anomalies, and it remains the leading cause of perinatal mortality and morbidity (4). The most critical mortality and morbidity associated with complications of preterm birth is before 34 weeks of gestation. The rate of preterm births has increased over the last 20 years due to the increase in multiple pregnancies through assisted reproductive techniques and the increase in the frequency of invasive obstetric procedures (5). The gestational age and maturity of the fetus increase the life expectancy of the newborn and not the birth weight (6). It has been found that 83% of neonatal mortality is due to births before 37 weeks' gestation (7,8).

The prediction or prevention of preterm birth has therefore become one of the most important issues in obstetrics. Pre-diagnosis of preterm birth and prevention by determining the risk factors is the best approach to reduce the preterm birth rate. Early detection of pregnant women at high risk of preterm birth is therefore an important step in reducing fetal morbidity and mortality (9). Comprehensive studies to determine the risk of preterm birth have been conducted on various factors ranging from simple pelvic floor measurements to digital examination and sonographic assessment of the cervix (10,11). In this study, we investigated the association between low maternal height and lower maternal BMI and preterm birth.

Material and Methods

This case-control study was conducted retrospectively at the Obstetrics-Gynecology Department between January 2009 and December 2014. This study was performed in accordance with the principles of the Helsinki Declaration, and it was approved by the GATA ethics committee (October 14, 2014; EGT.OGT: 50687469-1491-550-14/1648.4-1968).

Inclusion and Exclusion criteria

The study included singleton pregnancies with preterm delivery (>27 weeks' gestation to <37 weeks' gestation) with spontaneous labor and singleton pregnancies with delivery after 40 weeks' gestation. Pregnant women were excluded from the study if they had elevated liver enzymes, multiple pregnancies, polyhydramnios, induced labor due to FGR, preeclampsia or similar causes, placental abnormalities such as placenta previa, uterine abnormalities and surgery, group B streptococcus positivity, fetal abnormalities, had given birth before 27 and after 42 weeks of gestation, and smoked cigarettes.

Study Design

Patients who had a preterm spontaneous vaginal delivery and/or a cesarean section (CS) were included in the study group (Group I). Patients who had a postdated spontaneous vaginal delivery and/or cesarean section were included in the control group (Group II). A postdated pregnancy is defined as a pregnancy that has exceeded the expected date of delivery (more than 280 days - calculated according to the Naegele rule -to calculate the expected date of birth, subtract 3 months and add 7 days to the date of the last menstruation-). When comparing the groups, the aim of selecting post-dated pregnancies for the control group was to increase the significance by excluding term pregnancies (≥ 37 weeks' gestation and ≤ 40 weeks' gestation) between the two groups.

Data

541 pregnant women were included in the study. If the women did not know their exact week of gestation (due to early or late ovulation or an unknown last menstruation), gestational age was determined by the earliest ultrasound measurement. The weeks of

gestation were confirmed by measuring the crown-rump length (CRL) at the twelfth week in all pregnant women. A sample of approximately 295 pregnant women was included in Group I and a sample of approximately 246 pregnant women was included in Group II.

For the study, the data were taken from the patient files or the hospital files of the two groups. Patient demographics, gestational age at birth, smoking status, maternal height and BMI were recorded.In our hospital's antenatal clinic, height and weight are measured in a standardized way during the first trimester at the patient's first visit to the nurses' room and recorded in the patient's medical file. This data was taken from the patient's records and included in the study.

BMI was calculated using the following formula: Patient's weight (kg) / square of patient's height (m).

Ultrasound examination and fetal monitoring

Ultrasound measurements were performed using the General Electic Logiq S6®, 1.5 - 4.5 MHz probe (Waukesha, WI USA) to confirm gestational age, assess gross fetal anomalies, determine amniotic fluid volume, cervical length and placental implantation. A Philips AvalonTM FM20 cardiotocograph was used to detect uterine contractions and assess fetal behavior.

Statistical analysis

The SPSS 15.0 program for Windows Evaluation Version was used for the statistical analysis. Numbers, percentages, averages and standard deviations were used to analyze the data. The Kolmogorov-Smirnov test was used to check the conformity of the continuous variables with the normal distribution. For comparison between groups, the student t-test was used for continuous variables, while the chi-square test was used for discontinuous variables. Logistic regression analysis was performed to identify the variables (height and BMI) important for predicting preterm birth. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were determined using receiver operating characteristic (ROC) analysis to obtain cut-off values for detecting the role of maternal height and BMI in preterm birth. Statistical significance was assessed at the $p < 0.05$ level for all outcomes.

Results

In the study, 4893 patient records who had given birth in the Department of Obstetrics and Gynecology within the last 5 years were retrospectively analyzed. 541 of the 4893 patients who met the study criteria were selected. The average age of the patients in the study was 28 ± 6.7 years. The average height and weight of the patients were 160.6 ± 6.9 cm and 73.8 ± 12.4 kg, respectively. The average BMI was 28.6 ± 4.7 kg/m^2. 295 of 541 patients (54.5%) who had a preterm delivery were designated as the study group, while 45.5% (n:246) of patients who had a post-dated birth were designated as the control group.

The demographic parameters of the groups are shown in Table I.

Table I Comparison of the demographic parameters of the groups

	Group I (n=295)	**Group II** (n=246)	***p***
Age[a]	26 ± 5.4	30.3 ± 7.3	*<0.001*
Delivery Week[a]	31.6 ± 2.9	41.0 ± 0.8	*<0.001*
Height(cm)[a]	158.5 ± 4.8	163.2 ± 6.2	*<0.001*
BMI (kg/m^2)[a]	26.6 ± 3.4	31.1 ± 4.9	*<0.001*
Number of Births[b]			
0	133 (45.1)	101 (41.1)	
1	106 (35.9)	109 (44.3)	
2	38 (12.9)	30 (12.2)	*0.134*
3	14 (4.7)	5 (2.0)	
4	4 (1.4)	1 (0.4)	
Abortion[b]			
0	110 (37.3)	92 (37.4)	
1	85 (28.8)	77 (31.3)	*0.758*
2	100 (33.9)	77 (31.3)	
History of preterm[b]			
Yes	89 (30.2)	23 (9.3)	*<0.001*
No	206 (69.8)	223 (90.7)	

BMI: body mass index.

[a] Non-parametric data was expressed with mean and standart deviation;

[b] Parametric data was expressed with numbers and percentage.

In the logistic regression analysis performed to identify the factors influencing preterm birth, the odds ratio (OR) for age was 0.901 (95% confidence interval (CB): 0.864 – 0.938), for height: 0.728 (95% confidence interval: 0.682 – 0.777), for BMI: 0.630 (95% confidence interval: 0.575 – 0.690) and for retrospective preterm birth: 3.637 (95% confidence interval: 1.800 - 7.350) (Table II).

Table II Evaluation of the factors affecting preterm birth by logistic regression analysis

	ß	OR	%95 CB
Age	-0.105	0.901	0.864 – 0.938
Height	-0.318	0.728	0.682 – 0.777
BMI	-0.463	0.630	0.575 – 0.690
History of preterm	1.291	3.637	1.800 – 7.350

BMI: body mass index; ß: Logit Coefficient; OR: Odds Ratio; CB: Confidence Bounds; *p*: Logistic Regression Analysis

When these factors were analyzed using ROC analysis, the area under the curve (AUC) was 0.667 for age, 0.763 for BMI, 0.708 for height, and 0.604 for retrospective preterm birth. Each value was statistically significant (*p<0.001*) (Table III, Figure I).

Table III Evaluation of the factors affecting preterm birth by ROC analysis

	AUC	%95 CB	*p*
Age	0.667	0.621 – 0.713	*<0.001*
Height	0.708	0.665 – 0.752	*<0.001*
BMI	0.763	0.723 – 0.804	*<0.001*
History of preterm	0.604	0.557 – 0.651	*<0.001*

AUC: area under curve; BMI: body mass index; CB: Confidence Bounds; *p*: ROC Analysis

The values for sensitivity, specificity, PPV, NPV and accuracy were calculated for the variables height and BMI. For the height variable, the sensitivity for the point of best estimate, which was 165.5 cm, was 0.95, the specificity 0.37, the PPV 64%, the NPV 86% and the accuracy 68.5, while for the BMI variable, for the point of best estimate, which was 30.5 kg/m^2, the sensitivity was 0.87, the specificity 0.55, the PPV 70%, the NPV 78% and the accuracy 72.4% (Table IV).

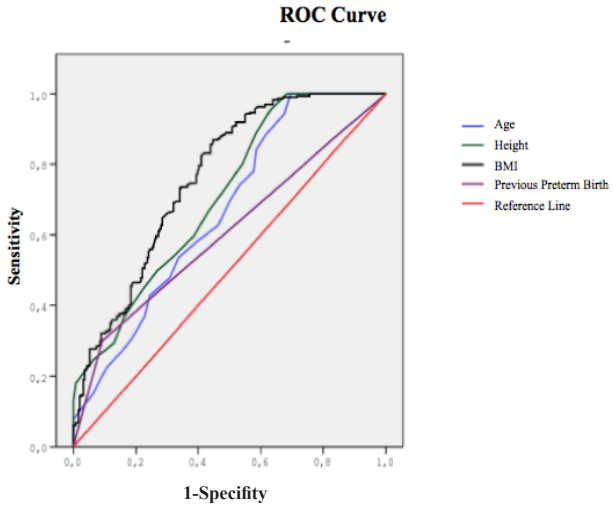

Figure I Illustration of the factors affecting preterm birth with ROC curve

Table IV The performance values for preterm birth in terms of height and BMI variables

		Sensitivity	Specificity	PPV	NPV	Accuracy
Height (cm)	152.5	0.13	1.0	1.0	0.49	0.524
	165.5	0.95	0.37	0.64	0.86	0.685
	166.5	1.0	0.32	0.64	1.0	0.691
BMI (kg/m^2)	21.3	0.06	1.0	1.0	0.44	0.487
	30.5	0.87	0.55	0.70	0.78	0.724
	34.7	1.0	0.24	0.61	1.0	0.654

BMI: body mass index; NPV: negative predictive value; PPV: positive predictive value

Discussion

Over the last 20 years, an increase in the preterm birth rate has been observed, possibly due to the increase in multiple pregnancies through assisted reproductive techniques as well as the increase in the frequency of invasive obstetric procedures (4). The proportion of preterm births in Turkey is about 15% (12). In present study, we found a preterm birth rate of 13.6% in our hospital, a tertiary center that admits high-risk patients from smaller centers. Thus, our aim was to predict and possibly prevent preterm births and its complications by identifying patients at high risk of preterm birth.

There are several studies investigating how different etiologic factors cause spontaneous preterm birth (1,13). In this study, we aimed to investigate whether maternal height and BMI can be used to predict preterm birth. We conclude that pregnant women with a small body size or a low BMI have a higher risk of preterm birth.

There are studies indicating that the most important demographic factor in the etiology of preterm birth is the young age of the mother, especially if she is 19 years old or younger (14,15). Lao et al. (14) showed that the risk of preterm birth increases in young pregnant women, while it is inversely proportional to the mother's body size. This increase in the risk of preterm birth in young women was associated with the underdeveloped anatomical body structure of young women. In our study, the mean age of mothers who had a preterm birth was 26 ± 5.4 years, while the mean age of postdate birth was 30.3 ± 7.3 years, with the difference being statistically significant (*p<0.001*). The results of the present study are consistent with these studies.

Pregnant women who have already had a preterm birth also have a higher risk of preterm birth in subsequent pregnancies (16,17,18). Schaaf et al. (16) have shown that pregnant women who have already had a preterm birth have an approximately 3-fold higher risk of a preterm birth in their next pregnancies. It has also been shown that pregnant women who have already had a preterm birth and subsequently experience a multiple pregnancy have a higher risk of preterm birth. El-Bastawissi et al. in the USA pointed out that the odds ratio (OR) for the risk of preterm birth with a previous preterm birth is 6 (18). In the present study, a statistically significant increase in the risk of preterm birth was found when patients who had a previous preterm birth were compared with those who had a later birth (*p<0.001*), and an OR of 3.637 was found.

In the meta-analysis examining maternal body size for its influence on preterm birth and abortion, it was found that pregnant women with smaller body size had a higher risk of preterm birth than pregnant women who were taller (19). The present study showed that the height of all pregnant women with preterm birth was less than 166.5 cm, while the height of all pregnant women with post-date birth was more than 152.5 cm. For the point of best estimate (the point at which the total amount of specificity and sensitivity is highest), which was 165.5 cm, the sensitivity was found to be 0.95 (meaning that 95% of pregnant women with a preterm birth are included), while the specificity was 0.37 (meaning that only 37% of pregnant women with a late birth are included).

Ehrenberg et al. (20) examined obese pregnant women with regard to the risk of preterm birth and their uterine activity. They conclude that obese/overweight women have a lower preterm birth rate before 35 weeks of gestation due to their lower uterine activity and contraction fraction compared to normal or underweight pregnant women. Apart from that study, Zhang et al. (21) found that dilation arrest was observed in pregnant women with high BMI in the first stage of labor, which in turn led to an increased cesarean section rate compared to pregnant women with normal or low BMI (OR: 3.54). This arrest of labor observed in the first stage of labor and the increase in cesarean section rate were associated with weaker myometrial contraction and lower Ca^{2+} concentration in obese pregnant women. A local study by Cnattingius et al. (22) in Sweden showed that with an increase in BMI, the risk of spontaneous preterm birth also increased, OR:1.58, when BMI was ≥30 kg/m^2.

In the study, the BMI of all pregnant women with preterm births was below 34.7 kg/m^2. In addition, the BMI of all pregnant women with a post-date birth was above 21.3 kg/m^2. When we set the best estimate for BMI at 30.5 kg/m^2, the sensitivity was 0.87 (meaning that 87% of pregnant women with preterm births are affected), while the specificity was 0.55 (meaning that 55% of pregnant women with late-term births are affected). Positive predictive value and negative predictive value were determined to be 70% and 78%, respectively. The accuracy for predicting preterm birth was calculated to be 72.4% when 30.5kg/m^2 was used as the best estimate. Our results showed that both BMI and maternal height were found to be significant predictors of preterm birth. However, BMI was the more useful criterion than maternal height.

In conclusion, there are different values/results in the literature regarding the importance and effect of BMI and maternal height in predicting preterm birth. In order to obtain an average result for these two criteria in our country, the distribution of BMI in a normal pregnancy, the distribution of weight gain by weeks of gestation and the mother's height should be determined. Since most preterm births occur in pregnancies without risk, we compared

BMI and maternal height between groups without considering the history of preterm birth. Even though we did not exclude the risk of history of preterm birth, it is obvious that mothers with the same height and approximately the same BMI had previous preterm births. Therefore, we believe that close monitoring of BMI and maternal height as thresholds from the beginning of pregnancy is an appropriate approach to reduce preterm birth and its complications. However, as this is a retrospective study, the results of the study require a prospective follow-up protocol to assess their validity.

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Investigation of Possible Predictive Factors, Clinical Characteristics, and Treatment in Vascular Behçet's Disease: Real-Life Data from a Single Center

Vasküler Behçet Hastalığında Olası Prediktif Faktörler, Klinik Karakteristikler ve Medikal Tedavinin Değerlendirilmesi: Tek Merkezden Gerçek Yaşam Verileri

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Investigation of Possible Predictive Factors, Clinical Characteristics, and Treatment in Vascular Behçet's Disease: Real-Life Data from a Single Center

ABSTRACT

Objective: The aim of this study was to investigate the phenotypes, predictive factors, and treatment approach of Behçet's patients with vascular involvement.

Material and Method: This retrospective study analyzed 123 patients with Behçet's disease, 28 of whom had vascular involvement, and were followed up in our center. The study presented the vascular involvement patterns of the patients along with their clinical characteristics and comorbid conditions. The drugs usage by the patients were analyzed based on the first line and current medications, duration of medical therapy, and drug retention rate.

Results: In Behçet's patients with vascular involvement, the male sex ratio was statistically higher compared to those without vascular involvement (60.7% vs 37.9%; OR=2.82 (1.17-6.77); *p=0.018*). The frequencies of Behçet's clinical manifestations, smoking, and comorbidities were similar in both groups. The most common subtype of vascular Behçet's is deep vein thrombosis (18; 64.2%), followed by superficial thrombophlebitis (5; 17.8%), neurovascular involvement (5; 17.8%), cardio-aortic (2; 7.1%) and pulmonary arterial (2; 7.1%). Azathioprine, glucocorticoids, and cyclophosphamide are the most preferred immunosuppressives in vasculo-Behçet's. Anticoagulant therapy was initiated in 67.8% (19; 28) of the patients at the first vascular event.

Conclusion: The study presented that male gender predicts vascular involvement in Behçet's disease, with deep vein thrombosis being the most common vascular subtype. Although immunosuppressive drugs represent the cornerstone of treatment for vasculo-Behçet's disease, most patients had also received anticoagulant therapy following the initial attack.

Keywords: Anticoagulant, Behçet's Disease, drug retention, immunosuppressive, real-world data, vascular involvement.

ÖZET

Amaç: Bu çalışmanın amacı vasküler tutulumu olan Behçet hastalarının tutulum paternlerini, prediktif faktörleri ve tedavi seçimlerini ortaya koymaktır.

Gereç ve Yöntem: Bu çalışmaya merkezimizde takipli 28'i vasküler tutulumlu olan 123 Behçet hastası retrospektif olarak dahil edildi. Hastaların vasküler tutulum paternleri diğer klinik karakteristikleri ve komorbid durumları ile sunuldu. Hastaların kullandıkları ilaçlar ilk başlanılan ajan, mevcut kullanılan ajan, kullanım süresi ve ilaçta kalım değişkenlerine göre analiz edildi.

Bulgular: Vasküler tutulumu olan Behçet hastalarında erkek cinsiyet oranı, vasküler tutulum olmayanlara göre istatistiksel olarak yüksekti (%60,7 vs. %37,9; OR=2,82 (1,17-6,77); *p=0,018*). Her iki grupta Behçet klinik tutulumları, sigara içimi ve komorbidite frekansları benzer bulundu. En sık görülen vasküler Behçet subtipi derin ven trombüsü (18; %64,2) olup onu sırasıyla süperfisyal tromboflebit (5; %17,8), nörovasküler tutulum (5; %17,8), kardiyo-aortik (2; %7,1) ve pulmoner arteriyel tutulum (2; %7,1) izledi. Vasküler Behçet'te en sık tercih edilen immunsupresifler azatioprin, glukokortikoid, siklofosfamid olup antikoagülan tedavi hastaların %67,8 (19; 28)'inde ilk vasküler olayda başlanmıştı.

Sonuç: Bu çalışmada erkek cinsiyetin Behçet Hastalığı'na bağlı vasküler tutulumu predikte ettiği gösterildi. Derin ven trombüsü en sık görülen vasküler Behçet subtipiydi. Vaskülo-Behçet'te immunsupresif ilaçlar ana tedavi olmasına rağmen hastaların büyük bir kısmı ilk atak sonrası antikoagülan tedavi de almıştı.

Anahtar Sözcükler: Antikoagülan, Behçet Hastalığı, gerçek yaşam verisi, ilaçta kalım, immünsupresif, vasküler tutulum.

Introduction

Behçet's disease (BD) is a multisystemic autoinflammatory vasculitis that affects multiple organs, including the mucocutaneous, ocular, vascular, neurological, and intestinal systems (1). The disease is characterized by pan-vasculitis, which affects veins and arteries of all sizes (2). Vascular involvement is the leading cause of mortality in BD, with particularly high mortality rates observed in cases of pulmonary and inferior vena cava involvement (2).

The frequency of vascular involvement in BD has been reported to range between 7% and 40% in different studies (3,4). The most common type of major vascular involvement is deep vein thrombosis (2). Arterial involvement is characterized by thrombosis and aneurysms and is less common than venous involvement (5,6). Superficial thrombophlebitis is considered a form of vascular involvement but is excluded from the definition of major vascular involvement.

The treatment of Vascular BD involves the use of immunosuppressive drugs (5). According to European Alliance of Associations for Rheumatology (EULAR) treatment recommendations, the first-line agents used are glucocorticoids (GC), azathioprine (AZA), and cyclophosphamide, although the specific choice may vary depending on the type of involvement (7). In cases of resistance or contraindication to immunosuppressives, biological therapies such as anti-TNF may be employed (7). The available evidence on the use of anticoagulant therapy for vascular involvement in BD is insufficient (6-8).

Many studies, including EULAR recommendations, provide drug recommendations based on the involvement patterns in vascular BD (2,5,8). However, the duration of immunosuppressive treatment remains unclear. Several Behçet's clinics have shared their experiences on this subject in the literature (2,4,5,8-10). In this respect, this study aimed to present the predictive factors, clinical characteristics, and treatment approaches of Behçet's patients followed up in our clinic, especially the subtypes of vascular involvement.

Material and Methods

Study design and patients

This retrospective study analyzed 123 patients with BD who were followed up at the rheumatology clinic of Kastamonu Training and Research Hospital between November 2022 and December 2023 and met the International Study Group Criteria of Behçet's disease (11). The study retrospectively evaluated the clinical and demographic data obtained from the patients' outpatient clinic visits every three months. The demographic data of patients with BD includes information on patient age, gender, age at diagnosis, duration of vascular involvement, body mass index, smoking, and comorbidities such as diabetes mellitus, hypertension, renal failure, coronary artery disease, and asthma/bronchial disease. The study recorded various symptoms in Behçet's patients, including oral aphthae, genital ulcers, papulopustular lesions, erythema nodosum, pathergy test positivity, ocular involvement, musculoskeletal involvement, intestinal involvement, neurological involvement, and vascular involvement.

The presence of vascular involvement was determined in 123 patients using clinical and imaging methods such as ultrasonography, CT angiography, and MRI angiography. The study analyzed vascular involvement patterns, first-line and current medications, duration of medication for each drug, number of patients who discontinued and restarted the medication along with the reasons in 28 patients diagnosed with vasculo-Behçet's.

The International Study Group Criteria of BD comprises five headings: oral aphthae, genital ulcer, ophthalmic involvement, skin involvement, and positive pathergy test (11). BD is diagnosed in individuals who have at least two of the other clinical findings in addition to oral aphthae (11).

This study was approved by the Kastamonu University, Faculty of Medicine, Ethics Committee of Clinical Research (date: 6/12/23; protocol number: 2023-KAEK-149). The study followed the Declaration of Helsinki and good clinical practice guidelines.

Statistical analysis

All statistical analyses were performed using SPSS version 26 (IBM Corp, Armonk, NYC). The normal distribution of variables was analyzed using visual (histogram) and analytical methods (Kolmogorov/Smirnov test). Descriptive statistics were presented as mean ± standard deviation for continuous variables and as frequency (n) and percentage (%) for categorical variables. Student-T test was used to compare

normally distributed variables between the groups with and without vascular involvement. Chi-square/Fisher exact tests were used to compare nominal (CI) variables. The odds ratios (95% confidence interval) were used to express the association between clinical characteristics and vascular involvement. *p value less than 0.05* was considered statistically significant.

Results

A total of 123 patients with BD were included in this study, of whom 28 (22.7%) had vascular involvement and 95 (77.3%) did not have vascular involvement. The male gender was significantly more predominant in patients with vascular involvement than in those without (60.7% vs 37.9%; OR=2.82(1.17-6.77); *p=0.018*). The mean age, body mass index, and disease duration were similar in both groups (*p>0.05*). The average duration of vascular involvement in the group with vascular Behçet's was 16.2±9.2 years (Table I).

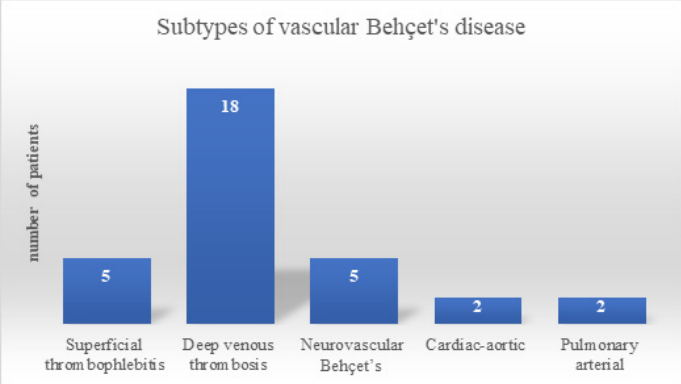

Figure I Classification of vascular involvement of Behçet's disease

The percentages of clinical involvement in Behçet's (oral aphthae, genital ulcer, papulopustular lesion, erythema nodosum, uveitis, arthralgia, intestinal and neuroparenchymal involvement) were similar in both groups, with and without vascular involvement (*p>0.05*). Additionally, both groups had similar rates of pathergy test positivity. The results of study revealed that variables other than gender had no statistically significant impact on vascular involvement (*p>0.05*) (Table I).

Table II shows the frequency of atherosclerosis-related risk factors for vascular involvement in Behçet's patients with and without vascular involvement. The results indicate that smoking was similar in both groups (46.4% vs 35.8%; *p=0.311*). Furthermore, the frequency of comorbidities, such as diabetes mellitus, hypertension, renal impairment, coronary artery disease, and pulmonary disease, was similar in both groups.

Table I Demographic and clinical characteristics of Behçet's patients with and without vascular involvement

	Vascular BD (n=28)	BD without vascular involvement (n=95)	*OR (95% CI)*	*P value*
Gender, male, n, %	17(60.7%)	36 (37.9%)	2.82(1.17-6.77)	***0.018***
Age, years, mean±SD	43.5±11.5	40.3±10.1		*0.195*
Disease duration, years, mean±SD	15.0±10.7	10.8±8.7		*0.135*
Duration of vascular involvement, years, mean±SD	16.2±9.2	-		
Body mass index, kg/m², mean±SD	27.1±3.9	26.3±5.2		*0.344*
Oral aphthous ulcer, n, %	28(100%)	94(98.9%)	0.98(0.96-1.01)	*0.587*
Genital ulcer, n, %	23(82.1%)	72(75.8%)	1.46(0.50-4.30)	*0.483*
Papulopustular lesion, n, %	19(67.8%)	60(63.2%)	1.23(0.50-3.01)	*0.650*
Erythema nodosum, n, %	18(64.3%)	52(54.7%)	1.55(0.64-3.71)	*0.322*
Pathergy positivity, n, %	20(71.4%)	69(72.6%)	0.94(0.37-2.40)	*0.901*
Uveitis, n, %	13(46.4%)	41(43.1%)	1.37(0.59-3.20)	*0.461*
Arthralgia/arthritis, n, %	19(67.8%)	65(68.4%)	0.97(0.39-2.40)	*0.955*
GIS involvement, n, %	1(3.5%)	1(1.1%)	3.48(0.21-57.51)	*0.356*
Neuroparenchyma involvement, n, %	3(10.7%)	2(2.1%)	5.58(0.88-35.23)	*0.077*

BD, Behçet's disease; SD, standard deviation; OR, odds ratio; CI, confidence interval; kg/m², kilogram/meter square, GIS, gastrointestinal system.

In the analysis of vascular Behçet's patients based on subtypes, deep vein thrombosis was found to be the most common (18; 64.2%). Superficial thrombophlebitis (5; 17.8%), neurovascular involvement (5; 17.8%), cardio-aortic (2; 7.1%), and pulmonary arterial (2; 7.1%) involvement were also detected, respectively (Figure I).

When examining the first line immunosuppressive treatments, glucocorticoids (27; 96.4%), azathioprine (18; 64.2%), and cyclophosphamide (9; 32.1%) were administered. Furthermore, 67.8% of patients received anticoagulant therapy upon diagnosis, despite the lack of conclusive evidence in vascular BD. Regarding to analysis of the current treatments of the patients, it was found that 17 (60.7%) patients used AZA and 7 (25%) patients used GC. Notably, no patients received cyclophosphamide. Furthermore, none of the patients were receiving anticoagulant treatment during their last treatment, while 4 patients were not receiving any form of treatment, including immunosuppressive and anticoagulant treatment (Figure II).

Table II Comorbidities in patients with of Behçet's patients with and without vascular involvement

	Vascular BD (n=28)	BD without vascular involvement (n=95)	OR (95% CI)	*P value*
Smoking, n, %	13(46.4%)	34(35.8%)	1.55(0.66-3.64)	*0.311*
Comorbidities, n, %				
-Diabetes mellitus	3(10.7%)	8(8.4%)	1.30(0.32-5.28)	*0.710*
-Hypertension	7(25.0%)	12(12.6%)	2.30(0.80-6.57)	*0.113*
-Renal failure	1(3.6%)	3(3.2%)	1.13(0.11-11.36)	*0.914*
-Coronary artery disease	3(10.7%)	4(4.2%)	2.73(0.57-13.00)	*0.194*
-Asthma/bronchial disease	2(7.1%)	3(3.2%)	2.35(0.37-14.87)	*0.350*

BD: Behçet's disease, OR, odds ratio; CI, confidence interval.

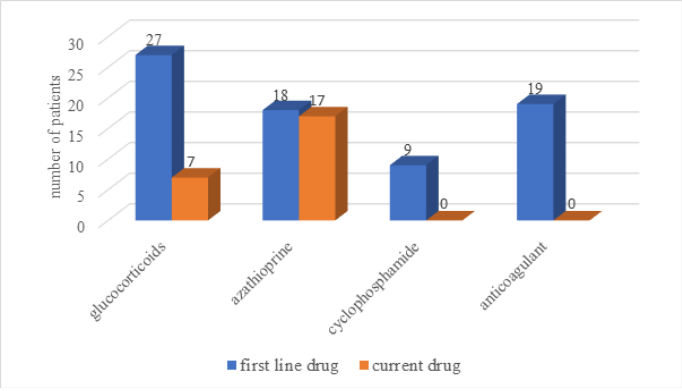

Figure II Drug retention rate of Behçet's disease, first line vs current treatment

The duration of use of immunosuppressive drugs was analyzed. AZA was used for the longest time with a mean of 11.2 (±5.8) years, followed by GC with 6.2 (±3.4) years, anti-TNF drugs with 3.5 (±1.2) years, and cyclophosphamide with 0.6 (±0.3) years (Table III). The mean duration of anticoagulant use was calculated to be 9.2 (±4.3) years.

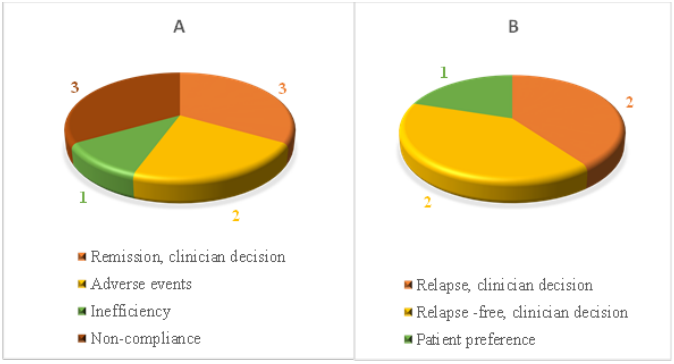

Figure III Reasons for discontinuation (A) and restarting (B) of immunosuppressive treatment

According to drug compliance of immunosuppressive treatment, it was found that treatment was discontinued for a period in 9 patients, with 5 of these patients subsequently restarting treatment. Figure III provides detailed information on the reasons for discontinuation and resumption of treatment.

Table III Duration of drug administration of vascular Behçet's patients

Drugs	Duration, year, mean (±SD)
Glucocorticoids	6.2 (±3.4)
Azathioprine	11.2 (±5.8)
Cyclophosphamide	0.6 (±0.3)
Anticoagulant	9.2 (±4.3)
anti-TNF	3.5 (±1.2)

TNF: Tumor necrosis factor.

Discussion

The study showed that the relative risk of male gender for vascular involvement was 2.82 (95% CI; 1.17 - 6.77; $p<0.05$) compared to female gender in patients with BD. This finding is consistent with previous studies on vascular Behçet's cohorts in the literature (4,10,12,13). Our study found that male gender was the only factor associated with vascular involvement. Other studies have shown a relationship between young age (4), erythema nodosum (12), ocular involvement

(12), neuroparenchymal involvement, and vascular involvement. Additionally, a retrospective study found a correlation between superficial thrombophlebitis and major vascular involvement (4).

No significant association was found between vascular BD and atherosclerosis-related factors, including smoking, diabetes mellitus, hypertension, and coronary artery disease, in our patients. The relationship between BD and atherosclerosis has been a controversial issue for years (6). A meta-analysis showed that subclinical atherosclerosis increased in patients with BD when evaluating coronary intima-media thickness (14). Furthermore, studies have demonstrated that patients with BD do not experience an increase in the frequency of coronary atherosclerosis, angina pectoris, or myocardial infarction (15,16).

The prevalence of vascular involvement in BD varies between ethnic groups. While it is less frequently observed (3-7%) in Far Eastern countries such as Japan, studies report a rate of around 40% in Türkiye (3,4). In this study, the prevalence of vascular BD was found to be 22.7% (28; 123). The most common presentation of vascular BD is deep vein thrombosis and superficial thrombophlebitis in the veins of the lower extremities (1,4,5,12,17). Neurovascular involvement characterized by thrombotic involvement in the venous sinuses of the brain is a vascular subtype of BD and is also classified as neuro-Behçet's. Consistent with the literature, this study found that deep vein thrombosis was the most common venous involvement, followed by superficial thrombophlebitis and sinus vein thrombosis. Although arterial lesions are less common in vascular BD (3-5%), they have a more severe course (2,4,5,10,12). Arterial involvement can be observed in all arterial structures, particularly the pulmonary artery. The study found arterial involvement in the pulmonary artery (2; 7.1%) and cardiac-aortic (2; 7.1%) vascular structures.

Immunosuppression is the primary treatment for vascular BD (2,5,7,8,18-20). The goal of immunosuppressive therapy is to reduce vessel wall inflammation and recanalization (2,5,7,8,19,20). In cases of venous involvement, treatment varies depending on the location and duration of the condition (acute/chronic). Glucocorticoids, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil and biological agents (TNF inhibitors) are commonly used in practice (2,5,7,8,18-20). In this study, the combination of azathioprine and corticosteroids was the first choice for the patient group. Another combination, which is especially preferred in the clinic for major arterial aneurysm and/or thrombosis, is cyclophosphamide and corticosteroids.

The duration of immunosuppressive treatment for vasculo-Behçet's disease is a controversial issue. Studies have shown that patients receiving azathioprine for DVT had a 45% frequency of vascular relapse (21). In a larger cohort of vascular Behçet's patients, relapse was observed in 44.7% of patients with a mean follow-up of 24.5 months (22). In the same study, it was found that the median duration of immunosuppressive treatment after the first vascular event was 24 months. The study also showed that relapse occurred at a median of 34.5 months (22), indicating that early discontinuation of immunosuppressive treatment may increase the risk of relapse. In our patient group, the mean duration of azathioprine use was 11.2 (±5.8) years and steroid use was 6.2 (±3.4) years, which is a relatively long duration. During the last one-year follow-up period, two patients had to restart immunosuppressive treatment due to relapse.

Anticoagulant drugs are a controversial issue in treating vascular BD. According to EULAR recommendations, anticoagulant therapy can be used if there is no pulmonary artery aneurysm (7). However, there is no prospective study on the use of anticoagulants. A study conducted in Türkiye at multiple centers found no additional benefit in terms of relapse rates when anticoagulant therapy was used in conjunction with immunosuppressive therapy, compared to immunosuppressive therapy alone (19). However, a retrospective study conducted in another cohort showed a positive effect of anticoagulant therapy (20). In our patient group, 67.85% (19; 28) of vascular Behçet's patients were started on anticoagulant therapy at the first vascular event. The patients used anticoagulants for an average of 9.2 (±4.3) years. Currently, no patients are receiving anticoagulant therapy.

Inflammation plays a central role in the pathogenesis of vascular involvement in BD. In addition, endothelial dysfunction leading to a tendency to thrombosis,

increase in procoagulant factors and dysfunction of tPA are other subheadings of the pathogenesis (5). However, the use of anticoagulant drugs in treatment is contradictory. In the latest recommendations of EULAR, anticoagulant therapy is recommended for the prevention of postthrombophilic syndrome which may be a complication of deep vein thrombosis (7).

One of the limitations of this study is that due to the retrospective nature of the study, relapses were evaluated within the period of our own follow-up and old relapses were evaluated according to patient declaration and imaging method. Therefore, relapse-time relationship and relapse-treatment relationship (immunosuppressive and anticoagulant) could not be obtained. Another limitation of the study is that due to its single-center design, subgroup analysis could not be performed in the vascular Behçet's group, in which vascular involvement of non-deep vein thrombus was rare. Therefore, the results of the study should be interpreted considering these situations. On the other hand, the most important strength of this study is that it provides detailed real-life data of patients with vascular BD.

This retrospective study found that vascular BD is more prevalent in men. The most common form of involvement in our patient group was deep vein thrombosis, consistent with previous studies. Additionally, this study showed that immunosuppressive drugs are the primary treatment for vasculo-BD, and anticoagulant therapy is frequently used in practice despite conflicting evidence. Additionally, there is a need for prospectively designed cohort studies and basic science research to determine the duration of immunosuppressive therapy and the effectiveness of anticoagulant therapy.

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Evaluation of Clinical Subacromial Impingement Test Positive Patients with Ultrasonographic Subacromial Impingement Test

Klinik Subakromial Sıkışma Testi Pozitif Hastaların Ultrasonografik Subakromial Sıkışma Testi ile Değerlendirilmesi

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Evaluation of Clinical Subacromial Impingement Test Positive Patients with Ultrasonographic Subacromial Impingement Test

ABSTRACT

Objective: Knowing which of the special clinical tests used in subacromial impingement syndrome is more successful in making the diagnosis is important for patient evaluation, determining if further examination is necessary, and arranging treatment. Utilizing sonographic impingement as a reference diagnostic technique, the study sought to evaluate how well clinical test results performed in diagnosing patients with subacromial impingement syndrome.

Material and Method: The study involved 42 patients with shoulder pain and at least one positive subacromial impingement test, including Neer, Hawkins, or Yocum tests. Dynamic sonographic compression of the tendon in the coracoacromial area was examined by abducting the shoulder. Dynamic sonographic compression findings were compared with clinical examination tests.

Results: In 40.5% of the patients, the ultrasonographic impingement test was positive. Hawkins test was positive in 81% of patients, Neer test was positive in 69% of patients, and Yocum test was positive in 78.6% of patients. A significant relationship was found between the ultrasonographically evaluated subacromial impingement test and the Neer test, but no significant relationship was found with other special tests (Hawkins and Yocum test) (*p=0.02, p=0.4, p=0.12,* respectively).

Conclusion: We have demonstrated a significant relationship between the ultrasonographic finding of dynamic subacromial impingement and the Neer test, which is a non-invasive and device-independent physical examination test.

Keywords: Dynamic sonographic impingement, Hawkins test, Neer test, shoulder pain, subacromial impingement syndrome, Yocum test.

ÖZET

Amaç: Subakromial sıkışma sendromunda kullanılan özel klinik testlerin tanıdaki başarısının bilinmesi hasta değerlendirmesinde, ileri tetkik gerekip gerekmemesi ve tedavi düzenlenmesi açısından önemlidir. Subakromial sıkışma sendromu tanılı hastalarda sonografik olarak sıkışma varlığını referans alarak klinik muayene testlerinin tanısal performansını belirlemek amaçlandı.

Gereç ve Yöntem: Çalışmaya Fizik Tedavi ve Rehabilitasyon polikliniğine şikâyeti omuz ağrısı olan ve muayenede en az 1 subakromial sıkışma testi pozitif olan (Neer, Hawkins veya Yocum testinden en az biri) 42 hasta dahil edildi. Omuza abdüksiyon yaptırarak korakoakromial alanda supraspinatus tendonuna ait dinamik sonografik sıkışma bulgusu değerlendirildi. Klinik muayene testleri ile dinamik sonografik sıkışma bulgusu karşılaştırıldı.

Bulgular: Hastaların %40,5'inde ultrasonografik olarak sıkışma testi pozitif idi. Hawkins testi %81 hastada, Neer testi %69 hastada, Yocum testi %78,6 hastada pozitif idi. Ultrasonografik olarak değerlendirilen subakromial sıkışma testi ile Neer testi arasında anlamlı ilişki saptandı, diğer özel testler (Hawkins ve Yocum testi) ile anlamlı ilişki saptanmadı (*p=0,02, p=0,4, p=0,12* sırasıyla).

Sonuç: Ultrasonografik dinamik subakromial sıkışma bulgusunun, non-invaziv ve cihaz bağımsız yapılabilen fizik muayene testlerinden Neer testi ile anlamlı ilişkisini göstermiş olduk.

Anahtar Sözcükler: Dinamik sonografik sıkışma, Hawkins testi, Neer testi, omuz ağrısı, subakromial sıkışma sendromu, Yocum testi.

Introduction

Shoulder pain impacting 16% to 26% of adults is the third most common cause of musculoskeletal complaints, and roughly 1% of adults seek medical attention each year for new shoulder pain (1). Soft tissues in the vicinity of the shoulder joint become painfully compressed in a clinical condition known as shoulder impingement syndrome. Patients experience pain when lifting their arms or lying on the affected side (2).

The coracoacromial ligament (CAL) joins the scapula's acromion and coracoid process, forming an osteoligamentous static limitation against upper humeral head displacement (3). The subacromial space is bounded above the lower surface of the acromion, acromioclavicular joint, and CAL, and below the head of the humerus (4). The gap is traversed by the long head of the biceps tendon, the subdeltoid bursa, and the supraspinatus and subscapularis tendons (5).

There are over 180 distinct shoulder physical examination tests reported in the literature, and deciding which ones to utilize is difficult. Furthermore, several labels for the same test may be used, or alternative positivity criteria may exist for the same test. Again, numerous physical examination tests of the shoulder have been used to diagnose a variety of shoulder conditions (6). Positive results from the subacromial impingement test during a dynamic sonographic evaluation of a shoulder with normal still images may point to rotator cuff issues (7).

Knowing which of the special clinical tests used in subacromial impingement syndrome is more successful in obtaining the diagnosis is significant for determining whether further testing is necessary and for treatment planning. Based on this, we aimed to examine the diagnostic performance levels of clinical test results in patients with subacromial impingement syndrome, using the sonographic impingement finding as the reference diagnostic method.

Materials and Methods

Before the Study, ethical approval was received from the local ethics committee (Ankara Dışkapı Training and Research Hospital, date: 04.04.2022 and decision no: 134/10). The study was conducted by the Declaration of Helsinki. Informed consent from the patients participating in this study was also obtained.

The study included 42 patients who presented to the physical medicine and rehabilitation outpatient clinic with shoulder pain (where all of them had positive painful arch test) and at least one positive subacromial impingement test (either the Neer, Hawkins, or Yocum test as they have high sensitivity in subacromial impingement syndrome test) (8-10). We also preferred these tests since we use them frequently in the outpatient clinic.

Exclusion criteria

The following conditions were not included in this study:

Those who have undergone a surgical procedure on the evaluated shoulder,

Those who have had steroid injections into the shoulder within the last 3 months,

Patients with a shoulder fracture and/or ongoing treatment due to a fracture,

Patients with frozen shoulder,

Patients with glenohumeral osteoarthritis, rotator cuff tendinitis-rupture, and subacromial bursitis,

Patients with bicipital tendonitis (since it frequently accompanies subacromial compression, it was excluded in order not to affect clinical test results.)

rheumatological disease, neuromuscular disease and/or serious comorbidities, cervical discopathy, and,

Those with a history of cervical trauma.

