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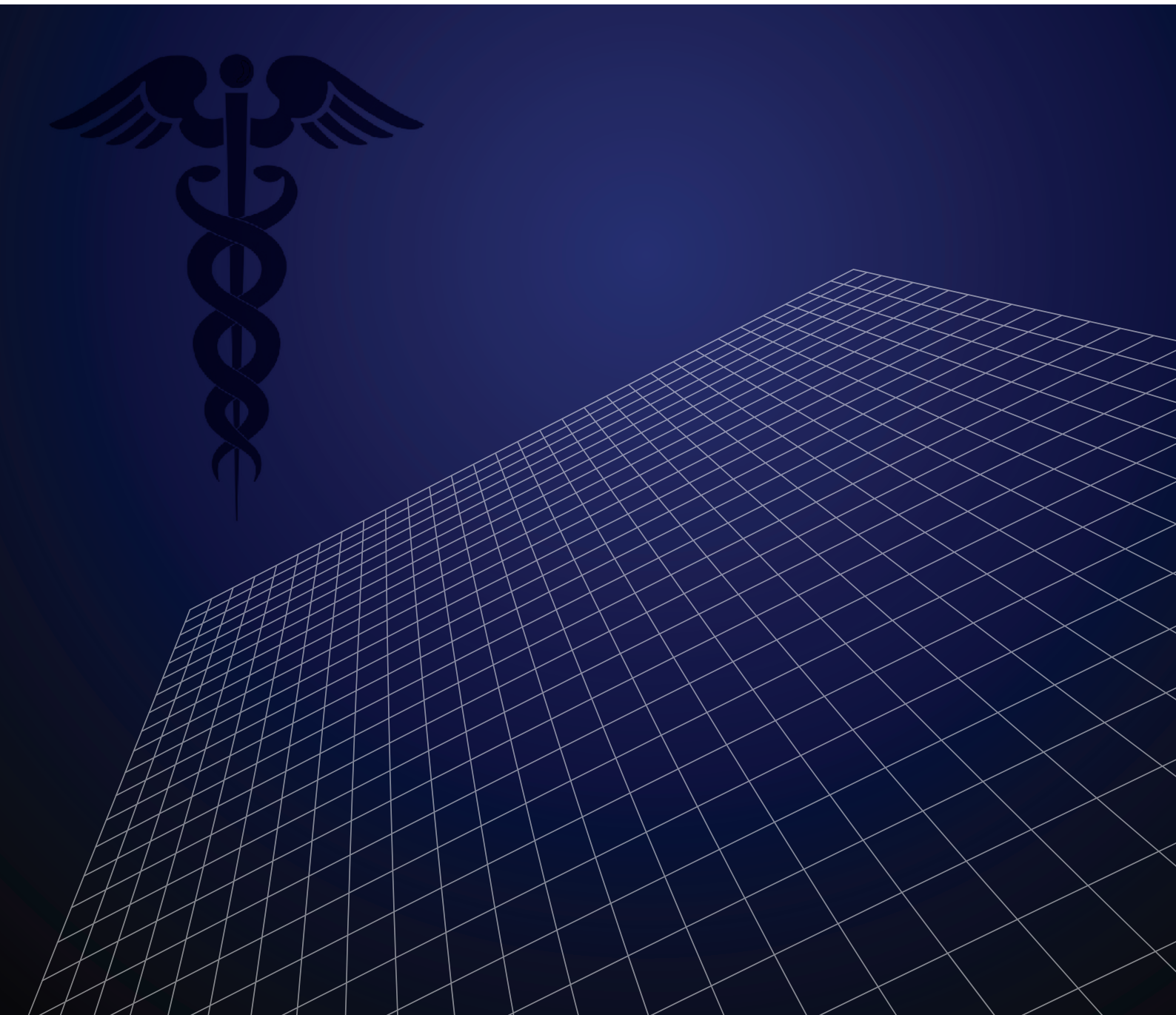

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To cite this article: Cabuk G, Cabuk AK. Efficacy and safety of Angio-Seal™ VIP vascular closure device compared to manual compression for access site hemostasis in patients who underwent antegrade common femoral artery puncture for popliteal and/or below the knee intervention. Turk J Clin Lab 2025; 2: 240-245.

Research Article

Efficacy and safety of Angio-Seal™ VIP vascular closure device compared to manual compression for access site hemostasis in patients who underwent antegrade common femoral artery puncture for popliteal and/or below the knee intervention

Angio-Seal™ VIP vasküler kapama cihazının, popliteal ve/veya diz altı müdahale için antegrad femoral arter ponksiyonu yapılan hastalarda girişim yeri hemostazı için etkililik ve güvenliği açısından manuel kompresyon ile karşılaştırılması

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Abstract

Aim: Antegrade common femoral artery puncture has become the preferred method for popliteal and below-the-knee interventions. There has been an increasing use of vascular closure devices aimed at reducing hospital stays and enhancing patient comfort. This study aimed to evaluate the efficacy and safety of the Angio-Seal™ VIP vascular closure device compared to manual compression for access site sealing in patients with popliteal and/or below-the-knee disease who underwent antegrade common femoral artery puncture.

Material and Methods: A total of 104 patients who underwent revascularization through antegrade common femoral artery puncture were randomly assigned to two groups based on the technique used for access site sealing: Angio-Seal™ VIP (n = 52) and manual compression (n = 52). The effectiveness of the two methods and the duration of hospitalization for both groups were analyzed. Complication rates were assessed during hospitalization and at a 3-month follow-up.

Results: Successful access site hemostasis without complications was achieved in 48 of 52 patients (92.30%) in the Angio-Seal™ VIP group and in 47 of 52 patients (90.38%) in the manual compression group (p = 0.42). Major complication rates did not differ between the Angio-Seal™ VIP (3.84%) and manual compression groups (3.84%, p = 1.00). However, the duration of hospitalization was significantly shorter in the Angio-Seal™ VIP group (10.4 hours vs. 28.6 hours, p = 0.03).

Conclusions: The Angio-Seal™ VIP device demonstrated safety and effectiveness comparable to manual compression for achieving hemostasis at the access site in patients undergoing antegrade common femoral artery puncture and was associated with a shorter duration of hospitalization.

Keywords: vascular closure device, antegrade, femoral, hemostasis

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Öz

Amaç: Antegrad femoral arter ponksiyonu, popliteal ve diz altı müdahaleler için tercih edilen yöntem haline gelmiştir. Hastanede kalış sürelerini azaltmayı ve hasta konforunu artırmayı amaçlayan vasküler kapatma cihazlarının kullanımı giderek artmaktadır. Bu çalışmanın amacı, popliteal ve/veya diz altı hastalığı olan ve antegrad femoral arter ponksiyonu yapılan hastalarda, girişim yeri hemostazının sağlanmasında, Angio-Seal™ VIP vasküler kapatma cihazının etkililiği ve güvenliğini manuel kompresyon ile karşılaştırmaktır.

Gereç ve Yöntemler: Antegrad femoral arter ponksiyonu ile revaskülarizasyon yapılan toplam 104 hasta, girişim yeri kapatma tekniğine dayanarak rasgele iki gruba atanmıştır: Angio-Seal™ VIP (n = 52) ve manuel kompresyon (n = 52). Her iki grup için yöntemlerin etkinlikleri ve hastaların hastanede kalış süreleri analiz edilmiştir. Komplikasyon oranları, hastanede yatış süresince ve 3 aylık takipte değerlendirilmiştir.

Bulgular: Angio-Seal™ VIP grubundaki 52 hastadan 48'inde (%92,30) komplikasyonsuz başarılı girişim yeri hemostazı sağlanmışken, manuel kompresyon grubundaki 52 hastadan 47'sinde (%90,38) bu başarı elde edilmiştir (p=0,42). Majör komplikasyon oranları Angio-Seal™ VIP (%3,84) ve manuel kompresyon grupları arasında (%3,84, p = 1,00) farklılık göstermemiştir. Ancak, hastanede kalış süresi Angio-Seal™ VIP grubunda belirgin şekilde daha kısa bulunmuştur (10,4 saate kıyasla 28,6 saat, p = 0,03).

Sonuçlar: Angio-Seal™ VIP cihazı, antegrad femoral arter ponksiyonu yapılan hastaların girişim yerinde hemostaz sağlamada, manuel kompresyon ile karşılaştırılabilir güvenlik ve etkinlik göstermiş ve daha kısa hastanede kalış süresi ile ilişkili bulunmuştur.

Anahtar Kelimeler: vasküler kapatma cihazı, antegrad, femoral, hemostaz

Introduction

The femoral artery is the most commonly preferred access site for popliteal and below-the-knee (BTK) endovascular interventions. While some operators favor a retrograde puncture with a crossover approach from the contralateral limb, others prefer an antegrade puncture of the common femoral artery (CFA) in appropriate cases due to several advantages, including improved pushability and support, as well as a shortened distance between the puncture site and the target lesion. The antegrade approach is particularly recommended when the operator needs to access the foot arteries for procedural success.

Manual compression and the use of vascular closure devices (VCDs) are the most commonly utilized methods for effectively sealing the arterial access site following an endovascular procedure. Several clinical trials have evaluated the effectiveness and safety of vascular closure devices for this purpose, demonstrating favorable outcomes [1-5]. The primary objectives of using these devices include reducing hospital stays, minimizing access site complications, and facilitating earlier patient mobilization. The fact that the type of anesthesia technique used can affect patients' length of hospital stay and the frequency of procedure-related complications underscores the importance of the hemostasis technique applied at the site of the intervention [6].

The Angio-Seal™ VIP is a plug-based VCD, and comprehensive data have supported its use regarding efficacy and safety in patients undergoing retrograde and antegrade CFA puncture site hemostasis. However, there is a lack of literature comparing conventional methods with Angio-Seal™ VIP for access site sealing, complications, and duration of hospitalization in patients with an antegrade CFA approach. Therefore, the aim of this study was to address this gap in the literature to some extent.

We compared the efficacy and safety of Angio-Seal™ VIP with manual compression for access site sealing in patients who underwent endovascular popliteal and/or BTK interventions through ipsilateral antegrade CFA access.

Material and Methods

Patient population

Over a 24-month period from 2022 to 2024, 93 out of 104 patients (64 male, 61.53%; age range 32-89 years) diagnosed with critical limb ischemia (n = 36) and Rutherford class 5/6 (n = 57), along with seven patients diagnosed with severe claudication unresponsive to medical/exercise therapy, underwent endovascular intervention via antegrade CFA access. Among all participants, four patients were primarily diagnosed with Buerger's disease. Seventy-eight patients (72.11%) had diabetes mellitus, and 14 patients had chronic

kidney disease (13.46%). Manual compression was performed in 52 patients, and Angio-Seal™ VIP VCD was applied in 52 patients for access site hemostasis. A total of 216 patient records were retrospectively matched by age, gender, BMI, risk factors, and Rutherford classification. We included 52 patients in each group from a total of 128 matched patients, randomly selected using a computer-based program that generates random numbers from those assigned to each patient. The sample size was calculated a priori using G-power software with 80% power and a 0.05 type I error rate. Our study received approval from the local ethics committee of Izmir City Hospital (2024/178) and was conducted in accordance with the Helsinki Declaration.

Study design and device deployment

This was a retrospective matched cohort study. Patients who underwent antegrade CFA puncture for endovascular intervention of popliteal and/or BTK disease were enrolled, and all variables associated with safety and efficacy were evaluated based on data taken from the database we carefully maintained.

All procedures were performed by a single operator with experience in over 200 cases of antegrade CFA puncture. A 6Fr vascular sheath (Terumo™) was used in all cases. Participants were evaluated using Doppler ultrasound and computed tomography angiography prior to the procedure. Fluoroscopic guidance, along with previously obtained information from CT angiography to determine the location of the bifurcation level, and Doppler ultrasound guidance were used in combination for the CFA puncture.

The Angio-Seal™ VIP device (St. Jude Medical, Minnetonka, MN, USA) consists of a polylactide/polyglycolide anchor, a collagen plug, and a suture contained within a specialized carrier system. When introduced, it achieves hemostasis by compressing the arterial puncture site between the anchor and the collagen plug. The device was deployed in accordance with the manufacturer's instructions but in an antegrade fashion. Patients with severe (>50%) proximal superficial femoral artery (SFA) disease and/or moderate to heavily calcified (graded by fluoroscopy and CT angiography) stenotic CFA, as well as those with a bypass graft at the puncture site, were excluded from the study.

The efficacy of closure with Angio-Seal™ VIP was defined by the device's ability to provide adequate hemostasis at the arterial puncture site without complications. After each successful device deployment, the access site was manually compressed for two minutes. For patients who did not receive Angio-Seal™ VIP, manual compressions were performed by the operator for a minimum of 15 minutes, starting four hours after the last intra-arterial heparin bolus, to achieve hemostasis. Patients were instructed to remain on bed rest for one hour and four hours following groin hemostasis in the Angio-Seal™ VIP and manual compression groups, respectively. An additional 2 kg sandbag was placed at the puncture site for three hours in the manual compression group. A nurse checked each patient's groin and pulses at 15 minutes, as well as at the 1st and 3rd hours after transferring them from the catheter laboratory to their beds. Patients in both the Angio-Seal™ group and the manual compression group were discharged promptly, barring any complications.

Complications were categorized as minor or major [6]. Minor complications included bleeding from the puncture site that did not require transfusion, hematomas ≤5 cm in diameter, and pseudoaneurysms that responded to ultrasound-guided manual compression. Major complications included hematomas >5 cm in diameter, bleeding requiring transfusion, pseudoaneurysms that did not respond to ultrasound-guided manual compression and required surgical intervention or percutaneous coil/thrombin embolization, arteriovenous fistula, retroperitoneal hemorrhage, plug embolism, groin infection, and vascular injury resulting in acute limb ischemia.

Patients were followed clinically and evaluated with Doppler ultrasound at one week and one month post-discharge.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 (SPSS, Chicago, IL, USA). The Kolmogorov-Smirnov test was utilized to assess the normal distribution of datasets. Categorical variables are expressed as numbers and percentages, while continuous variables are presented as mean ± standard deviation (SD) for normally distributed data and as median with interquartile ranges (25th–75th quartiles) for nonparametric data. The significance of differences between the two groups was evaluated, with two-tailed P values of <0.05 considered statistically significant.

Results

Baseline clinical characteristics of the two patient populations were similar (Table 1). The Angio-Seal™ VIP vascular closure device (VCD) was successfully deployed in all patients (100%). Successful access site hemostasis without complications was achieved in 48 of 52 patients (92.30%) in the Angio-Seal™ VIP group and in 47 of 52 patients (90.38%) in the manual compression group (p = 0.23).

Table 1. Baseline characteristics of study population. BMI; body mass index, CKD; chronic kidney disease.

Parameters		Angio-Seal™ VIP Group (n=52)	Manual Compression Group (n=52)	P value
Male (n, %)		33 (63.46%)	31 (59.61%)	0.09
Age (mean, range)		56.2 (±11.62)	57.6 (±12.08)	0.66
Diabetes mellitus (n, %)		37 (71.15%)	38 (73.07%)	0.12
Hypertension (n, %)		27 (51.92%)	23 (44.23%)	0.08
Dyslipidemia (n, %)		22 (42.30%)	24 (46.15%)	0.16
Smoking (n, %)		25 (48.07%)	27 (51.92%)	0.34
BMI (kg/m2) (mean, range)		24.2 (±3.62)	25.6 (±4.76)	0.82
CKD (n, %)		8 (15.38%)	6 (11.53%)	0.09
Rutherford classication (n, %)	3	3 (5.76%)	4 (7.69%)	0.15
	4	19 (36.53%)	17 (32.69%)	0.09
	5	16 (30.76%)	18 (34.61%)	0.22
	6	12 (23.07%)	11 (21.15%)	0.88
Buerger's disease (n, %)		2 (3.84%)	2 (3.84%)	1.00

In the Angio-Seal™ VIP group, three patients (5.76%) required extended manual compression (3 to 5 minutes) after deployment due to oozing from the puncture site; one patient (1.92%) developed a pseudoaneurysm that was treated with ultrasound-guided manual compression; one patient (1.92%) experienced a minor hematoma; one patient (1.92%) developed an arteriovenous fistula that was managed with a graft stent due to the patient's high surgical risk; and one patient (1.92%) had a major hematoma that required three units of blood transfusion and was clinically monitored, resolving within one week without surgical intervention. In the manual compression group, one patient (1.92%) had a minor hematoma; two patients (3.84%) developed pseudoaneurysms treated with thrombin embolization, while another pseudoaneurysm responded to external compression; and one patient (1.92%) experienced a major hematoma that necessitated surgery (Table 2).

The mean hospital stay was 10.4 hours for the Angio-Seal™ VIP group compared to 28.6 hours for the manual compression group (p = 0.03) (Table 2). No adverse events were reported during the 3-month follow-up period in either group.

Table 2. Main findings, complications, and duration of hospitalization of the study groups.

	Angio-SealTM VIP group (n=52)	Manual compression group (n=52)	p
Success rate of access site hemostasis (without complications) (n,%)	48 (92.30%)	47 (90.38%)	0.42
Major complications			
Hematoma >5cm or bleeding requiring blood transfusion (n,%)	1 (1.92%)	1 (1.92%)	
Pseudoaneurysm (needing for surgery) (n,%)	-	1 (1.92%)	
Arteriovenous fistula (n,%)	1 (1.92%)	-	
Total (n,%)	2 (3.84%)	2 (3.84%)	1.00
Minor complications			
Hematoma ≤5cm or bleeding not requiring blood transfusion (n,%)	1 (1.92%)	1 (2.77%)	
Pseudoaneurysm (responds to manual compression) (n,%)	1 (1.92%)	2 (3.84%)	
Total (n,%)	2 (3.84%)	3 (5.76%)	0.35
Duration of hospitalization (hours) (mean, range)	10.4 (±3.8)	0.6 (±6.7)	0.03

Discussion

Traditionally, contralateral CFA puncture with an "up and over" approach has been the preferred access for endovascular lower limb interventions. However, antegrade access has become increasingly common to mitigate the challenges associated with contralateral access, such as pushability, backup, torque control, and reaching the target site, especially in patients with popliteal and/or BTK disease [7,8]. Antegrade puncture of the ipsilateral CFA is generally preferred for popliteal and/or BTK interventions, provided the puncture site is not heavily calcified or stenotic. Nevertheless, antegrade puncture is technically more challenging than retrograde puncture and requires a longer learning curve.

VCDs have been widely adopted for access site sealing by many operators over the past two decades, providing immediate hemostasis without the need for external compression and prolonged bed rest. While vascular closure devices have been the standard for access site hemostasis in retrograde CFA punctures, their use for antegrade puncture site hemostasis has increased over the past decade [1-5].

Angio-Seal™ VIP, utilized in our study, is one of the most widely preferred VCDs due to its simple design, efficacy, and safety profile. Growing evidence in the literature encourages operators to adopt this device for antegrade CFA access site sealing. Numerous studies [9-14] have demonstrated its efficacy and safety in retrograde CFA puncture site sealing; however, several studies [1,5,7,16,17] have evaluated this VCD's use in antegrade approaches, with data primarily derived from retrospective analyses.

Lupattelli et al. [18] conducted a retrospective analysis of their data and found no statistically significant differences in overall complications between antegrade and retrograde CFA puncture site sealing using Angio-Seal™ VCD and manual compression (2.5%, 4.0%, and 4.5%, respectively). Lobby et al. [16] also reported no major complications associated with the use of Angio-Seal™ VCD in 58 patients undergoing antegrade CFA puncture. They performed manual compression instead of VCD in 7 patients due to severe CFA calcification at the puncture site, failure of device deployment in 4 patients, and one patient with superficial femoral artery dissection. In our study, we excluded patients with moderate to severe calcification at the puncture site, making this a non-determinant factor for access site hemostasis success or failure.

In a prospective trial, Minko et al. [15] identified obesity (BMI: 26.6 vs 28.8 kg/m^2, p = 0.04) as an independent risk factor for inadequate sealing with Angio-Seal™ VCD. Although this parameter was not analyzed in our study, the mean BMI was similar across both groups (Table 1). However, they [15] did not compare the efficacy and safety of this VCD with extrinsic compression as the conventional method in their investigation.

A meta-analysis [19] indicated that Angio-Seal™ VCD was non-inferior (and possibly favored) compared to manual compression concerning complications. Odds ratios (ORs) for hematoma events were 0.86 (95% CI 0.51–1.45, p = 0.78), for pseudoaneurysms 0.30 (95% CI 0.04–2.07, p = 0.93), for ischemic complications 0.80 (95% CI 0.22–2.94, p = 0.58), and for the need for surgery 0.83 (95% CI 0.18–3.85, p = 0.53). The analysis of total complications using Angio-Seal™ compared with manual compression also revealed no significant differences between the two groups (OR 0.84, 95% CI 0.53–1.34, p = 0.49). This meta-analysis [19] included a prospective randomized trial [20] which also determined that Angio-Seal™ was safe and effective compared to manual compression in terms of complications, additionally allowing for shorter hemostasis times. However, the trial [20] only included procedures involving retrograde femoral puncture.

A recent retrospective single-center study [21] reported a complication rate of 0.47% (46 of 9,754 cases) after VCD implantation, with complications ranging from claudication (n = 24) to acute limb ischemia (n = 19) and major bleeding (n = 3). They [21] found that female gender and diabetes mellitus were associated with major vascular complications. In our study, no major vascular complications such as acute limb ischemia, subsequent limb loss, or retroperitoneal hemorrhage were observed.

Limitations of the study

We did not analyze the cost-effectiveness of using Angio-Seal™ VIP; however, the shorter hospital stay demonstrated in both the literature and our study represents a significant factor in reducing costs [22]. Our sample size was relatively small due to the study being conducted at a single center over a limited time period, highlighting the need for further investigation into this device's efficacy and safety in larger cohorts. Additionally, patients with CKD and those classified as Rutherford class 6 were statistically different between the two groups. However, we believe this discrepancy may have resulted from simple randomization in our relatively small sample size and is unlikely to have influenced our results.

In conclusion the Angio-Seal™ VIP device proved to be a safe and effective method for access site hemostasis compared to manual compression in patients undergoing antegrade CFA puncture for endovascular popliteal and/or below-the-knee interventions, resulting in a significantly shorter duration of hospitalization in the Angio-Seal™ VIP group.

Declaration of conflicting interests

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

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Ethics approval

This study was approved by Izmir City Hospital Ethics Committee with protocol number 2024/178.

Authors' contribution

GÇ: developed the study concept, collected patient data, conducted the literature review, and performed the statistical analyses. AÇ: carried out all procedures and reviewed the final version of the manuscript. Both authors contributed to all stages of the study and share joint responsibility for the final manuscript.

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Research Article

Treatment satisfaction in erpidermolysis bullosa patients: the impact of demographic and clinical factors

Epidermolizis bülloza hastalarında tedavi memnuniyeti: demografik ve klinik faktörlerin etkisi

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Abstract

Aim: Epidermolysis bullosa (EB) is a hereditary disease which causes skin and mucous membrane blistering. While both standard and multidisciplinary care approaches exist for managing EB, the impact of care type on treatment outcomes remains incompletely understood, particularly across different EB subtypes. To compare treatment satisfaction and quality of life outcomes between standard versus multidisciplinary care approaches in pediatric EB patients, and to identify key demographic and clinical factors influencing these outcomes.

Material and Methods: This retrospective study evaluated 32 pediatric EB patients (age <16 years) receiving either multidisciplinary care (n = 18) or standard care (n = 14). Multidisciplinary care involved coordinated management by dermatologists, wound care specialists, pain management experts, psychologists and dedicated nurses, while standard care consisted of routine outpatient follow-up. Treatment outcomes were assessed using the validated Epidermolysis Bullosa Quality of Life (EB-QoL) scale at baseline and 6 months. Statistical analysis included repeated measures ANOVA, independent t-tests, and multiple regression analysis, with Levene's test confirming variance homogeneity.

Results: While baseline EB-QoL scores were comparable (44.8 ± 8.1 vs 45.2 ± 7.8, p = 0.876), the multidisciplinary care group showed significantly higher scores at 6 months (68.4 ± 9.2 vs 52.3 ± 8.7, p = 0.003). The magnitude of improvement varied by EB subtype, with Simplex patients showing the largest gains (baseline: 60.4 ± 7.2, 6-month: 71.2 ± 8.4) and Dystrophic patients the smallest (baseline: 38.6 ± 6.8, 6-month: 45.3 ± 7.8). Multiple regression analysis identified age (β = 0.324), BMI (β = 0.195), and multidisciplinary care (β = 0.468) as positive predictors of satisfaction, while disease duration (β = -0.286) and comorbidities (β = -0.245) had negative effects.

Conclusions: Multidisciplinary approaches to pediatric EB patients benefited from comprehensive care models. These results banner the magnitude of benefit, which relies heavily on skeletal structure. The severity of treatment outcomes was noticeably improved through the effect of structured multidisciplinary care. Each sub-type of EB affliction had improved treatment results but each diverged in the level of gain, which further enhances the need for individual tailored treatment protocols based on EB subtype classification and other parameters.

Keywords: epidermolysis bullosa, pediatric patients, multidisciplinary care, quality of life, psychosocial support

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Öz

Amaç: Epidermolizis bülloza (EB), deri ve mukoza zarında büllere neden olan kalıtsal bir hastalıktır. EB'nin yönetiminde hem standart hem de multidisipliner bakım yaklaşımları mevcut olmakla birlikte, bakım türünün tedavi sonuçları üzerindeki etkisi, özellikle farklı EB alt tipleri arasında tam olarak anlaşılamamıştır. Pediatrik EB hastalarında standart bakım ile multidisipliner bakım yaklaşımları arasındaki tedavi memnuniyeti ve yaşam kalitesi sonuçlarını karşılaştırmak ve bu sonuçları etkileyen temel demografik ve klinik faktörleri belirlemek.

Gereç ve Yöntem: Bu retrospektif çalışmada multidisipliner bakım (n = 18) veya standart bakım (n = 14) alan 32 pediatrik EB hastası (yaş <16) değerlendirildi. Multidisipliner bakım; dermatologlar, yara bakım uzmanları, ağrı yönetimi uzmanları, psikologlar ve özel hemşirelerden oluşan koordineli bir ekip tarafından sağlanırken, standart bakım rutin poliklinik takibinden oluşmaktaydı. Tedavi sonuçları, başlangıçta ve 6. ayda valide edilmiş Epidermolizis Bülloza Yaşam Kalitesi (EB-QoL) ölçeği kullanılarak değerlendirildi. İstatistiksel analizde tekrarlı ölçümler ANOVA, bağımsız örneklem t-testleri ve çoklu regresyon analizi kullanıldı, varyans homojenliği Levene testi ile doğrulandı.

Bulgular: Başlangıç EB-QoL skorları benzerken (44,8 ± 8,1 vs 45,2 ± 7,8, p = 0,876), multidisipliner bakım grubu 6. ayda anlamlı olarak daha yüksek skorlar gösterdi (68,4 ± 9,2 vs 52,3 ± 8,7, p = 0,003). İyileşme düzeyi EB alt tiplerine göre değişkenlik gösterdi; Simpleks hastalar en yüksek artışı (başlangıç: 60,4 ± 7,2, 6.ay: 71,2 ± 8.4), Distrofik hastalar en düşük artışı (başlangıç: 38,6 ± 6,8, 6.ay: 45,3 ± 7,8) gösterdi. Çoklu regresyon analizinde yaş (β = 0,324), VKİ (β = 0,195) ve multidisipliner bakım (β = 0,468) memnuniyetin pozitif belirleyicileri olarak saptanırken, hastalık süresi (β = -0,286) ve komorbiditeler (β = -0,245) negatif etki gösterdi.

Sonuçlar: Bulgularımız, yapılandırılmış multidisipliner bakımın tüm EB alt tiplerinde pediatrik hastaların tedavi sonuçlarını önemli ölçüde iyileştirdiğini, ancak faydanın hastalık şiddetine göre değiştiğini göstermektedir. Bu sonuçlar, EB alt tipi ve hasta özelliklerine göre bireyselleştirilmiş tedavi protokolleri içeren kapsamlı bakım programlarının uygulanmasını desteklemektedir.

Anahtar Kelimeler: epidermolizis bülloza, pediatrik hastalar, multidisipliner bakım, yaşam kalitesi, psikososyal destek

Introduction

Epidermolysis bullosa (EB) is a rare genetic disease characterized by skin and mucous membrane blistering due to mechanical trauma. The condition manifests in four main subtypes based on subcutaneous separation level and genetic mutation: EB Simplex, Junctional EB, Dystrophic EB, and Kindler syndrome [1,2]. EB profoundly impacts both physical and psychosocial quality of life, with patients requiring continuous wound care and experiencing significant pain management challenges [3,4].

Treatment approaches for EB typically fall into two categories: standard care and multidisciplinary care. Standard care involves routine outpatient follow-up with primary treating physicians, focusing on basic wound management and symptom control. On the other hand, multidisciplinary care allows treatment to be provided by a team of professionals which includes dermatologists, pain specialists, wound care nurses and psychologists. This type of team work consists of organized strategies for wound care, pain alleviation, and psychosocial aid [5,6]. The economic burden of EB management, particularly in severe dystrophic cases, poses substantial challenges for both families and healthcare systems, with ongoing wound care supplies representing a significant expense [7].

While the superiority of multidisciplinary care is generally accepted, quantitative evidence comparing outcomes between standard and multidisciplinary approaches remains limited. Furthermore, the differential responses of EB subtypes to these care approaches have not been systematically evaluated. This study aims to address these knowledge gaps by: first comparing quality of life outcomes between standard and multidisciplinary care approaches, second, analysing the impact of EB subtypes on treatment response, and third identifying key demographic and clinical factors that influence treatment satisfaction.

Previous research has extensively documented EB's genetic and clinical diversity. However, studies examining the role of comprehensive care models in patient outcomes remain scarce. While caregivers consistently report limited educational and professional opportunities, the mechanisms underlying these challenges are not fully understood [8,4]. Current treatment approaches predominantly focus on symptom management, with limited comparative analysis of

subtype-specific responses [9,5]. Recent advances in wound management and complication control show promise, but longitudinal outcome data remain insufficient [10,8].

The investigation, in this particular case, analyses how the care approach (standard versus multidisciplinary) impacts treatment satisfaction and quality of life across selected EB subtypes. Through consideration of these relationships together with relevant demographic and clinical information, we hope to propose criteria for improving EB patient care. Understanding these associations is crucial for establishing standardized care protocols and improving treatment outcomes in this challenging patient population.

Materials and Methods

This study was conducted in the Plastic Surgery Clinic of Şanlıurfa Metrolife Hospital, evaluating pediatric patients diagnosed with epidermolysis bullosa (EB). A total of 32 consecutive patients were enrolled, with 18 receiving multidisciplinary care and 14 receiving standard care. Multidisciplinary care encompassed coordinated wound management, pain control, and psychosocial support provided by a dedicated team of specialists, while standard care consisted of routine outpatient follow-up with primary treating physicians. After obtaining consent, participants were actively informed about study procedures.

Inclusion criteria specified participants below 16 years of age with clinical and genetic confirmation of EB, who had received treatment within the past six months. Both patient assent and parental/legal guardian consent were required. Exclusion criteria included uncontrolled systemic diseases, severe psychiatric disorders, surgical procedures other than EB in the last 6 months, and refusal to participate.

Questionnaires were administered age-appropriately under parental supervision. The study protocol was deemed ethically appropriate given its observational nature, approved care pathways, and comprehensive outcome assessment. The study adhered to Declaration of Helsinki principles and received Eskişehir City Health Practice and Research Center institutional ethics approval (Date: 17/10/2024, No: ESH/BAEK 2024/50).

Study design

This study was designed as a retrospective observational study. While randomization was not feasible due to the retrospective nature and care patterns being determined by standard clinical practice, we carefully evaluated group comparability through statistical analysis of baseline characteristics and EB subtype distribution. The ethics committee approved this design given the observational nature and absence of intervention allocation.

Measurement and calculation methods

Patient outcomes were assessed using the validated Turkish version of the Epidermolysis Bullosa Quality of Life (EB-QoL) scale, which evaluates physical symptoms, psychosocial impact, and treatment satisfaction. Measurements were conducted at baseline, 1 month, 3 months, and 6 months to track longitudinal changes. The scale demonstrates good internal consistency (Cronbach's α=0.89) and test-retest reliability (ICC=0.92).

Statistical Analysis

Data were analyzed using SPSS v25 software. Normality was assessed using Shapiro-Wilk test, while homogeneity of variances was confirmed through Levene's test. Between-group comparisons employed independent sample t-tests for continuous variables and chi-square tests for categorical data. Longitudinal changes were evaluated using repeated measures ANOVA. One-way ANOVA with post-hoc Tukey tests examined subtype differences. Multiple regression analysis assessed predictor effects, with model diagnostics including variance inflation factors, residual normality, and homoscedasticity tests.

Results

The mean age of pediatric epidermolysis bullosa (EB) patients was 8.4 ± 4.2 years, with comparable distribution between multidisciplinary and standard care groups (8.2 ± 4.0 vs 8.6 ± 4.4 years, p=0.786). Female patients predominated in both groups (61.1% vs 57.1%, p=0.654), comprising 59.4% of the total study population. Among disease subtypes, EB Simplex was most prevalent (43.8%), followed by Junctional EB (25.0%), Dystrophic EB (21.9%), and Kindler syndrome (9.3%), with similar distribution between care groups (p=0.892). Half of the participants (50.0%) were primary school students, while 37.5% were in preschool and 12.5% in secondary school, showing comparable educational levels between groups (p=0.945). Disease duration averaged 6.2 ± 3.8 years and was similar between groups (p=0.823). Common comorbidities included anemia (25.0%), malnutrition (18.8%), and contractures (15.6%), with no significant differences between care groups (p>0.05 for all). The mean body mass index (BMI) was 16.8 ± 2.4 kg/m^2, showing comparable values between multidisciplinary and standard care groups (16.6 ± 2.2 vs 17.0 ± 2.6 kg/m^2, p = 0.645) (Table 1).

Table 1. Demographic and clinical characteristics by type of care (n=32).				
Characteristic	Total (n=32)	Multidisciplinary care (n=18)	Standard care (n=14)	p-value
Age (years)	8.4 ± 4.2	8.2 ± 4.0	8.6 ± 4.4	0.786
Gender				0.654
- Female	19 (59.4)	11 (61.1)	8 (57.1)	
- Male	13 (40.6)	7 (38.9)	6 (42.9)	
EB Subtypes				0.892
- EB Simplex	14 (43.8)	8 (44.4)	6 (42.9)	
- Junctional EB	8 (25.0)	4 (22.2)	4 (28.6)	
- Dystrophic EB	7 (21.9)	4 (22.2)	3 (21.4)	
- Kindler Syndrome	3 (9.3)	2 (11.1)	1 (7.1)	
Education level				0.945
- Preschool	12 (37.5)	7 (38.9)	5 (35.7)	
- Primary school	16 (50.0)	9 (50.0)	7 (50.0)	
- Secondary school	4 (12.5)	2 (11.1)	2 (14.3)	
Disease duration (years)	6.2 ± 3.8	6.0 ± 3.6	6.4 ± 4.0	0.823
Comorbidities				
- Anemia	8 (25.0)	5 (27.8)	3 (21.4)	0.678
- Malnutrition	6 (18.8)	3 (16.7)	3 (21.4)	0.724
- Contractures	5 (15.6)	3 (16.7)	2 (14.3)	0.856
BMI (kg/m^2)	16.8 ± 2.4	16.6 ± 2.2	17.0 ± 2.6	0.645
Values are presented as mean ± SD or n (%). P-values were calculated using independent t-test for continuous variables and Chi-square test or Fisher's exact test for categorical variables. SD = Standard Deviation				

While baseline EB-QoL scores were comparable between groups (44.8 ± 8.1 vs 45.2 ± 7.8, p = 0.876), patients receiving multidisciplinary care showed markedly higher scores at 6 months compared to standard care (68.4 ± 9.2 vs 52.3 ± 8.7, p = 0.003). The magnitude of improvement was substantially greater in the multidisciplinary group, with a mean change score of 23.6 ± 4.8 points versus 7.1 ± 3.2 points in standard care (p < 0.001). The positive impact of multidisciplinary care was further supported by repeated measures ANOVA (F = 28.45, p < 0.001), with a large effect size (Cohen's d = 0.86, 95% CI: 0.42-1.30). Notably, the homogeneity of variances was confirmed (Levene's test: F = 0.234, p = 0.632), strengthening the validity of these findings. The balanced distribution of EB subtypes between groups (p = 0.892) suggests that the observed differences in outcomes were attributable to the care approach rather than disease subtype (Table 2).

Table 2. Satisfaction scores by type of care and statistical analysis (n=32).			
Characteristics	Standard Care (n=14)	Multidisciplinary care (n=18)	Statistical tests
EB-QoL score			
Baseline (T0)	45.2 ± 7.8	44.8 ± 8.1	p=0.876[1]
6-month (T1)	52.3 ± 8.7	68.4 ± 9.2	p=0.003*[1]
Change score (T1-T0)	7.1 ± 3.2	23.6 ± 4.8	p<0.001*[1]
EB subtype distribution			
EB simplex	6 (42.9%)	8 (44.4%)	p=0.892[2]
Junctional EB	4 (28.6%)	4 (22.2%)	
Dystrophic EB	3 (21.4%)	4 (22.2%)	
Kindler Syndrome	1 (7.1%)	2 (11.1%)	
Statistical parameters			
Levene's test	F=0.234		p=0.632[3]
Effect size (Cohen's d)	0.86		95% CI: 0.42-1.30
Repeated measures ANOVA	F=28.45		p<0.001*
EB-QoL Score = Epidermolysis Bullosa Quality of Life Scale (scored 0–100). Values presented as mean ± SD or n (%). [1]Independent samples t-test. [2]Chi-square test. [3]Test for homogeneity of variances. *Statistically significant (p < 0.05). Effect size interpretation: >0.2 small, >0.5 medium, >0.8 large.			

Analysis by EB subtypes revealed distinct quality of life patterns across groups. The EB Simplex group demonstrated the highest baseline scores (60.4 ± 7.2) and achieved the most favorable 6-month outcomes (71.2 ± 8.4), particularly in the multidisciplinary care setting (77.1 ± 8.9 vs 65.3 ± 7.8, $p < 0.001$). Junctional EB patients showed intermediate improvement (baseline: 48.2 ± 8.1; 6-month: 58.7 ± 9.2), with significantly better outcomes under multidisciplinary care (65.0 ± 9.8 vs 52.4 ± 8.6, p=0.008). Dystrophic EB patients had the lowest initial scores (38.6 ± 6.8) and showed modest improvement (6-month: 45.3 ± 7.8), though still benefiting from multidisciplinary care (49.1 ± 8.4 vs 41.5 ± 7.2, p=0.012). Kindler syndrome patients (n=3) showed intermediate response patterns (baseline: 44.5 ± 7.4; 6-month: 52.8 ± 8.9). Post-hoc analysis confirmed significant differences between EB Simplex and other subtypes (vs Junctional: $p = 0.002$; vs Dystrophic: $p < 0.001$; vs Kindler: $p = 0.004$), while also revealing a significant difference between Junctional and Dystrophic EB ($p = 0.024$). No significant differences were found in other subtype comparisons ($p > 0.05$) (Table 3).

Table 3. EB-QoL scores by EB subtypes and type of care (n=32).

EB Subtype	Total	Standard care	Multidisciplinary care	Statistical analysis
EB Simplex (n=14)				
n	14	6	8	F = 12.36
Baseline Score	60.4 ± 7.2	59.8 ± 7.0	61.0 ± 7.4	p = 0.845[1]
6-month Score	71.2 ± 8.4	65.3 ± 7.8	77.1 ± 8.9	p < 0.001*[2]
Junctional EB (n=8)				
n	8	4	4	F = 8.92
Baseline Score	48.2 ± 8.1	47.9 ± 7.8	48.5 ± 8.4	p = 0.912[1]
6-month Score	58.7 ± 9.2	52.4 ± 8.6	65.0 ± 9.8	p = 0.008*[2]
Dystrophic EB (n=7)				
n	7	3	4	F = 7.45
Baseline Score	38.6 ± 6.8	38.2 ± 6.5	39.0 ± 7.1	p = 0.876[1]
6-month Score	45.3 ± 7.8	41.5 ± 7.2	49.1 ± 8.4	p = 0.012*[2]
Kindler Syndrome (n=3)				
n	3	1	2	F = 4.23
Baseline Score	44.5 ± 7.4	44.0	45.0 ± 7.8	p = 0.924[1]
6-month Score	52.8 ± 8.9	48.6	56.9 ± 9.0	p = 0.038*[2]

Post-hoc Analysis (Tukey HSD) Results: EB Simplex vs Junctional EB: p = 0.002*. EB Simplex vs Dystrophic EB: p < 0.001*. EB Simplex vs Kindler: p = 0.004*Junctional EB vs Dystrophic EB: p = 0.024*. Junctional EB vs Kindler: p = 0.456. Dystrophic EB vs Kindler: p = 0.382. Notes: Values presented as mean ± SD unless otherwise noted [1]Between groups at baseline (ANOVA) [2]Between groups at 6 months (ANOVA) Levene's test for homogeneity of variances: p = 0.724 *Statistically significant (p < 0.05) EB-QoL = Epidermolysis Bullosa Quality of Life Scale (scored 0-100)

Multiple regression analysis revealed significant influences of both demographic and clinical factors on EB-QoL satisfaction scores. The model demonstrated strong explanatory power (R^2=0.684, Adjusted R^2 = 0.652, $F = 18.42$, $p < 0.001$), with satisfactory diagnostic measures (Durbin-Watson = 1.96). Among primary factors, age showed a positive association ($\beta = 0.324$, $p = 0.007$), while disease duration had a negative impact ($\beta = -0.286$, $p = 0.006$). BMI demonstrated a modest positive effect ($\beta = 0.195$, $p = 0.031$). In clinical factors, multidisciplinary care emerged as the strongest positive predictor ($\beta = 0.468$, $p = 0.003$), while EB subtype severity ($\beta = -0.412$, $p = 0.005$) and presence of comorbidities ($\beta = -0.245$, $p = 0.014$) showed negative associations. All variables demonstrated acceptable multicollinearity levels (VIF < 2.0), and model assumptions were met (Normality: $p = 0.342$, Homoscedasticity: $p = 0.456$) (Table 4).

Quality of life scores of pediatric EB patients who participated in the study showed significant differences in different subtypes. It was determined that the EB Simplex group had the highest quality of life score, while the Dystrophic EB group had the lowest scores. These differences were especially significant between EB Simplex and other subtypes. The scores of the Junctional EB and Kindler syndrome groups were closer to each other (Figure 1).

Longitudinal analysis of EB-QoL scores revealed divergent trajectories between care groups. Starting from comparable baseline scores (multidisciplinary: 44.8 vs standard: 45.2), the multidisciplinary care group showed progressively greater improvements at each time point (1 month: $p = 0.024$; 3 months: $p = 0.003$; 6 months: $p = 0.001$). Despite minor attrition in both groups (multidisciplinary: 18 to 17 patients; standard: 14 to 13 patients), the multidisciplinary approach demonstrated consistently superior outcomes. The improvement gradient was particularly pronounced in the first three months, followed by sustained gains through the six-month endpoint. While patients receiving standard care showed modest improvement over time, the rate and magnitude of progress were substantially higher in the multidisciplinary care group. These findings provide compelling evidence for the enhanced therapeutic benefit of multidisciplinary care in managing EB patients (Figure 2).

Table 4. Multiple regression analysis of factors influencing EB-QoL satisfaction scores (n=32)

Model parameters	Value	Statistical significance	β Coefficient	Standard error	t-value	VIF	p-value
R^2	0.684	F = 18.42	—	—	—	—	—
Adjusted R^2	0.652	p < 0.001*	—	—	—	—	—
Durbin-Watson	1.96	—	—	—	—	—	—
Independent variables							
Primary factors							
Age	—	—	0.324	0.112	2.893	1.24	0.007*
Disease duration	—	—	-0.286	0.098	-2.918	1.18	0.006*
BMI	—	—	0.195	0.086	2.267	1.15	0.031*
Clinical factors							
EB subtype†	—	—	-0.412	0.142	-2.901	1.32	0.005*
Multidisciplinary care‡	—	—	0.468	0.156	3.000	1.28	0.003*
Presence of comorbidities	—	—	-0.245	0.094	-2.606	1.21	0.014*

Model Assumptions: Normality (Shapiro-Wilk): p = 0.342; Homoscedasticity (Breusch-Pagan): p = 0.456; Multicollinearity: All VIF < 2.0 Notes: Dependent Variable: EB-QoL Score (0-100); *Statistically significant (p < 0.05); †EB Subtype coded as: EB Simplex=1, Junctional=2, Dystrophic=3, Kindler=4; ‡Multidisciplinary care coded as: Yes=1, No=0; VIF = Variance Inflation Factor

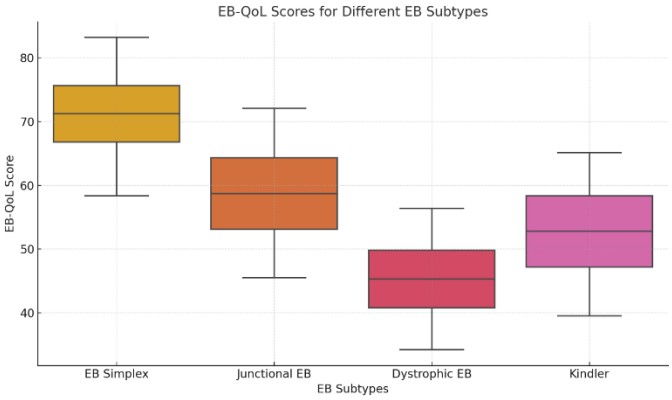

Figure 1. EB-QoL scores for different EB subtypes.

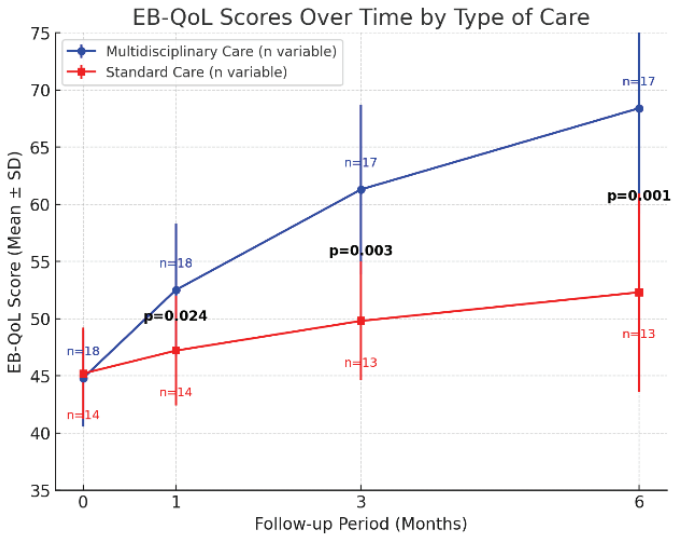

Figure 2. EB-QoL scores over time by type of care.

Discussion

Our study contributes to the knowledge of factors that affect the treatment satisfaction of young patients diagnosed with epidermolysis bullosa (EB). Our analysis has shown that the combination of multidisciplinary approach and psychosocial support considerably increases not only treatment satisfaction but the quality of life, and thus the necessity of individualized, integrated management is evident. As per our analysis, the subtypes of EB indicated a range of differences in quality of life scores along with clinical and demographic factors, which served as determinants of the outcome for the patients. This evidence gives clinicians' clear guidance on how to improve patient management and the treatment of EB as a whole.

Pediatric EB patients' quality of life has greatly benefited from such aspects and our analysis support this notion, which concurs with the existing literature asserting the need of multidisciplinary approach to wound care, complication control and psychosocial intervention. In their Italian reference center study, Retrosi et al demonstrated that a coordinated multidisciplinary team including dermatologists, pediatricians, endocrinologists, dieticians, dentists, plastic surgeons, digestive surgeons, geneticists, psychologists and dedicated nurses significantly improved EB treatment outcomes and increased patient satisfaction [11]. The differences in quality of life scores between EB subtypes may be explained by the diversity in the clinical course of the disease subtypes. In particular, the fact that the EB Simplex group had the highest quality of life scores was associated with the fact that this subtype had a milder disease profile. Polizzi et al, in their dental-focused study analysing oral manifestations, highlighted that a specialized dental care approach integrated within the overall treatment team was crucial for managing oral complications and improving quality of life in EB patients [12].

The strong effect of psychosocial support on treatment satisfaction and quality of life is also noteworthy in our findings. Thien et al showed that EB patients who received psychosocial support developed more effective coping mechanisms in their daily lives and this support increased treatment adherence [13]. Our findings reveal that a multidisciplinary approach is a critical tool in managing both the physical symptoms and psychosocial effects of EB. Data from the survey support the relevance of applying a multidisciplinary approach as well as an individual care strategy in EB treatment [14].

In our study, differences in quality of life scores between epidermolysis bullosa (EB) subtypes were clearly observed. The high quality of life scores observed in the EB Simplex group may be associated with the generally mild clinical picture of this subtype. The study by Bishnoi et al. also revealed that quality of life was less affected in EB Simplex patients compared to other subtypes [15]. In contrast, in more severe subtypes such as Dystrophic EB and Junctional EB, the increase in both physical and psychosocial burdens negatively affects quality of life. In a systematic review by Tang et al., it was reported that pain, nutritional deficiencies and chronic wounds were more prevalent in these groups and this situation had serious effects on quality of life [16].

It should also be highlighted that the aforementioned disparities in quality of life are a function of the clinical complications or the degree of access to treatment. In the study by Rogers et al., the effects of subtype-specific clinical complications on quality of life were emphasized [17]. In particular, contractures and chronic infections observed in dystrophic EB patients were found to affect the quality of life of this group more severely. These findings once again demonstrate the importance of personalized care strategies in the management of EB subtypes.

In our study, age, disease duration, BMI, and comorbidities were found to have significant effects on patient satisfaction. Decreased quality of life in individuals with longer disease duration reflects the long-term burden of a chronic disease. For example, as the disease duration increases in patients with epidermolysis bullosa, processes such as continuous renewal of skin and mucosal lesions, fibrosis, and inflammation negatively affect quality of life [18, 19]. However, it has been suggested that an increase in BMI provides better physical tolerance reflecting general health status and therefore contributes positively to quality of life [20]. Moreover, the presence of comorbidities (e.g., anemia or malnutrition) weakens the physical and psychological resilience of patients and decreases their overall satisfaction level [21].

In this study, the patients with epidermolysis bullosa (EB) who have received psychosocial support reported significantly greater increases in their quality of life and treatment satisfaction. This indicates that EB, being a chronic and rare disease, necessitates psychosocial support services. According to the literature, social support as well as good healthcare services help alleviate tensions and stress in patients and families, enhancing their life satisfaction. In particular, the effect of social support in reducing depression and improving quality of life may positively affect the mental health of these patients and caregivers [22]. In addition, satisfaction with health services has been consistently reported to be effective in reducing the depression level of caregivers [23]. However, parents of children with high dependency levels may not benefit sufficiently from support services due to the daily care burden [24,25].

When we compare the findings of our study with the results of similar studies in the literature, significant parallels are observed. Martin et al. (2019) showed that multidisciplinary care approach increased treatment satisfaction and quality of life in EB patients, and this finding supports the result that patients receiving multidisciplinary care in our study had higher EB-QoL scores [26]. In a study conducted by Angelis et al. (2016) in eight European countries, it was shown that patients' quality of life was significantly affected and this was associated with socioeconomic burden [27]. These findings explain the underlying reasons for the low quality of life scores in patients receiving standardised care in our study. In the comprehensive review by Chateau et al. (2023), the importance of the psychosocial effects of EB on both patients and caregivers was emphasised, which supports the importance of psychosocial support as a part of multidisciplinary care in our study [28]. In the qualitative study of Sangha et al. (2021), the difficulties experienced by EB patients in daily life, school and social interactions were examined in detail, and these findings explain the effects of age and disease duration on satisfaction that we found in our study [29].

In this context, families' relief service burden can be addressed by increasing their access to social resources and developing certain targeted programs.

However, the study design employed in this study, that is the retrospective one has its shortcomings. The incidence of information loss or inaccuracy that may result in data gaps negatively affects the precision of the results because data was

collected from recorded past events. Then again, to some extent, a retrospective review is not adequate to determine the cause and the effect. Consequently, the results should be taken cautiously in terms of causation and causality issues. Moreover, patient data came from a single site, therefore, the effects of the intervention as well as care standards exercised in other sites could not be compared to theirs. Additionally, more advanced multicenter studies will still be necessary to comprehend the full range of the psychosocial support and the multidisciplinary care services. Nonetheless, we do still add a major element of evidence on treatment satisfaction and quality of life of EB affected children.

In conclusion, this retrospective analysis of 32 pediatric EB patients demonstrates that multidisciplinary care - combining specialized wound management, systematic pain control, and structured psychosocial support - was associated with significantly better treatment outcomes compared to standard care. The magnitude of improvement varied by EB subtype, with Simplex patients showing the highest gains, though all subtypes benefited from the comprehensive approach. Our findings identified key factors affecting treatment success, including age, disease duration, and comorbidities. These results support implementing structured multidisciplinary care programs for pediatric EB patients, with treatment protocols tailored to individual patient characteristics and disease subtypes.

Declaration of conflicting interests

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

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Ethics approval

This study was approved by Eskişehir City Health Practice and Research Center Institutional Ethics Committee with protocol number (Date: 17/10/2024, No: ESH/BAEK 2024/50).

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Research Article

HER2-low expression in patients with hormone receptor positive and HER2 negative advanced breast cancer treated with ribociclib or palbociclib in combination with endocrine therapy

Hormon reseptörü pozitif, HER2 negatif metastatik meme kanseri tanısıyla ribosiklib veya palbosiklib ile letrozol kombinasyon tedavisi verilen hastalarda HER2-düşük ekspresyonunun önemi

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Abstract

Aim: Hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative breast cancer which represents the most common subgroup of metastatic breast cancer (MBC). Recently, further subclassification for HER2-negative tumors has emerged as HER2-low. There is limited knowledge regarding the effect of HER2-low expression on outcomes of patients with HR-positive and HER2-negative MBC treated with CDK 4/6 inhibitors plus hormonal therapy. Therefore, we evaluated survival parameters according to HER2-low status for this patient group in this study.

Material and Methods: As the Turkish Oncology Group (TOG) Project, retrospectively collected data from 423 patients with HR-positive/HER2-negative MBC treated with ribociclib and palbociclib plus letrozole therapy was assessed. Included patients had metastatic first-line therapy and endocrine-sensitive disease. Survival outcomes were compared between HER2-negative and HER2-low patient groups.

Conclusion: HER2-low status had no statistically significant impact on survival in patients treated with palbociclib or ribociclib plus letrozole.

Keywords: Cyclin-dependent kinase 4/6 inhibitors, palbociclib, ribociclib, hormone receptor positive and HER2 negative advanced breast cancer, HER2-low

Öz

Amaç: Metastatik meme kanserinin (MMK) en yaygın alt grubunu temsil eden hormon reseptörü (HR) pozitif, insan epidermal büyüme faktörü 2 (HER2) negatif meme kanseridir. Yakın dönemde HER2 negatif tümörler için daha ileri bir alt sınıflandırma olarak HER2-düşük terimi ortaya çıkmıştır. HER2-düşük ekspresyonunun, CDK 4/6 inhibitörleri ve hormonal tedavi kombinasyonuyla tedavi edilen HR-pozitif/HER2-negatif MMK'li hastaların sonuçları üzerindeki etkisine ilişkin sınırlı bilgi bulunmaktadır. Bu nedenle çalışmamızda bu hasta grubu için HER2-düşük durumuna göre sağkalım parametrelerini değerlendirdik.

Gereç ve Yöntemler: Türk Onkoloji Grubu (TOG) Projesi olarak Türkiye genelindeki 43 farklı tıbbi onkoloji merkezinden retrospektif olarak veri toplandı. Haziran 2016 ile Ağustos 2022 arasındaki dönemde Ribosiklib veya Palbosiklib ile letrozol kombinasyon tedavisi verilmiş HR-pozitif/HER2-negatif MMK'li 423 hastadan retrospektif olarak toplanan veriler değerlendirildi. Dahil edilen hastalar metastatik birinci basamak olarak tedaviye başlanan ve endokrin duyarlı hastalığa sahipti. Hastaların sağkalım sonuçları, HER2-negatif ve HER2- düşük hasta grubu arasında kıyaslandı.

Sonuç: HER2-düşük durumu, palbosiklib veya ribosiklib ile letrozol tedavisi alan hastalarda sağkalım üzerinde istatistiksel olarak anlamlı bir etki göstermedi.

Anahtar kelimeler: CDK4/6 inhibitörleri, metastatik meme kanseri, HER2-düşük ekpresyon

Introduction

Breast cancer (BC) is the most common cancer in women worldwide and the leading cause of cancer deaths among women [1]. In regard to treatment of metastatic hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative breast cancer which represents the most common subgroup of metastatic breast cancer (MBC), cyclin-dependent kinase (CDK) 4/6 inhibitors in combination with traditional endocrine therapy (ET) (an aromatase inhibitor or fulvestrant) has become the standard-of-care strategy [2-8]. Recently, further subclassification for HER2-negative tumors has emerged as HER2-low, which is defined as a score of 1+ on immunohistochemical (IHC) analysis or as an IHC score of 2+ and negative results on in situ hybridization (ISH) due to its potantial prognostic significance and treatment options [9-11]. Novel anti-HER2 antibody–drug conjugates have demonstrated substatial clinical activity in patients with

HER2-low MBC [12,13]. There is currently limited knowledge regarding the effect of HER2-low expression on outcomes of patients with advanced HR-positive and HER2-negative BC and treated with CDK 4/6 inhibitors plus hormonal therapy. Based on the current data, molecular profile of HR-positive and HER2-low BC may differ from that of HER2-zero disease [10]. Furthermore, the data regarding the prognostic significance of HER2-low expression in the advanced setting are conflicting [14-16]. The current study was therefore conducted to evaluate the survival parameters of the patients with metastatic HR-positive and HER2-negative BC treated with CDK 4/6 inhibitors plus letrozole according to HER2-low status.

Material and Methods

We retrospectively collected data from 43 different medical oncology centers in Turkey. 423 patients with HR-positive/ HER2-negative advanced breast cancer treated with ribociclib and palbociclib plus letrozole therapy between June 2016 and August 2022 were included. Due to reimbursement conditions in Turkey, all patients were ER-positive which was defined as at least 10% of cells staining positive, and CDK 4/6 inhibitors were limited to ribociclib and palbociclib. Included patients had either de-novo metastatic disease or endocrine-sensitive recurrent disease which relapsed >12 months after the completion of (neo) adjuvant ET. The outcome of the patients with HER2-0 (IHC score 0) and HER2-low (HER2 IHC score1+ or 2+ and ISH negative) tumors were compared. HER2 scored from both primary and metastatic tissue if present. For the patient with two pathology samples (primary and metastatic tissue), those with HER2-low levels in two samples were included.

Progression free survival (PFS) was calculated as the time from CDK 4/6 inhibitor treatment initiation to disease progression or death, whichever was earlier. Overall survival (OS) was defined as the time interval in months between the date of initiation of CDK 4/6 inhibitor treatment and death from any cause. Kaplan–Meier method were used to analyse survival data. Log-rank test was used to compare PFS and OS across groups. We conducted this study according to the Declaration of Helsinki. Ankara Bilkent City Hospital Ethics Committee approved the study protocol (2021, E2-21-1167). as a multicenter retrospective observational study.

Statistical Analysis

Progression free survival (PFS) was calculated as the time from CDK 4/6 inhibitor treatment initiation to disease progression or death, whichever was earlier. Overall survival (OS) was defined as the time interval in months between the date of initiation of CDK 4/6 inhibitor treatment and death from any cause. Median PFS (mPFS) and median OS (mOS) of the patients were calculated with the Kaplan-Meier method. Various clinical features were tested in a univariate analysis using Kaplan-Meier method and evaluated by Log-rank analysis. The p values <0.05 was considered statistically significant. SPSS Statistics version 26.0 was utilized for data analysis.

Results

In this study, 418 of the patients were female (98.8%). 75.7% of female patients were postmenopausal. Median age was 58 (25-90). While the HER2 IHC score was 0 in 285 of the patients (67.4%), the HER2 IHC score was 1+ and 2+ (HER2-low) in 138 patients (32.6%). Progesterone receptor expression was negative in 38 patients (9.1%). 196 patients had bone-only metastatic disease (46.3%). 9 patients had Central nervous system (CNS) metastases (2.1%) and 74 patients had liver metastases (17.5%). Table 1 shows patient characteristics.

The median follow up was 10.5 (95% CI, 9.7-11.4) months. Median OS could not be calculated at follow-up, with an estimated 81% of patients alive at 24 months. The median PFS was 29.4 months (95 CI, 16.2-42.7) for the entire cohort. In patients treated with ribociclib/palbociclib plus letrozole in the first-line and endocrine sensitive disease setting, there were no statistically significant difference in terms of mPFS between HER2-0 and HER2-low patients (36.2 and 29.4 months, p = 0.12) (Figure1). Compared with its HER2-0 counterpart, HER2-low expression seemed to have a better course in the mOS curves but there was no statistically significance (p = 0.49) (Figure2).

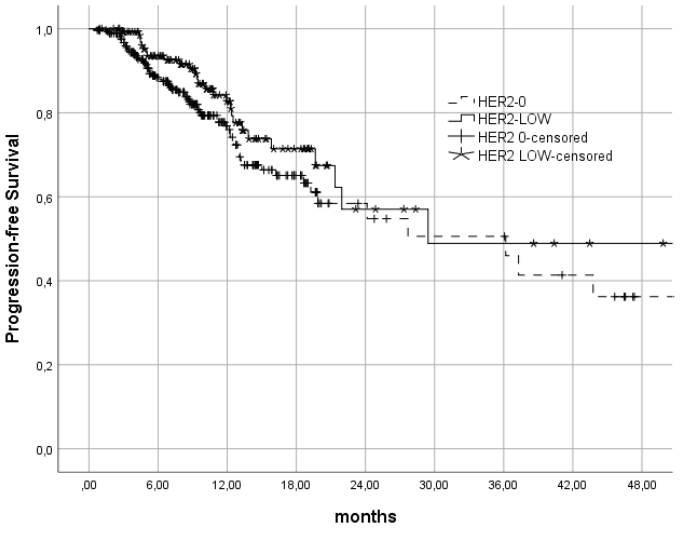

Figure 1. mPFS for HER2-0 and HER2-low patients in the entire cohort.

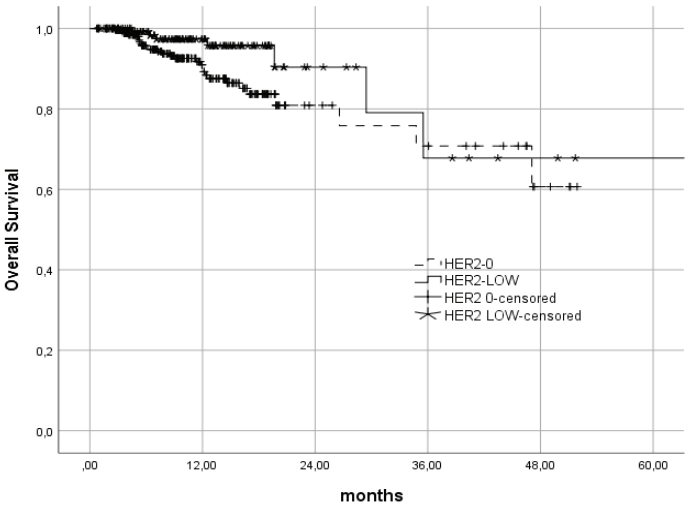

Figure 2. mOS for HER2-0 and HER2-low patients in the entire cohort.