Patient demographics (including age, gender, employment, and level of education), dominant shoulder, affected shoulder, comorbidities, and clinical shoulder examination tests were recorded. Professional groups such as plasterers, assembly workers, and construction workers were included in the group with heavy work above shoulder level. While one physician performed the clinical examination for each patient, another physician performed the US evaluation for each patient. Clinical tests and ultrasonographic evaluations of the patients were performed by different physicians. The physician performing in US was not informed about the patients' clinic. The patient underwent all US examinations while seated and with their shoulder in a neutral position.

Neer test: The person performing the examination

administers the Neer test while standing behind the patient. While one hand prevents scapular rotation, the other hand flexes the patient's arm forward, closing the gap between the greater tuberosity and the anteroinferior aspect of the acromion until the patient feels pain or full flexion. If the patient experiences pain before fully flexing the arm, the test is positive (11,12) (Figure Ia).

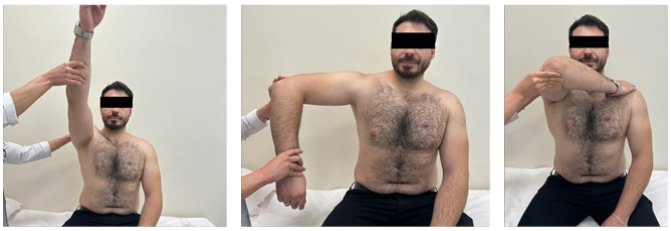

Figure I (a)Neer Test (b)Hawkins Test (c)Yocum Test

Hawkins Test: For the Hawkins test, the examiner flexes the arm to 90° with the elbow flexed at 90° and then slowly brings it into internal rotation. The test is positive if pain is experienced (13) (Figure Ib). *Yocum Test:* The Yocum test involves forcing the arm into abduction and flexing the elbow until the hand rests on the opposite shoulder. After that, the patient elevates their elbow without moving their shoulder. If the patient experiences discomfort during the maneuver, the test is termed positive (14) (Figure Ic).

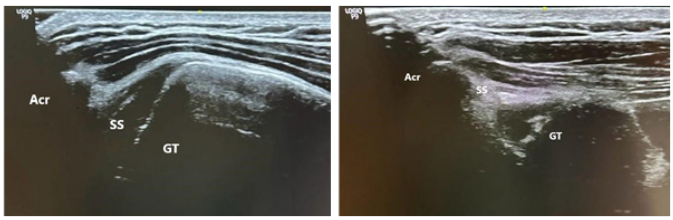

Figure II (a)Dynamic US testing for subacromial impingement in neutral position (Acr: acromion; SS: supraspinatus; GT: great tuberosity) (b)Dynamic US testing for subacromial impingement in abducted position (Acr: acromion; SS: supraspinatus; GT: great tuberosity)

Ultrasonographic Evaluation

First, with the probe on the lateral side of the shoulder, the supraspinatus tendon, subacromial bursa, and acromioclavicular joint were assessed in the transverse and longitudinal planes. Dynamic sonographic compression of the supraspinatus tendon in the coracoacromial area was examined by abducting the shoulder. The bicipital and subscapular tendons were evaluated from the anterior of the shoulder in two planes. The bicipital tendon was assessed both in the groove and distally. Externally rotating the shoulder was performed to examine the subscapularis tendon. From the posterior, the infraspinatus tendon and glenohumeral joint were assessed.

Table I Demographic and clinic data

Age (mean/SD)	54.2 (8.96)
Gender n (%)	
Female	31 (73.8)
Male	11 (26.2)
Education level n (%)	
Illiterate	5 (11.9)
Primary school	17 (40.5)
Middle school	3 (7.1)
High school	11 (26.2)
College	2 (4.8)
University graduate	4 (9.5)
Symptom duration n (%)	
3-6 months	15 (35.7)
6-12 months	8 (19)
>12 months	19 (45.2)
Occupation n(%)	
Heavy work above shoulder level	6 (14.3)
Light work above shoulder level	36 (85.7)
Dominant hand n (%)	
Right	42 (100)
Affected shoulder n(%)	
Right	26 (61.9)
Left	16 (38.1)
Comorbidity n(%)	
DM	10 (23.8)
HT	6 (14.3)
Thyroid disease	5 (11.9)
Renal disease	3 (7.1)
HL	2 (4.8)
Heart valve disease	2 (4.8)
COPD	1 (2.4)

DM: Diabetes mellitus; HT: Hypertension; HL: Hyperlipidemia; COPD: Chronic obstructive pulmonary disease

The patient was requested to raise their arm midway between flexion and abduction, with the hand in pronation and the elbow in extension, throughout the dynamic sonography evaluation. Between the acromion and the greater tubercle of the humerus,

in the coronal plane and along the supraspinatus tendon's long axis, was where the ultrasonic probe was positioned (15) (Figure IIa, Figure IIb).

Table II The rates of ultrasonographically evaluated subacromial impingement test and Neer test

	Sonographic dynamic imp finding is positive	Sonographic dynamic imp finding is negative	Total	*p**
Neer test is Positive n (%)	15 (35.8)	14 (33.3)	29 (69)	
Neer test is Negative n (%)	2 (4.8)	11 (26.2)	13 (31)	*0.02*
Total n (%)	17 (40.5)	25 (59.6)	42 (100)	

*: Pearson's chi-square test

Ultrasonographic subacromial impingement was considered positive in the presence of one of the 4 findings given below:
(a) "Bundling" or fluid expansion of the SA-SD bursa lateral to the pinch point in the coracoacromial arch (16,17),
(b) "bundling" of the supraspinatus tendon lateral to the pinch point in the coracoacromial arch (17,18),
(c) protrusion of the coracoacromial ligament (19),
(d) less commonly, complete "blocking" of supraspinatus tendon movement due to "upward displacement of the humeral head to prevent its passage under the acromion" (15).

Table III The rates of ultrasonographically evaluated subacromial impingement test and Hawkins test

	Sonographic dynamic imp finding is positive	Sonographic dynamic imp finding is negative	Total	*p**
Hawkins test is Positive	15 (35.8)	19 (45.2)	34 (81)	
Hawkins test is Negative	2 (4.8)	6 (14.3)	8 (19)	*0.4*
Total	17 (40.5)	25 (59.6)	42 (100)	

*: Pearson's chi-square test

Statistical analysis

The data were analyzed using the statistical software, Statistical Package for the Social Sciences (SPSS 22.0 for Windows). The Shapiro-Wilk test was utilized to assess the continuous variables in order to ascertain whether or not they displayed a normal distribution. For nominal variables, the data were reported as frequencies and percentages (%) in descriptive statistics. To investigate nominal variables, Pearson's Chi-Square test was used. When *p<0.05*, the results were considered significant.

Table IV The rates of ultrasonographically evaluated subacromial impingement test and Yocum test

	Sonographic dynamic imp finding is positive	Sonographic dynamic imp finding is negative	Total	*p**
Yocum test is Positive	11 (26.2)	22 (52.4)	33 (78.6)	
Yocum test is Negative	6 (14.3)	3 (7.14)	9 (21.4)	*0.12*
Total	17 (40.5)	25 (59.6)	42 (100)	

*: Pearson's chi-square test

Results

Of the total 42 patients, 31 were women (73.8%) and 11 (26.2%) were men. Average age: was 54.2. Demographic and clinic data of the patients are shown in Table I. The most common comorbidity was diabetes mellitus (10%), followed by hypertension with 6%, thyroid disease (hypothyroidism) with 5%, and renal disease (chronic renal failure) with 3%. 35.7% had symptoms for 3-6 months, 19% had symptoms for 6-12 months, and 45.2% had symptoms for more than 12 months. The dominant hand of all patients was right, and the right hand was affected in 61.9% of the patients. Ultrasonographic impingement test was positive in 40.5% of the patients. No pathology was detected in the bicipital tendon or subscapular tendon. The Hawkins test was positive in 81% of the patients, the Neer test was positive in 69% of the patients, and the Yocum test was positive in 78.6% of the patients. The ultrasonographically evaluated subacromial impingement test and the Neer test had a substantial relationship, but no significant connection was found with other specific tests (Hawkins and Yocum test). (*p=0.02, p=0.4*, and *p=0.12*, respectively). It is shown in Tables II, III, and IV.

Discussion

In this study, which we conducted to investigate the diagnostic performance levels of clinical test results by using the presence of sonographic impingement as a reference diagnostic method in patients diagnosed

with subacromial impingement syndrome, we demonstrated its significant relationship with the Neer test. Shoulder physical examination tests are clinical examination techniques developed to assist in the diagnosis of shoulder problems. The evidence for the validity and usability of tests presented in the literature is called into doubt (6).

The special subacromial impingement test may be positive for many shoulder problems. We wanted to show which test is more associated with compression of the supraspinatus tendon. In this study comparing clinically evaluated special subacromial impingement tests and sonographic subacromial impingement tests, we found that the Neer test is more related. For a physical examination of the shoulder, numerous clinical diagnostic tests have been devised, including the Neer, Hawkins, Yergason, Speed, drop arm, horizontal abduction, and painful arc tests. In cases of subacromial impingement and other shoulder diseases, these tests may be positive (20,21).

The sensitivity of the Hawkins-Kennedy test and the Neer impingement test were reported to be 62.5% and 68.8%, respectively, in a study by Somerville et al., whereas 88.9% and 77% in a study by Mac Donald et al. (22,23). Patients were examined for subacromial impingement syndrome using five physical examination tests (Neer, Hawkins-Kennedy, Jobe, painful arch, and external rotation resistance tests) in research where the surgical diagnosis was utilized as a reference (24). The painful arch test, the Jobe test, and the external rotation resistance test provide the best diagnostic benefit and reliability, while the Neer test is clinically effective for screening subacromial impingement syndrome (24). In their study by Sengul et al. (25), in which they investigated the diagnostic performance levels of clinical tests based on magnetic resonance imaging findings in patients with shoulder pain, they showed that the Neer test had 73% sensitivity, 20% selectivity, 92% positive predictive value, and 69% accuracy in detecting supraspinatus lesions. The Hawkins test was shown to have a sensitivity of 51%, a specificity of 40%, a positive predictive value of 92%, and an accuracy of 50%.

While the Yocum test did not have an adequate diagnostic performance level in detecting supraspinatus lesions, acromioclavicular joint pathologies, and glenohumeral effusion, it was found to have a high diagnostic performance level in detecting subacromial and subdeltoid effusion. We did not observe a significant relationship between the Yocum test and the dynamic ultrasonographic test. While tests for impingement and rotator cuff conditions were typically found to be sensitive, their selectivity was shown to be low (25).

In Calis et al.'s study (8), the subacromial injection test was employed as the standard reference test. The results showed that the most sensitive diagnostic tests were the horizontal adduction test (82.0%), Neer test (88.7%), and Hawkins test (92.1%). The drop arm test (97.2%), the painful arc test (80.5%), and the Yergason test (86.1%) were shown to have the best specificity. In our study, we did not find a significant relationship between the most sensitive Hawkins test and US findings.

Highly sensitive tests appear to have low specificity scores in comparison to highly specific tests, which appear to have low sensitivity levels. Although this finding implies that these diagnostic tests are insufficient for definitive diagnosis, it also implies that they serve a significant role in clinical evaluation (8). Fodor et al. (26) reported that the Hawkins test (72.2%) was the most sensitive and the Neer test (95.3%) was the most specific in detecting subacromial impingement syndrome in their investigation comparing clinical tests with US findings. In their study, Gismervik et al. (6) found that the Hawkins test had the highest diagnostic likelihood ratio (2.86) (sensitivity 0.58, specificity 0.67) for impingement syndrome. In our study, we found a significant relationship between the Neer test and dynamic ultrasonographic test.

Wang and colleagues (19) assessed the degree of CAL protrusion in the resting position and compared it to the degree of protrusion in different test procedures in their study. They concluded that the Hawkins-Kennedy impingement test caused more CAL protrusion than Neer's impingement test and that the introverted and horizontally abducted shoulder experienced the most substantial morphological alteration in the CAL. They concluded that subacromial impingement syndrome (SIS) can be diagnosed more accurately with high-resolution ultrasonography, which is also a useful technique for the dynamic

assessment of impinging structures in clinical settings. Physical examination alone is insufficient for a reliable diagnosis of subacromial impingement since the presentation is diverse and routine clinical tests may be erroneous (27, 28). A dynamic ultrasound examination that includes a clinically relevant and well-performed physical impingement test has value (29).

Conclusion

We have demonstrated a significant relationship between this important US finding and the Neer test, which is a non-invasive and device-independent physical examination test. In our study, magnetic resonance imaging (MRI) was not preferred due to its cost, long appointment, and imaging time, and most importantly, since subacromial compression is a dynamic finding and this cannot be achieved in MRI. Although the number of patients and the examination of a limited number of subacromial impingement tests are the limitations of our study, we think that our study is important and guiding in terms of showing which test is closest to the ultrasonographic result.

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Determining the Prevalence of Pain in Adult Patients Hospitalized in a University Hospital in Western Türkiye: An Observational Point Prevalence Study

Türkiye'nin Batısında Bir Üniversite Hastanesinde Yatan Erişkin Hastalarda Ağrı Prevelansının Belirlenmesi: Bir Gözlemsel Nokta Prevelans Çalışması

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Determining the Prevalence of Pain in Adult Patients Hospitalized in a University Hospital in Western Türkiye: An Observational Point Prevalence Study

ABSTRACT

Objective: Pain, called the fifth vital sign, is also known as an indicator of quality of life. This study aimed to investigate the prevalence and associated factors of pain in adult patients hospitalized in a university hospital in western Türkiye.

Material and Method: After obtaining ethical committee approval, this cross-sectional study investigated the prevalence of pain and associated factors in hospitalized patients who met the inclusion criteria using a face-to-face survey method between May 1-31, 2022. Sociodemographic data surveys were administered to the participants in the study. The Numeric Rating Scale (NRS) and the Brief Pain Inventory (BPI) were used to assess pain intensity. Pain intensity is defined as mild [1-3], moderate [4-6], or severe [7-10].

Results: The prevalence of pain was found to be 68.5% among the 762 people included in the study. The average NRS was found to be 6.33±2.24. Among the patients with pain, 60 (11.7%) had mild pain, 210 (41%) had moderate pain, and 242 (47.3%) had severe pain. A significant difference was found between the presence of pain according to gender (*p=0.034*). A moderate positive correlation was found between the worst pain intensity in the last 24 h and the least pain intensity in the last 24 h (*r=0.401, p<0.001*) and the average pain intensity in the last 24 h (*r=0.629, p<0.001*).

Conclusion: Pain prevalence and pain intensity were high in a university hospital in western Türkiye. Timely and appropriate treatments for pain management can prevent the development of complications and improve the quality of life of patients.

Keywords: Epidemiology, inpatients, pain, pain measurement, pain prevalence.

ÖZET

Amaç: Beşinci vital bulgu olarak adlandırılan ağrı aynı zamanda bir yaşam kalitesi göstergesi olarak bilinmektedir. Bu çalışmanın amacı Türkiye'nin batısında bir üniversite hastanesinde yatan erişkin hastalarda ağrı prevalansı ve ilişkili faktörlerini araştırmaktır.

Gereç ve Yöntem: Etik komite onayı alındıktan sonra hazırlanan bu kesitsel çalışmada dahil edilme kriterlerine uygun hospitalize hastalar 01-31 Mayıs 2022 tarihleri arasında yüzyüze anket yöntemi kullanılarak ağrı prevalansı ve ilişkili faktörler sorgulandı. Araştırmaya katılanlara sosyodemografik veri anketleri uygulandı. Ağrı yoğunluğunu değerlendirmek için Sayısal Derecelendirme Ölçeği (NRS) ve Kısa Ağrı Envanteri (BPI) kullanıldı.

Bulgular: Çalışmaya dahil edilen 762 kişinin ağrı prevelansı %68,5 olarak tespit edilmiştir. NRS ortalaması 6,33±2,24 olarak tespit edilmiştir. Ağrısı olan hastaların 60' ında (%11,7) hafif, 210' unda (%41) orta, 242' sinde (%47,3) şiddetli ağrı vardı. Cinsiyete göre ağrı varlığı arasında anlamlı farklılık tespit edilmiştir *(p=0.034)*. Son 24 saat en kötü ağrı şiddeti ile son 24 saat en hafif ağrı şiddeti *(r=0.401, p<0.001)* ve son 24 saatteki ortalama ağrı şiddeti *(r=0.629, p<0.001)* arasında pozitif yönde orta dereceli korelasyon ilişkisi tespit edilmiştir.

Sonuç: Ağrı prevelansı ve ağrı yoğunluğu Türkiye'nin batısında bulunan bir üniversite hastanesinde yüksek tespit edilmiştir. Ağrı yönetimindeki zamanında uygun tedaviler komplikasyon gelişimini önleyebilir ve hasta yaşam kalitesini artırabilir.

Anahtar Sözcükler: Ağrı, ağrı ölçümü, ağrı prevalansı, epidemiyoloji, yatan hastalar.

Introduction

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"(1). It is a complex and personal phenomenon that involves physical, sensory, and psychological factors. Pain is the leading cause of individual healthcare consultations and the most frequent symptom among hospitalized patients (2). Research indicates that nearly half of all hospitalized patients experience pain, with one in three reporting severe pain (3). The notion of pain as the "fifth vital sign" aims to encourage healthcare providers to be more attentive and careful about patients' pain complaints (4). Pain is known to hinder physical activity, affect sleep quality and anxiety, and contribute to a reduced quality of life and economic burden (5). However, inadequate pain management can lead to prolonged hospital stays, increased complications, higher healthcare costs, and repeated unnecessary hospitalizations (3). Therefore, healthcare providers play a crucial role in minimizing the impact of chronic pain and in supporting patients in maintaining their independent living abilities (6).

In the United States, the pain management survey was created by the Hospital Consumer Assessment of Healthcare Providers and Systems, and in Europe, the numeric rating scale (NRS) and a number of surveys have been used to determine the prevalence of pain in hospitalized patients (4). Studies conducted in different regions of the world have reported different results regarding prevalence of pain. The prevalence of pain in hospitalized patients in Canada, France, and Germany was found to be 71%, 40-90%, and 63%, respectively (7-9). Publications on the prevalence of pain are also reported to be quality indicators as they play a role in the adequate management of pain and the development of treatment strategies (10). In other words, the prevalence of pain in hospitalized patients can be defined as a quality indicator of healthcare (11). In addition, although there are some studies regarding the prevalence in Turkish society, studies regarding Turkish hospitals and inpatients are limited in the literature (12,13). Also, it has been reported that problems in pain management can cause patients to have serious functional disability, low quality of life, and significant health-related economic burdens (14). For this reason, the study to be conducted in a university hospital in the western region of Turkey is meaningful in terms of both showing the prevalence of pain and the factors affecting it and shedding light on the situation in our country on this issue. The aim of this study was to investigate the prevalence of pain and its associated factors in hospitalized in patients at Dokuz Eylül University Medical Faculty Hospital. The primary aim of this study is to determine the prevalence of pain, while the secondary aim is to determine the factors associated with pain severity.

Material and Method

Design and Setting

This cross-sectional study was conducted between 01-31 May 2022 on patients hospitalized at İzmir Dokuz Eylül University Faculty of Medicine Hospital, which has 1100 beds and is in the city of Izmir in the western region of Türkiye. Ethics committee approval was obtained before this cross-sectional study (İzmir Dokuz Eylül University Ethics Committee, Ethics Committee No:2022/02-22, Date:23.02.2022). The study protocol was in accordance with the Declaration of Helsinki as revised in 2013.

Sample

This study included patients of both sexes, aged 18 years and over, who had been hospitalized for at least 24 hours before the study, were willing to participate, and were conscious and able to speak. Patients in pandemic wards, pediatric patients, obstetric patients, patients who could not provide a pain anamnesis, and patients admitted for day surgery were excluded from the study (2, 15).

Sample Size

The sample size was computed with online calculator (https://www.calculator.net/sample-size-calculator.html). The primary endpoint was the prevalence of pain. For this purpose, we used the study of Mitello et al. (2). In their study involving 499 patients, they found the prevalence of pain to be 46.9%. Considering the number of patients included in this study, it was determined that 664 patients with marginal error of 5% and confidencel level of 99% should be included in the study. Considering that in addition to this rate, a 15% patient loss could occur, a plan was designed with 762 patients.

Measurement of Outcomes

Survey Form: The study used a survey that included sections on the patients' sociodemographic characteristics, as well as their medical diagnosis, length of hospital stays, other medical problems, mobility levels, and pain experiences (4,15).

Numeric Rating Scale (NRS): The study focused on the prevalence of pain, including its severity and duration. NRS is used to assess the intensity of pain in adults who can self-assess. It allows the intensity of pain to be determined on a scale of "0" (no pain) to "10" (maximum pain). Pain is defined as mild [1-3], moderate [4-6], or severe [7-10] (2,4).

Brief Pain Inventory (BPI): The Brief Pain Inventory (BPI) is a tool that assesses the severity of pain (BPI pain score) and the impact of pain on patients' daily functioning (BPI pain interference). Pain was rated on a scale of 0 (no pain) to 10 (the most severe pain you can imagine). In the interpretation of scores, the BPI pain score categorization is expressed as 7-10 for severe pain, 5-6 for moderate pain, 1-4 for mild pain, and 0 for the absence of pain. During the interview, the research assistant administered the BPI pain severity item, which includes 4 items in which patients rate their "worst pain", "least pain", "average pain" in the last 24 hours and "current pain". The scales for each item ranged from 0 to 10 (16-18).

Statistical analysis

We used the SPSS (Statistical Package for the Social Sciences) 24.0 package program to analyze the data of our research. We expressed frequent variables as number (n) and percentage (%). We used the Pearson chi-square and Fisher's exact test for group comparisons of frequency-indicating data. We examined the normal test assumptions of variables with continuous values using Kolmogorov, Smirnov and Shapiro-Wilk tests. We expressed variables with continuous values whose distribution pattern conformed to normal distribution as mean±standard deviation. We expressed variables with continuous values whose distribution pattern did not follow a normal distribution as mean ± standart derivation. We tested continuous value data using t test, Mann-Whitney U test, Kruskal Wallis test, considering the number of groups and normality test results. We considered *p values below 0.05* to indicate statistical significance.

Results

This study included a total of 762 patients who were hospitalized in the inpatient wards of İzmir Dokuz Eylül University Hospital. The mean age of the patients included in the study was 60.44±16.11, the median [minimum-maximum] was 63 [18-93]; the mean body weight (kg) was 74.8±14.1, the median was 74 [30-129]; the mean body length (cm) was 167.65±9.1, the median was 168 [145-197]; the duration of pain (months) was 12.26±38.41, the median was 3 [0-480]; the NRS average in all patients was 4.27±3.49, the median was 5 [0-10] and the NRS average in patients with pain was 6.33±2.24, the median was 6 [1-10].

Table I Pain Locations According to Gender

	Gender						
	Male (n=427)		Female (n=335)		Total		
	n	%	n	%	n	%	*p*
Head	38	13.6	40	16.5	78	15	*0.353*
Neck	32	11.5	37	15.3	69	13.2	*0.2*
Teeth	11	3.9	18	7.4	29	5.6	*0.083*
Abdomen	78	28	55	22.7	133	25.5	*0.172*
Upper Back	33	11.8	34	14	67	12.9	*0.45*
Lower Back	31	11.1	39	16.1	70	13.4	*0.095*
Knee	25	44.6	31	55.4	56	10.7	*0.157*
Upper Extremity	17	6.1	21	8.7	38	7.3	*0.258*
Feet	36	12.9	33	13.6	69	13.2	*0.806*
Hip	17	6.1	21	8.7	38	7.3	*0.258*
Shoulder	19	6.8	24	9.9	43	8.3	*0.199*
Chest	30	10.8	33	13.6	63	12.1	*0.314*
Other	7	2.5	9	3.7	16	3.1	*0.435*

Pearson Chi-Square Test, p<0.05 statistically significant

In this study, 453 (59.4%) patients were hospitalized in without surgery and 309 (40.6%) were hospitalized in surgery departments. Of these, 427 (56%) were male and 335 (44%) were female. A total of 232 (30.4%) participants stated that they were working. There were 209 (27.4%) patients with low economic status, 504 (66.1%) with medium economic status, and 49 (6.4%) with high economic status. The prevalence of findings accompanying pain is as follows: vomiting 62 (8.1%), nausea 93 (12.2%), fatigue 154 (20.2%), muscle weakness 153 (20.1%), loss of appetite 93

(12.2%), weight loss 92 (12.1%), dizziness 64 (8.4%), walking imbalance 75 (9.8%), insomnia 84 (11%), muscle cramps 50 (6.6%) and other symptoms 11 (1.4%). The number of patients who had previously received medication for pain was 298 (39.1%), 64 (8.4%) had medication and rehabilitation, 182 (23.9%) had medication and surgical treatment, and 44 (5.8%) had other treatments. The medication they used for their pain were as follows; paracetamol 437 (57.3%), non-steroidal anti-inflammatory drugs 101 (13.3%), narcotic analgesics 22 (2.9%), and other medications 39 (5.1%). 221 (29%) patients were not using any medication.

The ages of the patients in the study were as follows= <40y, n=101(13.3%); 41-60y, n=236 (31%); 61-70y, n=194, (25,5%), 71-80y, n=168 (22%) and >80, n=63 (8.3%). Pain was detected in 522 (68.5%) of the total 762 patients, whereas it was not detected in 240 (31.5%) patients. The most common area of pain was the abdomen 133 (25.5%), followed by the low back 70 (13.4%). No statistically significant differences were found between the painful areas according to sex (Table I). However, a significant difference was found between the sexes and the presence of pain (*p=0.034*). Pain was detected in 72.5% of women (n=243) and 65.3% of men (n=279). Acute pain was detected in 216 (28.3%) patients and chronic pain in 304 (39.9%) individuals among all patients. Cancer and vascular pain were detected in 73 (9.6%) and 122 (16%) patients, respectively. Statistically significant differences were found between educational status, the presence of cancer, and vascular pain according to whether the pain was acute or chronic, respectively (*p=0.029, p=0.036, p=0.026,* respectively) (Table II). Patients with comorbidities were as follows with their diseases and frequencies; diabetes was detected in 179 (23.5%), hypertension in 278 (36.5%), pulmonary disease in 51 (6.7%), and other diseases in 115 (5.1%).

Table II Evaluation of Factors Related to Pain Chronicity

Variable	Chronicity of Pain		*p*
	Acute (n=214, 41.3%)	Chronic (n=304, 58.7%)	
Age in Years			*0.832*
<40	36 (47.4)	40 (52.6)	
41-60	73 (41.2)	104 (58.8)	
61-70	57 (41)	82 (59)	
71-80	40 (39.6)	61 (60.4)	
>80	10 (37)	17 (63)	
Sex			*0.985*
Female	100 (41.5)	141 (58.5)	
Male	116 (41.6)	163 (58.4)	
Economic Situation			*0.811*
Mild	47 (39.8)	71 (60.2)	
Moderate	152 (42.5)	206 (57.5)	
High	17 (38.6)	27 (61.4)	
Education Status			*0.029*
Illiterate	4 (16)	21 (84)	
Literate	15 (27.8)	39 (72.2)	
Primary school	55 (44)	70 (56)	
Middle school	42 (42.9)	56 (57.1)	
High school	51 (41.5)	72 (58.5)	
Master's degree	17 (50)	17 (50)	
University	30 (52.6)	27 (47.4)	
Doctorate	2 (66.7)	1 (33.3)	
Pain Character			*0.652*
Manageable	15 (51.7)	14 (48.3)	
Throbbing	16 (47.1)	18 (52.9)	
Like a Shot Fired	2 (25)	6 (75)	
Like a knife stabbing	16 (39)	25 (61)	
Gnawing	9 (30)	21 (70)	
Sharp	6 (22.2)	21 (77.8)	
Soft	4 (40)	6 (60)	
Burning	8 (30.8)	18 (69.2)	
Exhausting	4 (26.7)	11 (73.3)	
Tiring	6 (37.5)	10 (62.5)	
Piercing	3 (42.9)	4 (57.1)	
Constantly annoying	9 (37.5)	15 (62.5)	
Numbness	10 (52.6)	9 (47.4)	
Awful	3 (30)	7 (70)	
Intolerable	6 (33.3)	12 (66.7)	
Department			*0.164*
Nonsurgical	89 (38.2)	144 (61.8)	
Surgical	127 (44.3)	160 (55.7)	
Presence of Cancer			*0.036*
Yes	22 (30.1)	51 (69.9)	
No	192 (43.1)	253 (56.9)	
Presence of Vascular Pain			*0.026*
Yes	61 (50)	61 (50)	
No	153 (38.6)	243 (61.4)	

p<0.05 statistically significant

Table III Demographic Data and Clinical Factors According to Pain İntensity

Variable	Intensity of Pain			p
	Mild	Moderate	Severe	
Age in Years				
<40	12 (15.8)	38 (50)	26 (34.2)	0.056
41-60	19 (10.9)	63 (36)	93 (53.1)	
61-70	21 (15.4)	48 (35.3)	67 (49.3)	
71-80	6 (6)	48 (48)	46 (46)	
>80	4 (14.3)	13 (46.4)	11 (39.3)	
Sex				
Female	35 (14.6)	101 (42.1%)	104 (43.3)	0.134
Male	27 (9.8)	109 (39.6)	139 (50.5)	
Economic Situation				
Mild	11 (9.4)	40 (34.2)	66 (56.4)	<0.001
Moderate	49 (13.8)	140 (39.3)	167 (46.9)	
High	2 (4.8)	30 (71.4)	10 (23.8)	
Current Job				
Housewife	8 (9.3)	21 (24.4)	57 (66.3)	<0.001
Retired	28 (12.1)	103 (44.6)	100 (43.3)	
Officer	5 (8.8)	26 (45.6)	26 (45.6)	
Employee	8 (12.9)	31 (50)	23 (37.1)	
Student	4 (30.8)	2 (15.4)	7 (53.8)	
Self-employment	8 (12.9)	31 (50)	23 (37.1)	
Other	0 (0)	17 (63)	10 (37)	
Pain Character				
Manageable	6 (20)	18 (60)	6 (20)	0.032
Throbbing	5 (14.7)	12 (35.3)	17 (20)	
Like a Shot Fired	1 (12.5)	5 (62.5)	2 (25)	
Like a knife stabbing	1 (2.4)	14 (34.1)	26 (63.4)	
Gnawing	5 (16.7)	13 (43.3)	12 (20)	
Sharp	2 (7.1)	13 (46.4)	13 (46.4)	
Soft	2 (20)	6 (60)	2 (20)	
Burning	4 (15.4)	15 (57.7)	7 (26.9)	
Exhausting	1 (6.7)	7 (46.7)	7 (46.7)	
Tiring	4 (25)	5 (31.3)	7 (43.8)	
Piercing	1 (14.3)	3 (42.9)	3 (42.9)	
Constantly annoying	2 (8.3)	14 (58.3)	8 (33.3)	
Numbness	0 (0)	4 (21.1)	15 (78.9)	
Awful	1 (10)	5 (50)	4 (20)	
Intolerable	5 (27.8)	5 (27.8)	8 (44.4)	
Department				
Nonsurgical	40 (17.2)	76 (32.8)	116 (50)	<0.001
Surgical	22 (7.8)	134 (47.3)	127 (44.9)	
Presence of Cancer				
Yes	6 (8.2)	19 (26)	48 (65.8)	0.003
No	53 (12.1)	191 (43.7)	193 (44.2)	
Presence of Vascular Pain				
Yes	12 (10)	74 (61.7)	34 (28.3)	<0.001
No	47 (12.1)	136 (34.9)	207 (53.1)	

p<0.05 statistically significant

Table IV Demographic Data and Clinical Factors by Departments

Variable		Departments		p
		Department of Non-Surgery	Department of Surgery	
Pain	+	234(44.8)	288(55.2)	**<0.001**
	-	219(91.3)	21(8.8)	
NRS	Mild Pain 1-3	40 (64.5)	22 (35.5)	**<0.001**
	Moderate Pain 4-6	76 (36.2)	134 (63.8)	
	Severe Pain 7-10	116 (47.7)	127 (52.3)	
Age in Years				
<40		55 (54.5)	46 (45.5)	**<0.001**
41-60		143 (60.6)	93 (39.4)	
61-70		94 (47.9)	101 (52.1)	
71-80		111 (66.1)	57 (33.9)	
>80		51 (81)	12 (19)	
Sex				
Female		218(65.1)	117(34.9)	**0.005**
Male		235(55)	192(45)	
Economic Situation				
Mild		144 (68.9)	65 (31.1)	**<0.001**
Modarete		289 (57.3)	215 (42.7)	
High		20 (40.8)	29 (59.2)	
Education Status				
Illiterate		27 (67.5)	13 (32.5)	**0.008**
literate		57 (67.1)	28 (32.9)	
Primary school		104 (60.8)	67 (39.2)	
Middle school		64 (44.8)	79 (55.2)	
High school		119 (63.6)	68 (36.4)	
Master's degree		30 (61.2)	19 (38.8)	
University		50 (60.2)	33 (39.8)	
Doctorate		1 (33.3)	2 (66.7)	
Marital status				
Never Married		44(66.7)	22(33.3)	**<0.001**
Married		313(56)	246(44)	
Widow/widower		82(75.9)	26(24.1)	
Divorced		14(48.3)	15(51.7)	
Current Job				
Housewife		112 (78.3)	31 (21.7)	**<0.001**
Retired		187 (54.5)	156 (45.5)	
Officer		39 (53.4)	34 (46.6)	
Employee		42 (55.3)	34 (44.7)	
Student		16 (94.1)	1 (5.9)	
Self-employment		47 (60.3)	31 (39.7)	
Other		8 (26.7)	22 (73.3)	
Pain Character				
Manageable		17 (56.7)	13 (43.3)	**0.022**
Throbbing		11 (32.4)	23 (67.6)	
Like a shot fired		3 (37.5)	5 (62.5)	
Like a knife stabbing		21 (51.2)	20 (48.8)	
Gnawing		11 (36.7)	19 (63.3)	
Sharp		12 (42.9)	16 (57.1)	
Soft		4 (40)	6 (60)	
Burning		9 (34.6)	17 (65.4)	
Exhausting		10 (66.7)	5 (33.3)	
Tiring		11 (68.8)	5 (31.3)	
Piercing		1 (14.3)	6 (85.7)	
Constantly annoying		12 (50)	12 (50)	
Numbness		13 (68.4)	6 (31.6)	
Awful		4 (40)	6 (60)	
Intolerable		14 (77.8)	4 (22.2)	
Presence of Cancer				
Yes		38(52.1)	35(47.9)	0.173
No		194(43.5)	252(56.5)	
Presence of Vascular Pain				
Yes		24(19.7)	98(80.3)	**<0.001**
No		208(52.3)	190(47.7)	

NRS= The Numeric Rating Scale, *p<0.05* statistically significant

Among all patients, 60 (8.1%) had an NRS final score of 1-3 (mild pain), 210 (27.6%) had 4-6 (moderate pain), and 243 (31.9%) had 7-10 (severe pain). Among the patients with pain (mild pain), 60 (11.7%), 4-6 (moderate pain) 210 (41%), and 7-10 (severe pain) 242 (47.3%) were detected. According to pain intensities, a significant relationship was detected between economic status, current job, pain character, department where the patient was hospitalized, presence of cancer, and vascular pain, respectively (*p<0.001, p<0.001, p=0.032, p<0.001, p=0.003, p<0.001*, respectively) (Table III). A significant relationship was detected between the presence and intensity of pain, age groups, sex, gender, economic status, educational status, marital status, current job, pain characteristics and presence of vascular pain in the patients according to the departments in which they were hospitalized, respectively (*p<0.001, p<0.001, p<0.001, p=0.005, p<0.001, p=0.008, p<0.001, p<0.001, p=0.022, p<0.001*) (Table IV).

Table V Correlation Relationship Between Brief Pain Inventory Subgroups

	Worst pain in the last 24 hours		Least pain in the last 24 hours		Average pain in the last 24 hours		Current Pain	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Worst pain in the last 24 hours	-	-	*0.401*	***<0.001***	*0.629*	***<0.001***	*0.302*	***<0.001***
Worst pain in the last 24 hours	*0.401*	***<0.001***	-	-	*0.572*	***<0.001***	*0.447*	***<0.001***
Worst pain in the last 24 hours	*0.629*	***<0.001***	*0.572*	***<0.001***	-	-	*0.453*	***<0.001***
Worst pain in the last 24 hours	*0.302*	***<0.001***	*0.447*	***<0.001***	*0.453*	***<0.001***	-	-

Pearson correlation test, *p<0.05* statistically significant

According to the BPI results of the patients included in the study median [minimum-maximum], the worst pain intensity in the last 24 hours was 8 [0-10], the least pain intensity in the last 24 hours was 3 [0-10], the average pain intensity in the last 24 hours was 5 [0-10] and the current pain was 4 [0-10]. A moderate positive correlation was found between the worst pain intensity in the last 24 hours and the least pain intensity in the last 24 hours (*r=0.401, p<0.001*) and the average pain intensity in the last 24 hours (*r=0.629, p<0.001*). A weak positive correlation was found between the worst pain intensity in the last 24 hours and the current pain intensity (*r=0.302, p<0.001*) (Table V).

Discussion

We found that the prevalence of pain in 762 hospitalized patients was 68.5%. The prevalence of pain was significantly higher in women than that in men. The average NRS was 6.33±2.24. 90% of the participants with pain had moderate or severe pain. Severe pain was higher in the non-surgical departments, while moderate pain was higher in the surgery departments.

Of the 762 patients included in our study, 59.4% were hospitalized in non-surgical departments and 40.6% in surgical departments. Of these, 56% were male and 44% were female. The prevalence of pain was found to be 68.5%. The NRS average score in patients with pain was found to be 6.33±2.24. The most common finding associated with pain was fatigue (20.2%), the most used analgesic for pain was Paracetamol (57.3%), and the most common painful body region was the abdomen (25.5%). The most common age range of the patients included in the study was 41-60 years (31%). While no significant difference was found between sex and painful body region, a significant difference was found between educational status and whether the pain was acute/chronic. A statistically significant difference was found between the pain intensity and the presence of cancer or vascular pain. A positive correlation was found between the worst, mildest, and average pain in the last 24 hours and the current pain.

Several studies have investigated, the prevalence of pain in hospitalized patients has been investigated in different studies. Das et al. (3) found the prevalence of pain in a teaching hospital in India was 70.6%, and Wu et al. (4) found it to be 69.5% in an academic medical center in Taiwan, Strohbuecker et al (7). found it to be 63% in a teaching hospital at a German university, while Wadensten et al. (19) found it to be 65% in a university hospital in Sweden. Our study is comparable to the literature with a pain prevalence of 68.5%. However, Damico et al. (20) found the prevalence of pain to be 38% in a study involving 26 centers in Italy. The difference in prevalence between studies can be explained by

differences in the inclusion/exclusion criteria in the study methodologies and differences between the departments where the studies were conducted.

In our study, the most common location of pain reported by patients was the abdomen (25.5%). Das et al. (3) also found that pain was most common in the abdomen, like our study. However, the results reported in the literature indicate that the most common location is the first site of musculoskeletal pain, followed by the abdomen (7). Silva et al. (21) found the most common location of pain was the abdomen (33.3%), in a study that examined the prevalence of pain in a hospital in Portugal. However, when they evaluated all musculoskeletal regions as a single region, musculoskeletal pain was the most common. Musculoskeletal pain affects 47% of the general population and causes a loss of quality of life (22). In our study, the prevalence was also found to be 59% when all musculoskeletal regions were evaluated as a single region. It can be stated that health care providers have a great responsibility to detect and treat both musculoskeletal pain and abdominal pain to improve patient quality of life.

In our study, the mean NRS score in patients with pain was 6.33±2.24. In different studies, the average NRS was 5.2 ± 3.33 and 6.27 ± 1.97, like our study (2,3). According to the NRS results in our study, mild pain was found in 11.7% of the patients, moderate pain in 41%, and severe pain in 48.8%. In a study conducted in India, mild, moderate, and severe pain were found in 9.4%, 41.1%, and 49.5% of patients, respectively, like our study (3). Sawyer et al. (8) reported severe pain in 25.8% of the patients and Silva et al. (21) reported severe pain in 28.8% of the patients. This difference can be explained by the differences in study methodologies and the cultural differences in how patients assess pain. In our study, it was observed that severe pain was significantly more common in cancer patients. Like our study, studies have shown that show that severe pain is significantly more common in cancer pain (3,23). This situation can be explained by the need for healthcare providers to prioritize cancer patients in terms of care and pain management. In our study, chronic pain was found in 58.7% of the patients with pain. Hutchcroft et al. (24) found chronic pain in 54% of patients, and Salomon et al. (8) found this in 44% of patients. On the other hand, some studies that have also found chronic pain at levels of 10% (3). This can be explained by the differences between the methodologies and the departments in which the studies were conducted. In addition, it can guide healthcare providers in preventing pain from becoming chronic.

In our study, we found no significant difference between patients in the non-surgery and surgery departments in terms of whether they had acute or chronic pain, but we did find a significant difference in pain intensity. Accordingly, severe pain was higher in non-surgical departments, whereas moderate pain was higher in surgical clinics. In contrast to the results of our study, it has been reported in the literature that pain lasting longer than 4 weeks is significantly more common in non-surgical departments (3). This can be explained by the fact that the definition of chronic pain is difference between studies. In our study, we defined patients who reported pain for ≥ 3 months as being in the chronic pain group.

In our study, we found that the prevalence of pain was significantly higher in women than that in men. A study conducted at a teaching hospital in France with 1478 participants also found that women reported more pain than men (8). The reason for this is not yet clear, but it has been reported in the literature that women are more likely to have a higher somatic response to pain stimuli than men. Women expressing pain have also been reported to have increased social acceptability (11). Future studies identifying the cause will clarify the difference in pain between the sexes.

In the current study, according to the BPI results, a moderate positive correlation was found between the worst, mildest, and average pain in the last 24 hours. Lorenz et al. (18) also found a moderate positive correlation between BPI parameters like our study. Considering the current pain processes of patients, it can be explained that the pain levels are in proportional ups and downs between these processes.

As a result of the surveys applied in the current study, it was determined that pain symptoms were more common in female patients than in the opposite sex, and the most common painful area was the abdomen and musculoskeletal region. Clinicians

should pay attention to these areas during patient examination and evaluation and should not ignore other areas. As it is known, the patient's response to pain questioning is affected by many factors, from the patient's clinical condition to his cultural status. The mean NRS value we obtained in patients hospitalized in a university hospital in Turkey will be a guide in questioning the level of pain experienced by doctors when examining patients during their clinical practice.

Our study has some limitations. It can be said that the results of the study cover hospitalized patients in a university hospital and will not be generalizable to a society with a large population. The answers given by the participants to the questions may lead to different results in different societies due to socio-cultural reasons. The fact that patients with no history taken a pain history were not included in our study is another important limitation. Conducting similar studies in patients who cannot have a pain history in the future will contribute to the field of science.

Conclusion

In this study, we investigated the prevalence of pain and its associated factors in a university hospital in Western Türkiye. Health care providers should be more attentive to patients about pain, which is an important quality of life indicator and is called the fifth vital sign, and that they should improve themselves in pain management. Factors affecting the quality of pain management include appropriate assessment, multidisciplinary, collaborative care planning, effective, cost-conscious, and safe treatment, and access to specialized care when needed. Pain prevalence detection and effective pain management improve the quality of life and ensure effective treatment delivery.