In HER2-low patient group, no significant differences were observed regarding mPFS (95 CI, 21.35, (18.3-24.4) and 29.4, (NE-NE) months) and mOS between patients receiving palbociclib letrozole or ribociclib letrozole in the follow-up period (p = 0.98 for mPFS, and p = 0.53 for mOS) (Figures 3,4).

"In the patient receiving palbociclib plus letrozole, no statistically significant differences in mPFS (Figure 5) and mOS were found between HER2-0 and HER2-low patients (p = 0.75 and p = 0.27, respectively).

Although mPFS curves showed a divergence from the first months in favor of HER2- low, no statistically significant differences in mPFS (Figure 6) and mOS were observed between HER2-0 and HER2-low patients who received ribociclib plus letrozole (p = 0.11 and p = 0.13, respectively)

In HER2-zero patient group, there was a numerically difference in favor of palbociclib plus letrozole in terms of mPFS, although it did not reach statistical significance (36.2 (8.3-64.0) and 24.1 (9.0-39.0), p = 0.1) (Figure 7).

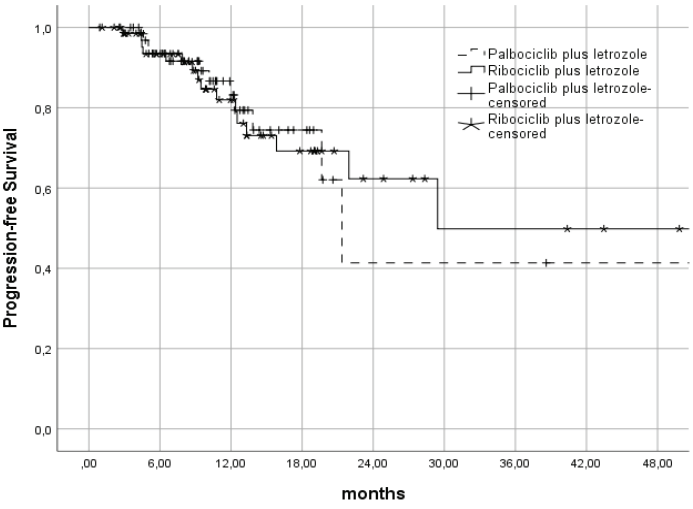

Figure 3. mPFS with palbociclib plus letrozole and ribociclib plus letrozole in HER2-low patients.

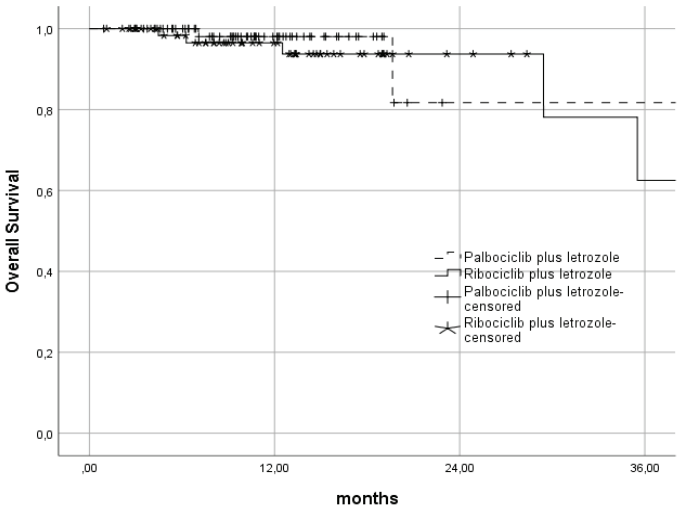

Figure 4. mOS with palbociclib plus letrozole and ribociclib plus letrozole in HER2-low patients.

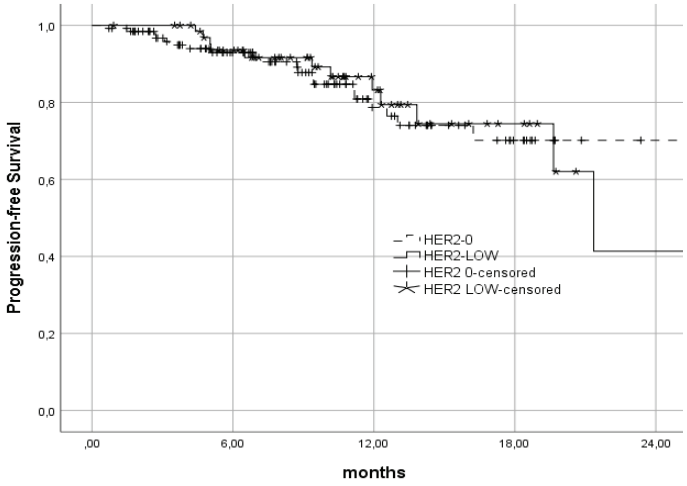

Figure 5. mPFS for HER2-0 and HER2-low in patients receiving palbociclib plus letrozole.

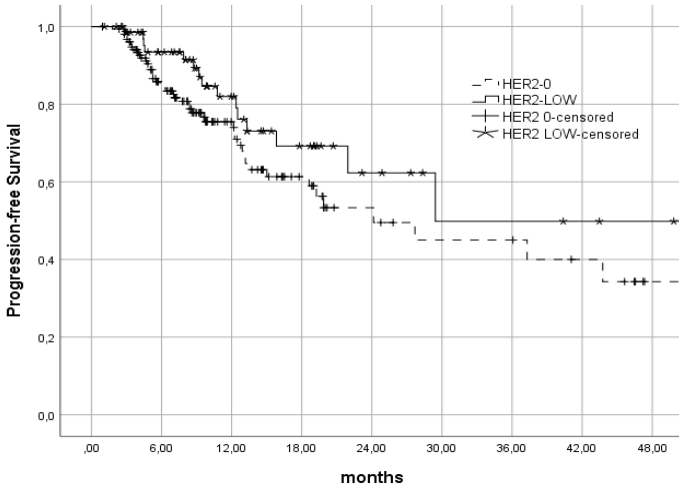

Figure 6. mPFS for HER2-0 and HER2-low in patients receiving ribociclib plus letrozole.

Table 1. Clinicopatological characteristics of the patients			
Characteristic	HER2-zero (n = 285) N (%)	HER2-low (n = 138) N (%)	p
Age (years, median)	58 (25-90)	58 (27-86)	
ECOG PS 0-1 2	 248 (88.6%) 32 (11.4%)	 126 (94.7%) 7 (5.3%)	 <0.045
Menopausal status Premenopausal Postmenopausal Men	 68 (23.9%) 215 (75.7%) 1 (0.4%)	 33 (21.5%) 116 (75%) 4 (3.5%)	0.70
Disease status De-novo Endocrine naive recurrent	 195 (68.4%) 90 (31.6%)	 67 (48.6%) 71 (51.4%)	 <0.001
Metastatic sites type Visceral +/- bone Bone-only	 161 (56.5%) 124 (43.5%)	 66 (47.8%) 72 (52.2%)	 0.94
Vissceral metastasis sites Liver CNS Lung	 48 (16.8%) 6 (2.1%) 92(32.4%)	 26 (18.8%) 3 (2.2%) 43(31.7%)	 0.61 0.60 0.80
Progesteron receptor negative	27 (9.5%)	11 (8.1%)	0.63
Treatment type Palbociclib-Letrozole Ribociclib-Letrozole	 129 (45.3%) 156 (54.7 %)	 67 (48.6%) 71 (51.4%)	0.52
ECOG PS: The Eastern Cooperative Oncology Group performance status CNS: central nervous system			

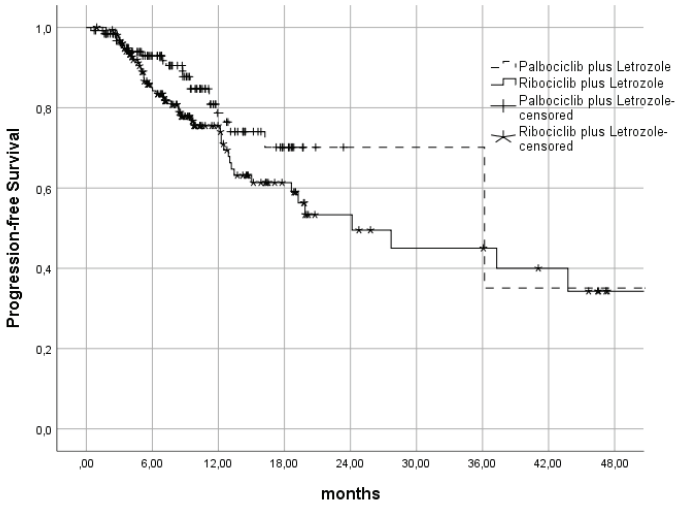

Figure 7. mPFS with palbociclib plus letrozole and ribociclib plus letrozole in HER2-zero patients.

Discussion

According to guidelines, BC is classically subdivided into three main groups as HR-positive and HER2-negative, HER2-positive, and triple-negative breast cancer (TNBC). As a relatively new entity, HER2-low-expressing tumors which are present in HER2-negative breast cancer represent approximately half of the cases in the entire breast cancer group. Recent data suggested that HER2-low rate was higher among HR-positive BC than HR-negative BC [17, 18]. More specifically, regarding advanced HR-positive HER2-low tumors, in DESTINY-Breast04 trial trastuzumab deruxtecan showed clinical benefit in patients who had received at least one line of therapy. Currently CDK 4/6 inhibitors plus ET are still accepted as the SoC therapy in the first line for this group of tumors.

Regarding data on CDK 4/6 inhibitors, only ribociclib among 3 agents in combination with ET demonstrated OS benefit in advanced HR-positive HER2-negative BC in the first-line treatment setting. After the release of OS data for MONALEESA-2, PALOMA-2, and MONARCH-3 [19-21], decisions regarding treatment selection in clinical practice continue to evolve. Before the completion of these data, ribociclib and palbociclib which provided reimbursement conditions in our country have been used since June 2016.

Our study cohort included patients with denovo metastatic or recurrent endocrine-sensitive disease diagnosed with HR-positive, HER2-negative MBC and treated with ribociclib or palbociclib plus letrozole as first-line therapy. Since providing reimbursement was relatively late in Turkey, the rate of the patients in our country pretreated with chemotherapy for metastatic disease before CDK4/6 inhibitor treatments were comperatively high. Therefore, the rate of patients who started CDK4/6 inhibitor treatment with a diagnosis of de novo disease was comparatively high in our cohorts [22]. In this study, we retrospectively evaluated whether HER2-low expression status has prognostic implication.

In our study, we found that there was no significant difference between HER2-low and HER2-0 in terms of treatment effectiveness. The efficacy of palbociclib or ribociclib and letrozole also did not differ significantly in the HER2-low patient group. A numerical inferior efficacy results of ribociclib were observed in the HER2-0 patient group that did not reflect statistical significance. In terms of patient characteristics, there was a statistically significant predominance of denovo disease in the HER2-0 group. However, mPFS or mOS were similar for the patients with denovo or endocrine sensitive relapsed disease ($p = 0.70$ and $p = 0.15$, respectively). Therefore, the numerical difference between both agents in the HER2-0 group can be more clearly demonstrated in terms of HER2 biology or the difference between the two agents with long-term follow-up.

There is controversy and limited data on the efficacy of CDK 4/6 inhibitors in patients with HR-positive and HER2-low tumors. One of the first analysis of Bao et al., in 106 patients with HR+/ERBB2– MBC treated with CDK4/6 inhibitors, they reported that HER2-low expression was associated with an inferior PFS (8.9 months; 95%CI, 6.49-11.30 months vs 18.8 months; 95%CI, 9.44-28.16 months; $p = 0.01$) [23]. This study included a heterogeneous patient group that received CDK 4/6 inhibitor treatment as a second or third line.

A Greek real-life data published later, evaluated the impact of low HER2 expression in metastatic HR-positive HER2-negative breast cancer treated with first-line CDK4/6 inhibitors and reported that despite numerical differences, treatment efficacy of CDK4/6 inhibitors was equal and independent of HER2 expression level [24].

In a cohort of 45 patients treated with palbociclib and either AI or fulvestrant according to treatment line, authors reported no significant differences in ORR (41.7% and 28.6%, respectively, $p = 0.360$) and mPFS (16.2 and 14.1 months, respectively, $p = 0.263$) between HER-2-zero and HER-2-low patients [25].

Based on the retrospective study of Lapuchesky LS et al., HER2-low expression did not show a statistically significant impact on patients with ER+/HER2-negative advanced breast cancer treated with CDK 4/6 inhibitors in the first-line setting [26]. In this study 70.4% of 186 patients received CDK4/6 inhibitors and endocrine therapy in the first-line treatment setting. They reported no statistically significant differences in PFS and OS between HER2-0 and HER2-low patients treated with CDK4/6 in the first-line setting.

An observational study also found that there were no association between HER2 status and clinical outcomes in 919 HR + /HER2- advanced BC patients treated with first-line ET plus CDK4/6 inhibitors [27]. Two other current studies investigating the role of HER2-low status, one from a single center showed a clearly numerically favorable PFS in the HER2-zero group, while the other multicenter study reported that HER2-low status was not associated with survival [28,29].

In our study, we could not show any difference in survival and prognosis between HER2-0 and HER2-low in the patient group with metastatic HR+/HER2- BC who received palbociclib or ribociclib combined with letrozole as first-line therapy. We believe that our study contributes to the literature with favorable number of patients and real-life data. However, the results should be evaluated considering the short follow-up period and the retrospective nature of the study. As interpreted in the systematic review, the predictive rather than the prognostic significance may be emphasized for HER2-low metastatic BC based on current level of evidence [30].

To sum up, based on our current knowledge, CDK 4/6 inhibitors in combination with ET is the standard treatment for HR-positive, HER2-low MBC. For the patients who progressed after SOC treatment, the optimal sequencing of ADCs in this setting and efficacy of combinations of ADCs with endocrine therapies or immunotherapies remain unclear. The search for an optimal HER2- low MBC treatment continues. In our study, HER2-low status did not show a statistically significant impact on treatment efficacy for patients treated with palbociclib or ribociclib plus letrozole. Results of prospective studies for this group of patients are awaited.

Declaration of conflicting interests

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

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Ethics Approval

The study protocol was approved by Ankara City Hospital Ethics Committee as a multicenter retrospective observational study in 22 December 2021 (E2-21-1167).

Author Contributions

Conception and design: MANS, SK, development of methodology, analysis and interpretation of data, and writing of the article: SK,MH,MANS, data acquisition: All authors, manuscript co-writing: All authors, final approval of manuscript: All authors. All authors revised the manuscript critically for important intellectual content and approved the version to be published.

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Research Article

Evaluation of ultrasonography and pathology results of incidental thyroid nodules detected on positron emission tomography-computed tomography: Single center results

Pozitron emisyon tomografi-bilgisayarlı tomografide insidental saptanan tiroid nodüllerinin ultrasonografi ve patoloji sonuçlarının değerlendirilmesi: Tek merkez sonuçları

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Abstract

Aim: We aimed to determine the thyroid pathologies of patients with thyroid incidentalomas detected on 18F-FDG PET-CT, to obtain clinical, imaging, histopathology, and surgical treatment results, and to reveal the relationship between 18F-FDG uptake patterns and Maximum Standard Uptake Values (SUVmax) and diagnostic results.

Material and Methods: Data from 1837 patients who underwent PET-CT for any reason between January 2021 and February 2024 were retrospectively analyzed. Demographic data, ultrasonography (USG) and 18F-FDG PET-CT images, surgical and histopathological data of all patients meeting the inclusion criteria were reviewed.

Results: Patients with uptake (n = 71) were evaluated with US and thyroid nodules were detected in 46 patients (46/1837) (2.5%). Of the 22 nodules that were performed fine needle aspiration biopsy (FNAB), 12 were benign pathologies. Among the six nodules that underwent surgery (2 Bethesda V, 3 Bethesda VI, and 1 Bethesda III), three were diagnosed as benign, while the other three (13.6%) were confirmed as malignant pathology (papillary thyroid carcinoma). The malignancy rate in nodules with focal uptake was 16.6% (3/18). No statistically significant difference was observed in the median SUVmax values between benign and malignant nodules (p = 0.164).

Conclusion: It is necessary to determine the need for diagnostic examinations, to reveal the results of diagnostic interventions, and to increase awareness, especially in patients with focal thyroid uptake observed on 18F-FDG PET-CT imaging. When focal uptake is detected on 18F-FDG PET-CT, it is important to perform FNAB if it is considered a risky nodule in terms of US, regardless of the SUVmax value.

Keywords: positron emission tomography-computed tomography, thyroid nodule, ultrasonography

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Öz

Amaç: ^{18}F-FDG PET-BT'de tiroid insidentoloması saptanan hastaların tiroid patolojilerini saptamayı, klinik, görüntüleme, histopatoloji ve cerrahi tedavi sonuçlarını elde etmeyi, 18F-FDG tutulum paternleri ve Maksimum Standart Uptake Değerleri(SUVmax) ile tanısal sonuçlar arasındaki ilişkiyi ortaya koymayı amaçladık.

Gereç ve Yöntemler: Ocak 2021 ile Şubat 2024 arasında herhangi bir nedenle PET-BT çekilen 1837 hastanın verileri retrospektif olarak analiz edildi. Dahil etme kriterlerini karşılayan tüm hastaların demografik verileri, ultrasonografi(USG) ve 18F-FDG PET-BT görüntüleri, cerrahi ve histopatolojik verileri incelendi.

Bulgular: Tutulum gösteren hastalar(n = 71) USG ile değerlendirilmiş, 46 hastada (%2,5) tiroid nodülü saptanmıştı . İnce iğne aspirasyon biyopsisi (İİAB) yapılan 22 nodülden 12'si benign olarak raporlanmıştı. Cerrahiye verilen 6 nodülün (2'si Bethesda V, 3'ü Bethesda VI ve 1'i Bethesda III) 3'ü benign, diğer 3'ü (%13,6) ise malign (papiller tiroid karsinomu) olarak sonuçlanmıştı. Fokal tutulum gösteren nodüllerdeki malignte oranı %16,6 (3/18) idi. Benign ve malign nodüllerin ortanca SUVmax değerleri arasında ise istatistiksel fark saptanmamıştı (p=0,164).

Sonuç: Özellikle 18F-FDG PET-BT görüntülemesinde fokal tiroid tutulumu gözlenen hastalarda tanısal incelemelere olan ihtiyacın belirlenmesi, sonuçlarının ortaya konulması ve farkındalığın artırılması için SUVmax değerinden bağımsız olarak ultrasonografik açıdan riskli nodüllere İİAB yapılması önemlidir.

Anahtar Kelimeler: pozitron emisyon tomografi-bilgisayarlı tomografi, tiroid nodülü, ultrasonografi

Introduction

Thyroid incidentaloma is often defined as an asymptomatic thyroid lesion detected incidentally during imaging studies performed for other reasons and whose frequency increases with age. The prevalence of thyroid nodules detected by imaging methods was 23.5% in the young population, while it was found to be 37% in those over the age of 65 [1]. Malignancy is detected in 5% of thyroid nodules. The incidence of thyroid cancer in Turkey in 2022 was reported as 6.4% [2].

Fluorine-18 fluorodeoxyglucose positron emission tomography-computed tomography (18F-FDG PET-CT) is an increasingly utilized functional imaging technique for the diagnosis, staging, and follow-up of oncological, cardiac, and neurological diseases. Therefore, increased diffuse or focal 18F-FDG uptake in the thyroid gland is frequently encountered in daily clinical routine 18F-FDG PET-CT. While these uptakes may be physiological, they can also be observed in toxic nodular goiter, multinodular goiter, thyroiditis, and thyroid malignancies. Incidental focal increased uptake in the thyroid gland detected on 18F-FDG PET-CT is observed in approximately 2-3%, and histopathological data indicate a malignancy risk of 35-40% in a significant portion of these cases [3-5]. The likelihood of malignancy increases in thyroid lesions demonstrating uptake on 18F-FDG PET-CT, whereas nodules without uptake are generally considered benign. Due to its high sensitivity and specificity, it can exclude malignancy in indeterminate thyroid nodules, particularly those larger than 15 mm, with a sensitivity of approximately 95-100% without requiring additional testing [6].

Evidence-based data have shown that thyroid incidentalomas are not rare, and the risk of malignancy, especially if the focal pattern is evident on 18F-FDG PET-CT, cannot be ignored, thus requiring further clinical and interventional evaluation [5]. Therefore, in this study, we aimed to determine the thyroid pathologies of patients with thyroid incidentalomas detected on 18F-FDG PET-CT, to obtain clinical, imaging, histopathology, and surgical treatment results, and to reveal the relationship between 18F-FDG uptake patterns and Maximum Standard Uptake Values (SUVmax) and diagnostic results.

Material and Methods

This study was conducted retrospectively by scanning hospital data records from the Endocrinology and Metabolism Diseases Clinic of our hospital between January 2021 and February 2024. A total of 1837 adult patients over the age of 18 who showed uptake in the thyroid gland on 18F-FDG PET-CT were included in the study. Patients with a previously diagnosed thyroid cancer, those with a "Maximum Standardized Uptake Value" (SUVmax) within normal physiological limits on 18F-FDG PET-CT, patients with repeat imaging, and those with incomplete medical data (ultrasonography, biopsy, pathology, etc.) were

excluded from the study. After the retrospective screening, demographic data, ultrasonography images, 18F-FDG PET-CT images, surgical, and histopathological data of all patients meeting the inclusion criteria were examined.

Ultrasonography (US) of the patients was performed by experienced endocrinologists with at least 5 years of experience, using a Hitachi HI VISION Preirus device (Hitachi Medical Systems, Tokyo, Japan) with a linear transducer probe of central frequency 7.5-15 MHz. Thyroid nodules were classified according to the European Thyroid Imaging Reporting and Data System (EU-TIRADS-2017), and the necessity of fine-needle aspiration biopsy (FNAB) was determined [7]. FNAB was performed using a 22 Gauge needle with an aspiration technique under US guidance, collecting samples from at least two different areas of the nodule. The samples were spread on glass slides, air-dried, and immediately sent to pathology. Giemsa-stained samples examined in the pathology department between 2021 and 2024 were retrospectively re-evaluated and reported according to the Bethesda 2023 Thyroid Cytology Reporting System [8].

18F-FDG PET/CT imaging was performed 60 minutes after FDG injection using a PET-CT scanner (Biograph 6; Siemens Medical Systems, Erlangen, Germany). FDG injection was performed after the patients had fasted for 6 hours and fasting blood glucose levels were below 150 mg/dl. 18F- FDG was administered intravenous at a dose of approximately 5.18 MBq/kg (0.14 mCi/kg). Immediately after the acquired CT scan for localization and attenuation correction, the PET scan was acquired in 5-7 bed positions with an imaging time of 4 minutes for each. 18F-FDG PET/CT images were reviewed by two experienced nuclear medicine physicians and visual and semiquantitative analysis of uptake in the thyroid gland was performed. Whereas focal 18F- FDG uptake was defined as a localized uptake covering less than an entire thyroid lobe, uptake covering at least one entire thyroid lobe was analyzed under the diffuse uptake category in this study. Due to the retrospective design of the study, interobserver agreement was not assessed. We also acknowledge that interobserver variability may influence the results. The study was approved by the ethics committee of the Ankara Training and Research Hospital (approval date and number: 17 April 2024-E-24/60). The study was performed in accordance with the Declaration of Helsinki.

Statistical Analysis

Data were analyzed using the SPSS 27 (Statistical Package for Social Sciences, Chicago, IL, USA). The normality of distribution was assessed using the Kolmogorov-Smirnov test. Normally distributed data were presented as mean ± standard deviation (SD) and n (%), while non-normally distributed data were expressed as median (minimum-maximum). The Mann-Whitney U test was used to compare non-parametric independent variables. The relationship between numerical variables was evaluated using the Spearman correlation test for non-normally distributed data. In this study, the statistical significance level was accepted as $p < 0.05$.

Results

Among 1837 patients who underwent 18F-FDG PET-CT imaging due to known or suspected cancer (excluding thyroid cancer), FDG uptake was detected in 124 patients. While 53 patients were excluded from the study, incidental thyroid uptake was found in 71 patients (3.8%) (Figure 1). Of these, 43 patients (2.3%) had focal uptake, while 28 patients (1.5%) had diffuse thyroid uptake. The mean age of the patients was 59.25 ± 13.17 years, with the majority being female (74.6%).

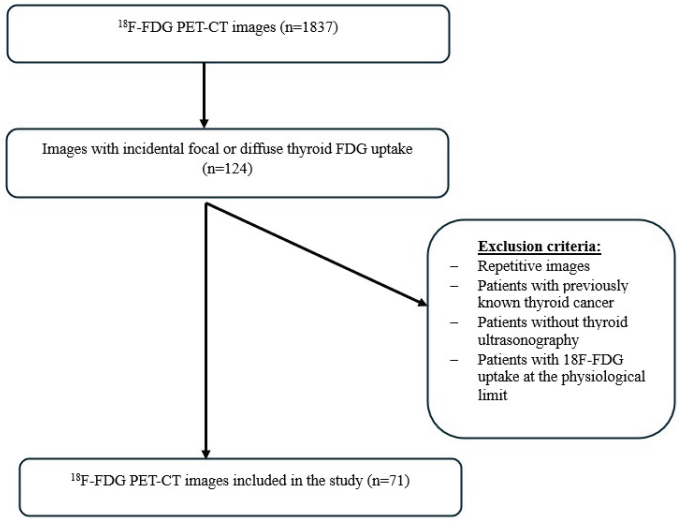

Figure 1. Flow diagram of the search strategy for focal or diffuse thyroid uptake on 18F-FDG PET-CT

Patients with uptake (n = 71) were evaluated with US and thyroid nodules were detected in 46 patients (46/1837) (2.5%) (Figure 2). The median nodule size was 1.5 cm (0.4-5.8 cm), with focal uptake present in 36 patients (78.3%) and diffuse uptake in 10 patients (21.7%). FNAB was performed in 18 of the focal uptake cases and 4 of the diffuse uptake cases. It was determined that the US findings of 25 patients without detected nodules were consistent with chronic thyroiditis, and the majority of these patients (72%) exhibited diffuse uptake on 18F-FDG PET-CT imaging.

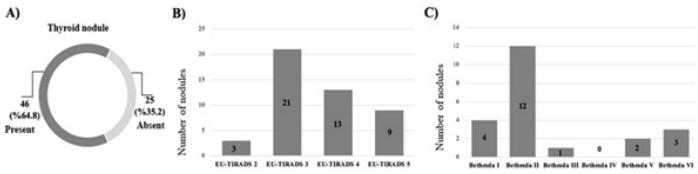

Figure 2. Evaluation of patients with focal or diffuse thyroid uptake on 18F-FDG PET-CT for the presence of nodules and nodule characteristics by Thyroid US, A) Presence of nodules on US, B) Distribution of nodules on US according to EU-TIRADS classification, C) Distribution of fine needle aspiration cytology result of nodules according to Bethesda categorization.

The indications for performing 18F-FDG PET-CT in 46 patients with thyroid nodules detected in US are listed in Table 1.

Table 1. Indications for 18F-FDG PET-CT in patients with nodules detected in ultrasonography.

Indications	N
Breast cancer	14
Colon cancer	7
Solitary pulmonary nodule	5
Gastric cancer	3
Lung cancer	3
Malignancy of unknown primary	3
Endometrial cancer	3
Squamous cell carcinoma	2
Non-Hodgkin lymphoma	2
Angiosarcoma	1
Laryngeal cancer	1
Other causes	3

Among the 46 nodules, 24 were considered benign or low-risk for malignancy according to the EU-TIRADS classification, with no further investigation recommended, and therefore, a biopsy was not performed (Figure 2) [7]. The remaining 22 patients had nodules with sonographic features requiring further evaluation, leading to fine-needle aspiration biopsy (FNAB). Among the 22 biopsied nodules, 12 were reported as benign (Bethesda II), two as suspicious for malignancy (Bethesda V), three as malignant (Bethesda VI), and one as atypia of undetermined significance (Bethesda III). Four biopsy results were reported as non-diagnostic (Bethesda I) (Figure 2) [8].

No surgical resection was performed on the 12 cytologically benign nodules. The four nodules were cytologically non-diagnostic (Bethesda I) and these patients refused surgical resection by their own decision. Among the six nodules that underwent surgery (2 Bethesda V, 3 Bethesda VI, and 1 Bethesda III), three were diagnosed as benign, while the other three (13.6%) were confirmed as malignant pathology (papillary thyroid carcinoma) [8]. All malignant nodules exhibited focal uptake on 18F-FDG PET-CT. The malignancy rate in nodules with focal uptake was 16.6% (3/18).

The median SUVmax value of the 71 incidental thyroid gland lesions (with either diffuse or focal uptake) was 4.59 (range: 2.3-17.6). There was no significant difference in SUVmax values between diffuse and focal uptake groups (diffuse uptake: 5.07 [2.3-12] vs. focal uptake: 4.4 [2.3-17.6], $p = 0.326$). The median SUVmax value of the 46 US-confirmed thyroid nodules was 4.45 (2.3-17.6), whereas the median SUVmax value of patients without detected nodules (n = 25) was 4.78 (2.3-12) ($p = 0.459$). Among patients with focal uptake and detected nodules, there was no significant difference in SUVmax values between those who underwent FNAB and those who did not (5.84 vs. 5.74, $p = 0.501$). The median SUVmax value of the 15 confirmed benign lesions was calculated as 4.59 (2.7-13.3), while the detailed characteristics of the three malignant nodules are presented in Table 2. No statistically significant difference was observed in the median SUVmax values between benign and malignant nodules ($p = 0.164$).

Finally, no correlation was found between SUVmax values and nodule size, Bethesda classification, or EU-TIRADS categorization (Table 3). However, a positive correlation was observed between the Bethesda classification and both nodule size and EU-TIRADS categorization ($r = 0.385$, $p = 0.008$ and $r = 0.550$, $p < 0.001$, respectively).

Table 2. Characteristics of thyroid nodules with proven malignancy.

Case	Size (cm)	SUVmax*	Pattern of uptake on PET/ CT	EU-TIRADS	Bethesda	Post-surgical diagnosis
1	3.2	5.7	Focal	5	VI	Papillary thyroid ca
2	1.4	5.5	Focal	5	VI	Papillary thyroid ca
3	5.8	14.4	Focal	5	V	Papillary thyroid ca

*Maximum Standard Uptake Values

Table 3. Evaluation of correlation analysis between SUVmax values and nodule size, Bethesda classification and EU-TIRADS.

	SUVmax	Nodule size	Bethesda	EU-TIRADS
SUVmax	N/A	r=0.048 p=0.750	r=0.139 p=0.359	r=0.188 p=0.210
Nodule size	r=0.048 p=0.750	N/A	r=0.385 p=0.008*	r=0.268 p=0.072
Bethesda	r=0.139 p=0.359	r=0.385 p=0.008*	N/A	r=0.550 p<0.001*
EU-TIRADS	r=0.188 p=0.210	r=0.268 p=0.072	r=0.550 p<0.001*	N/A

The relationship between numerical variables was evaluated with the Spearman correlation test for data that did not show normal distribution. $p<0.05$ was considered statistically significant. N/A: not applicable

Discussion

Nowadays, the prevalence of incidental thyroid nodules is increasing with the increasing frequency of diagnostic imaging. Different rates for the prevalence of incidental thyroid nodules detected by 18F-FDG PET-CT have been reported in the literature. In a meta-analysis, the prevalence in the included studies ranged between 0.16% and 11.74%, while the pooled prevalence was reported as 2.22% [9]. In our research, incidental thyroid gland uptake was found to be 3.8% and thyroid nodule prevalence was 2.5%.

As is known, uptake patterns in the thyroid gland and SUVmax values in 18F-FDG PET-CT are important in the diagnosis and follow-up of thyroid diseases. Focal thyroid uptake is highly suspicious for malignancy [9]. In the literature, focal thyroid uptake has been reported to be around 2% [3]. Similarly, this rate was found to be 2.3% in our study and focal uptake was seen in all malignant nodules. Another important point is that the SUVmax value is directly proportional to the malignancy of the thyroid nodule [4]. Different cut-off values have been reported in the literature to interpret the benign or malignant status of a thyroid nodule detected by 18F-FDG PET-CT according to the SUVmax value. For example, Kang et al. reported the cut-off value for SUVmax as 4.2 [10], while Bae et al reported the cut-off value for SUVmax as 3.5 [11]. On the contrary, Kim et al, Are et al, and Bogsrud et al reported no difference in SUVmax between benign and malignant lesions [12-14]. In our study, while the median SUVmax value of 15 benign lesions was 4.59, the median SUVmax value of 3 malignant lesions was 5.7 and no statistical difference was found between the median SUVmax values of benign and malignant nodules ($p = 0.164$). The fact that there were 3 malignant nodules prevented us from making a healthy statistic to determine the cut-off. However, numerically, all of the SUVmax values of the malignant nodules were above the cut-off values specified in the literature (SUVmax > 5.5). This may be due to the fact that the number of nodules biopsied in this study was small, and two of the malignant thyroid nodules were measured with lower SUVmax due to partial volume effects because of their small size [15]. We also explicitly note that limited sample size may have reduced the power to detect a statistically significant difference. Therefore, when focal uptake is seen on 18F-FDG PET-CT, we recommend FNAB if it is considered a risky nodule in terms of US, regardless of the SUVmax value.

When focal thyroid uptake is detected incidentally on 18F-FDG PET-CT, the thyroid should be evaluated with US. Biopsy is recommended for >1 cm EU-TIRADS-4/5 nodules and >2 cm EU-TIRADS-3 nodules. For <2 cm EU-TIRADS-2/3 nodules, follow-up with US at 6-12 month intervals is recommended [16]. Biopsy is not recommended for EU-TIRADS-2 nodules since no malignancy was detected in any of the studies [17]. EU-TIRADS-3/4/5 nodules <1 cm may be considered for biopsy only if there is a high risk and aggressive US features [18]. Diffuse FDG uptake in the thyroid gland may be physiological. However, it may also be seen in cases of increased gland activity or inflammation (Hashimoto's thyroiditis, Graves' disease, subacute thyroiditis, post-RAI treatment thyroiditis, etc.). For example, diffuse FDG uptake caused by chronic thyroiditis may hide the focal nodule at the base. Although the probability of malignancy is low in diffuse FDG uptake, this condition cannot be excluded [12]. Therefore, when necessary, an evaluation with ultrasound can guide decision-making. In our study, we decided to perform FNAB on four thyroid incidentalomas showing diffuse uptake after evaluating with the US. According to the American Thyroid Association (ATA) guideline, if there is diffuse FDG uptake in chronic lymphocytic thyroiditis proven by US and laboratory findings, further investigation is not required

[19]. The British Thyroid Association (BTA) guidelines state that thyroid nodules with focal uptake on 18F-FDG PET-CT are high-risk nodules and recommend US and TIAB [20]. To optimize clinical applicability, we use a follow-up strategy based on ultrasound risk stratification using the EU-TIRADS system. In our study, based on EU-TIRADS criteria, 24 of 46 nodules were not subjected to FNAB because they had benign and low-risk characteristics. Since the design of our study was retrospective, further investigation into the outcomes and follow-up of benign nodules could not be performed. According to some opinions, it has been reported that incidental thyroid nodules that are found to be malignant are overemphasized and further investigated despite the low mortality rate and mild prognosis [21]. In a consensus supporting this view, it was stated that further investigation may not be performed if the patient's 5-year life expectancy is low because the probability of the nodule being malignant is less than 15% [18].

In the literature, the malignancy rates of thyroid nodules showing FDG uptake have been reported at different rates. For example, in a meta-analysis including 22 studies, it was reported that the malignancy rate of thyroid nodules showing FDG thump was 35% [3]. In another meta-analysis, the malignancy rate was reported as 30.8% [9]. On the contrary, in other studies in the literature in which most of the thyroid nodules showing FDG uptake were followed up, this rate was reported to be around 15% and it was actually shown that the malignancy rate may be lower [22]. In our study, the malignancy rate in all nodules showing uptake (focal and diffuse) was found to be 13.6% (3/22), while the malignancy rate in nodules showing focal uptake was found to be 16.6% (3/18). Similarly, in the study of Elzein et al., 16 of 30 nodules in 1730 FDG PET/CT scans underwent FNAB and malignancy was detected in only 2 (12.5%) [23]. The relatively low malignancy rates in our study compared to the literature may be related to the risk classification we used to evaluate the nodules. In addition, the fact that not only histopathology but also cytopathology reports were used in some of the other studies in the literature to assess the risk of malignancy may have contributed to the higher detection of malignancy rates [12].

The pathology of the 3 malignant nodules in our study was reported as papillary thyroid carcinoma, the most common type of differentiated thyroid cancer in the literature [3]. Metastasis was not detected in any of the cases.

An association between thyroid nodules and breast cancer is known [24]. A recent study by Chen-Yu Ma et al. showed an increased frequency of thyroid nodules in patients with breast cancer (especially in hormone-positive breast cancer patients) [25]. In this study, breast cancer was found to be the most common malignancy accompanying thyroid nodules.

The first limitation of our study is the small number of patients, as the PET-CT device in our hospital has been in use since 2021. Secondly, only the EU-TIRADS classification was used as the US risk classification when evaluating nodules. Thirdly, since it was a retrospective study, some data cannot be accessed. On the other hand, the strength of our study is that the malignancy risk of the nodules was confirmed by histopathology.

In conclusion, this current study demonstrated that when focal uptake is observed on 18F-FDG PET-CT, FNAB should be performed if the nodule is considered ultrasonographically suspicious, regardless of the SUVmax value. During the diagnosis or follow-up of oncologic patients, thyroid uptake in PET-CT may be overlooked due to a focus on the primary malignancy, and therefore, these patients may not be referred to endocrinology clinics. To avoid missing such cases, it is essential to determine the need for diagnostic evaluation in patients with focal thyroid uptake in 18F-FDG PET-CT, to clarify outcomes through diagnostic interventions, and to increase awareness. Establishing optimal management will not only reduce unnecessary FNABs and subsequent surgeries but also allow for a personalized approach based on the primary malignancy, performance status, and survival of oncologic patients. Therefore, further guiding studies and clinical guidelines are needed for the diagnosis, management, and follow-up of incidental thyroid nodules showing uptake in PET-CT.

Declaration of conflicting interests

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Ethics Approval

The study was approved by the ethics committee of the Ankara Training and Research Hospital (approval date and number: 17 April 2024-E-24/60).

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Research Article

Clinical outcomes of sorafenib treatment in Child-Pugh B hepatocellular carcinoma patients: a retrospective single-center study

Child-Pugh B hepatoselüler karsinom hastalarında sorafenib tedavisinin klinik sonuçları ve prognostik faktörleri: retrospektif tek merkezli bir çalışma

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Abstract

Aim: Hepatocellular carcinoma (HCC) is a leading cause of liver-related mortality, particularly in patients with cirrhosis. sorafenib is the one of primary systemic therapies for advanced HCC. This study evaluates the clinical outcomes and prognostic factors of sorafenib treatment in this patient group.

Material and Methods: This retrospective, single-center study included 28 Child-Pugh B HCC patients treated with sorafenib. Patient characteristics, OS, and PFS were analyzed. Kaplan-Meier survival analysis and Cox regression were performed to identify prognostic factors, including TACE, TARE, and tumor size.

Results: Among 28 patients, 85.7% were male, and 89.3% had cirrhosis. Most (64.3%) underwent biopsy, and extrahepatic disease was rare (3.6%). HCC lesions were >5 cm in 67.9% of patients. Sorafenib resulted in SD (57.1%), PR (10.7%), and PD (32.1%). Median OS and PFS were 8.1 and 5.9 months, respectively. Cox regression analysis did not identify significant prognostic factors, as TACE, TARE, and tumor size showed no meaningful impact on survival. The median OS and PFS were 8.1 and 5.9 months, respectively. Most patients (57.1%) SD, while 32.1% had PD.

Conclusions: Sorafenib stabilized disease in most patients (57.1%), but 32.1% experienced progression, highlighting the need for improved patient selection and combination therapies. Compared to SHARP and Asia-Pacific trials, our study's outcomes differed due to the exclusive inclusion of Child-Pugh B score 7 patients. These findings underscore the importance of refining treatment strategies and identifying predictive biomarkers to optimize outcomes.

Keywords: hepatocellular carcinoma, sorafenib, child-B

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Öz

Amaç: Hepatoselüler karsinom (HCC), özellikle sirozu olan hastalarda karaciğerle ilişkili ölümlerin önde gelen nedenlerinden biridir. Sorafenib, ileri evre HCC için birincil sistemik tedavilerden biridir. Bu çalışma, Sorafenib tedavisinin klinik sonuçlarını ve prognostik faktörlerini değerlendirmektedir.

Gereç ve Yöntemler: Bu retrospektif, tek merkezli çalışma, Sorafenib ile tedavi edilen 28 Child-Pugh B HCC hastasını içermektedir. Hasta özellikleri, genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) analiz edilmiştir. Kaplan-Meier sağkalım analizi ve Cox regresyon analizi, transarteryel kemoembolizasyon (TACE), transarteryel radyoembolizasyon (TARE) ve tümör boyutu gibi prognostik faktörleri belirlemek için kullanılmıştır.

Bulgular: Çalışmadaki 28 hastanın %85,7'si erkek ve %89,3'ü sirozluydu. Çoğu (%64,3) biyopsi yapılmıştı ve ekstrahepatik hastalık nadirdi (%3,6). Hastaların %67,9'unda HCC lezyonları >5 cm idi. Sorafenib tedavisi ile hastaların %57,1'inde stabil hastalık (SD), %10,7'sinde kısmi yanıt (PR) ve %32,1'inde progresif hastalık (PD) gözlendi. Ortanca OS ve PFS sırasıyla 8,1 ve 5,9 ay olarak hesaplandı. Cox regresyon analizi, TACE, TARE ve tümör boyutunun sağkalım üzerinde anlamlı bir etkisi olmadığını gösterdi.

Sonuçlar: Sorafenib, hastaların çoğunda (%57,1) hastalığın stabil kalmasını sağladı, ancak %32,1'inde progresyon gözlendi. Bu durum, hasta seçiminin iyileştirilmesi ve kombine tedavi yaklaşımlarının değerlendirilmesi gerektiğini vurgulamaktadır. SHARP ve Asya-Pasifik çalışmalarına kıyasla, çalışmamızda yalnızca Child-Pugh B hastalarının dahil edilmesi nedeniyle farklı sonuçlar elde edilmiştir. Bu bulgular, tedavi stratejilerinin optimize edilmesi ve prognostik biyobelirteçlerin belirlenmesinin önemini ortaya koymaktadır.

Anahtar Kelimeler: hepatosellür kanser, sorafenib, child-B

Introduction

Hepatocellular carcinoma (HCC) is a primary liver malignant tumor that typically develops in the setting of chronic liver disease, particularly in patients with cirrhosis or chronic hepatitis B virus infection. Approximately 75% of primary liver tumors are HCC, with cholangiocarcinoma comprising most of the remaining cases [1]. Recent advances in imaging have increased the early detection rate of HCC. Curative therapies, such as hepatic resection, liver transplantation, and radiofrequency ablation, are possible in early-stage HCC and thus improve patient survival rates [2,3]. Otherwise, trans-arterial chemoembolization is an important locoregional treatment for patients with unresectable HCC [4]. Sorafenib is a multitargeted, orally active small molecule tyrosine kinase inhibitors (TKI) that inhibits Raf kinase and the vascular endothelial growth factor receptor (VEGFR) intracellular kinase pathway [5]. It was the first systemic agent to show an overall survival (OS) benefit for advanced HCC in a placebo-controlled trial [6].

The efficacy of sorafenib has been extensively studied, with pivotal trials such as the SHARP and Asia-Pacific studies establishing its role in improving OS and progression-free survival (PFS) in patients with advanced HCC. However, real world studies indicate significant variability in patient response, particularly among different liver function subgroups. The GIDEON study and other prospective analyses suggest that treatment outcomes may be influenced by factors such as Child-Pugh classification, prior locoregional therapies, and baseline tumor burden.

In this study, we aimed to evaluate the clinical outcomes of sorafenib treatment in a cohort of patients with advanced HCC, focusing on survival metrics and potential prognostic factors. Unlike previous large-scale studies, our analysis exclusively included patients classified as Child-Pugh B, allowing for a more detailed assessment of treatment response in this specific patient population. Additionally, we sought to determine the impact of trans-arterial chemoembolization (TACE) and trans-arterial radioembolization (TARE) and HCC lesion size on survival outcomes in this cohort.

Material and Methods

This study was conducted retrospectively on 28 patients who were diagnosed with HCC and used sorafenib between 2017 and 2023 at Gülhane Training and Research Hospital.

Patient demographic and clinical characteristics were extracted from medical records, including gender, cirrhosis status, biopsy status, and presence of extrahepatic disease. Tumor characteristics such as lesion size and metastatic involvement were also recorded. The primary endpoints were OS and PFS,

assessed using Kaplan-Meier survival analysis. Ethical approval for this study was obtained from the Gülhane Training and Research Hospital Ethics Committee, and the study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, the Ethics Committee of Gülhane Training and Research Hospital (2024/506) waived the obligation to obtain informed consent.

Stastistical Analysis

Cox-regression analysis was utilized to identify potential prognostic factors influencing survival outcomes. The independent variables examined included the administration of TACE and TARE procedures (performed vs. not performed) and HCC lesion size. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to determine statistical significance. OS was defined as the time from diagnosis to death from any cause, whereas PFS was defined as the time from the initiation of sorafenib treatment to disease progression.

All statistical analyses were performed using the IBM SPSS Statistics 27.0 software package. Continuous variables were described as medians (interquartile range (IQR)) and categorical variables as percentages. The Chi-square test was used to compare categorical variables, while the Mann-Whitney U test or Student's T-test was used to compare continuous variables. Survival curves and rates were estimated using the Kaplan-Meier method. The log-rank test was used to compare the survival outcomes between the groups. All reported p values were two-sided, and p values < 0.05 were regarded as statistically significant.

Results

An analysis of patient characteristics in this study, which included 28 patients, revealed that most of the study cohort was male (85.7%) and had underlying cirrhosis (89.3%). Additionally, a substantial proportion of patients (64.3%) had undergone a biopsy, while extrahepatic disease was observed in only a small fraction (3.6%).

None of the patients exhibited lung or bone involvement. Regarding HCC lesion size, 67.9% of patients had lesions larger than 5 cm. The analysis of responses to sorafenib indicates that most patients (57.1%) exhibited stable disease (SD), suggesting that sorafenib effectively maintains disease stability in a significant proportion of cases. A smaller percentage (10.7%) achieved a partial response (PR), while no patients achieved a complete response (CR). Progressive disease (PD) was observed in 32.1% of patients, highlighting the variability in treatment outcomes (Table 1).

Table 1. Baseline characteristics

Variable	Category	Count (n)	Percentage (%)
Gender	Male	24	85.7
	Female	4	14.3
Biopsy status	No	10	35.7
	Yes	18	64.3
Cirrhosis status	No	3	10.3
	Yes	25	89.3
Extrahepatic disease	No	27	96.4
	Yes	1	3.6
HCC lesion size	<5 cm	9	32.1
	>5 cm	19	67.9
TAKE rtatus	No	22	78.6
	Yes	6	21.4
TARE rtatus	No	23	82.1
	Yes	5	17.9
Best response to sorafenib	CR	0	0
	PR	3	10.7
	SD	16	57.1
	PD	9	32.1

The Kaplan-Meier survival analysis estimated a median OS was calculated as 8.1 months (95% CI: 6.274-10.059) (Figure 1). The median PFS time was 5.9 months (95% CI: 4.463–7.403) (Figure 2).

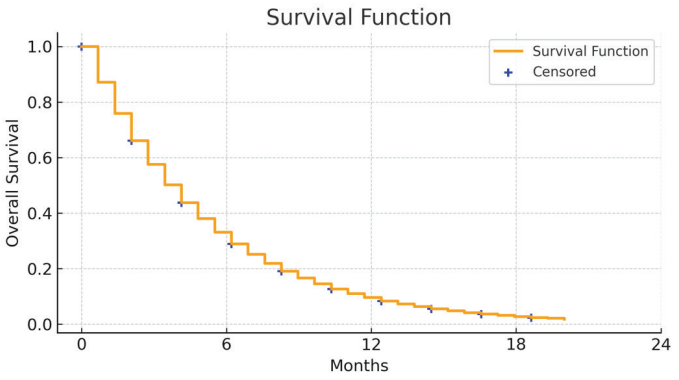

Figure 1. The median OS was calculated as 8.1 months (95% CI: 6.274-10.059)

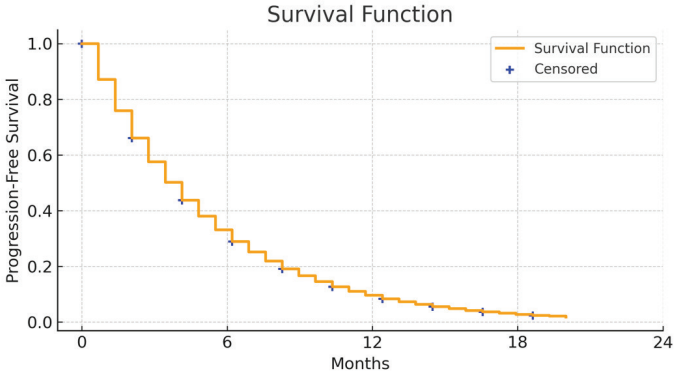

Figure 2. The median PFS time was 5.9 months (95% CI: 4.463–7.403).

A Cox-regression analysis was performed to evaluate the prognostic factors influencing patient outcomes. The variables included in the model were the presence of TACE (performed vs. not performed), TARE (performed vs. not performed), and HCC lesion size. None of the variables showed statistically significant associations with patient survival ($p > 0.05$ for all). Specifically, the HR for TACE (performed vs. not performed) was 1.39 (95% CI: 0.433–4.500, $p = 0.576$), indicating no significant impact on prognosis. Similarly, TARE (performed vs. not performed) had a HR of 0.78 (95% CI: 0.251–2.479, $p = 0.684$), suggesting no meaningful effect on survival. HCC lesion size also did not demonstrate a significant association with patient outcomes (95% CI: 0.351–2.198, $p = 0.781$).

Discussion

The findings of this study indicate that sorafenib treatment resulted in a SD response in most patients (57.1%), suggesting a role in disease stabilization rather than inducing tumor regression. This aligns with previous studies demonstrating that sorafenib provides a clinical benefit primarily by delaying disease progression rather than achieving high response rates [6,7].

Despite the observed disease stabilization, a significant proportion of patients (32.1%) exhibited PD, highlighting the need for improved patient selection criteria or combination therapies to enhance treatment effectiveness. The lack of CR and low PR rates (10.7%) emphasize the limited tumor shrinkage potential of sorafenib, reinforcing its role as a disease-modifying rather than curative agent in HCC management.

In the SHARP study, 95% of the patients were classified as Child-Pugh A, while the remaining 5% were Child-Pugh B. Based on the study findings, the median PFS and OS were measured as 5.5 months and 10.7 months, respectively [6]. In another study, the sorafenib Asia-Pacific trial, in which 97% of the patients were classified as Child-Pugh A, the median PFS and OS were reported as 6.5 months and 2.8 months, respectively [7]. The differences observed in our study may be attributed to the smaller patient cohort and the fact that all patients included were classified as Child-Pugh B, which could have influenced the treatment outcomes. T. Pressiani et al. conducted a prospective study on patients receiving sorafenib, in which the PFS and OS in the Child-Pugh B subgroup were determined to be 2.1 months and 3.8 months, respectively [8]. In an order prospective study conducted by M. Nakomo et al., which included a total of 365 patients, of whom 100 were classified as Child-Pugh B, the median PFS and OS were reported as 3.6 and 10.3 months, respectively [9]. In our study Kaplan-Meier survival analysis revealed a median OS of 8.1 and a median PFS of 5.9 months.

An analysis based on the results of the GIDEON study reported that in patients receiving sorafenib, those who underwent TACE had a median OS of 19 months and a median PFS of 8.4 months, whereas in patients who did not undergo TACE, the median OS and PFS were 9.8 months and 5.9 months, respectively [10]. In our study, the Cox-regression analysis did not identify significant prognostic factors among the examined variables (TACE and TARE procedures, HCC lesion size), suggesting that these clinical parameters may not serve as strong independent predictors of survival in patients treated with sorafenib. Unlike the GIDEON analysis, our study exclusively included patients classified as Child-Pugh B, which may have contributed to this difference in findings. The STAH trial, which randomized 339 patients with advanced HCC to receive sorafenib with or without concurrent TACE, demonstrated that the addition of TACE did not improve overall survival compared with sorafenib alone but was associated with a significant deterioration in liver function [11]. SORAMIC trial, which included 424 patients not eligible for TACE (90% classified as Child-Pugh A), showed that the addition of radioembolization to sorafenib did not lead to a significant survival benefit (median OS of 12.1 vs. 11.4 months) and was linked to increased rates of grade 3 or 4 adverse events [12] .These findings further emphasize the need for careful patient selection when considering combination approaches with sorafenib.

Overall, while sorafenib remains a standard treatment for advanced HCC, its limited efficacy highlights the importance of ongoing clinical investigations to identify novel therapeutic strategies that can improve patient prognosis and treatment response rates.

The analysis of responses to sorafenib indicates that most patients (57.1%) exhibited SD, suggesting that sorafenib effectively maintains disease stability in a significant proportion of cases. A smaller percentage (10.7%) achieved a PR, while no patients achieved a CR. PD was observed in 32.1% of patients, highlighting the variability in treatment outcomes. These findings underscore the need for further investigation into optimizing treatment efficacy and identifying predictive biomarkers for better patient stratification.

In conclusion, this study demonstrated that in the treatment of Child-Pugh B score 7 HCC patients, sorafenib primarily provides clinical benefit by delaying disease progression rather than achieving high response rates.

Declaration of conflicting interests

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Ethics approval

This study was approved by Gülhane Training and Research Hospital Ethics Committee with protocol number 2024/506

Authors' contribution

ÖFK: writing, original draft, methodology, investigation, data curation, conception, literature review, analisis, AT: writing, original draft, methodology, data curation, EKT: investigation, data curation, HA: investigation, data curation, supervision, NK: methodology, editing, critical review

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Research Article

Prognostic value of aggregate index of systemic inflammation in acute ischemic stroke mortality

Akut iskemik inmede sistemik inflamasyonun toplam indeksinin prognostik değeri

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Abstract

Aim: Systemic inflammation plays a key role in the pathophysiology of acute ischemic stroke (AIS), influencing disease severity and outcomes. The Aggregate Index of Systemic Inflammation (AISI) is a novel inflammatory biomarker that integrates multiple hematological parameters. This study aimed to evaluate the prognostic value of AISI in predicting 30-day mortality in AIS patients.

Material and Methods: This retrospective cohort study included patients diagnosed with AIS in the emergency department of a tertiary care hospital between January 1, 2022, and January 1, 2025. AISI was calculated as (Neutrophil count × Monocyte count × Platelet count) / Lymphocyte count, with all components expressed in absolute values ($\times 10^9$/L). The primary outcome was 30-day all-cause mortality. Logistic regression analysis was performed to assess the independent prognostic value of AISI. Model performance was evaluated using accuracy, sensitivity, specificity, and the area under the receiver operating characteristic curve (AUROC).

Results: A total of 663 AIS patients were analyzed, including 573 survivors (86.4%) and 90 non-survivors (13.6%). AISI values were significantly higher in non-survivors compared to survivors (755.4 ± 410.8 vs. 396.7 ± 216.1, $p < 0.001$). Multivariate logistic regression analysis identified AISI as an independent predictor of 30-day mortality (OR: 1.10, 95% CI: 1.02 - 1.19, $p = 0.040$). The AUROC for AISI was 0.820, indicating good discriminatory ability.

Conclusions: AISI was found to be an independent predictor of 30-day mortality in AIS patients, highlighting the potential role of systemic inflammation in stroke prognosis. Given its accessibility and ease of calculation, AISI could serve as a useful marker for early risk stratification in clinical practice. However, further prospective, multicenter studies are needed to validate its clinical utility and compare it with other established inflammatory indices.

Keywords: acute ischemic stroke, inflammation, mortality

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Öz

Amaç: Sistemik inflamasyon, akut iskemik inmenin (Aİİ) patofizyolojisinde kritik bir rol oynayarak hastalık şiddetini ve sonuçlarını etkiler. Sistemik İnflamasyonun Toplam İndeksi (AISI), birden fazla hematolojik parametreyi entegre eden yeni bir inflamatuvar biyobelirteçtir. Bu çalışmada, AISI'nin Aİİ hastalarında 30 günlük mortaliteyi öngörmedeki prognostik değeri değerlendirilmiştir.

Gereç ve Yöntemler: Bu retrospektif kohort çalışmasına, 1 Ocak 2022 ile 1 Ocak 2025 tarihleri arasında üçüncü basamak bir hastanenin acil servisinde Aİİ tanısı alan hastalar dahil edilmiştir. AISI, (Nötrofil sayısı × Monosit sayısı × Trombosit sayısı) / Lenfosit sayısı formülüyle hesaplanmış ve tüm bileşenler mutlak değerler ($\times 10^9$/L) cinsinden ifade edilmiştir. Birincil sonuç değişkeni, 30 günlük tüm nedenlere bağlı mortalite olarak belirlenmiştir. AISI'nin bağımsız prognostik değerini değerlendirmek için lojistik regresyon analizi yapılmış, model performansı doğruluk, duyarlılık, özgüllük ve alıcı işletim karakteristik eğrisi altındaki alan (AUROC) kullanılarak değerlendirilmiştir.

Bulgular: Toplam 663 Aİİ hastası analiz edilmiş, bunlardan 573'ü (%86,4) sağ kalırken, 90'ı (%13,6) yaşamını kaybetmiştir. AISI değerleri, yaşamını kaybeden hastalarda sağ kalanlara kıyasla anlamlı olarak daha yüksek bulunmuştur (755,4 ± 410,8 vs. 396,7 ± 216,1, $p < 0,001$). Çok değişkenli lojistik regresyon analizinde AISI, 30 günlük mortalitenin bağımsız bir prediktörü olarak belirlenmiştir (OR: 1,10, %95 GA: 1,02 - 1,19, $p = 0,040$). AISI için AUROC değeri 0,820 olup iyi bir ayırt edici güce işaret etmektedir.

Sonuçlar: AISI, Aİİ hastalarında 30 günlük mortalitenin bağımsız bir öngörücüsü olarak belirlenmiş ve sistemik inflamasyonun inme prognozundaki potansiyel rolünü ortaya koymuştur. Erişilebilirliği ve kolay hesaplanabilirliği göz önüne alındığında, AISI klinik uygulamada erken risk sınıflandırması için faydalı bir belirteç olarak kullanılabilir. Ancak, klinik kullanımının doğrulanması ve diğer yerleşik inflamatuvar indekslerle karşılaştırılması için daha fazla prospektif, çok merkezli çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: akut iskemik inme, inflamasyon, mortalite

Introduction

Acute ischemic stroke (AIS) remains a major global health burden and a leading cause of morbidity and mortality worldwide [1-3]. According to the Global Burden of Disease (GBD) 2021 database, the global incidence of ischemic stroke in 2021 was estimated at 7.8 million cases, with an age-standardized incidence rate of 92.39 per 100,000 people. While the incidence of ischemic stroke has shown a relative decline over the past three decades, it continues to contribute significantly to long-term disability and healthcare costs. The disability-adjusted life years (DALYs) associated with ischemic stroke were reported as 70.4 million in 2021, reflecting its substantial impact on global health systems [4]. Despite advances in acute management and secondary prevention strategies, ischemic stroke remains the second leading cause of death globally and disproportionately affects low- and middle-income countries [5]. Given the high disease burden, identifying prognostic markers that facilitate early risk stratification and improve patient outcomes remains a critical area of research.

Inflammation plays a crucial role in the pathophysiology of AIS, contributing to neuronal injury, blood-brain barrier disruption, and secondary brain damage [6]. Systemic inflammatory responses following an ischemic event are associated with poor clinical outcomes, including increased infarct volume, neurological deterioration, and higher mortality rates [7]. Several hematological biomarkers, including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII), have been studied as potential prognostic indicators in stroke patients [8-10]. Recently, the Aggregate Index of Systemic Inflammation (AISI) has been proposed as a novel marker that integrates multiple inflammatory parameters to provide a more comprehensive assessment of systemic inflammation. However, the prognostic utility of AISI in AIS patients remains largely unexplored [11]. Given the strong association between inflammation and stroke outcomes, evaluating the role of AISI in predicting mortality could enhance risk stratification and inform early therapeutic strategies.

We hypothesize that the AISI is an independent predictor of mortality in patients with AIS.

Material and Methods

This retrospective cohort study included patients diagnosed with AIS in the emergency department of a tertiary care hospital between January 1, 2022, and January 1, 2025. Ethical approval for the study was obtained from the Gazi Yaşargil Education and Research Hosptial's Ethics Committee (349, 07.02.2025). Due to the retrospective nature of the study, the requirement for informed consent was waived.

Patients aged 18 years or older who were diagnosed with AIS based on clinical evaluation and neuroimaging (CT or MRI) findings were included in the study. Those with hemorrhagic stroke, other non-ischemic cerebrovascular events, severe infection, malignancy, or autoimmune disease that could influence inflammatory markers were excluded. Additionally, patients receiving immunosuppressive or corticosteroid therapy or those with missing laboratory parameters necessary for the calculation of the AISI were not included in the final analysis.

Data were retrieved from the hospital's electronic medical records. Baseline demographic characteristics, including age, sex, and comorbid conditions such as hypertension, diabetes mellitus, and atrial fibrillation, were collected. Vital signs at admission, including blood pressure, heart rate, respiratory rate, oxygen saturation, and temperature, were recorded. Laboratory parameters, including neutrophil count, lymphocyte count, platelet count, monocyte count, hemoglobin, C-reactive protein (CRP), blood urea nitrogen (BUN), lactate, and creatinine levels, were extracted for analysis.

The AISI was calculated as (Neutrophil count × Monocyte count × Platelet count) / Lymphocyte count, with all components expressed in absolute values ($\times 10^9$/L) [12].

The primary outcome of this study was 30-day all-cause mortality, defined as death occurring within 30 days of hospital admission due to any cause. In cases where hospital records did not contain definitive mortality information, telephone follow-up with patients' relatives was conducted to verify the outcome.

Statistical Analysis

The data were analyzed using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were used to summarize the baseline characteristics of the patients. Continuous variables were presented as mean ± standard deviation (SD) for normally distributed data and median (interquartile range [IQR]) for non-normally distributed data. Categorical variables were summarized as frequencies and percentages. To compare continuous variables between the two groups, an independent samples t-test was used for normally distributed data, and the Mann-Whitney U test was used for non-normally distributed data. Categorical variables were compared using the Chi-square test or Fisher's exact test, depending on the expected frequency. A p-value of <0.05 was considered statistically significant. Multivariate logistic regression was conducted to identify independent risk factors for 30-day mortality, including variables with a p-value <0.20 from univariate analysis. The logistic regression model was fitted using standard procedures. The goodness of fit was assessed using the Hosmer-Lemeshow test, and model performance was evaluated using accuracy, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC). The dataset was split into training and test sets in an 80-20 ratio. ROC analysis was performed to evaluate the predictive performance of the AISI in predicting 30-day mortality. The optimal cutoff value for AISI was determined using the Youden index, and sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (-LR) were computed.