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The Role of Sedation and Local Anesthesia in Acute Subdural Hematoma Surgery in the Elderly Population

Yaşlı Populasyonda Akut Subdural Hematom Cerrahisinde Sedasyon Lokal Anestezinin Yeri

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The Role of Sedation and Local Anesthesia in Acute Subdural Hematoma Surgery in the Elderly Population

ABSTRACT

Objective: In the elderly population, subdural hematoma represents a significant cause of morbidity and mortality. The surgical and anesthesia techniques for managing this condition have progressively evolved. Unlike numerous studies that compare chronic cases managed under general anesthesia and sedation, our study uniquely focuses on acute subdural hematoma cases.

Material and Method: From 2020 to 2024, a retrospective study reviewed 54 patients aged 65 and older who underwent surgery for acute subdural hematoma. The patients were categorized into two groups: sedation (n=26) and general anesthesia (n=28). Data on surgical duration, hospital and intensive care unit stays, and mortality rates were collected from hospital archives. The general anesthesia group received midazolam, fentanyl, propofol, and rocuronium, while the sedation group received midazolam, fentanyl, and propofol. Subdural drains were universally placed and removed after postoperative brain computed tomography.

Results: The mortality rate was significantly lower in the sedation group compared to the general anesthesia group ($p=0.024$). Surgical duration was shorter in the sedation group ($p<0.001$), and the intensive care unit stay was also significantly reduced ($p<0.001$). There was no significant difference in regular ward stay between the groups ($p=0.212$). The time from surgery to discharge was significantly shorter in the sedation group ($p<0.001$). Sedation facilitated lower bleeding and medication doses, enabled early mobilization, and potentially increased the benefit-to-risk ratio of surgery.

Conclusion: While many studies compare general anesthesia and sedation in chronic subdural hematoma surgery, our study is the first to compare these approaches in elderly patients with acute subdural hematoma. We found shorter surgical times and lower complication rates with sedation.

Keywords: General anesthesia, sedation, subdural hematoma surgery.

ÖZET

Amaç: Yaşlı popülasyonda sık görülen subdural hematom, önemli bir morbidite ve mortalite nedenidir. Bu patolojinin cerrahisi ve anestezi uygulama teknikleri zamanla evrimleşmiştir. Genel anestezi ve sedasyon altında yapılan kronik subdural hematom cerrahilerinin karşılaştırılması literatürde çokça yer alırken, bu çalışmamızda farklı olarak benzer perspektiften akut subdural hematom vakaları tartışılacaktır.

Gereç ve Yöntem: 2020 - 2024 yıllarında akut subdural hematom nedeniyle opere edilen 65 yaş üzeri 54 hasta sedasyon (n=26) ve genel anestezi grubu (n=28) olarak iki gruba ayrılarak cerrahi süreleri, servis ve yoğun bakım ünitesi kalış süreleri ve mortalite oranları retrospektif olarak hastane arşivinden taranmıştır. Genel anestezi grubuna uygun dozda midazolam, fentanyl, propofol, roküronyum; sedasyon grubuna ise midazolam, fentanyl, propofol uygulanmıştır. Tüm hastalara subdural dren yerleştirilmiş ve postoperatif beyin tomografileri çekildikten sonra drenleri çekilmiştir.

Bulgular: Mortalite oranı, sedasyon grubunda genel anestezi grubuna kıyasla daha düşük olarak saptanmıştır ($p=0.024$). Cerrahi sürenin sedasyon grubunda daha kısa olduğu görülmüştür ($p<0.001$). Yoğun bakım ünitesinde kalış süresinin sedasyon grubunda anlamlı şekilde daha kısa olduğu belirlenmiştir ($p<0.001$). Gruplar arasında hastanede kalma süresi açısından bir fark saptanmamıştır ($p=0.212$). Ameliyat ile taburculuk arasında geçen sürenin sedasyon grubunda belirgin şekilde daha kısa olduğu görülmüştür ($p<0.001$). Sedasyon grubunda kanamanın az olması ve alınan ilaç dozunun düşük olması, hastaya erken mobilizasyon olanağı sağlamıştır. Bu durum, erken mobilizasyonu ve cerrahiden sağlanan fayda oranını artırmıştır.

Sonuç: Kronik subdural hematom cerrahisinde genel anestezi ve sedasyonu karşılaştıran birçok çalışma mevcutken, çalışmamız ileri yaş akut subdural hematom vakalarında genel anestezi ve sedasyonun karşılaştırıldığı ilk çalışmadır. Sedasyonla yapılan akut subdural hematom olgularında ameliyat süresi ve komplikasyon oranı daha düşük saptanmıştır.

Anahtar Sözcükler: Genel anestezi, sedasyon, subdural hematom cerrahisi.

Introduction

Chronic subdural hematomas (CSH) are typically drained by neurosurgeons via craniotomy under general anesthesia, using either double burr holes or a single burr hole. With advancements in endoscopic surgery, experienced surgeons can now successfully perform endoscopic subdural hematoma drainage (1). In recent years, for older adults where complications from general anesthesia are a concern, drainage of a subdural hematoma via a single burr hole under sedation has become increasingly widespread (2). As the use of high-speed drills and surgeon experience increase, the evacuation of subdural hematomas under sedation can be accomplished more efficiently. Consequently, the duration of postoperative admission to the critical care unit is minimized, surgical infection rates are reduced, and early mobilization becomes feasible, thereby enhancing overall surgical success rates (3). In extraordinary situations, such as pandemics, finding a place in intensive care units for neurosurgery cases can become challenging. This has prompted neurosurgeons to become faster and more practical. Advanced age patients with comorbidities often require general anesthesia and intensive care monitoring. However, selected cases performed under sedation can be monitored in the general ward (4). In the literature, the use and comparison of general anesthesia and sedation for CSH cases have been evaluated in many studies (5,6). Unlike other studies, this study evaluated acute subdural hematoma (ASH) cases in patients over the age of 65 who underwent surgery under both sedation and general anesthesia.

Material and Methods

ASH cases operated on by a single surgeon at a single center between 2020 and 2024 were retrospectively analyzed. The study included a total of 54 patients: 28 underwent surgery under general anesthesia (general anesthesia group) and 26 under sedation (sedation group). Patient data were obtained from the hospital database and included discharge reports, age, gender, length of stay in the ward and intensive care unit, duration of surgery, and mortality rates. Exclusion criteria included patients under 65 years of age, those with a history of cranial surgery, and those with bilateral subdural hematoma. All cases were operated on within the first week after hospital admission. Patients with a midline shift greater than 1 cm or hemiparesis were operated on the day of arrival. Patients with a midline shift less than 1 cm and without hemiparesis were monitored, and those who developed hemiparesis during follow-up underwent emergency surgery on the same day.

Surgery was performed under sedation for patients who could not tolerate general anesthesia. The general anesthesia group received midazolam 0.01 mg/kg, fentanyl 1 mcg/kg, propofol 3 mg/kg, and rocuronium 0.6 mg/kg. The sedation group received midazolam 0.01 mg/kg, fentanyl 0.5 mcg/kg, and propofol 1.5 mg/kg. Postoperatively, patients were evaluated by an anesthesiologist. Those who did not require intensive care were monitored in the neurosurgery ward, while patients experiencing respiratory distress, arrhythmia, or loss of consciousness were transferred to the intensive care unit. A subdural drain was routinely placed in all patients during surgery, and they were discharged after a routine postoperative control brain tomography was performed and the drains were removed. The general anesthesia and sedation groups were compared in terms of surgery time, mortality rates, and intensive care follow-up periods. This retrospective investigation received approval from the Hitit University Non-Entrepreneurial Research Ethics Board (No: 2024-08; date: 03/04/2024).

Statistical analysis

Statistical evaluations were conducted using SPSS (version 22.0; IBM, Armonk, NY). The surgical duration, lengths of stay in the ward and intensive care unit, the interval between the day of surgery and discharge, and mortality rates were compared between the groups using the Mann–Whitney U test. Statistical significance was set at a *p-value threshold of <0.05*.

Results

The study comprised 54 patients, including 29 males and 25 females. Midline shift was observed in 45 of these patients: 21 had a shift of 1.5 cm (±1 mm), and 24 had a shift of 1 cm (±1 mm). General anesthesia and craniotomy were preferred for patients with extensive midline shift. Most patients had a history

of trauma, although clear trauma information was not available for those with dementia. Of the 54 patients, 28 underwent general anesthesia and 26 received sedation. The average age of participants was 75.6 ± 6.3 years in the general anesthesia group and 84.2 ± 5.3 years in the sedation group (Table I). The general anesthesia group underwent craniotomy, while the sedation group underwent burr hole drainage, as illustrated in Figures I and II.

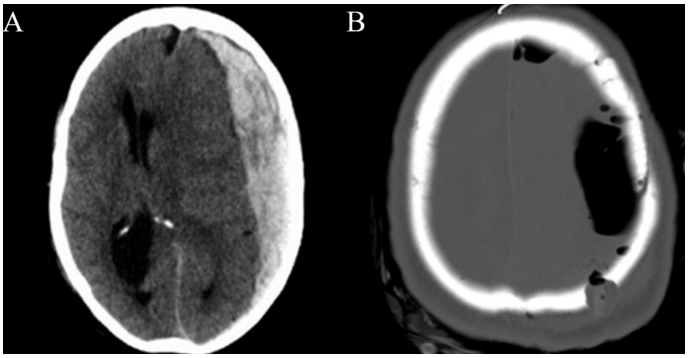

Figure 1 (A): Preoperative image of general anesthesia group, (B): Postoperative image of general anesthesia group with craniotomy defect

Table I Demographic characteristics of the participant population

	General Anesthesia Group	Sedation Group
Patients (n=54)	28	26
Sex • Female (n) • Male (n)	 13 15	 12 14
Age (mean ± standard deviation) (years)	75.6 ± 6.3	84.2 ± 5.3

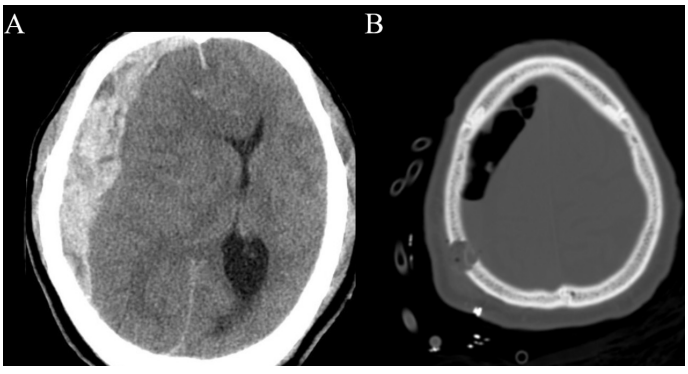

Figure 2 (A): Preoperative image of sedation group, (B): Postoperative image of sedation group with Burr Hole defect

All 26 patients in the sedation group were discharged, whereas five patients from the general anesthesia group passed away during their stay in the intensive care unit. Consequently, the mortality rate was significantly lower in the sedation group compared to the general anesthesia group (*p=0.024*). A significant difference in surgical duration between the groups was also detected (*p<0.001*). The average surgical duration was shorter in the sedation group compared to the general anesthesia group (23.6 ± 5.3 minutes vs. 59.6 ± 8.8 minutes) (Table II).

Table II Showing comparing analysis between the groups of sedation and general anesthesia

	General Anesthesia Group (n=28)	Sedation Group (n=26)	
Mortality (n)	5	0	*p=0.024*
Surgery duration (min)	59.6 ± 8.8	23.6 ± 5.3	*p<0.001*
Intensive care unit stay (days)	4.5 ± 3.9	0.58 ± 0.5	*p<0.001*
Hospital ward stay (days)	4.3 ± 2.7	5.2 ± 0.8	*p=0.212*
Hospital discharge length (days)	8.1 ± 2.5	5.8 ± 1.1	*p<0.001*

min: minutes

A notable disparity in postoperative intensive care unit stay length was observed between the groups (*p<0.001*). The average stay duration in the intensive care unit was shorter in the sedation group than in the general anesthesia group (0.58 ± 0.5 days vs. 4.5 ± 3.9 days). Conversely, no significant difference was noted in hospital ward stay duration between the cohorts (*p=0.212*). The mean duration of hospital ward stay was 4.3 ± 2.7 days in the general anesthesia group and 5.2 ± 0.8 days in the sedation group. The interval between the surgery date and discharge date was notably shorter in the sedation group compared to the general anesthesia group (mean interval, 5.8 ± 1.1 days vs. 8.1 ± 2.5 days; *p<0.001*) (Table II).

Discussion

For chronic subdural hematomas, numerous factors such as the patient's age, comorbidities, size of the bleed, and presence of midline shift affect the indication, type, and urgency of surgery. A craniotomy may be preferred in cases of acute-on-chronic hematoma or when there is a midline shift and edema caused by the hematoma General anesthesia is typically used for craniotomy. However, in recent years, hematoma evacuation via a single burr hole

has become more common in patients who are at higher risk for complications from general anesthesia. Patients who undergo surgery under sedation demonstrate cardiac and respiratory complications less frequently than those who undergo surgery under general anesthesia (7). Furthermore, patients with chronic subdural hematoma who undergo evacuation under local anesthesia and sedation experience fewer postoperative complications, shorter surgical times, and shorter hospital stays compared to those who undergo evacuation under general anesthesia (8). A study reported that surgeries performed under local anesthesia had shorter surgical times, lower mortality rates, and fewer postoperative complications compared to those performed under general anesthesia (9). Another study found that patients with chronic subdural hematoma who underwent surgery under local anesthesia and sedation had fewer postoperative complications and shorter hospital stays compared to those who underwent surgery under general anesthesia (10). Similarly, in our study, both the interval between surgery and discharge and the duration of stay in the intensive care unit were shorter for surgeries performed under local anesthesia and sedation compared to those performed under general anesthesia.

As an alternative, a mini craniotomy can be performed under sedation and local anesthesia. However, this procedure should be carried out only by experienced surgeons, as the use of high-speed drills during a sedation-assisted mini craniotomy can pose challenges due to the lack of head fixation (11). In experienced centers, surgeries for acute subdural hematomas have been successfully performed under sedation (12). The use of rigid or angled endoscopes in these procedures has been reported to increase the surgical success rate (13,14). In ASH surgery, procedures have traditionally been performed with general anesthesia and craniotomy. In contrast, for chronic subdural hematoma surgery, some surgeons prefer sedation and local anesthesia, particularly in older patients. There are no definitive criteria for determining the surgical method. Craniotomy may be preferred in cases with significant hemorrhage or when there is a risk of intraoperative loss of control. The surgeon's experience and speed also play a crucial role in the decision-making process. In extraordinary situations, such as pandemics, finding a place in intensive care units may become challenging, compelling surgeons to seek effective and practical solutions while maintaining surgical ethics and standards (15). Most of the cases were performed during the pandemic, and using sedation and local anesthesia for ASH surgery greatly increased the comfort of both the anesthesiologist and the surgeon, as well as the patients. The avoidance of intubation is also significant in terms of reducing the risk of coronavirus transmission. Further studies on this topic could be beneficial. This study highlights that ASH cases can be effectively managed with sedation and local anesthesia (16). The increased use of endoscopic techniques in subdural hematoma surgery has significantly accelerated the pace of research conducted in recent years (17). Considering all this information, it is anticipated that the use of a single burr hole under sedation for the surgical treatment of ASH will become more widespread in the future.

In conclusion; for patients deemed to possess heightened vulnerability to the adverse effects of general anesthesia, executing surgical procedures under sedation and local anesthesia holds promise in mitigating mortality rates and diminishing the length of intensive care unit residency. Therefore, it is an appropriate strategy to perform surgery under sedation and local anesthesia in elderly patient groups presenting with ASH.

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Comparison of the Efficacy of Dorsal Root Ganglion Pulsed Radiofrequency for 2 Minutes versus 4 Minutes in the Treatment of Chronic Lumbosacral Radicular Pain

Kronik Lumbosakral Radiküler Ağrı Tedavisinde Dorsal Kök Gangliyonu Darbeli Radyofrekansın 2 Dakikaya Karşı 4 Dakika Süreyle Uygulanmasının Etkinliğinin Karşılaştırılması

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Comparison of the Efficacy of Dorsal Root Ganglion Pulsed Radiofrequency for 2 Minutes versus 4 Minutes in the Treatment of Chronic Lumbosacral Radicular Pain

ABSTRACT

Objective: Pulsed radiofrequency treatment of the dorsal root ganglion has been increasingly used to treat lumbosacral radicular pain in recent decades. However, there is no consensus in the literature regarding issues such as pulsed radiofrequency application duration. This study aimed to determine the efficacy and incidence of adverse events between 2-minute and 4-minute pulsed radiofrequency for lumbosacral radicular pain.

Material and Method: This retrospective study included 160 patients who underwent 2-minute or 4-minute dorsal root ganglion pulsed radiofrequency treatment (Group-2 minutes 82 patients and Group-4 minutes 78 patients). The Numeric Rating Scale and Oswestry Disability Index scores before, 1 and 6 months after the interventions were evaluated to assess the effectiveness of the procedures. The rate of intervention-related adverse events was determined for both durations.

Results: Both the 2-minute and 4-minute procedures provided effective analgesia at 1 and 6 months compared with baseline. There was no difference in the pain scores between the two groups at the measurement times. At the 1-month follow-up, 50% or greater pain relief was achieved in 39% of patients in the 2-minute group compared to 50% in the 4-minute group, with no difference between the groups. There was no significant difference in the rate of procedure-related adverse events between the groups.

Conclusion: Although a higher success rate was achieved with 4-minute pulsed radiofrequency, there was no significant difference, and both 2 and 4-minute pulsed radiofrequency procedures provided safe and effective analgesia compared with baseline. Prospective studies with larger sample sizes are needed.

Keywords: Inflammation, pulsed radiofrequency treatment, radiculopathy.

ÖZET

Amaç: Dorsal kök ganglionunun pulsed radyofrekans tedavisi, son yıllarda lumbosakral radiküler ağrının tedavisinde giderek daha fazla kullanılmaktadır. Ancak pulsed radyofrekansın uygulama süresi gibi konularda literatürde bir fikir birliği bulunmamaktadır. Bu çalışmanın amacı lumbosakral radiküler ağrı tedavisinde 2 dakikalık ve 4 dakikalık pulsed radyofrekans uygulamaları arasındaki etkinliği ve yan etki insidansını karşılaştırmaktır.

Gereç ve Yöntem: Bu retrospektif çalışmaya 2 dakikalık veya 4 dakikalık dorsal kök ganglionu pulsed radyofrekans tedavisi uygulanmış 160 hasta dahil edildi (Grup-2 dakika 82 hasta ve Grup-4 dakika 78 hasta). İşlemlerin etkinliğini değerlendirmek için girişimlerden önce ve girişimlerden 1 ve 6 ay sonra Sayısal Derecelendirme Ölçeği ve Oswestry Engellilik İndeksi skorları değerlendirildi. Girişimlere bağlı advers olayların oranı her iki prosedür için de değerlendirildi.

Bulgular: Hem 2 dakikalık hem de 4 dakikalık pulsed radyofrekans prosedürleri, başlangıca kıyasla 1. ve 6. aylarda etkin analjezi sağladı. Ölçüm zamanlarında iki grup arasında ağrı skorları arasında fark yoktu. 1 aylık takipte, 2 dakika grubundaki hastaların %39'unda, 4 dakika grubundaki hastaların %50'sinde %50 veya daha fazla ağrı rahatlaması sağlandı ve gruplar arasında fark yoktu. Ayrıca işleme bağlı advers olay oranı açısından gruplar arasında anlamlı bir fark yoktu.

Sonuç: Her ne kadar 4 dakikalık pulsed radyofrekans ile daha yüksek bir başarı oranı elde edilmiş olsa da, gruplar arasında anlamlı bir fark yoktu ve hem 2 hem de 4 dakikalık dorsal kök ganglionu pulsed radyofrekans tedavisi, başlangıca kıyasla güvenli ve etkili analjezi sağladı. Daha geniş katılımlı prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: İnflamasyon, pulsed radyofrekans tedavisi, radikülopati.

Introduction

Lumbosacral radicular pain (LRP) is a common and debilitating condition that affects a significant proportion of the population. Epidemiological studies suggest that LRP has a prevalence rate with annual incidence estimates ranging from 5% to more than 15% and a lifetime prevalence of 60% to 90%. Approximately 10% of acute cases progress to chronic pain (1). While most cases of acute LRP resolve spontaneously, a significant percentage progress to chronic pain, resulting in significant disability and an impact on daily activities (2). Management of chronic LRP remains a challenge, with drug and physical therapy modalities showing variable success rates. Unfortunately, for a subset of patients, these treatments fail to alleviate pain, severely impacting their quality of life (3). Epidural corticosteroid injections provide significant relief for LRP and have demonstrated efficacy in reducing symptoms. However, several studies have indicated that the benefits are predominantly short-term, and the duration of pain relief is often limited (4, 5).

With a limited response to conventional treatments, dorsal root ganglion (DRG) pulsed radiofrequency (PRF) therapy has gained traction in recent decades as an alternative treatment for LRP. PRF therapy involves delivering short bursts of electrical energy to the affected nerve tissue to modulate pain signals without causing significant tissue damage. While the complete mechanism of action for PRF remains elusive, it is thought to impact synaptic transmission, gene expression, and inflammatory mediators without inducing substantial thermal damage or coagulation necrosis in nerve fibers (6). Despite its growing popularity, there is no consensus in the literature regarding the optimal PRF application duration, which often varies at the practitioner's discretion. Practitioners typically apply PRF for 4 or 2 minutes (min) per level (7, 8). However, there are centers that use 6 min or longer (9). Notably, PRF therapy is associated with very few complications, underscoring its potential as a safe treatment modality (10).

The primary aim of this study was to determine the efficacy of two commonly used durations of PRF application, 2 and 4 min, in the treatment of LRP. In addition, our secondary aim was to evaluate and compare the complication rates associated with these different durations. This investigation is intended to contribute to the establishment of evidence-based guidelines for PRF therapy in the treatment of LRP, potentially improving patient outcomes, and reducing the burden of chronic LRP.

Material and Method

Study Design and Participants

This retrospective study involved data collection at a single-center pain clinic in a tertiary-care hospital. Approval was obtained from the Ankara Etlik Şehir Hospital Clinic Research Ethics Committee (Date: 12.07.2023; Decision number: 2023-235). The data of patients who underwent intervention between October 2021 and January 2023 were reviewed. This study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion Criteria: Unilateral radicular low back pain extending below the knee; treatment limited to L4, L5, and S1 nerve roots; PRF treatment of the DRG at only two levels (according to magnetic resonance imaging (MRI) and clinical findings) in just one session; numeric Rating Scale (NRS) score ≥6 despite at least 3 months of conservative treatment, including physical therapy and drug combination therapy; compatibility with current clinical and physical examination findings and MRI; and short-term benefit (<1 month) from previous transforaminal epidural injection (TFEI).

Patients are routinely evaluated by neurosurgery, orthopedics, physical therapy and rehabilitation, and rheumatology before consulting us (this is the routine practice of the hospital and these departments are not part of the study), and the exclusion criteria were determined as follows: pain originating from inflammatory or degenerative conditions of the low back, hip, or knee; previous lumbar surgery; one or three levels of DRG PRF treatment; additional intervention in the same session; atypical or bilateral pain radiation; MRI evidence of extruded, sequestered, or migrated discs; presence of motor deficits; relative spinal stenosis (spinal canal sagittal diameter < 13 mm); myelopathy; lumbar fracture; positive piriformis provocation and tenderness; cancer; diabetes mellitus; coagulation disorders; use of antiplatelet or anticoagulant medications; presence of a cardiac pacemaker; psychiatric disorders; and allergies to

drugs used.

Dorsal Root Ganglion Pulsed Radiofrequency Procedure

All procedures were performed by pain specialists with at least five years of fluoroscopy experience. All necessary emergency medications and equipment were made available in the operating room before patient intervention. The patient was placed in the prone position, and a pillow was placed under the patient's abdomen to reduce lumbar lordosis. The C-arm fluoroscope was rotated and tilted to obtain an antero/posterior (A/P) image of the target lumbar vertebra. The C-arm was then rotated toward the affected side to obtain an oblique fluoroscopic image of the target lumbar vertebra. An oblique angle was applied until the spinous process approached the contralateral facet joint.

The inferior medial point of the pedicle was identified as the needle entry point. The skin and subcutaneous tissues were anesthetized with 1 mL of 2% lidocaine using a 27-gauge needle. A 10-mm active and 100-mm radiofrequency (RF) cannula (TOP Nuropole Needle, TOP Corporation, Tokyo, Japan) was advanced from the anesthetized point to the target. The cannula was advanced using a tunnel-vision technique (Figure IA). The depth of the needle was checked with lateral views. In the lateral view, the final depth of the needle was located between the middle and posterior thirds of the intervertebral foramen (Figure IB). An A/P fluoroscopic image of the epidurogram, which could include a nervegram, was obtained. On the A/P image, contrast medium (iohexol, 300 mg iodine/ml; GE Healthcare, Piscataway, NJ, USA) was spread below and medial to the pedicle shadow and outlined the target spinal nerve exiting the foramen (Figure IC). The RF cannula was then connected to an RF generator (TOP Lesion Generator, TOP Corporation, Tokyo, Japan). The tissue impedance was verified to be ≤ 350 Ω. For sensory stimulation, a paresthesia response was sought in the relevant dermatome at a current of 0.5 volt (V) at a frequency of 50 Hz. Subsequently, no contractile response was observed in the relevant myotome at a current of 1-1.5 V at a frequency of 2 Hz. After appropriate responses, PRF was applied at 42 °C for 120 s (Group-2 minutes) or 240 s (Group-4 minutes), depending on the practitioner's clinical approach. Patients were observed for at least 30 min after the procedure for possible complications.

Assessments

Demographic data (including patient age, sex, and relevant medical history), how many seconds (120 s or 240 s) PRF was applied to the patients for each level, and pain and functionality scores were extracted from hospital records.

Pain intensity was quantified using the NRS, in which patients rated their pain on a scale from 0 (no pain) to 10 (the most severe pain). The Oswestry Disability Index (ODI) was also used to measure the impact of pain on daily functioning. The ODI is a percentage scale, ranging from 0% (indicating no disability) to 100% (indicating the maximum possible disability), and is calculated based on patient responses to a series of ten questions about daily activities and pain (11). NRS and ODI scores were collected before the procedure and at follow-up intervals of 1- and 6-months post-treatment. Clinically significant pain relief was defined as a 50% or greater reduction in NRS score.

Adverse event rates were related to the DRG PRF procedure (procedure-related complications or post-procedural effects, with the majority of them being transient and non-serious.) were obtained from patient follow-up records and direct interviews.

Statistical Analysis

All analyses were performed using Jamovi Project (2022, Jamovi version 2.3) (computer software). The results of this study are expressed as frequencies and percentages. Normality analysis was performed using the Shapiro-Wilk test, skewness kurtosis, and histograms. All analyses were conducted using Jamovi Project (2022, Jamovi Version 2.3, Computer Software). Categorical variables are presented as absolute numbers with percentages. Categorical variables were compared using the chi-squared test or Fisher's exact test. Mann-Whitney U tests were used to compare the numerical dependent variables between the groups. Repeated measures were analyzed using Friedman's test with Bonferroni correction for multiple t-tests. Statistical significance was set at $p < 0.05$.

Results

A total of 182 patients, whose medical records were available, were screened for eligibility. After excluding 14 of these patients due to additional facet joint injections in the same session and 8 patients due to caudal epidural injections, the study was completed with 160 patients, and the final analysis included 82 patients in Group 2-minute (120 s PRF) and 78 patients in Group 4-minute (240 s PRF). A patient flowchart is shown in Figure II.

Table I Baseline demographics and clinical characteristics

Variables	Group-2 minutes (n=82)		Group-4 minutes (n=78)		
	Median (min-max)	Mean±SD	Median (min-max)	Mean±SD	*p value*
Age	59 (23-81)	58.8±10.7	55.5 (27-82)	55.2±12.9	*0.074**
Basal NRS	7 (7-10)	7.5±0.65	8 (6-10)	7.6±0.95	*0.354**
NRS-1 month	5 (0-8)	4.5±1.69	4 (1-9)	4.5±2.15	*0.714**
NRS-6 months	6 (2-10)	5.4±1.76	5 (2-9)	5.4±1.83	*0.899**
Basal ODI	50 (44-56)	49.5±2.9	50 (44-56)	49.7±2.6	*0.704**
ODI-1 month	38 (16-54)	33.3±11.6	27 (18-54)	32.4±12.9	*0.906**
ODI-6 months	44 (20-56)	37.2±11.4	31 (20-54)	35.5±11.4	*0.494**
Duration of pain (months)	9.5 (6-17)	10.4±3.4	10 (5-18)	10.6±3.1	*0.319**
Gender n(%)					
Female	38 (46.3)		52 (66.7)		*0.093***
Male	44 (53.7)		26 (33.3)		
Adverse Events n(%)					
None	75 (91.4)		69 (88.5)		*0.938***
Numbness	4(4.9)		5 (6.4)		
Dysesthesia	3 (3.7)		4 (5.1)		
Pain Side n(%)					
Left	39 (47.6)		38 (48.7)		*0.987***
Right	43 (52.4)		40 (51.3)		

Values are presented as mean ± standard deviation, median (min-max), number (%)
PRF: Pulsed radiofrequency; ODI: Oswestry Disability Index; NRS: Numerical rating scale
*: Mann Whitney U Test **: Chi-Square Test

The demographic and clinical characteristics of patients are shown in Table I. The groups were similar with respect to age, gender, duration of pain, and the side of treatment. Although procedure-related adverse events were observed in more patients in Group 4-minute (numbness 5 vs. 4 and dysesthesia 4 vs. 3), this difference was not statistically significant (*p>0.05*). These adverse events resolved spontaneously within one month, with the longest duration requiring no treatment.

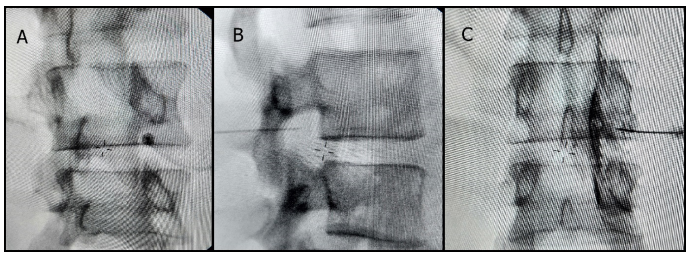

Figure I Fluoroscopy-guided dorsal root ganglion pulsed radiofrequency procedure
(A) shows the tunnel view of the radiofrequency cannula on the oblique fluoroscopic image. (B) shows the tip of the cannula in the foramen intervertebrale on a lateral fluoroscopic image. (C) shows the epidurogram of the existing nerve root.

When the NRS and ODI were evaluated within the groups, their changes over time were statistically significant. At the 1st and 6th month controls, there was a significant improvement in both NRS and ODI scores compared to baseline (*p<0.001*). However, there was no significant difference between the two groups at any time point (*p>0.05*). (Table II).

Table II NRS and ODI scores over time

Treatment Groups		NRS		ODI	
		Median(min-max) / Mean rank	*p value*	Median(min-max) / Mean rank	*p value*
Group-2 minute	Basal	7 (7-8) / 2.84		50 (48-52) / 5.84	
	1 month	5 (3-6) / 1.19	*<0.001*	38 (22-44) / 4.15	*<0.001*
	6 months	6 (4-7) / 1.97		44 (26-48) / 5.01	
Group-4 minute	Basal	8 (7-9) / 2.68		50 (48-52) / 5.72	
	1 month	4 (3-6) / 1.30	*<0.001*	27 (20-46) / 4.27	*<0.001*
	6 months	5 (4-7) / 2.02		31 (24-48) / 5.01	

Friedman test
PRF: Pulsed radiofrequency; ODI: Oswestry Disability Index; NRS: Numerical rating scale; min.-max.: minimum-maximum.

Pain relief of at least 50% was achieved in 39% of patients in Group 2-minute at the 1-month follow-up and in 32.9% at the 6-month follow-up. In comparison,

Group 4-minute exhibited a 50% response rate at the 1-month follow-up and 33.3% at the 6-month follow-up. There was no significant difference in the success rates between the groups at 1 month (*p=0.203*) and 6 months (*p>0.05*).

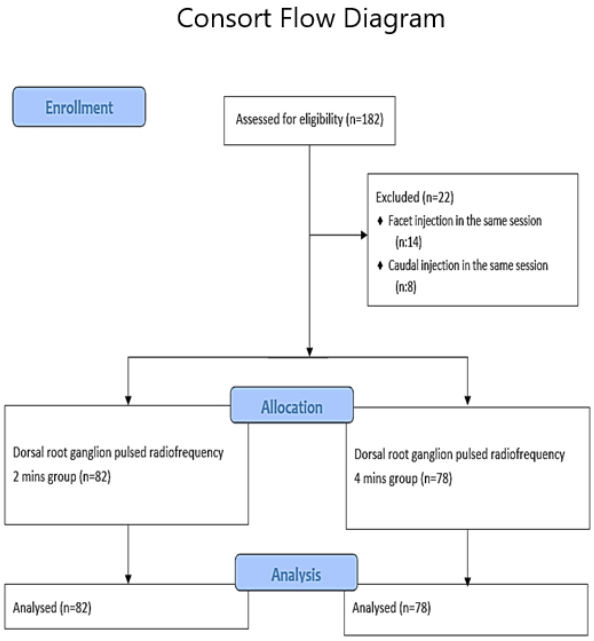

Figure II Patient flow chart

Discussion

In our study, 2-minute and 4-minute DRG PRF applications provided effective analgesia and improved functionality in the management of LRP refractory to conservative treatments, as observed at the first- and sixth-month assessments. Compared to baseline, both the NRS and ODI scores improved. Although there were no statistically significant differences in NRS and ODI between 2 min and 4 min PRF applications, the proportion of patients with 50% or greater pain relief was higher in Group 4-minute, 50% vs. 39% at 1 month, and 33.3% vs. 32.9% at 6 months. Adverse event rates were not significantly different between the groups.

A prospective study by Van Boxem et al. (7), which applied 4-minute DRG PRF per level for LRP, resulted in significant pain relief in 56.9% of patients at six weeks and 55.4% at six months. Conversely, a retrospective study by the same authors (8) using a 2-minute application per level reported a success rate of 22.9% at six months. The authors attributed the difference in results between these studies to the strict inclusion criteria used in the prospective study. In the first study, only patients with pathologies at the lumbar (L) 5 and sacral (S) 1 levels were included, resulting in a higher success rate. Because the L4 dermatome is not very specific, they did not include the L4 level in the study. However, the impact of different durations of PRF, 4-minute versus 2-minute, was not addressed. Our study showed, although not statistically significant, a higher success rate of 50% in Group 4-minute at the 1-month follow-up. In addition, our data included patients who underwent DRG PRF at the L4, L5, and S1 levels, which is more reflective of clinical practice than isolated applications at the L5 and S1 levels.

Another difference between the two studies by Van Boxem et al. is that the retrospective study included only patients with single-level DRG PRF, which had a lower success rate. Elevated levels of chemokine receptor 2 (CLR2), indicating chronic inflammation due to persistent DRG and nerve root compression, were found in both affected and adjacent DRGs (12). This finding suggests that multilevel DRG PRF applications may increase the likelihood of success. Our study included patients who underwent two-level DRG PRF based on clinical and MRI findings. Jyotsna et al. (13) combined 2-minute PRF with 1-minute continuous radiofrequency (CRF) lesioning (mean temperature 56°C ± 8°C for 60 seconds) per level in the treatment of chronic LRP and performed repeated sessions as pain resurged during follow-up. This approach resulted a significant pain reduction for an average of 4.7 months after two sessions in 40 of 50 patients. In the following period, they provided pain relief for an average of 4.3 months with 2-minute PRF+1-minute CRF, which they repeated for five sessions to 18 patients whose pain continued in the following period. In our country, RF applications can be performed only once a year within the framework of social insurance reimbursement, which does not allow for repeated interventions. Our study involved a single PRF session, and the potential for increased success with repeated procedures remains unexplored. Another important detail in this study by Jyotsna et al. (13) is the application of CRF to the DRG, the use of which has always been a reservation for pain specialists. Only one complication was reported in this study, and the patient had numbness that lasted

1 week. This complication was thought to be caused by CRF, rather than PRF.

Although PRF is generally known to have a low adverse event rate (10), one of the largest gaps in the literature is the lack of PRF-related adverse events. In our study, mild numbness was observed in five patients and dysesthesia in four patients in Group-4 minute, while numbness was observed in four patients and dysesthesia was observed in three patients in Group-2 minute, but there was no significant difference between the groups in terms of these adverse event rates. In addition, the longest lasting adverse event in our study was 1 month, which resolved spontaneously without treatment. Koh et al. (9) reported a transient pain increase in six patients in the PRF group and four patients in the sham group in their study comparing 6 mins PRF and sham electrode for LRP and recovered in 2-3 days on average. Although PRF seems to be non-destructive, there are publications indicating that it may cause minor changes in the DRG (14, 15). In the literature, the number of studies in which PRF was applied for 6 min per level is limited and Koh et al. (9) achieved a success rate of 48.4% at 2 months, while this rate was 19.4% in the sham group. At the 3rd month of control, a significant pain relief of 38.7% was observed in the PRF group. The literature gives a wide range of PRF success rates (from 30% to 80%) (8, 16, 17).

The mechanism of action of PRF involves the modulation of pain signals without causing significant nerve tissue damage (18). The predictive factors for PRF efficacy have been investigated. Van Boxem et al. (19) demonstrated in their study that they applied PRF for 4 min that a positive response to the diagnostic block before PRF and an age of 55 years or older may be predictive. Kim et al. (20) also found that short-term positive response to epidural injection prior to PRF was predictive. All participants in our study experienced short-term benefits (<1 month) from TFEI prior to PRF treatment. The absence of comorbid musculoskeletal pain was another predictor highlighted, emphasizing the importance of thorough systemic evaluation prior to interventional treatments, such as PRF, to minimize unnecessary procedures and increase success rates. Our study ensured that the patients underwent comprehensive examinations by orthopedics, neurosurgery, physical therapy and rehabilitation, and rheumatology to rule out non-LRP causes prior to PRF administration. Our study had several limitations. First, the follow-up period was limited to 6 months due to limitations in medical records. Second, we could not evaluate the effects of interventions on drug consumption. Third, our study had a retrospective design.

Conclusion

Although PRF application appears to be generally safe, minor adverse events can be observed, and increasing the duration of application did not increase the incidence of adverse events. A higher success rate was observed with 4-minute PRF application, although this was not clinically significant. Larger, randomized, prospective studies are needed to investigate the effects of varying PRF durations on treatment outcomes.

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The Effect of Thyroid Nodule Size and Characteristics on the Accuracy of Fine-Needle Aspiration Biopsy and the Risk of Malignancy

Tiroid Nodül Boyutu Ve Özelliklerinin İnce İğne Aspirasyon Biyopsisinin Doğruluğu Ve Malignite Riski Üzerine Etkisi

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The Effect of Thyroid Nodule Size and Characteristics on the Accuracy of Fine-Needle Aspiration Biopsy and the Risk of Malignancy

ABSTRACT

Objective: Ultrasound evaluation of nodule characteristics and FNAB is a simple, cost-effective method. However, its reliability in large nodules is controversial. This study aims to examine the impact of thyroid nodule size and characteristics on malignancy risk and FNAB accuracy as evaluated by ultrasound.

Material and Method: IThis retrospective study included 522 patients who underwent thyroidectomy between January 1, 2020, and January 1, 2024. The data included the patients' age, gender, preoperative thyroid ultrasound findings, preoperative FNAB pathology findings, operation notes, and postoperative pathology results colleected from hospital archives. Kruskal-Wallis Variance Analysis, ROC (Receiver Operating Characteristics) curve analysis, Bonferroni Corrected Mann-Whitney U Test, Chi-Square Tests, were used at statistical analysis.

Results: The median age was 49.45 years. The threshold value for nodule size in the X plane was 27 mm (*p<0.001*) when comparing preoperative FNAB with postoperative pathology. For nodules with X ≤ 27 mm, FNAB sensitivity was 0.842, the false predictive value was 0.636, and the false negative rate was 0.157. In this group, the mean age, nodule size, and two-dimensional area (X*Y) were significantly higher nodules, while isoechoic features were more common in benign nodules.

Conclusion: It was found that the risk of malignancy decreases with increasing age, nodule size, and two-dimensional area; the risk of malignancy increases with hypoechoic and microcalcification findings; and FNAB sensitivity decreases and the false negative value increases in nodules >27 mm.

Keywords: Fine-Needle aspiration biopsy, thyroid nodule, ROC analysis, ultrasound.

ÖZET

Amaç: Ultrasonografi, tiroid nodüllerinin özelliklerinin incelenmesi ve ince iğne aspirasyon biyopsisinin (İİAB) alınması noktasında kolay, avantajlı ve güvenlik-maliyet etkin bir yöntemdir. Bununla beraber, büyük nodüllerde güvenilirliği tartışmalıdır. Bu çalışmada amacımız ultrasondaki tiroid nodül boyutu ve özelliklerinin malignite riski üzerine ve ince iğne aspirasyon biyopsisinin doğruluğu üzerine etkisini incelemektir.

Gereç ve Yöntem: Çalışmaya, retrospektif olarak 01.01.2020 ile 01.01.2024 tarihleri arasında tiroidektomi operasyonu geçiren 522 hasta dahil edilmiştir. Yaş, cinsiyet, preoperatif ultrason bulguları, preoperatif İİAB sonuçları, ameliyat notları ve postoperatif patoloji bulguları arşivden araştırılmıştır. İstatistiksel analizde Kruskal-Wallis Varyans Analizi, ROC (Receiver Operating Characteristics) eğrisi analizi, Bonferroni Düzeltmeli Mann-Whitney U Testi ve Ki-Kare Testleri kullanılmıştır.

Bulgular: Medyan yaş 49,45 olarak bulundu. Preoperatif İİAB ile postoperatif patoloji uyumu incelendiğinde; nodülün X düzlemdeki boyutu için eşik değer 27 mm olarak bulundu (*p<0.001*). X ≤ 27 mm olan nodüllerde İİAB nin Sensivite 0.842, Yanlış prediktif değer 0.636 ve Yanlış Negatif Oran (FNR) 0.157 daha anlamlı bulundu. X ≤ 27 mm boyutta; yaş ortalaması, nodül X boyutu ve iki boyutlu alan (X*Y) benign grupta (*p<0.001*); X ≤ 27 mm ve X tüm boyutta hipoekoik ve mikrokalsifikasyon özelliği malign grupta, İzoekoik görünüm benign grupta anlamlı yüksek bulundu.

Sonuç: Yaş, nodül boyutu ve iki boyutlu alan artışıyla malignite riskinin azaldığı; hipoekojenite ve mikrokalsifikasyon bulgusunun malignite riskini arttırdığı; >27 mm nodüllerde İİAB nin sensivitesinin azaldığı ve false negatif değerinin arttığı görüldü.

Anahtar Sözcükler: İnce iğne aspirasyon biyopsisi, tiroid nodülü, ROC analizi, ultrasonografi.

Introduction

Thyroid nodules are a very commonly detected clinical condition (1). Before the advancement of imaging techniques, only 5-10% of patients had thyroid nodules detected by palpation (2). However, nowadays, thyroid nodules can be detected in 19-68% of randomly selected individuals via ultrasound (3). It is crucial for the clinician to accurately predict the benign or malignant nature of thyroid nodules to avoid unnecessary thyroidectomy and potential complications (4). Ultrasound is an easy method for obtaining nodule characteristics and performing fine-needle aspiration biopsy (FNAB), and it is useful in making surgical decisions for malignant or benign cases or follow up them according to the 2017 Bethesda thyroid cytopathology reporting system criteria (1-3). Although there are limited and suspicious findings depending on the radiologist; the absence of microcalcifications, the presence of regular borders and a halo, and iso-hyperechogenicity in nodule ultrasound features suggest benign nodules. FNAB is considered the gold standard diagnostic tool for thyroid nodules due to its simplicity, advantages, safety-cost effectiveness, and diagnostic specificity (5-6). Although, there are debates regarding its reliability in large (>30-40 mm) nodules. Some studies have reported that nodules larger than 40 mm have high false-negative rates of up to 30% in cytology (7-8), while other studies have suggested that nodule size does not adversely affect the reliability of FNAB (9-10). Our aim is investigate the effect of thyroid nodule size and characteristics on malignancy risk and the accuracy of fine-needle aspiration biopsy as assessed by ultrasound.

Material and Method

This retrospective study included 522 patients who underwent elective thyroid lobectomy or total thyroidectomy between January 1, 2020, and January 1, 2024, at the General Surgery Clinic of Samsun University Training and Research Hospital. Between 2018 and 2024, all patients aged 18 to 90 years who presented with thyroid compression symptoms (such as respiratory issues, swallowing difficulties, and voice problems) and were indicated for thyroidectomy based on fine-needle aspiration biopsy (FNAB) results were included in the study. Patients with a history of thyroid surgery, a history of malignancy in the neck region, those who presented with imaging and FNAB cytology results from external centers, patients with non-diagnostic FNAB pathology results, and individuals under the age of 18 were excluded from the study. Retrospective data collected included age, gender, preoperative thyroid ultrasound findings (lobe with the largest nodule, X size of the largest nodule, two-dimensional estimated nodule area (X*Y), nodule characteristics (hypoechoic, hyperechoic, isoechoic, halo finding, microcalcification, and macrocalcification findings), preoperative FNAB pathology findings, operation notes, and postoperative pathology results. The preoperative FNAB and postoperative pathology results were categorized using the Bethesda scoring system (11). The preoperative FNAB pathology results were compared with the postoperative pathology results to investigate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), false positive rate (FPR), and false negative rate (FNR) of FNAB and the thyroid ultrasound nodule findings with postoperative pathology results. When examining the concordance between preoperative and postoperative pathology, preoperative FNAB pathology results were categorized as Bethesda 2 (Group 1), Bethesda 3 and 4 (Group 2), and Bethesda 5 and 6 (Group 3); postoperative pathology results were categorized as Bethesda 2 (Group 1), Bethesda 4 (Group 2), and Bethesda 6 (Group 3). The study was approved by the Ethics Committee of of Samsun University Clinical Research with the protocol number GOKAEK 2024/4/14 on February 14, 2024. The study was conducted in accordance with research and ethical principles. Descriptive statistics were performed to provide information about the general characteristics of the study groups. Quantitative data were described using mean and standard deviation (x ± sd) as well as minimum and maximum values; qualitative data were described using number (n) and percentage (%). Differences between groups for quantitative variables were assessed using the Kruskal-Wallis Variance Analysis for independent groups. Bonferroni Corrected Mann-Whitney U Test was used for pairwise comparisons. Differences between groups for qualitative variables were assessed using Chi-Square Tests. Marginal Homogeneity Test

was used for dependent qualitative groups. ROC (Receiver Operating Characteristics) curve analysis was applied to determine cut-off values for nodule size based on preoperative and postoperative pathology concordance, and the area under the ROC curve (AUC) was evaluated. *P values less than 0.05* were considered statistically significant. Calculations were performed using statistical software (IBM SPSS Statistics 22, SPSS Inc., an IBM Co., Somers, NY).

Results

Between January 1, 2020, and January 1, 2024, there were 653 patients aged 18-90 who underwent thyroid lobectomy and total thyroidectomy due to thyroidectomy indication. Of these patients, 58 were excluded due to presenting with fine-needle aspiration biopsy (FNAB) and thyroid ultrasound results from different centers; 73 were excluded due to a history of previous thyroid surgery, history of neck malignancy, and nondiagnostic FNAB pathology results. Therefore, a total of 131 patients were excluded, and 522 patients were included in the study (Figure I). Among these 522 patients, 411 were female and 111 were male. The median age of the patients was found to be 49.45 years. A total thyroidectomy was performed on 430 patients, and a thyroid lobectomy was performed on 92 patients. When examining the distribution of qualitative values, the largest nodule was seen in the right lobe in 52.1% of the cases in preoperative ultrasound. In the ultrasound examination of nodule characteristics, 54% were hypoechoic in echogenicity; in the examination of calcification and halo findings, 14.4% had a halo finding, 13.8% had macrocalcification, and 12.2% had microcalcification. A total of 142 patients underwent thyroidectomy due to compression findings without preoperative fine-needle aspiration biopsy. Among the patients who underwent FNAB, the results were as follows: 116 patients (Bethesda 3) AUS/FLUS, 92 patients (Bethesda 2) Benign, 78 patients (Bethesda 4) Suspicious for Follicular Neoplasm, 39 patients (Bethesda 5) Suspicious for Malignancy, and 54 patients (Bethesda 6) Malignant. In the postoperative pathology examination, 261 patients were evaluated as Bethesda 2 Benign, 232 patients as Bethesda 6 Papillary Carcinoma, and 29 patients as Bethesda 4 Follicular Neoplasm (Table I). In the analysis of thyroid nodule sizes, the mean size in the X plane was 32.63 (3-89) mm, the mean size in the Y plane was 20.86 (0.9-79) mm, and the mean two-dimensional estimated area (X*Y) was 850.37 (6-6478) mm^2 (Table II). When examining the concordance between preoperative FNAB pathology Bethesda results and postoperative pathology Bethesda results, the ROC analysis for the nodule size in the X plane indicated a threshold value of 27 mm (*p<0.001*) (Figure II).

Table I Distribution of Qualitative Characteristics (n=522)

		n	%
Gender	Male	111	21.3
	Female	411	78.7
Preoperative Imaging	Right	272	52.1
	Left	217	41.6
	Isthmus	33	6.3
Ultrasound nodule characteristics	Hypoechoic	282	54.0
	Hyperechoic	102	19.5
	Isoechoic	138	26.4
Ultrasound nodule characteristics 2	None	297	56.9
	Halo Sign	75	14.4
	Microcalcification	63	12.1
	Macrocalcification	72	13.8
	Halo Sign- Microcalcification	7	1.3
	Halo Sign- Macrocalcification	3	0.6
	Microcalcification - Macrocalcification	5	1.0
Preoperative FNAB Pathology	None	142	27.20
	(Bethesda 2) Benign	93	17.81
	(Bethesda 3) AUS/FLUS	116	22.22
	(Bethesda 4) Suspicious for Follicular Neoplasm	78	14.95
	(Bethesda 5) Suspicious for Malignancy	39	7.48
	(Bethesda 6) Malignant	28	5.36
	(Bethesda 6) Malignant Papillary Carcinoma	26	4.98
Surgery	Thyroidectomy (Unilateral)	92	17.6
	Thyroidectomy (Bilateral)	430	82.4
Postoperative Pathology	(Bethesda 2) Benign	261	50.0
	(Bethesda 4) Follicular Neoplasm	29	5.6
	(Bethesda 6) Malignant Papillary Carcinoma	232	44.4

In the statistical analysis of the concordance between preoperative FNAB Bethesda score and postoperative pathology Bethesda score based on nodule size; no statistical difference was observed in the concordance between preoperative and

postoperative pathology for nodules with X ≤ 27 mm, while a statistically significant difference was found for nodules with X > 27 mm and for all nodules (*p<0.001*) (Table III). When examining the specificity, sensitivity, predictive, and proportional values of FNAB based on nodule size; for nodules with X ≤ 27 mm, sensitivity was highest at 0.842, with a positive predictive value (PPV) of 0.888 and a negative predictive value (NPV) of 0.275. The false predictive value was 0.636, and the false negative rate (FNR) was lowest at 0.157 (Table IV).

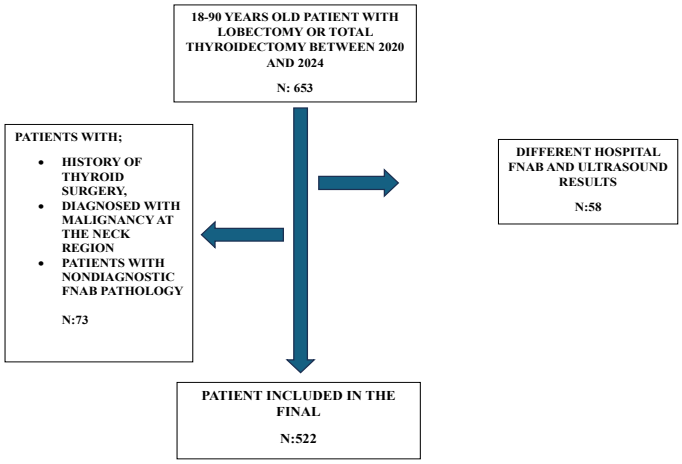


Figure I Table of included and excluded patients

Table II Distribution of Quantitative Values (n=522)

Measurement	Mean	SD	Min	Max
Age	49.45	12.54	18.00	87.00
Nodule Size X (mm)	32.63	17.72	3.00	89.00
Nodule Size Y (mm)	20.86	11.77	0.90	79.00
Nodule Two- Dimensional Area (mm^2)	850.37	864.03	6.00	6478.00

In the statistical analysis of quantitative measurements based on postoperative pathology Bethesda scoring; for patients with nodule size X ≤ 27 mm, the mean age, nodule X size, and two-dimensional estimated area (XY) in the Bethesda 2 Benign group were found to be statistically significantly higher compared to the Bethesda 6 Malignancy group (*p<0.001*). For patients with nodule size X > 27 mm, the two-dimensional area (XY) in the Bethesda 2 Benign group was statistically significantly higher compared to the Bethesda 6 Malignancy group (*p=0.006*). Across all sizes, the mean age in the Bethesda 2 Benign group was statistically significantly higher compared to the Bethesda 4 Follicular Neoplasm group (*p=0.006*). Additionally, the nodule X size and two-dimensional estimated area (X*Y) in the Bethesda 2 Benign group were statistically significantly higher compared to the Bethesda 6 Malignancy group (*p<0.001*) (Table V).

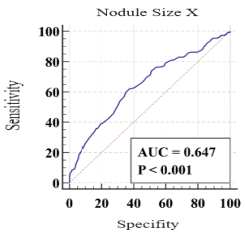
Table III Distribution of Qualitative Characteristics (n=522)

Nodule Size X ≤ 27 (n=233) (Bethesda 2)		**Post Operative Pathology**			***p***
		(Bethesda 4)	**(Bethesda 6)**		
Preop FNAB Pathology	**(Bethesda 2)**	21 (63.6)	-	12 (36.4)	*0.226*
	(Bethesda 3 ve 4)	71 (55.5)	11 (8.6)	46 (35.9)	
	(Bethesda 5 ve 6)	8 (11.1)	-	64 (88.9)	
Nodule Size X> 27 (n=289) (Bethesda 2)		**Postop Pathology**			*p*
		(Bethesda 4)	**(Bethesda 6)**		
Preop FNAB Pathology	**None**	84 (59.2)	12 (8.5)	46 (32.4)	***<0.001****
	(Bethesda 2)	41 (68.3)	1 (1.7)	18 (30.0)	
	(Bethesda 3 ve 4)	31 (47.0)	4 (6.1)	31 (47.0)	
	(Bethesda 5 ve 6)	5 (23.8)	1 (4.8)	15 (71.4)	
All Nodule Size X Values (n=522) (Bethesda 2)		**Postop Pathology**			*p*
		(Bethesda 4)	**(Bethesda 6)**		
Preop FNAB Pathology	**None**	84 (59.2)	12 (8.5)	46 (32.4)	***<0.001****
	(Bethesda 2)	62 (66.7)	1 (1.1)	30 (32.3)	
	(Bethesda 3 ve 4)	102 (52.6)	15 (7.7)	77 (39.7)	
	(Bethesda 5 ve 6)	13 (14.0)	1 (1.1)	79 (84.9)	

Marginal Homogeneity Test
p value is significant at 0.05 level.
(Bethesda 2) Benign (Bethesda 3) AUS/FLUS (Bethesda 4) Suspicious for Follicular Neoplasm (Bethesda 5) Suspicious for Malignancy (Bethesda 6) Malignant

In the statistical analysis of qualitative measurements based on postoperative pathology Bethesda scoring; no statistically significant relationship was found between gender, preoperative ultrasound nodule lobe, and postoperative pathology Bethesda groups for patients with nodule size X ≤ 27 mm, X > 27 mm, and

all sizes. For patients with X ≤ 27 mm (*p=0.016*) and all sizes (p*<0.001*), the hypoechoic characteristic of the nodule was found to be statistically significantly higher in the Bethesda 6 Malignant group, while the isoechoic characteristic was found to be statistically significantly higher in the Bethesda 2 Benign group. A statistically significant relationship was found between nodule halo and calcification findings and postoperative pathology Bethesda groups for patients with nodules of all sizes. The nodule halo finding was statistically significantly higher in the Bethesda 4 Follicular Neoplasm group, microcalcification finding was statistically significantly higher in the Bethesda 6 Malignant group, and Halo-Microcalcification finding was statistically significantly higher in the Bethesda 4 Follicular Neoplasm group (*p=0.006*) (Table VI).



Area Under Curve (AUC) for ROC Curve	Value
Area Under Curve (AUC)	0.647
Standard Error	0.0270
95% Confidence Interval	0.604 to 0.688
Z-Statistic	5.437
Significance Level P (Area=0.5)	**<0.001***
Youden index	**Value**
Youden Index J	**0.2469**
Threshold Value	**≤27**
Sensitivity	**62.09**
Specificity	**62.60**

Figure II Preoperative-Postoperative Pathology Concordance Nodule X Dimension Cut-off Value

Table IV Specificity, Sensitivity, Predictive Values, and Proportional Values of Fine Needle Aspiration Biopsy (FNAB) Based on Nodule Size

	Nodule Size X ≤ 27 (n=105)	Nodule Size X> 27 (n=79)	All Nodule Size X (n=184)
Sensitivity	0.842	0.454	0.724
Specificity	0.724	0.891	0.826
Positive Predictive Value (PPV)	0.888	0.750	0.858
Negative Predictive Value (NPV)	0.636	0.694	0.673
False Positive Rate (FPR)	0.275	0.108	0.173
False Negative Rat (FNR)	0.157	0.545	0.275

Table V Distribution of Quantitative Measurements by Postoperative Pathology Status

		Nodule Size X ≤ 27 (n=233)					Nodule Size X> 27 (n=289)					All Nodule Size X Values (n=522)				
	Groups	N	Mean±SD	Min-Max	p	Post Hoc p	N	Mean±SD	Min-Max	p	Post Hoc p	N	Mean±SD	Min-Max	p	Post Hoc p
Age	(Bethesda 2)	100	52.99±11.40	18.00-75.00		1-2:0.006*	161	49.42±12.90	20.00-87.00			261	50.79+12.45	18.00-87.00		
	(Bethesda 4)	11	41.09±11.13	21.00-58.00	***<0.001***	1-3:0.001*	18	45.39±11.67	29.00-67.00	*0.403*		29	43.76+11.47	21.00-67.00	***0.004***	1-2:0.006*
	(Bethesda 6)	122	47.58±12.52	20.00-82.00			110	49.85±12.56	26.00-81.00			232	48.66+12.56	20.00-82.00		
Nodul Size X (mm)	(Bethesda 2)	100	19.24±5.50	4.00-27.00			161	46.81±14.34	29.00-89.00			261	36.25+17.85	4.00-89.00		
	(Bethesda 4)	11	19.09±5.34	10.00-26.00	***<0.001***	1-3:<0.001*	18	42.72±11.34	30.00-70.00	*0.190*		29	33.76+14.98	10.00-70.0	***<0.001***	1-3:<0.001*
	(Bethesda 6)	122	14.94±6.28	3.00-27.00			110	43.39±11.88	28.00-85.00			232	28.43+17.03	3.00-85.00		
Nodule Two-Dimensional Area (mm^2)	(Bethesda 2)	100	270.14±146.25	12.00-675.00			161	1485.53±945.61	150.00-6478.00			261	1019.87+953.35	12.00-6478.0		
	(Bethesda 4)	11	287.27±170.46	100.00-589.00	***<0.001***	1-3:<0.001*	18	1158.39±784.56	400.00-3392.00	***0.003***	1-3:0.006*	29	827.97+754.41	100.0-3392.0	***<0.001***	1-3:<0.001*
	(Bethesda 6)	122	186.88±146.11	6.00-600.00			110	1190.00±743.28	270.00-3850.00			232	662.5+723.77	6.00-3850.0		

Kruskal Wallis Variance Analysis *p value is significant at 0.05 level.* Bonferroni Corrected Mann Whitney U Test was applied for binary comparisons. (Bethesda 2) Benign:1 (Bethesda 4) Follicular Neoplasm:2 (Bethesda 6) Papillary Carcinoma Malignant:3

Table VI Distribution of Qualitative Characteristics by Postoperative Pathology Status

Groups		Nodule Size X ≤ 27 (n=233)			Nodule Size X> 27 (n=289)			All Nodule Size X Values (n=522)		
(Bethesda 2)		Postop Pathology			Postop Pathology			Postop Pathology		
		(Bethesda 4)	(Bethesda 6)	(Bethesda 2)	(Bethesda 4)	(Bethesda 6)	(Bethesda 2)	(Bethesda 4)	(Bethesda 6)	
Gender	Male	23(23.0)	3(27.3)	15(12.3)	33(20.5)	6(33.3)	31(28.2)	56(21.5)	9(31.0)	46(19.8)
	Female	77(77.0)	8(72.7)	107(87.7)	128(79.5)	12(66.7)	79(71.8)	205(78.5)	20(69.0)	186(80.2)
		p: 0.079			*p: 0.226*			*p: 0.378*		
Preop USG Imaging Nodule Lobe	Right	48(48.0)	7(63.6)	62(50.8)	81(50.3)	10(55.6)	64(58.2)	129(49.4)	17(58.6)	126(54.3)
	Left	44(44.0)	4(36.4)	51(41.8)	75(46.6)	7(38.9)	36(32.7)	119(45.6)	11(67.9)	87(37.5)
	Isthmus	8(8.0)	-	9(7.4)	5(3.1)	1(5.6)	10(9.1)	13(5.0)	1(3.4)	19(8.2)
		p: 0.820			*p: 0.088*			*p: 0.263*		
Ultrasound	Hypoechoic	45(45.0)^{a}	6(54.5)^{ab}	81(66.4)^{b}	75(46.6)	10(55.6)	65(59.1)	120(46.0)^{a}	16(55.2)^{ab}	146(62.9)^{b}
	Hyperechoic	19(19.0)^{a}	3(27.3)^{a}	18(14.8)^{a}	33(20.3)	3(16.3)	26(23.6)	52(19.9)^{a}	6(20.7)^{a}	44(19.0)^{a}
	Isoechoic	36(36.0)^{a}	2(18.2)^{ab}	23(18.9)^{b}	53(32.9)	5(27.8)	19(17.3)	89(34.1)^{a}	7(24.1)^{ab}	42(18.1)^{b}
		p: 0.016			*p: 0.074*			***p<0.001***		
Ultrasound	None	57(45.2)	5(4.0)	64(50.8)	103(64.0)	8(44.4)	60(54.5)	160(61.3)^{a}	13(44.8)^{a}	124(53.4)^{a}
	Halo Sign	13(43.3)	3(10.0)	14(46.7)	26(16.1)	6(33.3)	13(11.8)	39(14.9)^{a}	9(31.0)^{b}	27(11.6)^{a}
	Microcalcification	12(31.6)	1(2.6)	25(65.8)	9(5.6)	2(11.1)	14(12.7)	21(8.0)^{a}	3(10.3)^{ab}	39(16.8)^{b}
	Macrocalcification	14(48.3)	1(3.4)	14(48.3)	21(13.0)	1(5.6)	21(19.1)	35(13.4)^{a}	2(6.9)^{a}	35(15.1)^{a}
	Halo Sign- Microcalcification	-	1(25.0)	3(75.0)	1(0.6)	1(25.0)	1(0.9)	1(0.4)^{a}	2(6.9)^{b}	4(1.7)^{ab}
	Halo Sign- Macrocalcification	3(100.0)	-	-	1(0.6)	-	1(0.9)	3(1.1)^{a}	-^{a}	-^{a}
	Microcalcification-Macrocalcification	1(33.3)	-	2(66.7)	-	-	-	2(0.8)^{a}	-^{a}	3(1.3)^{a}
		p: 0.219			*p: 0.072*			***p: 0.006***		

Chi-Square Test *p value is significant at 0.05 level*. Different letters in the same row indicate statistically significant difference (*p<0.05*).

Discussion

The diagnosis and treatment of thyroid nodules remain a significant concern due to controversial outcomes. With technological advancements, the use of ultrasound-guided FNAB has increased, becoming the gold standard in diagnosis (5-6). The sensitivity of FNAB in the literature is reported to be between 65-95% and specificity between 70-100% (12). However, the reliability of FNAB concerning nodule size remains controversial. Although FNAB can accurately detect large thyroid nodules, its limitations in differentiating malignancies persist. It should be noted that the accuracy of FNAB results can be influenced by multifactorial factors such as sample volume adequacy, sampling from the correct location, and correct interpretation of results (10,13). Some studies have shown no significant difference in false negatives, false positives, positive predictive values, and negative predictive values between the groups when the cutoff value for nodule size is set at 4 cm (8,14). Other studies have indicated a high rate of false negatives in nodules larger than 4 cm (13,15-16). Some studies have demonstrated that the false-negative rates for nodules >4 cm range between 7-50% (13,16-19). These findings suggest that relying solely on FNAB results may overlook malignancies and that thyroidectomy may be considered even in cases with benign biopsy results. Some studies have taken a nodule size of 3 cm as the cutoff value and found higher false-negative rates in nodules ≥3 cm compared to those <3 cm (7-8,14,20-22), while others have found low or no differences (15,23,24). In our study, the cutoff value for the concordance of preoperative FNAB pathology results and postoperative pathology results in the ROC analysis for nodule size in the X plane was found

to be 27 mm (*p<0.001*). Using this cutoff value, no statistical difference was observed in the concordance between preoperative and postoperative pathology for nodules with X ≤ 27 mm, whereas a statistically significant difference was found for nodules with X > 27 mm and for all nodules (*p<0.001*). In the examination of the specificity, sensitivity, predictive, and proportional values of FNAB based on nodule size; for nodules with X ≤ 27 mm, sensitivity was 0.842, positive predictive value (PPV) was 0.888, and false positive rate (FPR) was 0.275, all higher compared to nodules with X > 27 mm; false predictive value was 0.636, and false negative rate (FNR) was 0.157, both lower. In our study, the sensitivity, specificity, false positive, and false negative values of Fine-Needle Aspiration Biopsy (FNAB) based on nodule size were consistent with the literature. A cutoff value of 27 mm was identified as a distinct finding compared to other studies for nodule size. While the reliability of FNAB was high for nodules under 27 mm, it was demonstrated that the sensitivity of FNAB decreased for nodules larger than 27 mm.

Although fine-needle aspiration biopsy (FNAB) is the gold standard in pathological diagnosis, the ultrasound characteristics of thyroid nodules still assist clinicians in distinguishing between malignant and benign conditions. There is ongoing debate regarding nodule size as a predictive risk factor for malignancy. In the study by Albuja-Cruz et al. (7), the frequency of malignancy in nodules larger than 40 mm was found to be slightly lower compared to those smaller than 40 mm. Another study found no correlation between the size of nodules and the malignancy rate in nodules 40 mm and larger (10). Cavallo et al. (22) demonstrated that the risk increases inversely with nodule size. A meta-analysis found that the risk of malignancy is higher in nodules ≥30 mm compared to those <30 mm, but the rate decreases in nodules >60 mm (25,30). In our study, the mean size of nodules, particularly those ≤ 27 mm, was found to be statistically significantly higher in benign lesions, while no significant difference was observed in lesions > 27 mm. The mean size of all nodules was also statistically significantly higher in benign lesions. This indicates that the inverse relationship between nodule size and malignancy risk for nodules ≤ 27 mm is consistent with the literature. In the examination of all nodule sizes, particularly in nodules larger than 27 mm, we found that the risk of malignancy decreased with increasing nodule size, which contrasts with some studies in the literature. Additionally, when examining the estimated two-dimensional area of the nodule in relation to postoperative malignancy; the two-dimensional estimated area was statistically significantly higher in benign lesions for nodules ≤ 27 mm, > 27 mm, and all nodules. When reviewing the literature on the relationship between nodule ultrasound characteristics and malignancy, a study evaluating 255 patients found that nodules with combinations of hypoechoic, microcalcifications, and irregular borders had a higher rate of malignancy (26). Mandel et al. identified five features predictive of malignancy: hypoechogenicity, microcalcifications, irregular borders, absence or thick halo, and increased vascularity (27). In our study, the characteristics of thyroid nodules, specifically hypoechogenicity and microcalcifications, were found to be associated with malignancy, consistent with the literature. The presence of a halo was significantly associated with the Bethesda 4 Follicular Neoplasm group. Age and gender are important and debated risk factors for malignancy. Some authors report a higher proportional rate of malignancy in males, although there are studies that contradict this. Some studies have shown that malignant thyroid nodules are more common in females than males, with higher rates in the 20-30 decade for females and in the 30th decade for males (28-30). In our study, no significant relationship was found between gender and postoperative pathology; however, a significant relationship was observed between age and postoperative pathology. For nodules ≤ 27 mm and all sizes, Bethesda 2 Benign pathology was significantly higher in older age groups.

Based on these results, although the malignancy rate decreases in nodules larger than 27 mm in clinical practice, it should be noted that the sensitivity of FNAB is low. In treatment planning, USG features should also be considered in addition to FNAB results, and options such as repeated multiple FNABs in more experienced centers or diagnostic operations should be evaluated as practical alternatives. To

improve the accuracy of FNAB, it is recommended to enhance biopsy sampling techniques in experienced hands and to collaborate with more experienced pathologists.

In our study, although data were systematically collected from the hospital database, some patient data were inaccessible due to the absence of external center results in the data system. Therefore, the small patient population, single-center design, and retrospective nature of the study represent significant limitations. Future research should include multicenter, prospective studies with larger patient populations and encompass other populations.

Conclusion

In conclusion, our study demonstrated that the risk of malignancy decreases with increasing age, nodule size, and estimated two-dimensional area. The risk of malignancy increases in nodules with hypoechoic features and microcalcifications. The sensitivity of FNAB decreases in nodules larger than 27 mm, and the false-negative rate increases. While the risk of malignancy generally decreases with increasing nodule size, the reduction in the reliability of FNAB should be considered, and the presence of hypoechoic and microcalcification features in nodules should be taken into account. For nodules larger than 27 mm, repeat FNAB and diagnostic surgery may be recommended by the operator. Nonetheless, prospective studies with larger patient populations are needed to enhance the generalizability and reliability of our findings.

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The Naples Score: Can it Outperform Existing Scores in Predicting Gastric Cancer Mortality?

Naples Skoru: Mide Kanseri Ölümlerini Tahmin Etmede Mevcut Skorlardan Daha İyi Performans Gösterebilir mi?

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The Naples Score: Can it Outperform Existing Scores in Predicting Gastric Cancer Mortality?

ABSTRACT

Objective: Gastric cancer surgery, including curative and palliative procedures, is crucial for managing gastric cancer. Accurate assessment of nutritional status is essential for risk stratification and improving patient outcomes. This retrospective study aims to identify the most reliable predictors of postoperative mortality by investigating the correlation between four nutritional scores and the mortality rate following gastric cancer surgery.

Material and Method: This retrospective study evaluated 50 patients diagnosed with gastric adenocarcinoma and operated on at Hitit University Department of General Surgery between April 2021 and September 2023. Nutritional scores were calculated using albumin, cholesterol, neutrophil-to-lymphocyte ratio, and lymphocyte-to-monocyte ratio, along with mortality rates. Data collected included age, gender, operation type, laparoscopy usage, albumin, cholesterol, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, mortality rates, and TNM stages. Nutritional scores were calculated, and their predictive accuracy for mortality was assessed using time-dependent Receiver Operating Characteristic curve analysis.

Results: Significant differences in albumin levels, neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, and nutritional scores were found between deceased and surviving patients. Specifically, albumin levels were significantly lower in deceased patients (median = 3.5 mg/dL) compared to surviving patients (median = 4.1 mg/dL, *p=0.001*). The median neutrophil-to-lymphocyte ratio was higher in deceased patients *(p=0.005)*, and the median lymphocyte-to-monocyte ratio was lower in deceased patients *(p=0.009)*. Among the scores, the Naples Prognostic Score was significantly associated with mortality but was outperformed by the Prognostic Nutritional Index. The Prognostic Nutritional Index had the highest predictive accuracy with an Area Under the curve of 0.792, a sensitivity of 76%, and a specificity of 86.2%, outperforming the others.

Conclusion: Among the evaluated scores, the Prognostic Nutritional Index is the most effective predictor of prognosis. Its superior predictive accuracy suggests that the PNI can be utilized to enhance risk assessment and guide nutritional interventions in gastric cancer patients undergoing surgery.

Keywords: Gastric cancer, mortality, predictor.

ÖZET

Amaç: Küratif ve palyatif prosedürler dahil olmak üzere mide kanseri cerrahisi, mide kanserinin yönetiminde çok önemlidir. Beslenme durumunun doğru değerlendirilmesi, risk sınıflandırması ve hasta sonuçlarının iyileştirilmesi için esastır. Bu retrospektif çalışma, dört beslenme skoru ile mide kanseri cerrahisi sonrası mortalite oranı arasındaki ilişkiyi inceleyerek postoperatif mortalitenin en güvenilir öngörücülerini belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: Bu retrospektif çalışma, Nisan 2021 ile Eylül 2023 arasında Hitit Üniversitesi Genel Cerrahi Kliniğinde ameliyat edilen mide adenokarsinomu tanısı konulan 50 hastayı değerlendirdi. Beslenme skorları, albümin, kolesterol, nötrofil-lenfosit oranı, lenfosit-monosit oranı ve mortalite oranları kullanılarak hesaplandı. Toplanan veriler arasında yaş, cinsiyet, operasyon tipi, laparoskopi kullanımı, albümin, kolesterol, nötrofil-lenfosit oranı, lenfosit-monosit oranı, mortalite oranları ve TNM evreleri yer aldı. Beslenme skorları hesaplandı ve mortaliteyi öngörmedeki doğrulukları zaman bağımlı Alıcı İşletim Karakteristik eğrisi analizi kullanılarak değerlendirildi.

Bulgular: Albümin seviyeleri, nötrofil-lenfosit oranı, lenfosit-monosit oranı ve beslenme skorları arasında ölen ve hayatta kalan hastalar arasında anlamlı farklılıklar bulundu. Özellikle, albümin seviyeleri ölen hastalarda (medyan = 3,5 mg/dL) hayatta kalan hastalara kıyasla (medyan = 4,1 mg/dL, *p=0,001*) anlamlı derecede daha düşüktü. Ölen hastalarda medyan nötrofil-lenfosit oranı daha yüksekti (*p=0,005*) ve medyan lenfosit-monosit oranı daha düşüktü (*p=0,009*). Skorlar arasında, Naples Prognostic Skoru mortalite ile anlamlı derecede ilişkiliydi ancak Prognostic Nutritional Index tarafından aşıldı. Prognostic Nutritional Index, 0,792'lik bir eğri altındaki alan, %76 duyarlılık ve %86,2 özgüllük ile en yüksek öngörü doğruluğuna sahipti ve diğerlerini geride bıraktı.

Sonuç: Değerlendirilen skorlar arasında, Prognostic Nutritional Index prognozun en etkili öngörücüsüdür. Üstün öngörü doğruluğu, PNI'nin mide kanseri cerrahisi geçiren hastalarda risk değerlendirmesini geliştirmek ve beslenme müdahalelerini yönlendirmek için kullanılabileceğini önermektedir.

Anahtar Sözcükler: Mide kanseri, mortalite, öngörücü.

Introduction

Gastric cancer surgery, particularly curative procedures, remains a cornerstone in the management of gastric cancer (GC). According to established guidelines, palliative resections generally do not contribute to survival benefits except in emergency cases. GC ranks among the leading causes of cancer-related deaths worldwide. The prognosis is particularly poor in metastatic patients. The nutritional status of these patients is often worse due to gastrointestinal involvement and cancer-related cachexia. Impaired nutritional status and immune response are among the reasons for the short survival time in these patients (1). Despite advances in surgical techniques and perioperative care, postoperative mortality continues to be a significant concern, with rates varying based on a multitude of factors including patient nutritional status. Malnutrition, often observed in patients undergoing gastric cancer surgery, has been implicated in increased postoperative complications and mortality. Therefore, accurate assessment of nutritional status is crucial for risk stratification and improving patient outcomes (2).

Several nutritional scoring systems have been developed to evaluate the nutritional status and predict outcomes in surgical patients (3). Among these, the Naples Prognostic Score (NPS), Controlling Nutritional Status (CONUT) score, Prognostic Nutritional Index (PNI), and Systemic Inflammation Score (SIS) are widely recognized (4,5). Each of these scores integrates various biochemical and clinical parameters to provide a comprehensive assessment of a patient's nutritional and inflammatory status. The NPS incorporates albumin levels, total cholesterol, lymphocyte count, and neutrophil-to-lymphocyte ratio, reflecting both nutritional and systemic inflammatory conditions. The CONUT score, derived from serum albumin, total cholesterol, and lymphocyte count, similarly provides an indication of protein reserves, caloric depletion, and immune competence. The PNI, calculated using serum albumin concentration and total lymphocyte count, is another established predictor of surgical outcomes and overall prognosis. Lastly, the SIS combines the albumin level with the lymphocyte-to-monocyte ratio, emphasizing the role of systemic inflammation in patient prognosis. The Naples Prognostic Score (NPS) incorporates albumin levels, total cholesterol, lymphocyte count, and neutrophil-to-lymphocyte ratio, reflecting both nutritional and systemic inflammatory conditions (6). The CONUT score, derived from serum albumin, total cholesterol, and lymphocyte count, similarly provides an indication of protein reserves, caloric depletion, and immune competence (7). The Prognostic Nutritional Index (PNI), calculated using serum albumin concentration and total lymphocyte count, is another established predictor of surgical outcomes and overall prognosis (8). Lastly, the Systemic Inflammation Score (SIS) combines the albumin level with the lymphocyte-to-monocyte ratio, emphasizing the role of systemic inflammation in patient prognosis (9).

Previous studies have demonstrated the utility of these scores in various clinical settings, yet their comparative effectiveness in predicting prognosis specifically in gastric cancer patients remains underexplored (10). Understanding the relative predictive value of these scores can guide clinical decision-making and optimize perioperative care strategies.

This study aims to investigate the correlation between these four nutritional scores and the mortality rate following gastric cancer surgery. By evaluating the predictive accuracy of NPS, CONUT, PNI, and SIS, we seek to identify the most reliable predictors of prognosis, thereby facilitating better risk assessment and targeted nutritional interventions for patients undergoing gastric cancer surgery.

Material and Methods

This retrospective study evaluated 50 patients diagnosed with gastric adenocarcinoma and operated on at a single center between April 2021 and September 2023. Individuals under the age of 18 and above the age of 80, those with known hematological and oncological diseases, those with known vascular and endothelial diseases, and those whose data could not be accessed were excluded from the study. A total of 50 patients were included in the study after applying the exclusion criteria. Data collected included age, gender, operation type, laparoscopy usage, albumin, cholesterol, neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), mortality rates, Naples

score, CONUT score, PNI score, SIS score, and TNM stages. Survival analysis was performed to provide a more accurate assessment of patient outcomes. This study received ethical approval from the local ethics committee institutional review board (Protocol Number: 2023/178).

Statistical analyses were conducted using IBM SPSS Statistics for Windows software (version 26; IBM Corp., Armonk, N.Y., USA). Descriptive statistics were reported for categorical variables as counts and percentages, and for numerical variables as mean ± standard deviation for normally distributed variables and median (minimum-maximum) values for non-Gaussian distributed variables. The normal distribution of data was assessed using the Shapiro-Wilk test. Correlations between variables were evaluated using Pearson and Spearman correlation coefficients, depending on the data distribution. Comparison of numerical measurements between independent groups, such as age, cholesterol levels, and PNI, was assessed using the Student's t-test, while non-Gaussian distributed variables were assessed with the Mann-Whitney U test, considering the distribution of the data. Categorical variables such as gender, operation type, laparoscopy usage, mortality rate, Naples groups, and TNM stages were evaluated between research groups using the Chi-square test. Survival analysis was conducted using the Kaplan-Meier method, and the differences between groups were compared using the log-rank test. Cox regression analysis was employed for multivariate analysis of the parameters to determine their impact on survival. Receiver Operating Characteristic (ROC) curves were utilized to demonstrate the discriminative ability of nutritional scores. Cut-off values for these markers were determined using the area under the curve and the Youden index. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy values were calculated based on these cut-off values. Odds ratio values were computed for these cut-off points. A significance level of $p < 0.05$ was considered statistically significant.

Results

A total of 50 patients met the inclusion criteria for the study. The mean age of the patients was 65.58±10.67 years. Eighty percent of the patients were male. Sixty-six percent of the patients had undergone total gastrectomy, and thirty-four percent had undergone subtotal gastrectomy. Laparoscopy was used in forty-six percent of surgeries. Twenty-one patients had died during the follow-up period since undergoing the procedure.

Table I Demographic specifications of the patients and comparison between the patient groups

Variables		All Patients (n=50)	Alive (n=29)	Deceased (n=21)	p
Age		65.58±10.67	64.28±10.64	67.38±10.7	*0.315*
Gender	Male	40 (80%)	25 (86.21%)	15 (71.43%)	*0.286*
	Female	10 (20%)	4 (13.79%)	6 (28.57%)	
Operation Type	Subtotal	17 (34%)	9 (31.03%)	8 (38.1%)	*0.603*
	Total	33 (66%)	20 (68.97%)	13 (61.9%)	
Laparoscopic	Laparotomy	27 (54%)	15 (51.72%)	12 (57.14%)	*0.704*
	Laparoscopy	23 (46%)	14 (48.28%)	9 (42.86%)	
Albumin		3.95 (2.6-4.5)	4.1 (3.2-4.4)	3.5 (2.6-4.5)	***0.001***
Cholesterol		174.8±45.1	181.14±39.46	166.14±51.63	*0.250*
NLR		3.06 (1.27-109.6)	2.55 (1.27-6.51)	3.95 (1.77-109.6)	***0.005***
LMR		3.04 (1.26-7.36)	3.22 (1.27-7.36)	2.27 (1.26-4.5)	***0.009***
Naples Group	Naples Score 0	3 (6%)	2 (6.9%)	1 (4.76%)	***0.022***
	Naples Score 1-2	25 (50%)	19 (65.52%)	6 (28.57%)	
	Naples Score 3-4	22 (44%)	8 (27.59%)	14 (66.67%)	
CONUT		2 (0-10)	2 (0-5)	4 (0-10)	***0.004***
PNI		46.13±6.93	49.06±5	42.08±7.29	***<0.001***
SIS		1 (0-2)	1 (0-2)	2 (0-2)	***<0.001***
TNM	T1N0	9 (18%)	9 (31.03%)	0 (0%)	*0.053*
	T2N0	1 (2%)	1 (3.45%)	0 (0%)	
	T2N1	1 (2%)	0 (0%)	1 (4.76%)	
	T3N0	6 (12%)	5 (17.24%)	1 (4.76%)	
	T3N1	3 (6%)	0 (0%)	3 (14.29%)	
	T3N2	3 (6%)	2 (6.9%)	1 (4.76%)	
	T3N3	10 (20%)	3 (10.34%)	7 (33.33%)	
	T4N0	2 (4%)	1 (3.45%)	1 (4.76%)	
	T4N1	2 (4%)	1 (3.45%)	1 (4.76%)	
	T4N2	3 (6%)	2 (6.9%)	1 (4.76%)	
	T4N3	10 (20%)	5 (17.24%)	5 (23.81%)	

NLR: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, CONUT: Controlling Nutritional Status, PNI: Prognostic Nutritional Index, SIS: Systemic Inflammation Score Shapiro-Wilks test, Student t-test, Mann Whitney-U test, Chi-square test

When the subjects were divided into two groups based on mortality status, no statistically significant

Table II Optimal cut-off values for the distinction between alive and deceased groups and diagnostic indicators (Youden index)

Variables	Cut-Off	Diagnostic Values					ROC Curve			Odds Ratio		
		Sensitivity	Specificity	PPV	NPV	Accuracy	Area (SE)	95%CI	*p*	Odds Ratio	95%CI	*p*
Naples	≥4	66.7	72.4	63.6	75.0	70.0	0.690	0.536-0.843	***0.023***	5.25	1.551-17.767	***<0.001***
CONUT	≥4	61.9	89.7	81.3	76.5	78.0	0.740	0.584-0.895	***0.004***	14.083	3.191-62.150	***<0.001***
PNI	<44.95	76.0	86.2	80.0	83.3	82.0	0.792	0.650-0.935	***<0.001***	20	4.659-85.848	***<0.001***
SIS	≥2	76.2	72.4	66.7	80.8	74.0	0.755	0.617-0.892	***0.002***	8.4	2.306-30.603	***<0.001***

CONUT: Controlling Nutritional Status, PNI: Prognostic Nutritional Index, SIS: Systemic Inflammation Score

differences were identified between the two groups in terms of age or gender (*p=0.315* and *p=0.286*, respectively). Furthermore, no differences were identified regarding the type of operation or the use of laparoscopy (*p=0.603* and *p=0.704*, respectively). The median albumin level of 3.5 mg/dL (2.6-4.5) was observed to be significantly lower in patients who had died than in patients who were still alive (median = 4.1 mg/dL, 3.2-4.4; *p=0.001*) (Table I). There was no significant difference in cholesterol levels between the two groups (*p=0.250*). The median NLR of deceased patients was significantly higher than that of those still alive (*p=0.005*). The median LMR of the deceased patients was lower than that of patients who were still alive (*p=0.009*). There was no statistically significant difference between groups in terms of TNM stage (*p=0.053*) (Table I).

Table III Kaplan Meier Survival Analysis Results

Variables		Estimated Mean Survival Duration	Std. Error	95% Confidence Interval		Log-rank test statistical significance
				Lower Bound	Upper Bound	
PNI	≥44.95	37.157	1.216	34.773	39.540	*<0.001*
	<44.95	27.179	1.654	23.936	30.421	
CONUT	<4	36.194	1.229	33.784	38.604	*<0.001*
	≥4	26.650	1.862	23.000	30.300	
SIS	<2	36.731	1.379	34.028	39.433	*<0.001*
	≥2	29.296	1.698	25.967	32.625	
Naples	<4	35.849	1.411	33.083	38.615	*0.010*
	≥4	29.915	1.834	26.321	33.509	
Overall Estimated Survival Duration		33,150	1.207	30.785	35.516	

CONUT: Controlling Nutritional Status, PNI: Prognostic Nutritional Index, SIS: Systemic Inflammation Score

Table IV Multivariate Cox Regression Analysis Results

Variables	B	SE	Wald	Sig.	Exp(B)	95% CI for Exp(B)	
						Lower	Upper
Albumin	-1.470	0.454	10.478	0.001	0.230	0.094	0.560
NLR	0.032	0.012	7.288	0.007	1.032	1.009	1.057
PNI	-0.111	0.033	11.275	0.001	0.895	0.838	0.955
LMR	-0.465	0.206	5.079	0.024	0.628	0.419	0.941

NLR: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, PNI: Prognostic Nutritional Index

A statistical analysis of the nutritional scores of two groups revealed that the majority of deceased patients had a Naples score of 3–4 (66.67%), while the majority of the other group had a Naples score of 1–2 (65.52%). This difference was found to be statistically significant (*p=0.022*). Patients who died had a higher median CONUT score of 4 than patients who survived (median 2; *p=0.004*). Similarly, the SIS score of deceased patients was significantly higher compared to the other group (*p<0.001*). The PNI score of 49.06±5 was significantly higher in living patients compared to 42.08±7.29 in deceased patients (*p<0.001*).