Results

In this study, we analyzed a total of 663 patients diagnosed with AIS, consisting of 573 survivors (86.4%) and 90 deceased patients (13.6%). The mean age of survivors was 67.9 ± 11.8 years, significantly lower than that of deceased patients, who had a mean age of 75.9 ± 10.8 years (mean difference 8 years, 95% CI: 5.4 - 10.6, $p < 0.001$). The prevalence of hypertension was significantly higher in deceased patients (92.2%) compared to survivors (71.2%) ($p < 0.001$), while diabetes was more common among deceased patients (21.1%) compared to survivors (10.1%) ($p = 0.002$). Atrial fibrillation also occurred more frequently in deceased patients (17.8%) compared to survivors (5.8%) ($p < 0.001$). Systolic blood pressure was significantly higher in deceased patients (160.7 ± 14.7 mmHg) compared to survivors (149.5 ± 15.2 mmHg), with a mean difference of 11.2 mmHg (95% CI: 7.9 - 14.6), $p < 0.001$. Diastolic blood pressure was also significantly higher in deceased patients (86.9 ± 10.9 mmHg) compared to survivors (84.3 ± 9.8 mmHg), with a mean difference of 2.5 mmHg (95% CI: 0.3 - 4.8), $p = 0.024$. Respiratory rate (20.1 ± 5.5 bpm vs. 15.3 ± 4.1 bpm, $p < 0.001$) and oxygen saturation (91.7 ± 3.3% vs. 95.6 ± 1.9%, $p < 0.001$) were also significantly different between the two groups, with deceased patients showing higher respiratory rates and lower oxygen saturation. No significant difference in temperature was observed between the groups (36.8 ± 0.4°C vs. 36.8 ± 0.5°C, $p = 0.34$) (Table 1).

Table 1. Baseline demographic and clinical characteristics of patients with acute ischemic stroke.				
Parameter	Survivor (n=573)	Deceased (n=90)	p	Mean difference (95% CI)
Age (years)	67.9 ± 11.8	75.9 ± 10.8	<0.001	8 (5.4 - 10.6)
Sex (male)	348 (60.7%)	57 (63.3%)	0.639	
Hypertension	408 (71.2%)	83 (92.2%)	<0.001	
Diabetes	58 (10.1%)	19 (21.1%)	0.002	
Atrial fibrillation	33 (5.8%)	16 (17.8%)	<0.001	
Systolic BP (mmHg)	149.5 ± 15.2	160.7 ± 14.7	<0.001	11.2 (7.9 - 14.6)
Diastolic BP (mmHg)	84.3 ± 9.8	86.9 ± 10.9	0.024	2.5 (0.3 - 4.8)
Heart rate (bpm)	85.6 ± 10.1	84.6 ± 8.6	0.407	
Respiratory rate	15.3 ± 4.1	20.1 ± 5.5	<0.001	4.8 (3.9 - 5.8)
Oxygen saturation (%)	95.6 ± 1.9	91.7 ± 3.3	<0.001	3.9 (3.4 - 4.4)
Temperature (°C)	36.8 ± 0.4	36.8 ± 0.5	0.34	
Abbrev.: BP: Blood Pressure; bpm: Beats per minute				

Laboratory parameters revealed that neutrophil count was significantly higher in deceased patients (7.1 ± 1.5 × 10^9/L) compared to survivors (5 ± 1.2 × 10^9/L), with a mean difference of 2.1 × 10^9/L (95% CI: 1.8 - 2.4), p < 0.001. C-reactive protein (CRP) levels were significantly elevated in deceased patients (17.4 ± 4.7 mg/L) compared to survivors (10 ± 2.8 mg/L), with a mean difference of 7.4 mg/L (95% CI: 6.7 - 8.1), p < 0.001. Lactate levels were significantly higher in deceased patients (3 ± 0.5 mmol/L) compared to survivors (1.8 ± 0.4 mmol/L), with a mean difference of 1.2 mmol/L (95% CI: 1.1 - 1.3), p < 0.001. The AISI was also significantly higher in deceased patients (755.4 ± 410.8) compared to survivors (396.7 ± 216.1), with a mean difference of 358.7 (95% CI: 302.8 - 414.7), p < 0.001. No significant differences were observed for lymphocyte, monocyte, hemoglobin, creatinine, and platelet counts (Table 2).

Table 2. Laboratory parameters of patients with acute ischemic stroke at admission.				
Parameter	Survivor (n=573)	Deceased (n=90)	p	Mean difference (95% CI)
Neutrophil (10^9/L)	5 ± 1.2	7.1 ± 1.5	<0.001	2.1 (1.8 – 2.4)
Lymphocyte (10^9/L)	2 ± 0.5	2 ± 0.4	0.126	0.5 (0.4 - 0.6)
Monocyte (10^9/L)	0.6 ± 0.1	0.6 ± 0.2	0.058	
Hemoglobin (g/dL)	13.8 ± 1.2	13.8 ± 1.7	0.757	
CRP (mg/L)	10 ± 2.8	17.4 ± 4.7	<0.001	7.4 (6.7 - 8.1)
BUN (mg/dL)	21.2 ± 4	21.9 ± 4.6	0.146	
Creatinine (mg/dL)	1.6 ± 0.3	1.5 ± 0.4	0.127	
Platelet (103/µL)	251.4 ± 47.4	242.6 ± 41.1	0.097	
AISI	396.7 ± 216.1	755.4 ± 410.8	<0.001	358.7 (302.8 - 414.7)
Abbrev.: RDW: Red Cell Distribution Width, CRP: C-Reactive Protein, BUN: Blood Urea Nitrogen, AISI: Aggregate Index of Systemic Inflammation				

The multivariate logistic regression analysis revealed that hypertension (odds ratio [OR]: 3.67, 95% CI: 1.50 - 10.43, p = 0.003) and neutrophil count (OR: 2.98, 95% CI: 2.25 - 4.09, p < 0.001) were significant risk factors for 30-day mortality (Table 3).

Table 3. Multivariate logistic regression analysis for predicting 30-day mortality in acute ischemic stroke patients.		
Variable	OR (95% CI)	p
Hypertension	3.67 (1.50 - 10.43)	0.003
BUN	1.09 (1.00 - 1.19)	0.044
Neutrophil	2.98 (2.25 - 4.09)	<0.001
AISI	1.10 (1.02 - 1.19)	0.040
Hemoglobin	1.20 (0.87 - 1.65)	0.263
Temperature	1.06 (0.40 - 2.80)	0.911
Monocyte	1.84 (0.16 - 21.21)	0.626
Platelet	0.99 (0.98 - 1.01)	0.358

The AISI was significantly associated with 30-day mortality (OR: 1.10, 95% CI: 1.02 - 1.19, p = 0.040). Other factors, including BUN, hemoglobin, temperature, monocyte, and platelet counts, were not significant predictors. Model performance on both training and test sets showed an accuracy of 85.12% (95% CI: 82.1% - 87.6%) for the training set, with sensitivity and specificity of 94.50% and 67.28%, respectively. The positive predictive value (PPV) was 90.12%, while the negative predictive value (NPV) was 79.53%. Receiver operating characteristic analysis for AISI revealed an area under the curve (AUROC) of 0.820 (95% CI: 0.770 - 0.870), with an optimal criterion of 512.2 (Figure 1).

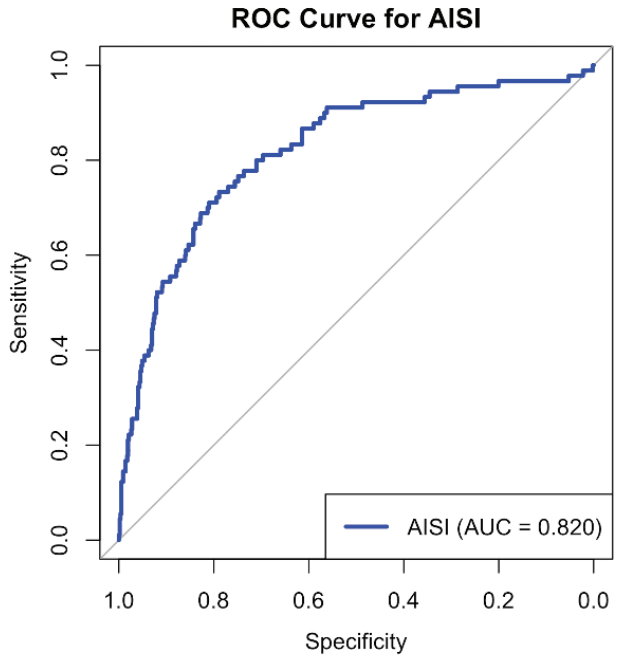

Figure 1. Receiver operating characteristic curve for the aggregate index of systemic inflammation (AISI) in predicting 30-day mortality.

Sensitivity was 62.1% (95% CI: 42.3 - 79.3%) and specificity was 88.6% (95% CI: 85.6 - 91%). The positive likelihood ratio (+LR) was 5.47 (95% CI: 3.82 - 7.83) and the negative likelihood ratio (-LR) was 0.43 (95% CI: 0.27 - 0.69) (Table 4).

Discussion

This study demonstrated that the AISI is an independent predictor of 30-day mortality in acute ischemic stroke patients. Higher AISI values were significantly associated with increased mortality risk, supporting its potential role in risk stratification.

Inflammation plays a pivotal role in the pathophysiology of AIS. Following an ischemic event, a cascade of inflammatory responses is initiated, contributing to both immediate and delayed neuronal injury. The initial phase involves the activation of resident immune cells, particularly microglia, which rapidly respond to ischemic insult by adopting a pro-inflammatory phenotype. This activation leads to the release of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α), exacerbating neuronal damage [13]. Concurrently, the ischemic environment disrupts the blood-brain barrier (BBB), increasing its permeability and allowing peripheral immune cells, including neutrophils and monocytes, to infiltrate the brain parenchyma. These infiltrating cells further amplify the inflammatory milieu through the production of reactive oxygen species (ROS) and additional cytokines, leading to oxidative stress and further compromise of neuronal integrity [14]. Recent studies have highlighted the dual role of neuroinflammation in AIS, where it can be both detrimental and beneficial. While acute inflammation contributes to tissue damage, it also facilitates debris clearance and tissue repair processes. The balance between these opposing effects is critical in determining clinical outcomes [15].

Table 4. Receiver operating characteristic analysis for aggregate index of systemic inflammation in predicting 30-day mortality.

Parameter	AUROC	Criterion	Sensitivity (95% CI)	Specificity (95% CI)	+LR (95% CI)	-LR (95% CI)
AISI	0.820 (0.770 - 0.870)	512.2	62.1 (42.3 - 79.3)	88.6 (85.6 - 91)	5.47 (3.82 - 7.83)	0.43 (0.27 - 0.69)

AUROC: Area Under Receiver Operating Characteristic Curve; +LR: Positive Likelihood Ratio; -LR: Negative Likelihood Ratio; CI: Confidence Interval

The AISI is a composite inflammatory marker incorporating neutrophil, monocyte, lymphocyte, and platelet counts, reflecting a broader spectrum of immune activation. AISI has been investigated in various clinical conditions, including hypertension, where it has been linked to increased cardiovascular risk, and idiopathic pulmonary fibrosis, where it correlates with disease severity and progression [16,17]. Studies have also explored its role in COVID-19-related inflammation and chronic obstructive pulmonary disease (COPD), suggesting its potential as a generalizable marker of systemic immune activation [18,19].

In the context of AIS, the prognostic value of AISI remains relatively underexplored. However, recent evidence by Göçmen et al. demonstrated that stroke patients exhibit significantly elevated AISI levels compared to healthy controls [11]. Their findings suggest that AISI is particularly high in hemorrhagic stroke cases and that an AISI threshold above 507.45 is associated with increased mortality risk. These findings are in agreement with the results of the present study, where AISI was identified as an independent predictor of 30-day mortality in AIS patients. The ability of AISI to capture multiple inflammatory pathways may explain its prognostic utility, offering a more comprehensive risk stratification tool compared to traditional inflammatory markers. Furthermore, the implementation of AISI in clinical practice, especially in emergency departments and stroke units, may offer practical advantages. As a rapid and cost-effective inflammatory

marker derived from routine hematological tests, AISI could be integrated into early risk stratification protocols. Identifying high-risk AIS patients upon admission may support timely clinical decision-making and resource allocation. Future multicenter studies should explore the generalizability of AISI across diverse patient populations and healthcare settings to better define its clinical utility. While AISI has shown promise as a prognostic indicator, further studies are required to determine its relative performance compared to other inflammation-based indices and to assess its clinical applicability in routine stroke management.

Limitations of the study

First, its retrospective design may introduce selection bias and limit the ability to establish causal relationships. Second, as a single-center study, the findings may not be generalizable to broader populations, and external validation in multicenter cohorts is needed. Third, the study lacks a control group, which limits the ability to compare AISI levels in stroke patients with those in healthy individuals or patients with other neurological conditions. Fourth, this study focused specifically on AISI and did not compare it with other inflammatory indices such as NLR, PLR, or SII. Future research should evaluate the relative prognostic performance of AISI alongside these markers. Finally, long-term outcomes beyond 30 days were not evaluated, and further studies are required to determine the prognostic value of AISI over extended follow-up periods.

In conclusion, this study demonstrates that the AISI is an independent predictor of 30-day mortality in acute ischemic stroke patients. The significant association between higher AISI values and increased mortality risk highlights the potential role of systemic inflammation in stroke prognosis. As an easily accessible hematological marker, AISI could contribute to early risk stratification in clinical practice. However further prospective, multicenter studies are needed to validate its prognostic utility.

Declaration of conflicting interests

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

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Ethical Approval

This study was approved by the Gazi Yaşargil Education and Research Hosptial's ethics committee (ethics committee ruling number: 349, date: 07.02.2025).

Authors' contribution

NES: Conceptualization, Methodology, Writing, Original Draft. MÖ: Data Collection, Formal Analysis, Supervision, Writing, Review & Editing.Both authors have read and approved the final version of the manuscript.

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Research Article

Effects of genetic polymorphisms of ERCC1, XRCC1, GSTP1, ABCB1, and CYP on prognosis of patients with non-small cell lung cancer receiving platinum-based chemotherapy

ERCC1, XRCC1, GSTP1, ABCB1 ve CYP genetik polimorfizmlerinin platin tabanlı kemoterapi alan küçük hücreli dışı akciğer kanseri hastalarının prognozu üzerine etkileri

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Abstract

Aim: Lung cancer has the greatest mortality rates among both men and women and is the primary cause of cancer-related fatalities globally. The effectiveness of chemotherapy as a treatment for lung cancer varies greatly from patient to patient. Genetic factors affect the effectiveness of chemotherapy.

Material and Methods: age of patients, types of lung cancer, smoking status, genetic profiles (ERCC-C8062A, ERCC G28152A, GSTP1-A313G, ABCB1-C1236T, ABCB1-C3435T CYP3A5*2B, CYP3A4*1B), clinical stages of cancer, and treatment were evaluated by Kaplan-Meier estimates, and a cox regression model was conducted to assess survival probability and hazard of death of different groups.

Results: Cox regression analysis revealed that ABCB1-C1236T and ABCBC-C3435T wild and heterozygous alleles, smoking, adenocarcinoma, and other types of cancer were used for predicting progression time in advanced-stage lung cancer patients. However, no variables were found to be significant predictors of progression time in early-stage lung cancer patients.

Conclusions: Overall, our results imply that genetic variables may play a substantial influence in the rate of lung cancer progression and emphasize the need for tailored medication in the treatment of this disease. Discovering genetic markers that can predict the advancement time of lung cancer could assist clinicians in customizing treatment approaches for individual patients and improving the prognosis for people afflicted with this dreadful disease.

Keywords: lung cancer, NSCLC, chemotherapy, polymorphism, platinum

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Öz

Amaç: Akciğer kanseri, hem erkekler hem de kadınlar arasında en yüksek ölüm oranlarına sahip ve küresel olarak kanserle ilişkili ölümlerde birinci sırada yer almaktadır. Kemoterapinin akciğer kanseri tedavisindeki verimliliği, genetik faktörlerin kemoterapinin etkinliğini etkilemesinden dolayı hastadan hastaya büyük ölçüde değişiklik göstermektedir.

Gereç ve Yöntemler: Hastaların yaşı, akciğer kanseri tipleri, sigara içme durumu, genetik profili (ERCC-C8062A, ERCC G28152A, GSTP1-A313G, ABCB1-C1236T, ABCB1-C3435T CYP3A5*2B, CYP3A4*1B), kanserin klinik evreleri ve tedavi yöntemleri Kaplan-Meier tahminleri ve farklı grupların sağ kalma olasılıkları ve ölüm tehlikesini değerlendirmek amacıyla yapılan Cox regresyon modeli ile değerlendirildi.

Bulgular: Progresyon süresinin tahmin etmek için akciğer kanseri hastalarının, ABCB1-C1236T ve ABCBC-C3435T yabanıl ve heterozigot alelleri, sigara içme, adenokarsinomun ve diğer kanser türlerini kullanarak Cox regresyon analizi ile ileri evre akciğer kanseri hastalarında progresyon süresini tahmin edilebileceği ortaya koyulmuştur. Ancak, erken evre akciğer kanseri hastalarında progresyon süresinin tahmin etmek için hiçbir değişken bulunamamıştır.

Sonuçlar: Genel olarak, sonuçlarımız genetik değişkenlerin akciğer kanseri ilerleme oranında önemli bir etkiye sahip olabileceğini ve bu hastalığın tedavisinde kişiye özel ilaç tedavisine olan ihtiyacı vurgulamaktadır. Akciğer kanserinin progresyon süresini tahmin edebilecek genetik belirteçlerin keşfedilmesi, klinisyenlerin bireysel hastalar için tedavi yaklaşımlarını özelleştirmelerine ve bu korkunç hastalıktan muzdarip kişilerin prognozunu iyileştirmelerine yardımcı olabilir.

Anahtar Kelimeler: akciğer kanseri, KHDAK, kemoterapi, polimorfizm, platin

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Lung cancer was the most diagnosed cancer in 2022, accounting for nearly 2.5 million new cases, which represents approximately 12.4% of all cancer cases worldwide. Therefore, new therapy and diagnosis strategies are quite essential [2].

Platinum-based chemotherapy is the first-line treatment for lung cancer patients. Chemotherapy medications containing platinum, such as cisplatin, carboplatin, and oxaliplatin, function by binding to DNA and interfering with cell division, causing the death of rapidly dividing cancer cells. These medications have been widely utilized for over four decades and have greatly contributed to the improving cancer survival rates. The success of platinum-based chemotherapy varies depending on the type and stage of cancer, the patient's age, overall health, and genetics. Some patients may develop resistance to platinum-based chemotherapy, while others may experience severe side effects [3]. Thus, biomarkers that can predict the response to platinum-based chemotherapy and enhance patient outcomes must be identified [4].

Genetic variations in genes related to drug metabolism, drug transport, and DNA repair are some of the variables that could affect the response to platinum-based chemotherapy. Polymorphisms are changes in DNA sequences that can affect how proteins encoded by those sequences function. Certain polymorphisms may result in increased or decreased enzyme activity, impacting chemotherapeutic drug metabolism. Others may affect DNA repair ability, leading to increased chemotherapy sensitivity or resistance. The discovery of genetic variables that may affect the rate at which lung cancer progresses is one field of study that has attracted a lot of interest lately.

Several studies have investigated the association between polymorphisms in genes involved in drug metabolism, DNA repair, and transport and the lung cancer progression. ERCC1 and XRCC1 are genes involved in DNA repair, while GSTP1, CYP3A4, CYP3A5, and ABCB1 are genes involved in drug metabolism and transport [5-8]. Polymorphisms in these genes might affect their function and, in turn, impact the response to chemotherapy and the overall prognosis of patients with lung cancer. The ERCC1 gene plays a critical role in the nucleotide excision repair pathway, which is responsible for removing DNA damage induced by chemotherapeutic agents such as cisplatin. Polymorphisms in ERCC1 have been associated with reduced DNA repair efficiency and increased cellular sensitivity to cisplatin-based chemotherapy [9]. Base excision repair is a process that corrects oxidative stress-induced DNA damage. This process is facilitated by the XRCC1 gene. Polymorphisms in the XRCC1 gene have been associated with a reduced capacity to repair DNA and an increased sensitivity to chemotherapy drugs such as cisplatin and etoposide [10]. GSTP1 is a gene involved in the metabolism of chemotherapy

drugs, including taxanes and platinum-based drugs. CYP3A5 is a gene involved in the metabolism of chemotherapeutic agents like docetaxel and paclitaxel. Polymorphisms in the GSTP1 and CYP3A5 genes have been linked to diminished drug metabolism, resulting in increased toxicity and diminished efficacy [6,7]. ABCB1 is a gene involved in the transport of chemotherapy drugs such as paclitaxel and vinblastine out of cells, resulting in diminished drug accumulation and efficacy. Polymorphisms in the ABCB1 gene have been linked to an increase in drug efflux and a reduction in drug accumulation, leading to a decrease in the efficacy of chemotherapy [8].

In this article, we aim to investigate the association between polymorphisms in the ERCC1, XRCC1, GSTP1, CYP3A4, CYP3A5, and ABCB1 genes and progression of lung cancer.

Material and Methods

Patient recruitment

This study was conducted at the Pamukkale University, Department of Medical Genetics and included 74 patients diagnosed with lung cancer. Patients were recruited from January 2013 to December 2016. The inclusion criteria were as follows: patients with histologically confirmed lung cancer, aged 18 years or older, and scheduled for platinum-based chemotherapy. Patients with a history of other cancers, autoimmune diseases, or concurrent infections were excluded. The study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Pamukkale University Non-Interventional Clinical Research Ethics Committee (Decision No: E-60116787-020-443429, dated October 31, 2023).

Genotyping

The Qiagen EZI DNA Blood Kit (Qiagen, Hilden, Germany) has been used to isolate gDNA from peripheral blood samples. Genotyping of the ERCC1-C8092A, ERCC1-T19007C, XRCC1-G28152A, GSTP1-A313G, ABCB1-C1236T, ABCB1-C3435T, CYP3A5*2B, and CYP3A4*1B polymorphisms was performed using the pyrosequencing method (PyroMark Q24) (Qiagen Hilden, Germany). After polymerase chain reaction (PCR) was conducted according to the manufacturer's protocol, GE Healthcare's streptavidin Sepharose HP (Waukesha, WI, USA) was bound to PCR products., followed by purification, washing, and denaturation steps for pyrosequencing. Genotyping was performed by two independent researchers who were blinded to the clinical data, using the PyroMark Q24 Advanced Software.

Chemotherapy regimen

All patients received platinum-based chemotherapy as the first-line treatment, consisting of either cisplatin or carboplatin, combined with a taxane or gemcitabine. The chemotherapy regimens were selected by the attending oncologists based on the patient's clinical characteristics and the tumor histology.

Follow-up and survival analysis

Patients were followed up every three months after the completion of chemotherapy. Follow-up evaluations included a physical examination, chest computed tomography (CT) scan, and laboratory tests. The primary endpoint of this study was progression time, defined as the duration between the initial diagnosis of cancer and the point at which the disease progresses or worsens. All progression data were obtained from medical records.

Variables

The evaluated variables included patient age, gender, lung cancer subtypes, number of affected individuals in the family, treatment and smoking status, ERCC1-C8092A, ERCC1-T19007C, XRCC1-G28152A, GSTP1-A313G, ABCB1-C1236T, ABCB1-C3435T, CYP3A5*2B, CYP3A4*1B, polymorphisms, and clinical cancer stages.

Statistical Analysis

The log-rank test and the Kaplan-Meier method were used to examine the relationship between polymorphisms and progression time. Utilizing the Cox proportional hazards model, 95% CIs and hazard ratios (HRs) were computed. Potential confounding factors, including smoking status, cancer subtypes (adenocarcinoma, squamous cell carcinoma, and others), and cancer stage, were adjusted in the multivariate analysis. Statistical analyses were conducted using SPSS software (version 25.0, IBM Corp., Armonk, NY, USA). A p-value of less than 0.05 was deemed statistically significant.

To ensure the accuracy of genotyping, 10% of the samples were randomly selected for repeat genotyping.

Results

Descriptive statistics

Descriptive statistics are shown in table 1. Of the 74 patients included in the study, 64 (86.5%) were male (38 in the advanced-stage group, 26 in the early-stage group), while 10 (13.5%) were female (2 in the advanced-stage group, 8 in the early-stage group). The median and average age at diagnosis of lung cancer were 61 (range: 40–78) and 60.43 ± 8.91 years, respectively. Fifty-six (75.7%) patients were active smokers, whereas 18 (24.3%) had never smoked. Seventeen out of 74 patients had a family history of cancer. Among them, 9 (52.9%) had first-degree relatives, 4 (23.5%) had second-degree relatives, and 3 (17.6%) had third-degree relatives affected by cancer (Table 1).

Table 1. Clinical and demographic characteristics of the patients.	
Variables	Frequency (n, %)
Age (n=74)	
<65	16 (21.6)
65-74	30 (40.5)
>75	28 (37.8)
Gender (n=74)	
Male	64 (86.5)
Female	10 (13.5)
Family history(n=17)	
First degree relatives	9 (52.9)
Second degree relatives	8 (47.1)
Number of affected relatives(n=17)	
1	10 (58.8)
2	4 (23.5)
3	3 (17.6)
Smoking (package/years) (n=53)	56 (71.6)
<40	21 (39.6)
41-59	26 (49.1)
>60	6 (11.3)
Subtypes of cancer	
Adenocarcinoma	16 (21.6)
Squamous cell carcinoma	37 (50.0)
Others	21(28.4)
Stages	
I-II	13 (17.6)
III	31 (42.9)
IV	30 (40.5)
Platin based chemotherapy	68 (91.9)
Events progressed secondary time	27 (36.5)

Survival tests

The median progression time of each polymorphism at each stage of lung cancer is shown in figure 1. Before implementing the Kaplan-Meier test, extreme values and outliers were excluded from the analysis. After excluding one extreme value (Patient 72) from the study, a statistically significant difference was found in the progression times of ERCC1-T19007C polymorphisms in the advanced-stage lung cancer group (log-rank test p-value: 0.04).

Figure 1. Median progression time of each polymorphism per stage of lung cancers.

Cox proportional hazard models

In this study, a Cox regression model was implemented to predict the progression time of advanced (stage IV) and early stage (stage I, stage II, and stage III) lung cancer patients. The variables were divided into two categories based on the stage of lung cancer. First, a univariate analysis was conducted to identify the variables that were significant in predicting progression time. A threshold of 0.1 was set for including variables in the analysis. Based on the results of the univariate analysis, six variables GSTP1-A313G, XRCC1-G28152A, ABCB1-C3435T, ABCB1-C1236T, cancer subtype, and smoking were selected for the multivariate Cox regression model.

Our Cox regression analysis revealed that the ABCB1-C1236T and ABCB1-C3435T wild-type and heterozygous alleles, smoking, adenocarcinoma, and other cancer types were significant predictors of progression time in advanced-stage lung cancer patients (Table 2). However, no variables were found to be significant predictors of progression time in early-stage lung cancer patients (Table 3).

Table 2. Prognostic factors affect progressing time in multivariate analysis in high stage lung cancer patients.		
Variables	Sig.	OR (95 CI %)
GSTP1-313		
A/A	0.278	
A/G	0.654	0.815(0.334-1.992)
3G/G	0.110	0.227(0.037-1.397)
XRCC1-28152		
G/G	0.127	
G/A	0.100	0.409(0.141-1.186)
A/A	0.087	0.324(0.089-1.179)
ABCB1-3435		
C/C	0.085	
C/T	0.049	0.311(0.098-0.993)
T/T	0.112	0.403(0.131-1.238)
ABCB1-1236		
C/C	0.060	
C/T	0.026	0.278(0.090-0.860)
T/T	0.972	1.020(0.330-3.159)
Subtype of cancer		
Adenocarcinoma	0.008	
Squamous cell carcinoma	0.677	1.255(0.431-3.649)
Others	0.006	0.262(0.101-0.681)
Smoking	0.041	3.480(1.055-11.477)

Table 3. Prognostic factors affect progressing time in multivariate analysis in early-stage lung cancer patients.

Variables	Sig.	OR (95 CI %)
GSTP1- 313		
A/A	0.481	
A/G	0.421	1.359 (0.644-2.869)
G/G	0.449	0.606 (0.166-2.215)
XRCC1- 28152		
G/G	0.382	
G/A	0.190	1.659 (0.778-3.539)
A/A	0.458	1.509 (0.510-4.469)
ABCB1- 3435		
C/C	0.838	
C/T	0.605	0.796 (0.334-1.894)
T/T	0.676	0.803 (0.287-2.248)
ABCB1-1236		
C/C	0.476	
C/T	0.562	1.336 (0.502-3.557)
T/T	0.224	1.994 (0.656-6.062)
Subtype of cancer		
Adenocarcinoma	0.208	
Squamous cell carcinoma	0.204	1.890 (0.708-5.047)
Others	0.091	2.080 (0.889-4.864)
Smoking status	0.296	0.641 (0.278-1.476)

Discussion

The treatment of lung cancer is a very difficult and long process because there are a lot of factor such as late diagnosis, inadequate treatment strategies, regular follow-up after treatment, tumor mutation burden, drug response and toxicity [11]. The first-line treatment for NSCLC is platinum-based chemotherapy, and a recent study showed that platinum-based chemotherapy is affected by inherent factors such as DNA repair, signaling, and metabolism [12]. In this study, we have aimed to examine the relationship between the GSTP-A313G (rs1695), CYP3A4*1B (rs2740574), CY3A5-2B (rs776746), ABCB1-C1236T (rs1128503), ABCB1-C3435T (rs1045642), ERCC1-C8092A (rs3212986), ERCC1-T19007C (rs11615) and XRCC1-G28152A (rs25487) genes polymorphisms and progression free survival in 72 patients who are receiving platinum-based chemotherapy. Our results particularly emphasize the importance of ERCC1 and ABCB1 polymorphisms in predicting progression time in advanced-stage NSCLC patients, while no significant predictors were observed for early-stage patients.

ERCC1 and DNA repair mechanisms

The statistically significant difference in progression times for the ERCC1-T19007C polymorphism (log-rank test $p = 0.04$) highlights the key role of ERCC1 in treatment outcomes. ERCC1 is a vital component of the nucleotide excision repair (NER) pathway, which is responsible for repairing platinum-induced DNA damage. Polymorphisms in ERCC1 may alter protein function, leading to differences in chemotherapy response.

Our findings align with earlier studies that reported associations between ERCC1 expression and chemotherapy resistance. For example, Olaussen et al. demonstrated that high ERCC1 expression correlates with poor responses to platinum-based therapies in NSCLC patients, supporting its role as a potential biomarker for chemotherapy sensitivity [13]. Similarly, a meta-analysis by Wei et al. (2011) revealed that ERCC1 polymorphisms, particularly T19007C, influence both overall survival and progression-free survival in NSCLC patients undergoing platinum-based regimens [14].

ABCB1 polymorphisms and drug resistance

Our multivariate Cox regression analysis identified ABCB1-C1236T and ABCB1-C3435T polymorphisms as significant predictors of progression time in advanced-stage NSCLC. ABCB1 (also known as P-glycoprotein) encodes a membrane-bound transporter that mediates drug efflux, reducing intracellular concentrations of chemotherapeutic agents like cisplatin.

Several studies support our observations regarding ABCB1 polymorphisms. For instance, a study by Kim et al. (2006) demonstrated that the C3435T polymorphism is associated with reduced drug efflux and improved chemotherapy efficacy [15]. Moreover, Jia et al. showed that genetic variations in ABCB1 could predict progression time and survival in patients receiving platinum-based chemotherapy, underscoring its clinical relevance as a predictive biomarker [16].

Smoking remains a critical determinant of lung cancer progression and treatment outcomes. Our findings confirm its association with shorter progression times in advanced-stage patients, reinforcing smoking cessation's importance in improving clinical outcomes. Active smokers exhibit increased DNA damage and resistance to platinum-based therapies, possibly due to smoking-induced alterations in DNA repair pathways [17].

Additionally, adenocarcinoma, identified as a significant predictor, is the most common histological subtype of NSCLC. Adenocarcinoma patients often present with distinct genetic and molecular characteristics, including EGFR and ALK

mutations, which influence treatment responses (18). Our results suggest that the cancer subtype should be carefully considered when predicting prognosis and tailoring therapies for advanced-stage NSCLC patients.

Early-stage NSCLC: challenges in prediction

Unlike advanced-stage patients, no significant predictors of progression time were identified in the early-stage group. This finding may reflect biological differences between early- and late-stage tumors or the limited power to detect associations due to the small sample size. Early-stage NSCLC patients often undergo surgical resection, which complicates comparisons with chemotherapy-treated advanced-stage patients.

Future research examining the clinical and genetic factors influencing disease development in early-stage non-small cell lung cancer (NSCLC) requires longer follow-up periods in a larger cohort.

Limitations and future directions

Limitations of the study: The results of this study suggest that ABCB1-C1236T and ABCB1-C3435T polymorphisms, smoking, and subtype of lung cancer are significant predictors of progression time in high-stage lung cancer patients. Individualized management and therapy of patients with lung cancer may benefit from these findings. However, note that there was a limited sample size (n = 72), and larger sample sizes are required for more research to validate these results and look into the underlying mechanisms of these correlations. In addition, the lack of significant predictors for early-stage lung cancer patients suggests that other factors may play a more important role in the progression of the disease at this stage.

The results of this analysis suggest that there is a significant difference in progression times between early-stage lung cancers and high-stage lung cancers. However, it is important to note that the log-rank test only tests for a difference in survival times and does not provide information on the direction of the difference. Further analysis is needed to determine which group has a longer or shorter survival time.

Future studies should concentrate on examining the functional implications of ERCC1 and ABCB1 polymorphisms as well as verifying these results in larger, multicenter cohorts. Integrating genetic markers with emerging biomarkers, such as PD-L1 expression and tumor mutation burden, may further enhance prognostic accuracy and guide personalized treatment strategies.

In conclusion, our study highlights the significant role of ERCC1 and ABCB1 polymorphisms, smoking status, and adenocarcinoma subtype in predicting progression time for advanced-stage NSCLC patients receiving platinum-based chemotherapy. These findings underscore the value of genetic and clinical predictors in optimizing treatment strategies for advanced NSCLC. However, to overcome the difficulties in validating these markers and predicting the prognosis of early-stage lung cancer, high-throughput data obtained from larger study groups and algorithms created using these data are needed.

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Ethics approval

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Authors contributions

ERK, AD: designed all experimental procedures of the study, ER, MTA: wrote the manuscript and analyzed data. GGD, FB: searched literature, collected data, HA: developed the theoretical framework. The final manuscript was read and approved by all authors.

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Araştırma Makalesi

Karpal tünel cerrahisi yapılan hastaların demografik özellikleri

Demographic characteristics of patients undergoing carpal tunnel surgery

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Öz

Amaç: Çalışmamızın amacı karpal tünel sendromu tanısı konularak cerrahi tedavi uygulanan hastaların demografik verilerini ortaya koymak ve sonuçlarımızı literatür eşliğinde tartışmaktır.

Gereç ve Yöntemler: Karpal tünel sendromu tanısı ile ortopedi ve travmatoloji kliniğinde 2023 ve 2024 yıllarında cerrahi tedavi uygulanan hastalar geriye dönük olarak hastane bilgi sisteminden taranmıştır. Hastaların dijital dosyalarından yaşı, cinsiyeti ve sağ/sol taraf bilgileri elde edilmiştir.

Bulgular: Çalışmaya 257 kadın, 75 erkek toplam 332 hasta dahil edildi. Kadın hasta sayısının erkek hasta sayından fazla olması istatiksel olarak anlamlı bulundu ($p < 0,001$). Hastaların ortalama yaşı 55.8 idi (yaş aralığı 19-88). Yaş gruplarına göre 5 farklı gruba ayrıldığında 46-58 yaş aralığında bulunan hasta sayısı diğer gruplara göre anlamlı olarak fazla idi ($p < 0,001$). Hastaların tümüne baktığımızda 185'i sağ elinden, 147'si sol elinden ameliyat oldu. Sağ elinden ameliyat olan hasta sayısının fazla olması istatiksel olarak anlamlı bulundu ($p < 0,005$).

Sonuç: Karpal sendromu nedeniyle ameliyat olan 332 hastalık retrospektif çalışmamızda hastaların kadın cinsiyet, sağ elden operasyon olma ve orta yaş etkilenimi daha belirgindir.

Anahtar Kelimeler: karpal tünel sendromu, nöropati, cerrahi

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Abstract

Aim: The aim of our study was to reveal the demographic data of patients who underwent surgical treatment for carpal tunnel syndrome and to discuss our results in light of the literature.

Material and Methods: Patients who underwent surgical treatment for carpal tunnel syndrome in the orthopedics and traumatology clinic during 2023 and 2024 were retrospectively screened using the hospital information system. Age, gender, and right/left side data were obtained from the patients' digital records.

Results: A total of 332 patients, comprising 257 females and 75 males, were included in the study. The number of female patients was significantly higher than the number of male patients ($p < 0.001$). The average age of the patients was 55.8 years (age range: 19–88). When divided into five age groups, the number of patients aged 46–58 was significantly higher than in other groups ($p < 0.001$). Of all patients, 185 underwent surgery on the right hand, and 147 on the left hand. The higher number of patients operated on the right hand was statistically significant ($p < 0.005$).

Conclusion: In our retrospective study of 332 patients operated for carpal tunnel syndrome, female gender, surgery on the right hand, and middle-aged patients were more prominently affected.

Anahtar Kelimeler: carpal tunnel syndrome, neuropathy, surgery

Giriş

Median sinirin el bileği seviyesinde karpal tünel içerisinde tuzaklanmasına bağlı olarak oluşan karpal tünel sendromu en sık görülen nöropatilerden birisidir [1]. Tünelin her iki yanını ve dorsalini kemik yapılar oluştururken volarde transvers karpal ligaman içeride kalan yapıların üzerine örtmektedir. Karpal tünel içerisinde sıkışma çoğunlukla idiopatik olsa da internal veya external etkenlere bağlı olarak da gelişebilmektedir [2]. Sıkışma sonrası median sinir üzerinde iletim bozulur. Bu sırada hastalar çoğunlukla ağrı ve uyuşmadan şikayet eder. Predispozan faktörler arasında sistemik inflamatuar hastalıklar, diyabet ve tiroid gibi endokrin problemler, gebelik, karpal tüneli daraltan yumuşak doku kitleleri, el bileğini sık kullanmak gibi etkenler sayılabilir [1].

Tanıda klinik öykü ve muayenede hastalar geceleri bilekte ağrı, uyuşma şikayeti ile uyanıp bu durumun ellerini sallamakla hafiflediğini tarif ederler. Muayenede kronik olgularda tenar bölgede atrofi ve duyu kusuru görülür. Hastalarda median sinir kompresyona uğratacak provakatif testler anlamlılık gösterir. Tanı çoğunlukla muayene ve anamnez ile konulur. Tanıyı doğrulamada ve ayırıcı tanıda elektromiyografi, laboratuvar testleri ve radyolojik görüntüleme yöntemlerinden yararlanılabilir [3].

Tedavide yeni başlangıçlı olgularda veya gebelik gibi geçici durumlarda konservatif tedavi etkili olabilmektedir. Konservatif tedavi seçenekleri arasında non-steroid antiinflamatuar ilaçlar, splint kullanımı, steroid enjeksiyonu gibi uygulamalar sayılabilmektedir [4]. Daha uzun süreli şikayetleri olan, kliniği daha ileri olan veya konservatif tedaviye istenen yanıt alınamayan olgularda cerrahi tedavi uygulanmaktadır. Cerrahi tedavide amaç transvers karpal ligamanı açarak tünel içindeki basıncı düşürmektir.

Çalışmamızın gayesi karpal tünel sendromu tanısı konularak cerrahi tedavi uygulanan hastaların demografik verilerini ortaya koymak ve sonuçlarımızı literatür eşiliğinde tartışmaktır.

Gereç ve Yöntemler

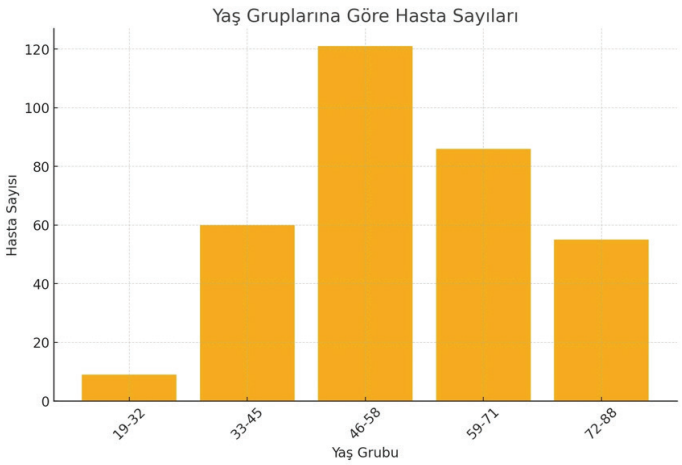
Bu çalışma için etik kurul onayı Pamukkale Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan alınmıştır (Onay No: 04, Tarih: 18.02.2025). Ayrıca, Denizli İl Sağlık Müdürlüğü'nden araştırma izin belgesi temin edilmiştir. Araştırma kapsamında, 2023 ve 2024 yılları arasında Pamukkale Üniversitesi Hastanesi Ortopedi ve Travmatoloji Kliniği'nde karpal tünel sendromu tanısıyla cerrahi tedavi uygulanan hastalar retrospektif olarak hastane bilgi sistemi üzerinden taranmıştır. Dahil edilen olguların dijital dosyalarından yaş, cinsiyet ve etkilenen ekstremitenin (sağ/sol) bilgileri kaydedilmiştir. Herhangi bir eksik veya hatalı veriye sahip olan hastalar çalışma dışı bırakılmıştır.

İstatistiksel Analiz

Elde edilen veriler, IBM SPSS Statistics (versiyon XX) programı kullanılarak analiz edilmiştir. Tanımlayıcı istatistikler olarak sürekli değişkenler için ortalama, standart sapma, minimum ve maksimum değerler; kategorik değişkenler için ise sayı ve yüzde değerleri raporlanmıştır. Gruplar arasındaki kategorik değişkenlerin karşılaştırılmasındaki-kare testi kullanılmıştır. Sürekli değişkenlerin iki bağımsız grup arasında karşılaştırılmasında ise bağımsız örneklem t-testi (verilerin normal dağılım gösterdiği varsayımı ile) veya normal dağılım sağlanmadığında Mann-Whitney U testi uygulanmıştır. Tüm istatistiksel testlerde $p < 0,05$ değeri anlamlı kabul edilmiştir.

Bulgular

Çalışmaya 257 kadın, 75 erkek toplam 332 hasta dahil edildi. Kadın hasta sayısının erkek hasta sayından fazla olması istatiksel olarak ta anlamlı bulundu ($p < 0,001$). Hastaların ortalama yaşı 55.8 idi (yaş aralığı 19-88). Yaş gruplarına göre 5 farklı gruba ayrıldığında 46-58 yaş aralığında bulunan hasta sayısı diğer gruplara göre anlamlı olarak fazla idi ($p < 0,001$). Hastaların yaş gruplarına göre dağılımı şekil 1 de gösterilmiştir. Erkek hastaların ortalama yaşı 56.2 olarak bulundu (yaş aralığı 22-85). Kadın hastaların ortalama yaşı 55.7 idi (yaş aralığı 19-88). Erkek hastalar ile kadın hastaların yaşları arasında istatiksel olarak anlamlı bir farklılık izlenmedi ($p > 0,005$). Hastaların tümüne baktığımızda 185'i sağ elinden, 147'si sol elinden ameliyat oldu. Sağ elinden ameliyat olan hasta sayısının fazla olması istatiksel olarak anlamlı bulundu ($p < 0,005$).



Şekil 1. Hastaların beş farklı yaş grubunda dağılımı görselde görüldüğü gibi orta yaş grubunda kümelenme mevcuttur.

Tartışma

Çalışmamızda ikinci basamakta bulunan bir sağlık kurumunda son 2 yılda karpal tünel cerrahisi yapılan hastalar değerlendirildiğinde, ameliyat olan hastaların kadın cinsiyette olması, sağ el tutulumu ve orta yaş grubunda bulunması araştırmamızın göze çarpan istatiksel olarak anlamlı demografik bulgularıdır.

Karpal tünel cerrahisi nedeniyle ameliyat olan hastaların anlamlı bir şekilde çoğunluğunu kadınlar oluşturmuştur. Kadınlardaki hormonal değişimler, özellikle gebelik ve menapoz dönemleri, karpal tünel sendromu görülme riskini arttırdığı literatürde paylaşılmıştır [5]. Gebelikte karşılaşılan karpal tünel sendromu genellikle üçüncü trimesterde görülmekte olup doğum sonrası çoğunluğu düzelmektedir [6].

Yaş dağılımına göre değerlendirildiğinde hastaların çoğunluğunun orta yaş grubunda yer aldığı izlendi. Umay ve arkadaşlarının, elektronöromiyografi sonrası karpal tünel sendromu tanısı konulan 119 hastalık çalışmasında da benzer olarak orta yaş grubunda etkilenme daha fazla çıkmıştır [7]. Yine Eren ve arkadaşlarının çalışmasında da orta yaş grubu daha fazla etkilenmiştir [8]. Bu sonuç kadın hastalar için hormonal değişimlerin görüldüğü gerek kadın gerek erkek hastalar içinse çalışma koşulları, sigara, obezite gibi etkenlere bağlı oluşabilecek kronik bası kliniğinin oturması ve semptomatik hale gelmesinin beklendiği yaş aralığı olarak yorumlanabilir.

Araştırmamızda ameliyat olan hastalarda sağ el oranı anlamlı olarak daha fazlaydı. Sağ elin sıklıkla baskın olması ve daha fazla kullanım nedeniyle kronik basıya maruz kalması bu durumu açıklayabilirdi. Kara ve arkadaşlarının mini açık cerrahi sonuçlarını yayımladığı çalışmalarında da sağ el bileği tutulumu anlamlı olarak daha fazlaydı [9]. Louie ve arkadaşlarının yaptığı cerrahi gevşetme sonrası on yıllık takip sonuçlarını bildirdiği araştırmada da yine dominant el tutulumu daha fazla olarak görülmektedir [10]. Bunun yanında cerrahi yapılmayan elektronöromiyografi çalışmalarında bu anlamlılık çok belirgin değildir [7,11]. Hastaların dominant ellerindeki tutulumun onlarda daha fazla şikayete yol açtığını ve ameliyat olurken dominant taraftan yana tercihte bulunduklarını düşünmekteyiz.

Araştırmamızın bazı kısıtlılıkları bulunmaktadır. Bunlardan bir tanesi retrospektif olarak gerçekleşmesidir. Bu tanı, tedavi ve takip sürecine hakim olmamızı kısıtlasa da bu araştırmada bir tedavi sonucunu ortaya koymaktan çok demografik verilerin ortaya konması amaçlanmıştır. Bu sebepten yazının geriye dönük bir çalışma olması sonuçlarımızı çok fazla etkilemeyeceğini düşünmekteyiz. Araştırmadaki 332 hastanın tamamı ikinci basamak sağlık kurumundan tek bir merkezden alınmıştır. Çok merkezli olması elbette ki çalışmanın gücünü arttıracaktır. Bunun yanında hasta sayısı literatürle karşılaştırıldığında iyi sayılabilecek bir rakam çalışmamızın güçlü yanlarındandır.

Sonuç olarak, karpal sendromu nedeniyle ameliyat olan 332 hastalık retrospektif çalışmamızda hastaların kadın cinsiyet, sağ elden operasyon olma ve orta yaş etkilenimi daha belirgindir.

Maddi destek ve çıkar ilişkisi

Araştırmacıların herhangi bir çıkar ilişkisi bulunmamaktadır.

Etik Kurul Onayı

Bu çalışma için etik kurul onayı Pamukkale Üniversitesi Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu'ndan almıştır (Onay No: 04, Tarih: 18.02.2025).

Yazarların Katkısı

ANA: yazım, makale gönderimi, ET: yazım, veri toplama

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Araştırma Makalesi

Gastrointestinal sistem maligniteli hastalarda demir eksikliği ve kronik hastalık anemisi ayırıcı tanısında soluble transferrin reseptör düzeylerinin yeri

The role of soluble transferrin receptor levels in the differential diagnosis of iron deficiency anemia and anemia of chronic disease in patients with gastrointestinal malignancy

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Öz

Amaç: Anemi, gastrointestinal malignite hastalarında sık görülen bir komplikasyondur. Bu çalışma, anemik gastrointestinal maligniteli hastalarda serum soluble transferrin reseptör (sTfR), sTfR/log ferritin indeksi ve hepsidin seviyelerinin demir eksikliği anemisi (DEA) ile kronik hastalık anemisi (KHA) ayırıcı tanısındaki rolünü araştırmayı amaçladı.

Gereç ve Yöntemler: Çalışmaya Ankara Numune Eğitim ve Araştırma Hastanesi'nde takip edilen gastrointestinal maligniteli 126 anemik hasta dahil edildi. Serum demir, total demir bağlama kapasitesi, ferritin, vitamin B12, folik asit, sTfR ve hepsidin seviyeleri ölçüldü ve sTfR/log ferritin indeksi hesaplandı. Transferrin saturasyonuna göre hastalar DEA (transferrin saturasyonu ≤ %20) ve KHA (transferrin saturasyonu > %20) olarak iki gruba ayrıldı. sTfR ve sTfR/log ferritin indeksinin tanısal performansı ROC analizi ile değerlendirildi.

Bulgular: sTfR düzeyi ve sTfR/log ferritin indeksi DEA grubunda KHA grubuna kıyasla anlamlı derecede yüksekti ($p < 0,001$). sTfR'nin DEA'yı belirlemede duyarlılığı %77,1 ve özgüllüğü %67,9 olarak bulundu (1,65 mg/L kesim noktası). Ferritin için duyarlılık %57,1, özgüllük ise %76,8 olarak hesaplandı. Hepsidin düzeyleri açısından iki grup arasında anlamlı fark bulunmadı.

Sonuç: sTfR ve sTfR/log ferritin indeksi, gastrointestinal maligniteli hastalarda DEA ile KHA ayırıcı tanısında faydalı parametrelerdir. Hepsidin seviyeleri, akut faz reaktanı özelliği nedeniyle ayırıcı tanıda etkili olmayabilir. sTfR ölçümünün standardizasyonu ve farklı hasta grupları için optimal kesim noktalarının belirlenmesi amacıyla daha geniş çaplı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: soluble transferrin reseptörü (sTfR), sTfR/log ferritin indeksi, hepsidin, gastrointestinal malignite

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Abstract

Aim: Anemia is a common complication in patients with gastrointestinal malignancies. This study aimed to investigate the role of serum soluble transferrin receptor (sTfR), sTfR/log ferritin index, and hepcidin levels in the differential diagnosis of iron deficiency anemia (IDA) and anemia of chronic disease (ACD) in anemic patients with gastrointestinal malignancies.

Material and Methods: The study included 126 anemic patients with gastrointestinal malignancies followed at Ankara Numune Training and Research Hospital. Serum iron, total iron-binding capacity, ferritin, vitamin B12, folic acid, sTfR, and hepcidin levels were measured, and the sTfR/log ferritin index was calculated. Based on transferrin saturation, patients were classified into two groups: IDA (transferrin saturation ≤20%) and ACD (transferrin saturation >20%). The diagnostic performance of sTfR and sTfR/log ferritin index was assessed using ROC analysis.

Results: The sTfR level and sTfR/log ferritin index were significantly higher in the IDA group compared to the ACD group ($p < 0.001$). The sensitivity and specificity of sTfR for identifying IDA were 77.1% and 67.9%, respectively, with a cutoff value of 1.65 mg/L. Ferritin showed lower sensitivity (57.1%) but higher specificity (76.8%). No significant difference was found in hepcidin levels between the two groups.

Conclusion: sTfR and the sTfR/log ferritin index are useful parameters for distinguishing IDA from ACD in patients with gastrointestinal malignancies. Hepcidin levels may not be effective due to their acute-phase reactant properties. Standardization of sTfR measurement and further large-scale studies are needed to determine optimal cutoff values for different patient populations.

Keywords: soluble transferrin receptor (sTfR), sTfR/log ferritin index, hepcidin, gastrointestinal malignancy

Giriş

Serum hemoglobin konsantrasyonunun yaşa ve cinsiyete göre ortalama değerin altında olması olarak tanımlanan anemi gastrointestinal malignitesi olan hastalarda sık karşılaşılan bir problemdir. Bu hasta grubunda anemi prevalansı kolon kanseri için %42,6, mide kanseri için %33,3 gibi yüksek oranlarda bulunmuştur [1].

Aneminin tedavi edilmediği takdirde kanser hastalarında yaşam kalitesinde azalma, daha kötü performans durumu, kognitif fonksiyonlarda bozulma, eşlik eden kardiyovasküler ve respiratuvar komorbid hastalıkların alevlenmesi, kemoterapi toleransında azalma ve tümör progresyonuna bağlı olarak erken ölümle ilişkili olduğu bilinmektedir [2].

Bu nedenle takibinde anemi saptanan malign hastalarda mutlaka etiyolojik neden araştırılarak düzeltilebilir nedenler varsa saptanmalı, nutrisyonel eksiklikler yerine konmalı, transfüzyon desteği veya eritropoetin (EPO) stimüle edici ajanlarla tedavi denenmelidir. Bu sayede anemi ile ilişkili halsizlik gibi semptomlar azalır, yaşam kalitesi artar, transfüzyon ihtiyacı azalır, kemoterapi toleransı artar, bilişsel fonksiyonlar düzelir.

Maligniteye sekonder kronik hastalık anemisi (KHA) ve kan kaybı veya geçirilmiş cerrahiye bağlı olarak demir eksikliği anemisi (DEA) bu hasta grubunda aneminin en sık karşılaşılan nedenleri olup konvansiyonel tetkikler bu iki hastalığın ayırıcı tanısında yetersiz kalabilmektedir.

Ferritin vücuttaki demir depolarının göstergesi olarak demir eksikliği tanısında oldukça önemli olmakla birlikte aynı zamanda akut faz reaktanı olması nedeniyle özellikle kronik hastalık anemisine eşlik eden demir eksikliği anemisinin tanımlanmasında yetersiz kalabilmektedir.

Serum soluble transferrin reseptörü (sTfR) demir eksikliği varlığında eritroid öncül hücrelerin demir ihtiyaçlarına bağlı olarak serumda arttığından ve enfeksiyon, inflamasyon gibi durumlardan etkilenmediğinden demir eksikliğini göstermede güvenilir bir belirteçtir [3-5]. Yine sTfr düzeyinin ferritinin logaritmasına bölünmesiyle elde edilen sTfR/log ferritin indeksinin DEA, KHA ayırıcı tanısında sensitivite ve spesifitesi yüksek bir metod olarak kullanılabileceği farklı çalışmalarda gösterilmiştir [6,7].

Hepsidin karaciğerde üretilen, duodenal demir absorbsiyonunu ve makrofajlardan demir salınımını inhibe eden bir proteindir [8]. Demir eksikliği varlığında demir absorbsiyonunu arttırmak için hepsidin düzeyi azalır. Ancak ferritin gibi hepsidin molekülü de bir akut faz reaktanıdır ve enfeksiyon, inflamasyon durumlarında düzeyi yükselir [9,10].

Bu çalışmada gastrointestinal sistem malignitesi olan anemik hastalarda aneminin en sık nedenleri olan DEA ve KHA ayırıcı tanısında sTfR, sTfR/log ferritin indeksi ve hepsidin düzeylerinin yeri araştırılmış ve farklı parametrelerin tanı değerlerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler

Ankara Numune Eğitim ve Araştırma Hastanesi Medikal Onkoloji Polikliniği'nde gastrointestinal sistem (mide, kolon) malignitesi nedeniyle takipli, anemisi olan 126 hasta dahil edilmiştir. Poliklinik kontrolleri esnasında anemisi saptanan (kadınlar için Hb < 12 gr/dL, erkekler için Hb < 13,5 gr/dL) hastaların demir, demir bağlama kapasitesi, ferritin, vitamin B12, folik asit düzeyleriyle birlikte hastanemizde rutin kullanılmayan sTfR ve hepsidin düzeylerinin değerlendirilmesi için hastalardan onamları alınarak fazladan bir tüp kan alındı. Transferrin saturasyonu (TS) ve sTfR/log ferritin indeksi hesaplanarak bulundu.

Daha sonra hastalar transferrin satürasyonuna (TS) göre %20 ve altında olanlar demir eksikliği anemisi (DEA), TS%20'nin üstünde olanlar kronik hastalık anemisi (KHA) olarak kabul edildi. Hastaların yaş, cinsiyet, tanı tarihi, malignitenin yerleşim yeri, evresi (metastatik- non metastatik), yapılan cerrahi, geliş şikayeti, aldığı tedavi, numune sırasında aktif kemoterapi alıp almaması, hemoglobin, hematokrit, lökosit, trombosit, MCV, demir, demir bağlama kapasitesi, transferrin saturasyonu, ferritin, B12, folik asit, sTfR, hepsidin, sTfR/log ferritin indeksi, daha önce transfüzyon alıp almadığı, transfüzyon sayısı, son transfüzyon tarihlerine bakılarak veriler kaydedildi.

sTfR ve hepsidin düzeyleri DRG tarafından sağlanan ELISA kitleri ile çalışıldı. sTfR düzeyi için sandwich immunassay tekniği kullanılırken hepsidin düzeyi ölçümünde solid faz immunoassay ölçüm tekniği kullanıldı. Hepsidin için beklenen değerler (erişkin hastalar için) 13,3-54,4 ng/mL iken aynı grupta sTfR için 0,9-3,3 mg/L olarak rapor edilmektedir. ELISA okumaları için synergy microplate okuyucu kullanılmıştır.

İnsan katılımcıları içeren çalışmalarda gerçekleştirilen tüm prosedürler, kurumsal ve/veya ulusal araştırma komitesinin etik standartlarına ve 1964 Helsinki Bildirgesi'nin daha sonraki değişikliklerine veya eşdeğer etik standartlara uygundur. Bu kesitsel çalışma için onay, Ankara Numune Eğitim ve Araştırma Hastanesi Klinik Araştırmalar Etik Kurulu tarafından 27.07.2011 tarih ve 211/2011 karar numarası ile verilmiştir.

İstatistiksel Analiz

Verilerin analizi SPSS for Windows 11.5 paket programında yapıldı. Sürekli değişkenlerin dağılımının normale uygun olup olmadığı Shapiro Wilk testi ile varyansların homojenliği ise Levene testiyle araştırıldı. Tanımlayıcı istatistikler sürekli değişkenler için ortalama ± standart sapma, ortanca (çeyrekler arası genişlik) ya da ortanca (en küçük – en büyük) olarak kategorik değişkenler ise olgu sayısı ve (%) biçiminde gösterildi. Gruplar arasında ortalamalar yönünden farkın önemliliği bağımsız grup sayısı iki olduğunda Student's t testi ile ikiden fazla grup arasındaki farkın önemliliği ise Tek Yönlü Varyans Analizi (One-Way ANOVA) ile incelendi. Gruplar arasında ortanca değerler yönünden farkın önemliliği bağımsız grup sayısı iki olduğunda Mann Whitney U testi ile ikiden fazla grup arasındaki farkın önemliliği ise Kruskal Wallis testi ile incelendi. Tek Yönlü Varyans Analizi sonucunun önemli bulunması halinde farka neden olan durumları tespit etmek amacıyla post hoc Tukey HSD testi kullanıldı. Kategorik değişkenler Pearson'un Ki-Kare veya Fisher'in Kesin Sonuçlu Ki-Kare testi ile değerlendirildi.

Demir eksikliği anemisi olan ve olmayan grupları ayırt etmede sTfR ölçümlerinin belirleyici olup olmadığı ROC analizi ile eğri altında kalan alan hesaplanarak değerlendirildi. Eğri altında kalan alanın önemli bulunması halinde en iyi kesim noktası Youden İndeks kullanılarak saptandı. Ayrıca, bu noktaya ilişkin duyarlılık, seçicilik, pozitif ve negatif tahmini değerler ile doğruluk oranları hesaplandı. Demir eksikliği anemisi olan ve olmayan grupları ayırt etmede ferritin ve sTfR düzeylerinin birlikte etkileri Çoklu Değişkenli Lojistik Regresyon analiziyle araştırıldı. Her bir değişkene ait odds oranı ve %95 güven aralıkları hesaplandı. P < 0,05 için sonuçlar istatistiksel olarak anlamlı kabul edildi.

Bulgular

Çalışmaya gastrointestinal sistem malignitesi nedeniyle takipli olan 126 hasta dahil edildi. Hastaların temel özellikleri Tablo-1'de özetlendi. Hastaların ortanca yaşı 62 (min-max: 28-86), 51'i (%43,7) kadındı. Tümör yerleşim yeri 66 (%52,4) hastada mide, 48 (%38,1) hastada sol kolon (rektum, rektosigmoid bölge ve inen kolon), 12 (%9,5) hastada sağ kolon idi.

Hastalar transferrin saturasyonlarına göre TS ≤ %20 olanlar DEA ve TS > %20 KHA olarak iki gruba ayrıldığında 70 (%55) hastanın DEA, 56 hastanın KHA (%45) olduğu görüldü. DEA olan hastaların 29'u (%41,4) kadın, 41'i (%58,6) erkek, KHA olan hastaların ise 26'sı (%46,4) kadın, 30'u (%53,6) erkekti. DEA ve KHA olan hastalar tümör lokalizasyonuna göre karşılaştırıldığında DEA olan 70 hastadan 36'sının (%51,4) mide, 7'sinin (%10,0) sağ kolon, 27'sinin (%38,6) sol kolon (rektum, rektosigmoid ve sol kolon) malignitesi olduğu görüldü. KHA olan hastaların ise 30'u (%53,6) mide, 5'i (%8,9) sağ kolon, 21'inde (%37,5) sol kolon malignitesi vardı. Uygulanan cerrahi yönteme göre DEA ve KHA görülme oranları açısından anlamlı fark bulunmadı. TS değerine göre DEA ve KHA olan hasta grupları klinik ve demografik özellikler açısından karşılaştırıldığında yaş, cinsiyet, tümör lokalizasyonu, yapılan operasyon dağılımları açısından anlamlı fark yoktu

Tablo 1. Hastaların genel özellikleri.

		n	%
Cinsiyet	Kadın	51	43,7
	Erkek	75	56,3
Tümör lokalizasyonu	Mide	66	52,4
	Sağ kolon	12	9,5
	Sol kolon*	48	38,1
Evresi	Metastatik	26	20,6
	Non-metastatik	100	79,4
Yapılan cerrahi	Total gastrektomi	24	19,0
	Subtotal gastrektomi	36	28,6
	Sağ kolektomi	13	10,3
	Sol kolektomi	46	36,5
	Palyatif cerrahi	1	0,8
	Yok	6	4,8
Geliş şikayeti	Anemi	8	6,3
	Kanama	33	26,2
	Diğer	85	67,5
Aldığı tedavi	KT	40	31,7
	KT+RT	55	43,7
	İzlem	31	24,6
Numune sırasında aktif kemoterapi	Var	4	3,2
	Yok	122	96,8
	Hayır	94	74,6

Tablo 2. Transferrin saturasyonuna göre demir eksikliği anemisi ve kronik hastalık anemisi olan hastaların gruplara göre demografik ve klinik özellikleri.