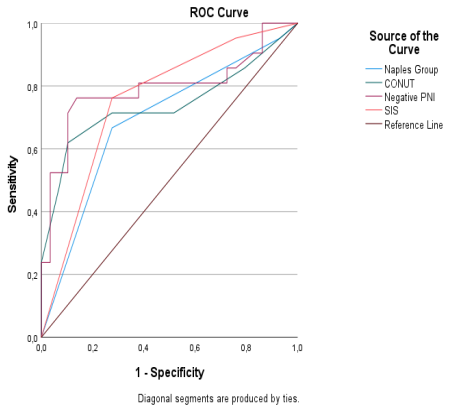

Figure I Receiver operating curve of prognostic scores in the distinction between groups

To assess the optimal values of Naples, CONUT, PNI, and SIS scores for distinguishing between alive and deceased patient groups, the area under the curve and the Youden index were employed in ROC analysis (Figure I and Table II). For the prediction of mortality, the most suitable Naples cut-off value was determined to be ≥4 with 66.7% sensitivity, 72.4% specificity, 63.6% positive predictive value, 75% negative predictive value, and 70% test accuracy (OR 5.25, 95% CI 1.551-17.767, *p<0.001*). Similarly, the optimal CONUT cut-off value was also found to be ≥4 with 61.9% sensitivity, 89.7% specificity, 81.3% positive predictive value, 76.5% negative predictive value, and 78% test accuracy (OR 14.083, 95% CI 3.191-62.150, *p<0.001*). The optimal PNI cut-off was <44.95 with 76% sensitivity, 86.2% specificity, 80.0% positive predictive value, 83.3% negative predictive value, and 82% test accuracy (OR 20, 95% CI 4.659-85.848, *p<0.001*). Lastly, the optimal SIS cut-off was ≥2 with 76.2% sensitivity, 72.4% specificity, 66.7% positive predictive value, 80.8% negative predictive value, and 74% test accuracy (OR 8.4, 95% CI 2.306-30.603, *p<0.001*). Among these prognostic scores, PNI was found to be slightly better than the other scores, with a higher area under the curve and a higher odds ratio. A PNI score under 44.95 increased the likelihood of mortality by approximately 19 times. To assess the survival analysis, both Kaplan-Meier and Cox regression analyses were performed. The median survival time for all patients was 30 months. For deceased patients, the median survival time was 24 months, while for surviving patients, it was 36 months. The Kaplan-Meier survival curves indicated that higher Naples, CONUT, and SIS scores were associated with shorter survival times, while a higher PNI score was associated with longer survival (Figures IIa, IIb, IIc, IId, and Table III). The mean estimated survival duration for patients whose Naples scores were 4 or higher was 29.91±1.83 months, while the mean estimated survival duration for patients with Naples scores lower than 4 was significantly higher at 35.84±1.41 months (*p=0.010*, Table III). Cox regression analysis further identified that albumin, NLR, LMR, and PNI were significant predictors of survival. Multivariate Cox regression analysis results indicated that lower albumin levels, higher NLR, lower LMR, and lower PNI scores significantly increased the risk of mortality (Table IV and Figure III for details). These findings highlight the importance of nutritional and inflammatory status in predicting postoperative outcomes in gastric cancer surgery patients.

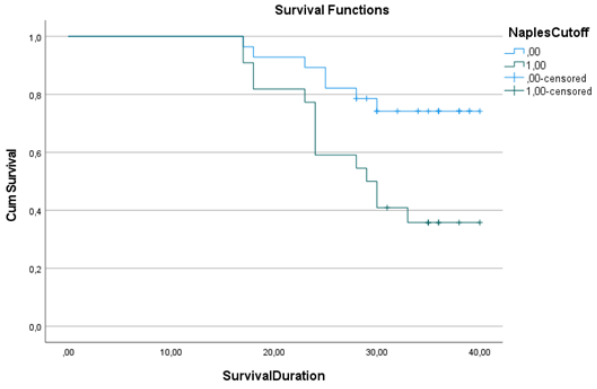

Figure IIa Kaplan Meier Survival Analysis Graph of Naples Score Cutoff

Table V Demographic specifications of the patients and comparison between the patient groups

Variables		Naples<4	Naples≥4	*p value*
Age		63.71±10.75	67.95±10.33	*0.165*
Gender	Male	22 (78.57%)	18 (81.82%)	*0.776*
	Female	6 (21.43%)	4 (18.18%)	
Operation Type	Subtotal	12 (42.86%)	5 (22.73%)	*0.136*
	Total	16 (57.14%)	17 (77.27%)	
Laparoscopic	Laparotomy	14 (50.00%)	13 (59.09%)	*0.522*
	Laparoscopy	14 (50.00%)	9 (40.91%)	
Albumin		4.15 (2.8-4.5)	3.61 (2.6-4.2)	*<0.001*
Cholesterol		192.64±45.81	152.18±32.96	*0.001*
NLR		2.47 (1.27-11.7)	3.97 (1.74-109.6)	*0.003*
LMR		3.74 (1.31-7.36)	2.35 (1.26-3.78)	*0.002*
Mortality	Alive	21 (75%)	8 (36.36%)	*0.006*
	Deceased	7 (25%)	14 (63.64%)	
CONUT		1.5 (0-10)	4 (1-9)	*0.005*
PNI		49.11±6.30	42.33±5.85	*<0.001*
SIS		1 (0-2)	2 (1-2)	*<0.001*
TNM	T1N0	9 (32.14%)	0 (0.00%)	*0.095*
	T2N0	1 (3.57%)	0 (0.00%)	
	T2N1	0 (0.00%)	1 (4.55%)	
	T3N0	4 (14.29%)	2 (9.09%)	
	T3N1	2 (7.14%)	1 (4.55%)	
	T3N2	2 (7.14%)	1 (4.55%)	
	T3N3	2 (7.14%)	8 (36.36%)	
	T4N0	1 (3.57%)	1 (4.55%)	
	T4N1	1 (3.57%)	1 (4.55%)	
	T4N2	2 (7.14%)	1 (4.55%)	
	T4N3	4 (14.29%)	6 (27.27%)	

NLR: Neutrophil-to-Lymphocyte Ratio, LMR: Lymphocyte-to-Monocyte Ratio, CONUT: Controlling Nutritional Status, PNI: Prognostic Nutritional Index, SIS: Systemic Inflammation Score

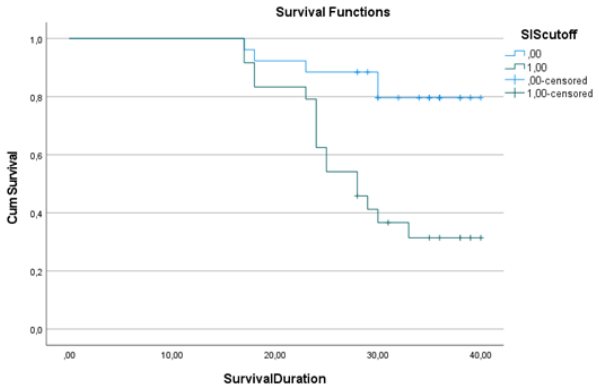

Figure IIb Kaplan Meier Survival Analysis Graph of SIS Cut-off

Further analysis was conducted by dividing patients into two groups based on the Naples score cut-off value of ≥ 4, as determined by the Youden index. Patients with Naples scores of 4 or higher were characterized by lower albumin levels, lower cholesterol levels, higher NLR, lower LMR, higher mortality rates, higher CONUT scores, lower PNI scores, and higher SIS scores (Table V).

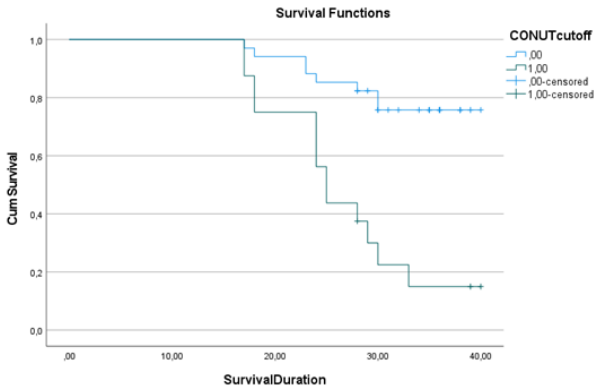

Figure IIc Kaplan Meier Survival Analysis Graph of CONUT Cutoff

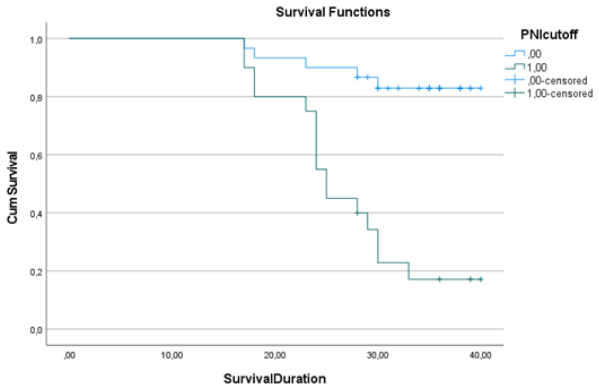

Figure IId Kaplan Meier Survival Analysis Graph of PNI Cutoff

These results further validate the importance of the NAPLES score in predicting patient outcomes. A higher NAPLES score indicates a worse prognosis, underscoring the relevance of nutritional and inflammatory status as critical factors in the postoperative survival of gastric cancer patients. The detailed statistical analysis emphasizes that patients with higher NAPLES scores tend to have poorer survival outcomes, highlighting the utility of this score in clinical decision-making and patient management.

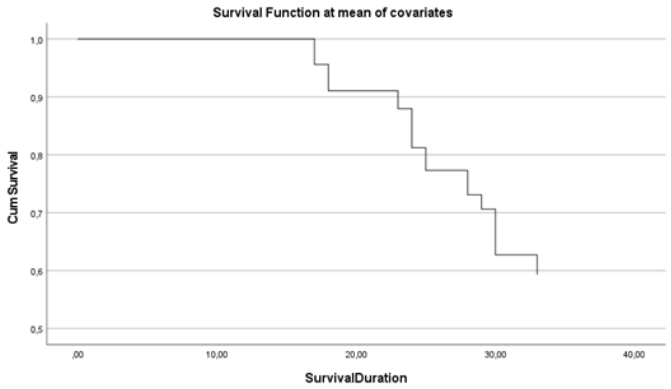

Figure III Cox Regression Analysis Graph

Discussion

This study aimed to compare the prognostic value of various nutritional and inflammatory scores in predicting mortality in patients undergoing gastric cancer surgery. Our findings revealed that Naples, CONUT, PNI and SIS scores were significantly associated with mortality and that PNI was superior to other scoring methods.

GC ranks among the leading causes of cancer-related deaths worldwide (11). The prognosis is quite poor in metastatic patients. The nutritional status of these patients is often worse due to gastrointestinal involvement and cancer-related cachexia. Impaired nutritional status and immune response are among the reasons for the short survival time in these patients (12).

In many studies, cancers have been shown to be affected by the immune response and related to nutritional status. This has led to the development of new biomarkers of the immune system and nutrition-based prognostic scoring systems (13).

The inflammatory response in the tumor may also play a role in the destruction of tumor cells and angiogenesis. The inflammatory response can

be altered by exposing tumors to radiotherapy and chemotherapy. Lymphocytes play an important role in this reaction. Lymphopenia in many tumors, including GC, is also associated with adverse effects and poor prognosis (14,15). On the other hand, increased tumoral neutrophil infiltration usually correlates with poor clinical features. Neutrophils play a role in tumor cell proliferation and tumor formation by activating cytokines and causing metastasis (16,17). Therefore, NLR and LMR have been evaluated in many studies, and increasing NLR and decreasing LMR are generally associated with worse outcomes (18).

Malnutrition is intricately linked to angiogenesis and tumor growth, thereby facilitating disease progression. Serum albumin levels serve as a crucial indicator of nutritional status and inflammatory burden, functioning as a negative acute phase reactant. Hypoalbuminemia is frequently associated with unfavorable outcomes in various malignancies (19). Our study similarly found that hypoalbuminemia correlates with poor prognosis in GC. Beyond albumin, cholesterol levels also reflect nutritional status, with low cholesterol being indicative of a poor prognosis (20). Therefore, nutritional status scores often include both albumin and cholesterol measurements.

This study shows that the NPS is an independent indicator of outcome in patients who undergo surgery for GC. By including all previously used biomarkers in the PNI, we covered both nutritional and inflammatory status. The PNI worsened with tumor progression, suggesting a strong correlation between tumor status and patient status, and was a significant predictor of long-term outcome. Its prognostic performance turned out to be much better than that of previous scoring systems and significantly improved the current prognostic model. Further analysis, based on the Naples score cut-off value of ≥ 4, demonstrated its significant prognostic value. Patients with Naples scores ≥ 4 had a worse prognosis compared to those with scores < 4. The median survival time for patients with Naples < 4 was 30 months, indicating better outcomes. This underscores the utility of the Naples score in clinical decision-making and highlights its importance in risk stratification and management of gastric cancer patients.

The two indicators that make up PNI are obtained by routine peripheral blood laboratory testing before surgery. We evaluated the predictive performance of various prognostic scores using time-dependent ROC curve analysis. The findings indicated that PNI had a higher area under the curve and a greater odds ratio compared to NPS, CONUT, and SIS, making it the most effective predictor.

This study has several limitations. Firstly, as a retrospective study, it is inherently subject to potential selection bias. Secondly, the lack of external validation and the fact that it was conducted at a single center with a moderate sample size might have diminished the strength of its findings. Future prospective and multi-institutional studies are required to validate these results.

In conclusion, PNI, CONUT, SIS, and NPS, which evaluate the calculated immune nutritional status, predict GC patient outcomes. PNI appears superior to others in this respect.

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The Impact of Bone Marrow Fibrosis on Transplant Outcomes in Multiple Myeloma Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

Otolog Kök Hücre Nakli Yapılan Multiple Myeloma Hastalarında Kemik İliği Fibrozisinin Nakil Sonuçlarına Etkisi

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The Impact of Bone Marrow Fibrosis on Transplant Outcomes in Multiple Myeloma Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

ABSTRACT

Objective: In newly diagnosed multiple myeloma, bone marrow fibrosis is observed in 8-57% of cases. In this retrospective study, we aimed to investigate the clinical and demographic characteristics of multiple myeloma patients with bone marrow fibrosis, as well as the impact of bone marrow fibrosis on engraftment and transplant outcomes following autologous hematopoietic stem cell transplantation.

Material and Method: Our study included 78 newly diagnosed multiple myeloma patients who received induction therapy and underwent autologous hematopoietic stem cell transplantation at our center between August 2016 and July 2023.

Results: Bone marrow fibrosis (grade I-III) was detected in 37 patients (47.5%). Patients with bone marrow fibrosis had a significantly higher percentage of bone marrow plasma cells compared to those without fibrosis (50% vs 35%, *p=0.007*). After autologous hematopoietic stem cell transplantation, time to neutrophil and platelet engraftment were significantly longer in the group with bone marrow fibrosis (Median time to neutrophil engraftment:14 vs 13 days, *p=0.005*, Median time to platelet engraftment:16 vs 13 days, *p=0.004*). The length of hospital stay after autologous hematopoietic stem cell transplantation was significantly longer in the group with bone marrow fibrosis (22 days vs 19 days, *p=0.047*). No significant differences were found regarding neutrophil and platelet engraftment days when considering clinical, demographic, and other transplant-related factors.

Conclusion: In conclusion, our study found that newly diagnosed multiple myeloma patients with bone marrow fibrosis had longer neutrophil and platelet engraftment times and longer hospital stays after autologous hematopoietic stem cell transplantation. There is a need for larger prospective studies to determine the optimal amount of CD34 (+) stem cells and to explore more effective use of supportive therapies and growth factors in this patient group.

Keywords: Autologous hematopoietic stem cell transplantation, bone marrow fibrosis, Multiple Myeloma, neutrophil engraftment, platelet engraftment.

ÖZET

Amaç: Yeni tanı multiple myelomda kemik iliğinde fibrozis %8-57 arasında görülmektedir. Bu retrospektif çalışmamızda, kemik iliğinde fibrozis olan multiple myelom hastalarının klinik ve demografik özellikleri ile kemik iliği fibrozisinin otolog hematopoetik kök hücre nakli sonrası engrafmana ve nakil sonuçlarına etkisini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışmamıza, Ağustos 2016 ile Temmuz 2023 tarihleri arasında merkezimizde multiple myelom tanısı ile indüksiyon tedavisi verilen ve otolog hematopoetik kök hücre nakli yapılan 78 hasta dahil edildi.

Bulgular: Hastaların 37'sinde (%47,5) kemik iliğinde grade I - III fibrozis saptanmıştır. Kemik iliğinde fibrozis saptanan hastalarda kemik iliği plazma hücre oranı anlamlı daha yüksek tespit edilmiştir (%50 vs %35, *p=0.007*). Fibrozisi olan ve olmayan multiple myelom hastalarının diğer klinik ve demografik özellikleri benzerdir. Otolog hematopoetik kök hücre naklinde verilen CD34(+) kök hücre miktarları ve melfalan dozları da her iki grup arasında benzerdir. Otolog hematopoetik kök hücre nakli sonrası, nötrofil ve trombosit engrafmanı, kemik iliğinde fibrozis olan grupta anlamlı olarak daha uzun tespit edilmiştir (Medyan nötrofil engrafman günü: 14 vs 13 gün, (*p=0.005*), medyan trombosit engrafman günü: 16 vs 13.gün, (*p=0.004).* Otolog hematopoetik kök hücre nakli sonrası hastanede kalış süresi, kemik iliğinde fibrozis olan grupta anlamlı daha uzun tespit edilmiştir (22 gün vs 19 gün, *p=0.047*). Hastaların nötrofil ve trombosit engrafman günü üzerine etki edebilecek diğer hasta, hastalık ve transplant ilişkili faktörler açısından anlamlı fark tespit edilememiştir.

Sonuç: Çalışmamız sonucunda, kemik iliğinde fibrozis tespit edilen, yeni tanı multiple myelom hastalarında otolog hematopoetik kök hücre nakli sonrası nötrofil ve trombosit engrafman günü ile hastanede kalış süresi daha uzun saptanmıştır. Bu hasta grubunda optimal CD34(+) kök hücre miktarının belirlenmesi, destek tedavilerin ve büyüme faktörlerinin daha etkin kullanımı ile ilgili daha geniş prospektif çalışmalara ihtiyaç duyulmaktadır.

Anahtar Sözcükler: Kemik iliği fibrozisi, Multiple Miyelom, nötrofil engrafmanı, otolog hematopoetik kök hücre nakli, trombosit engrafmanı.

Giriş

Multiple myelom (MM) klonal plazma hücrelerinin neoplastik proliferasyonu ile birlikte end organ hasarı olarak tanımlanan, böbrek yetmezliği, hiperkalsemi, anemi ve litik kemik lezyonları ile karakterizedir (1, 2). Tüm kanserlerin %1'ini, hematolojik malignitelerin ise %10'unu oluşturur ve ikinci en sık görülen hematolojik malignitedir (3, 4).

Transplanta uygun, yeni tanı MM hastalarında, indüksiyon kemoterapisini takiben otolog hematopoetik kök hücre nakli (OKHN) ve nakil sonrası idame tedavisi standart yaklaşım olarak kabul edilmektedir (5, 6). OKHN ile nakil öncesinde mobilize edilen hematopoetik kök hücreler, hazırlama rejimi olarak tanımlanan myeloablatif kemoterapi sonrası hastaya infüze edilmekte ve kök hücrelerin kemik iliği nişine yerleşerek hematopoezin yeniden başlaması hedeflenmektedir. Transfüzyon desteği olmaksızın, infüze edilen kök hücrelerin tekrar hematopoezi başlatması engrafman olarak adlandırılır (7). Çalışmalarda standardizasyonu sağlama amaçlı, nötrofil ve trombosit engrafmanı için objektif kriterler tanımlanmıştır. Yapılan çalışmalara göre nötrofil engrafmanı ortalama 11-15. günler arası, trombosit engrafmanı ise 11-18. günler arasında gerçekleşmektedir (7, 8). Engrafmanın 21 günden uzun sürmesi gecikmiş engrafman olarak tanımlanırken; 42 günü aşması ise primer engrafman yetmezliği olarak tanımlanmaktadır (9, 10).

MM mikroçevresi klonal plazma hücreleri, hücre dışı matriks proteinleri; adipositler ve fibroblastların oluşturduğu stromal hücreler; osteoblastlar, osteoklastlar, mezenkimal kök hücreler, inflamatuar hücreler, büyüme fatktörleri, sitokinler ve vasküler yapılardan oluşmaktadır. Kemik iliği mikroçevresinin, MM hücrelerinin büyüme ve hayatta kalmasını desteklediği, hücresel immüniteyi baskıladığı, böylece hastalık progresyonunda ve tedavi direncinde önemli rol oynadığına dair kanıtlar mevcuttur. Son yıllarda MM tedavisindeki büyük gelişmelere rağmen; sadece plazma hücrelerini hedefleyen tedavi başarısının sınırlı olması nedeni ile mikroçevreyi de hedefleyen tedavilerin önemi vurgulanmıştır (11-14).

Kemik iliğinde retikülin ya da kollajen lif artışı olarak tarif edilen kemik iliği fibrozisi, primer myelofibrozis gibi myeloproliferatif hastalıklarda görülebileceği gibi; lösemi, lenfoma, enfeksiyonlar, endokrinopatiler veya diğer solid malignitelere sekonder olarak da gelişebilir (15, 16). Kemik iliği fibrozisinde öne çıkan mekanizma Transforming Growth Faktör Beta (TGF-β) ve megakaryositlerden salınan diğer sitokinler olsa da, aslında çok daha kompleks bir alt yapısı olduğunu düşündüren kanıtlar mevcuttur (17). MM hastalarında tanı anında kemik iliği fibrozisi %8-57 oranında tespit edilmektedir (18-20). Biz çalışmamızda merkezimizde OKHN yapılmış olan yeni tanı MM hastalarında kemik iliği fibrozisi olan ve olmayan hastalardaki klinik, demografik özellikleri analiz etmeyi; kemik iliği fibrozisi olan hastalarda fibrozisin OKHN sonrası engrafmana ve nakil sonuçlarına etkisini araştırmayı amaçladık.

Gereç ve Yöntem

Çalışmamıza, Sağlık Bilimleri Üniversitesi Gülhane Eğitim ve Araştırma Hastanesi Hematoloji Bilim Dalında, MM tanısı ile indüksiyon tedavisi sonrası OKHN uygulanmış olan tüm hastalar dahil edilmiştir. Çalışmada Dünya Tabipleri Birliği Helsinki Bildirgesi ve iyi klinik uygulamalar kılavuzu ilkelerine bağlı kalınmış ve tüm hastalardan çalışmaya dahil edilmek üzere yazılı bilgilendirilmiş onam alınmıştır. Çalışmamız; Sağlık Bilimleri Üniversitesi Gülhane Tıp Fakültesi 22.08.2023 tarih ve 2023-312 sayılı onamı ile etik kurul onayı almıştır.

Çalışmaya Dahil Edilen Hastalar

Çalışmamıza, Ağustos 2016 – Temmuz 2023 tarihleri arasında, SBÜ GEAH Hematoloji Bilim Dalında, Uluslararası Myelom Çalışma Grubu (IMWG) tarafından 2014 yılında revize edilmiş tanı kriterlere göre MM tanısı konulmuş (2), OKHN'ne uygun olan, indüksiyon tedavisi/tedavileri sonrası yeterli kök hücre mobilizasyonu ve OKHN yapılmış olan 18-70 yaş arası toplam 78 hasta dahil edilmiştir. Tanı anında transplanta uygun olmayan ya da yeterli kök hücre mobilizasyonu yapılamayan veya transplanta uygun olmasına rağmen nakil olmayı kabul etmeyen hastalar çalışma dışı bırakılmıştır. Ayrıca takip ya da tedavi verilerine erişilemeyen, eksik takip verisi olan veya takipten çıkan hastalar da çalışma dışı bırakılmıştır. Öncesinde başka bir malignite nedeniyle kemoterapi/radyoterapi almış olanlar, Eastern Cooperative Oncology Group (ECOG) performans skoru >2 olanlar, sol ventrikül ejeksiyon fraksiyonu <%50 olanlar, ağır pulmoner komorbiditesi olanlar; yeterli karaciğer fonksiyonu olmayan hastalar; OKHN'ne

uygun olmayan grup olarak değerlendirilmiştir.

Tüm hastalar, international staging system (ISS) ve revize ISS evreleme sistemine göre evrelendirilmiş; hepsine tanı anında ve nakil öncesi dönemde kemik iliği biyopsisi yapılmıştır. Yüksek sitogenetik risk; 1q değişiklikleri, del(17p), t(4;14) ve t(14;16) olarak belirlenmiştir (21-23). Tanı anındaki kemik iliği fibrozisinin değerlendirilmesi için retikülin boyama yapılmış, fibrozis düzeyi Avrupa konsensüsü dikkate alınarak I-III arasında gradelenmiş; I düşük grade fibrozis, II-III ise yüksek grade fibrozis olarak tanımlanmıştır (24). Tanı anındaki kemik iliğinde grade II-III fibrozis tespit edilen hastalarda eşlik edebilecek hematolojik ve non-hematolojik diğer nedenler dışlanmıştır. Hastaların demografik verileri, tanı anı hemogram ile biyokimya sonuçları, genetik risk faktörleri, ISS ve R-ISS risk skorları, nakil öncesi almış oldukları kemoterapi protokolleri, nakil hazırlama rejimleri, mobilize/infüze edilen CD34(+) kök hücre sayısı, engrafman günleri, hastanede kalış süreleri retrospektif olarak analiz edilmiştir.

Tedavi Protokolleri

İndüksiyon Tedavileri

Hastaların yaş, performans, komorbiditeleri ve ilaca erişebilme gibi faktörlerine bağlı olarak hematopoetik kök hücre nakli öncesinde indüksiyon rejimi olarak VCd (Bortezomib 1,3 mg/m2, siklofosfamid 300 mg/m2, deksametazon 40 mg/hafta) ya da VRd (Bortezomib 1,3 mg/m2, lenalidomid 10-25 mg/gün, deksametazon 40 mg/hafta) tedavileri verildi. Birinci basamak indüksiyon rejimlerine yanıtın değerlendirilmesi, International Myeloma Working Group- 2016 (IMWG-2016) yanıt değerlendirme kriterlerine göre yapıldı (25). Minimum 4 siklus uygulanan indüksiyon tedavisiyle en az kısmi yanıt elde edilen hastalarda kök hücre mobilizasyonuna geçildi. 4 siklus tedavi ile en az kısmi yanıt elde edilemeyenlerde, ya da indüksiyon tedavisi esnasında progresif hastalığı olanlarda ikinci basamak tedavi verildi. İkinci basamak tedavi seçimi; yine yaş, performans, komorbidite, ilaca erişebilme faktörleriyle birlikte birinci basamak tedavi rejimine bağlı olarak belirlenmiştir.

Kök Hücre Mobilizasyonu ve Otolog Hematopoetik Kök Hücre Nakli

İndüksiyon tedavisi ile IMWG-2016 kriterlerine göre, en az parsiyel yanıt elde edilmiş olan hastalara kök hücre mobilizasyonu ve OKHN uygulanmıştır. Kök hücre mobilizasyon protokolü olarak hastalara tek başına granülosit koloni stimüle edici faktör (G-CSF) (2x5 mcg/kg/gün) ya da kemoterapi ile birlikte G-CSF uygulanmıştır. Periferik hematopetik kök hücreler, 2,5 kan volümü aferez ile santral/periferik kateter yardımı ile toplanmıştır. En az $2x10^6$/kg CD34(+) kök hücre toplanan hastalarda OKHN'ne ilerlenmiştir. Hastalara OKHN hazırlama rejimi olarak melfalan verilmiştir. Hastaların yaş, performans ve kreatinin klerensine göre melfalan dozu 140 mg/m^2 ya da 200 mg/m^2 olarak belirlenmiştir. Melfalan -2.günde, tek gün infüzyon olarak uygulanmıştır. 0.günde hematopoetik kök hücre infüzyonu verilmiştir. Tüm hastalara nakil sonrası +5.günden itibaren nötrofil engrafmanına kadar 5 mcg/kg/gün dozundan G-CSF uygulanmıştır. Transplantasyon sonrasında hastalara hemoglobin düzeyini en az 7 g/dl'de tutacak şekilde eritrosit süspansiyonu, platelet düzeyini ise 20000/mm^3'de tutacak şekilde trombosit transfüzyonu yapılmıştır.

Tanımlar

Nakil sonrası hastaların nötrofil ile trombosit engrafman günleri, hastanede kalış süreleri ve sağkalımları analiz edilmiştir. Nötrofil engrafmanı, mutlak nötrofil sayısının >500/mm^3 olduğu 3 ardışık günün ilk günü; trombosit engrafmanı replasman yapılmaksızın trombosit sayısının >20000/mm^3 olduğu ardışık 7 günün ilk günü olarak tanımlanmıştır. Hastaların hastanede yatış süreleri, kök hücre infüzyonundan itibaren (0. günden) hesaplanmıştır.

İstatistiksel analiz

Elde edilen veriler Windows Statistical Package For Social Sciences (SPSS) 23.0 kullanılarak analiz edildi. Sayısal değişkenler içinde normal dağılım gösterenler ortalama ± standart sapma olarak veya normal dağılım göstermeyenler ortanca (minimum-maksimum) olarak tanımlandı. Kategorik değişkenler yüzde olarak ifade edildi. Kolmogorov-Smirnov ve Shapiro-Wilk testleri ile dağılımın normalliği saptandıktan sonra sürekli değişkenler Mann-Whitney U testi veya Student t-testi ile, kategorik değişkenler ise Ki-kare testi veya Fisher's Exact testi ile karşılaştırıldı. *p değeri 0,05*'ten küçük hesaplandığında istatistiksel olarak anlamlı kabul edildi.

Bulgular

Merkezimizde OKHN uygulanmış toplamda 78

hasta dahil edildi. Çalışmaya alınan hastaların 46'sı (%58,9) erkek, 32'si ise (%41,1) kadındı. Hastaların medyan yaşı 60 (aralık: 40-70) olup, hastaların 53'ü (%67,9) 65 yaş ve altındaydı. Tanı anındaki biyopsi sonucuna göre hastaların 41'inde (%52,5) kemik iliğinde fibrozis tespit edilmezken, 37'sinde (%47,5) tanı anında grade I-III fibrozis saptandı. Kemik iliğinde fibrozisi olan ve olmayan hastaların demografik ve klinik verilerinin karşılaştırılmasında, fibrozis tespit edilen hastaların kemik iliğindeki medyan plazma hücre oranı anlamlı şekilde daha fazla tespit edildi (%50 vs %35, *p=0.007*). Ayrıca tanı anında kemik iliğinde >%50 plazma hücresi bulunan hasta oranı, fibrozis tespit edilen grupta anlamlı şekilde daha fazla bulundu (%43,2 vs %19,5, *p=0.037*). Hastaların tanı anındaki klinik, demografik özellikleri ve kemik iliği fibrozisinin varlığına göre analizi Tablo I'de özetlenmiştir.

Çalışmaya dahil edilen hastaların 63'üne (%80,7) birinci basamak indüksiyon tedavisi olarak VCd protokolü, 15'ine ise (%19,3) birinci basamak tedavi de VRd protokolü verilmiştir. Hastaların 45'ine (%56,7) nakil öncesinde 1 sıra tedavi, 33'üne ise (%43,2) >1 sıra tedavi uygulanmıştır. Kemik iliğinde fibrozis tespit edilen hastaların nakil öncesi tedavi verileri ve elde edilen yanıtları, kemik iliğinde fibrozis olmayan hastalar ile benzer tespit edilmiş olup anlamlı fark saptanmamıştır. Hastaların nakil öncesi aldığı tedavi verileri, elde edilen yanıtlar ve kemik iliği fibrozisinin varlığına göre nakil öncesi tedavilerin analizi Tablo II'de özetlenmiştir.

OKHN yapılan hastalara medyan 4,01x10^6/kg CD34(+) hematopoetik kök hücre infüze edilmiştir. Kemik iliğinde fibrozis tespit edilen hastalara medyan 4,19x10^6/kg (2,2-6,3x10^6/kg), fibrozis tespit edilmeyen hastalara ise medyan 3,86x10^6/kg (2-7,9 x10^6/kg) CD34(+) kök hücre infüze edilmiş olup her iki grup arasında infüze edilen kök hücre miktarları açısından anlamlı fark yoktur. Hastaların 62'sinde (%79,5) melfalan dozu 200 mg/m^2 verilmiş olup, 16 hastada (%20,5) melfalan dozu 140 mg/m^2 olarak belirlenmiştir. 16 hastanın 11'inde kreatinin klerensinin düşük olması, 5 hastada ise performans ve yaş dikkate alınarak melfalan dozu 140 mg/m^2 olarak belirlenmiştir. Kemik iliğinde fibrozis tespit edilen ve edilmeyen gruplar arasında melfalan dozu bakımından anlamlı fark tespit edilmemiştir.

Tablo I Hastaların tanı anındaki klinik ve demografik özellikleri

		Tüm Hastalar (n=78)	Kemik İliğinde Fibrozis Yok (n=41)	Kemik İliğinde Fibrozis Var (Grade I-III) (n=37)	*p değeri*
Yaş	Medyan - yıl	60 (40-70)	60 (42-70)	60 (40-70)	*0.471*
Yaş Grupları	≤65 yaş	53 (%67,9)	27 (%65,9)	26 (%70,3)	*0.676*
	>65 yaş	25 (%32,1)	14 (%34,1)	11 (%29,7)	
Cinsiyet	Erkek	46 (%58,9)	26 (%63,4)	20 (%54,1)	*0.401*
	Kadın	32 (%41,1)	15 (%36,6)	17 (%45,9)	
Lökosit Sayısı	Medyan-x10^9/L	6,1 (1,8-19)	6,2 (1,8-19)	6.1 (2,2-14,5)	*0.941*
Hemoglobin	Median - g/dl	10,4 (5,5-15,6)	10,7 (5,5-15,6)	10 (5,7-13,9)	*0.223*
Platelet	Medyan-x10^9/L	230 (91-535)	234 (140-456)	214 (91-535)	*0.970*
Laktat Dehidrogenaz	Medyan U/L	190 (101-791)	194 (101-791)	188 (105-387)	*0.600*
Albumin	Medyan – g/dl	3,5 (2,1-4,7)	3,5 (2,1-4,7)	3,4 (2,5-4,6)	*0.429*
β_2 Microglobulin	Medyan – mg/L	3,5 (1,1 – 20)	2,8 (1,1-55)	3,6 (2,2-30)	*0.419*
ISS Evresi	Evre I Evre II Evre III	17 (%21,8) 31 (%39,7) 30 (%38,5)	8 (%19,5) 18 (%43,9) 15 (%36,6)	9 (%24,3) 13 (%35,1) 15 (%40,6)	-
R-ISS evresi	Evre I Evre II Evre III	15 (%19,2) 48 (%61,6) 15 (%19,2)	8 (%19,5) 25 (%61) 8 (%19,5)	7 (%18,9) 23 (%62,2) 7 (%18,9)	-
Sitogenetik	Normal 1q t(4;14) t(14;16) t(11;14) del(17p) del(13q) Eksik	49 (%62,8) 5 (%6,4) 3 (%3,8) 1 (%1,2) 4 (%5,1) 4 (%5,1) 6 (%7,7) 6 (%7,7)	25 (%61) 3 (%7,3) 2 (%4,9) - 2 (%4,9) 3 (%7,3) 3 (%7,3) 3 (%7,3)	24 (%64,8) 2 (%5,4) 1 (%2,7) 1 (%2,7) 2 (%5,4) 1 (%2,7) 3 (%8,1) 3 (%8,1)	-
Yüksek Riskli Sitogenetik*	Evet	13 (%16,6)	8 (%19,5)	5 (%13,5)	*0.756*
Kemik İliği Plazma Hücre Oranı	Medyan (%)	%50(10-90)	%35 (10-90)	%50(10-90)	***0.007***
Kemik İliği Plazma Hücre Oranı	%10-50 >%50	54 (%69,2) 24 (%30,8)	33 (%80,5) 8 (%19,5)	21 (%56,8) 16 (%43,2)	***0.037***
Kemik İliği Fibrozis (Grade II-III)	Yok Var	61 (%78,2) 17 (%21,8)	41 (%100) -	20 (%54,1) 17 (%45,9)	-

ISS: International Staging System, R-ISS :Revised International Staging System

*1q kazanımı/amplifikasyonu, t(4;14), t(14;16) ve del(17)p

Nötrofil engrafmanı hastaların 77'sinde (%97) gözlenmiş olup, 1 hastada nötrofil engrafmanı öncesinde transplant ilişkili mortalite gelişmiştir. Tüm hastalar ele alındığında, nötrofil engrafmanı medyan 13.günde (10-46 gün) saptanmıştır. Kemik iliğinde fibrozis saptanmayan grupta nötrofil engrafmanı medyan 12.günde (10-46 gün) tespit edilirken, kemik

iliğinde fibrozis saptanan grupta medyan 14.günde (11-26 gün) gözlenmiştir. Kemik iliği fibrozisi olanlarda nötrofil engrafmanının anlamlı şekilde uzadığı tespit edilmiştir (*p= 0.005*).

Tablo II Hastaların Otolog Kök Hücre Nakli Öncesindeki Tedavileri ve Yanıt Durumu

		Tüm Hastalar (n=78)	Kemik İliğinde Fibrozis Yok (n=41)	Kemik İliğinde Fibrozis Var (Grade I-III) (n=37)	*p değeri*
Birinci Basamak Tedavi Rejimi	VCd VRd	63 (%80,7) 15 (%19,3)	33 (%80,4) 8 (%19,6)	30 (%81) 7 (%19)	*0.947*
Nakil öncesi kaç sıra tedavi aldığı	1 2 3	45 (%56,7) 22 (%28,2) 11 (%14,1)	23 (%56,1) 14 (%34,1) 4 (%9,8)	22 (%59,5) 8 (%21,6) 7 (%18,9)	-
Nakil öncesi kaç sıra tedavi aldığı	Medyan	1 (1-3)	1 (1-3)	1 (1-3)	*0.678*
İkinci Basamak Tedavi Rejimi	VRd	11 (%14,1)	7 (%17)	4 (%10,8)	-
	KRd	8 (%10,3)	5 (%12,2)	3 (%8,1)	
	Daratumumab-Bazlı	3 (%3,8)	2 (%4,9)	1 (%2,7)	
Nakil Öncesi Lenalidomid Tedavisi	Hayır Evet	40 (%51,2) 38 (%48,8)	20 (%48,7) 21 (%51,3)	21 (%54,1) 17 (%45,9)	*0.481*
Nakil öncesi Lenalidomid kür sayısı	≤4 Kür >4 Kür	31 (%39,7) 7 (%8,9)	17 (%41,5) 4 (%9,8)	14 (%37,8) 3 (%8,1)	*0.858*
Nakil Öncesi Radyoterapi	Evet	4 (%5,1)	3 (%7,3)	1 (%2,7)	*0.356*
Nakil Öncesi Hastalık Durumu**	CR VGPR PR	41 (%52,6) 21 (%26,9) 16 (%20,5)	23 (%56,1) 13 (%31,7) 5 (%11,2)	18 (%48,6) 10 (%27) 9 (%23,4)	-
Nakil Öncesi Hastalık Durumu	≥VGPR <VGPR	62 (%79,5) 16 (%20,5)	36 (%87,8) 5 (%12,2)	28 (%75,6) 9 (%24,4)	*0.163*

*VCd: Bortezomib, Siklofosfamid Deksametazon, VRd: Bortezomib, Lenalidomid Deksametazon, KRd: Karfilzomib, Lenalidomid, Deksametazon

** CR: Complete Response= Tam Yanıt, VGPR:Very good partial response (Çok iyi Kısmi Yanıt), PR: partial response (Kısmi Yanıt), SD:stabil disease (Stabil Hastalık)

Trombosit engrafmanı hastaların 74'ünde (%94,8) gerçekleşmiştir. 4 hastada ise trombosit engrafmanı gözlenmemiştir. 2 hastada trombosit engrafmanı öncesinde transplant ilişkili mortalite gelişmiştir. 2 hastaya ise uzamış izole trombositopeni nedeni ile Eltrombopag tedavisi verilmiştir. Tüm hastalar ele alındığında trombosit engrafmanı medyan 14. günde (9-44 gün) saptanmıştır. Kemik iliğinde fibrozis tespit edilmeyen grupta trombosit engrafmanı medyan 13.günde (10-25 gün) tespit edilirken, kemik iliğinde fibrozis saptanan grupta medyan 16.günde (9-44 gün) gözlenmiş olup, kemik iliği fibrozisi olanlarda trombosit engrafmanının anlamlı şekilde geç gerçekleştiği tespit edilmiştir (*p=0.004*).

Transplant sürecinde transfüze edilen kan ürünleri açısından değerlendirildiğinde, fibrozis olan ve olmayan hastalar arasında transfüze edilen eritrosit ve trombosit süspansiyonları açısından anlamlı fark saptanmamıştır. Transplant sürecinde hastanede kalış süresi tüm hastalar için medyan 21 gündür (12-105 gün). Hastanede kalış süresi; kemik iliğinde fibrozis gözlenmeyen hastalarda medyan 19 gün (13-105), kemik iliğinde fibrozisi olan hastalarda ise medyan 22 gün (12-81 gün) saptanmıştır. Kemik iliğinde fibrozisi olan hastaların anlamlı bir şekilde hastanede kalış süreleri daha uzun olduğu tespit edilmiştir (*p=0.047*). Hastaların transplant sonuçları ve fibrozisi olan olmayan hastalara göre verilerin analizi Tablo III'de özetlenmiştir.

Tablo III Otolog Kök Hücre Nakli Prosedürleri ve Nakil Sonuçları

		Tüm Hastalar (n=78)	Kemik İliğinde Fibrozis Yok (n=41)	Kemik İliğinde Fibrozis Var (Grade I-III) (n=37)	*p değeri*
Melfalan Dozu	140 mg/m^2 200 mg/m^2	16 (%20,5) 62 (%79,5)	9 (%22) 32 (%78)	7 (%18,9) 30 (%80,1)	*0.786*
İnfüze edilen CD34 (+) Kök Hücre Miktarı	Medyan – 10^6/kg	4,01 (2-7,9)	3,86 (2-7,9)	4,19 (2,2-6,3)	*0.339*
Nötrofil Engrafmanı Sağlanan hastalar		**77** (%98,7)	41 (%100)	36 (%97,3)	*0.972*
Nötrofil Engrafmanı	Medyan – Gün	13 (10-46)	12 (10-46)	13 (11-26)	***0.005***
Trombosit Engrafmanı Sağlanan hastalar		74 (%94,8)	39 (%95,1)	35 (%94,5)	*0.916*
Trombosit Engrafmanı	Medyan – Gün	14 (9-44)	13 (10-25)	16 (9-44)	***0.004***
Eritrosit Süspansiyonu	Medyan-Unite	1 (0-16)	1 (0-10)	1 (0-16)	*0.780*
Trombosit Süspansiyonu	Medyan-Unite	3 (1-28)	3 (1-13)	3 (1-28)	*0.325*
Hastanede kalış süresi	Medyan-Gün	21 (12-105)	19 (13-105)	22 (12-81)	***0.047***
Transplant İlişkili Mortalite		2 (%2,5)	1 (%2,4)	1 (%2,7)	*0.941*

Hastaların medyan nötrofil engrafman günü, medyan trombosit engrafman günü ve hastanede kalış süresi üzerine yapılan analizde, nötrofil ve trombosit engrafman günü ile hastaların yaşı, cinsiyeti, sitogenetik riski, ISS evresi, R-ISS evresi, tanı anındaki plazma hücre oranı, indüksiyon tedavi rejimi, nakil öncesi radyoterapi alıp almaması, nakil öncesi hastalık durumu ve melfalan dozu arasında anlamlı fark tespit edilmedi. Transplant öncesinde

>4 kür lenalidomid tedavisi alan hastaların, medyan hastanede kalış süresinin, ≤4 lenalidomid alan hastalara göre anlamlı şekilde daha uzun olduğu tespit edildi (*p=0.025*). Transplant öncesindeki lenalidomid kür sayısı ile medyan nötrofil ve trombosit engrafman günü açısından fark saptanmadı.

Tartışma

OKHN sonrası engrafman süresinin uzaması, getirdiği morbidite ve mortalite riskinin yanında ağır ekonomik yükler de oluşturmaktadır ayrıca halen birçok bilinmezliği barındırmaktadır. Çalışmamız sonucunda kemik iliğinde fibrozisi olan hastalarda olmayanlara göre, nötrofil ve trombosit engrafman zamanları ve hastanede kalış süreleri anlamlı olarak daha uzun bulunmuştur.

Koshiishi ve arkadaşlarının, OKHN yapılan 15 MM hastasını dahil ettikleri çalışmasında, hastaların 7'sinde kemik iliğinde fibrozis tespit edilmiştir. Hastaların nötrofil engrafman zamanı açısından, kemik iliğinde fibrozisi olan ve olmayan hastalar arasında anlamlı fark tespit edilmemiştir. Bu çalışmada hastaların trombosit engrafmanı ya da hastanede kalış süresi ile ilgili verilere yer verilmemiştir. Nötrofil engrafmanı açısından, analizdeki hasta sayısı oldukça az olması nedeni ile anlamlı fark oluşmayabileceği düşünülmüştür (26).

Soll ve ark. engrafman ve fibrozis ilişkisini araştırdıkları hematolojik maligniteli hastalarda (Akut/kronik lösemi, myelodisplastik sendrom (MDS) ve Lenfoma) yaptıkları çalışmada ise allojeneik hematopoetik kök hücre nakli ve OKHN yapılan toplam 203 hasta dahil edilmiştir. Tüm derecelerde fibrozisi (grade I-III) olan hastalarda trombosit engrafmanında 3 gün gecikme saptanmıştır. Grade II ve üzerinde fibrozisi olan grupta ise trombosit engrafmanında 7 gün (median 23 vs 30 gün), eritrosit engrafmanında 2 günlük gecikme tespit edilmiştir. Fibrozisi olan ve olmayan gruplar arasında nötrofil engrafman gününde fark görülmemiştir (27). Bu çalışmaya alınan hastaların tanıları, kullanılan hazırlama rejimleri ve yapılan nakil tipleri çalışmamızdan farklı olmakla birlikte, aynı çalışmamızda olduğu gibi fibrozisi olan hastaların trombosit engrafmanında uzama tespit edilmiştir.

Büyükkurt ve arkadaşlarının, kemik iliği fibrozisi ile engrafman arasındaki ilişkiyi araştırdıkları, 34 OKHN yapılmış hastanın dahil edildiği çalışmada; hastaların yarısında (17/34) kemik iliğinde fibrozis tespit edilmiştir. Çalışmaya alınan hastaların %73'ü de MM tanılıdır. Trombosit ve eritrosit engrafman günleri, grade II ve üzerinde fibrozisi olan grupta anlamlı olarak daha uzun tespit edilmiştir (18 güne karşı 12 gün). Nötrofil engrafmanı ile fibrozis arasında ise anlamlı fark tespit edilmemiştir. Ancak fibrozis derecesi arttıkça engrafman süresinin daha belirgin uzadığı ortaya konmuştur (28).

Scott ve arkadaşlarının akut myeloid lösemi (AML) ve MDS tanısı ile myeloablatif allojeneik hematopoetik kök hücre nakli yapılan; 113'ü kemik iliği fibrozisi olan toplam 471 hastayı araştırdıkları çalışmalarında ise fibrozisi olan grubun nötrofil engrafman süresinde istatistiksel açıdan anlamlı olarak 11 gün gecikme saptanmıştır (29).

Suyanı ve arkadaşlarının kemik iliği fibrozisinin OKHN sonuçlarına olan etkisini değerlendirdikleri çalışmalarına; OKHN yapılan 69 hasta dahil edilmiştir. Hastaların 19'unda kemik iliğinde grade I-III fibrozis tespit edilirken, 50 hastada fibrozis saptanmamıştır. Çalışmada MM tanısı olan 32 hasta mevcut olup bu hastaların yarısında (16/32) kemik iliğinde fibrozis tespit edilmiştir. OKHN yapılan ve kemik iliği fibrozisi olan hastalarda medyan nötrofil engrafman süresi 2 gün uzun tespit edilmiş olmasına rağmen nötrofil ve trombosit engrafman günleri açısından istatistiksel anlamlı fark bulunmamıştır. Hastalara transfüze edilen eritrosit ve trombosit süspansiyonu sayıları da benzer bulunmuştur. Ayrıca kemik iliği fibrozisinin sağ kalımı etkilemediğini raporlamışlardır (30). Bu çalışmada, bizim çalışmamızdan farklı olarak, OKHN yapılan hastaların yarısından daha azı MM tanılıdır. Kemik iliğinde fibrozis, MM tanılı hastaların %50'sinde mevcutken (16/32), MM dışı hastalarda fibrozis görülme oranı oldukça düşüktür (3/37, %8,1). Çalışmanın sadece MM tanılı olan hastalara yönelik bir alt grup analizi de bulunmamaktadır. Dahil edilen hasta grubunun heterojenitesi nedeni ile çalışmamızdan farklı olarak, bu çalışmada fibrozis ve engrafman arasında anlamlı bir ilişki tespit edilmemiştir.

Çalışmamızın bazı kısıtlılıkları bulunmaktadır. Çalışmamız retrospektif bir analizdir, dahil edilen hastaların tamamı, komorbiditeler, erişim problemleri nedeni ile aynı indüksiyon rejimini alamamıştır. Ayrıca kemik iliği fibrozisinin toplam sağkalım

ve progresyonsuz sağkalım üzerine etkileride irdelenememiştir. Çalışmamızın güçlü yönleri olarak, literatürdeki MM hastalarında kemik iliği fibrozisinin OKHN sonuçları üzerine etkisini değerlendiren diğer çalışmalara nazaran daha fazla hasta sayısına sahiptir. Ayrıca güncel ve yeni indüksiyon rejimleri ile tedavi edilen hastaları içermektedir.

Sonuç olarak bizim çalışmamızda, tanı anında kemik iliğinde fibrozis tespit edilen MM hastalarında, OKHN sonrası nötrofil ve trombosit engrafmanının anlamlı bir şekilde daha geç olduğu ve nakil sonrası hastanede kalış süresinin daha uzun olduğu saptanmıştır. Tanı anında kemik iliği fibrozis tespit edilen hastalarda, engrafman süresinin uzun olabileceği göz önünde bulundurulduğunda, OKHN sürecinde hastalara daha yoğun destekleyici tedaviler verilmesi gerekebilir. Ayrıca bu hasta grubunda, hazırlama rejiminin intensitesi, optimal CD34(+) kök hücre miktarının belirlenmesi ve büyüme faktörlerinin ve destek tedavilerin daha etkin kullanımı ile ilgili daha geniş prospektif çalışmalara ihtiyaç duyulmaktadır.

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The Impact of Hemovigilance Studies on Transfusion Practices: Single Centre Experience

Hemovijilans Çalışmalarının Transfüzyon Uygulamalarına Etkisi: Tek Merkez Deneyimi

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The Impact of Hemovigilance Studies on Transfusion Practices: Single Centre Experience

ABSTRACT

Objective: Blood product transfusion is one of the most commonly used medical interventions worldwide. However, transfusion-related adverse events (TRAEs) can cause morbidity and rarely even mortality. For this reason, hemovigilance studies have recently gained importance in terms of safe and effective implementation of transfusion.

Material and Method: Transfusion practices issued in the period of 2016-2023 were analyzed retrospectively. All TRAE including adverse reactions (AR) and adverse events (AE) were recorded. The impact of hemovigilance practices on the incidence of TRAE was analyzed by comparing the numbers and types of events between years.

Results: In the 8-year period between 2016 and 2023, a total of 135,506 blood products belonging to 45,571 patients were used. 172 adverse reactions (AR) were reported in 170 patients. The overall AR incidence was found to be 126.8 (/100000). The highest yearly AR rate was reported in 2018 with 168.04 (/100000). Since hemovigilance measures were tightened, a statistically significant decrease was recorded in ARs from the beginning of 2020 to date ($p<0.001$).

Conclusion: The result of the current study demonstrated that a reduction in ARs could be achieved with hemovigilance measures. Although some common TRAEs like allergy seem unlikely to prevent due to the underlying pathophysiological mechanisms, we hope that our study showing that some reactions can be reduced by hemovigilance will encourage clinicians and hemovigilance units. Even though hemovigilance studies are being conducted to improve transfusion safety, the most critical concern is reducing exposure to blood components.

Keywords: Hemovigilance, reaction, transfusion.

ÖZET

Amaç: Kan ürünü transfüzyonu dünya çapında en yaygın kullanılan tıbbi müdahalelerden biridir. Ancak transfüzyonla ilişkili advers olaylar (TRAE'ler), hastalarda morbiditeye ve hatta nadiren mortaliteye neden olabilir. Bu nedenle son yıllarda transfüzyonun güvenli ve etkin uygulanması açısından hemovijilans çalışmaları önem kazanmıştır.

Gereç ve Yöntem: 2016-2023 döneminde yayımlanan transfüzyon uygulamaları geriye dönük olarak incelendi. Olumsuz reaksiyonlar (AR) ve olumsuz olaylar (AE) dahil olmak üzere tüm TRAE kaydedildi. Hemovijilans uygulamalarının TRAE insidansına etkisi, yıllar arasında olay sayısı ve türü karşılaştırılarak analiz edildi.

Bulgular: 2016-2023 yılları arasında toplam 8 yıl boyunca toplam 45571 hasta için 135506 kan ürünü kullanıldı. 170 hastada 172 advers reaksiyon (AR) bildirildi. Genel AR insidansı 126,8 (/100000) olarak bulundu. Yıllık en yüksek AR oranı 168,04 (/100000) ile 2018 yılında bildirildi. Hemovijilans tedbirleri sıkılaştırıldığı için AR'lerde 2020 yılı başından bugüne istatistiksel olarak anlamlı bir düşüş kaydedildi *($p<0.001$)*.

Sonuç: Bu çalışmanın sonucu, hemovijilans önlemleriyle AR'lerde azalmanın sağlanabileceğini gösterdi. Alerji gibi yaygın görülen bazı TRAE'lerin altta yatan patofizyolojik mekanizmalar nedeniyle önlenmesi pek mümkün görünmese de bazı reaksiyonların hemovijilans ile azaltılabileceğini gösteren çalışmamızın klinisyenleri ve hemovijilans birimlerini teşvik edeceğini umuyoruz. Hemovijilans çalışmalarıyla daha güvenli transfüzyon yapılmaya çalışılsa da en önemli konu kan bileşenlerine maruziyetin en aza indirilmesidir.

Anahtar Sözcükler: Hemovijilans, reaksiyon, transfüzyon.

Introduction

Blood product transfusion is one of the most commonly used medical interventions worldwide. However, transfusion-related adverse events (TRAE) can cause morbidity and rarely even mortality. For this reason, hemovigilance studies have recently gained importance in terms of safe and effective implementation of transfusion (1). Hemovigilance strategies and processes begin with donor selection and continue through several phases such as blood component processing, providing the product to the patient, monitoring during and after transfusion at the bedside, and attempting to obtain information regarding adverse events. Based on those data, it must be used for preventing recurrence (1,2).

Due to its importance, the International Haemovigilance Network Database was established, with the participation of 25 countries, to ensure universal information transfer, and the results were published. They determined the rate of adverse reactions to transfusion of blood products was 660 per 100,000 individuals; nearly 3% of these were categorized as severe (1).

Blood transfusion has become a generally safe therapy as blood banking and transfusion medicine techniques have improved over the previous several decades. However, adverse events associated with blood transfusions might occur, thus their avoidance is a top priority in transfusion medicine. It is not clear whether hemovigilance studies prevent undesirable events. Some studies have shown it to be useful in preventing some transfusion reactions (3). However, it is often thought to be effective in reducing errors made during the transfusion process. In our study, we investigated whether hemovigilance studies in our center had an effect on adverse TRAE.

Material and Method

Transfusion practices in our tertiary referral hospital from 2016 to 2023 were analyzed retrospectively. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Hitit University Ethics Committee (Date: 03/04/2024 number: 2024-08). The number of blood products used, blood type, and how many patients were transfused were analyzed and recorded according to the years. Transfusion committee records, decisions regarding hemovigilance and subsequent practices were recorded. TRAE was classified and defined as adverse reactions (AR) and adverse events (AE) according to International Society for Blood Transfusion: Proposed standard definitions for surveillance of non-infectious adverse transfusion reactions (4). An AE is an undesirable and unintended occurrence before, during, or after the transfusion of blood or a blood component, which may be related to the administration of the blood or component. It does not necessarily result in a reaction in the recipient (4). An AR is an undesirable response or effect in a patient temporally associated with the administration of blood or a blood component (4). All hemovigilance notification sheets that were properly filled in with reports of ARs confirmed by a hematologist from the transfusion center were included. In our hospital, notification forms filled out by clinicians regarding transfusion reactions and adverse events that occur during or after transfusion are forwarded to the blood center hemovigilance unit. Regulatory and preventive activities are planned after the necessary information about these events and event-specific management practices are made. These forms are then archived. After an assessment is made by the transfusion medicine service, the final diagnosis is entered into the database and communicated to the primary clinical team. TRAEs are classified by physician on the transfusion medicine service. These records were analyzed, and the type and number of transfusion reactions and adverse events were recorded by year. The incidence and severity of transfusion reactions and adverse events were compared between years to determine whether hemovigilance procedures had an impact on them.

Statistical Analysis

Data obtained in the study were analyzed statistically using SPSS vn. 27 software (IBM SPSS Statistics 27). Frequency tables and descriptive statistics were used to interpret the findings. Demographic data were summarized with descriptive statistics. Numerical variables were presented as median (minimum-maximum) values, and categorical variables as

number (n) and percentage (%). Pearson-χ2 cross-tabulations were used to examine the relationships between two qualitative variables. A value of *<0.05* was accepted as statistically significant.

Results

In our center, which serves as a transfusion center in a tertiary care hospital, 135506 blood products were used for a total of 45571 patients for a total of 8 years between 2016 and 2023. The distribution of the products used by years is given in Table I.

Table I The distribution of the products used by years

Blood product type	Number (n)	Patients (n)
Erhtyrocyte suspension	86311	30076
Fresh Frozen Plasma	38924	11830
Pooled platelet	8174	2857
Apheresis platelet	620	408
Cryoprecipitate	1072	86
Whole blood	405	314
Total	135506	45571

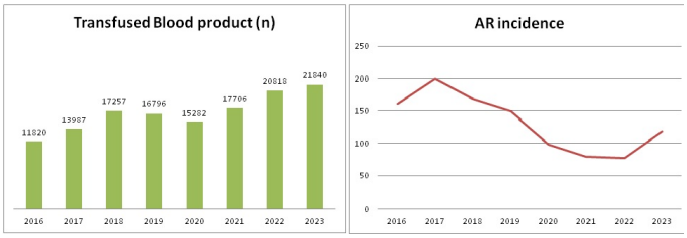

Figure I Distribution of transfused blood product (total number/year) and Adverse Reaction (AR) incidence (n/100000) among years

Hemovigilance studies performed during the 8-year follow-up period are given in Table II. During the follow-up period, 172 adverse reactions (AR) were reported in 170 patients. The total AR incidence was found to be 126.88/100000. The highest yearly AR rate was reported in 2018 with 168.04 (/100000). AR rates by years are given in Table III. It was observed that the most developed AR was allergic reactions (n=102, 59.3%). The number of AR types by year is given in Table IV. As of 2020, it was decided to record not only ARs but also transfer, service and clinician-related undesirable events that cause product destruction and make the necessary notifications. A total of 60 AEs were recorded in 3 years. The distribution of AEs was given in Table V. Since 2020, the number of nurses has been increased, hemovigilance measures have been tightened, and serious training has started to be provided. When AR was compared by years, it was found that the total incidence of AR decreased significantly starting from 2020 (*p<0.001*). ARs without allergic reactions were significantly decreased by the year of 2020 (*p<0.001* for Febrile nonhemolytic transfusion reaction (FNHTR), *p=0.011* for other types). The comparison of total and subtypes of AR by year was given in Table VI and graphical view was shown in Figure I. Since AE was registered after 2020, no comparison was made in this respect.

Table II Details of hemovigilance studies by year

Years	Newly added Hemovigilance Practices
2016	A decision was taken at the transfusion committee meeting and in-service training was provided to doctors and service personnel regarding blood and product applications.
2017	At the transfusion committee meeting, the administration was informed that the transfusion center needed to assign an additional hemovigilance nurse in accordance with the relevant legislation, as the annual requests exceeded 12000.
2018	Committee members were informed about 3-month transfusion reactions. It was decided to emphasize the sensitivity of the issue regarding control nursing to the clinical unit managers.
2019	It has been decided by the hospital management to provide periodic on-site training to all units twice a year. These trainings continue to be given by hemovigilance nurses to this day.
2020	The second hemovigilance nurse started working. Documents such as transfusion forms have begun to be checked more thoroughly. Field checks have also started to be carried out regularly. During the field controls, it was emphasized that a new vascular access should be opened for transfusion, and if there is an old vascular access, it should be used after washing with saline. Hemovigilance Guide has been updated. Emphasis has been placed on sending physician-nurse signatures and stamps to hemovigilance on transfusion follow-up and monitoring forms. In our center, the process of collecting whole blood from donors has been stopped, except in cases of necessity. Products other than whole blood coming from the regional center have begun to be used. From now on, it was decided to record not only undesirable reactions but also transfer, service and clinician-related undesirable events that lead to product destruction and make the necessary notifications.
2021	Information was provided by stating that the most important errors in protecting patient safety are preventable errors caused by improper authentication and incorrect barcoding.
2022	Training was given on confirming the patient's blood group by taking two blood group samples at different time intervals. Emphasis was placed on increasing the level of awareness for safe blood transfusion.
2023	General information is provided to new healthcare personnel in our hospital by providing orientation training on blood and blood products. Training was given to clinical support teams about the importance of safe blood transportation.

Table III Number of transfused blood products and incidence of adverse reactions

Years	Adverse reaction (AR, n)	Transfused Blood product (n)	Transfused Patients (n)	AR incidence (n /100000)
2016	19	11820	4110	160.74
2017	28	13987	4756	200.18
2018	29	17257	5639	168.04
2019	25	16796	5903	148.84
2020	15	15282	5782	98.15
2021	14	17706	6789	78.82
2022	16	20818	6232	76.85
2023	26	21840	6360	119.04
Total	172	135506	45571	126.88

Discussion

Blood transfusion is one of the most frequently used methods in daily practice in hospitals. Approximately 17,000 blood products are used annually in our center, confirming that transfusion is one of the frequently used modalities. It was determined that a total of 172 ARs developed in 8 years and a total of 60 AEs developed in the last 3 years. When compared in general, it was seen at a similar rate to the AR incidence reported in the world (1).

Table IV Types of Adverse Reactions

Years	Allergy	FNHTR	Angioedema	TACO	Hypotension	TRALI	Anaphylaxis
2016	6	10	2	1	0	0	0
2017	17	10	1	0	0	0	0
2018	15	8	0	1	4	1	0
2019	14	8	0	0	2	1	0
2020	11	3	0	0	1	0	0
2021	10	4	0	2	1	0	0
2022	11	2	0	0	0	0	0
2023	18	6	0	1	0	0	1
Total	102	51	3	5	8	2	1

FNHTR: Febrile nonhemolytic transfusion reaction, TACO: transfusion associated circulatory overload
TRALI: transfusion related acute lung injury

While ARs arise from immune or nonimmune causes blood product or recipient, AE events are often undesired events caused by either human or mechanical defects in the processes involved. In our center, AE has started to be recorded in the last 3 years and approximately 20 events are recorded per year. Among these, a situation that may also cause hemolytic AR and result in mortality is transfusion of different groups of blood products to a patient. An undesirable event may suddenly cause a serious undesirable reaction. It has been observed that 1 blood group incompatible erythrocyte suspension (ES) transfusion was performed in the last 3 years, and it did not cause a serious reaction. It was thought that the reason for this was that the patient had a stem cell transplant before. Researchers have documented a reduction in ABO incompatible red cell transfusions over the last 20 years, although bothdocument these 'never events' continue to occur indicating that further action is necessary. The most common AE event is when the clinician gives up transfusion for any reason after the blood product is prepared for the patient, and therefore the product is destroyed as wastage. Other adverse events that have reduced over time from interventions and policy setting prompted by analysis of hemovigilance data include transfusion associated acute lung injury (TRALI), bacterial infections, transfusion-associated graft-versus-host disease (TAGvHD), and post-transfusion purpura (PTP) (5). Similar to recent reports, our study showed that without allergic reactions, especially FNHTR was significantly decreased by hemovigilance studies. Since allergic reactions generally occur due to immune causes, this was an expected result for us.

Table V Distribution and characteristics of Adverse Events

Years	Cross match incompatable transfusion	Destruction due to transfer problems	Second product destruction due to previous reaction	Destruction due to the clinician giving up the transfusion decision	Patient refused
2021	1	1	2	1	0
2022	0	0	6	31	0
2023	0	1	2	14	1
Total	1	2	10	46	1

There has been a significant decrease in AR over the years, especially as of 2020. This is an important

result as it shows how important a role haemovigilance studies play. Hemovigilance practices are very important as a way to prevent all these. However, it is not clear to what extent the effects of hemovigilant applications on AR and AE are present. In general, issues involving transfusion safety have evolved significantly in recent years to now fully encompass the effectiveness of transfusion. New methods to evaluate transfusion safety and effectiveness under the name of hemovigilance studies need to be developed and implemented (6). At this stage, the most important tasks are to detect inappropriate practices, evaluate and analyze undesirable events, and, if possible, prevent their recurrence or take measures to prevent it. Several factors that have been shown to be associated with AR have been reported in some studies. It is conceivable that ARs can be reduced by paying attention to these risk factors. For example, it has been shown that leukopenia may be a risk for mild AR, and high body temperature may be a risk for moderate AR (7). In another study, it was demonstrated that beneficial strategies to avoid TRAE include judicious use of blood components, identification of high-risk patients, adherence to recommended clinical processes and awareness of TRAE pathophysiology (3). Since AE events started to be recorded in our center as of 2020, the effect of hemovigilance studies on them could not be evaluated by year.

Table VI Comparison of Adverse Reactions before and after the year 2020

	Periods (between years)		*p*
	2016-2019 (n=101)	2020-2023 (n=71)	
Incidence of total adverse reactions (n/100000)	168.72	93.85	***<0.001***
Incidence of allergic reactions (n/100000)	86.86	66.09	*0.089*
Incidence of FNHTR (n/100000)	60.14	19.82	***<0.001***
Incidence of other reactions (n/100000)	21.71	7.93	***0.011***

FNHTR: Febrile nonhemolytic transfusion reaction

As can be seen in our study, one of the most common ARs is allergic reactions (59.3%). The total number of allergic reactions was decreased by the year of 2020, but it is not statistically significant. Based on this result, we can consider allergic reactions developed because of immunological reasons so that it is unlikely to reduce or prevent allergy with hemovigilance studies. One of the most common undesirable events we encounter is that if an allergic reaction occurs to any blood product, the clinician gives up on subsequent transfusion and therefore destroys the product. Although it is actually an inappropriate approach in general, there have been recent results showing that this may be correct. The prophylactic approach in patients at risk of allergic reactions is a controversial issue. Pre-transfusion administration of antipyretic or antihistaminemedication could be considered in patients with a medical history of alergic AR. Randomised controlled trials did not find any benefit of premedication on allergic reaction prevention (3). In a single-center study published in 2020, acute reactions were significantly associated with transfusion history and receiving three or more units of blood (8). Similar to these results, meta-analysis still demonstrated that there is no recommendation that blood products should not be used again in patients who have previously developed allergic reactions. In fact, there is not enough evidence to use prophylactic treatment such as antihistamines and steroids in subsequent transfusions in a patient who has previously developed an allergic reaction (9). With all these data, clinicians do not need to give up transfusion decisions when necessary due to fear of previous reactions. What needs to be done is monitoring closely the patients with a history of allergic transfusion reactions when receiving subsequent transfusions.

However, it is a mystery whether the data in our study and in most hemovigilance studies around the world fully reflect what is actually happening. These data may not fully reflect reality; It depends on clinicians paying attention to these events, detecting them, and then keeping a report and informing the blood center and hemovigilance. Hemovigilance systems with voluntary declaration may underestimate TRAE incidence. These data may be less reflective than they should be, due to reasons such as clinicians not being aware of an event even if it occurs or not attributing this event to transfusion. For this reason, in order to reach real data, hemovigilance training should be provided to

clinicians to carefully monitor adverse events and report them to the blood center.

Conclusion

The result of the current study showed that a reduction in ARs could be achieved with hemovigilance measures. Although some common TRAEs like allergy seem unlikely to prevent due to the underlying pathophysiological mechanisms, we hope that our study showing that some reactions can be reduced by hemovigilance will encourage clinicians and hemovigilance units. Based on all these data, all blood banks and transfusion centers need to handle hemovigilance studies more seriously and strictly. Even though safer transfusion is tried to be done with hemovigilance studies, the most important issue is minimizing exposure to blood components.

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Why/ When/ How should I breastfeed?

Neden/ Ne Zaman/ Nasıl Emzirme(me)liyim?

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Why/When/How should I breastfeed?

ABSTRACT
Breastfeeding is one of the most powerful practices to support infant survival and well-being, starting in the first hours after birth, continuing exclusively with breast milk for six months, and continuing for up to two years with the provision of safe and appropriate complementary foods. Breastfeeding also promotes healthy growth and early childhood development. There are some unfavourable situations for the initiation and continuation of breastfeeding. These include failure to breastfeed, mode of delivery, newborn status, nipple problems, as well as many factors related to the infant or mother such as harmful habits, sleep problems, lack of care by health personnel, infectious diseases and breast cancer diseases. The aim of this review is to expand women's perspectives on breastfeeding in the postpartum period and to emphasise the benefits of breastfeeding for both mother and baby. .
Keywords: Breast Milk, breastfeeding, nursing, postpartum period.

ÖZET
Doğumdan sonraki ilk saatlerde başlayan, altı ay boyunca sadece anne sütü ile devam edilen ve güvenli-uygun tamamlayıcı gıdaların sağlanmasıyla iki yıla kadar devam eden emzirme, bebeklerin hayatta kalmasını ve refahını desteklemek için en güçlü uygulamalardan birisidir. Emzirme, sağlıklı büyümeyi ve erken çocukluk dönemlerinin gelişimini de destekler. Emzirmenin başlaması ve devam ettirilmesi açısından bazı olumsuz durumlar bulunmaktadır. Bunlar emzirmede başarısız olmak, doğum şekli, yenidoğan durumu, meme başı problemleri gibi bebeğe veya anneye ait birçok faktör olabileceği gibi zararlı alışkanlıklar, uyku sorunları, sağlık personelinin bakım eksikliği, bulaşıcı hastalıklar ve meme kanseri hastalıklarıdır. Bu derleme ile doğum sonrası dönemde kadınların emzirmeye yönelik bakış açılarını genişletmek, emzirmenin hem anne hem de bebek açısından yararlarını vurgulamak amaçlanmıştır.
Anahtar Sözcükler: Anne sütü, doğum sonu dönem, emzirme, hemşirelik.

Giriş

Anne sütü ile besleme evrensel olarak kabul edilen bir beslenme yöntemidir. Emzirmenin ve dolayısıyla anne sütünün hem anne hem de bebek için birçok faydası vardır. Bu nedenle, tüm kadınların gebelikten itibaren emzirmeye teşvik edilmesi sağlanmalıdır. Emzirme ve anne sütünün önemine dikkat çekmesi açısından bu derleme oldukça önemlidir. Emzirmenin ne zaman, nasıl ve ne şekilde yapılması gerektiğini aynı zamanda anne ve yenidoğan açısından önemine vurgu yapmak, amacıyla hazırlanmıştır.

Anne sütü tarih boyunca tüm bebekler için bilinen en iyi besin olmuştur. İlk 6 ay bebeğin ihtiyacı olan besinin %100'ünü, 6-12. ayda %50'sini ve 1. yaştan itibaren de %30'unu karşıladığı bilinmektedir (1). Anne sütü, nöronal membranların ana yapılarını oluşturan ve insan beyninin gelişimini pozitif olarak uyararak sinir sisteminin işleyişinde kritik rol oynayan dokosaheksaenoik asit (DHA) ve araşidonik asit (AA) gibi uzun zincirli çoklu doymamış yağ asitlerini içerir (2). Anne ve bebek arasındaki ten tene temas, prolaktin ve oksitosin üretimi gibi annenin hormonal tepkilerini uyarır ve bu da bilişsel gelişimi dolaylı olarak geliştirebilir (3). Laktasyon yenidoğanın anneyle olan tam bağımlı halinin sonlanıp daha bağımsız bir yaşama geçtiği dönem olarak tanımlanır. Yenidoğana sindirimi kolay besinler ve çeşitli immünolojik faktörleri sağlayan; nörolojik, hormonal ve ruhsal uyaranlar sonucunda gelişen laktasyon, plasentanın fonksiyonlarına benzer bir rol üstlenen meme ile sağlanmaktadır (4).

Memeler anatomik olarak, pectoralis majör kasının üzerine ve 2. ve 7. kostalar arasında orta hatta 5-7 cm kalınlıkta ve 10-12 cm çapında çift taraflı yerleşim gösteren organdır (5). Meme korpusu 15-20 lobdan, her lob 20-40 lobülden ve her lobül de 10-100 alveolden oluşur (6). Lobüller süt üreten hücreler olan laktositleri içerisinde barındırır. Bu sebeple süt üretimi lobüllerde gerçekleşir. Üretilen bu süt ise alveollerden duktuslar aracılığı ile meme ucuna akmaktadır (7). Anne sütü salınımı gebelikle birlikte başlar, dolaşımda yüksek miktarda progesteron hormonu vasıtasıyla kontrol altında tutulur. Doğum sonrası dönemde progesteron hormonu azalırken, prolaktin ve oksitosin hormonunun salınması, meme ucu uyarısına bağlı olarak süt sekresyonu başlar (8). Gebeliğin üçüncü ayının sonunda kolostrum adı verilen ön süt oluşur. Protein, vitamin ve mineral ile yenidoğanda pasif immünizasyon sağlayacak olan immunoglobülinleri içerir. Kolostrum genellikle gebeliğin 16. haftasından itibaren meme ucundan dışarı doğru akmaya başlar. Kolostrum sonrasında geçiş sütü salgılanırken, 14. gün sonunda matür (olgun) süt olma özelliğini kazanır (9). Memenin anatomik yapısı Şekil I. 'de gösterilmiştir (10).

Anne sütü bebek beslenmesinde en önemli kaynaktır. Dünya sağlık Örgütü (DSÖ), Birleşmiş Milletler Çocuklara Yardım Fonu (UNICEF) ve Amerikan Pediatri Akademisi (APA) gibi birçok uluslararası kuruluş emzirmenin doğumdan sonra başlatılmasının önemli olduğuna dikkat çekerken, ilk 6 ay boyunca yalnızca anne sütü ile beslenmelerini, 6 ay sonrasında emzirme ile birlikte ek besinlere başlanmasını önermektedir (7). Ülkemizde Türkiye Nüfus Sağlık Araştırması (TNSA) verilerine göre bebeklerin %71'i doğumdan sonraki ilk bir saat içinde emzirilmeye başlanmıştır ve emzirme oranları 4-5 aylık bebeklerde yüzde %14'e kadar gerilemektedir. TNSA (2018) verilerine göre ortanca emzirme süresi 16,7 aydır (11). Emzirme oranlarındaki düşüşün nedenlerini incelediğimizde anneye ait nedenler; emzirmede başarısızlık, doğumun şekli, sezaryen oranlarının artması, sütün yetersiz olduğu inancı, yenidoğanın durumu ve meme başı çatlakları, çökük meme başı, mastit, meme apsesi, annenin hastalıkları yer almaktadır. Yenidoğana ait nedenler ise iatrojenik obstetrikal sedasyon ve analjezik kullanımı, yenidoğanın ağzında aft, doğuştan metabolizma bozuklukları (galaktozemi, fenilketonüri), emme ve yutma refleksinin olmaması, konjenital malformasyonlar (tavşan dudak, yarık damak), serebral defektler, prematürite, düşük doğum ağırlığı, çoğul gebelikler, yenidoğana erken dönemde formula sütlerin verilmesidir (12). Tablo I'de Yenidoğanın emzirilmesine ilişkin kanıt önerileri sunulmuştur (13).

Neden emzirmeliyim?

Bebek için en uygun ve doğal besin kaynağı anne sütüdür. İçeriği bakımından bebeğin büyüme- gelişme açısından su dâhil tüm besin ögelerini içermektedir (14). İkinci altı aylık dönemde ise bebeğin gereksiniminin yaklaşık yarısı veya daha fazlasını, yaşamın ikinci yılında ise yaklaşık üçte birini sağlamaktadır. İçerdiği hormonlar, enzimler ve canlı hücreler ile birlikte bebeğin bağışıklık sistemini destekleyerek hastalıklara karşı koruma sağlamaktadır. Bu sebeplerden dolayı

bir bebeğin hem bebeklik süresince hem de ilerleyen yaşamında anne sütü almış olması büyük faydalar sağlamaktadır (15).

Tablo I Yenidoğanın emzirilmesine ilişkin kanıt önerileri

Yenidoğanın Emzirilmesine İlişkin Kanıt Önerileri	Kanıt Düzeyi ve Öneri Derecesi
Düşük doğum ağırlıklı bebeklerde dahil olmak üzere tüm yenidoğan bebekler, klinik olarak stabil olduklarında ve anneleri ve bebekleri hazır olduklarında doğumdan hemen sonra emzirilmelidir.	Güçlü öneri, kaliteli kanıt
Bebeğin anne ile ten teması sağlanması durumunda ilk saatte emzirme hemen başlatılmalıdır.	Güçlü öneri, orta kalite kanıt
Komplikasyonu olmayan yenidoğanlar, doğumdan hemen sonra ilk saatte anneleriyle cilt teması sağlanmalı, emzirilmeye çalışılmalı ve hipotermi önlenmelidir.	Güçlü öneri, düşük kaliteli kanıt

a) Yenidoğan üzerine etkileri

- Mortalite ve morbidite riskini azaltır.
- Altı ay ya da daha uzun süren emzirme, sonrasında otit riskini azaltır.
- Sindirimi kolaydır, nekrotizan enterokolit, inflamatuvar barsak hastalığı, çölyak hastalığına karşı koruyucudur (16).
- Alt solunum yolu enfeksiyonlarına bağlı olarak hastaneye yatış oranlarını azaltmaktadır.
- Atopik dermatit riskini azaltmaktadır (17).
- Obezite insidansında azalma görülür (18).
- Yaşamın ilerleyen dönemlerinde tip 1 ve tip 2 diyabet oranlarında düşüş görülmektedir.
- Bebeği en az altı ay süreyle emzirme sonucunda çocukluk çağı lösemi (ALL ve AML) riskinde azalma olduğu saptanmıştır (19).
- Ani bebek ölüm sendromunun önlenmesinde önemli role sahiptir.
- Nörogelişimsel puan skorlarında anne sütü alanlarda pozitif yönde artış görülmektedir (20).
- Anne sütünde bulunan IgA ve IgG; bakteri, virüs gibi yabancı protein moleküllerine bağlanarak, sindirim sisteminden absorbe olmasına engel olur (20).
- Erişkinlik döneminde kan basıncı ve kan kolesterol düzeylerini pozitif yönde etkiler.
- Anne sütü ideal elektrolit ve mineral bileşimi sayesinde bebeğin gereksinimini karşılayacak miktarda sodyum, potasyum, kalsiyum ve fosfor içermektedir (21).
- Alerjiye ilişkin solunum sorunları ve yiyecek alerji ileri anne sütüyle beslenen yenidoğanlarda daha az sıklıkla görülmektedir.
- Anne sütünde bulunan proteinin serbest biluribini bağladığı, bu sayede anne sütü ile beslenen bebeklerde hiperbiluribinemi vakalarına daha az rastlandığı bildirilmektedir (5).

b) Anne üzerine etkileri

- Emzirme esnasında anne ve bebeğin temas etmesi, bebeğin kokusu ve ısısı annede anti-stres etki yaratarak rahatlamasını sağlamaktadır. Bu sebeple emzirme eylemi anne için doğal bir sakinleştirici özelliği de taşımaktadır (22).
- Erken dönemde emzirmeye başlayan kadınlarda doğum sonrası kanama riski azalır ve bununla birlikte halsizlik, anemi, çarpıntı, çabuk yorulma gibi semptomlarda da azalma görülmektedir (22,23).
- Emzirme döneminde, total kolestorol, LDL ve trigliserid düzeyleri azalırken, HDL seviyeleri yüksek kalmaktadır. Aynı zamanda emzirme kan lipit düzeyini düşürerek anneyi kardiyovasküler hastalıkları riskine karşı korur.
- Emzirme ovulasyonu engelleyerek, laktasyonel amenoreye sebep olmaktadır. Emziren kadınlarda meme uçları ve areoladaki sinir liflerinin uyarılması sonucunda ön hipofizden prolaktin, arka hipofizden ise oksitosin hormonu salgılanır. Hipotalamus-hipofizer fonksiyonlar inhibe olurken, lutein ve foliküler hormonun salgılanmasının azalması sonucu adet döneminin erken başlaması da önlenmiş olur (24,25).
- Emzirme aynı zamanda kadını uterus ve over kanserlerine karşı korurken idrar yolu enfeksiyonları insidansını düşürmekte; osteoporoz oranlarını da azaltmaktadır (26).
- Gestasyonel diyabeti olan ve olmayan kadınlarda pankreas beta hücre fonksiyonunu uyardığı için tip 2 diyabet riskini azaltmaktadır.
- Emzirme günlük olarak 500 kalori yakmakta ve bu da gebelik döneminde alınan kiloların verilmesini kolaylaştırmaktadır (27).
- Emziren kadın vücudunda üretilen feromonlar sayesinde emzirmeyen kadınlara oranla cinsel istek ve cinsel fantezilerinin daha yüksek olduğu bulunmuştur (28,29).
- Postpartum dönemde annenin izlemi anne-bebek sağlığının korunması, geliştirilmesi açısından elzemdir. Emzirme eyleminin annelik rolleri gelişiminde ve uyumunda artma, kadının özgüvenini arttırıcı özellikleri

de bulunmaktadır (30).

- Emzirme, annenin iyilik halini olumlu yönde etkilemekte ve doğum sonrası depresyon riskini azaltmaktadır (31).
- Sosyal ve ekonomik yönden de önemli olan emzirme bireysel ve kurumsal bazda kazanç sağlamaktadır. Hastane kalış süresinin kısalması, kullanılan ilaç miktarının azalması gibi faktörlere bağlı olarak ülke ekonomisine de katkıda bulunur. Ayrıca çevre kirliliği oranlarını da azaltmaktadır (32).

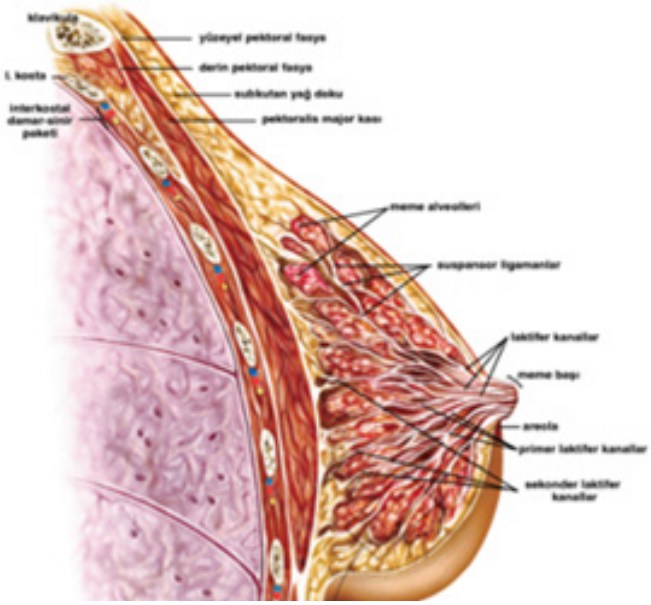
Neden emzirme kesintiye uğrar?

a) Yetersiz Süt Üretimi ve Algısı

Yetersiz süt üretimi algısı; anne sütünün miktarının veya besleyiciliğinin bebeğin açlığını ve beslenme ihtiyaçlarını karşılamada yetersiz olduğuna dair inancıdır (33). Yetersiz süt üretimi algısı anneler tarafından yaygın olarak benimsenmişken, gerçekte yetersiz süt üretimi annelerin %1-5'ini etkilemektedir (34). Bu algıyı etkileyen faktörler incelendiğinde en yaygın sebebin bebeğin sürekli ağlaması olduğu görülmüştür (33). Yetersiz süt üretimi algısı ile emzirme öz yeterliliği arasındaki ilişkiyi belirlemek amacıyla yapılan bir çalışmada, emzirmeyi ileri anne yaşının, yükseköğrenim düzeyinin ve yüksek gelir durumunun, çocuğun erkek cinsiyetinin, gebeliğin planlanmasının, çok doğum yapmanın, emzirme eğitiminin ve emzirmek için planlanan sürenin, olumlu yönde etkilediği bulunmuştur (35). Yetersiz süt üretimi algısı ile baş edebilmek için anne-bebek etkileşimi arttırılmalı, ilk haftada risk altındaki emziren annelere daha fazla odaklanılmalı ve memelerde yeterli stimülasyonu sürdürmek için emzirme desteği sunulmalıdır (33,36).

b) Meme Başı ile İlgili Sorunlar

Meme başı ağrısı ve meme çatlağı doğum sonrası erken dönemde görülen en yaygın emzirme sorunlarındandır. Bu sorunlar emzirmenin erken bırakılması ile yakından ilişkilidir (37). Fiziksel bulgular; memede kırmızı veya beyaz çizgiler, çatlak, yarık, meme ucunda kanama, kabarıklık, kabuklanma bir veya her iki meme ucunda görülebilmektedir. Meme başı ağrısı ve meme çatlağının nedenleri arasında; yenidoğanın memeye uygun şekilde yerleştirilememesi, düz veya içe dönük meme başı, dil bağı, enfeksiyonlar, damak anomalileri ve mastit bulunmaktadır (37). Meme başı ağrısı %34 ve %97 prevalansı ile emziren annelerde en sık görülen şikâyetlerden biri olup yetersiz süt üretimi algısından sonra emzirmeyi erken bırakmanın ikinci nedenidir (38). Yapılan bir çalışmada, doğum sonrası hastaneden taburcu edilmeden önce annelerin %79'u meme başı ağrısı yaşadıklarını, postpartum dönem meme başı ağrısı ve çatlağı görülme oranı sırasıyla birinci haftada %72 ve %58, ikinci haftada %59 ve %33, dördüncü haftada %43 ve %24, sekizinci haftada %20 ve %8 oranında bulunmuştur (39). Meme başı ağrısı ve çatlağının önlenmesinde önemli bir yaklaşım, bebeğin memeye uygun yerleştirmesi ve memeden uygun ayrılmasıdır. Bebek kendiliğinden emmeyi bırakmadan, memeden çekilmemelidir. Meme başı ağrısı ve çatlağı, temiz ve kuru tutulduğunda 7-10 günde kendiliğinden geçecektir (37-39).