	DEA (n=70)	KHA (n=56)	p
Yaş	61,0±13,3	60,8±9,9	0,926
Cinsiyet			0,574
Kadın	29 (%41,4)	26 (%46,4)	
Erkek	41 (%58,6)	30 (%53,6)	
Yerleşim yeri			0,964
Mide	36 (%51,4)	30 (%53,6)	
Sağ kolon	7 (%10,0)	5 (%8,9)	
Sol kolon	27 (%38,6)	21 (%37,5)	
Yapılan operasyon			
Total gastrektomi	11 (%15,7)	13 (%23,2)	0,287
Subtotal gastrektomi	20 (%28,6)	16 (%28,6)	-
Sağ kolektomi	8 (%11,4)	5 (%8,9)	0,647
Sol kolektomi	25 (%35,7)	21 (%37,5)	0,836
Palyatif cerrahi	-	1 (%1,8)	-

Hastaların 32'sine (%25,4) takipleri süresince ortalama 3 ünite (1-40) eritrosit süspansiyonu transfüzyonu uygulanmıştı. Hastalar hematolojik parametrelerine göre karşılaştırıldığında transfüzyon alan hastaların ortalama ferritin değeri transfüzyon almayan hastalara göre daha yüksek, Hb değeri ise daha düşük bulundu (Tablo 3).

Tablo 3. Tüm olgular içerisinde kan transfüzyonu alan (T) ve almayan (Tx) grupların laboratuvar ölçümlerinin karşılaştırılması.

	T	Tx	p
Ferritin (ng/mL)	60,5 (326,5)	33,5 (75,2)	0,036
sTFR (mg/L)	0,5 (1,0)	1,0 (1,0)	0,240
Hepsidin (ng/mL)	23,2 (8,8)	23,0 (13,7)	0,915
Demir (µg/dL)	62,0 (70,7)	46,5 (37,7)	0,297
Demir bağlama kapasitesi (mg/dL)	257,5 (113,0)	289,5 (131,7)	0,134
Hemoglobin (gr/dL)	10,9±1,1	11,8±1,0	<0,001
Hematokrit	33,0±3,2	35,9±2,9	<0,001

Serum demiri, TDBK, sTfR ve hepsidin düzeyleri arasında transfüzyon alan ve almayan grup arasında anlamlı fark yoktu. DEA ve KHA olan gruplar klinik ve demografik özellikler açısından karşılaştırıldığında yaş, cinsiyet, tümör lokalizasyonu, yapılan operasyon dağılımları açısından iki grup arasında anlamlı fark yoktu.

Değerlendirme anında tüm hastaların ortanca Hb değeri 11,7 gr/dL iken (8,4 gr/dL-13,4 gr/dL) kadın hastaların ortanca Hb değeri 11,2 gr/dL, erkek hastaların ortanca Hb değeri 11,8 gr/dL idi. MCV değerlerine bakıldığında toplamda 26 (%20,6) hastanın MCV değeri 80'in altındaydı. DEA olan hastaların %30'unda, KHA olan hastaların ise %8,9'unda mikrositer anemi mevcuttu.

Hastalar tümör lokalizasyonuna göre Hb, Hct, demir, TDBK, sTfR, hepsidin, ferritin düzeylerine göre karşılaştırıldığında mide kanseri olanlarda Hb değeri sol kolon kanseri olanlardan anlamlı şekilde daha düşük bulundu ($p = 0,014$). Diğer hematolojik parametrelerin tümör lokalizasyonuna göre anlamlı olarak değişmediği görüldü.

DEA ve KHA olarak gruplanan hastaların ferritin ve sTfR değerlerine bakıldığında DEA grubunda ortalama ferritin değeri 22 ng/mL iken KHA grubunda 59 ng/mL ($p < 0,001$), sTfR düzeyi DEA grubunda 2,2 mg/L iken KHA grubunda 1,5 mg/L ($p < 0,001$) bulundu. sTfR/log ferritin indeksi değerlerine bakıldığında DEA grubunda bu oran ortalama 1,5 iken KHA grubunda 0,8 idi ($p < 0,001$) (Tablo 4).

Tablo 4. Demir eksikliği anemisi ve kronik hastalık anemisi olan hastaların ferritin, sTfR, sTfR/log ferritin indeksi ve hepsidin düzeylerinin karşılaştırılması.

	DEA (n=70)	KHA (n=56)	p
Ferritin (ng/mL)	22,0 (65,5)	59,0 (99,5)	<0,001
sTfR (mg/L)	2,2 (1,3)	1,5 (0,6)	<0,001
Hepsidin(ng/mL)	21,7 (12,4)	23,6 (11,5)	0,456
sTfR/log ferritin indeksi	1,5 (2,2)	0,8 (0,5)	<0,001
<1	20 (%28,6)	36 (%64,3)	
1-2	21 (%30,0)	19 (%33,9)	
>2	29 (%41,4)	1 (%1,8)	

Hastalar sTfR/log ferritin indeksine göre 1'in altında olanlar, 1-2 arası olanlar ve 2'nin üstünde olanlar olarak gruplandırıldığında DEA olan hastaların %41,4'ünde 2'nin üstünde, %30'unda 1-2 arasında, %28,6'sında ise 1'in altında, KHA olan hastaların ise %64,3'ünde 1'in altında, %33,9'unda 1-2 arasında, %1,8'inde ise 2'nin üstündeydi. sTfR düzeyinin 1,65 mg/L'nin üzerinde olmasının DEA varlığını gösterdiği düşünülerek yapılan analizler sonucunda sTfR'nin DEA varlığını göstermede sensitivitesi %77,1 spesifitesi %67,9 bulundu. Ferritin için ise 30 ng/ml kesim noktası alındığında sensitivite % 57,1 spesifite %76,8 bulundu (Tablo 5).

Tablo 5. Demir eksikliği anemisi ve kronik hastalık anemisi olan grupları ayırt etmede kesim noktalarına göre sTfR ve ferritinin tanısal performans düzeyleri.

		sTFR	Ferritin
Olgu Sayısı		N=126	N=126
Kesim Noktası		>1.65	≤30
Duyarlılık	GP/(GP+YN)	54/70 (%77,1)	40/70 (%57,1)
Seçicilik	GN/(GN+YP)	38/56 (%67,9)	43/56 (%76,8)
PTD	GP/(GP+YP)	54/72 (%75,0)	40/53 (%75,5)
NTD	GN/(YN+GN)	38/54 (%70,4)	43/73 (%58,9)
Doğruluk	(GP+GN)/(N)	92/126 (%73,0)	83/126 (%65,9)
p değeri		<0,001	<0,001

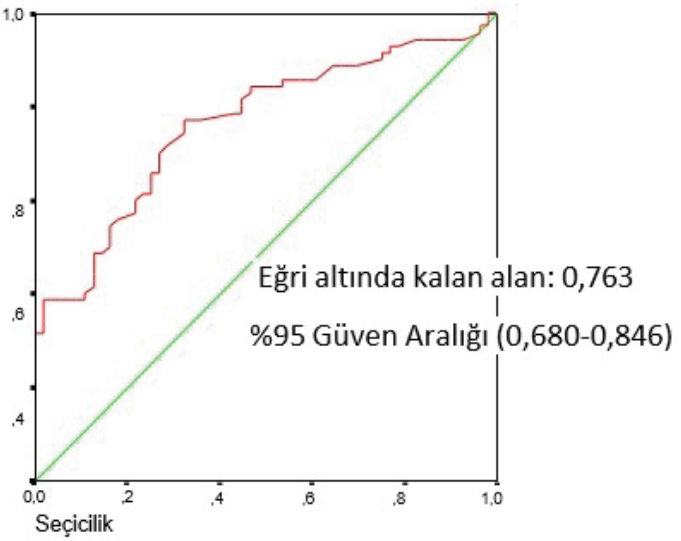
GP: Gerçek Pozitif, YN: Yalancı Negatif, GN: Gerçek Negatif, YP: Yalancı Pozitif, PTD: Pozitif Tahmini Değer, NTD: Negatif Tahmini Değer

Çoklu değişkenli lojistik regresyon analizine göre demir eksikliği anemisi (DEA) olan ve kronik hastalık anemisi (KHA) olan grupları ayırt etmede sTfR ve ferritinin etkileri incelendiğinde sTfR için 1,65 mg/L kesim noktası alındığında odds oranı 5,83 ferritin için ise 3,27 bulunmuştur. Ferritin için gastrointestinal maligniteli hastalardan oluşan bu popülasyonda kesim noktası 30 ng/ml kabul edildi (Tablo 6).

Tablo 6. Çoklu değişkenli lojistik regresyon analizine göre demir eksikliği anemisi ve kronik hastalık anemisi olan grupları ayırt etmede sTfR ve ferritinin etkilerinin birlikte incelenmesi.

	Odds oranı	%95 Güven aralığı	p
sTFR>1.65	5,832	2,571-13,227	<0,001
Ferritin≤30	3,271	1,403-7,625	0,006

DEA varlığında ferritin değerinin 30'un altında olması beklenirken sTfR düzeyi için farklı çalışmalarda farklı kesim noktaları bulunmuş olmakla birlikte bizim çalışmamızda sTfR için yapılan ROC eğrisinde eğri altında kalan alan 0,763 ve kesim noktası 1,65 mg/L bulundu (Şekil 1).



Şekil 1. Demir eksikliği anemisi olan ve kronik hastalık anemisi olan grupları ayırt etmede serum TFR'ye ilişkin ROC eğrisi.

Tartışma

Gastrointestinal sistem malignitesi olan hastalarda demir eksikliği anemisi ve kronik hastalık anemisi sık karşılaşılan problemlerdir. Gastrointestinal sistem malignitesi olan anemik hastalarda enflamatuar olaylardan etkilenmeyen, fonksiyonel demir durumu ve eritropoetik aktiviteyi değerlendirmede güvenilir bir parametre olan sTfR'nin DEA ile KHA ayırıcı tanısındaki yerini araştırdığımız bu çalışmada DEA olan hastalarda sTfR düzeyi KHA olan hastalardan anlamlı şekilde daha yüksek bulundu. Lee ve ark. yaptığı çalışmada erişkin, anemik, endoskopik olarak malign lezyonu olan hastalarda DEA tanısında ferritin için 44 ng/ml kesim noktası kabul edildiğinde sensitivitesinin %72, spesifitesinin ise %70 olduğu gösterilmiştir [11]. Bizim çalışmamızda gastrointestinal sistem malignitesi olan hastalarda DEA varlığını göstermede ferritin için 30 ng/ml kesim noktası alınmış ve sensitivitesi %57, spesifitesi %76 bulunmuştur.

Demir eksikliği durumunda hücrelerin artan demir ihtiyacına bağlı olarak hücre yüzeyinde TfR ve serumda ölçülen sTfR düzeylerinde artış olur. Suominen P. ve arkadaşlarının romatoid artritli anemik hastalarda sTfR ve sTfR/log ferritin indeksinin DEA varlığını göstermede tanısal değerini incelediği çalışmada retrospektif olarak bakıldığında oral demir tedavisinden fayda gören hastaların bazalde bakılan sTfR konsantrasyonu ve sTfR/log ferritin indeks değerlerinin demir tedavisinden sonra anlamlı olarak değiştiği ve bu değerlerin kemik iliği demir depolarının boyanması ve ferritin değerlerine kıyasla daha etkili olduğu (sTfR, sTfR/log ferritin indeks, kemik iliği boyaması ve ferritin için sırasıyla etkinlik değerleri, %93,3, %93,3, %83,8, %80,7) bulunmuş olup sTfR ve sTfR/log ferritin indeksi değerlerinin

DEA, KHA ayırıcı tanısında kullanışlı parametreler olduğu ve kemik iliği depo demirinden bağımsız olarak fonksiyonel demir eksikliğini de gösterebilecekleri sonucuna ulaşılmıştır [12]. Bizim çalışmamızda da DEA olan hastalarda sTfR düzeyi KHA olan hastalara göre daha yüksek bulunmuş olup ayırıcı tanıda kullanılabilecek bir parametre olduğu gösterilmiştir.

Frank ve arkadaşlarının farklı parametrelerin DEA ile KHA ayırıcı tanısında tanısal güçlerini değerlendirdiği bir çalışmada laboratuar testlerinin tanısal gücü TDBK > sTfR > MCV > TS = RDW > serum demir konsantrasyonu şeklinde olduğu bulunmuş ve sTfR değerinin rutin ölçümünün TDBK ölçümüne göre bir üstünlüğü olmadığı ve ek yarar sağlamayacağı sonucuna ulaşılmıştır [13]. Ancak bu çalışmada hastalar ferritin değerlerine göre DEA ve KHA olarak gruplandırılmış olup ferritinin KHA olan hastalarda demir depolarını göstermede sensitivite ve spesifitesinin düşük olmasından dolayı sTfR'nin etkinliği düşük bulunmuş olabilir. Bizim çalışmamızda hastalar TS değerine göre DEA ve KHA gruplarına ayrılmış olup sTfR ölçümünün ferritinden daha sensitif olduğu bulunmuştur.

Kemoterapinin sTfR düzeyini düşürücü etkisi bilinmekle birlikte kemoterapiden bağımsız olarak malignitenin başlı başına sTfR düzeyini düşürücü etkisinin olup olmadığı net değildir. Farklı çalışmalarda solid malignitesi olan hastalarda EPO düzeyinin anemi derecesine göre düşük saptandığı, anemiye yetersiz EPO yanıtı olduğu, ayrıca kemoterapiye bağlı kemik iliği supresyonunun sTfR düzeyini düşürdüğü gösterilmiştir [14]. Bu nedenle sTfR düzeyinin KHA olan hastalarda DEA varlığını göstermede uygun olmayacağını söyleyen çalışmalarda KHA olan hasta popülasyonunda malignitesi olan hastaların varlığı sonuçları etkilemiş olabilir. Spesifik olarak solid malignitesi olan hasta gruplarında sTfR ve sTfR/log ferritin indeksinin DEA ve KHA ayırıcı tanısındaki yeri kesin olarak belirlenmemiştir.

Berlin ve arkadaşlarının anemisi olan, ferritin değeri normal veya yüksek olup sTfR düzeyi yüksek olan hastalarda yapılan endoskopi sonuçlarını incelediği çalışmada sTfR düzeyi yüksek olan hastaların %68'inde kolonik polip, kolon kanseri, duodenal ülser, mide kanseri, kolit, atrofik gastrit, eroziv gastrit ve anjiodisplazi gibi demir eksikliğine neden olacak bir patolojik bulguya rastlanmıştır ve yüksek sTfR düzeylerinin gastrointestinal kanamaya bağlı DEA varlığını göstermede ferritin normal veya yüksek olduğunda iyi bir belirteç olacağı sonucuna varılmıştır [15].

DEA varlığını ve DEA, KHA birlikteliğini göstermede hem vücut demir depoları, hem demirin eritropoez için kullanılabilirliği, hem de kemik iliğindeki total eritroid kütlenin değerlendirilmesine olanak sağlayan sTfR/log ferritin indeksinin bu iki parametrenin ayrı ayrı değerlendirilmesinden daha sensitif ve spesifik bir gösterge olabileceği Punnonen K. ve arkadaşlarının yaptığı çalışmada gösterilmiştir [6]. sTfR/log ferritin indeksinin 1'in altında olması KHA tanısını desteklerken DEA ve DEA, KHA birlikte olması durumunda bu oran 2'nin üstünde olmaktadır [6,7]. Ancak bunun aksine sTfR ve sTfR/log ferritin indeks ölçümünün tanısal gücünün incelendiği 10 farklı çalışmadan derlenen Infusino I. ve arkadaşları tarafından derlenen bir metaanaliz sonucunda ise hem sTfR, hem sTfR/logferritin indeksinin DEA ve KHA ayırımında kullanılabileceği belirtilmekle birlikte sTfR için odds oranı 22.9, sTfR/log ferritin indeksi için odds oranı 9.5 olmasına dayanarak sTfR'nin tek başına sTfR/log ferritin indeksinden daha etkili olduğu gösterilmiştir [16]. Bizim çalışmamızda da DEA olan hastaların sadece %41,4'ünde sTfR/logferritin indeksi 2'nin üstünde, %30'unda 1-2 arasında iken

%28,6'sında ise 1'in altındaydı. KHA olan hastaların ise %64,3'ünde 1'in altında, %33,9'unda 1-2 arasında, %1,8'inde 2'nin üstündeydi. DEA ve KHA olan gruplar arasında bu oran karşılaştırıldığında ise sTfR/log ferritin indeksi DEA grubunda ortalama 1,5 iken KHA grubunda 0,8 idi ve bu fark istatistiksel olarak anlamlı idi ($p < 0,001$).

Yapılan farklı çalışmalarda DEA varlığını belirlemede sTfR düzeyi için farklı kesim noktaları belirlenmiştir. sTfR ve sTfR/log ferritin indeksinin DEA tanısındaki yerinin araştırıldığı 9 ayrı çalışmanın değerlendirilmesinden oluşan Koulaouzidis A. ve arkadaşları tarafından yayınlanan bir derlemede bulunan sTfR kesim noktası değerleri ve sTfR, sTfR/log ferritin indeksinin sensitivite ve spesifite analizlerinin sonuçları incelendiğinde sTfR için DEA olanlarda ortalama değer Punnonen ve ark. 1997 yılında yaptığı çalışmada 6,2 ± 3,5 mg/L, Suominen ve ark. 2000 yılında yaptığı çalışmada 2,92 ± 0,76 mg/L, Hanif ve ark. 2005 yılında yaptığı çalışmada ise 9.68 ± 2,48mg/L bulunmuştur [17]. Bizim çalışmamızda DEA olan hastalarda ortalama sTfR değeri 2,2 ± 1,3 mg/L, DEA tanısı için sTfR kesim noktası olarak 1,65 mg/L bulundu. Hastaların %96.8'i aktif kemoterapi almıyor olmasına rağmen sTfR düzeylerinin yapılan farklı çalışmalarda bulunan değerlerden düşük saptanması malignitenin kemoterapiden bağımsız olarak başlı başına sTfR düzeyini düşürücü etkisi olmasına bağlı olabilir. Ayrıca sTfR ölçüm yöntemlerinde standardizasyon olmaması ve farklı hasta grupları için normal referans aralıklarının net belirlenmemiş olması da bu farklılıklara yol açabilir.

DEA ve KHA ayırıcı tanısında ve DEA ile KHA birlikteliğini göstermede sTfR ve sTfR/logferritin indeks ölçümünün tanısal gücünün incelendiği Infusino I. ve arkadaşları tarafından 2012

yılında yayınlanan bir metaanaliz sonucunda ise sTfR için genel olarak sensitivite %86 (%82-89), spesifite %75 (%71-79) bulunmuştur [16]. Bizim çalışmamızda DEA varlığını göstermede sTfR'nin sensitivitesi %77, spesifitesi % 68, ferritinin ise sensitivitesi %57, spesifitesi %76 bulunmuştur. Tanısal doğruluk değerlerine baktığımızda sTfR için 92/126 (%73,0), ferritin için 83/126 (%65,9), odds oranı ise sTfR için 5,832 ferritin için 3,271 olduğu görülmüştür. sTfR için daha önce yapılan diğer çalışmalardan daha düşük sensitivite ve spesifite sonuçlarının bulunması hastaların DEA ve KHA olarak gruplandırılmasında TS değerinin baz alınmasından, kemik iliği incelemesi yapılmamış olmasından ve hasta grubumuzun malignitesi olan hastalardan oluşuyor olmasından kaynaklanıyor olabilir.

Hepsidin demir metabolizmasındaki anahtar rolünün keşfinden sonra DEA tanısındaki yeri üzerine çok sayıda çalışma yapılan bir moleküldür. İntestinal demir absorbsiyonunu ve makrofajlardan demir salınımını engelleyerek negatif demir dengesi sağlayan hepsidin molekülünün düzeyi demir eksikliği varlığında vücudun artan demir gereksinimine bağlı olarak düşer. Ancak hepsidin aynı zamanda inflamasyon varlığında özellikle IL-6 ve diğer sitokinler aracılığıyla sentezi artan ve kronik hastalık anemisi patogenezinde anahtar rol oynayan bir moleküldür. Pasricha SR ve arkadaşlarının 261 anemik olmayan hastanın serum ferritin, sTfR/log ferritin indeks ve hepsidin konsantrasyonlarını ölçerek hepsidin düzeyinin DEA tanısındaki yerini araştırdığı çalışmada hepsidin için 8 ng/mL sınır alındığında sensitivite %41.5, spesifite %97.6, 18 ng/mL sınır alındığında sensitivite %79.2, spesifite %85.6 bulunmuştur [18]. Ancak bu çalışmada hasta popülasyonu sağlıklı, anemisi olmayan reprodüktif dönemdeki kadınlardan oluşmaktadır. Bizim çalışmamızda DEA ve KHA olan hastalar arasında hepsidin düzeyleri arasında anlamlı fark olmadığı, DEA olan hastalarda hepsidin düzeyinde düşüş olmadığı görülmüştür. Bu durum malignite varlığının hepsidin düzeyinde artışla sonuçlanmasına bağlı olabilir. Kronik hastalıkların seyrinde görülen anemi patofizyolojisinde hepsidin artışına bağlı ortaya çıkan fonksiyonel demir eksikliği önemli bir yer tutmaktadır. Thomas C ve arkadaşları hepsidin düzeyinin DEA ile KHA ayırıcı tanısındaki yerini araştırmışlar ve retikülosit hemoglobin içeriği ile kombine edildiğinde hepsidin düzeyi ölçümünün ayırıcı tanıda kullanılabileceği sonucuna varmışlardır [19]. Goodnough LT ve arkadaşlarının yaptığı çalışmada DEA varlığında vücudun demir ihtiyacındaki artışa bağlı hepsidin düzeyinde artış olduğu, KHA varlığında ise patogenetik olarak ortaya çıkan sitokinlerin etkisiyle hepsidin düzeyinde artış olduğu gösterilmiş olup ayırıcı tanıda hepsidin düzeylerinin kullanılabileceği fakat KHA'ya eşlik eden DEA varlığında kullanışlı olmayacağı sonucuna varılmıştır [20]. Bizim çalışmamızda da DEA ve KHA olan hastalar arasında hepsidinin anlamlı olarak değişmediği gösterilmiş olup bu sonuç malignitesi olan hastalarda DEA olsada sitokin ilişkili hepsidin artışının daha etkili olmasına bağlı olabilir.

Sonuç olarak gastrointestinal sistem malignitesi olan anemik hastalarda DEA ve KHA ayırıcı tanısında sTfR ölçümü ferritin ölçümünden daha sensitif bir yöntem olarak kullanılabilir. sTfR/log ferritin indeksi DEA olan hastalarda sTfR artışı ve ferritin düşüşüne paralel olarak yükselmekte olup malignitesi olan hastalarda bu oran için kesim noktalarının belirlenmesi açısından daha geniş çaplı çalışmalar gerekmektedir. Hepsidin düzeyi malignitesi olan hastalarda akut faz yanıtı olarak yükseldiğinden KHA'ya eşlik eden DEA varlığını göstermede etkili değildir. sTfR ölçümü sensitivite ve spesifitesi tanı için ideal altın standart olarak kullanılacak bir test olmadığını gösterse de DEA, KHA ayırıcı tanısında ferritinden daha etkili, sensitivitesi ve doğruluk oranı daha yüksek bir yöntem olarak malignitesi olan hastalarda özellikle kronik hastalık anemisine eşlik eden demir eksikliğini göstermede tanısal test olarak tercih edilebilir. Konvansiyonel tetkiklerin ayırıcı tanıda yetersiz kaldığı ve kemik iliği incelemesi yapılamayacak hastalarda sTfR düzeyine bakılarak, yüksek saptanması durumunda demir tedavisi başlanıp yanıt izlenebilir ancak ölçüm yöntemlerinin standardize edilmesi gerekmekte olup, farklı hasta gruplarındaki kesim noktası değerlerinin belirlenmesi için geniş çaplı çalışmalara ihtiyaç vardır.

Maddi destek ve çıkar ilişkisi

Araştırmacıların herhangi bir çıkar ilişkisi bulunmamaktadır.

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Yazarların katkısı

PP: çalışmanın tasarımı, verilerin toplanması, istatistiksel analizlerin gerçekleştirilmesi ve makalenin yazımı, EZ: çalışmanın genel denetimi, yazının düzenlenmesi ve bilimsel açıdan eleştirel değerlendirilmesi, FB:rutin tetkikler dışında sTfR ve hepsidin düzeylerinin laboratuvar analizlerini gerçekleştirdi; sTfR/log ferritin indeksi hesaplamalarını yaptı, BC: çalışma fikrinin oluşumuna katkı sağladı; yazım sürecinde bilimsel değerlendirme ve düzenlemelerde yer aldı, SA:

çalışmanın planlanmasında destek verdi; yazının gözden geçirilmesi ve bilimsel katkı sağlanması süreçlerine katıldı, EA: akademik danışmanlık sağladı ve araştırmanın genel yönlendirilmesine katkıda bulundu.

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Research Article

Multidisciplinary management of cancer patients: hospitalisation and consultation characteristics

Kanser hastalarının multidisipliner yönetimi: hastaneye yatış ve konsültasyon özellikleri

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Abstract

Aim: Cancer is one of the leading causes of death. Cancer patients have long-term hospitalisations for a wide variety of reasons. This study aims to emphasize the importance of a multidisciplinary approach in cancer treatment by evaluating the hospitalisation and consultation characteristics of patients hospitalised in the Medical Oncology Service of Etlik City Hospital.

Material and Methods: The demographic, clinical, biochemical, hospitalisation, discharge status, and consultation characteristics of a total of 376 patients hospitalised in the Medical Oncology Service between May and June 2024 were evaluated. Patients for whom consultation was requested and those for whom consultation was not requested were analysed comparatively. Patient data were retrieved retrospectively from the hospital's archive and automation system.

Results: The median length of hospitalisation was five days (range: 1-43), and 17.3% of patients had a hospital stay exceeding 21 days. A total of 15.2% of patients were transferred to the intensive care unit, while 3.7% were referred to the palliative care ward. The data indicates that consultations were requested for 72.6% of patients, most frequently from infectious diseases (38.3%), cardiology (26.3%), and radiology (22.1%) departments. Compared to patients without consultation requests, those for whom consultations were requested exhibited significantly lower albumin/globulin ratios ($p < 0.001$), more advanced disease stages ($p < 0.01$), and prolonged hospitalisation durations ($p < 0.001$)

Conclusions: Challenges in the management of oncology patients require the coordinated efforts of multiple specialities. A multidisciplinary approach is essential to prevent complications, increase treatment efficacy and improve clinical outcomes.

Keywords: cancer, hospitalisation characteristics, consultation, multidisciplinary approach

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Öz

Amaç: Kanser önde gelen ölüm nedenlerinden biridir. Kanser hastalarının çok çeşitli nedenlerle uzun süreli hastane yatışları vardır. Bu çalışma Etlik Şehir Hastanesi Tıbbi Onkoloji Servisinde yatan hastaların yatış ve konsültasyon özelliklerini değerlendirerek kanser tedavisinde multidisipliner yaklaşımın önemini vurgulamayı amaçlamaktadır.

Gereç ve Yöntemler: Mayıs-Haziran 2024 tarihleri arasında Tıbbi Onkoloji Servisinde yatan toplam 376 hastanın demografik, klinik, biyokimyasal, yatış, taburculuk ve konsültasyon özellikleri değerlendirildi. Konsültasyon talep edilen hastalar ile konsültasyon talep edilmeyen hastalar karşılaştırmalı olarak analiz edilmiştir. Hasta verileri hastanenin arşiv ve otomasyon sisteminden retrospektif olarak elde edilmiştir.

Bulgular: Ortanca hastanede yatış süresi beş gündü (1-43) ve hastaların %17,3'ünün hastanede kalış süresi 21 günden uzundu. Hastaların %15,2'si yoğun bakım ünitesine, %3,7'si de palyatif servisine nakledilmiştir. En sık konsültasyon istenen 3 klinik enfeksiyon hastalıkları (%72,6), kardiyoloji (%38,3) ve radyoloji (%22,1) idi. Konsültasyon istenen hastalarda, albümin/globulin oranı anlamlı düzeyde daha düşük ($p < 0,001$), hastalık evresi daha ileri ($p < 0,01$) ve hastanede yatış süresi daha uzun ($p < 0,001$) bulundu.

Sonuçlar: Onkoloji hastalarının tedavisinde karşılaşılan zorluklar, birden fazla uzmanlık alanının koordineli çabalarını gerektirmektedir. Komplikasyonları önlemek, tedavi etkinliğini artırmak ve klinik sonuçları iyileştirmek için multidisipliner bir yaklaşım şarttır.

Anahtar Kelimeler: kanser, hastaneye yatış özellikleri, konsültasyon, multidisipliner yaklaşım

Introduction

Cancer is an increasingly significant health problem on a global scale. Despite considerable progress in the management and treatment of cancers, they continue to be among the leading causes of death. Within our own nation, cancers rank as the second most prevalent cause of mortality, surpassed only by cardiovascular diseases [1,2]. The increase in life expectancy, due in part to earlier diagnosis and novel therapies, has led to a concomitant increase in the number of cancer outpatients and emergency department visits [3]. The management of cancer patients requires the collaboration of several medical disciplines, namely medical oncology, surgery, pathology, radiation oncology and other relevant specialties. This underscores the imperative for a multidisciplinary approach to cancer treatment [4].

The aim of our study was to evaluate the reasons for hospitalisation, length of stay, discharge status and consultation processes of patients hospitalised in the oncology ward, to reveal the difficulties in treatment processes and to emphasise the necessity of evaluating oncology patients not only by oncologists but also by other medical branch physicians. In this direction, we aimed to show the importance of a multidisciplinary approach.

Material and Methods

The present retrospective study was designed to evaluate the admission and consultation characteristics of patients admitted to the medical oncology service of Etlik City Hospital between May and June 2024. The study was conducted in accordance with the Declaration of Helsinki and approved by the Scientific Research Evaluation and Ethics Committee of Etlik City Hospital with the approval number BADEK-2024-1243 on 18 December 2024.

Hospitalisation characteristics were evaluated by location, reason, duration and discharge status. The number of consultations and the most frequently requested clinics were determined as consultation characteristics. Subsequently, a comparative analysis was conducted of the sociodemographic, clinical, hospitalisation and laboratory parameters of patients who requested consultation and those who did not. All the data relating to the patients were obtained from the hospital's automation system and patient records retrospectively. The records were anonymised in such a way that patient identity information was kept confidential and collected in a database.

Statistical Analysis

The collected data were analysed using SPSS 22.0 software. Continuous variables were characterised by median (minimum-maximum) and interquartile range (IQR) values, while categorical variables were presented as frequency and percentage. Pearson Chi-Square test was used to evaluate the differences between patients with and without consultation, and $p < 0.05$ was considered statistically significant. The objective of this method was to conduct a detailed analysis of the hospitalisation and consultation processes of patients hospitalised in the ward.

Results

The median age of the 376 patients hospitalised in the medical oncology service in May-June 2024 was 63 years (20-90 years), with a male-to-female ratio of 55.1% to 44.9%. The most prevalent primary diagnosis was lung cancer (28.2%), followed by gastric cancer (12.8%), colorectal cancer (11.7%) and breast cancer (10.1%). The majority of patients were found to be in a metastatic stage (66.8%), and 53.2% had at least one comorbidity, with hypertension (31.4%) and diabetes (22.3%) being the most prevalent. Patients' demographic and clinical characteristics are shown in table 1.

Table 1. Sociodemographic and clinical characteristics.	
Age median (range) year	63.0 (20.0-90.0)
Sex	No (%)
Male	207 (55.1)
Female	169 (44.9)
Primary	No (%)
Lung	106 (28.2)
Breast	38 (10.1)
Pancreas	22 (5.9)
Gastric	48 (12.8)
Colorectal	44 (11.7)
Sarcoma	13 (3.4)
Bladder	6 (1.6)
Colangiocarcinoma	12 (3.2)
Jinecological	31 (8.2)
Testis	10 (2.7)
Head & neck	19 (5.1)
Kidney	6(1.6)
Primary unknown	6 (1.6)
Other	15 (3.9)
Stage	No (%)
Metastatic	251 (66.8)
Non-metastatic	125 (33.2)
Comorbidity	No (%)
Yes	200 (53.2)
No	176 (46.8)
Comorbidity	No (%)
Hypertension	118 (31.4)
Diabetes Mellitus	84 (22.3)
Coronary artery disease	64 (17.0)
Cerebrovascular disease	27 (7.2)
Asthma/COPD	38 (10.1)
Thyroid (hypo/hyper) disease	22 (5.9)
Other	36 (9,6)
Abb: COPD: Chronic Obstructive Pulmonary Disease	

When the admission and discharge features of the patients were evaluated, it was found that the majority were admitted from the oncology outpatient clinic (64.1%) and the emergency department (21.5%), while transfers from the intensive care unit (4.5%) and other clinics to the oncology service were less common. The most common reason for hospitalisation was maintenance of oncological treatment (44.4%), followed by infectious causes (13.6%), palliative care (16.5%) and interventional procedures (12.8%). The median length of stay was five days (range: 1-43 days) and 15.3% of patients required hospitalisation for more than 21 days. In terms of discharge status, the majority of patients (79.5%) were discharged home, while 15.2% were referred to the intensive care unit and 3.7% to palliative care. The mortality rate was 0.8%. The admission and discharge characteristics of the patients are detailed in table 2.

Table 2. Hospitalisation- discharge futures of the hospitalisation.	
Referred department	N (%)
Oncology outpatient clinic	241 (64.1)
Emergency	81 (21.5)
Transfer from intensive care	17 (4.5)
Transfer from thoracic medicine/surgery	10 (2.7)
Transfer from general surgery/surgical oncology	7 (1.9)
Transfer from gynecooncology	6 (1.6)
Transfer from other clinics	14 (3.8)
Cause for hospitalisation	No (%)
Infection	51 (13.6)
Maintenance of oncologial treatment	167 (44.4)
Electrolyte imbalace	24 (6.4)
Blood transfusion	20 (5.3)
Palliative Care	62 (16.5)
Interventional procedures	48 (12.8)
Other	4 (1.1)
Duration of hospitalisation median (range) days	5.0 (1.0-43.0)
Duration of hospitalisation	No (%)
1-7 days	202 (53.7)
8-21 days	109 (29.0)
>21 days	65 (17.3)
Discharge status	No (%)
Discharged	299 (79.5)
Transfer to intensive care ward	57 (15.2)
Transfer to palliative service	14 (3.7)
Transfer to other clinics	3 (0.8)
Exitus	3 (0.8)

The median haemoglobin (Hgb) value was 10.9 g/dL (9.2-12.3), while the total protein and albumin levels were 62 g/L (56.0-68.0) and 35 g/L (30.0-39.9), respectively. The median albumin/globulin ratio was 1.30 (1.07-1.59). Patients' enrolled laboratory parameters are shown in table 3.

Table 3. Biochemical parameters at the time of hospitalisation.	
	Median (IQR)
Hgb (g/dL)	10.9 (9.2-12.3)
Lenfosit (109/L)	1.03 (0.60-1.63)
Platelet (109/L)	220.0 (140.0-318.0)
Total protein (g/L)	62.0 (56.0-68.0)
Albümin (g/L)	35.0 (30.0-39.9)
Globulin (g/L)	27.0 (23.0-31.0)
Albumin/globulin	1.30 (1.07-1.59)

When analysing the consultation status of the patients, it was found that 72.6% of the patients requested a consultation in at least one department and the median of the number of consultations was 2 (range: 0-7). The most commonly requested specialties were infectious diseases (38.3%), cardiology (26.3%), radiology (22.1%) and radiation oncology (14.7%). Supporting specialties such as palliative care (16.5%), intensive care (16.2%) and anaesthesia/analgesia (7.2%) were also included in significant proportions. The departments for which consultation was requested are summarised in table 4.

Table 4. Clinics for consultation.	
Consultation	N (%)
Yes	273 (72.6)
No	103 (27.4)
Number of clinics consulted median (IQR)	2.0 (0-7.0)
Consultant clinics	No (%)
Radiation oncology	55 (14.7)
Infectious diseases	144 (38.3)
Anaesthesia/algology	27 (7.2)
General surgery/surgical oncology	37 (9.8)
Nutrition	29 (7.7)
Gynecooncology	3 (0.8)
Cardiology	99 (26.3)
Thoracic diseases/surgery	55 (14.7)
Radiology	83 (22.1)
Physiotherapy and rehabilitation	13 (3.5)
Psychiatry	62 (16.5)
Palliative clinic	18 (4.8)
Intensive care	61 (16.2)
Urology	19 (5.1)
Ophthalmic diseases	9 (2.4)
Ear-nose-throat	16 (4.3)
Neurosurgery	12 (3.2)
Neurology	26 (6.9)
Nephrology	20 (5.3)
Other	81 (21.6)

When the relationship between consultation status and clinical characteristics of the patients was examined, consultation rates were more common in hospitalisations due to infectious conditions, palliative care and interventional procedures ($p < 0.001$). Albumin/globulin ratio was lower in the consultation group ($p < 0.001$). In addition, patients who were consulted were found to be at a more advanced stage ($p < 0.01$) and had a longer hospital stay (61.9%; 8 days or more) compared to patients who were not consulted ($p < 0.001$). The relationships between consultation status and clinical characteristics of the patients are summarized in table 5.

Discussion

The most common cancers in men worldwide are lung, prostate and colorectal, while the most widespread cancers in women are breast, colorectal and lung [5]. The incidence of cancer increases with age and the presence of comorbidities [6-8]. Studies in the published literature show that the incidence of cancer is more in men [9-11]. In our study as well, the results were consistent with the literature indicating that cancer incidence is associated with factors such as age, gender, and comorbidities [8,9].

Güneysu et al. found that 43.5% of the total hospitalisations in the medical oncology service were outpatient (outpatient clinic or appointment system), 48.8% were from the emergency unit and 7.7% were from other units [5]. In a study by Sadik et al. titled "Characteristics of cancer patients admitted to the emergency department within one year", it was reported that approximately 60% of oncology patients admitted to the emergency department were hospitalised [8]. In our study as well, the majority of patients were admitted from medical oncology outpatient clinics, while a portion were admitted through emergency services. This finding highlights the need for oncology wards to be structured in a way that accommodates both scheduled treatment processes and urgent admissions, indicating that both sources play a significant role in patient flow.

In studies in the literature, the principle cause for admission of cancer patients to emergency departments or oncology outpatient clinics were dyspnoea, pain, general condition disorder and gastrointestinal symptoms [12-14]. In our study, hospital admissions were predominantly due to the continuation of oncological treatments. This finding underscores the critical role of oncology wards not only in managing complications but also in maintaining continuity of planned treatment protocols. The frequent occurrence of infectious conditions, palliative care needs, and interventional procedures among the causes of admission further highlights the clinical diversity of oncology inpatients and the necessity for multidisciplinary management. The fact that our hospital is a large metropolitan referral center serving patients from surrounding provinces significantly contributes to this heterogeneity.

In our study, it was observed that the length of hospital stay varied considerably, with a subset of patients experiencing prolonged admissions. Additionally, a notable proportion of patients were transferred to intensive care or palliative care units, indicating that many of them had advanced-stage disease and complex clinical conditions. Variations in hospital stay duration and discharge status reported in the literature [15–17] may be influenced by the clinical characteristics of the patient population, the availability of palliative care services, and differences in institutional capacity. In particular, the effectiveness and accessibility of palliative care services appear to be key factors that directly impact the length of hospital stay and discharge planning.

Studies in the literature show that cancer patients are mostly anaemic in laboratory parameters and are at risk of malnutrition [18]. In our study, it was found that the patients were anaemic and albumin levels were low. Low albumin/globulin ratio, longer hospital stay and higher proportion of metastatic patients in the consulted group suggest that these patients have more severe clinical conditions and are more prone to malnutrition.

Table 5. Correlation of consultations with patients' clinical characteristics and parameters.

	No Consultation n (%) (103)	Consultation n (%) (273)	P
Sex			
Male	52 (50.5)	155 (56.8)	0.30
Female	51 (49.5)	118 (43.2)	
Primary			
Lung	29 (28.2)	77 (28.2)	
Breast	17 (16.5)	21 (7.7)	
Pancreas	6 (5.8)	16 (5.9)	
Gastric	8 (7.7)	40 (14.7)	
Colorectal	12 (11.6)	32 (11.7)	
Sarcoma	7 (6.8)	6 (2.2)	
Bladder	0 (0.0)	6 (2.2)	
Colangiocarcinoma	0 (0.0)	12 (4.4)	
Jinecological	12 (11.7)	19 (7.0)	0.003
Testis	6 (5.8)	4 (1.5)	
Head & neck	2 (2.0)	17 (6.2)	
Kidney	1 (1.0)	5 (1.8)	
Primary unknown	0 (0.0)	6 (2.2)	
Other	3 (2.9)	12 (4.3)	
Stage			
Metastatic	53 (51.5)	198 (72.5)	<0.001
Non-metastatic	50 (48.5)	75 (27.5)	
Cause for hospitalisation			
Infection	6 (5.8)	45 (16.5)	
Maintenance of oncologial treatment	84 (81.6)	83 (30.4)	
Electrolyte imbalace	3 (2.9)	21 (7.7)	
Blood transfusion	6 (5.8)	14 (5.1)	<0.001
Palliative care	1 (1.0)	61 (22.3)	
Interventional procedures	3 (2.9)	45 (16.5)	
Other	0 (0.0)	4 (1.5)	
Comorbidity			
Yes	55 (53.4)	121 (44.3)	0.13
No	48 (46.6)	152 (55.7)	
Comorbidity			
Hypertension	31 (30.1)	87 (31.9)	0.79
Diabetes Mellitus	20 (19.4)	64 (23.4)	0.39
Coronary artery disease	18 (17.5)	46 (16.8)	0.26
Cerebrovascular disease	5 (4.9)	22 (8.1)	0.36
Asthma/COPD	7 (6.8)	31 (11.4)	0.26
Thyroid (hypo/Hyper) Disease	9 (8.7)	13 (4.8)	0.75
Other	13 (12.6)	10 (3.6)	0.41
Duration of hospitalisation			
1-7 days	95 (92.2)	107 (39.2)	
8-21 days	5 (4.9)	104 (38.1)	<0.001
>21 days	3 (2.9)	62 (22.7)	
Albumin/globulin			
Low	21 (20.4)	167 (61.2)	<0.001
High	82 (79.6)	106 (38.8)	

Abb: COPD: Chronic Obstructive Pulmonary Disease, Pearson's Chi-Square Test

In a study by Aytekin et al (2014), an analysis of consultations for patients hospitalised in a medical oncology ward revealed that 43.5% of patients required consultation from at least one specialty, with radiology, infectious diseases, and general surgery being the most frequently consulted departments [19]. Conversely, our study identified infectious diseases, cardiology, and radiology as the most commonly consulted specialties. Furthermore, substantial consultation rates were observed from other specialties, including intensive care, palliative care, anesthesiology and pain management, radiation oncology, and general surgery. These findings underscore the essential role of coordinated, team-based care in treating individuals with cancer, stressing the importance of integrated efforts beyond oncology alone.

The necessity of multidisciplinary evaluation in oncology care is well-supported by numerous studies in the literature [20–22]. In our study, patients who required consultations were more to be at advanced disease stages, experienced longer hospital stays, and exhibited more severe clinical and laboratory profiles. These results emphasize the critical importance of inter-specialty collaboration and the multidisciplinary approach in addressing the complex management needs of cancer patients. Specifically, the contributions of supportive care specialties are vital in improving treatment efficacy and managing complications, particularly in patients with advanced disease.

Limitations of the study

This study has several limitations. Firstly, the retrospective and single-center design may limit the generalizability of the findings to broader populations. Secondly, the study period was limited to only two months, which may not reflect potential seasonal variations or institutional fluctuations in admission and consultation patterns. Additionally, due to the retrospective design, some clinical or laboratory variables that may have impacted outcomes could not be comprehensively evaluated. Future prospective and multi-center studies with longer follow-up periods are needed to validate these findings.

In conclusions, it has been observed that cancer patients have long hospitalisations for a wide variety of reasons. The treatment of these patients is a challenging process that requires the collaboration of multiple clinical specialties. The high rate of referral to intensive care units underlines the management challenges and highlights the critical need for specialized care. A multidisciplinary approach is essential in the management of cancer patients to prevent complications, increase treatment efficacy and improve patient outcomes.

Conflict of interest

The authors declare that they have no institutional associations or financial support that could be perceived as a potential conflict of interest related to the content of this manuscript.

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Ethical Statement

Approval was obtained from the Etlik City Hospital 'Scientific Research Evaluation and Ethics Committee' before the commencement of the study. The ethics committee approval date is 18/12/2024, and the approval number is 2024-1243.

Author Contributions

All authors confirm their substantial contributions to the conception and design of the study, data acquisition, analysis, and interpretation equally. They have all critically revised the content, approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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Araştırma Makalesi

Travmatik unilateral transtibial ve transfemoral amputasyonu olan bireylerde düşme korkusunun karşılaştırılması

Comparison of fear of falling in individuals with traumatic unilateral transtibial and transfemoral amputation

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Öz

Amaç: Alt ekstremite amputasyonu olan bireyler uzuv kayıplarından dolayı düşme riski altındadır. Protez kullanan bireylerde düşme korkusunun artması bireylerin rehabilitasyon sürecini ve yaşam kalitelerini olumsuz etkileyebilir. Travmatik unilateral transtibial amputasyonu (TTA) ile transfemoral amputasyonu (TFA) olan bireylerin düşme korkusunun karşılaştırılması ve düşme korkusu ile ilişkili olabilecek faktörlerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışma kesitsel olarak planlandı. Çalışmaya 18-65 yaş arası unilateral TTA olan 30 birey ve TFA olan 30 birey dahil edildi. Vizüel Analog Skala (VAS) ile sağlam ekstremite, ampute ekstremite ve bel ağrısının şiddeti belirlendi. Numerik Derecelendirme Ölçeği (NRS) kullanılarak genel protez, soket, protez ayak ve varsa protez diz eklemi memnuniyetleri sorgulandı. Son 1 yıl içerisinde düşme sayısı not edildi. Bireylerin düşme korkusu ise Uluslararası Düşme Etkinlik Ölçeği (FES-I) ile değerlendirildi.

Bulgular: Çalışmaya dahil edilen bireylerin son bir yıl içerisinde %56.7'si en az bir defa düşme yaşadığını belirtti. TTA ve TFA grupları arasında VAS sağlam ve rezidüel ekstremite ağrısı, son bir yıl içerisindeki düşme sayısı arasında istatistiksel olarak anlamlı fark saptandı (sırasıyla p = 0,011, p = 0,017, p = 0,024). VAS sağlam ekstremite ağrısı ve düşme korkusu arasında TTA grubunda istatistiksel olarak anlamlı bir ilişki saptandı (p = 0,004). VAS bel ağrısı ile düşme korkusu arasında ise hem TTA hem de TFA grubunda istatistiksel olarak anlamlı ilişki saptandı (sırasıyla p = 0,039, p = 0,043). Amputasyondan sonra geçen süre ile düşme korkusu arasında TFA grubunda anlamlı bir ilişki saptandı (p = 0,027).

Sonuçlar: TTA olan bireylerde düşme korkusu, sağlam ekstremite ağrısı ve bel ağrısı ile ilişkilidir. TFA olan bireylerde ise düşme korkusu bel ağrısı ve amputasyondan sonra geçen süre ile ilişkilidir. Ampute bireyleri olumsuz etkileyebilecek olan düşme korkusunun önlenmesi için sağlam ekstremite ağrısı ve bel ağrısı gibi ilişkili faktörlerin belirlenmesi önemlidir. Düşme korkusunu önlemek için ilişkili olabilecek bu faktörlere yönelik rehabilitasyon uygulamalarının planlanması gerekmektedir.

Anahtar kelimeler: transtibial amputasyon, transfemoral amputasyon, düşme, düşme korkusu

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Abstract

Aim: Individuals with lower limb amputation are at risk of falling due to limb loss. Increased fear of falling in prosthesis users may negatively affect the rehabilitation process and quality of life. The aim of this study was to compare the fear of falling in individuals with traumatic unilateral transtibial amputation (TTA) and transfemoral amputation (TFA) and to determine the factors that may be associated with the fear of falling.

Material and Methods: This is a cross-sectional study. The study included 30 individuals with unilateral TTA and 30 individuals with TFA, aged 18-65 years. The Visual Analogue Scale (VAS) was used to determine the severity of intact limb, amputated limb and low back pain. The Numeric Rating Scale (NRS) was used to assess satisfaction with the overall prosthesis, socket, prosthetic foot, and prosthetic knee joint. The number of falls in the past year was recorded. Fear of falling was assessed using the Falls Efficacy Scale International (FES-I).

Results: Among the individuals included in the study, 56.7% reported at least one fall in the last year. There was a statistically significant difference between TTA and TFA groups in terms of VAS intact and residual limb pain and number of falls in the last year ($p = 0.011$, $p = 0.017$, $p = 0.024$, respectively). A statistically significant relationship was found between VAS intact extremity pain and fear of falling in the TTA group ($p = 0.004$). A statistically significant relationship was found between VAS low back pain and fear of falling in both TTA and TFA groups ($p = 0.039$, $p = 0.043$, respectively). There was a significant relationship between the time since amputation and fear of falling in the TFA group ($p = 0.027$).

Conclusion: Fear of falling is associated with intact limb pain and low back pain in unilateral TTA individuals. In unilateral TFA individuals, fear of falling was associated with low back pain and time since amputation. In order to prevent fear of falling, which may negatively affect amputees, it is important to identify associated factors such as intact limb pain and low back pain. In order to prevent fear of falling, rehabilitation practices should be planned for these related factors.

Keywords: transtibial amputation, transfemoral amputation, falls, fear of falling

Giriş

Alt ekstremite amputasyonu (AEA) kas gücü, yürüme ve denge gibi fiziksel işlevleri olumsuz etkilemektedir. AEA sonrası oluşan yürüme asimetrisi sebebiyle enerji tüketiminin arttığı yeni yürüyüş paternleri gelişir [1]. Ampute birey tarafından benimsenen yeni yürüyüş paternlerinde denge kontrolündeki eksiklikler sebebiyle de düşme riski artar [2]. Düşme; ölüm veya ciddi yaralanma ile sonuçlanabilen, fonksiyonel kısıtlılık ve sakatlığa neden olabilen önemli bir sağlık sorunu olarak karşımıza çıkmaktadır [3].

Alt ekstremite amputasyonu sebebiyle protez kullanan bireylerde düşme korkusu artar ve bu korku nedeniyle bireylerin sosyal katılımları azalırken sağlıkla ilişkili yaşam kaliteleri de olumsuz etkilenebilir [1,2]. Düşme korkusunun bireylerin rehabilitasyon sürecini de olumsuz etkileyebileceği belirtilmektedir [4]. Düşme riski, ampute bireylerde dengenin bozulması nedeniyle amputasyon anından protez kullanmaya başladıktan birkaç yıl sonrasına kadar yüksektir [5]. Unilateral alt ekstremite amputasyonu olan bireylerin %52'sinin son 1 yıl içinde düştüğünü, %49'unun düşme korkusu yaşadığı belirtilmektedir [6]. Düşme ile ilişkili faktörler arasında ileri yaş, kas güçsüzlüğü, eşlik eden kronik hastalıklar, yürüme ve denge bozuklukları, görme bozuklukları, mental durum değişikliği ve çoklu ilaç kullanımı yer almaktadır [6,7]. Transfemoral amputasyonu (TFA) olan bireylerde bel ağrısı, artralji, rezidüel ekstremite veya protezle ilgili sorunlar düşme riskini arttıran sebepler arasında olduğu belirtilmiştir [5].

Transtibial amputasyonu (TTA) ve TFA olan bireylerde düşme korkusunu karşılaştıran ve düşme korkusu ile ilişkili faktörleri inceleyen literatürde az sayıda çalışma bulunmaktadır. Bu çalışmanın amacı, travmatik unilateral TTA ile TFA olan bireylerin düşme korkusunun karşılaştırılması ve düşme korkusu ile ilişkili olabilecek faktörlerin belirlenmesidir.

Gereç ve Yöntemler

Katılımcılar ve çalışma dizaynı

Bu araştırma kesitsel bir çalışma olarak planlanmıştır. Ocak 2024 ve Haziran 2024 tarihleri arasında 3. basamak bir hastanenin ortopedik rehabilitasyonu kliniğinde tedavi alan ve polikliniklere başvuran TTA ve TFA olan bireyler çalışmaya alındı. Çalışmaya 18-65 yaş arası, unilateral TTA veya TFA olan, amputasyondan sonra geçen süre ≥ 1 yıl olup ve protezini aktif

olarak kullanan 60 birey dahil edildi. 30 kişide TTA mevcut iken 30 kişide TFA mevcuttu. Bilateral alt ekstremite amputasyonu ya da herhangi bir seviye üst ekstremite amputasyonu, görme veya işitme problemi, nörolojik hastalığı, kırık veya osteoporozu olan bireyler çalışma dışı bırakıldı. Araştırma için Ankara Bilkent Şehir Hastanesi Etik Kurulundan onay alındı (Tarih:13.12.2023 no: E1-23-4437). Çalışma Helsinki Deklarasyonu Prensiplerine uygun olarak yürütülmüştür.

Demografik ve klinik veriler

Bireylerin cinsiyet, yaş, boy, kilo, amputasyon tarihi, kullandığı protez, protezi günlük kullanım süresi, yardımcı cihaz kullanımı kaydedildi. Vizüel Analog Skala (VAS) ile sağlam ekstremite, ampute ekstremite ve bel ağrısının şiddeti belirlendi. Nümerik Derecelendirme Ölçeği (NRS) kullanılarak genel protez, soket, protez ayak ve varsa protez diz eklemi memnuniyetleri sorgulandı. Son 1 yıl içerisinde düşme sayısı not edildi. Bireylerin düşme korkusu ise Uluslararası Düşme Etkinlik Ölçeği (FES-I) ile değerlendirildi. FES-I, 16 farklı günlük yaşam aktivitesi sırasında düşme ile ilgili endişe düzeyi hakkında bilgi sağlar. Her soru 1'den (hiç endişe duymam) 4'e (çok endişe duyarım) kadar 4 puan ile değerlendirilir. Bu ölçek denge ve yürüme ölçümleri ile ilişkilidir. Düşme riski ve fonksiyonel kapasitedeki azalmayı ön görme konusunda güvenilirliğe sahiptir [8]. FES-I'in Türkçe geçerliliği ve güvenilirliği gösterilmiştir [9].

İstatistiksel Analiz

SPSS versiyon 23 (IBM Corp., Armonk, NY, ABD) kullanılarak istatistiksel analizler yapıldı. Kolmogorov-Smirnov testi kullanılarak değişkenlerin normal dağılıma uygunluğuna bakıldı. Tanımlayıcı analiz verileri kategorik değişkenler için sayı (yüzde) ve sürekli değişkenler için ortalama ± standart sapma şeklinde sunuldu. Kategorik değişkenler için Ki-kare testi kullanıldı. Normal dağılım gösteren verilerde Bağımsız grup t testi kullanılırken normal dağılmayan verilerde Mann-Whitney U testi kullanılarak ikili karşılaştırmalar yapıldı. Düşme korkusu ve ilişkili faktörler arasındaki ilişki Spearman korelasyon katsayısı ile belirlendi. İstatistiksel olarak $p \leq 0,05$ anlamlı kabul edildi.

Bulgular

Travmatik alt ekstremite amputasyonu olan toplam 60 erkek birey çalışmaya dahil edildi. Katılımcıların yaş ortalaması 39,51 ± 10,53, amputasyon sonrası geçen süre ortalaması

171,81 ± 138,67 ay ve günlük protez kullanım süresi ortalaması 12,86 ± 3,71 saatti. Amputasyon tarafı 40 (%66,7) kişide sağ taraf ve 20 (%33,3) kişide sol taraftı. En sık amputasyon nedeni 30 (%50) kişide olmak üzere mayın yaralanmasıydı. 54 (%90) kişi herhangi bir yardımcı cihaz kullanmıyordu. Amputasyon sonrası geçen süre, günlük protez kullanım süresi, amputasyon tarafı ve yardımcı cihaz kullanımında TTA ve TFA grupları arasında istatistiksel olarak anlamlı bir fark saptanmadı (Tablo 1).

Son 1 yıl içerisinde bireylerin %56,7'si en az 1 defa düşme yaşadığını belirtti. TFA grubunun %67,7'si son 1 yıl içerisinde düşme yaşadığını ifade ederken, TTA grubunun %44,8'i ifade etti. Son 1 yıl içerisindeki düşme sayısı, VAS sağlam ve rezidüel ekstremite ağrısı açısından TTA ve TFA grupları arasında istatistiksel olarak anlamlı fark saptandı (sırasıyla $p = 0,011$, $p = 0,017$, $p = 0,024$). VAS sağlam ve rezidüel ekstremite ağrısı TTA grubunda yüksek iken son 1 yıl içerisindeki düşme sayısı TFA grubunda daha yüksekti. VAS bel ağrısı, soket konforu, protez ayak memnuniyeti, genel protez memnuniyeti ve FES-I değerlerinde iki grup arasında istatistiksel olarak anlamlı fark saptanmadı. FES-I değeri TTA grubunda 26,06 ± 7,80 olarak saptanırken TFA grubunda 24,80 ± 5,54'idi (Tablo 2).

TTA grubunda, VAS sağlam ekstremite ağrısı ve düşme korkusu arasında istatistiksel olarak anlamlı ilişki saptandı ($p = 0,004$). VAS bel ağrısı ile düşme korkusu arasında ise hem TTA hem de TFA grubunda istatistiksel olarak anlamlı ilişki saptandı (sırasıyla $p = 0,039$, $p = 0,043$) Amputasyondan sonra geçen süre ile düşme korkusu arasında TFA grubunda anlamlı ilişki saptandı ($p = 0,027$) (Tablo 3). TTA ve TFA gruplarında amputasyondan sonra geçen süreleri ile düşme sayısı arasında ilişki saptanmadı (sırasıyla $p = 0,842$, $p = 0,261$).

Tartışma

Bu çalışmada TTA ve TFA olan bireyler arasında düşme korkusu açısından bir fark saptanmadı. İki grup arasında düşme sayısı, sağlam ekstremite ağrısı ve rezidüel ekstremite ağrısı açısından fark saptandı. TTA olan bireylerde düşme korkusu, sağlam ekstremite ağrısı ve bel ağrısı ile ilişkilidir. TFA olan bireylerde ise düşme korkusu, bel ağrısı ve amputasyondan sonra geçen süre ile ilişkilidir.

Alt ekstremite amputasyonu olan bireyler uzuv kayıplarından dolayı kas güçsüzlüğü, kas iskelet sistemindeki kısıtlılıklar ve asimetri nedeniyle düşme riski altındadır. Bu bireylerin her yıl %52'sinin düştüğü ve %75'inin tekrarlayan düşmeler yaşadığı belirtilmektedir [10]. Unilateral AEA olan bireylerin yarısından fazlası yılda en az bir düşme yaşarken, amputasyonu olmayan

Tablo 1. Demografik özellikler.				
	Toplam amputasyon grubu (n=60)	Unilateral transtibial amputasyon grubu (n=30)	Unilateral transfemoral amputasyon grubu (n=30)	p
Yaş (yıl)	39,51±10,53	39,00±11,23	40,03±9,94	0,620
VKI (kg/m2)	25,79±4,00	25,62±4,42	25,96±6,60	0,748
Amputasyondan sonra geçen süre (ay)	171,81±138,67	155,90±144,70	187,73±132,88	0,164
Günlük protez kullanım süresi (saat)	12,86±3,71	12,90±3,61	12,83±3,86	0,947
Amputasyon tarafı				0,273
Sağ	40 (66,7)	18 (60)	22 (73,3)	
Sol	20 (33,3)	12 (40)	8 (26,7)	
Amputasyon nedeni				0,412
Mayın	30 (50)	17(56,7)	13 (43,3)	
Patlayıcı madde	15 (25)	8 (26,7)	7 (23,3)	
Roket	4 (6,7)	2(6,7)	2 (6,7)	
Ateşli silah yaralanması	11 (18,3)	3(10)	8 (26,7)	
Yardımcı cihaz kullanım durumu				0,549
Yok	54 (90)	27 (90)	27 (90)	
Tek kanedyen	5 (8,3)	3 (10)	2 (6,7)	
Çift kanedyen	1 (1,7)	0 (0)	1 (3,3)	
VKI: Vücut Kitle İndeksi, Mann-Whitney U testi, Bağımsız T testi, Ki-kare testi, Toplam grubun demografik özellikleri, Demografik özellikler açısından transtibial amputasyon grubu ve transfemoral amputasyon gruplarının karşılaştırılması				

Tablo 2. Klinik özellikler açısından transtibial amputasyon grubu ve transfemoral amputasyon gruplarının karşılaştırılması.			
	Unilateral transtibial amputasyon grubu (n=30)	Unilateral transfemoral amputasyon grubu (n=30)	p
VAS-sağlam ekstremite ağrısı (cm)	3,36±3,30	1,20±1,84	0,011*
VAS-rezidüel ekstremite ağrısı (cm)	4,50±3,51	2,33±2,53	0,017*
VAS-bel ağrısı (cm)	3,03±2,99	2,30±2,50	0,355
Soket konfor memnuniyeti	6,66±3,18	7,50±2,59	0,365
Protez ayak memnuniyeti	7,50±2,60	6,46±3,32	0,277
Genel protez memnuniyeti	7,53±2,56	6,43±3,27	0,221
Düşme sayısı	1,03±1,40	2,33±2,39	0,024*
FES-I	26,06±7,80	24,80±5,54	0,778
VAS: Vizüel Analog Skala, FES-I: Falls Efficacy Scale-International, Mann-Whitney-U testi, * p<0,05 değeri istatistiksel olarak anlamlı			

Tablo 3. Transtibial amputasyon grubu ve transfemoral amputasyon grubunda klinik özellikler ile düşme korkusu arasındaki ilişki.				
	Unilateral transtibial amputasyon grubu (n=30)		Unilateral transfemoral amputasyon grubu (n=30)	
	r	p	r	p
VAS-sağlam ekstremite ağrısı (cm)	0,511	0,004*	0,286	0,125
VAS-rezidüel ekstremite ağrısı (cm)	0,161	0,395	0,324	0,081
VAS-bel ağrısı (cm)	0,378	0,039*	0,372	0,043*
Soket konfor memnuniyeti (cm)	-0,100	0,599	-0,343	0,064
Protez ayak memnuniyeti (cm)	-0,272	0,146	-0,095	0,617
Genel protez memnuniyeti (cm)	-0,284	0,129	-0,219	0,245
Düşme sayısı	0,219	0,244	-0,238	0,204
Amputasyondan sonra geçen süre (ay)	0,080	0,675	0,403	0,027*
VAS: Vizüel Analog Skala, FES-I: Falls Efficacy Scale-International, Spearman Testi, * p<0,05 değeri istatistiksel olarak anlamlı				

bireylerin %26'sı yılda en az bir düşme yaşar [11]. Çalışmamızda da literatüre benzer şekilde son bir yıl içerisinde çalışmaya katılan bireylerin %56,7'si düşme yaşadığını belirtmiştir.

Düşme, vücutta ciddi yaralanmalara neden olabilirken sonrasında oluşabilecek düşme korkusu uzun süreli immobilizasyona sebep olarak birçok komplikasyona yol açabilir. Düşme korkusunun artması tekrarlayan düşmelerin oluşmasına neden olabilir [12]. Düşme sonrası kırıklar, düşme korkusu, protez kullanımının azaltılması ve ardından gelen sosyal geri çekilme görülebilmektedir [7]. Barnett ve ark. yaptığı çalışmada alt ekstremite protezi kullanan her beş TTA olan bireyden biri rehabilitasyon sırasında düşmekte olduğu bulunmuştur. Bu bireylerden bir yıldan daha az protez kullanım deneyimi olanların düşme korkusu daha yüksek bulunmuştur. Protez kullanan bireylerde protez deneyimindeki artışın düşme riski için önleyici olduğu belirtilmiştir [1]. Çalışmamızda, TTA olan bireylerde amputasyondan sonra geçen süre ile düşme korkusu arasında bir ilişki saptanmadı. TFA olan bireylerde ise amputasyondan sonra geçen süre ile bir ilişki saptandı. Bildiğimiz kadarıyla literatürde amputasyondan sonra geçen süre ile düşme korkusu arasındaki ilişkiyi inceleyen bir çalışma bulunmamaktadır. Bu konuda prospektif daha fazla çalışmaya ihtiyaç vardır.

Transfemoral amputasyonu olan bireylerde amputasyon seviyesinin TTA olan bireylere göre daha proksimalde olması nedeniyle daha fazla fonksiyonel bozukluğa neden olmaktadır. TFA olan bireyler denge bozukluğu ve fiziksel yetersizlik nedeniyle düşme açısından daha risklidir [13]. Düşme ve düşme korkusu TFA olan bireyler arasında yaygındır ve yıllık düşme oranları %66'ya kadar çıkmaktadır [14]. TFA olan bireylerin rehabilitasyondan sonraki 1 yıl içinde düşme olasılığı TTA olan bireylere göre 1,4 kat daha fazla bulunmuştur [15]. Benzer şekilde çalışmamızda TFA olan bireylerin %67,7'si, TTA olan bireylerin ise %44,8'i son bir yıl içerisinde düşme yaşadığını ifade etmiştir. Düşme korkusu açısından ise her iki grup arasında anlamlı bir fark saptanmamıştır. TFA ve TTA olan bireylerde postür ve denge gibi faktörlerin amputasyon seviyesinden etkileniyor olması amputasyon seviyesinin düşme korkusunu da etkileyeceğini düşündürüyor olsa da düşme korkusunu etkileyebilen ve çalışmamızda incelenmeyen depresyon gibi diğer faktörlerin etkisi ile TFA ve TTA olan bireylerde düşme korkusu açısından bir fark saptanmamış olabilir [16,17].

Pauley ve ark.'nın yaptığı çalışmada düşme ile ilişkili risk faktörleri arasında sırt veya eklem ağrısı, TFA seviyesi, rezidüel ekstremite veya protezle ilgili dört veya daha fazla sorun olması yer aldığı belirtilmiştir. Düşme korkusuyla ilişkili risk faktörleri arasında ise son bir yıl içinde bireyin daha önce düşmüş olması bulunmaktadır [18]. Engenheiro ve ark. yaptığı bir çalışmada bel ve eklem ağrısı ile güdük ve protezle ilgili yaşanan sorunların düşme riskini arttırdığı belirtilmiştir [5]. Bel ve her iki alt ekstremite ağrısı düşme olasılığının artmasıyla ilişkili değiştirilebilir faktörler olarak tanımlanmıştır. Amputasyondan sonraki bir yıllık dönemde rezidüel ekstremite, sağlam ekstremite ve bel ağrısı olan bireylerde, bu üç bölge ağrısı olmayan bireylere kıyasla, tekrarlayan düşme bildirme olasılığının 6,5 kat arttığı belirtilmiştir [19]. Çalışmamızda da benzer şekilde düşme korkusu ile bel ağrısı ve sağlam ekstremite ağrısı arasında ilişki saptanmıştır. Sağlam ekstremite ağrısı ile düşme korkusu arasındaki ilişkinin sadece TTA olan bireylerde olmasının nedeni çalışmamıza dahil edilen TTA olan bireylerin sağlam ekstremite ağrısının TFA olan bireylere göre daha fazla olması olabilir.

Çalışmamızın bazı kısıtlılıkları bulunmaktadır. Ampute bireylerin düşme korkusunu etkileyebilecek denge, duygu durumları ve depresyon gibi faktörler bu çalışmada incelenmemiştir. Çalışmaya dahil edilen ampute bireylerin daha önce aldıkları rehabilitasyon programları değerlendirmeye dahil edilmemiştir. Protez kullanan toplum içerisinde yaşayan travmatik amputasyonu olan erkek bireyler incelenmiştir. Bu nedenle ampute bireylerin genelini yansıtmıyor olabilir. Bu çalışmanın kesitsel olması nedensel ilişkinin anlaşılmasını zorlaştırıyor olabilir.

Sonuç olarak, düşme korkusu TTA olan bireylerde sağlam ekstremite ağrısı ve bel ağrısı ile ilişkilidir. TFA olan bireylerde düşme korkusu, bel ağrısı ve amputasyondan sonra geçen süre ile ilişkilidir. Ampute bireyleri olumsuz etkileyebilecek olan düşme korkusunun önlenmesi için sağlam ekstremite ağrısı ve bel ağrısı gibi ilişkili faktörlerin belirlenmesi önemlidir. Bu bireylerin rehabilitasyon programında bu ilişkili faktörlerin göz önünde bulundurulması ve düşme korkusunu önlemek için rehabilitasyon uygulamalarının planlanması gerekmektedir. Bu konu ile ilgili daha fazla prospektif çalışmaya ihtiyaç bulunmaktadır.

Maddi destek ve çıkar ilişkisi

Araştırmacıların herhangi bir çıkar ilişkisi bulunmamaktadır. Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur.

Etik kurul onayı

Araştırma için Ankara Bilkent Şehir Hastanesi Etik Kurulundan onay alındı (Tarih:13.12.2023 No: E1-23-4437).

Yazarların katkısı

GKK: çalışmanın konsept ve tasarımlarının oluşturulması, verilerin toplanması, makalenin taslağının hazırlanması ve yazımı MÖA: çalışmanın konsept ve tasarımlarının

oluşturulması, makalenin taslağının hazırlanması ve yazımı, makalenin gözden geçirilmesi ve düzenlenmesi AP: verilerin toplanması NK: makalenin taslağının hazırlanması ve yazımı, makalenin gözden geçirilmesi ve düzenlenmesi YD: verilerin analizi, makalenin gözden geçirilmesi ve düzenlenmesi KA: makalenin gözden geçirilmesi ve düzenlenmesi

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Araştırma Makalesi

Gastrointestinal stromal tümörler: Tek merkez deneyimi-demografik ve patolojik bulguların analizi

Gastrointestinal stromal tumors analysis of demographic and pathological findings: Single center experience

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Öz

Amaç: Gastrointestinal stromal tümörler (GİST), gastrointestinal sistemin en sık görülen mezenkimal neoplazmları olup sıklıkla mide ve ince bağırsaktan kaynaklanmaktadır. Nadir görülmelerine rağmen, son yıllarda moleküler biyoloji ve hedefe yönelik tedavi alanındaki gelişmeler klinik sonuçları anlamlı düzeyde iyileştirmiştir.

Bu tek merkezli retrospektif çalışmanın amacı, GİST tanısı almış hastaların demografik, patolojik ve tedaviye ilişkin özelliklerini değerlendirmek; rekürrenssiz sağkalım (RFS) süresini ve tedaviye bağlı tolerabiliteyi gerçek yaşam koşullarında incelemektir.

Gereç ve Yöntemler: Eylül 2022 ile Eylül 2024 tarihleri arasında Ankara Etlik Şehir Hastanesinde GİST tanısı almış hastaların tıbbi kayıtları retrospektif olarak incelenmiştir. Demografik özellikler, tümör lokalizasyonu, mitotik indeks, immünohistokimyasal belirteçler, KIT/PDGFRA mutasyon durumu, cerrahi ve sistemik tedavi verileri, advers olaylar ve sağkalım sonuçları analiz edilmiştir. RFS, tedavi başlangıcından itibaren nüks, ölüm veya son takip tarihine kadar geçen süre olarak tanımlanmıştır.

Bulgular: Toplam 46 hasta çalışmaya dahil edilmiş olup, ortanca yaş 62,9 yıl (Aralık: 41,8–82,0) ve %58,7'si erkekti. Tümörlerin en sık yerleşim yerleri mide (%60,9) ve ince bağırsak (%34,8) idi. Tüm hastalara cerrahi rezeksiyon uygulanmış, %84,8'inde R0 rezeksiyon sağlanmıştır. Hastaların %58,7'sine adjuvan imatinib tedavisi verilmiş, bu grubun %19,6'sında advers etki bildirilmiştir. Ortanca 16,8 aylık takip süresi boyunca 4 hastada (%8,7) nüks saptanmış, 1 hasta (%2,2) yaşamını yitirmiştir. Ortanca RFS'ye ulaşılamamıştır. Tümör boyutu, rezeksiyon durumu ve diğer klinik değişkenler ile RFS arasında tek değişkenli analizde istatistiksel olarak anlamlı ilişki saptanmamıştır.

Sonuç: Bu çalışma, GİST hastalarının gerçek yaşam verilerine dayalı klinik ve patolojik özelliklerine ışık tutmaktadır. Bulgular literatürle büyük ölçüde uyumlu olsa da, hasta sayısının sınırlı oluşu ve kısa takip süresi nedeniyle uzun dönem prognostik faktörlerin daha net belirlenebilmesi için prospektif ve çok merkezli çalışmalara ihtiyaç duyulmaktadır.

Anahtar Kelimeler: gastrointestinal stromal tümör, gerçek yaşam verisi, hedefe yönelik tedavi, rekürrenssiz sağkalım, imatinib, yan etkiler

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Abstract

Aim: Gastrointestinal stromal tumors (GISTs) represent the most common mesenchymal neoplasms of the gastrointestinal tract, frequently arising from the stomach and small intestine. Despite their rarity, recent advances in molecular biology and targeted therapies have significantly improved clinical outcomes.

This single-center retrospective study aimed to characterize the demographic, pathological, and treatment-related features of patients diagnosed with GIST, and to evaluate recurrence-free survival (RFS) and treatment tolerability under real-world clinical conditions.

Material and Methods: We retrospectively reviewed medical records of patients diagnosed with GIST at Ankara Etlik City Hospital between September 2022 and September 2024. Data regarding demographic characteristics, tumor localization, mitotic index, immunohistochemical profile, KIT/PDGFRA mutation status, surgical outcomes, targeted therapy administration, adverse events, and survival metrics were analyzed. RFS was defined as the time from treatment initiation to recurrence, death, or last follow-up.

Results: A total of 46 patients were included, with a median age of 62.9 years (range: 41.8–82.0); 58.7% were male. The most common tumor sites were the stomach (60.9%) and small intestine (34.8%). All patients underwent surgical resection, with R0 resection achieved in 84.8%. Adjuvant imatinib therapy was administered to 58.7% of patients, and adverse effects were reported in 19.6% of those treated. During a median follow-up of 16.8 months, recurrence occurred in 4 patients (8.7%) and 1 patient (2.2%) died. Median RFS was not reached. Tumor size, resection margin status, and other clinical variables showed no statistically significant association with RFS in univariate analysis.

Conclusions: This study provides insight into the clinical and pathological characteristics of GIST patients in a real-world setting. While the findings are largely consistent with existing literature, the limited sample size and short follow-up period underscore the need for prospective, multicenter studies to better define long-term prognostic factors and optimize treatment strategies.

Keywords: gastrointestinal stromal tumor, real-world evidence, targeted therapy, recurrence-free survival, imatinib, adverse events

Giriş

Gastrointestinal stromal tümörler (GIST), gastrointestinal sistemin en yaygın mezenkimal tümörleri olup, genellikle mide ve ince bağırsak kaynaklı olarak karşımıza çıkmaktadır [1]. GLOBOCAN 2022 verilerine göre, GİST insidansı yılda yaklaşık 13.000 yeni vaka olup, bu tümörlerin gastrointestinal maligniteler arasında göreceli olarak düşük prevalansa sahip olduğunu göstermektedir [2]. Erkeklerde ve kadınlarda benzer oranlarda görülmekle birlikte, ortalama tanı yaşı 60 civarındadır [3].

GIST'lerin patogenezinde, hücre yüzeyinde yer alan tirozin kinaz reseptörleri olan KIT (CD117) ve PDGFRA genlerinde meydana gelen kazanılmış mutasyonlar belirleyici rol oynamaktadır. Bu mutasyonlar, reseptörlerin liganda bağımlı olmayan sürekli aktivasyonuna neden olarak hücresel proliferasyonu tetikler. İmatinib, bu yolağı hedef alarak özellikle KIT mutasyonu taşıyan GIST'lerde etkili bir tirozin kinaz inhibitörüdür [4].

Tümörün gastrointestinal sistem içerisindeki lokalizasyonu, klinik bulgular üzerinde belirleyici bir rol oynamaktadır. Mide kaynaklı GIST'ler sıklıkla dispepsi veya gastrointestinal sistemden kanama gibi semptomlarla kendini gösterirken, ince bağırsak yerleşimli tümörlerde intestinal obstrüksiyon veya akut batın bulguları daha ön planda olabilmektedir. Bununla birlikte, bazı küçük boyutlu lezyonlar klinik olarak sessiz seyredebilir ve sıklıkla endoskopik ya da radyolojik incelemeler sırasında rastlantısal (insidental) olarak tespit edilmektedir. Bu klinik farklılıklar, hem tanı sürecinde uygulanacak algoritmaları hem de bireyselleştirilmiş tedavi stratejilerinin belirlenmesini doğrudan etkilemektedir. [5].

GIST tanısında; endoskopik ultrasonografi (EUS), bilgisayarlı tomografi (BT) ve manyetik rezonans görüntüleme (MRG) gibi ileri görüntüleme yöntemleri yaygın olarak kullanılmakta olup, kesin tanı ise histopatolojik inceleme ve immünohistokimyasal belirteçlerin değerlendirilmesi sonucunda konulmaktadır. [6,7].

Tedavi seçenekleri evreye, tümörün büyüklüğüne, mitotik aktivitesine ve lokalizasyonuna bağlı olarak değişkenlik göstermektedir. GIST tedavisinde cerrahi müdahale, küratif yaklaşımın temelini oluşturmaktadır. 2000'li yılların başında imatinib'in klinik kullanıma girmesiyle GİST tedavisinde

sağkalımda anlamlı artışlar gözlenmiştir. Yüksek risk taşıyan olgularda adjuvan imatinib tedavisi standart öneri haline gelmişken, ileri evre hastalarda ise imatinib başta olmak üzere çeşitli tirozin kinaz inhibitörleri, sistemik hastalık kontrolü sağlamak amacıyla kullanılmaktadır. Ayrıca, belirli oligometastatik durumlarda (örneğin izole karaciğer metastazı) bu ajanlar neoadjuvan ya da dönüştürücü (conversional) tedavi amacıyla da tercih edilebilmektedir. Bu tür vakalarda tam kür sağlanamasa bile, uzun süreli sağkalım oranlarına ulaşmak mümkün olabilmektedir [8,9].

Bu çalışmanın amacı, Ankara Etlik Şehir Hastanesi'nde GİST tanısı almış ve takibi sürdürülen hastaların demografik, klinik ve histopatolojik özelliklerini retrospektif olarak analiz etmek; uygulanan cerrahi ve sistemik tedavi yaklaşımlarını, tedaviye bağlı advers etkileri ve rekürrenssiz sağkalım (RFS) sonuçlarını değerlendirmektir. Ayrıca, prognostik faktörlerin RFS üzerindeki potansiyel etkilerini belirlemek hedeflenmiştir.

Gereç ve Yöntemler

Bu çalışma, Ankara Etlik Şehir Hastanesi'nde yürütülen, retrospektif, tanımlayıcı ve tek merkezli bir araştırmadır. Çalışmaya, 1 Eylül 2022 ile 30 Eylül 2024 tarihleri arasında histopatolojik olarak gastrointestinal stromal tümör (GİST) tanısı almış, en az 6 aylık klinik takibi bulunan ve eksiksiz medikal kayıtlarına erişilebilen hastalar dahil edilmiştir. Eksik veriye sahip olan, histopatolojik tanısı net olmayan ya da takibi 6 aydan kısa süren hastalar çalışma dışı bırakılmıştır. Etik onay, Ankara Etlik Şehir Hastanesi Klinik Araştırmalar Etik Kurulu tarafından alınmıştır (Karar No: AEŞH-BADEK1-2025-077).

Hasta verileri, hastane bilgi yönetim sistemi, patoloji arşivi ve manuel hasta dosyaları kullanılarak retrospektif olarak taranmış; elde edilen bilgiler iki bağımsız araştırmacı tarafından çapraz doğrulama yöntemiyle kontrol edilerek veri bütünlüğü sağlanmıştır. Kayıt altına alınan parametreler arasında yaş, cinsiyet, eşlik eden komorbiditeler; tümör lokalizasyonu, boyutu, mitotik indeks, evresi, Ki-67 proliferasyon indeksi, rezeksiyon durumu ve KIT/PDGFRA mutasyon durumu gibi histopatolojik değişkenler ile uygulanan cerrahi ve sistemik tedavi yaklaşımları, tedavi süresi ve advers olay profili yer almaktadır.

Çalışmanın birincil sonlanım noktası, rekürrenssiz sağkalım (RFS) olarak tanımlanmıştır. RFS, cerrahi veya sistemik tedavi başlangıcından itibaren hastalığın lokal ya da uzak nüksünün saptandığı tarih, ölüm tarihi ya da son klinik takip tarihi arasında geçen süre olarak hesaplanmıştır

İstatistiksel Analiz

Çalışmada elde edilen veriler, IBM SPSS Statistics for Windows, versiyon 30.0 (IBM Corp., Armonk, NY, USA) yazılımı kullanılarak analiz edilmiştir. Tanımlayıcı istatistikler kapsamında sürekli değişkenler ortalama ± standart sapma veya medyan (minimum–maksimum) değerleri ile, kategorik değişkenler ise frekans ve yüzde oranlarıyla ifade edilmiştir. Sağkalım analizleri kapsamında, rekürrenssiz sağkalım (RFS) süreleri Kaplan-Meier metodu ile hesaplanmış; sağkalım eğrileri gruplar arasında log-rank testi kullanılarak karşılaştırılmıştır. RFS üzerinde etkili olabilecek prognostik faktörlerin belirlenmesi amacıyla tek değişkenli Cox regresyon analizi uygulanmıştır. Çok değişkenli analizler için yeterli örneklem büyüklüğü sağlanamaması nedeniyle yalnızca tek değişken modeller raporlanmıştır. Tüm istatistiksel testlerde anlamlılık düzeyi $p < 0,05$ olarak kabul edilmiştir.

Bulgular

Çalışmaya toplam 46 hasta dahil edilmiştir. Biyolojik cinsiyet dağılımı 27 erkek (%58,7) ve 19 kadın (%41,3) şeklindedir. Tanı anındaki ortanca yaş 62,9 yıl olup, yaş aralığı 41,8 ile 82,0 yıl arasında değişmektedir. Tümör lokalizasyonları açısından en sık mide (%60,9; n = 28), ardından ince bağırsak (%34,8; n = 16) ve kolon (%4,3; n = 2) yerleşimi saptanmıştır. Eşlik eden komorbid hastalıklar arasında hipertansiyon (%45,7; n = 21) ve diabetes mellitus (%30,4; n = 14) en sık bildirilen durumlar olmuştur. Hastaların detaylı demografik ve histopatolojik özellikleri Tablo 1'de sunulmuştur.

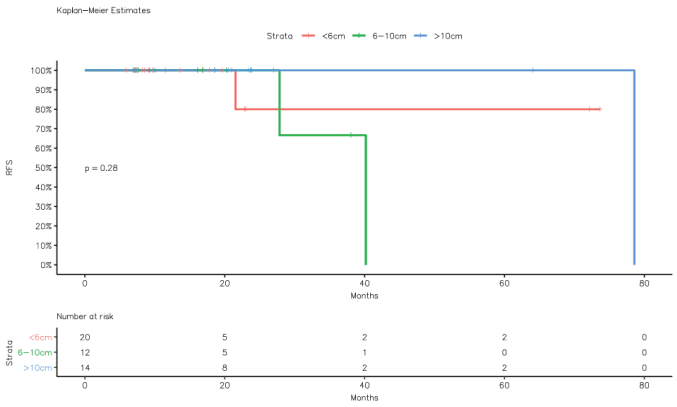
İncelenen tüm hastalara cerrahi rezeksiyon uygulanmıştır. Patolojik değerlendirme sonucunda, 39 hastada (%84,8) R0, 7 hastada (%15,2) R1 rezeksiyon sağlandığı bildirilmiştir. Cerrahi sonrası 27 hasta (%58,7) adjuvan imatinib tedavisi almış olup, bu grubun 9'unda (%19,6) tedaviye bağlı advers etkiler gözlenmiştir. Grade 4 düzeyinde halsizlik gelişen 2 hastada tedavi sonlandırılmış, 6 hastada ise geçici tedavi araları verilmiş ve ardından tedaviye devam edilmiştir. Bir hastada QTc süresi 455 msn olarak ölçülmüş, ancak doz değişikliği yapılmaksızın tedavi sürdürülmüştür.

Ortanca takip süresi 16,8 ay olan kohortta 4 hastada (%8,7) nüks gelişmiş; bunların biri lokal, üçü uzak metastaz şeklinde seyretmiştir. Bu hastaların ikisine cerrahi rerezeksiyon, diğer ikisine ise sistemik imatinib tedavisi uygulanmıştır. Takip boyunca yalnızca 1 hasta (%2,2) eksitus olarak kaydedilmiştir. Tahmini ortanca sağkalım süresi 86,2 ay olup, güven aralığı hesaplamalarında alt ve üst sınır değerlere ulaşılamamış, bu nedenle sonuçlar "non-reached (NR)" olarak raporlanmıştır (Tablo 2).

Tablo 1. Hastaların tanı anında demografik ve patoloji özellikleri.	
Yaş yıl, median (Aralık)	62,9(41,8-82,0)
Cinsiyet, n (%)	
Kadın	19 (41,3)
Erkek	27 (58,7)
Ek hastalık, n (%)	
0	7(15,2)
1	20(43,5)
2	9(19,6)
3≤	9(19,6)
Ek hastalık, n (%)	
Hipertansiyon	21(45,7)
Diabetes Mellitus	14(30,4)
Diğer	24(52,2)
Lokalizasyon, n (%)	
Mide	28(60,9)
Duodenum	9(19,6)
Jejunum/ileum	7(15,2)
Kolon	2(4,3)
Tanı, n (%)	
EUS ile	10(21,7)
Rezeksiyon ile	36(78,3)
EUS'ta yüksek risk, n (%)	
Var	6(13,0)
Yok	4(8,8)
EUS'ta yüksek risk, n (%)	
Düzensiz sınır	0(0)
Kistik alanlar	5(10,9)
Ülserasyon	0(0)
Ekojenik odaklar	1(2,2)
Heterojenite	0(0)
Evre, n (%)	
T1N0M0	1(2,2)
T2N0M0	19(41,3)
T3N0M0	10(21,7)
T3N1M1	2(4,3)
T4N0M0	11(23,9)
T4N1M0	1(2,2)
T4N0M1	2(4,3)
Tümör boyutu, n (%)	
<6cm	20(43,5)
6-10cm	12(26,1)
>10 cm	14(30,4)
İmmunohistokimya, n (%)	
CD117	45(97,8)
DOG-1	45(97,8)
CD34	33(71,7)
SMA	16(34,8)
S100	3(6,5)
Ki67skoru (%) median (Aralık)	7,5(1,0-50,0)
Mitoz 50 HPF/5mm2 , n (%)	
≤5	28(60,8)
>5	18(39,1)
EUS: Endoskopik Ultrasonografi CD117: Farklılaşma Kümesi SMA: Düz Kas Aktini HPF: Yüksek büyütme alanı	

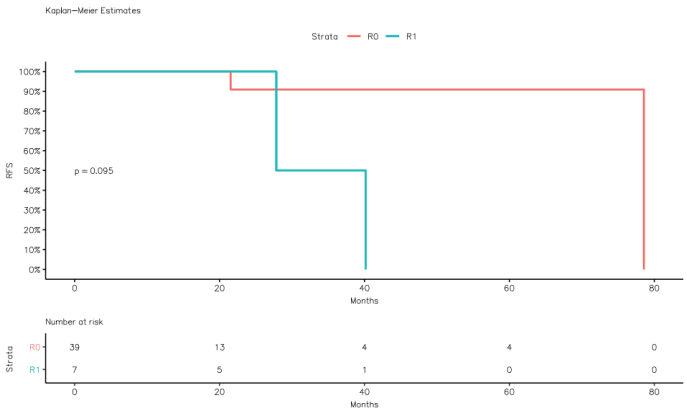
Tablo 2. Hastalara uygulanan tedaviler ve sağkalım sonuçları.	
Neoadjuvan tedavi, n (%)	
Evet	2(4,3)
Hayır	44(95,7)
Neoadjuvan ne aldı?	
Imatinib	2(100)
Neoadjuvan ne kadar süre median(hafta)(Aralık)	24(22-26)
Operasyon, n (%)	
Evet	46(100)
Hayır	0(0,0)
Operasyon, n (%)	
R0	39(84,8)
R1	7(15,2)
Moleküler analiz, n (%)	
Bakılmamış	42(91,3)
Bakılmış	4(8,7)
PDGFR ALFA, n (%)	
Pozitif	1(25)
Negatif	3(75)
BRAF, n (%)	
Pozitif	0(0.0)
Negatif	3(100)
NTRK, n (%)	
Pozitif	0(0.0)
Negatif	3(100)
Adjuvan Imatinib, n (%)	
Aldı	27(58,7)
Almadı	19(41,3)
Imatinib ne kadar süre aldı median (Aralık)(ay)	20,0(1,0-56,0)
Yan etki, n (%)	
Evet	9(19,6)
Hayır	18(39,1)
Yan etki, n (%)	
Grade3 Dermatit	1(2,2)
Grade 3 Ödem	2(4,3)
Grade 4 Halsizlik	2(4,3)
BFT bozukluğu	2(4,3)
QT uzaması (455msn)	1(2,2)
Grade 3 Nötropeni	1(2,2)
Yan etki sonrası Imatinib, n (%)	
Devam	1(2,2)
Ara verildi	6(13,2)
Kesildi	2(4,3)
Nüks, n (%)	
Evet	4(8,7)
Hayır	42(91,3)
Nüks, n (%)	
Lokal	1(2,2)
Uzak Metastaz	3(6,5)
Nükste tedavi, n (%)	
Rerezeksiyon	2(4,3)
Imatinib	2(4,3)
Exitus, n (%)	
Evet	1(2,2)
Hayır	45(97,8)
Median takip süresi ay	16,8
PDGFR ALFA: Trombosit Kaynaklı Büyüme Faktörü Reseptörü Alfa BRAF: B-raf proto-onkogen serin/treonin kinaz NTRK: Nörtotrofik Tirozin Kinaz Reseptörü ,BFT: Böbrek Fonsiyon Testleri	

Tanı anındaki tümör boyutu ile rekürrenssiz sağkalım (RFS) arasındaki ilişki değerlendirildiğinde; çapı <6 cm olan tümörlerde ortanca RFS süresine ulaşılamamış (Not Reached, NR), 6–10 cm aralığındaki tümörlerde ortanca RFS 40,1 ay (%95 güven aralığı [GA]: 27,8–NR), >10 cm olan tümörlerde ise 78,5 ay olarak hesaplanmıştır. Ancak, tümör boyutu grupları arasında RFS açısından istatistiksel olarak anlamlı bir fark saptanmamıştır (log-rank testi, p = 0,28) (Şekil 1).



Şekil 1. Tümör boyutuna göre RFS Kaplan-Meier eğrileri.

Rezeksion sonrası rezidü tümör durumu ile rekürrenssiz sağkalım (RFS) arasındaki ilişki incelendiğinde; R0 rezeksiyon uygulanan hastalarda ortanca RFS süresine ulaşılamamış (NR), R1 rezeksiyon yapılan hastalarda ise ortanca RFS 34,0 ay (%95 güven aralığı: 27,8–NR) olarak hesaplanmıştır. Gruplar arası karşılaştırmada, RFS açısından istatistiksel anlamlılığa ulaşmayan ancak sınırda anlamlılık düzeyine yakın bir fark gözlenmiştir (log-rank testi, p = 0,09) (Şekil 2).



Şekil 2. Rezüdü tümöre göre RFS Kaplan-Meier eğrileri.

Hastaların demografik özellikleri ile uygulanan tedavi yaklaşımlarının rekürrenssiz sağkalım (RFS) üzerindeki etkileri tek değişkenli Cox regresyon analizi ile değerlendirilmiştir. Cinsiyet, tümör lokalizasyonu, tümör boyutu, Ki-67 indeksi, mitotik aktivite, cerrahi rezeksiyon sonrası rezidü durumu ve adjuvan imatinib tedavisi alma durumu ile RFS arasında istatistiksel olarak anlamlı bir ilişki saptanmamıştır (p > 0,05). Bu bulgular doğrultusunda, herhangi bir değişkenin RFS üzerinde belirgin etkisi görülmemiştir. Ayrıca, çok değişkenli analizlerin güvenilir biçimde yapılabilmesi için gerekli olan örneklem büyüklüğüne ulaşılamadığından, çok değişkenli modelleme yapılmamıştır.

Tablo 3. Demografik özellikleri ve uygulanan tedavilerin RFS üzerine tek değişkenli analizi.

Değişken	p	HR (%95CI)
Cinsiyet Kadın Erkek	0,46	0,39(0,03-4,62)
Lokalizasyon Mide Duodenum Jejunum/ileum	0,95	0,92(0,07-10,9)
Tümör boyutu <6cm 6-10cm >10 cm	0,47	0,58(0,13-2,50)
Ki67skoru % ≤7.5 >7.5	0,56	2,04(0,18-23,0)
Mitoz 50 HPF/5mm2 ≤5 >5	0,72	1,56(0,12-19,0)
Operasyon R0 R1	0,54	6,07(0,54-67,7)
Adjuvan Imatinib Aldı Almadı	0,50	3,61(0,10-14,5)
HPF: Yüksek büyütme alanı		

Tartışma

Bu çalışmada, GİST tanısı almış 46 hastalık bir kohort retrospektif olarak analiz edilmiş ve elde edilen bulgular mevcut literatür ile karşılaştırılmıştır. GİST'ler, mide ve ince bağırsak kaynaklı olmak üzere gastrointestinal sistemin en sık görülen mezenkimal tümörleri arasında yer almaktadır. Moleküler düzeyde, KIT ve PDGFRA gen mutasyonlarının hastalık biyolojisinde temel rol oynadığı gösterilmiş; bu bulgu, tirozin kinaz inhibitörlerinin etkinliğini açıklamakta ve kişiselleştirilmiş tedavi yaklaşımlarını mümkün kılmaktadır [10,11].

Çalışmamızda hastaların %58,7'si erkek, ortanca yaş ise 62,9 yıl olarak saptanmıştır. Bu dağılım, literatürde bildirilen

50–70 yaş aralığı ve hafif erkek predominansı ile uyumludur [12,13]. Tümörlerin %60,9'unun mide, %34,8'inin ince bağırsak ve %4,3'ünün kolon lokalizasyonlu olması da önceki epidemiyolojik çalışmaları desteklemektedir. Mide GİST'lerinin daha sık görülmesine karşın, ince bağırsak yerleşimli tümörlerin daha agresif seyir gösterebildiği bilinmektedir [14,15].

Çalışma popülasyonunun tamamına cerrahi rezeksiyon uygulanmış olup, R0 rezeksiyon oranı %84,8 olarak hesaplanmıştır. Bu oran, hastaların çoğunun lokalize ve rezektabl evrede olduğuna işaret etmektedir. R1 rezeksiyon oranı %15,2 olup literatürle paralellik göstermektedir; zira yüksek riskli olgularda mikroskobik rezidü hastalık riski daima göz önünde bulundurulmalıdır [16].

Rezeksiyon türü ile RFS ilişkisi değerlendirildiğinde; R0 rezeksiyon yapılan hastalarda ortanca RFS'ye ulaşılamazken, R1 rezeksiyon yapılan grupta bu süre 34,0 ay olarak hesaplanmıştır. İstatistiksel olarak anlamlılığa ulaşmayan ancak klinik açıdan anlamlı sayılabilecek bir fark saptanmıştır ($p = 0,09$). Bu bulgu, R0 cerrahinin prognoz üzerindeki olumlu etkisine dair literatürdeki verilerle örtüşmektedir [17].

Hastaların %58,7'si adjuvan imatinib tedavisi almış olup, bu grupta %19,6 oranında tedaviye bağlı advers etkiler gözlenmiştir. Grade 4 düzeyinde halsizlik nedeniyle iki hastada tedavi sonlandırılmış, diğerlerinde geçici doz kesintileri ile tolere edilebilirlik sağlanmıştır. Bu sonuçlar, daha önce yayınlanmış çalışmalarda bildirilen advers etki profiliyle uyumludur [18,19].

Takip süresince dört hastada (%8,7) rekürrens gözlenmiş; bunların biri lokal, üçü uzak metastaz olarak saptanmıştır. Bu hastalara güncel kılavuzlar doğrultusunda rerezeksiyon veya sistemik imatinib tedavisi uygulanmıştır [20,21].

Çalışmamızda tahmini ortanca sağkalım süresi 86,2 ay olarak hesaplanmış olup, alt ve üst güven aralığına ulaşılamamıştır. Bu durum, cerrahi sonrası GIST hastalarında uzun sağkalım süresine işaret etmekte ve imatinib tedavisinin sağkalımı olumlu yönde etkileyebileceğini düşündürmektedir [22,23]. Ancak kısa takip süresi, bu bulgunun yorumlanmasında sınırlayıcıdır.

Tek değişkenli analiz sonuçlarına göre; cinsiyet, lokalizasyon, tümör boyutu, mitotik indeks, Ki-67 skoru, rezeksiyon tipi ve adjuvan imatinib kullanımı gibi değişkenlerin RFS üzerinde anlamlı etkisi saptanmamıştır ($p > 0,05$). Bununla birlikte, bu tür klinik değişkenlerin etkisinin istatistiksel anlamlılığa ulaşamaması, örneklem büyüklüğünün sınırlı olması ile ilişkili olabilir. Çok değişkenli analiz planı metodolojik olarak düşünülmüş olsa da, güvenilir bir model oluşturmak için gereken vaka sayısına ulaşılamamış, bu nedenle çok değişkenli istatistiksel modelleme yapılmamıştır. Literatürde benzer örneklem büyüklüğüne sahip çalışmalarda da bu sınırlılıklar sıkça vurgulanmaktadır [8].

Bu çalışmanın bazı sınırlılıkları mevcuttur. Öncelikle, tek merkezli ve retrospektif tasarımı, veri standardizasyonunu sınırlamıştır. Hasta sayısının görece az olması, özellikle alt gruplar arasında yapılan analizlerin istatistiksel gücünü zayıflatmıştır. Moleküler analizlerin yalnızca sınırlı sayıda hastada yapılabilmiş olması, belirli prognostik belirteçler hakkında alt analizlerin gerçekleştirilememesine neden olmuştur. Ayrıca, ortanca takip süresinin kısa olması, sağkalım verilerinin tam olgunlaşmasına engel teşkil etmektedir. Bu nedenlerle bulgular dikkatli yorumlanmalı ve ileriye dönük güçlü metodolojilere sahip çalışmalara gereksinim olduğu göz önünde bulundurulmalıdır.

Sonuç olarak, bu çalışma GIST hastalarında tümör lokalizasyonu, cerrahi rezeksiyon tipi ve adjuvan imatinib tedavisi gibi klinik ve patolojik faktörlerin rekürrenssiz sağkalım üzerindeki etkilerini değerlendiren ve gerçek yaşam verilerine dayanan güncel bir analiz sunmaktadır. Elde edilen bulgular, mevcut literatür ile büyük ölçüde örtüşmekte ve GIST'lerin kliniğe yansıyan seyri hakkında önemli ipuçları sağlamaktadır. Sınırlı örneklem büyüklüğüne ve kısa takip süresine rağmen, çalışmamız gerçek yaşam pratiğinde GIST yönetimine dair değerli katkılar sunmakta; özellikle cerrahi sınır durumu ve adjuvan tedavi kararlarının hasta prognozuna etkisini vurgulamaktadır. Bu veriler, daha büyük örneklemlerle ve uzun dönem takip verileriyle desteklenecek çok merkezli, prospektif çalışmalara temel oluşturabilir.

Maddi destek ve çıkar ilişkisi

Araştırmacıların herhangi bir çıkar ilişkisi bulunmamaktadır. Çalışmayı maddi olarak destekleyen kişi/kuruluş yoktur.

Etik kurul onayı

Etik onay, Ankara Etlik Şehir Hastanesi Klinik Araştırmalar Etik Kurulu tarafından alınmıştır (Karar No: AEŞH-BADEK1-2025-077).

Yazarların katkısı

SÇ: çalışma fikrini geliştirdi, hasta verilerini topladı, literatür taramasını gerçekleştirdi ve istatistiksel analizleri yaptı, EEK: tüm işlemleri gerçekleştirdi ve makalenin son halini gözden geçirdi. Her iki yazar da çalışmanın tüm aşamalarına katkıda bulundu ve makalenin son halinden ortak sorumluluk taşımaktadır.

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Research Article

Association between second trimester maternal hypothyroidism and congenital heart diseases in fetuses: a retrospective study

Maternal hipotiroidi ile fetal konjenital kalp hastalıkları arasındaki ilişki: retrospektif bir çalışma

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Abstract

Aim: This study aimed to investigate the association between second-trimester maternal hypothyroidism and congenital heart diseases (CHDs) in fetuses.

Material and Methods: This retrospective study was conducted at Obstetrics and Pediatrics Training and Research Hospital between June 2022 and December 2024. The patient group comprised mothers of children diagnosed with major CHDs, while the control group included mothers of children without CHDs or with minor anomalies not requiring intervention. Maternal thyroid status was determined by second-trimester TSH levels: >4.0 mIU/mL was classified as hypothyroid, while 0.2–4.0 mIU/mL was considered euthyroid. Statistical analyses, including ROC analysis, regression analysis, Chi-square test, Fisher's exact test, and Mann-Whitney U test, were performed using SPSS 25, with $p < 0.05$ considered significant.

Results: The median TSH level was significantly higher in the CHD group compared to controls ($p = 0.002$). Logistic regression analysis revealed that each unit increase in maternal TSH levels increased the risk of fetal CHD by 1.47 times (95% CI: 1.212–1.792, $p < 0.001$). ROC analysis determined an optimal TSH cutoff of 1.795 mIU/mL (AUC = 0.627; sensitivity: 59.6%, specificity: 59.4%). While differences in CHD subgroups were observed, including conotruncal and valvular defects, these did not reach statistical significance ($p > 0.05$).

Conclusion: The study suggests a potential association between maternal hypothyroidism and fetal CHD.

Keywords: maternal hypothyroidism, congenital heart disease, fetal echocardiography, thyroid function

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Öz

Amaç: Bu çalışma, ikinci trimesterdeki maternal hipotiroidi ile fetal konjenital kalp hastalıkları (KKH) arasındaki ilişkiyi araştırmayı amaçladı.

Gereç ve Yöntemler: Bu retrospektif çalışma, Haziran 2022 ile Aralık 2024 tarihleri arasında Kadın Doğum ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi'nde gerçekleştirildi. Hasta grubu, majör konjenital kalp hastalığı tanısı alan çocukların annelerinden oluşurken, kontrol grubu KKH olmayan veya müdahale gerektirmeyen minör anomalilere sahip çocukların annelerini içeriyordu. Annelerin tiroid durumu, ikinci trimesterde ölçülen TSH seviyelerine göre belirlendi: >4,0 mIU/mL hipotiroid, 0,2-4,0 mIU/mL ötiroid olarak kabul edildi. İstatistiksel analizler arasında ROC analizi, regresyon analizi, Ki-kare testi, Fisher'ın kesin testi ve Mann-Whitney U testi yer almakta olup, tüm analizler SPSS 25 kullanılarak gerçekleştirildi ve $p < 0,05$ anlamlı kabul edildi.

Bulgular: Medyan TSH seviyesi, KKH grubunda kontrol grubuna göre anlamlı derecede daha yüksek bulundu ($p = 0,002$). Lojistik regresyon analizinde, maternal TSH seviyelerindeki her bir birimlik artışın fetal KKH riskini 1,47 kat artırdığı tespit edildi (95% CI: 1,212–1,792, $p < 0,001$). ROC analizi, TSH için optimal eşik değerini 1,795 mIU/mL olarak belirledi (AUC = 0,627; duyarlılık: %59,6, özgüllük: %59,4). Konotrunkal ve valvüler defektler gibi KKH alt gruplarında farklılıklar gözlenmiş olsa da, bu farklar istatistiksel anlamlılığa ulaşmadı ($p > 0,05$).

Sonuç: Çalışma, maternal hipotiroidizm ile fetal KKH arasında potansiyel bir ilişki olabileceğini göstermektedir.

Anahtar Kelimeler: maternal hipotiroidizm, konjenital kalp hastalığı, fetal ekokardiyografi, tiroid fonksiyonları

Introduction

Congenital heart diseases (CHDs) occur in approximately 1% of live births and account for one-third of all major congenital anomalies [1]. However, this prevalence may vary depending on regional and environmental factors [2,3]. As one of the most common congenital anomalies in newborns, CHDs are responsible for 30-50% of infant mortality associated with congenital anomalies [4-7].

The causes of CHDs have been linked to a combination of genetic predisposition and various environmental risk factors, such as maternal illnesses, teratogen exposure, and maternal phenylketonuria [2,8]. However, the genetic, epigenetic, and environmental foundations of these defects remain incompletely understood [9]. Despite advancements in diagnosis and treatment, CHDs continue to play a significant role in childhood morbidity and mortality, underscoring the critical importance of early detection and identification of risk factors [4].

Thyroid hormones play a critical role in maintaining the health of both the mother and fetus during pregnancy. During this period, the thyroid gland increases its production of thyroxine (T4) and triiodothyronine (T3) by approximately 50%, with a corresponding rise in daily iodine requirements. While these physiological changes occur seamlessly in healthy pregnancies, thyroid dysfunctions can emerge in many women as a result of pathological processes. Common thyroid disorders during pregnancy include hypothyroidism, hyperthyroidism, and nodular thyroid diseases, all of which can lead to significant complications before, during, or after pregnancy [10].

Maternal hypothyroidism can have significant adverse effects on pregnancy outcomes and fetal development [11-15]. Overt hypothyroidism, in particular, has been associated with an increased risk of complications such as preterm birth, low birth weight, pregnancy loss, gestational hypertension, and impaired neurodevelopment in the fetus [13,16,17]. Studies have also shown that maternal hypothyroidism can impact various systems, including the cardiovascular system, and has been linked to CHD [18-20]. Population-based studies in this field have yielded conflicting results regarding the risk posed by thyroid disorders on CHD [18,21].

In this study, we aimed to investigate the relationship between CHDs and second-trimester maternal hypothyroidism, considering the high prevalence of maternal hypothyroidism in our region.

Material and Methods

Study design

This retrospective study was conducted at the Giresun Obstetrics and Pediatrics Training and Research Hospital between June 2022 and December 2024. Initially, pediatric cardiology clinic records were reviewed to identify children diagnosed and followed with major CHDs during this period. The maternal second-trimester thyroid function tests of these children were collected, forming the patient group. For the control group, children without CHD or with minor cardiac anomalies that did not require intervention were identified during the same period, and their mothers' second-trimester thyroid function tests were gathered.

Thyroid function testing

Pregnant women with a TSH level above 4.0 mIU/mL were classified as hypothyroid and referred to an endocrinologist for further evaluation and levothyroxine treatment. Women with TSH levels between 0.2 and 4.0 mIU/mL were considered euthyroid [10].

Exclusion criteria

Participants meeting any of the following criteria were excluded: presence of systemic diseases, pregnancies achieved via in vitro fertilization, smoking, biochemical or hematological abnormalities, congenital fetal anomalies such as liver or neurological defects, gestational diabetes or hypertension, chronic hypertension, acute or chronic infections (e.g., fever, urinary tract infections, hepatitis), renovascular diseases, maternal morbid obesity, pre-pregnancy hypothyroidism or use of thyroid medication due to other endocrine disorders, other endocrine conditions, missing medical records or unavailable data.

Echocardiographic evaluation

Transthoracic echocardiographic assessments were performed using a Philips Affiniti 50 device (Philips Healthcare, Best, Netherlands) by an experienced pediatric cardiologist. Congenital heart diseases identified in the study were categorized into two groups as (1) Major CHDs: Moderate-to-large ventricular septal defects (VSD), moderate-to-severe pulmonary stenosis/atresia, moderate-to-severe aortic stenosis (valvular), arcus hypoplasia/aortic coarctation, situs inversus totalis/dextrocardia, atrioventricular septal defects (AVSD), Tetralogy of Fallot, truncus arteriosus, transposition of the great arteries (TGA), pulmonary artery sling, double outlet right ventricle (DORV), hypoplastic left heart syndrome (HLHS), and Ebstein's anomaly and (2) Minor CHDs: Defects not requiring surgical or transcatheter intervention, such as patent ductus arteriosus (PDA), patent foramen ovale (PFO), atrial septal defects (ASD), and mild valvular regurgitation or stenosis.

Thyroid hormone measurement

Venous blood samples were collected in BD Vacutainer SST II Advance tubes during routine second-level ultrasonography. The samples were centrifuged at 1500×g for 10 minutes to obtain serum. Thyroid-stimulating hormone (TSH) and free T4 levels were measured using a Roche Cobas e601 analyzer (Roche Diagnostics GmbH, Mannheim, Germany).

This study was approved by the Giresun Education and Research Hospital Ethics Committee (approval date: 25.12.2024; approval number: 2024/02). The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Written informed consent was obtained from the patients prior to inclusion in the study.

Statistical Analysis

All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro-Wilk test. As a result, numerical variables, including maternal age, maternal weight, TSH levels, and FT4 levels, were found not to follow a normal distribution. Therefore, non-parametric tests were used for these variables. Numerical data were expressed as median (25–75 percentiles), while categorical data were presented as counts and percentages [n (%)]. Differences between categorical variables were evaluated using the Chi-square test. In cases where expected cell counts were insufficient, Fisher's exact test was applied. Comparisons between numerical variables across groups were conducted using the Mann-Whitney U test. For TSH levels, which showed statistical significance, receiver operating characteristic (ROC) analysis was performed to determine diagnostic value and cutoff points. A significance level of $p < 0.05$ was considered statistically significant for all analyses. Confidence intervals were calculated at a 95% confidence level.

Results

A total of 301 pregnancies were included in the study. The median age of the participants was 28 years (25–32), and the median weight was 68 kg (61.5–78). Among the pregnancies, 99.3% were singleton, and 0.7% were twin pregnancies. According to laboratory data, the median TSH level measured during the second trimester was 1.79 mIU/mL (Table 1).

When comparing the control group with the CHD group, TSH levels were found to be significantly higher in the CHD group ($p = 0.002$). However, no significant differences were observed between the groups in terms of maternal age, weight, thyroid status, history of diabetes, smoking, or trisomy ($p > 0.05$) (Table 2).

The area under the curve (AUC) was calculated as 0.627 (95% confidence interval: 0.563–0.690) and found to be statistically significant ($p < 0.001$). According to the Youden index, the optimal cutoff value for TSH was determined to be 1.795 mIU/mL, providing a sensitivity of 59.6% and a specificity of 59.4% (Table 3) (Figure 1).

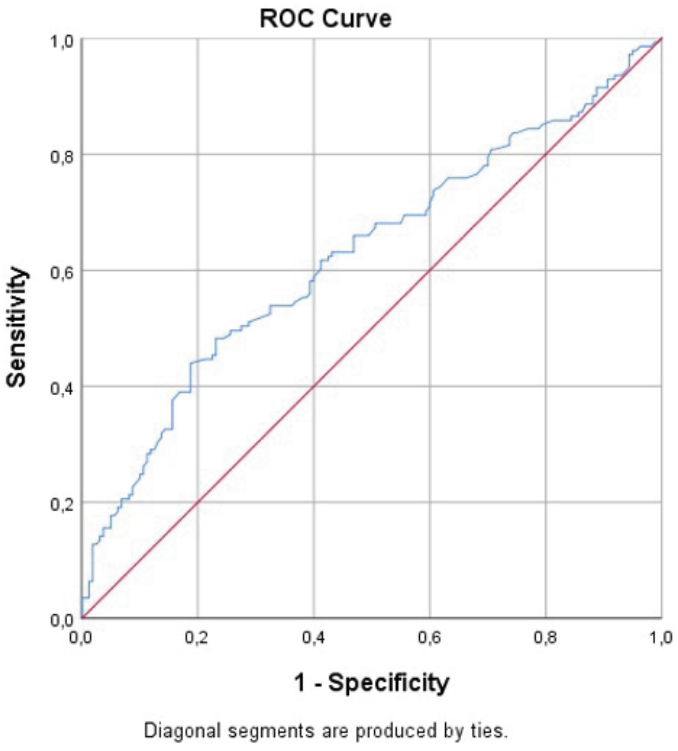

Figure 1. Receiver operating characteristic (ROC) curve for TSH levels in predicting congenital heart disease.

Table 1. Demographic, clinical, and laboratory characteristics of all participants.		
Characteristics		All participants (n=301)
Demographic data		
Maternal age (years)	28 (25–32)	
Maternal weight (kg)	68 (61.5–78)	
Number of fetuses n(%)	1	299 (99.3%)
	2	2 (0.7%)
Gestational weeks		21 (18-24)
Laboratory data		
TSH (mIU/mL)		1.79 (1.28–3.50)
T4 (ng/dl)		1.2 (0.5-3.3)
Clinical findings		
Diagnostic groups n(%)	Normal echocardiographic findings/minor anomalies (PFO, PDA, ASD, small VSD)	160 (53.2)
	VSD (At least moderate VSD)	59 (19.6)
	Pulmonary stenosis	22 (7.3)
	Arcus hypoplasia/aortic coarctation	9 (3.0)
	Tetralogy of Fallot	8 (2.7)
	Situs inversus totalis	13 (4.3)
	TGA	1 (0.3)
	Truncus arteriosus	1 (0.3)
	Pulmonary artery sling	2 (0.7)
	DORV	1 (0.3)
	HLHS	1 (0.3)
	AVSD	7 (2.3)
	Aortic stenosis/Bicuspid aortic valve	16 (5.3)
	Ebstein's anomaly	1 (0.3)
History of diabetes n(%)	No	298 (99.0)
	Yes	3 (1.0)
Smoking status n(%)	No	285 (94.7)
	Yes	16 (5.3)
History of trisomy n(%)	No	296 (98.3)
	Yes	5 (1.7)
Thyroid status n(%)	Euthyroidism	250 (83.1)
	Hypothyroidism	51 (16.9)
Cardiac anomaly classification n(%)	Healthy group and Minor CHD	160 (53.2)
	Major CHD	141 (46.8)

Abbrev.: ASD: Atrial Septal Defect, AVSD: Atrioventricular Septal Defect, CHD: Congenital Heart Disease, DORV: Double Outlet Right Ventricle, HLHS: Hypoplastic Left Heart Syndrome, PDA: Patent Ductus Arteriosus, PFO: Patent Foramen Ovale, TGA: Transposition of the Great Arteries, TSH: Thyroid-Stimulating Hormone, VSD: Ventricular Septal Defect.
Numerical variables are presented as median (25–75 percentiles). Categorical variables are presented as counts and percentages(%)..

Table 2. Comparison of participants with and without congenital heart disease.				
Characteristics		Control group (n=160)	Major CHD group (n=141)	p
Maternal age (years)		28 (25-32.75)	28 (25.5-31)	0.377*
Maternal weight (kg)		67 (62-77)	70 (60.5-78)	0.134*
TSH (mIU/mL)		1.55 (0.5-6.8)	3.05 (0.5-11.58)	0.002*
T4 (ng/dl)		1.2 (0.7-2.2)	1.3 (0.6-2.7)	0.234*
Thyroid Status	Euthyroid	144 (90)	106 (75.2)	0.001***
	Hypothyroidism	16 (10)	35 (24.8)	
History of diabetes n(%)	No	158 (98.8)	140 (99.3)	1.000**
	Yes	2 (1.2)	1 (0.7)	
Number of fetuses n(%)	1	160 (100)	139 (98.6)	0.219**
	2	0 (0)	2 (1,4)	
Smoking status n(%)	No	151 (94.4)	134 (95)	1.000***
	Yes	9 (5.6)	7 (5)	
History of trisomy n(%)	No	158 (98.8)	138 (97.9)	0.668**
	Yes	2 (1.2)	3 (2.1)	

Abbrev.: CHD: Congenital Heart Disease, TSH: Thyroid-Stimulating Hormone
Numerical variables are presented as median (minimum-maximum values). Categorical variables are presented as counts and percentages (%). *Mann-Whitney U test, ** Fisher Exact test, *** Pearson Chi-Square test. Statistical significance was set at p< 0.05. Bold values indicate statistically significant differences.

Table 3. ROC Analysis results of TSH levels for predicting congenital heart disease.

Risk Factor	AUC (95% Confidence Interval)	Cuttoff According to Youden index	p	Sensitivity (%)	Specificity (%)
TSH	0.627 (0.563-0.690)	1.795	<0.001	59.6%	59.4%

Abbrev.: AUC: Area Under the Curve, CI: Confidence Interval, TSH: Thyroid-Stimula ing Hormone.

Table 4. Logistic regression results for TSH and CHD risk.

Variable	B	S.E.	Wald	df	Sig. (p-value)	Exp(B) (Odds ratio)	95% CI for Exp(B) (Lower - upper)
TSH	0.388	0.100	15.089	1	0.000	1.474	1.212 - 1.792

Abbrev.: B: Coefficient, CHD: Congenital Heart Disease, CI: Confidence Interval, df: Degrees of Freedom, Exp(B): Exponentiated Coefficient (Odds Ratio), S.E.: Standard Error, Sig.: Significance, TSH: Thyroid-Stimulating Hormone, Wald: Wald Test Statistic.

It was found that each unit increase in maternal TSH levels increased the risk of fetal CHD by 1.47 times, and this relationship was statistically significant ($p < 0.001$) (Table 4).

In this table evaluating the impact of maternal hypothyroidism on subgroups of major CHD, differences were observed in certain subgroups such as conotruncal defects, septal defects, and valvular anomalies in the hypothyroid group; however, these differences did not reach statistical significance ($p > 0.05$) (Table 5).

Table 5. Distribution of embryologic and clinical cardiac classifications and TSH levels among participants with and without hypothyroidism.

Characteristics	Euthyroid (n=106)	Hypothyroidism (n=35)	p
TSH Levels (mIU/mL) median (min-max)	1.55 (0.5-2.96)	4.26 (3.03-11.58)	<0.001*
Embryologic heart classification			
Conotruncal (Fallot, TGA, DORV, Truncus, pulmonary artery sling)	8 (7.5%)	5 (14.3%)	0.157**
Left ventricular outflow obstruction (Aortic coarctation, arcus hypoplasia, HLHS, aortic stenosis)	6 (5.7%)	6 (17.1%)	
Valvular defects (pulmonary stenosis, bicuspid aorta, AVSD, Ebstein's anomaly)	34 (32.1%)	10 (28.6%)	
Septal defects (VSD)	48 (45.3%)	11 (31.4%)	
Situs anomalies (Situs inversus)	10 (9.4%)	3 (8.6%)	
Detailed cardiac classification			
VSD	48 (45.3%)	11 (31.4%)	0.291**
Pulmonary stenosis	17 (16.0%)	5 (14.3%)	
Aortic coarctation/arcus hypoplasia	5 (4.7%)	4 (11.4%)	
Fallot tetralogy	4 (3.8%)	4 (11.4%)	
Situs inversus totalis-dextrocardia	10 (9.4%)	3 (8.6%)	
TGA	0 (0.0%)	1 (2.9%)	
Truncus arteriosus	1 (0.9%)	0 (0.0%)	
Pulmonary artery sling	2 (1.9%)	0 (0.0%)	
DORV	1 (0.9%)	0 (0.0%)	
HLHS	0 (0.0%)	1 (2.9%)	
AVSD	6 (5.7%)	1 (2.9%)	
Aortic stenosis/bicuspid aorta valve	11 (10.4%)	5 (14.3%)	
Ebstein's anomaly	1 (0.9%)	0	

Abbrev.: ASD: Atrial Septal Defect, AVSD: Atrioventricular Septal Defect, CHD: Congenital Heart Disease, DORV: Double Outlet Right Ventricle, HLHS: Hypoplastic Left Heart Syndrome, PDA: Patent Ductus Arteriosus, PFO: Patent Foramen Ovale, TGA: Transposition of the Great Arteries, TSH: Thyroid-Stimulating Hormone, VSD: Ventricular Septal Defect.
*Mann Whitney U test, **Fisher Exact test. Statistical significance was set at $p< 0.05$. Bold values indicate statistically significant differences. Categorical variables are presented as counts and percentages (%).

Discussion

Our study results, consistent with the literature, indicate an association between maternal hypothyroidism and fetal CHD. Through regression analysis, we determined that each one-unit increase in TSH levels raises the risk of fetal CHD by 1.47 times.

Maternal hypothyroidism is a frequently encountered clinical condition, with its prevalence ranging from 2% to 17%, influenced by factors such as diagnostic criteria, the stage of pregnancy, and regional differences [22-24]. Numerous studies have indicated an association between maternal hypothyroidism and a heightened risk of congenital heart defects in the fetus, as well as cardiovascular conditions later in life during long-term follow-up [20, 25, 26]. The

precise pathways through which maternal hypothyroidism may lead to fetal heart disease remain unclear. However, it is thought to disrupt the normal developmental processes of the fetal heart in various ways. Research has also demonstrated that cardiac remodeling is influenced by the reactivation of embryonic genes, a process that may be influenced by thyroxine [20]. Hypothyroid mothers have been found to experience placental dysfunction, suggesting that thyroid hormones may have both direct and indirect roles in the maturation of the cardiovascular system. Additionally, thyroid hormones play a critical role in the formation of cardiac septa and the development of outflow tracts [27,28].

Ahad et al. [28] investigated the impact of maternal hypothyroidism on both the structural and functional aspects of the fetal heart. This study holds particular significance as it was conducted in Pakistan, where the prevalence of hypothyroidism is notably high. Unlike our study, they did not find a significant difference between the groups in terms of CHDs. However, in their evaluation of functional parameters, a significant difference was observed only in isovolumetric relaxation time. Additionally, while no significant differences in CHDs were found, the study identified significant differences in tricuspid, mitral, and aortic annulus measurements between the groups, with lower measurements reported in the hypothyroid group [28]. This reduction was particularly emphasized in the fetal left heart structures of the hypothyroid group. However, it is believed that this reduction does not lead to structural stenosis or hypoplasia. In our study, when groups were formed based on thyroid status, no significant impact of maternal hypothyroidism was observed in the analysis comparing subgroups of CHDs, particularly those related to left heart structures.

In a cross-sectional case-control study conducted by Grattan and colleagues over a 17-month period, a significantly higher prevalence of CHD was observed in infants born to mothers with maternal hypothyroidism [29]. Regression analysis revealed that maternal hypothyroidism was associated with a 1.68-fold increased risk of CHD [29]. In our study, we found that each one-unit increase in maternal TSH levels increased the risk of fetal CHD by 1.47 times. Furthermore, in the same study by Grattan et al. [29], heterotaxy, a subgroup of CHDs, was reported to occur significantly more frequently in the maternal hypothyroidism group. However, in our study, no significant differences were found among the subgroups of CHDs.

In the studies conducted by Liu et al. [18] and Browne et al. [21], it was similarly observed that maternal thyroid disorders, without detailed categorization, significantly increased the risk of fetal CHDs. Liu et al. [18] reported the most significant associations between maternal thyroid disorders and conotruncal defects, while Browne et al. [21] highlighted a notable relationship with left ventricular outflow tract obstruction heart defects. However, since these studies did not differentiate between hypothyroidism and hyperthyroidism, it is unclear which specific thyroid dysfunction contributed to these outcomes. As a result, a direct comparison with our study cannot be made.

In a nationwide population-based cohort study using Danish national registry data, Miao et al.[30] observed a significant increase in the incidence of cardiovascular diseases, such as hypertension, arrhythmias, and acute myocardial infarction, in children born to mothers with hypothyroidism. However, since infants with congenital anomalies were excluded from the study design, the relationship between maternal hypothyroidism and CHDs could not be assessed [30].

In their study, Dong et al. identified an association between elevated maternal FT4 levels and an increased risk of fetal CHDs. Additionally, they demonstrated that the free-to-total thyroxine proportion serves as a better indicator for this relationship. This association was found to be stronger when these markers were assessed between the 12th and 18th weeks of pregnancy, while measurements taken after the 18th week showed no significant changes [19]. In our study, while we found a significant relationship between elevated TSH levels and CHDs, FT4 levels did not exhibit any significant effect. Based on the findings of Dong et al.[19], evaluating thyroid function tests between the 12th and 18th weeks of gestation might have influenced the FT4 results in our patient population.

Limitations of the study

This study primarily focused on evaluating maternal hypothyroidism based on TSH and FT4 parameters, without accounting for potential risk factors such as diet, genetic predisposition, and environmental influences. Additionally, the small sample size, reliance on data from a single center, and the relatively short study period are significant limitations that should be acknowledged. Additionally, we did not gather information on the duration of maternal hypothyroidism before achieving a state of euthyroidism, nor did we evaluate the extent of fetal exposure to maternal hypothyroidism during this time. Furthermore, our study does not provide information on whether patients received medication or were monitored clinically without treatment. These factors are significant limitations, as they may impact fetal outcomes and should be taken into account in future research. We believe that to better understand the relationship between maternal hypothyroidism and fetal cardiac health, larger-scale,

multicenter, and prospective studies are needed. Such studies should also investigate the effects of maternal hypothyroidism on fetal cardiac rhythm and functional heart disorders.

In conclusion, This study suggests a potential association between maternal hypothyroidism and fetal structural heart diseases, emphasizing the importance of routine thyroid function screening during the second trimester of pregnancy. Future large-scale studies are needed to further elucidate this relationship and to better understand how optimizing maternal thyroid function may positively impact fetal cardiac health.

Declaration of conflicting interests

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

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Ethics approval

The study was approved by the Institutional Ethics Review Board for Clinical Research of Giresun Education and Research Hospital Ethics Committee (approval date: 25.12.2024; approval number: 2024/02). Written informed consent was obtained from the patients prior to inclusion in the study.

Author contributions

Conceptualization, visualization, investigation, formal analysis, data curation writing – original draft: BY, methodology, resources, supervision writing – review & editing: MA,BY, Each author reviewed and approved the published version of the study.

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Research Article

The effect of HbA1c on coronary artery bypass grafting mortality and morbidity in concomitant diabetes mellitus and coronary artery disease

Diyabetes mellitus ve koroner arter hastalığı birlikteliğinde hba1c'nin koroner baypas mortalitesi ve morbiditesine etkisi

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Abstract

Aim: In our study, we aimed to comparatively examine the effect of HbA1c levels and diabetes disease on patients undergoing isolated coronary bypass surgery.

Material and Methods: 200 consecutive patients (152 male, 48 female, mean age 61.1) who underwent coronary artery bypass surgery (CABG) in our hospital were included in the study. The patients were divided into two groups. Group 1 consisted of patients with HbA1c ≥6.5 % (n=100) and group 2 consisted of patients with HbA1c <6.5% (n = 100). In group 1 all the patients were diabetic while in group 2, 30 patients were diabetic. There was no difference in preoperative risk factors between the groups.