Şekil I Meme anatomik yapısı

Meme başı ile ilgili sorunlar arasında; düz, içe çökük, küçük veya büyük meme başı yer almaktadır (32). Düz ve içe çökük meme başına sahip 90 kadın ile yapılan bir çalışmada; manuel yöntem, lastik bant ve enjektör yöntemi ile emzirme durumları karşılaştırılmıştır. Bu üç müdahalenin üstünlüklerinin eşit olduğu bulunmuştur (40). Meme ile ilgili sorunlar, eğer mümkün ise gebelik döneminde tedavi edilmeli ancak hemşirelik girişimleri gerekiyorsa doğumdan sonra başlanmalıdır. Meme ucunun emzirmeden önce yuvarlanması, düz meme ucunun erektil hale gelmesine, bu da bebeğin daha kolay kavramasına yardımcı olmaktadır. Emzirme öncesi birkaç dakika meme pompasının kullanımıda, çökük meme ucunun çıkmasını kolaylaştırabilir (24).

Engorjman, memede artan vaskülarite ve konjesyon

ile süt birikimi durumudur. Genellikle her iki memede de görülebilmektedir. Meme yüzeyindeki ciltte kızarma, sıcaklık artışı, areolanın gerginleşmesi ve sertleşmesi ile karakterizedir. Eğer engorjman gelişir ve müdahale edilmez ise bebek memeyi rahat kavrayamaz ve süt akımı olamayacağından yenidoğanın beslenmesi olumsuz etkilenecektir. Erken dönemde tespit edilmesi ve tedavi edilmesi emzirmenin devamı için önemlidir (41).

Mastitis, emzirmenin yaygın bir komplikasyonudur. Kadınlar için büyük acı ve ıstıraba neden olur ve bazı annelerin bebeklerini istedikleri kadar emzirmelerini engelleyebilir. Tıkalı kanallar, memelerin sütle çok dolu olması, meme uçlarının çatlaması ve bebeğin doğru şekilde memeyi tutamaması gibi birçok faktör mastit gelişimine katkıda bulunur. Mastitis bir veya her iki memede ortaya çıkabilir ve meme ağrısı, kızarıklık, şişlik ve grip gibi bir dizi semptomla ilişkilendirilebilir. Semptomlar iki- üç gün, birkaç hafta veya daha fazla sürebilir (42,43). Mastitin erken dönem yönetimi oldukça önemlidir. Memelerin aktif olarak boşaltılması, çoğu durumda mastit gelişimini önlediği bildirilmiştir. Meme boşaltma işe yaramaz ise antibiyotik ile tedavi edilmelidir. Mastit tedavisinde yeni bir yaklaşım olan probiyotik kullanımı ile ilgili çalışmalar devam etmektedir (43).

c) Annenin Hastalıkları

Anne hastalandığı zaman alınan ilaçlar veya annenin genel durumuna bağlı olarak emzirme geçici olarak ertelenebilir. Ancak aniden emzirmenin kesilmesi mastite yol açabilir (24).

d) İlaçlar ve emzirme

Emzirme döneminde kullanılan birçok ilaç, anne sütüne belli oranlarda geçmektedir. Emzirme döneminde alınan bazı ilaçların güvenli olduğu belirtilmektedir. Birçok ilacın bebek için çok az yan etkisinin olduğu, bebek tarafından alınan dozun genellikle maternal dozun %1'den daha az olduğu saptanmıştır (24). Bir annenin ilaç kullanırken emzirmesi çok az durumda kontrendikedir. Kanser ilaçları alıyorsa, radyoaktif maddelerle tedavi ediliyorsa, psikiyatrik ilaç veya antikonvülzanlar kullanıyorsa emzirmenin durdurulması gerekebilir (44,45).

Ne zaman emzirmeliyim?

Dünya Sağlık Örgütü (DSÖ) doğumun hemen ardından bebeğin yalnızca anne sütü alması gerektiğini ve altı ay sonrasında ise ek besinlerle birlikte emzirmenin iki yaşa kadar devam ettirilmesini önermektedir. Doğum sonrası ilk 30 dakika- 1 saat içerisinde tüm annelerin bebeklerini emzirmesi sağlanmalıdır. İlk bir saatte bebek sık sık emzirilmeli ve en az on dakika bu eylem devam ettirilmelidir (46).

Bebeğin emme sıklığı ve zamanı isteğine göre ayarlanmalıdır. Belirli bir saat ya da zaman kavramı bulunmamaktadır. Eğer bebek her ağladığında emzirme eylemi gerçekleştirilir ise bu geç bir bulgu olarak kabul görmektedir. Emme hareketlerinin olması, elini ağzına götürmesi, kol ve bacaklarını gergin tutması gibi davranışlar bebeğin emme eylemine hazır oluşluğunu gösteren bulgulardır (47).

Emzirme döneminde hala tartışılan bir diğer konu ise tandem emzirmedir. Tandem emzirme; kadının doğum sonrasında yenidoğan bebeğini ve henüz emzirme döneminde olan iki yaşın altındaki diğer bebeğini de emzirmeye devam etmesi olarak tanımlanmaktadır (48,49). Darol ve ark. yaptıkları çalışma sonuçlarına göre bir yıldan daha uzun süre emzirme ve iki çocuğu aynı anda besleme, anne sütünün kalitesini olumsuz yönde etkilemediği; aksine, emzirme süresinin artmasıyla birlikte sütün bileşiminin, çocukların değişen ihtiyaçları tarafından belirlendiği şekilde evrim geçirdiğini göstermektedir (50). Tandem emzirme döneminde kadınlarda yorgunluk, geceleri sık uyanma, toplumdan uzaklaşma gibi olumsuzluklar da yaşanmaktadır. Yapılan kısıtlı çalışmalar sonucunda iki farklı yaştaki bebeğin emzirilmesinin anne, yenidoğan ve büyük bebek açısından olumsuz sonuçları olmadığı tespit edilmiştir (47,50,51).

Ne zaman emzirmemeliyim?

Anneler bazı özel durumlarda örneğin ciddi bir hastalığının olması ya da bebeğe geçebilecek hastalığa sahip olmaları durumunda bebeğin emzirilmemesi gerekebilir.

HIV pozitif kadınların emzirmeye devam etmesi konusu hala tartışmalıdır. DSÖ, tedavi endikasyonu olan gebe kadınların, anneden bebeğe HIV geçişini azaltmak için antiretroviral tedaviye ulaşımının sağlanmasını ve emzirilmenin desteklenmesini; anne sütü almayan bebeklerin beslenmesi için uygun formül mama ile beslenmenin sağlanmasını önermektedir (15).

Hepatit A, B, C' ye sahip annelerin bebeklerini emzirmelerinde herhangi bir sakınca yoktur. Hepatit

B'li anneden doğan bebekler, emzirmeye başlamadan önce hepatit immunoglobülin uygulanması, hepatit B aşısının ilk dozunun yapılması önerilmektedir. İlk doz aşıdan bir ay sonra, ikinci doz altı ay sonra, üçüncü doz aşının yapılması önerilmekte ve bu süre zarfında bebeğin emzirilmesinde de herhangi bir sakınca bulunmamaktadır. Profilaksi uygulandıktan sonra annelerin emzirme için desteklenmesi önerilmektedir (52).

Latent tüberküloz tedavisi alan kadınlar için emzirme teşvik edilirken; aktif tüberküloz geçiren kadınların emzirmeleri ve bebeğe yakın temasları kesin olarak önerilmemektedir. Aktif tüberküloz tedavisine başladıktan en az iki hafta sonra emzirmeleri önerilmektedir (53).

Memede aktif herpes simpleks virüsü lezyonu olan annelerin emzirmesi önerilmez. Lezyon iyileşinceye kadar etkilenen memeden sağılan süt bebeğe verilmemelidir (54).

Maternal varisella zoster virüsü varlığında, annenin bulaştırıcılığı geçene kadar, anne ve bebeğin geçici izolasyonu (72 saat içinde yeni lezyonlar oluşmadıysa ve mevcut lezyonlar üzerinde iyileşme oluncaya kadar) gerekmektedir. Bu süre boyunca varisella zoster immunoglobülini alan bebekler anne sütü alabilirler (24).

Annede yüksek miktarda alkol tüketimi, uyuşturucu ve madde bağımlılığı varsa emzirme bu durumlarda da kontraendikedir (7).

Nasıl emzirmeliyim?

Anne sütü yapımı, bebeğin sık aralıklarla ve aynı zamanda doğru tekniklerle emzirilmesi sonucu artış gösterir. Ayrıca doğru teknikle emzirme yöntemi meme başı çatlakları gibi sık görülen meme sorunlarının önlenebilmesi için de önemlidir. Emzirme esnasında annenin ve bebeğin genel durumu ile memelerin durumuna dikkat edilmelidir. Bu sebeple anne- bebek pozisyonu, bebeğin memeye yerleşmesi ve emme etkinliği değerlendirilmelidir (21). Önemli bir diğer madde ise bebeğin memeye doğru yerleşmesidir. Doğru yerleştiğini anlamak için aranması gereken özellikler arasında; areolanın bebeğin alt çenesine yakın olan kısmı, üstte kalan kısma kıyasla bebeğin ağzına daha fazla oranda yerleşmiş olmalı, bebeğin alt çenesi annenin memesine temas etmeli, bebeğin yanakları dolgun olmalı, bebek ritmik bir şekilde emmeli ve emme esnasında yutkunma sesleri duyulmalıdır (55).

Şekil II Bebeği memeye yerleştirme

Emzirme zamanlarında bebek aç, altı kuru, ortamın ılık olması gerekmektedir. Kadın en rahat pozisyonu seçmeli aksi takdirde let- down refleksi engellenmekte bu da annenin yorulmasına sebebiyet vermektedir. Annenin rahat edebilmesi için kolçağı olan bir sandalye, ayakların uzatılabileceği bir tabure bulundurulmalıdır. Emzirilen taraftaki ayağın kaldırılması da yarar sağlamaktadır. Kullanılan pozisyon hangisi olursa olsun diğer el ile meme desteklenmeli, başparmak yukarı, diğer dört parmak aşağıda olacak şekilde (C tutuşu) tutulmalıdır (24). U tutuş tekniği ise; tek el ile meme alttan desteklenir, aynı elin başparmağı, areolanın dış kenarı üzerinde parmak ucu yukarı bakacak şekilde işaret parmağı diğer kenarı kavisli bir şekilde yerleştirilerek tutulur (25). Şekil II'de bebeğin memeye nasıl yerleştirmesi gerektiği gösterilmiştir (56).

Şekil III Beşik tutuş tekniği

Temel emzirme pozisyonları arasında beşik tutuşu, çapraz beşik tutuşu, futbol tutuşu, kaydırma pozisyonu ve yan yatarak emzirme sayılabilir.

Beşik tutuşu (kucaklama tekniği): Bebek meme hizasına ve memeye yakın tutulur, bebeğin alt kolu annenin memesinin alt kısmına yerleştirilebilir. Anne bebeği kolunun üzerine alır, başını ve gövdesini destekler. Genellikle C tutuş tekniği ile kullanılır. Şekil III'de beşik tutuş tekniği gösterilmiştir (56).

Şekil IV Çapraz beşik tutuş tekniği

Çapraz beşik tutuşu (ters kucaklama tekniği): Bebeğin başının olduğu kolun tersine diğer kol ile bebeğin gövdesi desteklenir. Bebeğin başını tutan el sabit dururken diğer el sadece meme başının bebeğe yönlendirilmesi için kullanılır (25). Şekil IV'de çapraz beşik tutuş tekniği gösterilmiştir (56).

Şekil V Futbol tutuş tekniği

Futbol tutuşu: Genellikle ikiz, preterm, sezaryen ile doğum yapan anneler tarafından tercih edilmektedir. Ayrıca büyük memeye sahip kadınlarda emzirmeyi kolaylaştırdığı için tercih edilir. Anne emzirdiği taraftaki eliyle bebeğin baş ve boynunu alttan tutar ve ön kolu ile bebeğin sırtını destekler, bebek başı futbol topu gibi tutulur. Bebeğin ayakları ise annenin sırt tarafına doğru uzanır, bebeğin altı yastık ile desteklenerek hafifçe yükseltilmesi ve annenin bebeği kaydırma ihtiyacı da böylelikle azaltılmış olur. Şekil V'de futbol tutuş tekniği gösterilmiştir (56).

Kaydırma pozisyonu: Bebekler emerken bir tarafa yatarak emmek isteyebilirler. Diğer memeyi emzirmek için bebek diğer tarafa çevrildiğinde huzursuz olup emmek istemeyebilir. Bu gibi durumlarda bebeğin istemediği tarafa doğru çevirmeden ve vücut pozisyonunu değiştirmeden kaydırma yapılarak bebeğin diğer memeyi emmesi sağlanır (24).

Şekil VI Yan yatarak emzirme tekniği

Yan yatarak emzirme: Özellikle sezaryen doğum yapan kadınlarda tercih edilen bir pozisyondur. Ayrıca dinlendirici özelliği olması sebebiyle tüm kadınlarda kullanılabilmektedir. Burada dikkat edilmesi gereken husus ise bebeğin annenin kolunun üzerine yatmaması, kolun serbest kalması gerekliliğidir. Bebeğin burnu meme ucu ile aynı hizada olmalı, anne ve bebeğin sırtı battaniye ya da yastıkla desteklenmelidir (57). Şekil VI'da yan yatarak emzirme tekniği gösterilmiştir (56).

Emzirme sürecinde anne için öneriler

a) Anne emzirme öncesi:

- Annenin düzenli olarak beslenmesi, günlük enerji ihtiyacına en az 750 kalorinin ilave edilmesi gerekmektedir.
- Emzirme öncesi rahat bir pozisyonda olması gerekir.
- Eller su ve sabun ile yıkanmalıdır.
- Meme başı ve meme su ile yıkanmalıdır.
- Meme ucu süt salınımını kolaylaştırmak için uyarılabilir.
- Bol ve geniş elbiseler tercih edilebilir, sıkmayan sütyen kullanılmalıdır (58).

b) Anne emzirme sırasında:

- İlk gün bebek her istediğinde her meme beşer dakika, sonraki günlerde her bir meme on beş dakika boyunca emzirilmelidir.
- Bebek meme başına yaklaştırılarak yanak veya ağız köşesinin uyarılması ile refleks olarak ağzını açması sağlanmalı ve meme başı kısmının tamamını ağzına

almalıdır.
- Bebek bir memeyi tam olarak boşalttıktan sonra diğer meme ile emzirmeye devam edilmelidir. Bir sonraki emzirme de ise son bırakılan memeden başlanmalıdır.
- Emzirme esnasında bebeğin burnunun açık olduğuna dikkat edilmelidir (59).

c) Emzirme sonrasında:
- Her emzirme sonrasında meme başları su ile yıkanıp kurulanmalıdır.
- Gerekirse açıkta bırakılarak havayla temas ile kuruması beklenebilir.
- Bebeğin gazı çıkarılmalı ve bunun için anneye eğitim verilmelidir (59).

Sonuç

Anne sütü bebeğin büyüme ve gelişmesi için gerekli olan tüm besinleri içeren, bebeğin gelecekteki sağlıklı yaşamını destekleyen eşsiz bir besindir. Postpartum dönemde annelerin bebeklerini emzirmeleri anne bebek iletişiminin sağlanması ve bebeğin gelişimi için kilit rol oynamaktadır. Emzirmenin değerlendirilmesi ve danışmanlık hizmetleri anne sütü ile beslenmenin doğru ve uzun süre devam etmesi açısından önemlidir. Sonuç olarak doğum sonrası dönemde emzirme hem anne hem de bebek açısından hayati bir öneme sahiptir. Bu dönemde kadınlara emzirme teknikleri, beslenme hakkında eğitimler verilmeli, destek olunmalı, cesaretlendirilmeli, emzirmeye teşvik edilmeli ve multidisipliner yaklaşım benimsenmelidir.

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The Predictors of Outcome in Patients that Require Management in Intensive Care Units: A Narrative Review

Yoğun bakım ünitelerinde tedavi gerektiren hastalarda prognostik belirteçler: Derleme

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The Predictors of Outcome in Patients that Require Management in Intensive Care Units: A Narrative Review

ABSTRACT
Intensive care units stand as the frontline battlegrounds where medical warriors combat the most critical illnesses and injuries. Within the labyrinth of intensive care units, where every moment teeters between life and death, prognostic markers emerge as beacons of guidance amidst uncertainty. In recent years, researchers have identified several novel mortality predictors in the intensive care population. In this review, we aimed to examine the clinical and laboratory markers that have been proposed in recent years to evaluate prognosis in the intensive care unit population and to review the literature on this topic. Management of patients in intensive care units is a dynamic process and reliable risk stratification models and prognostic markers are needed for this purpose. Novel prognostic indicators could serve as reliable diagnostic and prognostic tools in critically ill patients.
Keywords: Intensive care, marker, mortality, predictor, prognosis.

ÖZET
Yoğun bakım üniteleri, tıbbi savaşçıların en kritik hastalıklar ve yaralanmalarla mücadele ettiği ön cephe savaş alanlarıdır. Her anın yaşamla ölüm arasında gidip geldiği yoğun bakım ünitelerinin labirentinde, belirsizlik ortamında yol gösterici işaretler olarak prognostik belirteçler ortaya çıkıyor. Son yıllarda araştırmacılar yoğun bakım popülasyonunda birçok yeni mortalite belirteçleri tespit etmektedirler. Bu derlemede, yoğun bakım ünitesi popülasyonunda prognozu değerlendirmek için son yıllarda önerilen klinik ve laboratuvar belirteçlerin incelenmesi ve bu konuyla ilgili literatürün gözden geçirilmesi amaçlandı. Yoğun bakım ünitelerindeki hastaların yönetimi dinamik bir süreçtir ve bu amaçla güvenilir risk sınıflandırma modellerine ve prognostik belirteçlere ihtiyaç vardır. Yeni prognostik göstergeler, kritik hastalarda güvenilir tanı ve prognostik araçlar olarak hizmet edebilir.
Anahtar Sözcükler: Belirteç, mortalite, öngördürücü, prognoz, yoğun bakım.

Introduction

The struggle against serious conditions takes place in intensive care units (ICUs). Subjects in ICU require more careful management and swiftness in interventions. Patients in ICU are vulnerable and need to round-the-clock care, monitored with precision, and supported with a delicate balance of science and compassion (1). Since the population in ICU requires prompt and attentive care, markers for prediction of outcome of those patients need to emerge. These indicators should serve well in assessing the progress of the patients' treatment and forecasting their future outlook. Biomarkers and prognostic indicators shed light on the path for clinicians, aiding in navigating the fine line between decision-making and care planning for ICU patients (2). In recent years, researchers have identified several novel mortality predictors in the intensive care population, leveraging advanced statistical techniques, biomarkers, and data-driven approaches. Some of these include machine learning models, serum biomarkers, genetic markers, multiomic approaches, physiological indices, and dynamic predictors (3, 4). In this current review, our objective was to analyze the clinical and laboratory indicators that have been suggested in recent years for assessing prognosis among patients in the intensive care unit, and to survey the existing literature concerning this subject.

Machine Learning Models

Advanced machine learning algorithms have been devised to discern intricate patterns within the mortality rates of intensive care patients and to scrutinize extensive datasets encompassing these individuals. These models include a wide range of clinical variables, such as vital signs, laboratory values, and demographic factors, to predict patients' prognoses with high accuracy. These models include automatic algorithms, decision-making models, kidney damage prediction models and survival prediction models (5-8).

Biomarkers

Emerging markers like procalcitonin, copeptin, and soluble trigger receptor expressed on myeloid cells (sTREM-1) demonstrate potential in forecasting mortality among critically ill patients (9-11). These biomarkers reflect underlying inflammatory processes, severity of infection, and organ dysfunction, providing valuable information about the patient's prognosis.

Genetic Markers

Variations in genetics might influence individuals' susceptibility to critical illness and their prognosis within the intensive care unit. Genome-wide association studies (GWAS) have pinpointed genetic markers linked to heightened mortality risk in conditions such as sepsis, acute respiratory distress syndrome, and septic shock (12-14).

Multiomic Approaches

The molecular mechanisms underlying the diseases of critically ill patients are possible by integrating data from multiple omics platforms, including genomics, transcriptomics, proteomics and metabolomics. Within this context, multiomic analyses have uncovered fresh biomarkers and therapeutic targets linked to mortality among the intensive care unit population (4, 15).

Physiological Indices

New physiological indices such as the Shock Index, Oxygenation Index, and Sequential Organ Failure Assessment (SOFA) score provide quantitative measurements of hemodynamic instability, respiratory failure, and organ dysfunction, respectively. Therefore, they assist clinicians in evaluating disease severity and forecasting the likelihood of death in critically ill patients (16-18).

Dynamic Predictors

Dynamic variables, such as changes in clinical parameters over time (e.g., trends in vital signs, laboratory values, and severity scores), provide valuable prognostic information in the intensive care unit (19). Monitoring dynamic indicators allows early detection of clinical deterioration and timely intervention to improve patient prognosis. APACHE-II score is among these dynamic markers (20). The identification of new determinants of mortality in the critical care population represents a significant advance in critical care medicine. With the integration of the latest technologies and innovative approaches, it is aimed to improve risk stratification, optimize treatment strategies and ultimately improve survival rates in critically ill patients.

Laboratory Markers of Prognosis in ICU

New indicators based on laboratory markers in the critical care population include a range of biomarkers and laboratory data-derived measurements that

provide valuable information regarding patient prognosis. Some examples may include procalcitonin, C-reactive protein, lactate, troponin, blood urea nitrogen and creatinine, hemogram-derived indices, and inflammatory cytokines. These markers have been examined in assessing outcomes of patients in intensive care.

Procalcitonin

Bacterial infections and systemic inflammation trigger the release of procalcitonin (PCT), which is a peptide precursor of calcitonin (21). Elevated PCT has been associated with increased mortality in critically ill patients, particularly those with sepsis and septic shock (22). It is also useful in deciding treatment. Monitoring PCT levels can aid in early detection of infection and guide antibiotic therapy decisions (23).

Procalcitonin is a valuable indicator of sepsis and systemic inflammation. PCT levels increase in response to bacterial infections and systemic inflammation, making it a valuable marker in identifying sepsis and other infectious conditions in intensive care patients. High PCT levels are associated with the presence and severity of bacterial infections and help clinicians distinguish between infectious and noninfectious causes of systemic inflammation. Procalcitonin also allows dynamic monitoring of the condition of patients in intensive care. Serial measurement of PCT levels provides valuable information about the patient's response to treatment and resolution of the infection. A decrease in PCT levels over time is indicative of a positive response to treatment; persistently high or increasing PCT levels may indicate ongoing infection or treatment failure. Dynamic monitoring of PCT levels helps clinicians optimize antibiotic therapy and identify patients at higher risk of adverse outcomes.

Procalcitonin holds prognostic significance in cases of sepsis and septic shock. Elevated levels of PCT upon admission to the intensive care unit or during the initial phases of sepsis have been linked to heightened disease severity and poorer outcomes. High PCT levels are associated with higher mortality rates, longer hospital stays, and increased rates of organ dysfunction in septic patients. Monitoring PCT levels can help clinicians assess the severity of infection, predict patient outcomes, and guide treatment decisions, including antibiotic therapy. Procalcitonin has an important action in prognosis and management decisions in ICU population. It provides valuable information about the presence and severity of infection, predicts patient outcomes, and guides antibiotic therapy. Integrating PCT measurement into clinical practice enhances patient care, promotes antibiotic stewardship, and mitigates the burden of antibiotic-resistant infections in the intensive care unit.

C-reactive protein

C-reactive protein (CRP) is an acute phase reactant produced by the liver in response to inflammation. High CRP levels are associated with a wide variety of inflammatory conditions, including diabetic nephropathy, thyroiditis, diabetic neuropathy, and hepatitis (24-27). Moreover, a recent work found association between Covid-19 mortality and CRP based inflammatory markers (28). CRP has also shown an association with heightened mortality rates among critically ill patients (29). Serial measurement of CRP levels can help assess the severity of inflammation and monitor response to therapy.

Lactate

Lactate is a byproduct of anaerobic metabolism and serves as a marker of tissue hypoperfusion and organ dysfunction (30). High levels of lactate, especially in cases of sepsis and septic shock, correlate with higher mortality rates among ICU patients. Additionally, lactate clearance, representing the speed at which lactate levels diminish with treatment, has emerged as a prognostic factor in critically ill patients (31-33).

Troponin

Troponin is a marker of myocardial injury and is commonly elevated in patients with acute coronary syndromes and other cardiac conditions. Heightened troponin levels have been linked to elevated mortality rates in critically ill patients, especially among those diagnosed with sepsis and acute respiratory distress syndrome (34, 35). Serial measurement of troponin levels can help identify patients at higher risk of adverse cardiac events.

Creatinine and Blood Urea Nitrogen

Creatinine and blood urea nitrogen (BUN) are markers of renal function and are commonly monitored in critically ill subjects. Elevated levels of creatinine and BUN are associated with acute kidney injury

(AKI) and increased mortality in the ICU (36, 37). Changes in renal function over time can help predict patient outcomes and guide renal replacement therapy decisions.

Inflammatory cytokines

Inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and interleukin-8 (IL-8) play key roles in the immune response and inflammatory cascade (38). High levels of these cytokines have been associated with increased mortality, especially in critically ill patients with sepsis and systemic inflammatory response syndrome (SIRS) (39). Measurement of cytokine levels may help identify patients at higher risk for poor outcomes and guide immunomodulatory therapy. New mortality predictors based on laboratory indices in the intensive care population provide valuable information for risk stratification, treatment guidance, and prognosis in critically ill subjects. Integrating these biomarkers into clinical practice may help improve patient outcomes and optimize resource allocation in the ICU.

Interleukin-6

Interleukin-6 (IL-6) plays a critical role in the inflammatory response and has emerged as an important biomarker for prognosis in the intensive care unit (ICU) population. It has important actions in assessing the severity of the disease (40). IL-6 is a pro-inflammatory cytokine produced by various cell types, including immune cells, endothelial cells, and fibroblasts, in response to infection, tissue damage, or inflammation. Elevated levels of IL-6 in the bloodstream indicate the presence and severity of systemic inflammation, a common occurrence in critically ill patients afflicted with conditions like sepsis, septic shock, and acute respiratory distress syndrome (ARDS) (41). High levels of IL-6 have been associated with increased disease severity and worse outcomes in ICU patients (42). Elevated IL-6 levels have been linked to an increased risk of mortality, prolonged hospital stays, and higher rates of organ dysfunction across various critical illnesses. Monitoring IL-6 levels may help clinicians identify patients at higher risk of adverse outcomes and guide treatment decisions. IL-6 levels measured early in the course of critical illness have prognostic value in predicting the patient (43). Numerous studies have indicated that elevated IL-6 levels upon admission to the intensive care unit or during the initial phases of the disease are correlated with heightened mortality and poorer outcomes among critically ill patients. Additionally, IL-6 levels may be linked to the occurrence of complications such as acute kidney injury (AKI), acute respiratory failure, and multiple organ dysfunction syndrome. Given its central role in the inflammatory response, IL-6 has emerged as a potential therapeutic target in critical care medicine (44). Strategies aimed at modulating IL-6 activity, such as the use of IL-6 inhibitors or monoclonal antibodies targeting the IL-6 receptor, are being investigated for their potential to alleviate inflammation and improve outcomes in critically ill patients.

Interleukin-8

Interleukin-8 (IL-8) is a potent chemokine involved in the recruitment and activation of neutrophils, which are key factors in the inflammatory response (45). In the ICU population, IL-8 has been associated with a variety of critical illnesses and serves as a marker of prognostic significance. IL-8 is released in response to infection, tissue damage, and inflammation. In critically ill patients, elevated IL-8 levels often reflect the presence of systemic inflammation, especially in conditions such as sepsis, septic shock, and acute respiratory distress syndrome (46). Sustained release of IL-8 may lead to excessive inflammatory response, contributing to tissue damage and organ dysfunction. High levels of IL-8 have been associated with increased disease severity and worse outcomes in intensive care patients. Elevated IL-8 levels upon admission to the intensive care unit or during the initial phases of critical illness have been correlated with elevated mortality rates, prolonged hospital stays, and increased incidence of organ failure (47). Tracking IL-8 levels can aid clinicians in gauging the extent of inflammation and forecasting patient outcomes. IL-8 has been demonstrated to contribute to the development of organ dysfunction in critically ill patients (48). Excessive levels of IL-8 may contribute to endothelial dysfunction, microvascular damage, and the development of acute lung injury. IL-8-mediated neutrophil recruitment and activation may also contribute to tissue damage in other organs such as the kidneys, liver, and gastrointestinal tract.

Strategies aimed at modulating IL-8 activity are being investigated for their potential to improve outcomes in critically ill patients (49). Hence, monitoring IL-8 levels could assist in directing clinical management and pinpointing patients who might gain from specific therapeutic interventions targeting the modulation of the inflammatory response.

Tumor necrosis factor-alpha

Tumor necrosis factor-alpha (TNF-alpha) is an inflammatory cytokine that holds a pivotal role in immune response and inflammation. In the critical care population, TNF-alpha has been studied extensively for its role and prognostic significance in various critical illnesses (50). It is produced primarily by activated macrophages and other immune cells in response to infection, tissue damage, or inflammation. In critically ill patients, elevated TNF-alpha levels often reflect the presence of systemic inflammation, especially in conditions such as sepsis, septic shock, and acute respiratory distress syndrome (51). TNF-alpha contributes to the recruitment and activation of immune cells, leading to amplification of the inflammatory response. High TNF-alpha levels have been associated with increased disease severity and worse outcomes in intensive care patients. Elevated TNF-alpha levels upon admission to the intensive care unit or during the initial phases of critical illness have been correlated with elevated mortality rates, prolonged hospital stays, and increased incidence of organ failure (52). Monitoring TNF-alpha levels can help clinicians assess the severity of inflammation and predict the outcome of the patients. TNF-alpha has been demonstrated to contribute to the pathogenesis of organ dysfunction in critically ill individuals. Overproduction of TNF-alpha can result in endothelial dysfunction, microvascular damage, and the onset of multiple organ failure (53). TNF-alpha-mediated inflammation contributes to tissue damage in various organs, including the lungs, kidneys, liver, and gastrointestinal tract.

There are also novel inflammatory indexes that have been used in various clinical conditions, including assessing the outcome of the critically ill patients. These include systemic inflammatory index (SII), Hemoglobin-Albumin-Lymphocyte-Platelet (HALP) score, uric acid to HDL cholesterol ratio (UHR), and prognostic nutritional index (PNI).

Systemic Inflammatory Index

In the field of modern medicine, the systemic inflammatory index stands out as a versatile tool that serves as both a diagnostic aid and a prognostic indicator in a wide disease variety. Based on the complex interplay of immune responses in the body, this index provides invaluable information about the severity and progression of various medical conditions. From acute infections to chronic inflammatory disorders, the systemic inflammatory index provides a quantitative measurement of the body's inflammatory burden, guiding healthcare professionals in their decision-making processes.
The systemic inflammatory index plays a crucial role in inflammatory conditions, serving as a quantitative measure of the body's overall inflammatory response (54, 55). In such instances, the immune system undergoes dysregulation, resulting in an overabundance of pro-inflammatory cytokines and other mediators. The systemic inflammatory index (SII), frequently derived from indicators like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC), furnishes clinicians with an overview of the systemic inflammatory condition. SII assists in diagnosing inflammatory conditions. Elevated levels of inflammatory markers can indicate the presence and severity of inflammation, helping clinicians differentiate between inflammatory and non-inflammatory conditions (56). Additionally, SII serves as a prognostic indicator, offering insights into the progression and severity of inflammatory diseases. High levels of inflammatory markers may indicate a more aggressive disease course or an increased risk of complications. Furthermore, SII is useful in guiding treatment decisions by monitoring the response to therapy. Changes in inflammatory marker levels over time can indicate the effectiveness of treatment and help clinicians adjust therapeutic strategies accordingly.

Hemoglobin-Albumin-Lymphocyte-Platelet (HALP) Score

HALP score is a composite index obtained from hemoglobin, albumin, lymphocyte and platelet levels in the blood. This score acts as a prognostic marker in Hemoglobin levels and indicates the oxygen carrying capacity of the blood. Low hemoglobin levels (anemia) may reflect underlying chronic diseases, nutritional

deficiencies, or bone marrow disorders. Albumin is a protein synthesized by the liver and serves as a marker of nutritional status and liver function. Low albumin levels may indicate malnutrition, liver disease, inflammation, or other underlying chronic conditions. Lymphocytes are a type of white blood cell that plays a role in the body's immune response. Decreased lymphocyte count may indicate impaired immune function, chronic infections, autoimmune diseases, or bone marrow disorders. Platelets are blood cells that play a role in clotting and wound healing. Abnormal platelet counts may indicate bleeding disorders, inflammatory conditions, or bone marrow disorders.

The HALP score combines these four components to provide a comprehensive assessment of the patient's nutritional and inflammatory status. Low HALP score, indicating low hemoglobin and albumin levels and/or high lymphocyte and platelet levels; It is associated with increased mortality and poor outcomes in a variety of diseases, including cancer, cardiovascular disease, chronic kidney disease, and sepsis (57). Clinicians use the HALP score as a prognostic tool to assess disease severity, predict clinical outcomes, and guide treatment decisions. It helps identify high-risk patients who may need more intensive monitoring or aggressive interventions to improve their prognosis. Additionally, monitoring changes in HALP score over time can provide valuable information about the patient's response to treatment and disease progression (58, 59).

In the intensive care population, HALP score serves as a valuable prognostic tool for assessing the severity of illness and predicting clinical outcomes. Low hemoglobin levels in critically ill patients can indicate various conditions such as anemia, hemorrhage, or impaired oxygen delivery (60). Monitoring hemoglobin levels as part of the HALP score helps clinicians identify patients who may require blood transfusions or additional interventions to optimize oxygenation and tissue perfusion. Serum albumin levels are commonly decreased in critically ill subjects because of factors such as inflammation, fluid shifts, and nutritional deficiencies. Low albumin levels are associated with increased morbidity and mortality in the ICU population. The HALP score incorporates albumin as a marker of nutritional status and disease severity, helping clinicians assess the overall inflammatory and metabolic state of critically ill patients (61). Changes in lymphocyte counts can reflect the degree of immune dysregulation and inflammatory response in critically ill patients. Lymphopenia is common in severe infections, sepsis, and systemic inflammatory syndromes. Monitoring lymphocyte counts, as part of the HALP score, aids in identifying patients with compromised immune function and predicting outcomes (62). Platelet counts are closely monitored in the ICU population due to their role in hemostasis and thrombosis. Thrombocytopenia, characterized by low platelet counts, can occur secondary to sepsis, disseminated intravascular coagulation (DIC), or drug-induced thrombocytopenia (63). Elevated platelet counts may indicate underlying inflammation or a hypercoagulable state (64). Including platelet counts in the HALP score allows clinicians to assess coagulation status and predict the risk of bleeding or thrombotic events in critically ill patients.

Uric acid to HDL-cholesterol Ratio (UHR)

The ratio of uric acid to high-density lipoprotein (HDL) cholesterol is a novel metabolic and inflammatory marker. Uric acid is a byproduct of purine metabolism and has antioxidant properties but can also contribute to inflammation when present in excess. HDL cholesterol, often referred to as "good" cholesterol, has anti-inflammatory and antioxidant properties and helps remove excess cholesterol from the bloodstream. UHR's diagnostic and prognostic role have been studied in various conditions such as hypertension, hepatic steatosis, type 2 DM, thyroiditis, metabolic syndrome, prediabetes, diabetic kidney disease and even new onset diabetes (65-70). UHR stands as a potential prognostic indicator in critically ill patients, especially among those diagnosed with sepsis and systemic inflammatory response syndrome. Uric acid and HDL cholesterol both contribute to inflammation and oxidative stress (71).

In critically ill patients, UHR has been proposed as a marker of oxidative stress and inflammation. Elevated levels of uric acid and decreased levels of HDL cholesterol are common in conditions such as sepsis and SIRS, where inflammation and oxidative stress play key roles in pathogenesis. UHR may reflect the balance between pro-inflammatory and

anti-inflammatory processes in these patients.

Studies have suggested that a higher UHR is associated with increased disease severity and worse outcomes in critically ill patients (72). Elevated UHR has been correlated with higher mortality rates, longer hospital stays, and increased rates of complications such as acute kidney injury, acute respiratory distress syndrome, and multi-organ dysfunction syndrome. The UHR holds promise as a reliable marker of prognosis in critically ill subjects, providing insights into disease severity and predicting clinical outcomes. Further research is needed to better understand the mechanisms underlying this ratio and its potential as a therapeutic target in critical care medicine.

Prognostic nutritional index (PNI)

The prognostic nutritional index (PNI) is a parameter that reflects both the nutritional and immunological status of the individual. In the context of inflammation, PNI may be a useful tool in assessing the severity and prognosis of inflammatory conditions (73). PNI includes serum albumin levels, which are commonly used as markers of nutritional status. During inflammation, as in acute or chronic diseases, there is often a decrease in serum albumin due to factors such as decreased synthesis, increased catabolism, or leakage into tissues. A low serum albumin level indicates malnutrition or inflammatory processes (74). PNI also includes the lymphocyte count, which reflects the body's immune response. Inflammation can lead to changes in lymphocyte number due to factors such as cytokine release, cell migration and apoptosis (75). The decrease in lymphocyte count is often associated with systemic inflammation and immune suppression. PNI provides a comprehensive assessment of the patient's condition by combining markers of both nutritional and immunological status. In inflammatory conditions, a low PNI is associated with worse prognosis, including increased risk of complications, longer hospital stay, and higher mortality rates. It serves as a prognostic indicator of patient outcomes. Monitoring changes in PNI over time may also help assess response to treatment in inflammatory conditions. Improvements in PNI may indicate successful management of inflammation, whereas persistent or worsening low PNI may indicate treatment failure or disease progression. In summary, the prognostic nutritional index (PNI) is a valuable tool in assessing the nutritional and immunological status of patients with inflammation. It provides information about prognosis, helps guide treatment decisions, and can be used to monitor response to treatment.

In intensive care patients, the prognostic nutritional index (PNI) plays an important role in assessing disease severity, predicting outcomes, guiding nutritional interventions, and monitoring response to treatment. ICU patients often experience significant physiological stress and metabolic changes. Including markers of both nutritional status (such as serum albumin) and immune function (such as lymphocyte count), PNI provides a comprehensive assessment of the patient's overall condition. Low PNI at the time of intensive care unit (ICU) admission may indicate higher disease severity and increased risk of complications (76). PNI serves as a prognostic indicator for intensive care patients. Several studies have shown that a low PNI is associated with worse outcomes in critically ill patients, including increased mortality, longer ICU stays, and higher complication rates. Therefore, PNI may help clinicians identify patients who may require closer monitoring or more aggressive interventions (76). Adequate nutrition is essential for the recovery of critically ill patients. However, many intensive care patients are at risk of malnutrition due to factors such as hypermetabolism, catabolism, and decreased oral intake. PNI can guide nutritional assessment and support strategies by identifying patients at higher risk of malnutrition. Patients with low PNI may benefit from early initiation of enteral or parenteral nutrition to prevent further deterioration of nutritional status and improve clinical outcomes. Monitoring changes in PNI over time can help assess the patient's response to treatment and nutritional support. While improvements in PNI may indicate a positive response to treatment, a decreasing PNI may signal treatment failure or ongoing physiological stress. Regular monitoring of PNI allows clinicians to adjust treatment plans and nutritional support strategies accordingly (77). PNI can be used to risk stratify critical care patients and help clinicians prioritize resources and interventions based on disease severity and predicted outcomes.

Patients with low PNI may require more intensive monitoring, aggressive nutritional support, or early intervention to reduce complications and improve prognosis. Overall, the prognostic nutritional index (PNI) is a valuable tool in the management of intensive care patients, providing valuable information on disease severity, prognosis, nutritional status, and response to treatment. Its integration into clinical practice can help optimize patient care and improve outcomes in the critical care setting.

Hemogram Indices

Hemogram indices have been reported as reliable diagnostic markers of inflammation in various conditions. For instance, aside from its function in detecting anisocytosis, RDW has been proposed as a new inflammatory indicator in several inflammatory conditions, such as functional bowel conditions, autoimmune diseases, rheumatoid arthritis, degenerative vertebral conditions, malignancy, autoimmune hepatitis, gastrointestinal conditions, and even Covid-19 infection (78-81). Another example could be mean platelet volume (MPV), which has been linked to type 2 DM, diabetic nephropathy, hypothyroidism, infections, vertebral discopathies, irritable bowel disease, gastrointestinal conditions, rheumatoid arthritis, obesity, mortality in ICU population, and liver fibrosis (82-85). All of these conditions are associated with inflammation as intensive care management does.

Recent studies on critically ill patients revealed that hemogram markers could be used as prognostic indicators. Mean platelet volume, which refers the size of circulating thrombocytes, has been suggested as a marker of outcome in patients in ICU (86). Another study suggested use of hemogram markers as screening and prognosis tools in ICU patients (87). These indices were also useful in detecting patients with poor prognosis in Covid-19 patients that require intensive care management (88). These data suggest that hemogram markers are reliable prognostic markers for patients in ICU.

Conclusion

Management of patients in ICU is a dynamic process and reliable risk stratification models and prognostic markers are needed for this purpose. Novel prognostic indicators could serve as reliable diagnostic and prognostic tools in critically ill subjects.

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Multimodal Imaging of a Choroidal Metastasis Secondary to Breast Cancer: A Case Report

Meme Kanserine Sekonder Gelişen Koroidal Metastazda Multimodal Görüntüleme: Olgu Sunumu

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ABSTRACT
Metastasis is the most common intraocular malignancy. These lesions are the smallest metastases in the human body that can be directly detected with a biomicroscope. Choroidal metastasis most commonly originates from primary cancer of the breast and lungs. Breast cancer is the most common type of cancer in women. In this case, a 42-year-old female with choroidal metastasis secondary to breast cancer is presented using multimodal imaging.
Keywords: Breast cancer, choroidal metastasis, multimodal imaging.