Results: Both groups had similar mortality rates. There was no difference in postoperative cerebrovascular accident, myocardial infarction, renal dysfunction, reoperation, atrial fibrillation, sepsis and superficial local infections. There was also no statistical difference in operative data, intensive care unit and hospital stay amongst the groups. In group 1, five patients had mediastinitis whilst there were no cases in group 2 and this was statistically significant (p = 0.030). Multivariate analysis revealed that an increase in postoperative blood glucose levels on the second postoperative day was predictive for mediastinitis (p = 0.036). ROC analysis showed that HbA1c >7.65% was the threshold value for occurrence of mediastinitis with a sensitivity of 80% and specificity of 65.6%.

Conclusion: As a result, poor control of blood glucose levels following CABG is a risk factor for infection and HbA1c is a significant marker for identification of preoperative infection risk.

Keywords: HbA1c, coronary artery bypass surgery, diabetes mellitus, mediastinitis

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Öz

Amaç: Çalışmamızda izole koroner bypass ameliyatı uygulanan hastalarda HbA1c düzeyi ve diyabet hastalığının etkisini karşılaştırmalı olarak incelemeyi amaçladık.

Gereç ve Yöntemler: Çalışmaya hastanemizde koroner baypas cerrahisi geçiren ardışık 200 hasta (152 erkek, 48 kadın, yaş ortalaması 61,1) dahil edildi. Hastalar iki gruba ayrıldı. Grup 1, HbA1c seviyesi ≥ %6,5 olan hastalardan (n = 100) ve grup 2, HbA1c seviyesi < %6,5 olan hastalardan (n = 100) oluşuyordu. 1. gruptaki hastaların tamamı diyabetik iken 2. gruptaki hastaların 30'u diyabetikti. Gruplar arasında ameliyat öncesi risk faktörleri açısından fark bulunmamaktaydı.

Bulgular: Her iki grupta da benzer ölüm oranları vardı. Postoperatif serebrovasküler olay, miyokard enfarktüsü, renal disfonksiyon, reeksplorasyon, atriyal fibrilasyon, sepsis ve yüzeyel lokal enfeksiyonlar açısından fark görülmedi. Gruplar arasında operasyon verileri, yoğun bakım ünitesinde kalış süresi ve hastanede kalış süresi açısından da istatistiksel olarak anlamlı fark saptanmadı. Grup 1'de 5 hastada mediastinit görülürken, grup 2'de hiç mediastinit görülmedi ve bu istatistiksel olarak anlamlıydı (p = 0,030). Multivaryant analizlerine göre, ameliyat sonrası ikinci günde kan şekeri düzeyindeki artışın mediastinit açısından öngörücü olduğu saptandı (p = 0,036). ROC analizi HbA1c > %7.65 değerinin, %80 duyarlılık ve %65 özgüllük ile mediastinit için eşik değer olduğunu gösterdi.

Sonuçlar: Sonuç olarak, koroner baypas cerrahisi sonrası kan şekeri düzeylerinin yetersiz kontrolü enfeksiyon için bir risk faktörüdür ve HbA1c preoperatif enfeksiyon riskinin belirlenmesinde önemli bir belirteçtir.

Anahtar Kelimeler: HbA1c, koroner arter baypas cerrahisi, diyabetes mellitus, mediastinit

Introduction

Diabetes mellitus (DM) is a major global contributor to morbidity and mortality, often leading to both microvascular and macrovascular complications [1]. Reducing glycated hemoglobin (HbA1c) levels to below 7%, a key indicator of effective glycemic control, has been shown to significantly decrease diabetes-related complications [2].

Coronary artery bypass grafting (CABG) is a well-established surgical intervention with favorable long-term outcomes, particularly when internal thoracic artery (IMA) grafts are utilized. Optimal management of atherosclerosis-promoting factors is crucial to the success of CABG. Numerous studies have demonstrated that diabetic patients experience higher rates of postoperative mortality and morbidity [3,4].

Postoperative complications such as acute renal failure, deep sternal wound infections, and prolonged hospital stays are more frequently observed in patients with type 1 DM compared to non-diabetic individuals [3]. Diabetic patients are at heightened risk for infections at both the sternotomy and leg graft sites. Aggressive perioperative glycemic control using insulin infusions [4], targeting blood glucose levels below 150 mg/dL postoperatively, has been shown to reduce early mortality and morbidity after cardiac surgery [5].

The American Diabetes Association recommends HbA1c measurement for long-term glucose monitoring in diabetic individuals [6]. HbA1c is a stable glycated hemoglobin complex formed by the irreversible binding of glucose to hemoglobin, reflecting glycemic control over the preceding 90–120 days. In 2008, the International Expert Committee established an HbA1c threshold of 6.5% for diagnosing diabetes, contingent on adherence to international standardization protocols [7].

This study aimed to evaluate the impact of HbA1c levels on outcomes in patients undergoing isolated CABG by stratifying them into two groups based on preoperative HbA1c levels.

Material and Methods

Study population

A total of 200 patients who underwent isolated CABG were enrolled. Patients were divided into two groups based on preoperative HbA1c levels: Group 1 (HbA1c ≥ 6.5%) and Group 2 (HbA1c < 6.5%). All patients in Group 1 had diabetes, whereas 30 patients in Group 2 were diabetic (p < 0.001). There were no statistically significant differences between the groups regarding age, sex, biochemical parameters, or other risk factors (Table 1).

Study end points

Blood glucose levels were measured preoperatively, intraoperatively, and on postoperative days 1, 2, and 3. Lengths of stay in the intensive care unit (ICU) and hospital were recorded. Complications during the follow-up period were considered clinical endpoints and included mortality, cerebrovascular accident (CVA), myocardial infarction (MI), arrhythmia, renal dysfunction, atrial fibrillation (AF), reoperation, deep sternal infection, sepsis, superficial local

infection, and combined infection (deep + superficial). All patients were monitored in the hospital's outpatient clinic for six months postoperatively.

Diabetes treatment

In Group 1, 16 patients received no treatment, 2 were managed with diet alone, 50 were on oral antidiabetic drugs (OADs), 18 on insulin therapy, and 14 on a combination of OADs and insulin. In Group 2, among the 30 diabetic patients, 3 received no treatment, 2 were managed with diet, and 25 were on OAD therapy.

Perioperative glycemic control

Insulin infusion was administered following the Portland Protocol. OADs and/or insulin were continued until the day of surgery, provided fasting blood glucose levels were <200 mg/dL. Patients with higher levels received insulin until stabilization below 200 mg/dL. During surgery, a solution of 25 U crystalline insulin in 250 mL saline was infused intravenously at 10 mL/hour. Blood glucose levels were monitored hourly, with insulin dosing adjusted accordingly.

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Türkiye Yüksek İhtisas Training and Research Hospital.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation; categorical variables were presented as frequencies and percentages. Group comparisons were performed using the Mann–Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables. Intragroup comparisons were analyzed with the Wilcoxon signed-rank test. Receiver operating characteristic (ROC) analysis was used to determine the HbA1c cut-off for predicting mediastinitis. Logistic regression analysis identified independent predictors of mediastinitis. A p-value <0.05 was considered statistically significant. Analyses were conducted using SPSS v15.0 (SPSS Inc., Chicago, IL, USA).

Results

No significant difference in early (30-day) mortality was observed between the groups: 4 deaths (3%) in Group 1 and 3 in Group 2 (Table 2). No group differences were observed in rates of reoperation, CVA, MI, arrhythmia, renal failure, or sepsis (Table 2). Postoperative complications occurred in 21 patients in Group 1 and 13 in Group 2, though this difference was not statistically significant (p = 0.132, Table 3). ICU and hospital stay durations did not differ significantly (Table 3). The groups were comparable regarding the number of distal anastomoses, aortic cross-clamp time, and cardiopulmonary bypass (CPB) duration (Table 4). Off-pump CABG was performed in 3 patients in Group 1 and 5 in Group 2; the rest underwent CPB.

Superficial local infections were documented in 4 patients in Group 1 (1 sternal, 3 saphenous sites) and 2 patients in Group 2 (saphenous site only), with no statistically significant difference (p = 0.341) (Table 5). The only complication found statistically significant in this study was deep sternal infection development. While 5 patients developed deep sternal infection in Group 1, it was not observed in any patient in Group 2 (p: 0.030) (Table 5). In these patients, the diagnosis of medisatinitis was confirmed by computed tomography. Debridement and sternal fixation were performed in 4 patients, and omentoplasty was additionally performed in 1 patient in Group 1. One patient did not undergo surgery, treated with antibiotic therapy for 30 days. One of these patients was a patient revised due to hemodynamic instability in the early postoperative period, and this patient died due to sepsis in the second postoperative month. When the two groups were compared in terms of combined infection development, the difference was observed to be statistically significant (p:0.030) (Table 5).

Multivariate logistic regression analysis identified elevated blood glucose on postoperative day 2 as the sole independent predictor of mediastinitis (p = 0.036) (Table 6).

Group 2 exhibited statistically significant daily fluctuations in blood glucose, whereas Group 1 showed no significant reduction from day 1 to day 2 (p = 0.086), although other changes were significant (Figure 1).

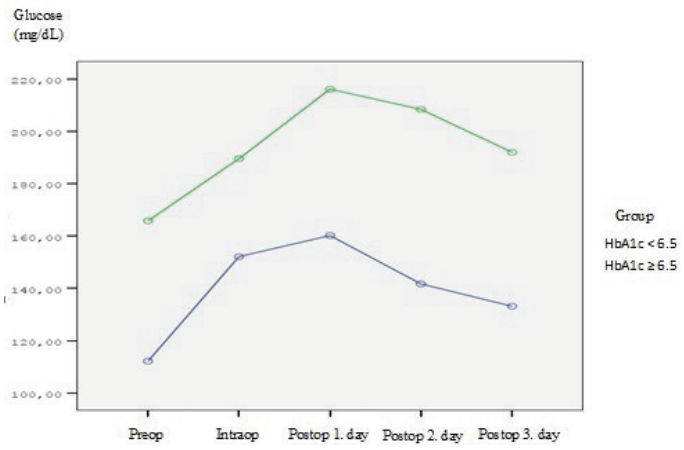

Figure 1. Daily changes of glucose measurement of the study patients according to HbA1c value.

ROC analysis demonstrated an area under the curve (AUC) of 0.737 for HbA1c in predicting mediastinitis. A threshold of

7.65% yielded 80% sensitivity and 65.6% specificity.

Discussion

Cardiovascular mortality is two to five times higher in diabetic patients than in non-diabetic individuals [8]. Several studies have shown elevated postoperative mortality and morbidity in this population [9,10]. However, tight perioperative glycemic control via insulin infusion has been associated with improved outcomes [11,12]. These results draw attention to the importance of strict glycemic control in the period after CABG.

Our findings revealed similar early mortality in both HbA1c groups. Although some previous studies reported no significant effect of diabetes on CABG outcomes [7], Bundhun et al. found increased mortality among diabetic patients in a meta-analysis of 11 studies involving 12,965 patients [9].

Pathophysiologic mechanisms underlying poorer outcomes in diabetic patients include end-organ damage, metabolic derangements, electrolyte disturbances, increased myocardial oxygen demand, and immune dysfunction. Hyperglycemia impairs neutrophil function, increases infection susceptibility, and disrupts coagulation and endothelial function. Some studies [13,14] found that high glucose values were an important risk factor for wound site infections, and there was a high correlation between maintaining glucose control and reduction in infection and sternal opening rates. In our study, deep sternal infection was significantly more common in the high-HbA1c group. Although superficial infections were not statistically different, the combined infection rate was. One of the 5 patients with mediastinitis underwent reoperation due to hemodynamic instability in the early postoperative period and the etiology may be re-surgery instead of poor glycemic control in this patient. Logistic regression identified postoperative day 2 hyperglycemia as a significant risk factor, underscoring the importance of tight glycemic control after CABG. Therefore, maintaining blood glucose control with aggressive treatment after surgery is of great importance in terms of reducing the risk of postoperative infection development. Alserius et al. reported that HbA1c > 6% was associated with an increased risk of superficial sternal infection and mediastinitis after CABG in a study of 605 patients [15]. Halkos et al. reported that HbA1c elevation was significantly associated with an increased risk of deep sternal infection after CABG and found the cut-off value as 7.8% for this complication [16]. In our study, we found the cut-off value of HbA1c as 7.65% for deep sternal infection with a sensitivity of 80% and specificity of 65.6%. In contrast, Göksedef et al. reported that HbA1c elevation did not pose a risk for mediastinitis development after CABG, but mediastinitis and local sternal infection were more common in the patients with high intraoperative blood glucose levels [17]. In our study, we found that high blood glucose levels on the 2nd postoperative day were significantly continued in the HbA1c ≥ 6.5% group with more common mediastinitis and superficial local infection compared to the other group. Interestingly, 30% of patients in the low-HbA1c group had diabetes but experienced no mediastinitis, suggesting that well-controlled diabetes may not pose an increased infection risk. Our findings support the notion that poor glycemic control, rather than the diagnosis of diabetes itself, is the primary risk factor.

Diabetes is also considered as an independent risk factor for neurological complications after CABG, and delirium and stroke are the most common of these complications. Zhongmin Li et al. [18] argued that there was no increase in neurological complications in diabetic patients. In our study, neurological events were observed in 3 patients in Group 1 and 1 patient in Group 2, but this difference was not statistically significant.

According to the results of the Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) study of 1800 patients, revascularization was more observed in diabetic patients after both CABG and percutaneous coronary intervention (PCI) compared to non-diabetic patients [19]. In this study, postoperative MI findings were observed in 3 patients in the HbA1c ≥6.5% group and 2 patients in the other group, but this difference was not statistically significant. Long-term follow-up studies will be more appropriate to evaluate revascularization after coronary bypass surgery. Therefore, our study is not suitable for evaluating this complication since it involves the early period after CABG.

Atrial fibrillation is the most common arrhythmia observed after cardiac surgery [20,21]. Apart from the proven classical risk factors, new mechanisms have now been introduced especially considering the role of inflammation in AF pathophysiology. One of the newly identified risk factors is the HbA1c levels in diabetic patients. There are studies demonstrating an inverse correlation between HbA1c levels and postoperative AF and showing that the incidence of AF is decreased in the presence of high HbA1c levels [22]. Iguchi et al. [23] showed that the incidence of AF was higher in patients with HbA1c level below 6.5% in a population study. Contrary to these data, Dublin et al. [24] showed that the risk of developing AF increased with increasing HbA1c levels in a population-based study on 1410 patients newly diagnosed with AF. In our study, although it

was not statistically significant, AF was observed in 9 patients in the HbA1c <6.5% group, while it was observed in 5 patients in the other group. Although the effect of HbA1c level on AF is still controversial, one alleged mechanism is the emergence of higher doses of insulin need for postoperative blood glucose regulation is protective for AF development.

Given the high morbidity and mortality of mediastinitis, delaying elective CABG in patients with HbA1c ≥ 7.65% to allow for better glycemic optimization may be advisable. Tight glycemic regulation is endorsed by the American Heart Association, particularly targeting blood glucose <180 mg/dL perioperatively [25]. It will be possible on the day of surgery with high doses of insulin therapy even in patients with poor glycemic control. As in our study, the patients with good blood glucose regulation in the long term have a lower risk of developing complications after CABG. Thus, HbA1c, which is an indicator of long-term glycemic control, is a valuable method that can be used to evaluate preoperative risks for cardiac surgery, especially infection.

Limitations of the study

This study was conducted at a single center with a limited sample size. The findings pertain to early postoperative outcomes; long-term effects of HbA1c on CABG complications warrant further investigation in larger, multicenter studies.

In conclusion, effective glycemic control significantly reduces the risk of infection following CABG. HbA1c is a reliable measure of long-term glucose regulation and may serve as a useful preoperative risk stratification tool.

Declaration of conflicting interests

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

Table 1. Baseline clinical and laboratory characteristics of the study patients according to the HbA1c value

Variable	Group 1 (HbA1c ≥ 6.5)	Group 2 (HbA1c < 6.5)	p value
Age	59.90 ± 8.67	62.30 ± 10.48	0.057
Sex (male/female)	71 / 29	81 / 19	0.098
Diabetes Mellitus	100	30	<0.001
Hypertension	71	75	0.524
Dyslipidemia	35	31	0.547
Peripheral arterial disease	4	1	0.184
Smokers	38	34	0.556
Chronic obstructive pulmonary disease	22	21	0.863
Body mass index (kg/m^2)	28.9 ±4.3	28.3±4.4	0.414
Ejection fraction(%)	53.48 ±9.3	54.18±8.8	0.673
Creatinine (mg/dL)	0.98±0.31	0.97±0.22	0.516
HbA1c (%)	8.87±1.8	5.65±0.5	<0.001
WBC (/mm^3)	8308.80±1983.2	7671.50±1860.4	0.017
Urine proetin(mg/L)	12	8	0.346
Preopertive glucose>180(mg/dL)	49	3	<0.001

Table 2 Postoperative outcomes of the study patients according to the HbA1c value

Variable	Group 1 (HbA1c ≥ 6.5)	Group 2 (HbA1c < 6.5)	p value
Mortality	4	3	0.702
Cerebrovascular accident	3	1	0.315
Myocardial infarction	3	2	0.653
Arrhythmia	5	1	0.098
Acute renal failure	2	1	0.563
Atrial fibrillation	5	9	0.270
Mediastinitis	5	0	0.030
Sepsis	3	1	0.315
Superficial local infection	4	2	0.341
Reoperation	5	2	0.251

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Ethics approval

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Türkiye Yüksek İhtisas Training and Research Hospital.

Authors' contributions

ST; Designed and performed experiments, analyzed data and co-wrote the paper. HZİ, AÖ, EUÜ,VB,CLB.; Performed experimentes. EUÜ; Performed bioinformatic analyzes. BTT; Designed experiments and co-wrote the paper. HZİ., UÜ, CLB; Supervized the research.

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Research Article

The effect of overweight and patient position changes on perfusion index after anesthesia induction

Fazla kilo ve hasta pozisyon değişikliklerinin anestezi indüksiyonundan sonra perfüzyon indeksi üzerindeki etkisi

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Abstract

Aim: The relative variability in the perfusion index (PI) observed after anesthesia induction, due to the effect of surgical positions, is influenced by multiple factors. The aim of this study was to investigate changes in PI in patients undergoing surgery in the supine, prone, and sitting positions, and to assess the effect of body mass index (BMI) on the relative change in PI (ΔPI).

Material and Methods: This is a prospective cross-sectional observational study. A total of 82 patients were enrolled between June 2023 and December 2023, including individuals over 18 years of age. The study investigated the effects of different patient positions (supine, sitting, and prone) and BMI on the relative change in perfusion index.

Results: Of the patients, 52.4% were male (n = 43). It was found that 43.9% of the patients had a BMI greater than 25 kg/m^2 (n = 36). The operations were performed in the prone position in 32.9% of cases (n = 27), supine position in 32.9% (n = 27), and sitting position in 34.1% (n = 28). No statistically significant difference was observed in the PI value at 0 minutes across all groups. The PI values at 10, 20, and 30 minutes were highest in Group 1 patients. It was found that the PI values were statistically higher in patients with a BMI <25 at all time intervals ($p < 0.001$). The ability of a BMI of 25 or greater to predict ΔPI after anesthesia induction was analysed, and the area under the ROC curve showed a sensitivity of 91% and specificity of 93%. The cut-off value, according to the maximum Youden index, was 0.96, with a confidence interval of 91-99% ($p < 0.001$).

Conclusion: The change in the PI value after anesthesia induction was found to be greater in patients positioned prone. This change significantly impacts ΔPI, particularly when the BMI ≥ 25 cut-off is applied.

Keywords: patient positions, perfusion index, obesity, anesthesiology

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Öz

Amaç: Anestezi indüksiyonundan sonra cerrahi pozisyondaki değişiklikle gözlenen perfüzyon indeksi (PI) değerindeki değişiklik birçok faktörden etkilenir. Bu çalışmanın amacı sırtüstü, yüzüstü ve oturma pozisyonlarında ameliyat edilen hastalarda PI'daki değişikliği ve vücut kitle indeksinin (VKİ) PI'daki (ΔPI) bağıl değişiklik üzerindeki etkisini araştırmaktır.

Gereç ve Yöntemler: Bu prospektif kesitsel gözlemsel bir çalışmadır. Haziran 2023 ile Aralık 2023 arasında 18 yaş üstü, sırtüstü, oturma ve yüzüstü pozisyonlarda olmak üzere toplam 82 hasta kaydedildi ve hasta pozisyon değişiklikleri ve VKİ değerlerinin ΔPI üzerindeki etkileri araştırıldı.

Bulgular: Hastaların %52,4'ünün erkek olduğu (n: 43) görüldü. Hastaların %43,9'unun (n:36) BKİ'sinin 25 kg/m2'nin üzerinde olduğu görülmüştür. Cerrahi operasyonlar %32,9 yüzüstü pozisyonda (n:27), %32,9 sırtüstü pozisyonda (n:27) ve %34,1 oturur pozisyonda (n:28) gerçekleştirilmiştir. Tüm gruplarda PI 0 değerinde istatistiksel olarak anlamlı bir fark olmadığı görülmektedir. PI 10-20-30 değerinin grup 1 hastalarında en yüksek düzeyde olduğu görülmektedir. Tüm zaman aralıklarında BKİ <25 olan hasta gruplarında PI değerlerinin istatistiksel olarak daha yüksek olduğu görülmektedir (p<0,001). BKİ 25 olan hastaların anestezi indüksiyonu sonrası ΔPI'yi tahmin etme yeteneği incelendiğinde, ROC eğrisi altında kalan alanın duyarlılığı %91, özgüllüğü ise %93 olarak bulunmuştur. Maksimum Youden indeksine göre kesme değeri %91-99 güven aralığıyla 0,96'dır (p<0,001).

Sonuç: Anestezi indüksiyonundan sonra PI'deki bağıl değişimin yüzüstü pozisyondaki hastalarda daha yüksek olduğu bulunmuştur. BMI≥25 kesme değeri kabul edilirse bu değişim ΔPI'yi yüksek oranda etkiler.

Anahtar Kelimeler: hasta pozisyonları, perfüzyon indeksi, obezite, anesteziyoloji

Introduction

It is common for certain vital signs to be affected after anesthesia induction, with hypotension and bradycardia being the most common. Several factors can contribute to the hypotensive effects of anesthetic induction [1]. In obese patients, hemodynamic parameters are influenced by changes in patient position during surgery. Blood pressure abnormalities after anesthesia induction are common in obese individuals. Additionally, bradycardia and hypotension may occur due to reduced venous return to the heart, which is caused by increased intrathoracic pressure during mechanical ventilation. This may lead to changes in the pulmonary vascular system and the patient's hemodynamics. In addition to these effects, the position in which the patient is placed during anesthesia may reduce venous return to the heart, alter ventilation and perfusion in the dependent regions of the lungs, and influence hemodynamic parameters [2]. Obesity is assessed using the Body Mass Index (BMI), which is calculated by dividing a person's body weight by the square of their height (kg/m^2). Individuals with a BMI greater than 30 are classified as obese [3]. Obese patients are at increased risk of certain complications during anesthesia, such as difficulties with intubation and mechanical ventilation. In addition, compared to patients with a normal BMI, they tend to have higher peak airway pressures during mechanical ventilation and may experience lower blood pressure [4]. Hypotension and reduced venous return to the heart in obese patients can increase myocardial workload and oxygen demand [5-6]. The Perfusion Index (PI) is the ratio of pulsatile to non-pulsatile blood flow, as measured by pulse oximetry. It is commonly used to assess peripheral perfusion and sympathetic nervous system activity. The Pleth Variability Index (PVI) quantifies changes in the amplitude of the plethysmographic waveform in response to respiratory variations and is considered to reflect intravascular volume status [7].

The hypothesis of our study was that changes in body position after the induction of general anesthesia, as well as obesity, influence the perfusion index (PI) values. In this study, we investigated changes in hemodynamic parameters and PI values in patients with a BMI of 25 or higher and those with a normal BMI, following anesthesia induction in the prone, sitting, and supine positions.

Material and Methods

Study design

We conducted a prospective, cross-sectional observational study, and obtained ethics committee approval from the Amasya University Ethics Committee (Approval No: 2023000046-1).The study adhered to the ethical principles outlined in the declaration of Helsinki. The study was registered

at ClinicalTrials.gov (ID: NCT96742619). In preparing our report, we adhered to the CONSORT checklist and followed the guidelines outlined in the STROBE statement. Written consent was obtained from all participants.

Inclusion criteria

A total of 82 patients aged over 18 years were enrolled between June 2023 and December 2023. The study included patients undergoing laparotomy in the supine position, shoulder surgery in the sitting position, and lumbar disc herniation surgery in the prone position.

Exclusion criteria

Patients under 18 years of age, those with peripheral circulation problems, heart failure, or heart valve disease, and patients unable to orient themselves were excluded from the study.

Patient and data collection

Patients scheduled for surgery in the prone position were classified as Group 1, those scheduled for surgery in the sitting position as Group 2, and those scheduled for surgery in the supine position as Group 3. All patients were then transferred to the operating room. Peripheral intravenous (IV) access was established using a 20 Gouge IV cannula. Patients were fasted for 6 hours and administered 500 cc of lactated Ringer's solution intravenously prior to transfer to the operating room.

Protocol

Premedication was administered 10 minutes prior to surgery with 1 mg IV midazolam and 40 mg IV pantoprazole. Routine monitoring included electrocardiography (ECG), oxygen saturation (SpO_2), pulse oximetry, non-invasive blood pressure (NIBP), and mean arterial pressure (MAP), all of which were recorded. PI and Pleth Variability Index (PVI) values were measured using the finger probe of a PI device (Masimo Corp, Irvine, CA, USA) placed on the right index finger. All values were recorded at minute 0. Body Mass Index (BMI) values (kg/m^2) were calculated using height and weight measurements for all participants. Preoperative data including age, sex, room temperature, and BMI were also recorded.

For anesthesia induction, propofol 1.5-2 mg/kg IV, fentanyl 1-2 mcg/kg IV, and rocuronium 0.6 mg/kg IV were administered, followed by bag-mask ventilation. After achieving muscle relaxation, patients were intubated and connected to a mechanical ventilator. A 50% oxygen (O_2)-air mixture was administered, with tidal volume set to 6-8 ml/kg, frequency 12-15/min, PEEP: 5 cm H_2O, and sevoflurane 2% MAC was used to maintain anesthesia. The patient was positioned in either the supine, prone, or sitting position for surgery. HR, SpO_2, MAP, PI, and PVI values were recorded at 10, 20, and 30 minutes post-positioning.

During the intraoperative period, Ringer's lactate was infused at 4-8 ml/kg/min, with 250 ml administered if MAP was <65 mm Hg. If MAP remained <65 mm Hg despite fluid administration, 1-2 mg of norepinephrine was given intravenously. At the end of the surgical procedure, the muscle relaxant effect was reversed with 200 mg IV sugammadex. Patients with adequate spontaneous respiration and muscle strength were extubated and transferred to the post-anesthesia care unit.

HR, MAP, PI, and PVI values were recorded at 10, 20, and 30 minutes. The relative change in PI value (ΔPI) at 30 minutes post-surgery was calculated using the formula: $\Delta PI = (PI_{30} - PI_0) / PI_0$.

Statistical Analysis

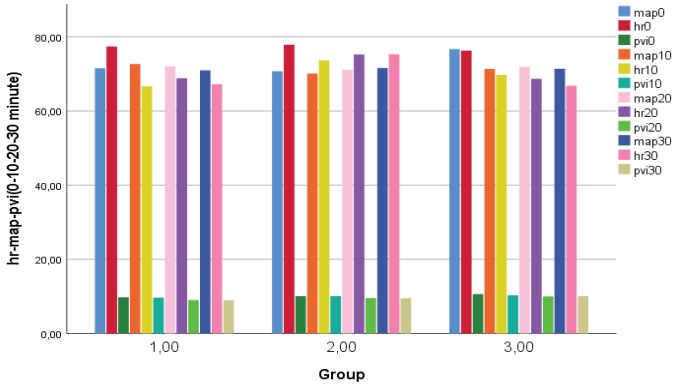
The study by Min JY et al [8] was used to calculate the sample size. The sample size of patients was calculated using G-Power 3.1.9.4. The effect size was calculated to be 0.39 with a type 1 error of 0.05 (the power of the study was 0.80) and the total number of patients was 80. To avoid missing data, 82 patients were included in the study. Data were analysed using IBM SPSS statistical package, version 25.0 (Chicago, IL, USA). Kolmogorov-Smirnov tests were used to analyse the normality of the data distribution. Continuous numerical data were expressed as standard deviation and median range. Demographic characteristics were summarised as frequency percentages. One-way ANOVA analysis with post-hoc Bonferroni correction was used to analyse group variables. Independent samples t-test and Mann-Whitney U test were used to analyse PI values at different time points in patients with normal and above normal BMI values. Pearson correlation analysis was used to determine the possible relationship between BMI and relative change in PI. A value of $p<0.05$ was considered statistically significant. An ROC curve was calculated using the best cut-off value. A BMI of 25 or higher was used as the cut-off value. Youden index to measure the ability of BMI variability to predict ΔPI after induction of anesthesia.

Results

A total of 82 patients data were analysed. It was found that 52.4% of the patients were male (n: 43). It was found that 43.9% of the patients had a BMI greater than 25 kg/m2 (n: 36). The operation was performed in 32.9% prone position (n: 27), 32.9% supine position (n: 27) and 34.1% sitting position (n: 28). Age, sex, BMI and room temperature of the groups were presented in Table 1.

Table 1. Demographic characteristics and room temperature values.		
	n	Mean±SD
Gender M/F	43/39	
Age (years)		45.5±16.7
BMI (kg/m2)		25.09±4.2
Room temperature°C		22.5±1.3
M:male, F:female, BMI:Body mass index, SD:Standard deviaation		

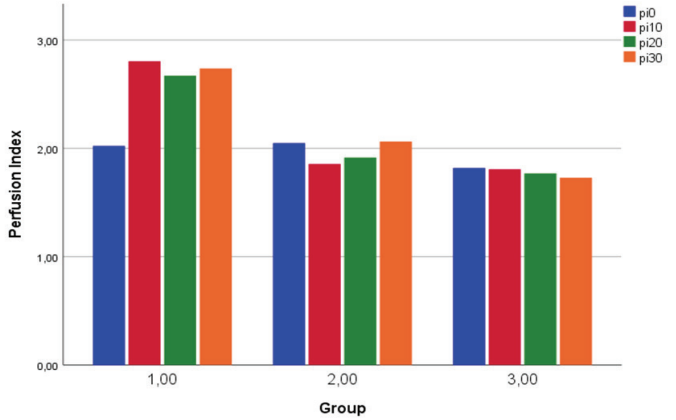
The PI values at 0, 10, 20 and 30 minutes are presented in Figure 1 (PI 0, PI 10, PI 20 and PI 30) for each group. No statistically significant difference was observed in the PI 0 values across the groups. The PI 10 value was higher in Group 1 patients ($p < 0.001$), with no difference observed between Groups 2 and 3 ($p = 0.967$). Similarly, the PI 20 value was higher in Group 1 patients ($p = 0.002$), with no difference observed between Groups 2 and 3 ($p = 0.758$). The PI 30 value was higher in Group 1 patients ($p < 0.001$), with no difference observed between Groups 2 and 3 ($p = 0.407$).



Map:Mean arterial pressure, hr:Heart rate, pvi: pleth variability index

Figure1: Comparison of PI values of groups at different time points

MAP, HR, and PVI values are presented in Figure 2. No statistically significant differences were observed across the groups at any time during anesthesia.



Pi: perfusion index

Figure 2: Comparison of hemodynamic parameters of groups at different time points

The PI values at 10, 20, and 30 minutes after anesthesia induction in patients with BMI values above normal (≥25 kg/m^2) and below normal (<25 kg/m^2) are presented in Table 2. It was observed that PI values were statistically higher in patients with BMI <25 at all time intervals ($p < 0.001$ for all comparisons).

Table 2. Comparison of PI values in patients with BMI ≥25 and BMI<25.				
Gropus	N	Mean Rank	Sum of Ranks	p
		PI 0		
BMI≥25	36	18.7	674.5	<0.001
BMI<25	46	59.3	2728.5	
		PI 10		
BMI≥25	36	24.8	894.5	<0.001
BMI<25	46	54.3	2508.5	
		PI 20		
BMI≥>25	36	21.1	756.5	< 0.001
BMI<25	46	57.3	2646.5	
		PI 30		
BMI≥25	36	18.9	681.0	<0.001
BMI<25	46	59.1	2722.0	
BMI: Body Mass Index. PI:perfusion Index				

There was a moderate negative correlation between BMI and ΔPI values (Pearson correlation coefficient - 0.76 and p<0.001). The rate of patients with a body mass index ≥25kg/m2 was 43.9% (n:26). To examine the change in PI value after induction of anesthesia according to the BMI variable, a ROC curve was constructed. The ability of patients with BMI of 25 to predict the ΔPI after induction of anesthetic was investigated. The area under the ROC curve showed a sensitivity of 91% and a specificity of 93%. The cut-off value according to the maximum Youden index was 0.96 with a confidence interval of 91-99% (p<0.001) (Figure 3).

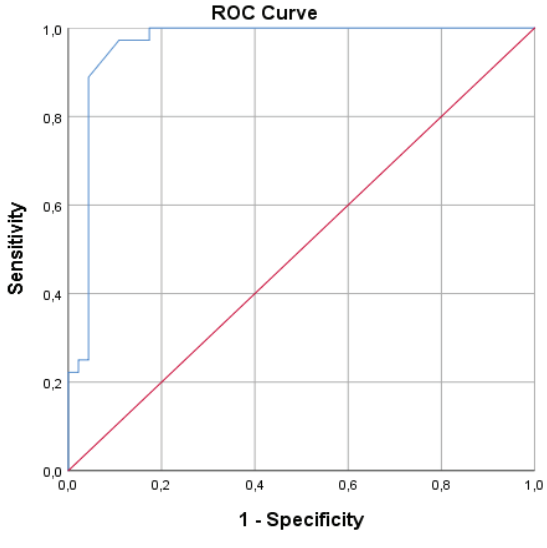


Figure 3: Area under the ROC curve

PI values of patients with BMI ≥ 30 and BMI < 30 at different time periods are presented in Table 3. No statistically significant difference was observed in the PI 0 value between the two groups. However, the PI 10, PI 20, and PI 30 values were significantly lower in patients with BMI ≥ 30 compared to those with BMI < 30 (p = 0.001, p < 0.001, p < 0.001, respectively).

Table 3. Comparison of PI values in patients with BMI ≥30 and BMI<30.

	BMI<30 (n=67)	BMI>30 (n=15)	p
PI 0	2.17±0.65	1.86±0.86	0.604
PI 10	2.30±0.80	1.46±0.73	<0.001
PI 20	2.32±0.81	1.24±0.38	<0.001
PI 20	2.46±0.85	0.85±0.14	<0.001

PI: Perfusion Index BMI: Body Mass Index (ıt is presented Mean±SD)

Discussion

The aim of this study was to investigate the effect of different patient positions and BMI on the PI during the intraoperative period. Initial findings showed that patients in Group 1 had statistically higher PI values after the induction of anesthesia (Figure 1). No significant difference in PI values was observed between the groups at the 0-minute time point before surgery. However, PI values measured at 10, 20, and 30 minutes were significantly higher in Group 1 compared to Groups 2 and 3. The PI provides valuable information regarding changes in organ perfusion, intraoperative fluid status, arterial blood pressure, and systemic hypoxia [9-10]. Consequently, we observed higher PI values in Group 1 patients, likely due to the change in patient positioning compared to the other groups.

In our study, as shown in Figure 2, the PI was lower in patients with a BMI ≥ 25. Considering the variable nature of the PI, we examined its relative variability using the Youden index, with a BMI cut-off of ≥25, to monitor changes in PI in overweight individuals. It was observed that a BMI ≥ 25 had an inverse effect on the relative variability of the PI (Table 3 - Figure 3).

In a study by Smith et al. [11], patients were positioned sitting after anesthesia induction, and a decrease in systemic blood pressure and PI values was observed within the first few minutes of positioning. It was suggested that a decrease in blood volume in the intrathoracic region might explain these changes. In patients placed in the supine position, increased intrathoracic pressure was thought to contribute to changes in PI by reducing cardiac index and blood flow. Similarly, in a study by Tapar et al. [12], the PI was highest in the Trendelenburg position, and, consistent with our findings, PI values were observed to be higher in patients operated in the prone position compared to those in the sitting or supine positions.

Obesity prevalence has been rising globally, with rates now reaching 35-42% [13]. Obesity triggers a cascade of events that predispose individuals to the development of high-flow heart failure. Symptoms of high-flow heart failure progress due to increased diastolic pressure and consequently increased intravascular volume [14]. In the early stages of obesity, patients may experience conditions such as diastolic dysfunction, atrial dilation, and increased cardiac output [15-16]. Our study also demonstrated that PI values decreased more significantly in obese individuals compared to non-obese individuals.

Limitations of our study include the exclusion of different types of surgeries and surgical procedures. Additionally, the relatively small sample size and the single-center design of the study may influence the results. Future studies may benefit from examining the relative change in PI in morbidly obese patients, as this could provide valuable insights into intraoperative management.

In conclusion, the PI was lower in patients with a BMI ≥ 25, and the relative change in PI was negatively correlated. The area under the curve (AUC) indicated that a BMI ≥ 25 negatively affected the relative variability of PI. It was observed that the PI was higher in the prone position compared to the supine and sitting positions. Additionally, the relative change in PI had a negative effect in individuals with a BMI ≥ 25. These results highlight the importance of monitoring PI in obese and overweight individuals with BMI above normal.

Ethical Approval

This study is approved by Amasya University Institution's Ethics Committee (2023000046-1).

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Authors Contribution

HTD conducted the study, inputted and analysed the data, and wrote the manuscript. MK, MK, ST and FK conducted the study, collected the data, and performed follow-ups. MK. HTD and ST,designed the study. OÖK Conducted the study, interpreted the data, and revised the manuscript. All the authors have read and approved the final version of the manuscript. All authors contributed equally to the manuscript and have read and approved the final version.

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Research Article

Causes of in-hospital cardiopulmonary arrests and mortality during the follow-up of elderly patients in the emergency department: a retrospective study

Acil serviste yaşlı hastaların takipleri sırasında hastane içi kardiyopulmoner arrestlerin ve mortalitenin sebepleri: retrospektifbir çalışma

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Abstract

Aim: This study aimed to identify the factors affecting the development of cardiopulmonary arrest (CPA), the probability of return of spontaneous circulation (ROSC), and survival rates in elderly patients admitted to the emergency department.

Material and Methods: A retrospective analysis was conducted on data from 500 patients aged 65 years and older who presented with CPA at Esenyurt Necmi Kadıoğlu State Hospital's emergency department between September 1, 2022, and August 31, 2024. Data were collected from the hospital's electronic medical records, including demographic information, comorbidities, clinical characteristics, resuscitation procedures, and survival rates. Statistical analysis was performed using SPSS version 26.0.

Results: The mean age of the patients was 79.67 ± 8.99 years, with hypertension (52.6%), COPD (40.2%), and cardiovascular diseases (35.4%) being the most common comorbidities. Patients who achieved ROSC had earlier initiation of resuscitation, and oxygen support along with mechanical ventilation significantly improved ROSC rates ($p < 0.05$). The 24-hour survival rate was 65% ± 10, the 30-day survival rate was 45% ± 10, and the in-hospital mortality rate was calculated as 55% ± 10.

Conclusion: Effective management of comorbidities and timely interventions are essential for reducing CPA risk and improving survival rates in elderly patients. Early and efficient resuscitation strategies significantly improve survival outcomes. Further studies with larger cohorts are recommended to optimize clinical management protocols.

Keywords: cardiopulmonary arrest, return of spontaneous circulation, elderly patients, emergency department, comorbidities, survival rates, resuscitation, hypertension, COPD, cardiovascular disease

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Öz

Amaç: Bu çalışma, acil servise başvuran yaşlı hastalarda kardiyopulmoner arrest (KPA) gelişimini etkileyen faktörleri, spontan dolaşımın geri dönme (SDGD) olasılığını ve sağkalım oranlarını belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: 1 Eylül 2022 - 31 Ağustos 2024 tarihleri arasında Esenyurt Necmi Kadıoğlu Devlet Hastanesi acil servisine KPA ile başvuran 65 yaş ve üzeri 500 hastanın verileri retrospektif olarak analiz edildi. Veriler, hastanenin elektronik tıbbi kayıtlarından elde edilerek demografik bilgiler, komorbiditeler, klinik özellikler, resüsitasyon işlemleri ve sağkalım oranları incelendi. İstatistiksel analizler SPSS sürüm 26.0 kullanılarak yapıldı.

Bulgular: Hastaların ortalama yaşı 79,67 ± 8,99 yıl olup, en yaygın komorbiditeler hipertansiyon (%52,6), KOAH (%40,2) ve kardiyovasküler hastalıklar (%35,4) olarak tespit edildi. SDGD sağlayan hastalarda resüsitasyona daha erken başlandığı ve oksijen desteği ile mekanik ventilasyonun SDGD oranlarını anlamlı derecede artırdığı görüldü ($p < 0,05$). 24 saatlik sağkalım oranı %65 ± 10, 30 günlük sağkalım oranı %45 ± 10 ve hastane içi mortalite oranı %55 ± 10 olarak hesaplandı.

Sonuç: Komorbiditelerin etkili yönetimi ve zamanında yapılan müdahaleler, KPA riskini azaltmada ve yaşlı hastalarda sağkalım oranlarını iyileştirmede kritik öneme sahiptir. Erken ve etkili resüsitasyon stratejileri sağkalım sonuçlarını önemli ölçüde iyileştirmektedir. Klinik yönetim protokollerini optimize etmek için daha geniş hasta gruplarıyla yapılacak ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: kardiyopulmoner arrest, spontan dolaşımın geri dönmesi, yaşlı hastalar, acil servis, komorbiditeler, sağkalım oranları, resüsitasyon, hipertansiyon, KOAH, kardiyovasküler hastalıklar

Introduction

Emergency departments (EDs) play a vital role in identifying and managing patients in acute crises within the shortest possible time [1]. Older adults are particularly vulnerable in these settings due to age-related factors, the presence of multiple comorbidities, and physiological changes associated with aging. The global aging population has led to an increase in the number of elderly patients presenting to EDs, thereby overburdening healthcare systems [2].

Morbidity and mortality associated with in-hospital cardiopulmonary arrest (CPA) are significantly higher in elderly patients compared to younger individuals. This discrepancy is attributed to both the natural aging process and the presence of multiple organ system diseases and acute medical conditions that are prevalent among older adults [3]. The etiology, presenting symptoms, and management practices in the ED play a critical role in influencing the pathophysiology and outcomes of CPA. Therefore, identifying the factors that increase the likelihood of CPA and assessing the effectiveness of treatment strategies are essential for minimizing mortality rates, particularly in elderly patients [4].

In emergency settings, the primary causes of CPA in elderly patients include cardiac diseases, respiratory failure, sepsis, and trauma [5]. Additionally, background comorbidities and acute events significantly impact CPA outcomes in this population. The outcomes of CPA differ between elderly and younger patients, underscoring the importance of early intervention and targeted management strategies [6]. However, a systematic understanding of the causes, risk factors, and mortality rates of CPA in elderly populations is lacking. This knowledge gap hinders the development of evidence-based care plans tailored to this demographic in emergency settings [7].

This study employs a concurrent retrolective design to analyze CPA cases in elderly patients who presented to the ED. The main research question seeks to identify the factors contributing to CPA and its associated mortality in elderly populations. Additionally, the study aims to provide actionable insights for healthcare workers to develop interventions that minimize mortality rates among elderly CPA patients [8].

Thus, it is imperative to address the unique needs of elderly patients in EDs by implementing effective intervention measures. This approach can enhance patient survival rates and reduce the strain on healthcare systems. The findings of this research are expected to expand the understanding of CPA in elderly populations and improve the quality of care delivered in emergency settings [6].

Material and Methods

This retrospective study was conducted by analyzing the data of 500 patients aged 65 and older who presented to the emergency department of Esenyurt Necmi Kadıoğlu State Hospital between September 1, 2022, and August 31, 2024. The aim of the study was to evaluate the incidence of in-

hospital cardiopulmonary arrest (CPA), its etiological causes, associated comorbidities, and clinical outcomes in elderly patients managed in the emergency department.

Study population

Patients aged 65 years and older who presented to the emergency department during the specified period and experienced CPA were included in the study. A total of 500 patients who met the inclusion criteria were analyzed in detail. Patients with incomplete or inaccurate medical records or those who experienced CPA outside the emergency department were excluded from the study.

Data collection

Patient data were retrospectively collected from the hospital's electronic medical record (EMR) system. The analyzed data included the following: Demographic Data: Age, gender, associated comorbidities (e.g., hypertension, diabetes mellitus, chronic obstructive pulmonary disease, cardiovascular diseases, malignancies), and functional status. Clinical Characteristics: Presenting complaints (e.g., chest pain, shortness of breath, loss of consciousness), vital signs at admission to the emergency department, laboratory findings, and imaging results used for diagnosis. Comorbidities: Associated chronic conditions and their management (e.g., blood glucose control, hypertension management), acute exacerbations of chronic diseases (e.g., acute left heart failure, chronic kidney failure). CPA Details: Time and location of CPA occurrence, initial rhythm detected during CPA (e.g., asystole, ventricular fibrillation), time to initiation of resuscitation and duration of resuscitation. Treatment and Interventions: Pre-CPA interventions (e.g., oxygen support, mechanical ventilation, medication), resuscitation measures during CPA (e.g., defibrillation, CPR, medication). Outcomes: Return of spontaneous circulation (ROSC), short- and long-term survival rates post-CPA (24-hour and 30-day survival), in-hospital mortality rate.

Statistical Analysis

Data analysis was performed using SPSS version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), while categorical variables were presented as frequencies and percentages. Categorical variables were analyzed using the chi-square test or Fisher's exact test. Continuous variables were analyzed using the independent t-test or Mann-Whitney U test. Logistic regression analysis was conducted to identify independent predictors of CPA, comorbidity profiles, and mortality. A p-value of <0.05 was considered statistically significant.

Results

Descriptive statistics

The average age of the participants was calculated as 79.67 ± 8.99 years. The age range varies between 65 and 95 years. The median age was determined as 79.5 years. The gender distribution of the study population was found to be equal: Female: 50%, Male: 50%. The distribution of comorbidities included hypertension (52.6%), diabetes mellitus (46.8%), COPD (40.2%), cardiovascular disease (35.4%), and malignancy (25.6%). Emergency department admission complaints were chest pain (35.4%), shortness of breath (34.2%), and loss of consciousness (30.4%)(Table 1).

Table 1. Demographics and comorbidities of patients.

Variable	Value
Mean age (years)	79.67 ± 8.99
Age range	65 - 95
Gender (Female/male)	50% / 50%
Hypertension	52.6%
Diabetes Mellitus	46.8%
COPD	40.2%
Cardiovascular disease	35.4%
Malignancy	25.6%

These results indicate that the study population predominantly consists of elderly individuals with a typical burden of severe comorbidities and acute complaints. Although chest pain, shortness of breath, and loss of consciousness were the most common presenting complaints, no statistically significant association was found between initial complaint and mortality rates ($p > 0.05$). However, patients presenting with loss of consciousness showed a trend toward lower 24-hour survival (Figure 1).

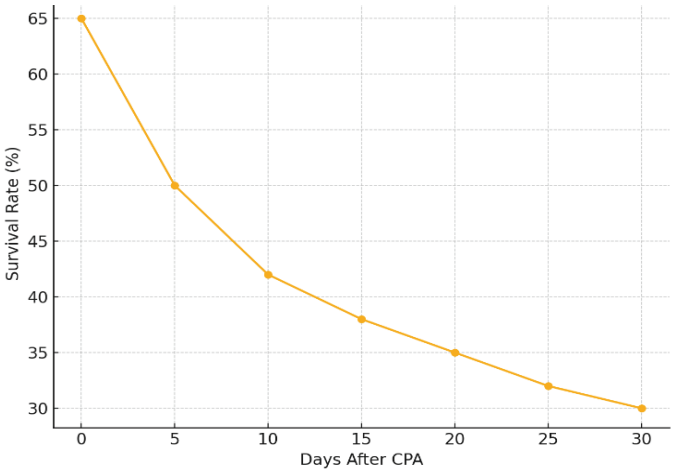

Figure 1. Comparison of 24-hour survival rates according to initial presenting complaint. Although no statistically significant association was found between presenting complaint and mortality ($p > 0.05$), patients presenting with loss of consciousness demonstrated a trend toward lower 24-hour survival.

Analysis of factors associated with cardiopulmonary arrest (CPA)

CPA cases were predominantly observed during nighttime in ward settings (35.0%), followed by the intensive care unit (33.4%), and daytime ward (31.6%). Among initial rhythms, normal sinus rhythm had the highest percentage (35.0%), followed closely by asystole (33.8%) and ventricular fibrillation (31.2%). Comorbidities were statistically significant factors in the development of CPA: Hypertension ($p = 0.001$), Diabetes Mellitus ($p = 0.005$), COPD ($p=0.003$), Cardiovascular Disease ($p = 0.008$), and Malignancy ($p = 0.015$). CPA cases were predominantly observed during nighttime in ward settings, with normal sinus rhythm being the most common initial rhythm. Comorbidities such as hypertension and COPD showed a strong association with CPA occurrences.

Resuscitation and intervention methods analysis report

Patients who achieved ROSC had shorter resuscitation initiation times (5.06 ± 2.75 minutes vs. 5.60 ± 2.88 minutes). Resuscitation duration for patients who achieved ROSC was 16.69 ± 7.85 minutes compared to 17.06 ± 7.69 minutes for those who did not achieve ROSC. Oxygen support ($p = 0.002$) and mechanical ventilation ($p = 0.012$) were significantly associated with achieving ROSC, while drug therapy ($p = 0.090$) was not. Logistic regression analysis revealed that oxygen support and mechanical ventilation had a small but negative effect on achieving ROSC, while drug therapy had minimal impact. These findings highlight the importance of the timing and effectiveness of interventions in achieving ROSC success.

Survival and mortality analysis estimated results

The 24-hour survival rate was 65% ± 10, while the 30-day survival rate was 45% ± 10. The in-hospital mortality rate was found to be 55% ± 10. Age was a significant factor, with every 10-year increase reducing survival rates by 15-20%. Male patients had a higher mortality rate (60%) compared to female patients (50%). Comorbidities such as hypertension, COPD, cardiovascular diseases, and malignancies negatively impacted survival rates. Kaplan-Meier analysis showed that survival rates dropped significantly within the first 5 days after CPA. Cox regression analysis showed that hypertension (1.30), COPD (1.35), and malignancy (1.50) significantly increased the risk of mortality. Early interventions and aggressive management of comorbidities were emphasized as critical for improving survival outcomes. (Table 2).

Table 2. Survival rates after CPA.

Outcome	Rate
24-Hour Survival	65% ± 10
30-Day Survival	45% ± 10
In-Hospital Mortality	55% ± 10

Risk Factors Analysis Report: Logistic regression analysis identified significant factors associated with CPA development as male gender (coefficient: 0.1958), cardiovascular disease (0.1222), hypertension (0.0602), and diabetes mellitus (0.0549). Advanced age had a limited impact (coefficient: -0.0037). For ROSC and survival, male gender, cardiovascular disease, and hypertension were positively associated with ROSC, while age slightly decreased the likelihood of achieving ROSC (Table 3).

Table 3. Factors significantly affecting CPA.

Factor	p
Hypertension	0.001
Diabetes Mellitus	0.005
COPD	0.003
Cardiovascular disease	0.008
Malignancy	0.015

Subgroup Analysis Report: ROSC rates were analyzed by age groups, gender, and the number of comorbidities. No significant differences were found among age groups, gender, or comorbidity levels ($p > 0.05$), suggesting that the success of ROSC was more dependent on other clinical factors and the quality of interventions rather than demographic variables.

Discussion

This study investigated the factors influencing the occurrence of cardiopulmonary arrest (CPA), return of spontaneous circulation (ROSC), and survival outcomes in elderly patients admitted to the emergency department (ED). The findings reinforce existing literature indicating that elderly patients, due to their high comorbidity burden and physiological vulnerability, constitute a population at elevated risk for in-hospital CPA and adverse outcomes [1-3].

Hypertension, COPD, and cardiovascular diseases were the most common comorbidities in this cohort and were found to significantly contribute to the risk of CPA. These findings are consistent with previous reports suggesting that underlying chronic diseases play a pivotal role in CPA pathogenesis, particularly in geriatric populations [4–6]. Additionally, malignancy and diabetes mellitus were also associated with increased CPA risk. As supported by Bonnesen K et al. [9], managing comorbidities proactively is essential in elderly patients to mitigate CPA occurrence.

Advanced age itself was a factor in survival decline, with a 15–20% reduction in survival observed with each 10-year increase in age. This aligns with Zanders R et al. [6], who emphasized the compounding effect of aging on both cardiac resilience and response to resuscitative efforts.

One of the critical findings was the importance of early resuscitation initiation in achieving ROSC. Patients who attained ROSC had shorter times to the initiation of CPR. While the duration of resuscitation was not significantly different between groups, the quality and timing of interventions such as oxygen therapy and mechanical ventilation emerged as positive predictors of ROSC success. This supports prior studies by Wang M et al. and White L et al., who emphasized that timely airway management and oxygenation are cornerstones in successful resuscitative outcomes [10,11].

Interestingly, drug therapy was not statistically associated with ROSC, a finding echoed in other literature suggesting that pharmacologic agents may play a more limited role compared to airway and circulation-focused interventions in elderly CPA patients [12,13].

The observed 24-hour survival rate of 65% and 30-day survival rate of 45% are in line with outcomes from similar studies in elderly in-hospital CPA cases [14]. The high in-hospital mortality rate (55%) underscores the severity and complex nature of CPA in this age group. Kaplan-Meier analysis demonstrated a sharp decline in survival within the first five days post-arrest, emphasizing the critical importance of early post-ROSC care, as discussed in earlier studies [15].

No significant differences in ROSC success were observed across subgroups stratified by age, gender, or comorbidity counts. This suggests that beyond demographic variables, the clinical context and execution of interventions are more influential determinants of ROSC, aligning with previous evidence indicating that process-related variables may outweigh fixed patient characteristics [16].

Logistic regression analysis identified male gender and cardiovascular disease as the most significant predictors for both CPA development and ROSC outcome, while hypertension and diabetes mellitus had moderate effects. Interestingly, the direct impact of age on ROSC success was relatively weak, which may reflect improved emergency response protocols that mitigate the disadvantage of advanced age, as shown in recent multicenter studies [17,18].

The findings of this study suggest that clinical efforts in elderly patients at risk of CPA should focus on: rigorous and proactive management of chronic conditions (especially hypertension, COPD, and cardiac disease), ensuring rapid initiation of resuscitation in the event of CPA, and optimizing the use of oxygenation and mechanical ventilation during resuscitative efforts. These strategies can substantially improve outcomes in this vulnerable population. Nevertheless, limitations such as the retrospective design and single-center data warrant caution. Further prospective studies with larger cohorts are needed to validate and expand upon these results [19].

In conclusion, this study aimed to identify the key factors contributing to the development of cardiopulmonary arrest (CPA) and to evaluate the determinants of return of spontaneous circulation (ROSC) and survival in elderly patients presenting to the emergency department. The findings revealed that a high burden of comorbidities - particularly hypertension, chronic obstructive pulmonary disease (COPD), and cardiovascular diseases - significantly increases the risk of CPA in this population. Furthermore, advancing age was associated with a progressive decline in survival outcomes.

Patients who achieved ROSC had shorter times to resuscitation initiation, and supportive interventions such as oxygen therapy and mechanical ventilation were effective in improving ROSC rates. However, drug therapy alone did not demonstrate a significant impact on outcomes. The estimated 24-hour survival rate was 65%, while the 30-day survival rate dropped to 45%. In-hospital mortality remained high at 55%. Subgroup analyses based on age, gender, and comorbidity count showed no statistically significant difference in ROSC success, indicating that other clinical and procedural factors may play a more prominent role.

Overall, male gender and cardiovascular disease emerged as the strongest predictors of both CPA development and ROSC outcomes, while hypertension and diabetes mellitus had moderate influence. Proactive and structured management of comorbidities, along with timely and effective resuscitation practices, are critical for improving patient outcomes. Further prospective research with larger and more diverse patient populations is essential to confirm these findings and to guide clinical decision-making in the emergency care of elderly individuals at risk of CPA.

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No funding was received for this study.

Conflicts of Interest

The author declares no conflicts of interest.

Ethical Approval

This study was approved by the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Approval No: E-10840098-202.3.02-765, Date: 24/01/2025)

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Research Article

Evaluation of the association between nomophobia, mindful eating, and nutritional status

Nomofobi, yeme farkindaliği ve beslenme durumu arasindaki ilişkinin değerlendirilmesi

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Abstract

Aim: The prevalence of nomophobia, defined as the fear of disconnecting from the mobile phone connection, has increased with the excessive use of mobile phones. Nomophobia is known to lead to various psychological problems such as low self-esteem, extroverted personality, social phobia, social anxiety and panic disorder, as well as unhealthy eating behaviors. For this reason, it is stated that it is important to raise awareness about the possible harms of excessive smartphone use and to inform all age groups.

Material and Methods: This study was conducted on university students between the ages of 18-30, who are smartphone users and whose smartphone usage time is at least 1 hour per day. Data were collected through face-to-face interviews with the participants using a questionnaire form. "24-hour Dietary Recall" was used to determine the daily nutrients consumption levels of the students; 'Nomophobia Questionnaire (NMP-Q)' was used to determine nomophobia levels; and 'Mindful Eating Questionnaire-MEQ' was used to evaluate eating awareness.

Results: The study included 622 participants (48.2% female; mean age: 19.2 ± 2.0 years). Higher nomophobia levels were significantly associated with lower mindful eating scores ($p < 0.001$), and a negative correlation was observed between the two variables. Additionally, it has been determined that the energy coming from fat in individuals' daily energy intake is above the recommended levels and has an unbalanced distribution.

Conclusion: This study revealed that increased nomophobia levels in university students are associated with decreased eating awareness and unbalanced eating patterns. The findings indicate that smartphone addiction may have adverse effects on eating behaviors and that this relationship should be addressed more comprehensively in terms of public health.

Keywords: eating habits, mindful eating, nomophobia, nutrition, smartphone addiction

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Öz

Amaç: Cep telefonu bağlantısından kopma korkusu olarak tanımlanan nomofobinin yaygınlığı, akıllı telefonların aşırı kullanımıyla birlikte artmıştır. Nomofobinin sağlıksız beslenme davranışlarına yol açtığı bilinmektedir. Bu çalışmanın amacı, üniversite öğrencilerinde nomofobi ve yeme farkındalığı arasındaki ilişkileri inceleyerek mobil cihaz bağımlılığının yeme farkındalığı ve beslenme durumu üzerindeki etkilerini anlamaktır.

Gereç ve Yöntemler: Bu çalışma, akıllı telefon kullanıcısı olan ve akıllı telefon kullanım süresi günde en az 1 saat olan 18-30 yaş aralığındaki üniversite öğrencileri üzerinde yürütülmüştür. Veriler, katılımcılarla anket formu kullanılarak yüz yüze görüşmeler yoluyla toplanmıştır. Öğrencilerin günlük besin tüketim düzeylerini belirlemek amacıyla "24 Saatlik Geriye Dönük Besin Tüketim Kaydı"; nomofobi düzeylerini belirlemek amacıyla 'Nomofobi Anketi'; yeme farkındalığını değerlendirmek amacıyla 'Yeme Farkındalığı Anketi' kullanılmıştır.

Bulgular: Çalışmaya 622 katılımcı (kadın %48,2; yaş ortalaması: 19,2 ± 2,0 yıl) katılmıştır. Daha yüksek nomofobi düzeyleri daha düşük yeme farkındalığı puanlarıyla anlamlı şekilde ilişkili bulunmuştur ($p<0,001$) ve iki değişken arasında negatif korelasyon gözlenmiştir. Ayrıca bireylerin günlük enerji alımlarında yağdan gelen enerjinin önerilen seviyelerin üzerinde olduğu ve dengesiz bir dağılıma sahip olduğu belirlenmiştir.

Sonuç: Bu çalışma, üniversite öğrencilerinde artan nomofobi düzeylerinin, azalan yeme farkındalığı ve dengesiz yeme düzenleriyle ilişkili olduğunu ortaya koymuştur. Bulgular, akıllı telefon bağımlılığının yeme davranışları üzerinde olumsuz etkileri olabileceğini ve bu ilişkinin halk sağlığı açısından daha kapsamlı bir şekilde ele alınması gerektiğini göstermektedir.

Anahtar Kelimeler: akıllı telefon bağımlılığı, beslenme durumu, internet bağımlılığı, yeme davranışı

Introduction

Nomophobia or NO MObile PHone Phobia, defined as the fear of disconnection from the mobile phone connection, is used to describe the psychological state experienced. The term Nomophobia was created according to the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria and labeled as "phobia of certain things" [1]. Although nomophobia is not included in the DSM-V criteria, it is recommended that nomophobia be included in the DSM-V criteria since it is thought that the incidence of nomophobia and the interest in nomophobia will increase accordingly [2]. Especially in the 21st century, the rapid increase in the use of and dependence on cell phones and other technological devices has increased the incidence of nomophobia. For this reason, it is emphasized that the public should be informed about nomophobia and the negative side effects of excessive use of mobile phones [3].

Excessive use of mobile phones, which has become widespread globally, can lead to various psychological problems such as low self-esteem, extroverted personality, social phobia, social anxiety, and panic disorder. Nomophobia is reported to show symptoms such as anxiety, respiratory irregularities, tremors, sweating, agitation, disorientation, and tachycardia [1,4]. Nomophobia is considered as a modern age phobia that has entered our lives as a by-product of interaction with smartphones. Nomophobia is a form of behavioral addiction to mobile phones and manifests itself as psychological and physical addiction symptoms. Given the negative effects of chronic mobile phone use, studies have generally focused on somatic effects [5].

It is reported that the prevalence of nomophobia is higher in women and young people. The prevalence of nomophobia varies between studies, ranging from 6% to 73%. This difference is due to differences in assessment criteria [6]. It is known that the prevalence of nomophobia is high especially among university students. It is usually seen at younger ages and is associated with anxiety-depression symptoms. In addition, it has been observed that the incidence of nomophobia is higher in individuals with high anxiety, hyperactivity and fear of loneliness [7]. Therefore, it is emphasized that nomophobia is a health problem that negatively affects the person, causing psychological problems, physical, and behavioral changes [8].

Nomophobia is associated with dietary behaviors. It has been reported that as nomophobia increases, daily consumption of meat, fish, eggs, vegetables, milk, and dairy products decreases [9]. In addition, smartphone addiction in individuals leads to some eating behavior disorders and obesity [10]. Smartphone addiction leads to an increase in body weight by affecting eating attitudes. The effect of eating behavior disorders on the emergence of smartphone addiction should be taken into consideration. Multidisciplinary

solutions are needed to prevent this addiction, which may increase over time. For this reason, it is recommended that dietary habits and lifestyle should also be taken into consideration for the prevention and development of an intervention for smartphone addiction among university students [11].

This study aims to understand the effects of mobile device addiction on eating awareness and nutritional status by examining the relationships between nomophobia and eating awareness in university students in detail. In particular, it is thought that investigating how healthy eating habits are affected by the increased use of smartphone and how eating awareness provides a balance against these effects will be a useful approach to improve both individual and public health.

Material and Methods

Study samples

This study was conducted on a total of 622 university students between November 2024 and February 2025. Participants who were continuing their education at the university, between the ages of 18-30, were smartphone users, had a smartphone usage time of at least 1 hour per day, did not have any psychological illness, and voluntarily agreed to participate in the study were included in the study.

Participants were selected on a voluntary basis among undergraduate students between the ages of 18-30 from different faculties and departments of the university. The settings in which the research will be conducted were determined as classrooms, laboratories or study rooms in the relevant departments of the university. Data were collected through face-to-face interviews with the participants using a questionnaire form. In order to protect the confidentiality of the participants, all data were kept anonymized and only accessible to the research team.

Tools

In the study, a questionnaire form created by the researchers and some scales were used. The sections in the questionnaire form and the scales to be used are given below.

General information: Demographic information of the participants was questioned.

Eating habits: The general eating habits and meal consumption status of the participants were questioned.

Smartphone usage habits: Participants were questioned about their smartphone usage habits.

Anthropometric measurements: Participants' height (cm) and body weight (kg) were questioned.

24-hour dietary recall: Through this form, the foods consumed by the individuals the day before and how much of these foods they consumed were questioned and recorded in detail through retrospective recall.

Nomophobia questionnaire (NMP-Q)

Nomophobia levels of the participants were measured with the Nomophobia Questionnaire (NMP-Q). The scale developed by Yıldırım and Correira [12] includes 20 items. It is a 7-point Likert-type scale based on self-report (1=strongly disagree, 7=strongly agree). A minimum of 20 and a maximum of 140 points can be obtained from the scale. At the end of the scale, 0-20 points range indicates no nomophobia, 21-60 points range indicates low level of nomophobia, 61-100 points range indicates moderate level of nomophobia, and 101-140 points range indicates high level of nomophobia. The scale has 4 sub-dimensions: inability to communicate, losing online connection, inability to access information, and sacrificing comfort.

Mindful eating questionnaire-MEQ

The Mindful Eating Questionnaire (MEQ) was used to assess participants' mindfulness of eating. The scale was developed by Framson et al., [13] to measure the quality of attention to eating. Its adaptation into Turkish was conducted by Köse et al., [14] in 2016. The scale consists of 30 questions and 7 sub-factors in total and each question is scored between 1-5. The sub-factors of the scale are; Mindless Eating, Emotional Eating, Eating Control, Awareness, Eating Discipline, Conscious Eating and Interference. While the minimum score that can be obtained from the scale is 30, the maximum score is 150 [14].

Statistical Analysis

SPSS 23.0 (IBM Corp., Armonk, NY) package program was used for statistical analyses. Descriptive statistics are presented as frequency (n), percentage (%), mean, standard deviation (SD), median and interquartile range (IQR). The assumption of normal distribution was checked by Shapiro Wilk test. In the analysis of the difference between the measurements of two independent groups, the Mann-Whitney U, and the Independent T Test was used. Spearman correlation test and Pearson correlation test were used to determine the relationships between continuous variables. Significance $p < 0.05$ values were considered statistically significant.

Results

Table 1 presents the general characteristics of the participants. A total of 622 participants, 48.2% female, participated in the study. The mean age of the participants was 19.2 ± 2.0 years, and the

mean body mass index (BMI) was 23.9 ± 3.7 kg/m^2. The average daily screen time was determined to be 5.62 ± 1.62 hours, and the majority of participants (96.5%) used a smartphone, 2.4% used a tablet, and 1.1% used a computer. Device use while eating was quite common, with 91.0% of participants reporting using a device. The total mean score of the nomophobia scale was 75.7 ± 32.3. When the distribution of nomophobia levels was examined, it was found that 7.7% of the participants had no nomophobia, 19.0% had low, 40.7% had moderate, and 32.6% had high levels of nomophobia. The total mean score of the eating consciousness scale was 130.1 ± 32.3. Statistically significant differences were found between the mean eating awareness scale scores of the participants according to their level of nomophobia; it was observed that the mean eating awareness scale scores decreased as the level of nomophobia increased (p<0.001) (Figure 1). In addition, a negative significant relationship was found between the nomophobia scale score and the eating awareness scale score (p < 0.001) (Figure 2). Table 2 shows the participants' daily energy and macronutrient intakes. The mean daily energy intake was 2059.1 ± 469.2 kcal; the energy proportions from carbohydrates, protein, and fat were 45.8 ± 8.1%, 14.0 ± 2.8%, and 40.2 ± 8.0%, respectively.

Table 1. Demographic characteristics of the study group.

Variables	(n=622)
Age, years	19.2 ± 2.00
Female, n(%)	300 (48.2%)
Body mass index, kg/m2	23.9 ± 3.70
Average screen usage time, hours	4.62 ± 1.62
Most used technological device, n(%)	
Phone	600 (96.5%)
Tablet	15 (2.4%)
Computer	7 (1.1%)
Use of devices during meals, n(%)	566 (91.0%)
Device use while consuming snacks, n(%)	567 (91.2%)
Monitoring of food amount while using the device, n(%)	138 (22.2%)
Change in eating habits if device is not used, n(%)	530 (85.2%)
Device use extends meal time, n(%)	530 (85.2%)
Smoking, n(%)	101 (16.2%)
Average Nomophobia scale score	75.7 ± 32.30
Nomophobia level, n(%)	
None	48 (7.7%)
Low	118 (19.0%)
Medium	253 (40.7%)
High	203 (32.6%)
Average eating awareness scale score	130.1 ± 32.30

Data are given as mean ± standard deviation or percentage [n (%).

Table 2. Evaluation of daily energy and macronutrient consumption of study groups.

Variables	(n=622)
Energy (kcal)	2059.1 ± 469.20
Carbohydrate (g)	162.6 ± 63.60
Carbohydrate (%TE)	45.8 ± 8.10
Protein (g)	70.4 ± 20.10
Protein (%TE)	14.0 ± 2.80
Fat (g)	154.3 ± 89.90
Fat (%TE)	40.2 ± 8.00
Fiber (g)	26.1 ± 8.30

Data are given as mean ± standard deviation or percentage [n (%). TE; total energy.

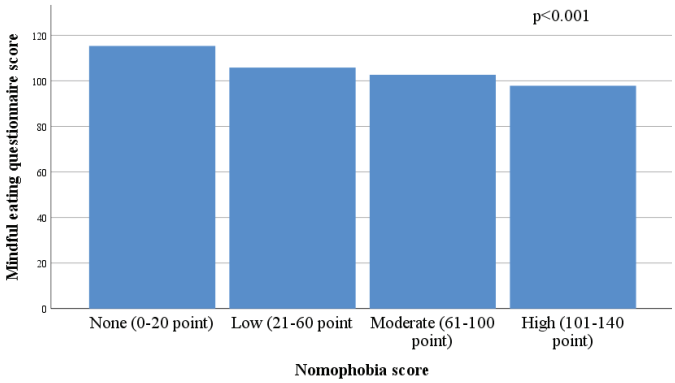

Figure 1. Average eating awareness scale score according to nomophobia levels

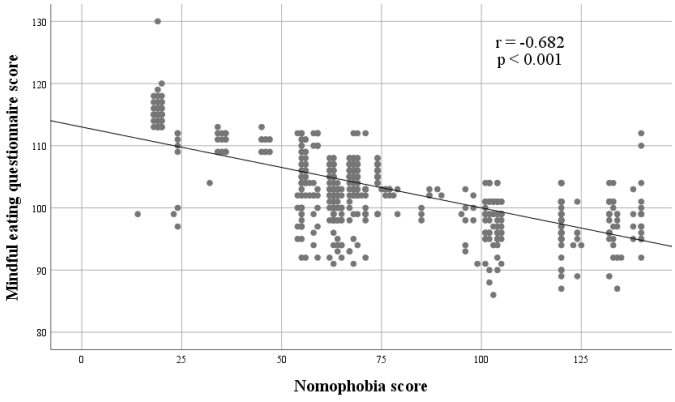

Figure 2. Correlation of nomophobia scores and eating awareness scale scores

Discussion

Smartphone addiction is reported to be associated with eating disorders, body weight and obesity. For this reason, it is stated that it is important to raise awareness about the possible harms of excessive smartphone use and to inform all age groups. Especially in university students, it is important to increase participation in sports and art activities that can be beneficial for

their mental, social and physical health and to encourage young people to establish face-to-face social relationships [15]. The aim of this study is to examine the possible relationship between nomophobia, eating habits, and eating awareness in university students. University students who agreed to participate in the study were questioned about their eating habits, mobile device usage habits, and 24-hour Retrospective Food Consumption Record. In addition, "Nomophobia Questionnaire (NMP-Q)" developed by Yıldırım and Correira in 2015 and "Mindful Eating Questionnaire (MEQ)" developed by Framson et al., were used.

In a study conducted by Farooqui et al., among medical students, 17.9% of students had mild nomophobia, while 60% had moderate nomophobia and 22.1% had severe nomophobia [16]. Dixit et al., reported that the prevalence of nomophobia in university students in India was 18.5% [17]. In a systematic review of 370 articles, Notara et al., emphasized that nomophobia was observed in 15.2%-99.7% of the participants and psychological, emotional, social, and physical side effects were observed due to excessive smartphone use [18]. In this study, more than half of the participants were found to have moderate (40.7%) and high (32.6%) levels of nomophobia, 7.7% had no nomophobia, and 19.0% had low nomophobia. These results are parallel to those in the literature and show that smartphone addiction is widespread among students in Turkey.

Rahme et al., reported that 1089 (48.3%) of the participants had moderate nomophobia, while 349 (15.5%) exhibited severe nomophobia. Higher hyperthymic temperament was associated with less nomophobia, while higher irritable temperament was associated with more nomophobia 19. In addition, it was found that reward addiction was positively associated with "Smartphone Addiction" and "Loss of Control" factors in nomophobia [19].

Nomophobia and feeding behaviors are closely related. Jahrami et al., reported a relationship between nomophobia and eating addiction. It was observed that Body Mass Index (BMI) and restricted eating attitude increased as smartphone addiction increased [20]. In a study conducted in Brazilian university students, smartphone addiction was found to be associated with eating disorders, bulimic behavior and social pressure to eat in the general eating disorders classification [21]. In this study, eating awareness, which expresses the level of consciousness and attention of individuals when eating, was evaluated, not eating disorders directly. The results showed that eating awareness scores decreased as the level of nomophobia in individuals increased. Decreased eating awareness can be associated with an increased risk of eating disorders. When evaluated from this perspective, low eating awareness scores in individuals with high levels of nomophobia in the study may cause negative changes in eating behaviors and an increased risk of eating disorders.

Yılmaz et al., investigated the effects of problematic internet and smartphone use on nutritional behaviors and abnormal body weight status in university students. It was observed that there was a negative relationship between nutritional behaviors and problematic internet and smartphone use. It was found that individuals with smartphone addiction consumed less cereals, fruits, and vegetables [22]. Similarly, this study determined that individuals' daily energy intake from fat was above the recommended levels. This finding shows that an adverse change in diet quality due to smartphone use is effective in food consumption and macronutrient distribution, providing important findings supporting the relationship between technology addiction and dietary patterns. It is also reported that nomophobia affects diet and meal timing. Especially, this is an important risk factor for obesity. It is reported that individuals with smartphone addiction have a higher BMI. It has also been observed that as the rate of addiction increases, the BMI increases [23].

Çelik et al., reported that problematic internet use is significantly associated with eating disorders. It is stated that long-term smartphone use leads to more fast-food consumption and triggers unhealthy eating habits [24].

Smartphone addiction is considered as a possible risk factor for eating disorders, obesity, and overweight. Considering that smartphone use is increasing and will increase over time, it is recommended that smartphone use should be taken into consideration to prevent obesity, which is an important public health problem [15]. It is reported that students with problematic internet usage lead an unhealthy lifestyle and show symptoms of depression and eating disorders more frequently. Increasing internet usage in young people may lead to eating disorders and unhealthy eating habits, as there are various contents that promote anorexia and bulimia in social media. Being overly preoccupied with the internet, neglecting sleep and ignoring negative emotions while online are seen as important predictors of eating disorders [25].

In conclusion, this study has shown that as the level of nomophobia increases in university students, eating awareness decreases, and unbalanced patterns are seen in eating habits. It is thought that nomophobia can negatively affect healthy eating behaviors by negatively affecting

individuals' attention at the time of eating, which can lead to undesirable changes in eating behaviors in the long term. The data obtained from the study show that phone addiction can also affect eating behaviors. Therefore, it is important to address the relationship between phone addiction and eating patterns more comprehensively and to develop preventive public health strategies in this regard.

Conflict of Interest

The authors have no conflict of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethical Approval

This study was approved by Suleyman Demirel University Health Sciences Ethics Committee Subcommittee with the letter dated 05/11/2024, numbered 09/83. All stages of the study were conducted within the framework of ethical rules.

Authors contributions

Concept: AK,KT; Supervision: AK,MY.; Materials: AK,MY; Data: AK,MY; Analysis: KT, AK; Literature search: MY,KT; Writing: KT,AK, MY; Critical revision: AK,KT.

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Research Article

The cluster of differentiation 47 expression in rectal cancer and efficacy of neoadjuvant therapies

Rektal kanserde farklılaşma kümesi 47 ekspresyonu ve neoadjuvan tedavilerin etkinliği

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Abstract

Aim: To investigate the relationship between CD47 expression levels, clinicopathological features, and survival in rectal cancer.

Material and Methods: It was designed as a retrospective case-control study. CD47 was analyzed in tumor tissue from patients with stage II and III rectal cancer who received neoadjuvant treatment. Patients were classified as negative, low, or high based on the CD47 H score. The pathological features of the disease, responses to neoadjuvant treatment, and overall survival were examined in relation to CD47.

Results: There were CD47 negative (n = 19, 31%), low (n = 18, 30%), and high (n = 24, 39%) patients. CD47 positivity was more common in female patients (p = 0.023). No significant differences were observed between the groups regarding relapse (p = 0.822), tumor location (p = 0.379), T stage (p = 0.360), preoperative lymph node status (p = 0.332), tumor grade (p = 0.801), perineural invasion (PNI) (p = 0.160), lymphovascular invasion (LVI) (p = 0.294), budding (p = 0.043), CEA level (p = 0.413), neoadjuvant treatment type (p = 0.650), T downstaging (p = 8.39), N downstaging (p = 0.530), surgery type (p = 0.717), pathological complete response (p = 0.747), tumor regression score (p= 0.836), positive surgical margin (p = 0.309), or (p = 0.028). The 5-year OS was 88% for patients with negative CD47, 74% for those with low CD47, and 57% for high CD47 (p=0.035).

Conclusion: Pretreatment CD47 score is important in terms of survival and prognosis in rectal cancer. The function of CD47 is more complex and needs to be further studied.

Keywords: rectal cancer, CD47, prognosis, survival

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Öz

Amaç: Rektum kanserinde CD47 ekspresyon düzeyinin klinikopatolojik özellikler ve sağkalım ile ilişkisini araştırmak.

Gereç ve Yöntemler: Retrospektif bir vaka-kontrol çalışması olarak tasarlandı. CD47 ekspresyonu, neoadjuvan tedavi alan evre II ve III rektum kanseri hastalarının tümör dokusundan çalışıldı. Hastalar CD47 H skoruna göre negatif, düşük veya yüksek olarak kategorize edildi. Hastalığın patolojik özellikleri, neoadjuvan tedaviye yanıtlar ve genel sağkalım CD47 ile ilişkili olarak incelendi.

Bulgular: CD47 negatif (n = 19, %31), düşük (n = 18, %30) ve yüksek (n = 24, %39) hastalar vardı. CD47 pozitifliği kadın hastalarda daha sıktı (p = 0.023). Gruplar arasında nüks (p = 0.822), tümör lokalizasyonu (p = 0.379), T evresi (p= 0.360), preoperatif lenf nodu durumu (p=0.332), tümör gradesi (p = 0.801), perinöral invazyon (PNİ) (p = 0.160), lenfovasküler invazyon (LVİ) (p = 0. 294), tomurcuklanma (p=0.043), CEA düzeyi (p = 0.413), neoadjuvan tedavi tipi (p=0.650), T evre azalması (p = 8.39), N evre azalması (p = 0.530), cerrahi tipi (p = 0.717), patolojik tam yanıt (p = 0.747), tümör regresyon skoru (p=0.836), pozitif cerrahi sınır (0.309) (p = 0.028) bakımından anlamlı fark yoktu. 5 yıllık OS, negatif CD47 için %88, düşük CD47 için %74 ve yüksek CD47 için %57 idi (p = 0.035).

Sonuç: Tedavi öncesi CD47 skoru rektum kanserinde sağkalım ve prognoz açısından önemlidir. CD47'nin işlevi daha karmaşıktır ve daha fazla çalışılması gerekmektedir.

Anahtar Kelimeler: rektum kanseri, CD47, prognoz, sağkalım

Introduction

Approximately 5-10% of rectal cancer patients are diagnosed at a locally advanced stage. These individuals undergo multimodal treatments, including radiotherapy, chemotherapy, and surgical intervention [1,2]. Neoadjuvant treatment of rectum cancer involves chemoradiotherapy (CRT) or short-course radiotherapy. Total mesocolic excision is performed after neoadjuvant treatment [3,4]. In recent years, there has been a trend toward the preoperative administration of full-dose chemotherapy and CRT, characterized as total neoadjuvant treatment (TNT) [5]. There is still a need for additional evidence regarding tumor behavior. Personalized treatment planning that considers the patient's characteristics and the disease may improve treatment outcomes.

Increased expression of the Cluster of Differentiation 47 (CD47) has been observed in various tumors, including ovarian cancer, gastric cancer, lung squamous cell carcinoma, bladder cancer, and breast cancer[6-9]. Research indicates that CD47 levels are elevated in colorectal cancer (CRC) cells compared to non-neoplastic colonic mucosa [10-11]. However, the clinical significance of this situation has been a matter of curiosity.

CD47 is involved in multiple cellular functions, significantly influencing areas such as cell proliferation, apoptosis, adhesion, migration, and various immune responses [8]. CD47, which is present on tumor cells, plays a crucial role in helping these cells evade detection by the immune system, primarily by preventing macrophages from engulfing them. Understanding how this mechanism functions is crucial, as it reveals the strategies that cancer cells use to evade the immune system responses. CD47 expression in CRC has been associated with activation of various oncogenic pathways and an immune-intensive tumour microenvironment (TME).

The expression of genes associated with damage-related molecular patterns positively correlates with the CD47 levels expression. In tumors exhibiting high levels of CD47, there was a notable activation of key oncogenic pathways, including the transforming growth factor beta, angiogenesis, phosphoinositide 3-kinase, and mitogen-activated protein kinase [12]. Additionally, the expression levels of several adaptive immune checkpoint genes and the estimated presence of immune cells in the tumor microenvironment (TME) were significantly increased in tumors with high CD47 expression [12]. By focusing on this signal, we can potentially improve the efficacy of immunotherapies, enabling the immune system to better identify and eliminate tumor cells [13-15]. Multiple antibodies and CD47 inhibitors have been investigated, many of which are currently in clinical trials [16,17].

This study explored CD47 expression in patients with

locally advanced rectal cancer, assessing response rates to neoadjuvant therapy and its influence on survival. The investigation analyzed the correlation between CD47 expression, clinicopathological features, and clinical outcomes, aiming to determine its potential use in clinical practice.

Patients and Methods

Study Design and Sample

This investigation was structured as a retrospective, case control study based at a single center. The local ethics committee approved the study protocol (ethical approval#: 2025-02/19 on February 20, 2025). The research adhered to the ethical guidelines set forth in the Declaration of Helsinki. Given the study's retrospective nature and the anonymity of the data, written informed consent was not obtained from the participants.

The population for the study included all rectal cancer patients followed up at the tertiary oncology center from 2010 to 2022. Data for the research were sourced from the patients' medical records and the hospital's information system. The study's inclusion criteria were being 18 years of age or older, having stages II or III rectum cancer, and having neoadjuvant treatment. Conversely, the study excluded individuals under 18 years of age, those admitted with metastatic or stage I rectal cancer, and those with a second primary cancer. Additionally, patients whose clinical data were lost during follow-up, those who did not proceed with surgery after neoadjuvant treatment, and those with insufficient archived tumor tissue for immunohistochemical analysis were als. All patients were followed up at 3-6 month intervals in the Oncology Center outpatient clinics. Recurrences, metastases, and types of metastases were recorded during the follow-up visits. Overall survival (OS) was defined as the duration from a diagnosis of rectal cancer to either death or the most recent follow-up. Patients' TNM stages based on clinical and radiographic findings and after surgery based on the American Joint Committee on Cancer (AJCC) staging system, 8 th edition undergoing neoadjuvant treatmen [18]. Recurrences, metastases, and types of metastases were recorded during the follow-up visits. The time from rectal cancer diagnosis to death or the last follow-up was defined as overall survival (OS). Modified Ryan Grading system was used to evaluation of neoadjuvant treatment pathological response.

Immunohistochemical Study and Evaluation of CD47 Expressions

From blocks of patients who were diagnosed with rectum cancer, sections measuring 3 microns in thickness were sliced and placed onto adhesive-coated slides. Following this, the CD47 primary antibody (rabbit monoclonal, EPR21794, diluted 1:2000, from Abcam, Cambridge, UK) was used for incubation. To ensure staining accuracy, tissue samples were processed in conjunction with positive control tonsil tissue for CD47, and negative control liver tissue for CD47 was also incorporated into the study. All immunohistochemical staining procedures were carried out using the Roche Ventana Benchmark Ultra automated device, located in Tucson, AZ, USA. Pathologist then evaluated the stained slides. The intensity of CD47 expression was categorized as follows: 0 for none, 1 for weak, 2 for moderate, and 3 for strong staining. The staining extent was classified as: 0 = 0%, 1 = 1–19%, 2 = 20–50%, and 3 = more than 50%. The H-score for CD47 was computed in an identical manner and was grouped into three categories based on the H-score: negative (0), low (1–3 points), and high (4–6 points) (Figures 1a,b). [12].

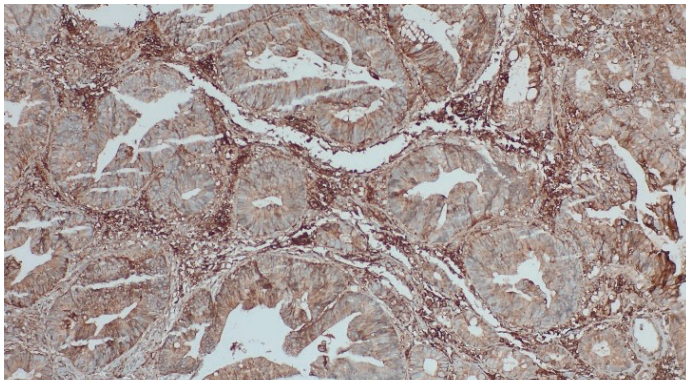

Figure 1A. CD47 positive rectal cancer.

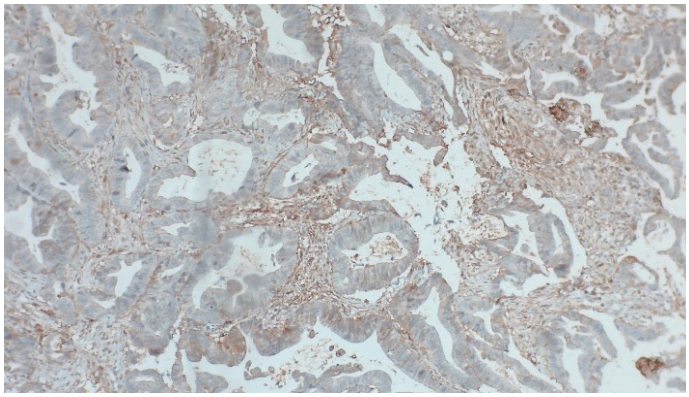

Figure 1B. CD47 negative rectal cancer.

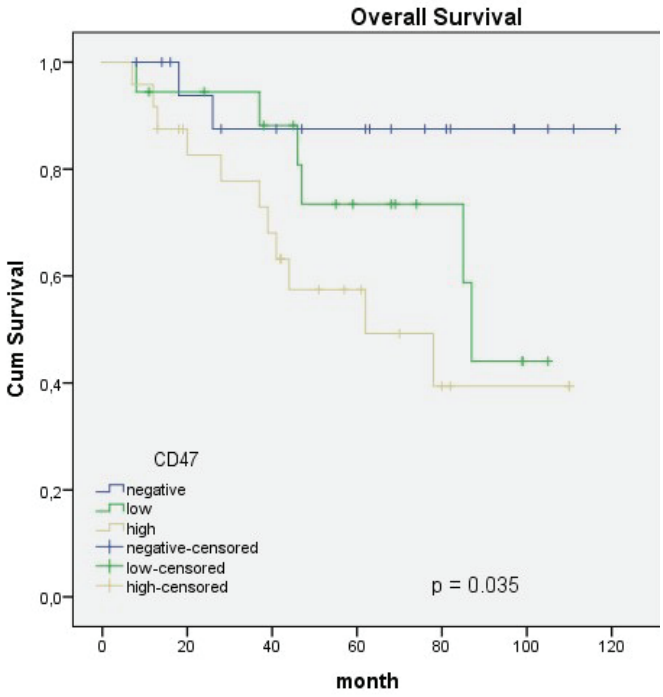

Figure 2. The Kaplan-Meier survival analysis with Log Rank test showing the survival outcomes

Statistical Analysis

Statistical analyses were performed utilizing the Statistical Package for Social Sciences (SPSS) version 23, developed by IBM SPSS Inc. in Chicago, IL, USA. To compare categorical variables, Pearson's chi-square test was used, while Fisher's exact test was applied when expected values were too low. Overall survival (OS) rates were estimated via the Kaplan–Meier approach, and differences in survival between groups were assessed using the log-rank test. For multivariate survival analyses, hazard ratios (HRs) alongside 95% confidence intervals (CIs) were determined through the Cox proportional hazard regression model. A statistical significance threshold was set at $p < 0.05$ for all tests.

Results

The study sample consisted of 61 consecutive non-metastatic rectal cancer patients, who were divided into three groups: CD47 negative (n = 19, 31%), low (n = 18, 30%), and high (n = 24, 39%). There were statistically significant differences between the groups in terms of gender (p = 0.023). CD47 positivity was more frequent in female patients. No significant differences were found between the groups in terms of relapse (p = 0.822), tumor localization (p = 0.379), T stage (p = 0.360), preoperative lymph node status (p = 0.332), tumor grade (p = 0.801), perineural invasion (PNİ) (p = 0.160), lymphovascular invasion (LVİ) (p = 0.294), budding (p = 0.043), CEA level (p = 0.413), neoadjuvant treatment type (p = 0.650), T downstaging (p = 0.839), N downstaging (p = 0.530), surgery type (p = 0.717), pathological complete response (p = 0.747), tumor regression score (p = 0.836), positive surgery margin (p = 0.309). Table 1 displays a comparison of the groups' characteristics.

When the effect of CD47 on OS was evaluated by the Kaplan-Meier test, 5-year OS was 88% for negative CD47, 74% for low CD47, and 57% for high CD47 (p = 0.035). Figure 2 shows the OS curves of the groups. In evaluating prognostic factors affecting OS, high CD47 levels were statistically significantly different in multivariate analysis (HR: 5.57, 95% CI: 1.25-26.58, p = 0.024). Table 2 shows the prognostic factors affecting OS.

Discussion

This study mainly focused on the prognostic effects of CD47 and demonstrated that high CD47 expression might be a marker of poor prognosis in locally advanced rectal cancer, independent of poor pathological features of the tumor.

Research indicates that CD47 expression is higher in CRC and metastatic lymph nodes than in normal tissue [19]. It was revealed that CD47 expression levels in CRC positively correlate with the activity of several oncogenic signaling pathways, including MAPK, PI3K, angiogenesis, and TGF-β. This suggests that various upstream oncogenic signaling pathways influence the transcriptional regulation of CD47, which in turn enhances downstream signaling pathways [20]. CD47 is reported to influence the tumor microenvironment by promoting M2 polarization and Tregs, contributing to the development of an immunosuppressive tumor microenvironment [21]. It is shown that high CD47 expression is associated with an increased amount of various types of immune cell infiltration into the tumor microenvironment. Regarding the CMS classification, CD47-high tumors exhibited a significantly greater proportion of CMS1 and CMS4 compared to CD47-low tumors. CMS1 is characterized by enhanced infiltration of cytotoxic T cells and NK cells, whereas CMS4 is characterized by increased infiltration not only of T cells but also of fibroblastic cells, endothelial cells, and myeloid cells [22].

Table 1. Clinicopathologic features of groups.

CD47	Negative n (%)	Low n (%)	High n (%)	p
Gender: Male Female	 17 (90) 2 (10)	 12 (67) 6 (33)	 12 (50) 12 (50)	0.023
Carcinoembryonic antigen Normal (<2.5 ng/ml) High	 11 (69) 5 (31)	 11 (85) 2 (15)	 12 (63) 7 (37)	0.413
Localization Middle Distal	 10 (53) 9 (47)	 9 (50) 9 (50)	 8 (33) 16 (67)	0.379
Grade 1 2 3	 4 (21) 12 (63) 3 (16)	 3 (33) 10 (56) 2 (11)	 9 (38) 13 (54) 2 (8)	0.801
Preop T stage T3 T4	 10(53) 9 (47)	 6 (33) 12 (67)	 8 (33) 16 (67)	0.360
Preop N stage N(-) N(+)	 6 (32) 13 (68)	 3 (17) 15 (83)	 9 (38) 15 (62)	0.332
Lymphovascular İnvasion No Yes	 18 (95) 1 (5)	 15 (83) 3 (17)	 23 (96) 1 (4)	0.294
Perinueral invasion No Yes	 15 (79) 4 (21)	 17 (94) 1 (6)	 17 (71) 7 (29)	0.160
Extracapsular extension No Yes	 17 (90) 2 (10)	 16 (89) 2 (11)	 23 (96) 1 (4)	0.661
Treatment Chemoradiotherapy Total Neoadjuvant Treatment	 11 (58) 8 (42)	 13 (72) 5 (28)	 16 (67) 8 (33)	0.650
Surgery Type Low anterior recestion Ab- dominoperineal resection	 14 (74) 5 (26)	 14 (78) 4 (22)	 16 (67) 8 (33)	0.717
T downstage No Yes	 7 (37) 12 (63)	 5 (28) 13 (72)	 8 (33) 16 (67)	0.839
N downstage No Yes	 7 (37) 12 (63)	 9 (50) 9 (50)	 8 (33) 16 (67)	0.530
Complete Response No Yes	 16 (84) 3 (16)	 16 (89) 2 (11)	 22 (92) 2 (8)	0.747
Regression Scor Grade 0 Grade1 Grade2 Grade3	 3 (16) 3 (16) 10 (52) 3 (16)	 2 (11) 3 (17) 9 (50) 4 (22)	 2 (8) 3 (12) 10 (42) 9 (38)	0.806
Surgical Margine Negative Positive	 18 (95) 1 (5)	 16 (89) 2 (11)	 19 (79) 5 (21)	0.309
Relaps No Yes	 15 (79) 4 (21)	 13 (72) 5 (28)	 17 (21) 7 (29)	0.822

Table 2. The The prognostic factors affecting overall survival.

Variable	N (%)	5 year OS (%)	p value	HR (65% CI)	p value
CD47					
Negative	19 (31)	88	0.035	1	
Low	18 (30)	74		3.47 (0.69-17.34)	0.129
High	24 (39)	57		5.57 (1.25-26.58)	0.024
Gender					
Male	41 (67)	72	0.059		
Female	20 (33)	49			
Carcinoembryonic antigen Normal (<2.5 ng/ml)	40 (85)	68	0.337		
High	7 (15)	86			
Localization					
Middle	27 (44)	69	0.844		
Distal	34 (56)	68			
Grade					
1	16 (28)	81	0.133		
2	35 (60)	62			
3	7 (12)	67			
Preop N status					
Negative	18 (30	82	0.208		
Positive	43 (70)	67			
Treatment					
Chemoradiotherapy	40 (66)	72	0.945		
Total Neoadjuvant Treatment	21 (34)	72			
T downsstage					
No	20 (33)	58	0.048		
Yes	41 (67)	78			
N downstage					
No	24 (39)	72	0.901		
Yes	37 (61)	71			
Complete Response		70			
No	54 (89)	100	0.272		
Yes	7 (11)				
TM regression					
Grade 0	7 (11)	100			
Grade 1	9 (15)	67	0.569		
Grade 2	29 (48)	72			
Grade 3	16 (26)	57			
Surgical Margine					
Negative	53 (87)	71	0.244		
Positive	8 (13)	58			

Oh H et al. examined how CD47 expression affects the oncogenic traits of CRC and its importance for CRC patient prognosis. [23]. The expression of CD47 showed a significant correlation with PNI, LVI, cellular differentiation, cancer staging, the depth of invasion, lymph node metastasis, and distant metastasis. Tian OS et al. conducted a study examining the connection between CD47 expression levels and various clinical and pathological factors in colon cancer tissues. These factors comprise gender, age at diagnosis, T stage, N stage, and the overall TNM stage [24]. CD47 expression was significantly linked to both N stage and overall clinical stage of the disease, but not to sex, age, or T stage. While the immune system serves as the primary defense against tumors, an inflammatory cell-rich microenvironment may eventually aid tumor development. This scenario is often linked to unfavorable clinical outcomes. In our study, there were no differences in clinicopathological characteristics between the groups, as we examined a selected, limited cohort with locally advanced disease. Furthermore, methodological differences in assessing CD47 may also be associated with varying results.

In colon cancer, a significant correlation was found between CD47 and immune cell infiltration around the tumour. The potential role of this in supporting the speculation that CD47 contributes to tumour escape from the immune system by promoting a dysfunctional T-cell environment [25]. Spatial profiling indicated increased infiltration of myeloid cells and a shift in macrophage populations from pro-inflammatory to immune-suppressive subsets, accompanied by the upregulation of the CD47/SIRPα axis. This shift highlights the role of CD47 in creating an immunosuppressive tumor microenvironment [26]. Literature includes studies that question the effect of CD47 on survival in colorectal cancer patients. In one study, CD47 positivity was linked to short relapse-free survival. However, in a multivariate analysis that included factors such as T stage, N stage, and TNM stage, it did not appear as an independent factor affecting survival [19]. This difference in survival may be attributed to the adverse clinicopathological features associated with CD47 in tumors. Nonetheless, it has been proposed that CD47 facilitates CRC progression by promoting tumor cell apoptosis and angiogenesis, resulting in low survival rates among these patients [23]. It showed that CD47-positive CRCs had poor survival [27,28]. However, there are also studies in the literature that support the opposite view [20,24]. Our study indicates that elevated CD47 expression correlates with a poorer prognosis. In a multivariate analysis incorporating tumor clinicopathological characteristics, it was identified as an independent factor influencing overall survival. While there was no statistical link between neoadjuvant treatment response and CD47 expression, none of the patients exhibiting high CD47 levels achieved a pathological complete response. This clinical finding implies that CD47 positivity may contribute to treatment resistance, leading to a reduced survival. There is a pressing need for innovative treatment strategies that can modify the tumor microenvironment and enhance treatment responses in the neoadjuvant therapy for CD47-positive locally advanced rectal cancer, potentially leading to improved survival outcomes.

It showed that the microenvironment of the primary tumor and the microenvironment of metastasis may differ in CRCs, which may contribute to the heterogeneity of the disease. [24]. This inconsistency might stem from variations in study methodologies and samples, along with the specific characteristics of the subjects studied. Therefore, further research is essential to explore the specific mechanisms by which CD47 impacts various cancer types and how patient prognosis might be enhanced through the regulation of CD47 expression.

It is important to recognize the limitations of this study. The retrospective design and potential selection biases should be taken into account. The number of patients who received TNT is small, and the observation period for this group is short. Additionally, the study does not specify the percentages of molecular subtypes of rectal tumors.

In conclusion, this study showed that pretreatment CD47 score is significant for survival and prognosis in rectal cancer patients. However, the literature's findings on the relationship between CD47 expression and prognosis are inconsistent and contradictory. This indicates that the role of CD47 is more complex and requires further investigation.

Competing interests

The authors have no conflict of interest to disclose.

Funding

The authors confirm that this is a self-funded study.

Ethics Approval and Consent to Participate

The present study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Sivas Cumhuriyet University on November 16, 2023 (permit # 2023-11/12)

Availability of data and materials

The datasets are available from the corresponding author upon reasonable request.

Authors' contributions

MU: Conceptualization, Methodology, Writing- Original draft preparation; MY: Data curation, Writing- Original draft preparation, Validation; EE: Conceptualization, Methodology, Validation; BY: Writing- Reviewing and Editing, Supervision.

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Research Article

A retrospective study in patients with portal vein thrombosis

Portal ven trombozu olan hastalarda retrospektif bir çalışma

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Abstract

Aim: To investigate into the age, gender as well as the etiology of portal vein thrombosis in patients diagnosed with the illness.

Material and methods: The medical records of patients with portal vein thrombus (PVT), who referred to the internal medicine and gastroenterology policlinic at Dursun Odabaş Education and Research Hospital at the Faculty of Medicine in Yuzuncu Yil University between 01.01.2011 and 31.12.2013 were retrospectively analyzed.

Results: As a result of the screening within the context of various parameters, a mild dominance of males was observed (M/F = 39/31), The average diagnosis of the illness in males was found to be 47 within the context of the age; this score was 41 in females. More than one thrombophilic factors were determined in 26 patients and there was a known history of liver cirrhosis in 15 patients, as well as myeloprolifirative disease found in 16 patients. Besides these, 13 of the patients were diagnosed to have idiopathic PVT.

Conclusion: PVT should be taken into consideration in the middle and later age patients in the differential diagnosis of abdominal pain, and any underlying disease like liver cirrhosis or thrombophilia should certainly be investigated.

Keywords: Portal vein thrombosis, etiyology, age,gender

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Öz

Amaç: Bu çalışmada, portal ven trombozu tanısı almış hastalarda yaş, cinsiyet ve etiyoloji açısından değerlendirme yapılması amaçlanmıştır.

Gereç ve Yöntem: Yüzüncü Yıl Üniversitesi Tıp Fakültesi Dursun Odabaş Eğitim ve Araştırma Hastanesi İç Hastalıkları ve Gastroenteroloji polikliniğine 01.01.2011 ile 31.12.2013 tarihleri arasında başvuran portal ven trombozu (PVT) olan hastaların tıbbi kayıtları retrospektif olarak analiz edilmiştir.

Bulgular: Çeşitli parametreler çerçevesinde yapılan tarama sonucunda, erkeklerde hafif bir baskınlık olduğu gözlemlenmiştir (E/K=39/31). Hastalığın tanı aldığı yaş ortalaması erkeklerde 47, kadınlarda ise 41 olarak bulunmuştur. Yirmi altı hastada birden fazla trombofilik faktör tespit edilmiş, 15 hastada karaciğer sirozu öyküsü mevcutken, 16 hastada ise miyeloproliferatif hastalık saptanmıştır. Bunların yanı sıra, 13 hastada idiopatik PVT tanısı konulmuştur.

Sonuç: Orta ve ileri yaş hastalarda karın ağrısının ayırıcı tanısında PVT mutlaka göz önünde bulundurulmalı, altta yatan karaciğer sirozu veya trombofili gibi hastalıklar mutlaka araştırılmalıdır.

Anahtar Kelimeler: portal ven trombozu, etiyoloji, yaş, cinsiyet

Introduction

Portal vein thrombosis (PVT) is an uncommon medical condition and a significant cause of asymptomatic portal hypertension (PHT).(1) Numerous prothrombotic factors and local abdominal pathologies can contribute to the development of PVT. Therefore, understanding the age, gender, and etiological distribution of the disease is crucial for appropriate management and follow-up.

PVT results from thrombus formation in the main branch or intrahepatic branches (right or left) of the portal vein. It may also involve the splenic vein or superior mesenteric vein.(2) In some cases, it occurs in the absence of underlying liver disease, termed idiopathic PVT. Historically, PVT was often equated with extrahepatic portal vein obstruction (EHPVO).(1)

PVT is a leading cause of non-cirrhotic portal hypertension worldwide and accounts for approximately 30% of esophageal variceal bleeding and a significant portion of variceal hemorrhage in pediatric patients(3). The increased use of Doppler ultrasonography (Doppler USG) has led to a rise in diagnoses in recent years. The lifetime risk of developing PVT in the general population is estimated to be around 1% (4).

Over time, the recognized etiological spectrum of PVT has expanded. Many cases once deemed idiopathic have now been attributed to thrombophilic conditions or local predisposing factors—approximately 60% and 30%, respectively. Some patients may present with multiple prothrombotic factors. One study reported that 87% of PVT patients had at least one risk factor, including intra-abdominal inflammation (5).

Liver function is generally normal or near-normal unless cirrhosis is present. Elevated alkaline phosphatase (ALP) levels may be observed in portal hypertensive biliopathy. Liver size and weight tend to remain within normal limits, although regenerative nodules and atrophy may occur due to hepatocyte apoptosis and compensatory arterial vasodilation (6).

Material and Methods

Subjects

This retrospective cohort study was conducted at the Internal Medicine and Gastroenterology outpatient clinics of Dursun Odabaş Training and Research Hospital, Van Yüzüncü Yıl University, between January 2011 and December 2013. Ethical approval was obtained from the institutional review board.

Seventy adult patients diagnosed with PVT during the study period were included. Diagnosis was confirmed using clinical history, physical examination, complete blood count, liver function tests, evaluation of inherited and acquired thrombophilic markers, Doppler ultrasonography (USG), computed tomography (CT), and/or the presence of esophageal varices. Patients with no identifiable etiology were classified as idiopathic PVT.

Of the 70 patients, 16 (22.8%) had underlying chronic myeloproliferative disorders, 26 (37.5%) had one or more thrombophilic conditions, and 15 (21.4%) had pre-existing liver cirrhosis. Thirteen patients (18.3%) were categorized as idiopathic.

Statistical Analysis

Statistical analysis was performed using SPSS version 10.0.

Continuous variables were presented as mean and range; categorical variables were summarized as frequencies and percentages. For group comparisons, the Student's t-test was used for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. Pearson or Spearman correlation coefficients were calculated for associations. Categorical variables were compared using the Z test and Chi-square test. A p-value of <0.05 was considered statistically significant.

Results

A total of 70 patients diagnosed with PVT were evaluated based on clinical history, laboratory data, and ultrasonographic findings. Demographic, radiologic, and biochemical characteristics are summarized in the following sections.

Among the 70 patients, 31 (44.3%) were female with a mean age of 41.48 years, and 39 (55.7%) were male with a mean age of 47.33 years. The age difference was not statistically significant (p = 0.5) (Table1).

Myeloproliferative disorders—such as polycythemia vera, essential thrombocythemia, or chronic myeloid leukemia—were found in 16 patients (22.8%). Elevated ALP levels (>300 U/L) were found in 17 patients (24.2%) and elevated GGT levels (>60 U/L) in 20 patients (28.4%), with no statistically significant difference between them (p = 0.12) (Table2).

Five patients (7.1%) were previously diagnosed with diabetes mellitus (DM), which did not differ significantly from the general population rate (p = 0.07). Direct bilirubin levels were above 1 mg/dL in five patients (7.1%), but ALP and GGT elevations were more pronounced.

ALT levels were elevated in 16 patients (22.8%) and AST levels in 17 (24.2%), with comparable elevation rates among PVT patients (p = 0.01). CRP levels were elevated (>5 mg/L) in 31 patients (44.2%), attributed to acute inflammation in some and chronic PVT with secondary infection in others. (Table2)

In 26 patients (37.5%), at least one deficiency in Protein C, Protein S, or Antithrombin III was identified. Factor V Leiden mutation was evaluated in 29 patients and found to be absent in all. USG data from 60 patients showed that 31 (51.6%) had a portal vein diameter >12 mm, and 24 (40%) had a splenic vein diameter >10 mm.

Thrombus localization was as follows: 50 patients (71.4%) had isolated portal vein thrombosis; 4 (5.7%) had portal and superior mesenteric vein involvement; 1 (1.4%) had thrombus involving the portal, superior mesenteric, and splenic veins; and 4 (5.7%) had portal and splenic vein thrombosis (Table3).

Ultrasound imaging revealed splenomegaly (>12 cm) in 38 patients (63.3%) and hepatomegaly (>14 cm) in 14 patients (23.3%). Splenomegaly was significantly more frequent than hepatomegaly (p = 0.02) (Table 4).

Table 1. Demographic characteristics of the patients.

		Frequene	%		Mean	Std Deviation
Gender	Female	31	44.3	Age	41.48	13.28877
	Male	39	55.7		47.3333	17.52041
	Total	70	100			

Table 2. Laboratory values of the patients.

WBC	70	2.30	31.3	7.6043	4.59238
HB	70	7.7	20.4	13.1057	2.76074
HCT	70	23	62.5	39.2886	8.02938
AST	70	13	197	37.9429	34.61167
ALT	70	7	190	32.9571	30.47044
GLC	70	68	389	113.3286	55.10878
PLT	70	32	749	229.2714	161.48324
ALP	70	54	885	271.8857	161.3444
GGT	70	7	515	60.3143	79.34433
D.BIL.	70	0.1	25	0.75	3.06966
CRP	70	3	108	16.6857	25.43337

WBC: White blood cell count, HB: Hemoglobi, HCT:Hematocrit, AST: Aspartate aminotransferase, ALT:Alanine aminotransferase, GLC: Glucose, PLT: Platelet Count, ALP: Alkaline phosphatase, GGT:Gamma-glutamyl transferase, D.BIL: Direct bilirubin, CRP: C-reactive protein

Table 3. The location of thrombus.

	Frequency (n)	Percent(%)	Valid Percent(%)	Cumulative Percent(%)
PV	50	71.4	71.4	71.4
PV+SMV	4	5.7	5.7	77.1
PV+SMV+SV	1	1.4	1.4	78.6
PV+SV	4	5.7	5.7	84.3
SMV	1	1.4	1.4	85.7
SV	2	2.9	2.9	88.6
Non	8	11.4	11.4	100
Total	70	100	100	

PV; portal vein, SMV; superior mesenteric vein, SV; splenic vein

Table 4. Liver and spleen size.

	N	Minimum	Maximum	Mean	Std. Deviation
Spleen	38	13	26	17.9342	3.60212
Liver	25	12	21	17.12	2.22336

Discussion

This retrospective study investigated the etiological, demographic, and biochemical characteristics of 70 patients with PVT. PVT accounts for approximately 30–35% of cases of portal hypertension in adults. It may present with or without underlying liver disease and is associated with either acute or chronic thrombotic occlusion of the portal venous system. The estimated prevalence of primary PVT is between 1 and 9 per 100,000 population, and it can occur at any age (7).

Acute PVT may be asymptomatic or present with abdominal pain, fever, and symptoms of bowel ischemia(8). Without timely treatment, it may progress to intestinal necrosis and peritonitis. Chronic PVT may cause cavernous transformation and portal hypertension and is often discovered during the evaluation of hypersplenism or variceal bleeding (9). Portal cholangiopathy, a rare complication of chronic PVT, can result in cholestasis (10).

Etiologies of PVT include liver cirrhosis, myeloproliferative disorders, neonatal omphalitis or umbilical vein catheterization, localized abdominal inflammation, and inherited or acquired prothrombotic conditions. While some causes are genetic, PVT itself is not considered a hereditary disease. Idiopathic cases account for 20–40% of presentations (11,12).

Previous studies, including those by Rajani et al., have documented thrombophilic factors in 22%, myeloproliferative diseases in 11%, malignancies in 7%, infections in 8%, and idiopathic PVT in 40% of patients (11). Autopsy studies in Japan and Sweden found PVT incidences of 0.05% and 1%, respectively, indicating regional variation(.13)

In our study, 37.5% of patients had thrombophilic disorders, 21.4% had cirrhosis, 22.8% had myeloproliferative disease, and 18.3% were idiopathic. There was no significant sex or age difference. Non-invasive imaging such as Doppler USG, CT, and MRI effectively identified PVT and its complications. MRI is particularly useful in diagnosing portal cholangiopathy.

In acute PVT, differential diagnoses should include all causes of abdominal pain, while in chronic cases, portal hypertension of non-hepatic origin should be considered (14,15) Genetic counseling is advised in hereditary thrombophilia (16,17). Acute PVT treatment includes anticoagulation for 3–6 months and management of the underlying cause (18). Surgical intervention may be necessary in cases of bowel infarction (19,20).

Chronic PVT management focuses on treating complications of portal hypertension using beta-blockers, band ligation, sclerotherapy, TIPS, splenectomy, or portosystemic shunts (21,22).

Patients diagnosed early and treated appropriately have favorable outcomes, though prognosis depends on comorbidities and age (23). In our cohort, splenomegaly was more common than hepatomegaly. While liver enzymes were elevated in some patients, there was no significant difference between ALP and GGT. These elevations may reflect portal biliopathy from cavernous transformation.

Hepatic steatosis was detected in only 5 of 70 patients (8.3%), significantly lower than the estimated community prevalence (20–25%). This finding suggests that PVT patients may have a lower prevalence of hepatic steatosis.

Limitations of this study include its retrospective design, small sample size, and potential biases. Although data were collected over three years, only 70 eligible cases were analyzed.

In conclusion, portal vein thrombosis should be considered in the differential diagnosis of abdominal pain in middle-aged adults. Evaluation for underlying liver cirrhosis or hereditary thrombophilia is essential. Portal biliopathy appears to be a common cause of cholestasis in these patients. The observed lower prevalence of hepatic steatosis in PVT patients requires further prospective investigation.

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Research Article

Prognostic role of systemic immune-inflammation index in patients with nasopharyngeal cancer

Nazofarenks kanserli hastalarda sistemik immün-inflamasyon indeksinin prognostik rolü

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Abstract

Aim: This study aimed to evaluate the prognostic significance of the systemic immune-inflammation index (SII) in patients with nasopharyngeal carcinoma (NPC).

Material and Methods: This retrospective study included 42 patients diagnosed with NPC between January 2014 and January 2020. Clinical data, hematological parameters, and survival outcomes were collected. Disease stage was classified using the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System. Pre-treatment SII values were calculated using complete blood count data (platelets × neutrophils / lymphocytes).

Results: The mean patient age was 54.0 ± 13.8 years, with a male predominance (66.7%). Most patients presented with advanced disease (AJCC Stage III–IV). Higher pre-treatment SII values were significantly associated with poorer overall survival (OS) and progression-free survival (PFS). Multivariate Cox regression analysis confirmed that elevated SII independently predicted reduced OS (HR: 1.06; 95% CI: 1.02–1.09; $p < 0.001$). ROC analysis identified optimal SII cut-off values of >610 for OS (sensitivity: 73.9%, specificity: 60.0%) and >580 for PFS (sensitivity: 75.0%, specificity: 57.1%). Kaplan–Meier analysis demonstrated significantly lower OS and PFS in patients with elevated SII (log-rank $p < 0.001$).

Conclusion: Elevated SII is a strong and independent prognostic marker for poor outcomes in NPC patients and may guide personalized clinical management.

Keywords: nasopharyngeal carcinoma, systemic immune-inflammation index, prognosis, survival analysis, inflammation

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Öz

Amaç: Bu çalışmanın amacı, nazofarenks karsinomlu (NPC) hastalarda sistemik immün-inflamasyon indeksinin (SII) prognostik önemini değerlendirmektir.

Gereç ve Yöntemler: Bu retrospektif çalışmaya Ocak 2014 ile Ocak 2020 arasında NPC tanısı alan 42 hasta dahil edildi. Klinik veriler, hematolojik parametreler ve sağkalım sonuçları toplandı. Hastalığın evresi, Amerikan Kanser Ortak Komitesi (AJCC) Evreleme Sisteminin 8. baskısı kullanılarak sınıflandırıldı. Tedavi öncesi SII değerleri, tam kan sayımı verileri (trombositler × nötrofiller / lenfositler) kullanılarak hesaplandı.

Bulgular: Hastaların ortalama yaşı 54,0 ± 13,8 yıl olup, erkek hastalar çoğunluktaydı (%66,7). Hastaların çoğunluğu ileri evrede (AJCC Evre III-IV) tanı aldı. Yüksek tedavi öncesi SII değerleri, anlamlı olarak daha kötü genel sağkalım (OS) ve progresyonsuz sağkalım (PFS) ile ilişkili bulundu. Çok değişkenli Cox regresyon analizinde, artmış SII'nin bağımsız olarak azalmış OS'yi öngördüğü gösterildi (HR: 1,06; %95 GA: 1,02–1,09; $p < 0,001$). ROC analizi ile OS için optimal SII eşik değeri >610 (%73,9 sensitivite, %60,0 spesifisite), PFS için >580 (%75,0 sensitivite, %57,1 spesifisite) olarak belirlendi. Kaplan-Meier analizinde yüksek SII olan hastaların OS ve PFS süreleri anlamlı derecede düşük bulundu (log-rank $p < 0,001$).

Sonuç: Artmış SII, NPC hastalarında kötü prognozun güçlü ve bağımsız bir belirtecidir ve kişiselleştirilmiş klinik tedavi yönetiminde yol gösterici olabilir.

Anahtar kelimeler: nazofarenks karsinomu, sistemik immün-inflamasyon indeksi, prognoz, sağkalım analizi, inflamasyon

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant epithelial tumor of the nasopharynx with a distinct geographical distribution, particularly prevalent in East and Southeast Asia (1). It is also etiologically linked to Epstein–Barr virus (EBV) infection, and despite NPC's sensitivity to radiotherapy, a significant subset of patients still experience treatment failure. Indeed, up to one-third of NPC patients develop locoregional recurrence or distant metastasis after primary chemoradiotherapy, leading to poor survival outcomes (2). This variability in patient outcomes underlines the need for reliable prognostic biomarkers to improve risk stratification and guide individualized therapy in NPC (3).

Inflammation has increasingly been recognized as playing a pivotal role in cancer progression and metastasis (4). NPC is no exception: its tumor microenvironment is characterized by abundant inflammatory cell infiltration and elevated cytokine levels that promote tumor growth and spread (5). Consistent with this, clinical studies have shown that elevated systemic inflammation-based markers – such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) – are associated with worse survival in NPC patients (6-8). These findings suggest that the host's inflammatory response can significantly influence NPC progression and prognosis.

Among the various inflammation-related indices, the Systemic Immune-Inflammation Index (SII) has emerged as a novel composite prognostic indicator. SII is derived from peripheral blood neutrophil, platelet, and lymphocyte counts, reflecting the balance between host inflammatory response and immune status (9). High SII values have been linked to adverse outcomes in several solid tumors, and recent evidence indicates a similar prognostic impact in NPC. In fact, a meta-analysis of six studies found that NPC patients with an elevated pretreatment SII had significantly poorer overall and progression-free survival compared to those with low SII (10). This highlights SII as a promising candidate biomarker for risk stratification in nasopharyngeal carcinoma.

While previous research in Turkey has investigated the prognostic significance of SII in head and neck cancers, to our knowledge, no study has specifically addressed its role in Turkish patients with NPC cohorts. This study aimed to evaluate the prognostic role of the SII in patients with NPC.

Patients and Methods

This retrospective study was conducted on adult patients diagnosed with nasopharyngeal carcinoma who were followed at the Department of Otorhinolaryngology, Dicle University, between January 2014 and January 2020. The study was approved by the Dicle University Medical Faculty Ethics Committee for Non-Interventional Studies (25.09.2024 - No: 245) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision). The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

During the study period, a total of 96 patients followed

for NPC were retrospectively evaluated. Inclusion criteria included histopathologically confirmed NPC, receipt of either radiotherapy or chemotherapy, and availability of a complete blood count taken within two weeks prior to the initiation of treatment. All patients included in the study had a confirmed diagnosis of NPC, and their disease stage was classified using the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System, which is specifically adapted for nasopharyngeal carcinoma. Additionally, all patients received routine intensity modulated radiotherapy. Exclusion criteria were: histological types other than squamous cell carcinoma, a previous malignancy, autoimmune or chronic inflammatory diseases, acute infections, and insufficient clinical data. Forty-two patients who met the exclusion and inclusion criteria were included in the analyses.

Data collection

The hospital's electronic information system and patient files were used to gather demographic and clinical data. The collected variables encompassed age, gender, ECOG performance status, T and N classifications, overall stage, anthropometric data (height and weight), treatment strategy, and pre-treatment hematologic parameters including neutrophils, lymphocytes, platelets, and monocytes. NLR was defined as the ratio of the absolute neutrophil count to the absolute lymphocyte count, and PLR as the ratio of the platelet count to the lymphocyte count, both derived from complete blood count values. SII was determined using the formula: platelet count × neutrophil count ÷ lymphocyte count (all in 10^9/L).

All patients were evaluated over a 5-year follow-up period. Overall survival (OS) was defined as the time from diagnosis to the date of last follow-up or death from any cause. Progression-free survival (PFS) was defined as the time from diagnosis to disease progression or death.

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) software. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Variables with a normal distribution were presented as mean ± standard deviation (SD), whereas non-normally distributed variables were expressed as median and interquartile range (IQR: 25th–75th percentiles). Categorical variables were presented as counts and percentages. To evaluate the prognostic relevance of potential factors, univariate Cox regression analyses were conducted. Variables with $p < 0.25$ were subsequently entered into a multivariate Cox regression model with 95% confidence intervals (CIs). ROC curve analysis was performed to evaluate the prognostic accuracy of SII, and the optimal cut-off point was determined using the Youden index, which identifies the value with the highest combined sensitivity and specificity. Survival outcomes were analyzed using the Kaplan–Meier method, and differences between groups were assessed with the log-rank test. A p-value < 0.05 was considered statistically significant in all analyses.

Results

The study included 42 patients with a mean age of 54.0 ± 13.8 years, of whom 28 were men (66.7%) and 14 were women (33.3%). The mean body mass index was 25.5 ± 4.3. T1–T2 staging was observed in 35.7% of patients, and N0–N1 in 31%, with most patients classified within AJCC stage III–IV. A total of 45.2% of patients received adjuvant chemotherapy (Table 1). The mean OS was 31 months, and the estimated OS for 1-, 3- and 5-year was were 81%, 62%, and 43%, respectively.

Univariate Cox regression analysis identified age, N stage, overall stage, and SII as statistically significant factors associated with overall survival. An increase in age was associated with a 1.27-fold higher risk of mortality (HR: 1.27; 95% CI: 1.02–1.53; p = 0.016). Similarly, patients with N stage 2–3 had a significantly increased risk of death compared to those with N stage 0–1, with a 2.45-fold elevated hazard (HR: 2.45; 95% CI: 1.06–5.70; p = 0.037). Patients with AJCC stage III–IV disease had a 1.88-fold increased risk of mortality compared to those with stage I–II (HR: 1.88; 95% CI: 1.20–2.95; p = 0.031). Additionally, higher SII values were significantly associated with worse survival outcomes (HR: 1.07; 95% CI: 1.03–1.10; p < 0.001) (Table 1).

Multivariate Cox regression analysis revealed that age, overall stage, and SII remained independent predictors of mortality. Age remained significant (HR: 1.29; 95% CI: 1.04–1.61; p = 0.018), as did advanced stage disease (HR: 1.93; 95% CI: 1.16–3.22; p = 0.012). SII also retained independent prognostic value, with each unit increase conferring a 1.06-fold increase in mortality risk (HR: 1.06; 95% CI: 1.02–1.09; p < 0.001) (Table 2).

ROC analysis showed that the SII had moderate discriminative ability for predicting OS (AUC: 0.684; 95% CI: 0.566–0.802) with an optimal cut-off value >610, yielding 73.9% sensitivity and 60.0% specificity. For PFS, the AUC was 0.662 (95% CI: 0.548–0.775), with an optimal cut-off value >580, sensitivity of 75.0%, and specificity of 57.1%. Both analyses were statistically significant (p < 0.001) (Table 3).

Kaplan–Meier analysis demonstrated significantly reduced OS and PFS in patients with elevated SII. Patients with SII > 610 had significantly worse OS compared to those with SII ≤ 610 (HR = 1.8; 95% CI = 1.3-2.2; log-rank p < 0.001). Similarly, patients with SII > 580 showed significantly shorter progression-free intervals (HR = 1.6; 95% CI = 1.2-1.9; log-rank p < 0.001) (Figure 1).

Table 1. Characteristics of the study population and univariate analysis of factors associated with overall survival.

			Survival	Univariable Regression	
	Alive n = 22	Deceased n = 20	HR	95% CI	p
Age, years	50.4 ± 14.6	58.3 ± 13.6	1.27	1.02-1.53	0.016*
Gender, n (%)					
Female	8 (36.4)	6 (30.0)	ref		
Male	14 (63.6)	14 (70.0)	1.44	0.55-3.76	0.454
BMI, kg/ m2	25.1 ± 3.5	25.7 ± 4.6	1.05	0.85-1.16	0.347
T stage, n (%)					
1-2	10 (45.5)	7 (35.0)	ref		
3-4	12 (54.5)	13 (65.0)	1.36	0.54-3.42	0.509
N stage, n (%)					
0-1	9 (40.9)	4 (20.0)	ref		
2-3	13 (59.1)	16 (80.0)	2.45	1.06-5.70	0.037*
AJCC stage					
I-II	7 (31.8)	4 (20.0)	ref		
III-IV	15 (68.2)	16 (80.0)	1.88	1.20-2.95	0.031*
Adjuvant chemotherapy, n (%)	10 (45.5)	9 (45.0)	1.27	0.61-2.63	0.523
NLR	2.2 ± 0.8	2.5 ± 0.7	1.52	1.12-2.05	0.018*
PLR	226.2 ± 44.8	243.7 ± 61.9	1.05	1.01-1.10	0.035*
SII	539.6 ± 142.4	688.3 ± 153.8	1.07	1.03-1.10	<0.001*

The data are expressed as the mean ± SD or IQR (25th–75th percentiles).or n (%).* indicates statistical significance at p < 0.05. AJCC, American Joint Committee on Cancer; BMI, Body Mass Index; CI, Confidence Interval; HR, Hazard Ratio; NLR, Neutrophil-To- Lymphocyte Ratio; PLR, Platelet-To-Lymphocyte Ratio; ref, Reference Category; SII, Systemic Immune-Inflammation Index; T stage, Primary Tumor Stage; N stage, Nodal Stage

Table 2. Independent predictors of mortality.

Variables	Multivariable Regression		
	HR	95% CI	p
	1.29	1.04-1.61	0.018*
AJCC stage			
I-II	ref		
III-IV	1.93	1.16-3.22	0.043*
SII	1.08	1.02-1.13	<0.001*

* indicates statistical significance at p < 0.05. AJCC, American Joint Committee on Cancer; BMI, Body Mass Index; CI, Confidence Interval; HR, Hazard Ratio; NLR, Neutrophil-To-Lymphocyte Ratio; PLR, Platelet-To-Lymphocyte Ratio; ref, Reference Category; SII, Systemic Immune-Inflammation Index; T stage, Primary Tumor Stage; N stage, Nodal Stage

Table 3. The diagnostic performance of the Systemic Immune-Inflammation Index in predicting overall survival (OS) and progression-free survival (PFS).

ROC Curve findings	OS	PFS
Area under the curve	0.684	0.662
Standard error	0.060	0.058
95% Confidence interval	0.566–0.802	0.548–0.775
P -value	<0,001*	<0,001*
Threshold value	>610	>580
Sensitivity (%)	73.9	75.0
Specificity (%)	60.0	57.1

* indicates statistical significance at p < 0.05. S>II, Systemic Immune-Inflammation Index.

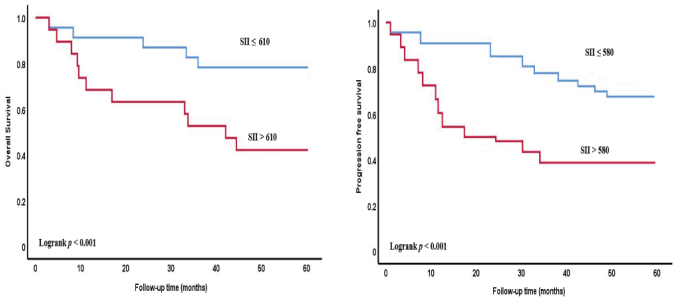

Figure 1. Axial magnetic resonance imaging (MRI) illustrating measurement of the interpeduncular angle (IPA).