ÖZET
Metastazlar, en sık izlenen göz içi maligniteleridir. Bu lezyonlar insan vücudunda biyomikroskopla doğrudan tespit edilebilen en küçük metastazları oluşturur. Koroid metastazları en sık meme ve akciğerin primer kanserinden kaynaklanır ve meme kanseri kadınlarda izlenenen en sık kanser türüdür. Bu olguda, meme kanserine sekonder koroid metastazı izlenen 42 yaşındaki kadın hasta multimodal görüntüleme kullanılarak sunulmuştur.
Anahtar Sözcükler: Koroidal metastaz, meme kanseri, multimodal görüntüleme.

Introduction

Breast cancer is the most common type of cancer in women and the most common malignancy in the world. More than 2.26 million newly diagnosed breast cancer cases were observed in women in 2020, accounting for 12.5% of all newly diagnosed cancers (1). Most breast cancer patients in the United States are diagnosed early, only 5% of patients present at the metastatic stage (2). The most common sites of metastasis are the bone, lung, liver, and soft tissues. This study uses multimodal imaging including color fundus photography, fundus fluorescein angiography (FFA), Enhanced depth imaging-optical coherence tomography (EDI-OCT), and ocular ultrasonography (US) to report the case of a 42-year-old female with choroidal metastasis (CM) of breast carcinoma.

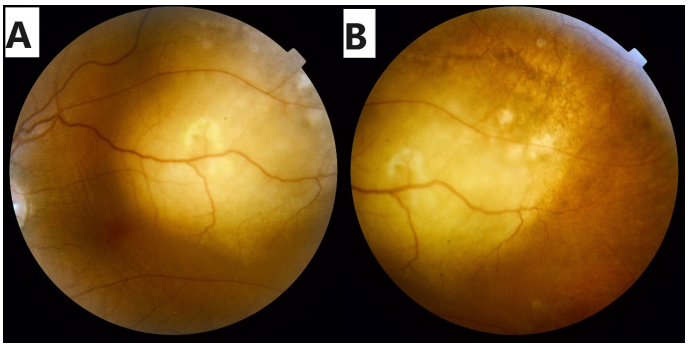

Figure I Color fundus photograph revealed: A) solitary, creamy white-yellowish, elevated choroidal lesion along the superotemporal arcade; B) typical leopard skin pigmentation at the superotemporal border of the metastatic lesion.

Case Report

A 42-year-old female presented with blurred vision in her left eye she had experienced for approximately two weeks. She had a history of infiltrating ductal carcinoma of the breast, for which she had undergone breast-conserving surgery, followed by chemotherapy and radiation therapy four years before. On presentation, the best corrected visual acuity was 10/10 in the right eye and 7/10 in the left. In both eyes, anterior segment examination was unremarkable, and intraocular pressure was normal. The fundus of the right eye was unremarkable. In the left eye, a solitary, creamy white-yellowish, and elevated choroidal lesion measuring approximately 5-disc diameters by 5-disc diameters along the superotemporal arcade (Figure Ia) and typical leopard skin pigmentation at the superotemporal border of the lesion (Figure Ib) were observed. On FFA, relatively hypofluorescence in the early venous phase (Figure IIa) and a non-homogeneous dye leakage in the middle and lower areas of the lesion with pinpoint leakage at the borders of the lesion in the late venous phase (Figure IIb) were perceived. EDI-OCT revealed an elevated dome-shaped choroidal hyporeflective lesion, subretinal fluid with a hyperreflective speckle, compression of the choriocapillaris, hyperreflective alterations in the outer retina, loss of the interdigitation and ellipsoid zone (Figure III). A highly echogenic, plateau-shaped choroidal mass was observed on B-scan US (Figure IV). The patient was diagnosed with CM secondary to breast cancer and referred to the center where she had previously received treatment. Written informed consent was obtained from the patient who participated in this study.

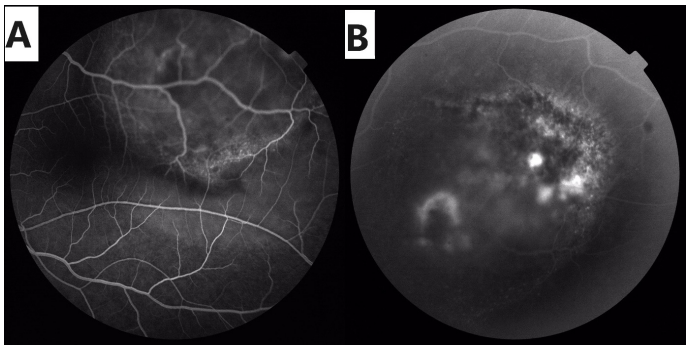

Figure II FFA revealed: A) relative hypofluorescence in the early venous phase; B) non-homogeneous dye leakage in the middle and lower areas of the lesion with pinpoint leakage at the borders of the lesion in the late venous phase.

Discussion

Metastasis is the most common intraocular malignancy than primary cancers. These lesions are the smallest metastases in the human body that can be directly detected with a biomicroscope. Due to its rich vascular supply and fenestrated choriocapillaris, the uveal system is the primary ocular site for metastasis in 99% of cases. Exactly 88% of uveal metastases are observed in the choroid. Choroidal metastatic lesions are localized in 80% of cases between the equator and the macula, 12% at the macula, and 8% between the equator and the ora serrata (3). The choroid is one of the most vascularized tissues in the body, and 80%–85% of ocular blood flow reaches the choroid. Short posterior ciliary arteries are

considered the entry route for uveal embolization of metastatic cells. Some studies indicated that the left eye was more frequently involved, and it has been proposed that this is related to the more direct path to the eye provided by the left common carotid originating from the aorta (4). Optic disc (5) and retina/vitreous (6) metastasis have also been reported extremely rare.

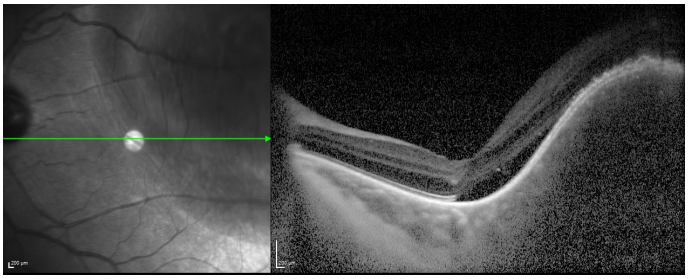

Figure III EDI-OCT revealed an elevated dome-shaped choroidal hyporeflective lesion, subretinal fluid with a hyperreflective speckle, compression of the choriocapillaris, hyperreflective alterations in the outer retina, and loss of the interdigitation and ellipsoid zone.

The incidence of CM has increased over the years due to the improvement in diagnostic techniques and the increase in the survival rate of patients due to available treatments. However, the incidence of CM is higher than reported, probably due to underdiagnosis in patients in poor general conditions. CM usually manifests within 2 to 4 years of the diagnosis of the primary tumor (7). Late presentation of uveal metastasis is extremely rare (8).

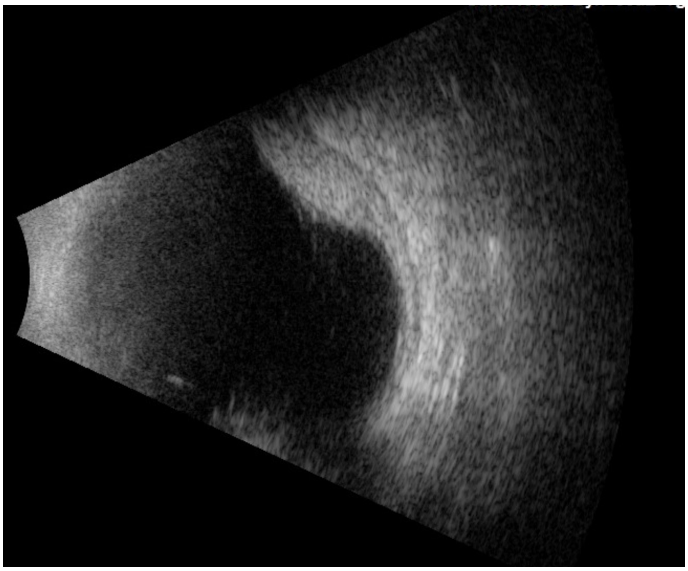

Figure IV B-scan US revealed a highly echogenic, plateau-shaped choroidal mass.

CM most commonly originates from primary cancer of the breast (37%–47% of cases) and lungs (20%–27% of cases). In a study conducted on 420 patients with uveal metastases, 34% had no history of malignancy at the time of ocular diagnosis. In patients with no known malignancy, the primary tumor sites were breast (35%) and lung (7%); the primary site could not be found in approximately 50% of patients. CMs in breast cancer are frequently more bilateral (33%) and multifocal (32%) compared to other primary neoplasms (3).

CM appears as creamy white, pale yellow, or flat plateau-shaped masses with subretinal fluid. Macrophages containing lipofuscin and changes in the retinal pigment epithelium (RPE), which cause brown pigmentation on the lesion, may result in a "leopard skin" appearance. An orange color can be seen in metastases originating from carcinoid tumors and renal cell or thyroid carcinomas (4).

The most common symptom in patients with CM is blurred vision due to macular involvement, subretinal fluid, or exudative retinal detachment. Other symptoms include photopsia, floater, metamorphopsia, scotoma, and ocular pain. Ocular pain may develop due to inflammation, tumor necrosis, neovascular glaucoma, microscopic scleral involvement, and invasion of the ciliary nerves. No symptoms are observed in 13% of patients (3,4,9).

In differential diagnosis, amelanotic melanoma or naevus, lymphoma, choroidal hemangioma, choroidal osteoma, eccentric disciform process, and posterior scleritis should be considered. CM can generally be diagnosed by fundus examination, but auxiliary diagnostic methods and tools should sometimes be used. Furthermore, these diagnostic tools can be beneficial in predicting the clinical course of metastatic lesions.

FFA may help distinguish CM from choroidal melanoma. In FFA, the lesion, which usually shows relative hypofluorescence in the arterial filling and early venous phase, gradually acquires hyperfluorescence in the late venous phase. However, hyperfluorescence is seen at earlier stages in amelanotic melanoma and hemangioma, mostly in the form of spots. CM also contains dilated retinal capillaries with a pinpoint leakage at the tumor border in 74% of cases, compared to melanoma in 16% of cases.

The double circulation pattern, mostly seen in choroidal melanoma, is rare in CM (10). Indocyanine green angiography shows a blockage in choroidal fluorescence and irregular staining on the surface. US allows the differentiation of metastases from other intraocular masses, especially melanomas. On A-scan US, the metastatic lesion shows a high initial spike, moderate-high internal reflection, and a high spike belonging to the sclera at the posterior border. B-scan US demonstrates moderate to high acoustic echogenicity. These findings differentiate choroidal metastatic masses from uveal melanomas, which are usually mushroom-shaped and show acoustic space and choroidal excavation on US. The internal acoustic reflectivity of choroidal hemangioma is higher than in choroidal metastatic lesions. CMs are generally small, posteriorly located, and suitable for OCT imaging. EDI-OCT may be more sensitive than US in evaluating small metastatic tumors at presentation and after treatment (11). Neoplasms that are 1 mm thick may not be detected by US, but EDI-OCT can detect these subclinical CMs (12). An irregular (lumpy-bumpy) anterior contour, overlying choriocapillaris thinning, plateau-shaped tumor, posterior shadowing, shaggy photoreceptors, subretinal fluid with high reflective speckles, thickening of RPE, loss of external limiting membrane, abnormality of photoreceptors, and loss of inner segment/outer segment junction are common EDI-OCT imaging features of CM (11-13). The most characteristic finding is an irregular "lumpy-bumpy" anterior tumor surface of a metastatic lesion. Highly reflective speckles in the subretinal fluid are thought to be shedded photoreceptor outer segments. "Shaggy photoreceptors" can describe the swelling and elongation of the photoreceptors. Improvement of shaggy photoreceptors has been reported in treated patients with CM and is associated with the resolution of subretinal fluid (11). While no blood flow within the metastatic lesion and absence of pathological blood flow at external retinal layers are observed in OCT-angio imaging, a dense irregular vascular network is observed in choroidal melanomas, hemangiomas, and osteomas (14). It has been suggested that the lack of blood flow within the metastatic lesion may result from shadowing artifacts of the RPE on the underlying tumor neovascularization or by a fringe washout due to higher flow speed inside the tumor (4).

In conclusion, it should be remembered that visual symptoms may be a sign of intraocular metastatic lesions in patients with a history of malignancy. The distinctive characteristics of choroidal lesions can be better understood with multimodal imaging.

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Efficacy of Continuous Renal Replacement Therapy in Metformin Intoxication: Case Report

Metformin Zehirlenmesinde Sürekli Renal Replasman Tedavinin Etkinliği: Olgu Sunumu

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Efficacy of Continuous Renal Replacement Therapy in Metformin Intoxication: Case Report

ABSTRACT
Metformin-associated lactic acidosis is seen in conditions that disrupt haemodynamics such as renal failure, hepatic failure, sepsis, septic shock or in acute poisoning. Since the mortality rate of metformin-associated lactic acidosis is high, early diagnosis and treatment is important in reducing mortality. Continuous renal replacement therapy is preferred especially in clinical conditions such as severe metabolic acidosis with haemodynamic instability, intoxication, hyperkalaemia and volume overload. In our patient with lactic acidosis due to metformin intoxication, we aimed to emphasise the efficacy of continuous renal replacement therapy because of the lack of response despite two intermittent haemodialysis and haemodynamic instability.
Keywords: Continuous renal replacement therapy, critical care, metformin, poisoning.

ÖZET
Metformin ilişkili laktik asidoz böbrek yetmezliği, karaciğer yetmezliği, sepsis, septik şok gibi hemodinamiyi bozan durumlarda ya da akut zehirlenmelerde görülür. Metformin ilişkili laktik asidozun mortalitesi yüksek olduğu için erken tanı ve tedavi mortaliteyi azaltmakta önemlidir. Sürekli renal replasman tedavisi özellikle hemodinamik anstabilite ile seyreden ciddi metabolik asidoz, zehirlenme, hiperkalemi, aşırı volüm yükü gibi klinik durumlarda tercih edilmektedir. Metformin zehirlenmesine bağlı gelişen laktik asidozlu olgumuzda iki kez aralıklı hemodiyaliz uygulanmasına rağmen yanıt alınamaması ve hemodinamik anstabilitesi olması nedeniyle hastaya uygulanan sürekli renal replasman tedavisinin etkinliğini vurgulamayı amaçladık.
Anahtar Sözcükler: Metformin, sürekli renal replasman tedavisi, yoğun bakım, zehirlenme.

Giriş

Metformin böbrek fonksiyonları normal hastalarda insülin direncinde ve Tip 2 diyabetik hastalarda hiperglisemi için ilk basamakta kullanılan biguanid grubu oral antidiyabetiktir (1). Antihiperglisemik bir ajan olup ancak tek başına kullanıldığında hipoglisemiye neden olmaz (2). Metformin ilişkili laktik asidoz böbrek yetmezliği, karaciğer yetmezliği, sepsis, septik şok gibi hemodinamiyi bozan durumlarda ya da akut zehirlenmelerde görülür (3). Laktik asidozda bulantı, kusma, ishal gibi gastrointestinal bulgular ve hipotansiyon görülebilir. Metformin ilişkili laktik asidozun mortalitesi yüksek olduğu için erken tanı ve tedavi mortaliteyi azaltmakta önemlidir. Sürekli renal replasman tedavisi (SRRT) özellikle hemodinamik anstabilite ile seyreden ciddi metabolik asidoz, zehirlenme, hiperkalemi, aşırı volüm yükü gibi klinik durumlarda tercih edilmektedir (4). Olgumuzda metformin zehirlenmesine bağlı gelişen laktik asidozda aralıklı hemodiyaliz tedavisi sonrası uygulanan SRRT'nin etkinliğini vurgulamayı amaçladık.

Olgu Sunumu

32 yaşında kadın hasta insülin direnci ve anksiyete nedeniyle kullanmakta olduğu ilaçlarını suisid amaçlı alımından (metformin 1000 mg [100 tablet] ve medazepam 10 mg [20 tablet]) iki saat sonra acil servise bulantı, kusma, uyku hali, sersemlik şikayetleri ile başvurdu. Acil serviste hasta çok sayıda ilaç aldığı için süre bir saatin üzerinde olsa da orogastrik lavaj ve aktif kömür (1 gr/kg), pantoprazol (40 mg intravenöz) ve ondansetron (4 mg intravenöz) uygulandı. Laboratuvar değerlerinde Glukoz: 76 mg/dL, kreatinin: 0,8 mg/dL – Arteriyel kan gazında (AKG); pH: 7,30 PO_2: 30,5 mmHg PCO_2: 41,4mmHg HCO_3: 22,4 mmol/L Laktat: 3,5 mmol/L olarak saptandı (Tablo I ve Tablo II). Hastanın takibinde metabolik asidoz, laktat artışı olması nedeniyle (Tablo I, preHD) acil yoğun bakıma alınarak hemodiyaliz (HD) uygulanması planlandı. Dört saat, antikoagülansız 200 ml/dk pompa hızı ile HD yapıldıktan sonra AKG'de metabolik asidoz ve laktat düzeyi yüksekliği devam etti (Tablo I, post1HD). Hemodiyaliz sonrası takiplerinde AKG'de pH: 7,16 PO_2: 33,3 mmHg PCO_2: 40,9 mmHg HCO_3: 13 mmol/L Laktat: 27 mmol/L olması nedeniyle tekrar nefroloji kliniğinin önerileri alınarak ikinci kez HD planlandı. 280 ml/dk akım hızı ve heparinli (6000 U) altı saatlik HD sonrası hastanın kontrol AKG'de, asidoz düzelmedi ve laktat düzeyi normalin çok üzerinde seyretmeye devam etti. Bunun üzerine nefroloji kliniği önerisi ile hasta anestezi yoğun bakım ünitesine alınarak, SRRT uygulanmasına karar verildi. (Tablo I, post2HD)

Tablo I Hastanın acil, HD ve SRRT tedavileri sürecindeki kan gazı değişiklikleri

	Acil	preHD	Post1HD	Post2HD	postSRRT	sonAKG
pH	7,30	7,10	7,16	7,19	7,45	7,48
PO_2 (mmHg)	30,5	48,6	33,3	45,6	40,5	38,9
PCO_2 (mmHg)	41,4	38,8	40,9	29,7	42,9	51,2
Laktat (mmol/L)	3,5	11,2	22	27	3,1	1,1
HCO_3 (mmol/L)	22,4	14,6	13	12,5	30	35
Glukoz (mg/dL)	73	149	72	72	105	120

Tablo I: Acil: Hastanın Acil servise geliş değerleri. preHD: Hemodiyaliz tedavisinden önceki değerler. Post.1HD: Birinci Hemodiyaliz tedavisi sonrası değerler. Post.2HD: İkinci Hemodiyaliz tedavisi sonrası değerler. postSRRT: SRRT sonrası değerler. sonAKG: Hastanın taburcu edilmeden önceki kan gazı değerleri.

Hasta yoğun bakıma spontan solunumda, bilinci açık, Glasgow koma skoru (GKS): 15 olarak getirildi. Acil yoğun bakım takibinde hipotansif seyrettiği (TA: 67/35 mmHg) için norepinefrin infüzyonu uygulanmaktaydı. Monitörize edilen hastanın vital bulguları TA: 94/56 mmHg, Nabız:90/dk, SpO_2: %99 olarak saptandı ve Glukoz: 96 mg/dL olarak ölçüldü. Sağ femoral venden çift lümenli 12F x 20 cm ikinci HD kateteri takıldı.

Nefroloji kliniğinin önerileri doğrultusunda SRRT tedavisi başlandı ve antikoagülasyon amaçlı sitrat kullanıldı. Cihazdan ve hastadan alınan kan gazı kontrolleri ile iyonize kalsiyum düzenlendi. Başlangıçtan iki saat sonra alınan kan gazında hasta serumunda iCa (HiCa) düzeyi: 0,76 olduğu için kalsiyum infüzyon hızı %10 artırıldı. Filtredeki iCa (FiCa) düzeyi: 0,20 olduğu için sitratlı pompa hızı 0,3 mmol/L azaltıldı. İki saat sonraki kan gazında HiCa: 0,85 geldiği için kalsiyum infüzyonu %5 artırıldı. FiCa: 0,27 yani hedef

aralıkta olduğu için değişiklik yapılmadı. Devamında 4 saat aralıklarla cihazdan ve hastadan alınan kan gazlarında HiCa ve FiCa düzeyleri hedef aralıkta olduğu için değişiklik yapılmadan takip edildi. (HiCa hedef aralığı: 1-1,2 mmol/L, FiCa hedef aralığı: 0,25-0,35 mmol/L)

Tablo II Hastaya ait laboratuvar değerleri

	Glu	BUN	Krea	ALT	AST	Ca	Na	K	CRP	PCT
Acil	76	10	0,84	10	24		138	4	<2	
YBÜ	88	6	1,05	30	68		138	3,3	<2	3.3
preSRRT	86	9	1,54	34	39	7,6	138	3,4		
SRRT	105	16	1,54	35	55	9,4	134	3,4	3,16	
postSRRT	145	14	1,22	30	38	11,6	134	3,5	8,37	0,15
Taburcu	127	15	0,92	24	19	8,7	137	3		

Tablo II; Glu: Glukoz, BUN: Kan Üre Azotu, Krea: kreatinin, ALT: Alanin transaminaz, AST: Aspartat transaminaz, Ca: Kalsiyum, Na: Sodyum, K: Potasyum, CRP: C-reaktif protein, PCT: Prokalsitonin, YBÜ: Yoğun Bakım Ünitesi, preSRRT: SRRT öncesindeki değerler, SRRT: Sürekli Renal Replasman Tedavisi, postSRRT: SRRT sonrasındaki değerler.

Yaklaşık olarak 16 saat SRRT yapılan hastanın kontrol AKG sonuçları giderek düzeldi. Uygulanan SRRT sonlandırıldığında, kan gazı değerleri normal sınırlarda bulunurken laktat düzeyinde anlamlı bir düşüş görüldü (Tablo I, postSRRT). Vital bulguları ise TA: 99/63 mmHg, Nb: 92/dk, SpO_2: %99 olarak saptanırken kan Glukoz değeri 105 mg/dL olarak ölçüldü. Yatışının ikinci gününde norepinefrin infüzyon dozu azaltılarak kapatıldı. Hasta yoğun bakım ünitesinde üç gün kaldı. Yoğun bakım süresince GKS:15 puandaydı. Sıvı tedavisi serum fizyolojik infüzyonu ile yapıldı. Servis takibinde taburculuk öncesi kan gazı değerleri normal sınırlarda ve laktat düzeyi 1,1 mmol/L olarak bulundu (Tablo I, sonAKG). Vital bulguları ise TA: 92/61 mmHg, Nb: 91/dk, SpO_2: %95 olarak saptandı ve kan Glukoz değeri 120 mg/dL olarak ölçüldü. Hasta şifa ile taburcu edildi. Tedavi sürecindeki klinik ve laboratuvar verilerinin akademik amaçlı bir yazıda kullanılması için hastadan onam alındı.

Tartışma

Metformin ilişkili laktik asidoz böbrek ve karaciğer yetmezliği gibi komorbid durumların dışında daha çok akut zehirlenmelere bağlı ortaya çıkmaktadır. Yapılan çalışmalarda da gösterildiği üzere kan gazı ve laktat değerlerinin mortalitede etkili olması nedeniyle laktik asidozun prognozu kötü seyretmektedir (3,5). Olgumuzu kabul ettiğimizde kan gazı değerleri normal olsa da kısa bir sürede laktat düzeyi (27 mmol/L) yükseldi. Ancak SRRT tedavisi ile AKG ve laktat düzeyi normal seviyelere geriledi. Hasta yoğun bakım ünitesinden servis katına devredildiği zaman kan gazı değerleri normal aralığa gerilemişti ve laktat düzeyi 1,1 mmol/L olarak hasta taburcu edildi.

Metformin tek başına kullanıldığı durumlarda hipoglisemi görülmez ancak diğer antidiyabetiklerle kullanıldığında hipoglisemi görülebilmektedir. Akut metformin zehirlenmelerinde diğer durumları da düşünerek hipoglisemi açısından kan şekeri takibi önerilir (2). Hipoglisemi açısından yakın takip edilen olgumuzda hipoglisemi saptanmadı.

Zehirlenmelerde suda çözünebilen ve proteine bağlanması düşük oranda olan ilaçlar RRT ile temizlenebilmektedir. Birçok antibiyotiğin aşırı alımlarında bu yöntem başarılı olmaktadır (6). Olgumuzda aşırı dozda alınan metformin plazma proteinlerine ihmal edilebilir düzeyde bağlandığından RRT ile plazmadan uzaklaştırılabilir. Metformin zehirlenmelerinde laktat düzeyi>15 -20 mmol/L ve pH<7,00 - 7,10 ise, hastada şok bulguları varsa ve destek tedavilerinin yetersiz kaldığı hastalarda renal replasman tedavisi (RRT) düşünülmelidir. Öncelikle aralıklı HD tercih edilmeli ancak hemodinamik olarak stabil olmayan hastalarda SRRT uygulanmalıdır (7). Olgumuzda da iki seans hemodiyaliz sonrasında bilinç düzeyinde anlamlı bir değişiklik görülmemesine rağmen laktat seviyesinin 20'nin üzerinde, kan gazında pH değerinin 7,19 gelmesi ve norepinefrin infüzyonu uygulanmasına rağmen kan basıncı değerlerinin düşük seyretmesi üzerine SRRT tedavisine geçilmesi uygun görüldü.

Kanama riski olmaması, daha uzun filtre ömrü sağlaması ve heparine göre daha güvenli hasta takibi yapmamızı sağladığı için SRRT'yi sitrat antikoagülasyonu ile yapmayı tercih ettik (8). Sitrat antikoagülasyonu artmış kanama riskinde, heparin ilişkili trombositopenide ve hiperkalsemide tercih edilebilmektedir. Heparin kullanımı ile ortaya çıkan

hücresel ve enzimatik mekanizmalarda öngörülemeyen bir doz-etki ilişkisi proinflamatuvar ve antiinflamatuvar yolaklarda zararlı olabilecek ve tahmin edilemeyen girişimlere neden olabilmektedir. Heparin hastanın kanama riskini artırırken, hastada kullanılan diyaliz devresinin ömrünü de kısalttığı belirtilmektedir (9). Olgumuzun hemodinamik olarak stabil olmaması, şok bulgularının ve eşlik eden metabolik asidoz tablosunun varlığı nedeniyle hastaya sitratlı SRRT uygulamaya karar verildi. Ayrıca yapılan çalışmalarda sitrat ile diyaliz devresi ömrü daha uzun, kanamanın daha az ve kan transfüzyonu ihtiyacının da daha az olduğu belirtilmiştir (9).

Sürekli RRT uygulamalarında sitrat kullanımı, cerrahi uygulanan hastalarda, genç hastalar ve sepsisli hastalarda ve ileri derecede organ yetmezliği olan hastalarda daha yararlı bulunmuştur (9). Olgumuz da genç hastaydı, organ yetmezliği olmamasına rağmen tedavinin başlangıcında uygulanan hemodiyaliz tedavilerine rağmen laktat düzeyi normalin çok üstünde seyretti. Bu nedenle sitratlı SRRT'nin daha etkili olacağı düşünüldü.

Ayrıca şiddetli metabolik asidozu (pH<7,10 - 7,20) olan hastalara sodyum bikarbonat tedavisi önerilmektedir. Ancak hipokalsemi, hipernatremi, laktat artışı gibi dezavantajları göz ardı edilmemelidir. Laktat metabolize edildiğinde bikarbonat oluşturduğu için laktik asidoza neden olan asıl sebep düzeltilirse sodyum bikarbonat tedavisine gerek kalmamaktadır (10). Olgumuzda şiddetli asidemi görülmediği için erken dönemde HD ve sonrasında SRRT uygulanması ile asidoz tablosu sodyum bikarbonat uygulamadan kontrol altına alınabilmiştir.

Sonuç

Tip 2 diyabet ve insülin direncinde tek başına ya da diğer antidiyabetiklerle kombine olarak kullanılan metforminin daha çok akut zehirlenmede ve diğer komorbid durumların varlığında laktik asidoz oluşturma potansiyeli vardır. Çok yüksek laktat seviyelerinde, destek tedavilerine rağmen devam eden şok bulguları olan hastalarda SRRT düşünülmelidir. Ayrıca zehirlenme vakalarında diğer nedenleri ekarte edip erken tanı koymak, doğru tedavi yöntemleri uygulamak mortaliteyi önemli derecede azaltmaktadır. Metformin zehirlenmelerinde literatürde ciddi asidemi ve laktik asidozda RRT kullanımının önerildiği, özellikle hemodinamisi anstabil ve hipotansif hastalarda SRRT kullanımının fayda sağlayacağı belirtilmektedir. Olgumuzda da bu şekilde hızlı bir klinik düzelme elde edildiği kanaatindeyiz.

Kaynaklar

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Pneumomediastinum Mistaken as Angioedema: Case Report

Anjiyoödem Sanılan Pnömomediastinum: Olgu Sunumu

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Pneumomediastinum Mistaken as Angioedema: Case Report

ABSTRACT
Pneumomediastinum and massive subcutaneous emphysema are clinical conditions that can occur during head and neck surgeries, bronchoscopy and tracheostomy, after thoracic trauma, rarely during dental procedures and sometimes spontaneously. Patients often present with symptoms such as swelling of the face, neck and sometimes the whole body, difficulty swallowing, shortness of breath, chest pain and skin crepitus. These findings usually develop suddenly and sometimes may occur within hours or days. A 48-year-old man is applies to the hospital with complaint chest pain due to a fall in the garden. If no pathology is thought to be present as a result of the X-ray, the patient is prescribed ibuprofen for pain relief and discharged. Patient who presents with what appears to be angioedema after taking ibuprofen is found to have pneumomediastinum. In the cases mentioned in the report and initially thought to be angioedema, seeing that the lips are not swollen and feeling subcutaneous crepitation, i.e. even just inspecting and palpating the patient, will distract the clinician from angioedema in a few seconds and direct him/her to the correct diagnosis and perform examinations in the direction of pneumomediastinum.
Keywords: Angioedema, blunt trauma, emergency medicine, pneumomediastinum, thoracic surgery.

ÖZET
Pnömomediastinum ve masif subkutan amfizem baş ve boyun ameliyatları, bronkoskopi ve trakeostomi gibi girişimler sırasında, toraks travması sonrasında, nadiren dental işlemler sırasında ve bazen de spontan olarak ortaya çıkabilen klinik durumlardır. Hastalar sıklıkla yüz, boyun ve bazen tüm vücutta şişlik, yutma güçlüğü, nefes darlığı, göğüs ağrısı ve ciltte krepitus gibi semptomlarla başvururlar. Bu bulgular genellikle aniden gelişir ve bazen saatler veya günler içinde ortaya çıkabilir. 48 yaşında erkek hasta bahçede düşmeye bağlı göğüs kafesinde ağrı şikâyeti ile hastaneye başvurur. Çekilen röntgen sonucunda herhangi bir patoloji olmadığı düşünülen hastaya ağrı kesici olarak ibuprofen reçete edilir ve taburcu edilir. İbuprofen aldıktan sonra anjiyoödem kliniği ile başvuran hastada pnömomediastinum olduğu tespit edilir. Vakada bahsedilen ve ilk etapta anjioödem düşünülen durumlarda dudakların şişmediğinin görülmesi ve cilt altı krepitasyonunun hissedilmesi, yani hastanın sadece inspeksiyon ve palpasyonla muayene edilmesi bile birkaç saniye içinde klinisyeni anjioödemden uzaklaştırıp doğru tanıya yönelmesini ve pnömomediastinum yönünde tetkikler yapmasını sağlar.
Anahtar Sözcükler: Acil tıp, anjioödem, göğüs cerrahisi, künt travma, pnömomediastinum.

Introduction

Pneumomediastinum and massive subcutaneous emphysema are clinical conditions that can occur during head and neck surgeries, bronchoscopy and tracheostomy, after thoracic trauma, rarely during dental procedures and sometimes spontaneously (1,2). Patients often present with symptoms such as swelling of the face, neck and sometimes the whole body, difficulty swallowing, shortness of breath, chest pain and skin crepitus (3). In patients presenting with such complaints, a differential diagnosis of other clinical conditions, many of which are life-threatening, such as angioedema, allergic reactions, cellulitis, and myocardial infarction, should be made. Feeling crepitus in the swollen parts of the body and preserving the lips despite swelling of all areas of the face are pathognomic in terms of subcutaneous emphysema (4). If there is a history of new drug use in the application of such cases, the first diagnosis that comes to the clinicians' mind is usually angioedema and glucocorticoid, antihistamine and oxygen therapy are the first treatment options. Since angioedema is life-threatening, rapidly progressive condition that affects the airway, and is diagnosed by clinical evaluation. Clinicians must protect the airway and then initiate antihistamine, glucocorticoid, and epinephrine treatments. There is no routine imaging technique to diagnose classic angioedema cases, except for patients who complain of abdominal pain due to hereditary angioedema (5). For this reason, inexperienced clinicians may have difficulty in diagnosing pneumomediastinum before imaging techniques. In this case report, a case of traumatic pneumomediastinum, which was thought to be angioedema based on clinical evaluation and was referred to a higher center with this preliminary diagnosis, will be presented.

Case Presentation

A 48-year-old man is applied to the hospital with chest pain due to a fall in the garden. He had a history of hypertension. In his history, it was learned that while he was doing gardening, he tripped and fell on a stone to the right. A posteroanterior chest radiography was taken for the patient whose vital signs were within normal limits (Figure Ia).

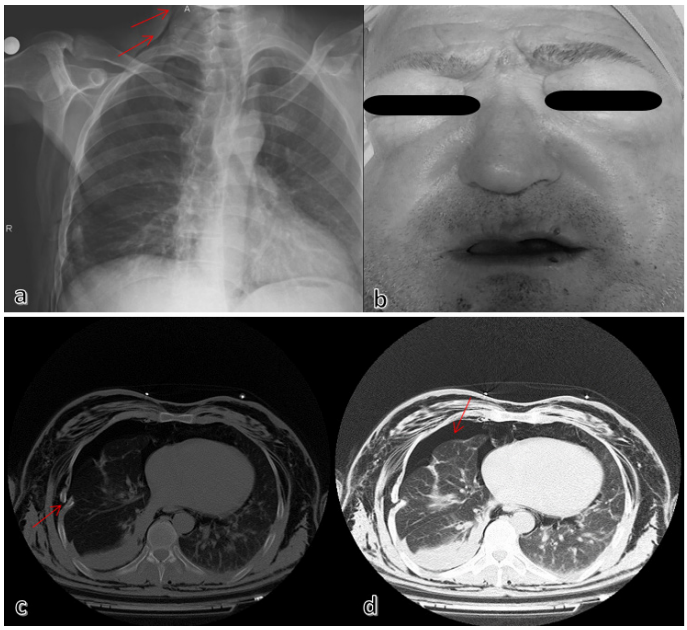

Figure I: A. Chest radiograph at initial presentation B. Image of edema on the face of a patient who cannot open his eyes spontaneously C. Traumatic rib fracture (red arrow) D. Traumatic pneumothorax (red arrow)

The patient, whom no pathology was considered as a result of the X-ray, was prescribed ibuprofen as an analgesic and discharged from the emergency department. The next day, the patient applied to the same hospital with complaints of sudden swelling in the face, eyes and neck, and shortness of breath. The patient, who states that his complaints started after taking an ibuprofen tablet, was considered to have angioedema, and glucocorticoid and antihistamine treatment was started, and he was referred to our hospital's emergency department by ambulance with the preliminary diagnosis of angioedema. When the patient was admitted to the emergency department of our hospital, his general condition was fair-good, he was conscious, oriented and cooperative. There was swelling all over his face and neck, so he could not open his eyes spontaneously (Figure Ib). His vital signs were, blood pressure: 140/90 mmHg, pulse: 94/min, temperature: 36,5 °C, respiratory rate: 16/min, SpO2: 94% on room air. According to the anamnesis taken from the patient's relative, it was learned that the patient fell the day before, he was given painkillers because he had pain in the chest area, and today, after using the medicine, he suddenly developed swelling in the body and shortness of breath. On physical examination, there was crepitus on the edematous area on the face and neck, there was no

edema on the lips, there was no uvula edema, lung sounds were deep, no rhonchi were heard, other system examinations were normal. In the tomography scans performed with the preliminary diagnosis of traumatic pneumomediastinum, the patient showed rib fracture due to trauma (Figure Ic), pneumothorax (figure Id), and pneumomediastinum and widespread subcutaneous emphysema (Figure II). The patient was consulted with thoracic surgery for chest tube application, observation and continuation of the treatment, and was admitted to the hospital.

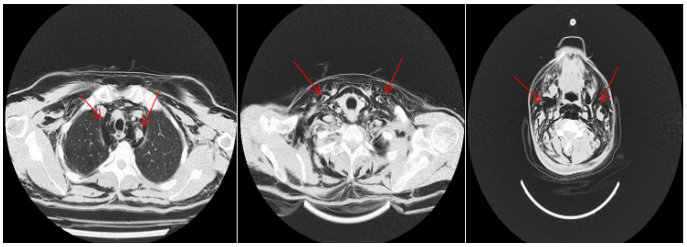

Figure II Pneumomediastinum and widespread subcutaneous emphysema

Discussion

Pneumomediastinum, by definition, means the presence of air in the mediastinum. Its mechanism can be explained by the passage of air from the airways, lungs or digestive organs to this area. Etiology can be divided into spontaneous pneumomediastinum, which is more likely to be seen in smokers, and secondary pneumomediastinum, which occurs after triggering by the iatrogenic causes, trauma or chronic diseases (6). The most common symptom at presentation is chest pain, which is located in the retrosternal region, followed by shortness of breath and subcutaneous emphysema. Even if patients appear well, anxiety, tachypnea, and tachycardia may be detected during clinical evaluation (7). Although chest radiography is usually sufficient for diagnosis; It is useful to perform computerized tomography to determine the degree of pneumomediastinum, to confirm whether pneumothorax is accompanied in the presence of widespread subcutaneous emphysema, and in suspicious cases when the diagnosis cannot be clearly made with chest radiography (6). After diagnosis, patients should be kept under observation in the hospital for at least 24 hours with bed rest, analgesia, oxygen support, if necessary, antibiotics to prevent mediastinitis, and chest radiography for follow up. Additionally, a chest tube should be applied in the presence of pneumothorax (7). Although angioedema and pneumomediastinum show serious similarities clinically, the most practical way to differentiate is to know that the lips are not swollen in pneumomediastinum and to feel subcutaneous crepitation when we touch the patient (8).

Pneumomediastinum is a serious clinical condition in addition to rib fracture and pneumothorax in patients with isolated thoracic trauma or multitrauma involving the thorax. Although it is easy to make a diagnosis in cases where widespread subcutaneous emphysema is observed immediately after trauma, it should not be forgotten that it may develop hours or days after the trauma and that the clinician may be misled by mentioning the patient's medicine use history, as in the case example. In the case example, although the chest X-ray taken on the first day does not show any obvious pathologies such as air density in the mediastinum, pneumothorax, rib fracture, when examined carefully, subcutaneous air density is seen near the neck (Figure Ia), and this is the information that can be used as a clue for doctors who works in centers without tomography. In such cases, seeing that the lips are not swollen and feeling subcutaneous crepitation, that is, examining the patient only with inspection and palpation, allows making the correct diagnosis within a few seconds.

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Unravelling the Complexity of Spleen Evaluation: A Critical Analysis of Ultrasonography Studies

Dalak Değerlendirmesinin Karmaşıklığının Çözülmesi: Ultrasonografi Çalışmalarının Eleştirel Bir Analizi

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Dear Editor,

I am writing to offer my opinion and reflection on the article titled "Evaluation of Spleen with Ultrasonography: Single Measurement or Volume Detection" authored by Olga Metin and Defne Gurbuz, published in Hitit Med J 2023;5(2): 90-94(1). The study presents a thorough investigation into the relationship between splenic dimensions and volume among patients attending gastroenterology outpatient clinics. While the study demonstrates methodological integrity and provides valuable insights, several areas merit critical examination.

The methodology employed in the study, which involved ultrasonographic measurements conducted by a single skilled radiologist, ensures consistency and reduces inter-observer variability. However, the sample size of 245 patients, while not insignificant, may limit the generalizability of the findings. This limitation is particularly notable given the exclusion of individuals with known conditions that may induce splenomegaly, narrowing the applicability of the results to a broader clinical population. The study's findings reveal significant correlations between splenic volume and factors such as height, weight, waist circumference, and body surface area (BSA), alongside a negative correlation with age. These results are consistent with existing literature, emphasizing the influence of anthropometric factors on splenic size (2). However, relying solely on correlation coefficients without deeper multivariate analysis could overlook potential confounding variables impacting these relationships.

Moreover, the observation of higher splenic volume in male patients compared to females, while aligning with some previous studies, lacks a comprehensive exploration of hormonal influences or lifestyle factors contributing to these differences. A more nuanced discussion on the biological underpinnings of gender disparities in splenic volume would strengthen the argument. The inverse relationship between splenic volume and age, though noteworthy, lacks exploration into the physiological mechanisms driving this change. An investigation into the role of aging on spleen functionality alongside volumetric changes would provide a more comprehensive understanding of the clinical implications of this finding. While the use of the prolate ellipsoid formula for calculating splenic volume is well-established, acknowledging the limitations of ultrasonography as an operator-dependent technique is crucial. Future research should compare these findings with measurements obtained via more operator-independent modalities like CT or MRI to validate the accuracy and consistency of ultrasonographic assessments (3).

The discussion on racial and ethnic differences in spleen size and volume is pertinent, yet the article could delve further into socioeconomic and environmental factors influencing these metrics (4). Considerations of variations in diet, physical activity, and access to healthcare would enrich the discussion. In summary, while the article provides valuable insights into the relationship between splenic volume and anthropometric factors, a deeper exploration of physiological, hormonal, and environmental influences is warranted. Additionally, expanding the study to include a larger and more diverse population, alongside comparisons with other imaging modalities, would enhance the robustness and applicability of the findings.

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Response From Editor:

The spleen plays a critical role in maintaining overall health. It is mobile and its shape and position vary considerably among healthy individuals, which can complicate accurate measurement of its size and the interpretation of splenic conditions on different imaging modalities. Splenic size may differ depending on age, gender, body mass index, and racial differences. Metin & Gurbuz investigated the relationship between splenic dimensions and volume among patients attending gastroenterology outpatient clinics and concluded that splenic volume measurements correlated with width of spleen, and decreased with age, and was correlated with body surface area and weight. And herein, Sakarie Mustafe Hidig pointed out some potential confounding factors which might impact these relationships; mainly the sample size, need of deeper multivariate analysis, potential effects of hormonal influences, lifestyle, socioeconomic and environmental factors. Ultrasound is a non-invasive, low-cost method for assessing the spleen without ionizing radiation, capable of detecting various abnormalities. However, defining standards for spleen via sonography is challenging. This study of Metin & Gurbuz and fine contribution of Sakarie Mustafe Hidig will guide to the design of future prospective, multicenter, randomized, robust studies.

Ass. Prof. Dr. Tolga Düzenli (Editor of HMJ)