The red lines indicate the angle formed between the medial aspects of the cerebral peduncles at the midbrain level.

Discussion

In this study, we found that an elevated pretreatment SII was associated with significantly poorer outcomes in NPC patients. Those with high SII values had lower OS and PFS rates compared to patients with low SII. Notably, our results indicate that SII can stratify NPC patients by risk. To the best of our knowledge, this is the first study to demonstrate the prognostic value of SII in the Turkish NPC patients.

Chronic inflammation is now recognized as a key driver in cancer progression, including NPC (10). NPC tumors often elicit

a systemic inflammatory response that correlates with disease severity. Inflammatory cells and mediators in the tumor microenvironment can promote angiogenesis, invasion, and immunosuppression, thereby facilitating tumor progression. For example, neutrophils – the most abundant immune cells in blood – can secrete pro-tumor factors (e.g. vascular endothelial growth factor, proteases) and suppress cytotoxic T-cell activity, fostering NPC invasion and metastasis (11). Conversely, lymphocytes (T cells, B cells, NK cells) are crucial for anti-tumor immunity; a reduction in lymphocyte count or function impairs immune surveillance and has been associated with worse outcomes in NPC (12, 13). Platelets also play a role by protecting tumor cells and aiding metastatic spread. Activated platelets release cytokines that support tumor cell extravasation and shield circulating cancer cells from NK cell–mediated lysis (14,15). Consistent with these mechanisms, clinical studies have observed that higher neutrophil and platelet counts (reflecting pro-tumor inflammation) and lower lymphocyte counts (reflecting weak immune response) are associated with more aggressive NPC and poorer survival (16-18). This link between systemic inflammation and NPC progression provides a rationale for investigating blood-derived inflammatory markers as prognostic indicators.

In the present study, both NLR and PLR were found to be associated with 5-year mortality. Among the inflammatory indices derived from blood counts, the NLR and PLR have been widely studied in NPC. These ratios serve as surrogates for the balance between pro-tumor inflammation and anti-tumor immunity. Numerous studies have confirmed that an elevated NLR or PLR is associated with advanced tumor burden and poorer survival outcomes in NPC (19-24). The prognostic value of NLR and PLR likely stems from their reflection of underlying biology: a high NLR indicates neutrophilia, which can promote tumor growth and suppress immunity, coupled with relative lymphopenia (impaired immune defense), while a high PLR indicates thrombocytosis (platelet-driven tumor progression) alongside lymphopenia.

By incorporating neutrophil and platelet counts together (rather than separately as in NLR or PLR), SII captures a broader spectrum of the systemic inflammatory response. This appears to translate into better risk stratification. Jiang et al. reported that in a cohort of over 300 NPC patients, SII had a higher area under the ROC curve for 3-year and 5-year survival than either NLR or PLR, indicating better discriminatory ability (21). In that study, all three indices showed significant associations with survival on univariate analysis, but SII emerged as the strongest independent predictor in multivariate modeling (hazard ratio for OS ~2.3 for high SII, compared to ~1.7 for NLR). Even after applying propensity score matching to balance baseline characteristics, SII remained an independent prognostic factor, whereas the predictive value of NLR and PLR was less pronounced. The authors concluded that "the prognostic value of SII is superior to PLR, NLR and MLR" in NPC (21). This finding has been echoed by others – a systemic review noted that composite indices like SII are more accurate in prognostic prediction than NLR or PLR in the NPC population (11,25). The enhanced performance of SII is biologically plausible: it simultaneously accounts for two tumor-promoting components (neutrophils and platelets) and the key tumor-fighting component (lymphocytes), thereby providing a more comprehensive measure of the immune-inflammatory balance. While NLR and PLR are useful and indeed prognostic in NPC, SII appears to yield superior prognostic information by virtue of its integrated formulation.

The results of the present study reinforce the prognostic significance of SII in NPC and align well with the existing body of literature. In our cohort, patients with higher SII experienced significantly worse outcomes, mirroring the adverse survival impact of elevated SII reported in prior studies (11,21,25). A 2022 meta-analysis pooling six studies (2169 patients) found that NPC patients with high SII had a 1.7-fold higher hazard of death and a ~1.6-fold higher risk of disease progression compared to those with low SII (10). Similarly, a 2023 systematic review including nine studies confirmed that SII is an independent predictor of both OS and PFS in NPC, with combined hazard ratios on the order of 1.7–1.8 for OS and 1.6–1.7 for PFS in favor of low SII (11). Xiong et al. reported that among 319 locally advanced NPC patients treated with chemoradiotherapy, those with high pretreatment SII had significantly shorter OS and PFS; furthermore, SII remained an independent predictor when controlling for clinicopathological factors (HR of 2.6 for OS and 1.3 for PFS) (26). These studies have identified optimal SII cut-off values in the mid-hundreds (generally ~400–700) to distinguish high- and low-risk patients. Despite these differences, the pattern is consistent: patients with SII above the optimal cut-off have markedly worse survival outcomes (including OS and disease-free/progression-free survival) compared to those below the cut-off. In the present study, the hazard ratios of SII for both OS and PFS were consistent with the existing literature. Notably, the magnitude of risk associated with high SII in our analysis (hazard ratios for OS and PFS) is comparable to that reported in earlier series and meta-analyses, lending credence to the reproducibility of this marker

across different populations. We also observed that SII provided independent prognostic value beyond the AJCC stage, which is consistent with most published data where SII remained significant in multivariable models (21).

Evidence from Turkey and other non-endemic regions echoes the prognostic significance of these markers, though published data are more limited. In a Turkish single-center study on NPC, patients with an elevated NLR (≥3) before treatment had substantially worse survival than those with lower NLR values (27). The same study and others also observed trends of higher PLR being associated with poorer outcomes, although NLR often emerged as the more significant predictor (27, 28). Until now, SII has not been extensively reported in Turkish NPC cohorts. This study contributes to the current evidence base by offering findings from a non-endemic population, indicating that the prognostic utility of SII is not exclusive to East Asian populations.

This study has several limitations that should be acknowledged. First, its retrospective design introduces potential selection bias and limits the ability to establish causal relationships. Although multivariate analyses were performed, unmeasured confounding factors may have influenced the results. Second, the sample size was relatively small, which may limit the statistical power and generalizability of the findings. Third, as a single-center study, the patient population may not fully represent broader demographic or geographic variations in nasopharyngeal carcinoma, particularly in non-endemic regions. Fourth, although SII was found to be a significant prognostic indicator, it can be influenced by non-cancer-related factors such as subclinical infections, concurrent inflammatory or hematologic conditions, and medication use, which may have affected pre-treatment blood counts. Finally, there remains no universally accepted cut-off value for SII in NPC; variability in thresholds across studies may impact its reproducibility and clinical applicability. Future multicenter prospective studies with larger and more diverse cohorts are needed to validate the prognostic utility of SII and to determine standardized reference values.

In conclusion, this study demonstrated that an elevated pre-treatment SII independently predicts poorer overall and progression-free survival outcomes in nasopharyngeal carcinoma patients. SII is an easily accessible, cost-effective biomarker that could improve risk stratification and guide clinical management.

Funding

The authors declared that this study has received no financial support.

Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was approved by the Dicle University Medical Faculty Ethics Committee for noninterventional studies (25.09.2024 - No: 245).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

Authors' contribution

Concept – G.K., Design- G.K., Data collection and/or processing - G.K. and B.H., Analysis and/or interpretation - G.K. and B.H., Writing – G.K., Critical review- B.H. All authors read and approved the final version of the manuscript.

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Research Article

Evaluation of apparent diffusion coefficient measurements and magnetic resonance imaging findings in benign and malignant gynecologic masses

Benign ve malign jinekolojik kitlelerde görünen difüzyon katsayısı ölçümlerinin ve manyetik rezonans görüntüleme bulgularının değerlendirilmesi

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Abstract

Aim: This study aimed to investigate the differences in magnetic resonance imaging (MRI) findings and various apparent diffusion coefficient (ADC) measurements between benign and malignant gynecologic masses.

Material and Methods: MRI images of 102 patients with pelvic masses, examined between June 2016 and November 2018, were retrospectively reviewed. Patients were categorized histopathologically as benign or malignant, by lesion composition (cystic, solid, mixed), and according to anatomical location (ovary, uterus, tube, cervix). Three ADC measurement methods were applied: diffuse ADC (dADC) from large ROIs covering the entire lesion, focal ADC (fADC) from small ROIs placed on the darkest regions of each slice, and specific ADC (sADC) calculated as the mean of the three lowest fADC values.

Results: According to lesion composition, solid lesions demonstrated lower ADC values than mixed lesions, yet no differences were observed between benign and malignant categories within each lesion composition. In ovarian and uterine masses, the value of ADCs showed no significant differences between benign and malignant groups. For cervical masses, the mean ADCs were higher in benign masses compared to malignant masses (dADC: 2.4±0.2 vs. 1.1±0.3, p=0.002; fADC : 2.3±0.2 vs. 0.7±0.1, p=0.001; sADC: 2.2±0.2 vs. 0.6±0.02, p=0.001).

Conclusion: Among various ADC measurement strategies, focal and specific ADC values more clearly reflected diffusion differences between benign and malignant gynecologic masses, particularly in cervical lesions. ADC values were affected by lesion composition, yet within each composition subgroup, benign and malignant lesions exhibited comparable values.

Keywords: Gynecologic masses, diffusion-weighted imaging, apparent diffusion coefficient, malignant, cervical cancer

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Öz

Amaç: Bu çalışma, benign ve malign jinekolojik kitleler arasında manyetik rezonans görüntüleme (MRG) bulguları ve çeşitli görünen difüzyon katsayısı (ADC) ölçümleri açısından farkları araştırmayı amaçlamaktadır.

Gereç ve Yöntemler: Haziran 2016 ile Kasım 2018 tarihleri arasında incelenen, pelvik kitleye sahip 102 hastanın MRG görüntüleri retrospektif olarak değerlendirildi. Hastalar histopatolojik olarak benign (n=82) veya malign (n=20) şeklinde, lezyon kompozisyonuna (kistik, solid, mikst) ve anatomik lokalizasyona (over, uterus, tüp, serviks) göre sınıflandırıldı. Üç ADC ölçüm yöntemi uygulandı: tüm lezyonu kapsayan geniş ROI'lerden elde edilen diffüz ADC (dADC), her kesitteki en koyu bölgelere yerleştirilen küçük ROI'lerden elde edilen fokal ADC (fADC) ve en düşük üç fADC değerinin ortalaması olarak hesaplanan spesifik ADC (sADC).

Bulgular: Lezyon kompozisyonuna göre solid lezyonlar, mikst lezyonlardan daha düşük ADC değerleri gösterdi, ancak her bir lezyon kompozisyonunda benign ve malign kategoriler arasında farklılık gözlenmedi. Over ve uterin kitlelerde, ADC değerleri benign ve malign gruplar arasında anlamlı fark göstermedi. Servikal kitlelerde benign lezyonların ortalama ADC değerleri malign gruba kıyasla daha yüksekti (dADC için 2,4±0,2 ve 1,1±0,3, p=0,002; fADC için 2,3±0,2 ve 0,7±0,1, p=0,001; sADC için 2,2±0,2 ve 0,6±0,02, p=0,001).

Sonuç: Farklı ADC ölçüm yöntemleri arasında, özellikle servikal lezyonlarda, fokal ve spesifik ADC değerleri benign ve malign jinekolojik kitleler arasındaki difüzyon farklılıklarını daha açık şekilde yansıtmıştır. ADC değerleri lezyon kompozisyonundan etkilense de her kompozisyon alt grubunda iyi huylu ve kötü huylu lezyonlar benzer değerler gösterdi.

Anahtar kelimeler: Jinekolojik kitleler, difüzyon ağırlıklı görüntüleme, görünen difüzyon katsayısı, malign, servikal kanser

Introduction

Gynecological masses originating in the ovaries, uterus, fallopian tubes, or cervix present a common diagnostic challenge, as accurate preoperative differentiation between benign and malignant lesions is crucial for guiding appropriate management. The main goal of imaging evaluation is to distinguish malignant tumors from benign ones and thereby determine the optimal surgical or therapeutic strategy [1, 2]. Magnetic resonance imaging (MRI) provides excellent soft-tissue contrast and detailed anatomical information for characterizing pelvic masses; however, even with high-resolution conventional MRI, reliably predicting malignancy can be difficult [3-5]. This limitation has prompted growing interest in advanced MRI techniques such as diffusion-weighted imaging (DWI) to improve lesion characterization.

DWI is an MRI sequence that quantifies the random motion of water molecules within tissues, and the derived apparent diffusion coefficient (ADC) values offer a quantitative measure of tissue cellularity and integrity. Malignant tumors often contain densely packed, hypercellular tissue that restricts water diffusion, causing markedly lower ADC values relative to less cellular benign lesions [6-8]. By incorporating ADC measurements into routine pelvic MRI protocols, radiologists can move beyond purely morphological assessment and potentially improve the distinction between benign and malignant gynecologic masses. In addition to its diagnostic value, ADC is also used to determine treatment response and prognosis during chemotherapy [9-11].

We hypothesize that malignant gynecological masses exhibit distinct quantitative ADC values and conventional MRI characteristics compared to benign lesions, and that ADC measurements can improve diagnostic accuracy in differentiating these entities. Therefore, the aim of this study is to investigate whether conventional MRI findings and quantitative ADC values differ between benign and malignant gynecological masses.

Material And Methods

This retrospective study was conducted using data from patients who underwent magnetic resonance imaging (MRI) with a preliminary diagnosis of pelvic mass at the Department of Radiology, Cumhuriyet University Faculty of Medicine, between June 2016 and November 2018. The study was approved by the Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (Date: 20.02.2019, Approval No: 2019-02/26) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision). The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

During the study period, 115 patients who underwent MRI

examinations due to a preliminary diagnosis of pelvic mass were retrospectively evaluated. Inclusion criteria encompassed individuals aged from 15 to 94 years who had pelvic masses identified, accompanied by postoperative histopathology results and clinical follow-up data. After applying exclusion criteria, specifically the absence of pelvic mass detection (n = 7) or missing histopathological and clinical follow-up records (n = 6), a total of 102 patients were enrolled in the final analysis.

Study Protocol

The hospital's electronic information system and patient files were used to gather demographic and clinical data. Imaging findings of the patients were collected via the Picture Archiving and Communication System (PACS).

Pelvic MRI and diffusion MRI examinations were conducted using a 1.5 Tesla MRI system (Magnetom Aera, Siemens, Erlangen, Germany) equipped with a dedicated body coil. The standard pelvic MRI protocol included T1A-weighted imaging (TR=484 ms, TE=12 ms, slice thickness 5 mm), T2A-weighted imaging (TR=3880 ms, TE=96 ms, slice thickness 5 mm), fat-suppressed T2 sequences (TR=4210 ms, TE=95 ms, slice thickness 5 mm), HASTE imaging from T2 sequences (TR=1400 ms, TE=102 ms, slice thickness 6 mm), and VIBE imaging from fat-suppressed T1 sequences (TR=6.69 ms, TE=2.39 ms, slice thickness 3 mm). DWI was performed with TR=5700 ms, TE=104 ms, and slice thickness 5 mm.

MRI Evaluation of Pelvic Masses

Pelvic masses detected via MRI were categorized based on anatomical origin into four groups: uterine, ovarian, tubal, and cervical. Additionally, lesions were classified according to their nature as solid, cystic, or mixed. Lesion sizes were measured in three dimensions (transverse, anterior-posterior, and craniocaudal), and their volumes were calculated. T1- and T2-weighted signal characteristics of lesions, along with the presence of hemorrhagic foci, were also assessed. After intravenous contrast administration, lesions were evaluated for staining characteristics and classified into four enhancement patterns: homogeneous, heterogeneous, circumferential, and septal enhancement.

Diffusion-weighted Imaging and ADC Measurement

DWI was routinely performed before contrast administration using single-shot echo-planar imaging with diffusion-sensitive gradients applied at three b-values (50, 400, and 800 mm^2/s) along the x, y, and z axes. ADC maps were generated automatically. Three different ADC measurement approaches were used. First, a circular region of interest (ROI) ≥37 mm^2 was placed in each axial slice covering the lesion, and the average ADC value (diffuse ADC; dADC) was calculated. Second, focal ADC (fADC) was measured by placing a smaller ROI of 10 mm^2 specifically on the darkest region within each axial slice. Lastly, the specific ADC (sADC) was calculated as the arithmetic mean of the three lowest focal ADC values (Figure 1-4).

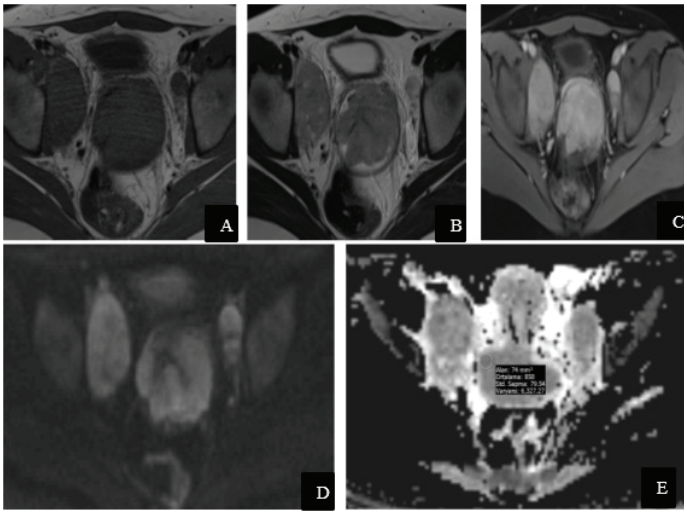

Figure 1. Solid lesion located in the uterine cervix. The lesion is hypointense on T1-weighted **(A)** and T2-weighted **(B)** images, measuring 50×43×27 mm (transverse × anterior-posterior × craniocaudal). It demonstrates intense homogeneous enhancement on post-contrast T1-weighted images **(C)**. Areas of diffusion restriction are observed at b=1000 s/mm^2 on DWI **(D)**, with a mean ADC value of 0.66×10^{-3} mm^2/s measured on the ADC map **(E)**. Histopathological diagnosis: Squamous cell carcinoma.

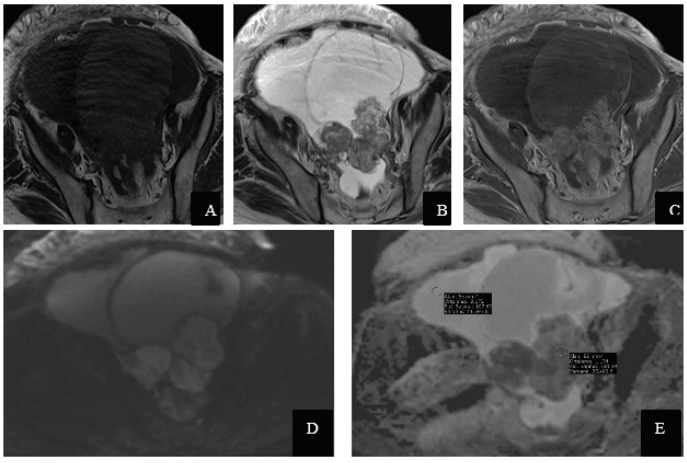

Figure 2. Mixed solid-cystic lesion located in the pelvic region. The lesion has lobulated contours and measures 156×102×122 mm (anterior-posterior × medial-lateral × craniocaudal), demonstrating hypointensity on T1-weighted images (A) and heterogeneous hyperintensity on T2-weighted images (B). Solid components and

septa show intense enhancement on post-contrast T1-weighted imaging (C). Prominent diffusion restriction is observed in the solid components at b=1000 s/mm^2 on DWI (D), with an average ADC value of 1.13×10^{-3} mm^2/s measured on the ADC map (E). Histopathological diagnosis: Tubal serous carcinoma.

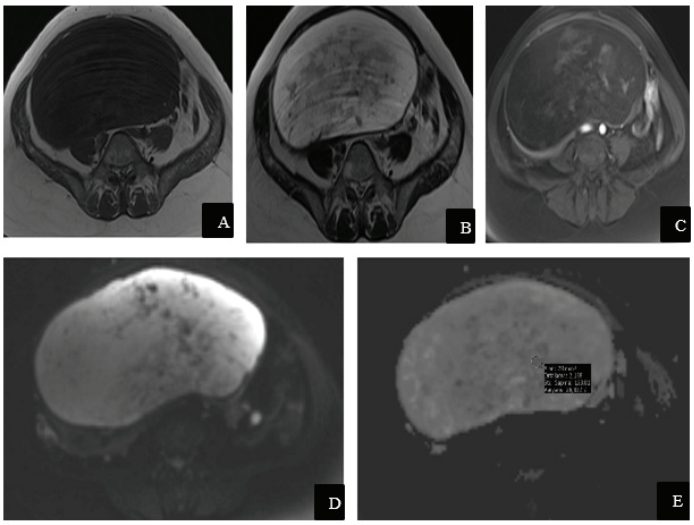

Figure 3. A pelvic mass originating from the uterine parenchyma, filling the pelvic cavity. The lesion measures 242×125×271 mm (craniocaudal × anterior-posterior × transverse) and is characterized as expansile and solid with well-defined borders. It is hypointense on T1-weighted (A) and heterogeneously hyperintense with cystic necrotic areas on T2-weighted images (B). On post-contrast T1-weighted imaging (C), heterogeneous enhancement is observed predominantly in the central regions. DWI at b=1000 s/mm^2 (D) shows diffusion restriction, with an ADC value of 2.18×10-^{3} mm^2/s measured on the ADC map (E). Histopathological diagnosis: Cystic degenerated leiomyoma.

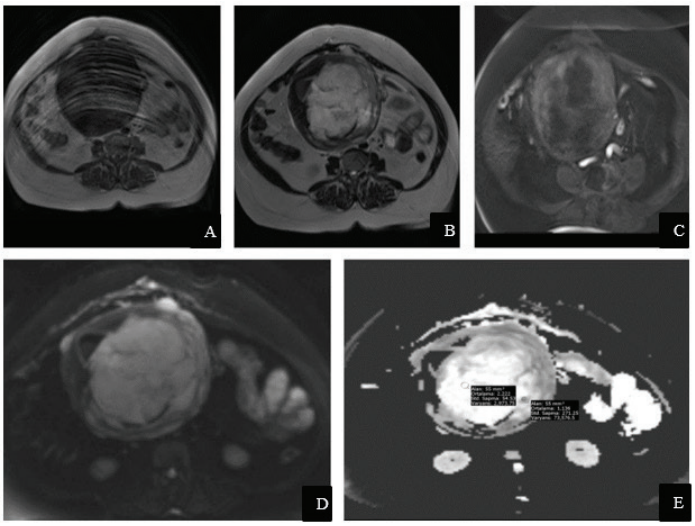

Figure 4. Solid uterine lesion characterized as a well-circumscribed, expansile mass measuring 93×53×52 mm (transverse × anterior-posterior × craniocaudal). It demonstrates hypointensity on T1-weighted (A) and heterogeneous hyperintensity on T2-weighted images (B). Post-contrast T1-weighted imaging (C) reveals cystic necrotic areas and intense enhancement within the solid portions of the lesion. Areas of diffusion restriction are seen at b=1000 s/mm^2 on DWI (D), with an ADC value of 1.13×10^{-3} mm^2/s measured on the ADC map (E). Histopathological diagnosis: Leiomyosarcoma.

MRI and DWI findings, including ADC values, were compared between histologically confirmed benign and malignant pelvic masses. Additionally, separate comparative analyses were performed to assess the diagnostic accuracy of MRI, DWI, and ADC metrics specifically for ovarian and uterine lesions.

Statistical Analysis

The SPSS 26.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk test. Quantitative variables were summarized as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Continuous variables were compared between benign and malignant groups using the Independent-Samples T-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. A p-value below 0.05 was considered statistically significant.

Results

A total of 102 masses were evaluated, including 82 benign and 20 malignant cases. Out of 102 cases, 91 underwent surgery, while 11 were followed clinically. Among the 55 ovarian lesions assessed, benign lesions accounted for 48 cases, including 14 endometriomas, 10 simple ovarian cysts, 7 mature cystic teratomas, 5 hemorrhagic cysts, 5 fibrothecomas, 3 mucinous cystadenomas, 3 serous papillary cystadenofibromas, and 1 serous cystadenoma. The 7 malignant lesions included 4 serous carcinomas, 2 Krukenberg tumors, and 1 Sertoli-Leydig cell tumor. Thirty-three uterine lesions comprised 28 leiomyomas, 3 endometrial cancers, and 2 leiomyosarcomas. Of the 11 cervical masses identified, 6 benign lesions were Nabothian cysts, and the remaining 5 were malignant squamous cell cervical cancers.

The mean age of patients with malignant masses was higher than those with benign masses (54.3 ± 19.1 vs. 40.3 ± 13.6 years, p = 0.001). Malignant masses were predominantly mixed (60.0%), while benign masses were mostly cystic (57.3%). The ovary was the most common localization overall (53.9%), although malignancies occurred notably more frequently in cervical (25.0%). Regarding pitting patterns, malignant masses most commonly showed heterogeneous patterns (85.0%),

while no pitting pattern was detected in 47.6% of benign lesion. There was no significant difference between benign and malignant masses in terms of mean dADC values (both 1.7 ± 0.7, p = 0.903). However, mean fADC (1.1 ± 0.6 vs. 1.5 ± 0.7, p = 0.025) and mean sADC values (0.9 ± 0.5 vs. 1.4 ± 0.7, p = 0.026) were significantly lower in malignant masses compared to benign ones. The demographic and clinical characteristics of patients are given in Table 1.

In solid and mixed masses, the mean ADC values showed no significant differences between benign and malignant groups (Table 2). In ovarian and uterine masses, the value of ADCs showed no significant differences between benign and malignant groups. For cervical masses, the mean ADCs were higher in benign masses compared to malignant masses (2.4 ± 0.2 vs. 1.1 ± 0.3, p = 0.002 for dADC; 2.3 ± 0.2 vs. 0.7 ± 0.1, p = 0.001 for fADC; 2.2 ± 0.2 vs. 0.6 ± 0.02, p = 0.001 for sADC) (Table 3). Additionally, the normal cervical stroma of 10 control cases without cervical involvement was evaluated, and the mean ADC values were as follows: diffuse ADC, 1.7 ± 0.3×10^{-3} mm^2/s; focal ADC, 1.7± 0.2×10^{-3} mm^2/s; specific ADC, 1.7 ± 0.7×10^{-3} mm^2/s.

Table 1. Demographic characteristics and ADC values of benign versus malignant masses.

Variables	All population n = 102	Benign n = 82	Malign n = 20	P-value
Age, years	43.0 ± 15.6	40.3 ± 13.6	54.3 ± 19.1	0.001*
Nature, n (%)				
Cystic	47 (46.1)	47 (57.3)	-	0.001*
Solid	33 (32.3)	25 (30.5)	8 (40.0)	
Mixed	22 (21.6)	10 (22.2)	12 (60.0)	
Localization				
Ovary	55 (53.9)	48 (58.5)	7 (35.0)	<0.001*
Uterus	33 (32.3)	28 (34.2)	5 (25.0)	
Tuba	3 (2.9)	-	3 (15.0)	
Cervix	11 (10.8)	6 (7.3)	5 (25.0)	
Pitting pattern				
No	39 (38.3)	39 (47.6)	-	0.001*
Homogeneous	5 (4.9)	4 (4.9)	1 (5.0)	
Heterogeneous	45 (44.1)	28 (34.1)	17 (85.0)	
Environmental	10 (9.8)	8 (9.8)	2 (10.0)	
Septal	3 (2.9)	3 (3.7)	-	
Diffuse ADC, x10-3 mm2/sn	1.7 ± 0.7	1.7 ± 0.7	1.7 ± 0.7	0.903
Focal ADC, x10-3 mm2/sn	1.4 ± 0.7	1.5 ± 0.7	1.1 ± 0.6	0.025*
Specific ADC, x10-3 mm2/sn	1.3 ± 0.7	1.4 ± 0.7	0.9 ± 0.5	0.026*

Table 2. Comparison of ADC values in solid and mixed masses by malignancy status.

Nature	Benign	Malign	P-value
Solid	n = 25	n = 8	
Diffuse ADC, x10-3 mm2/sn	1.1 ± 0.3	1.0 ± 0.2	0.846
Focal ADC, x10-3 mm2/sn	0.8 ± 0.3	0.8 ± 0.2	0.609
Specific ADC, x10-3 mm2/sn	0.8 ± 0.2	0.8 ± 0.3	0.918
Mixed	n = 10	n = 12	
Diffuse ADC, x10-3 mm2/sn	1.7 ± 0.6	2.0 ± 0.8	0.125
Focal ADC, x10-3 mm2/sn	1.2 ± 0.5	1.3 ± 0.6	0.667
Specific ADC, x10-3 mm2/sn	1.0 ± 0.5	1.1 ± 0.6	0.578

Table 3. Comparison of ADC values in the differentiation of benign and malignant according to localization.

Localization	Benign	Malign	P-value
Ovary	n = 48	n = 7	
Diffuse ADC, x10-3 mm2/sn	1.8 ± 0.7	2.2 ± 0.6	0.172
Focal ADC, x10-3 mm2/sn	1.6 ± 0.7	1.7 ± 0.7	0.951
Specific ADC, x10-3 mm2/sn	1.5 ± 0.8	1.4 ± 0.7	0.814
Uterus	n = 28	n = 5	
Diffuse ADC, x10-3 mm2/sn	1.4 ± 0.5	1.5 ± 0.5	0.679
Focal ADC, x10-3 mm2/sn	1.0 ± 0.3	0.9 ± 0.2	0.268
Specific ADC, x10-3 mm2/sn	0.9 ± 0.3	0.8 ± 0.2	0.458
Cervix	n = 6	n = 5	
Diffuse ADC, x10-3 mm2/sn	2.6 ± 0.6	1.1 ± 0.3	0.002*
Focal ADC, x10-3 mm2/sn	2.5 ± 0.2	0.7 ± 0.1	0.001*
Specific ADC, x10-3 mm2/sn	2.5 ± 0.3	0.6 ± 0.2	0.001*

Discussion

This study provides valuable insight into the role of diffusion-weighted MRI in characterizing pelvic masses by employing three distinct ADC measurement strategies. We defined dADC as the average ADC from a large ROI encompassing the entire lesion, fADC as the ADC from small ROIs placed on the darkest (most diffusion-restricted) region of the lesion on each slice, and sADC as the mean of the three lowest fADC values. This approach captures tumor heterogeneity by comparing whole-lesion diffusion with the most restricted areas. ADC values did not differ significantly between benign and malignant groups based on the nature (solid, cystic, mixed) of the lesions. However, a significant difference was noted in ADC values according to lesion localization, specifically within cervical lesions, where malignant lesions exhibited lower ADC values compared to benign lesions.

In our cohort, patients with malignant masses were significantly older on average than those with benign lesions (mid-50s vs. early 40s), and the malignant tumors more frequently exhibited complex mixed (solid-cystic) morphology with heterogeneous internal characteristics. These clinical and imaging features are recognized red flags for malignancy and are consistent with prior observations that adnexal and cervical malignancies tend to occur at older ages and often present with solid components on imaging [12-14]. Despite these features, our diffusion MRI results highlight a nuanced picture. Despite solid masses having lower ADC values than mixed masses, these values did not significantly differ between benign and malignant groups. Also, ovarian and uterine lesions showed no ADC value differences between benign and malignant classifications. However, malignant cervical lesions exhibited significantly lower ADC values compared to their benign counterparts.

Solid masses tend to have markedly lower ADC values than lesions with cystic portions. The reason is that a completely solid tumor affords little free space for water movement – water molecules are hindered by cell membranes, intracellular organelles, and sometimes fibrous matrix. By contrast, if a tumor is mixed (solid-cystic) or contains cystic areas (fluid-filled regions), the fluid allows relatively unhindered Brownian motion of water, which drives the ADC upward in those areas. In practical terms, a simple fluid-filled cyst will appear bright on an ADC map (high ADC) since water diffusion is nearly free, whereas a densely cellular solid tumor nodule appears dark on the ADC map (low ADC) due to restricted diffusion [15, 16]. Numerous studies have confirmed this dichotomy: cystic tumor components exhibit higher ADC values than solid tumor components (this holds true for both benign and malignant lesions) [1]. Rousell et al. evaluated 54 pelvic masses, measuring ADC separately from cystic and solid components. Mean ADC values for benign and malignant lesions from cystic components were $2.\pm0.5\times10^{-3}$ mm^2/s and $2.\pm0.5\times10^{-3}$ mm^2/s, without significant differences. Similarly, solid component ADC values for benign and malignant lesions were $1.2\pm0.6\times10^{-3}$ mm^2/s and $1.0\pm0.2\times10^{-3}$ mm^2/s, respectively, also showing no significant difference [17]. The results of our study are consistent with these observations.

In ovarian and uterine masses, the differences in diffusion metrics between benign and malignant lesions were not statistically significant. One likely explanation is the overlap in ADC values caused by lesion heterogeneity. Certain benign ovarian tumors such as fibromas, teratomas and endometriomas) can exhibit unusually low ADC values due to their contents, overlapping with the restricted diffusion seen in malignancies [1, 18]. Granular studies have found,

for example, that the mean ADC of solid components was not significantly different between benign and malignant ovarian tumors in some series [16]. Similarly, benign uterine fibroids with dense fibrous tissue may show very low ADC (a "T2 blackout" effect), mimicking the diffusion restriction of uterine sarcomas [19]. Tamai et al. observed that sarcomas had lower average ADC values than normal myometrium and degenerated leiomyomas with no overlap. However, they noted overlapping ADC values with ordinary and cellular leiomyomas [20]. These overlapping diffusion patterns diminish the statistical separation between benign and malignant groups, which aligns with recent studies reporting conflicting or inconclusive ADC findings in ovaries and uterus when lesion composition is diverse.

In contrast, cervical lesions showed clear and significant differences in all three ADC measures between benign and malignant cases. Cervical cancers are typically highly cellular, and this dense cell packing markedly restricts water diffusion, resulting in much lower ADC values in malignant tumors compared to normal or benign cervical tissue [21]. Previous studies have identified mean ADC values of about 1.0–1.1×10^{-3} mm^2/s, which are considerably lower than those observed in normal cervical stroma, typically between 1.5–2.1×10^{-3} mm^2/s [22-25]. Differences by histology have also been observed – squamous cell carcinomas typically show slightly lower ADC values than adenocarcinomas, a finding attributed to histologic differences (e.g. squamous tumors often being more densely cellular, whereas adenocarcinomas may have glandular mucin that increases water diffusivity) [26]. The current study did not allow comparisons across different histological types because of insufficient sample numbers. Although the dADC values for cervical lesions obtained in our study were consistent with the literature, our findings indicate that the fADC and sADC measurements demonstrated more substantial differences. In effect, the true tissue diffusion coefficient (slow ADC/dADC) drops in cancers, and even the perfusion-related diffusion component is reduced: intravoxel incoherent motion analysis confirms that both the pure diffusivity D and the perfusion fraction f are significantly lower in cervical carcinomas compared to normal cervical tissue [27]. These microstructural differences make ADC a valuable diagnostic biomarker in cervical cancer. Importantly, ADC values also carry prognostic information. Lower ADC tends to correlate with more aggressive tumor features – for instance, well-differentiated (Grade I) cervical cancers showed significantly higher ADC (~1.04×10–3 mm^2/s) than poorly differentiated Grade III tumors (approx. 0.67×10–3 mm^2/s) [28]. Similarly, the most diffusion-restricted tumors often indicate aggressive pathology: lesions with lymphovascular space invasion have significantly lower minimum ADC than tumors without lymphovascular invasion [29]. Consistently, pretreatment ADC has been linked to outcomes: tumors with very low ADC (high diffusion restriction) are associated with greater risk of recurrence and poorer survival, whereas higher ADC values tend to portend a more favorable prognosis [30].

This study has several limitations. First, its retrospective and single-center design introduces a potential selection bias and may limit the generalizability of the findings to broader populations. Second, the sample size—especially the number of malignant lesions—was relatively small, which may limit the statistical power of subgroup analyses, particularly those stratified by localization (e.g., cervix, ovary, uterus). Third, ROI placement was performed manually, and despite efforts to standardize it, some degree of subjectivity in selecting the darkest areas or lesion borders is inevitable. Fourth, lesion composition was heterogeneous within each group; for example, benign ovarian lesions included both simple cysts and endometriomas, which may have different diffusion characteristics despite falling under the same histopathological category. Finally, histological subtypes and tumor grades—particularly among malignant cases—were not analyzed separately, though these features are known to influence ADC values and may partially explain intragroup variability. These limitations suggest that further prospective studies with larger, balanced cohorts and blinded, multi-reader designs are warranted to validate the diagnostic and prognostic performance of ADC metrics in gynecological masses.

Conclusion

ADC values in gynecologic masses can vary based on the nature of masses and anatomical structures evaluated. Solid lesions and malignant cervical masses typically show lower ADC measurements. However, in ovarian and uterine lesions, considerable overlap in ADC values limited diagnostic performance, highlighting the need for cautious interpretation. While focal ROI strategies may enhance the sensitivity of DWI for detecting malignancy, ADC values alone are insufficient as stand-alone diagnostic tools due to lesion heterogeneity and compositional variability. Therefore, ADC metrics should be integrated with conventional MRI findings and clinical context for a more accurate and comprehensive evaluation of gynecologic masses.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (Date: 20.02.2019, Approval No: 2019-02/26).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

Authors' contribution

Concept – B.Ş. and O.S., Design- B.Ş. and O.S., Data collection and/or processing – B.Ş., G.Y., N.B., and O.S., Analysis and/or interpretation - B.Ş., G.Y., N.B., and O.S., Writing – B.Ş., Critical review- B.Ş., G.Y., N.B., and O.S. All authors read and approved the final version of the manuscript.

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Research Article

Evaluation of interpeduncular angle values according to age and gender by magnetic resonance imaging

Manyetik rezonans görüntüleme ile yaşa ve cinsiyete göre interpedünküler açı değerlerinin değerlendirilmesi

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Abstract

Aim: This study aimed to evaluate the prognostic significance of the systemic immune-inflammation index (SII) in patients with nasopharyngeal carcinoma (NPC).

Material and Methods: This retrospective study included 42 patients diagnosed with NPC between January 2014 and January 2020. Clinical data, hematological parameters, and survival outcomes were collected. Disease stage was classified using the 8th edition of the American Joint Committee on Cancer (AJCC) Staging System. Pre-treatment SII values were calculated using complete blood count data (platelets × neutrophils / lymphocytes).

Results: The mean patient age was 54.0 ± 13.8 years, with a male predominance (66.7%). Most patients presented with advanced disease (AJCC Stage III–IV). Higher pre-treatment SII values were significantly associated with poorer overall survival (OS) and progression-free survival (PFS). Multivariate Cox regression analysis confirmed that elevated SII independently predicted reduced OS (HR: 1.06; 95% CI: 1.02–1.09; $p < 0.001$). ROC analysis identified optimal SII cut-off values of >610 for OS (sensitivity: 73.9%, specificity: 60.0%) and >580 for PFS (sensitivity: 75.0%, specificity: 57.1%). Kaplan–Meier analysis demonstrated significantly lower OS and PFS in patients with elevated SII (log-rank $p < 0.001$).

Conclusion: Elevated SII is a strong and independent prognostic marker for poor outcomes in NPC patients and may guide personalized clinical management.

Keywords: nasopharyngeal carcinoma, systemic immune-inflammation index, prognosis, survival analysis, inflammation

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Öz

Amaç: Bu çalışma, sağlıklı yetişkin bir popülasyonda manyetik rezonans görüntüleme (MRI) kullanarak interpedünküler açı (IPA), pontomesensefalik açı (PMA) ve pontomedüller açı için normatif, yaşa ve cinsiyete göre tabakalandırılmış referans değerleri belirlemeyi amaçlamaktadır.

Gereç ve Yöntemler: Bu retrospektif çalışmaya Ocak 2018 ile Aralık 2020 arasında beyin MRI'ı çekilen 290 sağlıklı yetişkin hasta (124 erkek, 166 kadın; ortalama yaş: 43,1 ± 16,7 yıl) dahil edildi. IPA, PMA ve pontomedüller açılar, standartlaştırılmış aksiyel ve orta sagital T1 ağırlıklı spin-eko MRI dizilerinde ölçüldü. Sınıflandırma şu şekildeydi: 18-24 yaş (genç yetişkinler), 25-33 yaş (yetişkinler), 34-48 yaş (erken orta yaşlı), 49-64 yaş (orta yaşlı), ≥65 yaş (yaşlı).

Bulgular: Ortalama IPA 75,5° ± 10,2, PMA 57,0° ± 10,2 ve pontomedüller açı 133,8° ± 10,6 idi. Erkek ve kadınlar arasında herhangi bir açısal ölçümde anlamlı bir fark gözlenmedi ($p > 0,05$). Ancak, özellikle orta yaşlı ve yaşlı gruplarında, ilerleyen yaşla birlikte IPA değerlerinde anlamlı bir artış gözlendi ($p < 0,001$). IPA yaşla orta düzeyde pozitif bir korelasyon gösterdi ($r = 0,372$; $p < 0,001$), PMA ve pontomedüller açı ise yaşla anlamlı bir korelasyon göstermedi. Üç açısal parametre arasında anlamlı bir korelasyon bulunamadı.

Sonuç: IPA değerleri yaşla birlikte önemli ölçüde artarken, PMA ve pontomedüller açılar yetişkinlik boyunca nispeten sabit kaldı. Bu bulgular, beyin sapı açısal ölçümleri için normatif, yaşa ve cinsiyete göre sınıflandırılmış referans verileri sağlar ve bu da klinik tanılamada, özellikle spontan intrakraniyal hipotansiyon ve nörodejeneratif sendromlar gibi durumlarda, bunların kullanımını artırabilir.

Anahtar Kelimeler: interpedinküler açı, pontomesensefalik açı, pontomedüller açı, manyetik rezonans görüntüleme, beyin sapı morfolojisi, normatif veriler

Introduction

The interpeduncular angle (IPA) is a neuroanatomical measurement defined as the angle formed between the cerebral peduncles of the midbrain on axial magnetic resonance imaging (MRI) (1). In particular, spontaneous intracranial hypotension – a syndrome of low cerebrospinal fluid pressure - is associated with downward displacement of brain structures ("brainstem slumping") that markedly narrows the IPA (2). Although recent studies have shown that IPA is lower in patients with intracranial hypotension compared to healthy individuals, it appears to be elevated in patients with idiopathic normal pressure hydrocephalus (iNPH) and comparable in those with progressive supranuclear palsy (PSP) (3).

In addition to the IPA, other quantitative brainstem angular measurements - such as the pontomesencephalic angle (PMA) - offer further insight into midbrain and pontine anatomy. The configuration of subarachnoid cisterns - shaped in part by arachnoid membrane attachments - may influence multiple brainstem angular measurements, including both the PMA and the pontomedullary angle (4). The PMA is defined at the junction of the midbrain and pons, formed by the anterior surface of the midbrain and the superior surface of the pons. This angle also decreases in pathological states such as spontaneous intracranial hypotension (5). On the other hand, the pontomedullary angle, a sagittal measure between the pons and medulla (6), remains under-characterized in the literature.

Although clinical interest in brainstem morphometry has grown in recent years, there remains a notable lack of well-established reference values or nomograms for angular brainstem measurements in routine MRI interpretation. This absence is particularly evident in the case of the IPA, for which no large-scale normative data exist across the adult lifespan. Preliminary observations suggest that IPA values may be influenced by demographic factors such as sex, with males potentially exhibiting higher angles than females (7). These findings are consistent with broader studies of brainstem structure that have documented age- and sex-related variations in other angular metrics, including the PMA (8). However, comprehensive age- and sex-specific reference values for the IPA, PMA, and pontomedullary angle have yet to be systematically established.

To address this gap, this study aimed to provide age- and sex-stratified reference values for multiple brainstem angular measurements - including the IPA, PMA, and pontomedullary angle - in a healthy adult population.

Material and Methods

This retrospective study was conducted using cranial MRI scans obtained between January 2018 and December 2020 from adult individuals who had presented to Adana Yüreğir State Hospital for various non-neurological reasons. The study was approved by the Cukurova University Non-Interventional Clinical Research Ethics Committee (Date: 05.11.2021, Decision No: 2021/116-60) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision). The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

During the study period, a total of 290 patients who had undergone cranial MRI were retrospectively evaluated. Patients with known neurological disease, radiologically confirmed brainstem pathology, or inadequate image quality due to motion artifacts or technical limitations were excluded. The exclusion process was conducted by an experienced neuroradiologist with over 20 years of experience, who also confirmed the suitability of each case for angular measurements.

Study Protocol

The hospital's electronic information system and patient files were used to gather demographic and clinical data. MRI images were retrieved from the hospital's digital archive, and subject eligibility was determined through radiological screening. For subgroup analysis, participants were stratified into six age groups based on predefined age ranges to examine age-related variations in brainstem angular measurements (9, 10). The classification was as follows: 18–24 years (young adults), 25–33 years (adults), 34–48 years (early middle-aged), 49–64 years (middle-aged), ≥65 years (elderly).

MRI Acquisition

MRI examinations were performed using a 1.5-Tesla scanner (GE Signa Excite HD; GE Medical Systems, Milwaukee, WI, USA). The routine cranial MRI protocol included axial and mid-sagittal T1-weighted spin-echo sequences. Axial images were acquired with repetition time (TR) of 1173 ms, echo time (TE) of 8.9 and 35.5 ms, a slice thickness of 5 mm with a 0.4 mm interslice gap, and a matrix size of approximately 320 × 224. Mid-sagittal images were obtained using comparable parameters optimized for anatomical clarity. No intravenous contrast was administered.

Image Analysis and Measurements

All images were reviewed on the hospital's workstation using Karmed PACS software (Kardelen Software, Türkiye). Each parameter was measured twice, at least two weeks apart, using identical zoom levels, and the arithmetic mean of the two measurements was recorded as the final value for analysis. The IPA was measured on axial T1-weighted images at the level of the corpus mamillare. Lines were drawn along the medial borders of the cerebral peduncles, and the anteriorly converging angle between them was recorded (Figure 1). The PMA was assessed on the mid-sagittal plane as the angle between tangents to the anterior surfaces of the midbrain and pons (Figure 2). The pons-bulbus angle, also referred to as the pontomedullary angle, was measured on the same sagittal image as the angle formed between tangents to the inferior pons and the superior medulla oblongata (Figure 2).

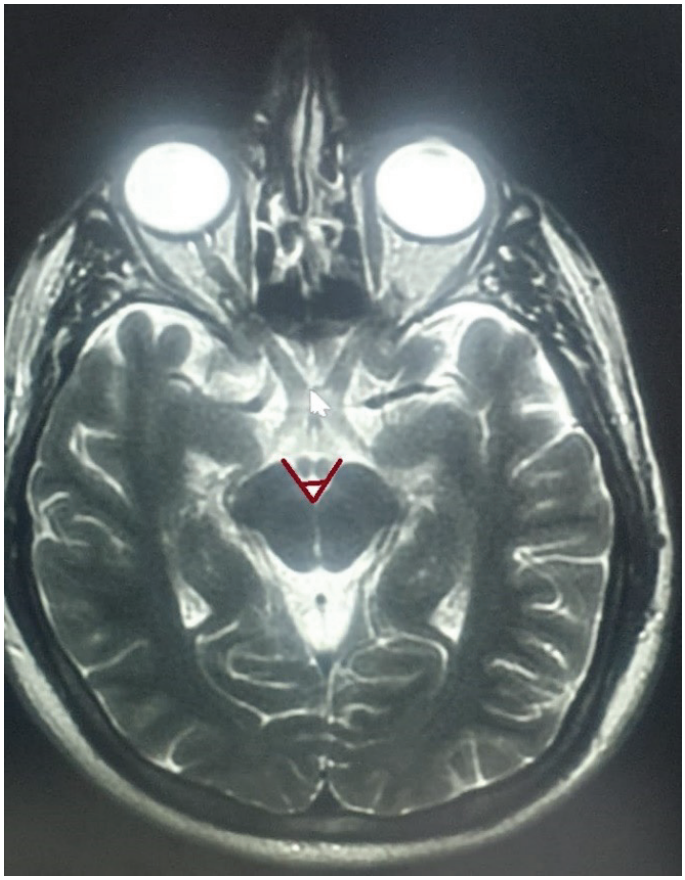

Figure 1. Axial magnetic resonance imaging (MRI) illustrating measurement of the interpeduncular angle (IPA). The red lines indicate the angle formed between the medial aspects of the cerebral peduncles at the midbrain level.

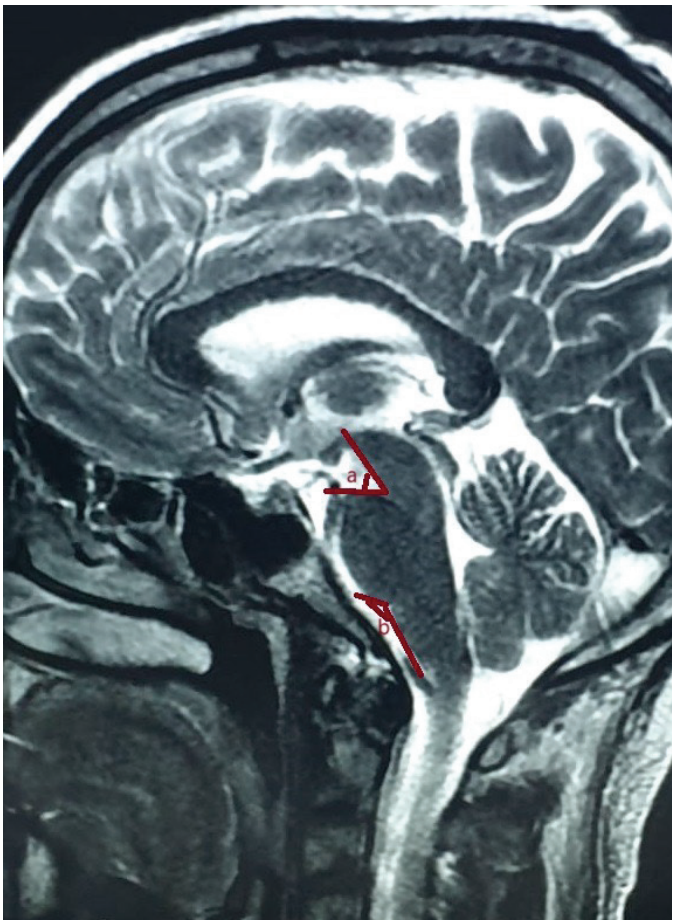

Figure 2. Sagittal magnetic resonance imaging (MRI) demonstrating the measurement of the pontomesencephalic angle (a) and the pontomedullary angle (b).

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) software. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Variables with a normal distribution were presented as mean ± standard deviation (SD), whereas non-normally distributed variables were expressed as median and interquartile range (IQR: 25th–75th percentiles). For comparisons between two independent groups, the Student's t-test was used for normally distributed data, while the Mann–Whitney U test was applied for non-normally distributed data. In comparisons involving more than two groups, one-way ANOVA was used for parametric data, and the Kruskal–Wallis test was employed for non-parametric data. When significant differences were observed, post hoc pairwise comparisons were conducted using the Bonferroni test (for ANOVA) or Dunn's test (for Kruskal–Wallis), as appropriate. The relationships between angular measurements (IPA, PMA, and PBA) were assessed using Pearson's correlation coefficient for parametric variables and Spearman's rank correlation coefficient for non-parametric variables. A p-value < 0.05 was considered statistically significant in all analyses.

Results

The study included 290 patients with a mean age of 43.1 ± 16.7 years, of whom 124 were men (42.8%) and 166 were women (57.2%). The mean IPA was 75.5° ± 10.2, with a range from 46.7° to 99.7°. The PMA had a mean of 57.0° ± 10.2 and values ranging between 30.7° and 96.8°. The pontomedullary angle showed a considerably wider distribution, with a mean of 133.8° ± 10.6, with a range from 102.3° to 158.7° (Table 1).

Comparative analysis of brainstem angular measurements between male and female participants did not reveal any statistically significant differences. The mean IPA was 74.8° ± 10.9 in females and 76.3° ± 9.2 in males ($p = 0.202$). Similarly, the PMA showed close values across gender, with a mean of 56.8° ± 10.7 in females and 57.3° ± 9.4 in males ($p = 0.660$). The pontomedullary angle was nearly identical between the two groups (133.9° ± 10.4 in females vs. 133.8° ± 10.9 in males, $p = 0.956$) (Table 1).

Age-based analysis revealed a statistically significant difference in IPA values across the five age groups. Both the middle-aged and elderly groups exhibited similar IPA values, which were higher on average compared to those of the younger age group (Young adults: 72.3° ± 8.2 vs. Adults: 71.6° ± 10.8 vs. Early middle-aged: 73.8° ± 9.9 vs. Middle-aged: 79.4° ± 9.4 vs. Elderly: 81.4° ± 9.0; $p < 0.001$). In contrast, IPA values among the younger three groups (young adults, adults, and early middle-aged) remained relatively close, showing no significant differences between them. The mean PMA and pontomedullary angle showed no significant differences among age groups (Table 2).

While age showed a positive correlation with the IPA ($r = 0.372$; $p < 0.001$), it was not significantly associated with either the PMA ($r = 0.008$; $p = 0.994$) or the pontomedullary angle ($r = -0.043$; $p = 0.468$) (Figure 3). No significant correlation was found among the IPA, PMA, and pontomedullary angles (Figure 4).

Table 1. Gender-based comparison of interpeduncular, pontomesencephalic, and pontomedullary angles.

Variables	All population n = 290	Female n = 166	Male n = 124	p
Age, years	43.1 ± 16.7	43.3 ± 16.9	42.8 ± 16.6	0.827
IPA, °				
mean ± SD	75.5 ± 10.2	74.8 ± 10.9	76.3 ± 9.2	0.202
min-max	46.7 - 99.7	46.7 - 99.7	56.5 - 97.7	
IQR	68.0 - 82.7	67.0 - 82.7	69.8 - 83.1	
PMA, °				
mean ± SD	57.0 ± 10.2	56.8 ± 10.7	57.3 ± 9.4	0.660
min-max	30.7 - 96.8	30.7 - 86.9	31.6 - 96.8	
IQR	50.2 - 63.1	49.6 - 62.6	50.7 - 63.8	
PBA, °				
mean ± SD	133.9 ± 10.6	133.9 ± 10.4	133.8 ± 10.9	0.956
min-max	102.3 - 158.7	102.3 - 154.9	106.1 - 158.7	
IQR	126.4 - 141.4	127.3 - 140.8	124.9 - 141.8	

The data are expressed as the mean ± SD, IQR (25th–75th percentiles). IPA, interpeduncular angle; PBA pontomedullary angle; PMA, pontomesencephalic angle.

Table 2. Age-based comparison of interpeduncular, pontomesencephalic, and pontomedullary angles.

Variables	Young adults n = 42	Adults n = 55	Early middle-aged n = 87	Middle-aged n = 70	Elderly n = 36	p
IPA, °						
mean ± SD	72.3 ± 8.2	71.6 ± 10.8	73.8 ± 9.9	79.4 ± 9.4	81.4 ± 9.0	<0.001*
min-max	55.7 – 95.0	46.7 - 96.1	51.1 - 95.3	54.8 - 99.7	59.4 - 98.0	
IQR	67.0 - 78.0	62.2 - 80.9	65.9 - 82.1	73.3 - 86.2	75.7 - 87.2	
PMA, °						
mean ± SD	57.0 ± 10.4	57.3 ± 8.0	57.0 ± 11.0	56.1 ± 10.4	58.4 ± 10.5	0.870
min-max	38.4 - 84.4	39.7 - 72.6	31.6 - 96.8	30.7 - 86.9	38.5 - 78.7	
IQR	53.1 - 60.5	51.9 - 63.6	49.6 - 63.8	49.6 - 62.1	50.6 - 65.8	
PBA, °						
mean ± SD	136.5 ± 10.1	131.4 ± 10.7	133.7 ± 10.1	135.4 ± 10.5	131.9 ± 11.5	0.077
min-max	107.6 - 154.9	102.3 - 150.5	111.9 - 151.8	106.1 - 158.7	107.8 - 154.9	
IQR	130.9 - 143.4	124.1 - 139.4	124.6 - 140.8	127.2 - 142.9	125.3 - 141.0	

The data are expressed as the mean ± SD, IQR (25th–75th percentiles). * P-value <0.05 shows statistical significance. Bold characters show the difference between groups. IPA, interpeduncular angle; PBA pontomedullary angle; PMA, pontomesencephalic angle.

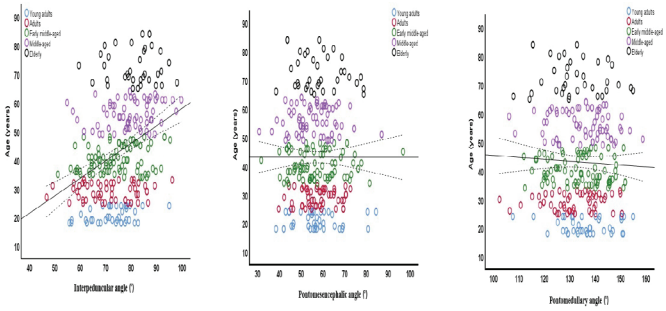

Figure 3. Association of age with ınterpeduncular, pontomesencephalic, and pontomedullary angles.

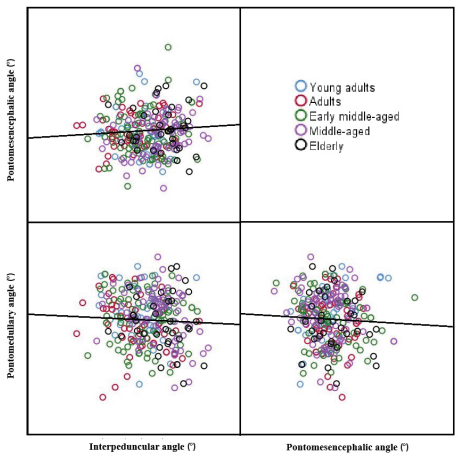

Figure 4. Correlation between interpeduncular, pontomesencephalic, and pontomedullary angles.

Discussion

This study presents one of the largest datasets to date investigating the variation of the IPA, PMA, and pontomedullary angle across age and sex in a healthy adult population. The findings demonstrate that while these angular measurements do not differ significantly by sex, the IPA increases notably in individuals aged 49 years and above. In contrast, PMA and PBA values remain stable across all age groups. The absence of significant correlations among the three angles, along with the age-related constancy of PMA and PBA, suggests a relative anatomical stability of the incisural and pontomedullary cisternal configurations in healthy adults. These results underscore the potential of the IPA as a morphometric marker sensitive to age-related changes, whereas the PMA and PBA appear less influenced by age or sex in the normative population.

In recent years, the IPA has drawn attention as an objective MRI-based indicator of spontaneous intracranial hypotension (7,11). The current literature reports conflicting findings regarding IPA values and their variation with age and sex in healthy individuals. Fatterpekar et al. (12) investigated the role of IPA in diagnosing PSP–Richardson Syndrome and reported an average IPA of 51.2° in the healthy control group. Wang et al. (7) reported that the mean IPA in the control group was approximately 56.3°, with males exhibiting a significantly wider IPA (~64°) compared to females (~53°). However, their study did not evaluate the association between age and the IPA (7). Nevertheless, in a transcranial ultrasound study conducted among adults aged 18 to 50, no significant effect of age or sex on IPA was identified (13). In a large-scale magnetic resonance morphometry study by Debnath et al., the mean IPA was reported as 76.4° ± 9.4, with a gradual widening observed beginning in the fifth and sixth decades of life. The study also noted that females may exhibit IPA values 1–2 degrees higher than males; however, this minimal difference was considered clinically negligible (8). In our cohort, IPA measurements aligned with those reported by Debnath et al., with a noticeable elevation observed in both middle-aged and older adults.

It is known that mild volumetric atrophy occurs in the midbrain (mesencephalon) and brainstem with aging. This condition may lead to a greater separation between the cerebral peduncles, resulting in a relative increase in cerebrospinal fluid (CSF) volume within the interpeduncular cistern (14). Indeed, Wang et al. (7) demonstrated that in cases of intracranial hypotension, the IPA was significantly reduced (from approximately 56° in controls to around 25° in hypotension), and that this reduction in IPA correlated with downward displacement of the brainstem (brain stem slumping). The authors suggested that the angle between the peduncles may be related to the CSF volume in the interpeduncular cistern, indicating that the IPA decreases when the CSF volume is reduced and widens when the volume increases (7). From this perspective, the expansion of the subarachnoid spaces in response to mild brain tissue shrinkage (atrophy) in advanced age may be a factor explaining the increase in the interpeduncular angle. In other words, the age-related increase in the distance between the peduncles is associated with the compensatory expansion of CSF around the brainstem to fill the surrounding space. This may be particularly relevant when distinguishing conditions associated with midbrain atrophy, such as PSP. Indeed, it has been reported that the IPA is significantly widened in PSP patients and demonstrates high sensitivity in differentiating PSP from Parkinson's disease (15). On the other hand, Ugga et al. (16) compared IPA measurements in iNPH, PSP, and control groups, all predominantly composed of elderly individuals. In that study, the average IPA in healthy controls was 75.5°, showing no significant difference compared to PSP patients, but was found to be elevated in those with iNPH (16). Therefore, a larger-than-normal IPA observed in an older individual may not always reflect pathology; the influence of age-related variation should be considered.

In the present study, measurements of both the PMA and the pontomedullary angle demonstrated no statistically significant association with either age or gender. Previous studies have reported a wide range of PMA values in healthy controls, varying between 39° and 65°, and emphasized that PMA does not significantly vary with gender (8, 17). A study involving healthy individuals from the Turkish population showed that the average PMA was greater in females (52°) than in males (56.8°). It was further noted that PMA declined in the 46–65 age group and increased again beyond the age of 65 (18). This apparent variability in PMA across age may reflect underlying anatomical and developmental changes of the brainstem. According to morphometric studies, the PMA tends to be broader in childhood, narrows during adolescence and adulthood as the pons enlarges relatively, and then widens again in older age due to pontine atrophy (8). However, such fluctuations are relatively minor, typically within a 2–4° range. The PMA reflects the curvature at the midbrain–pons junction, which is largely constrained by craniovertebral architecture. Given that the skull base angle remains stable

throughout life in healthy individuals, significant age-related variation in PMA is not generally expected. This may explain the lack of correlation between IPA and either the PMA or the pontomedullary angle. Notably, pronounced changes in PMA are observed primarily in pathological conditions, such as severe brainstem compression or anatomical deformities. Similarly, the pontomedullary angle—formed between the pons and medulla—is structurally stable and typically varies only in the presence of marked pathology. For instance, in cases of advanced brainstem atrophy, such as in olivopontocerebellar degeneration, a "flattening" of the pontomedullary angle (i.e., loss of its normally mild curvature) has been described (19).

This study has certain limitations. The retrospective design and single-center data usage introduce classic limitations such as potential selection bias and limited generalizability. Additionally, the sample size may be a limiting factor, particularly in detecting differences within subgroup analyses. A further limitation is that the present study focused exclusively on healthy subjects, thereby excluding the potential influence of pathological conditions. Future research involving various clinical populations could better elucidate the diagnostic and prognostic relevance of these parameters. Lastly, the fact that the measurements were performed manually and based on visual assessment may introduce the risk of interobserver and intraobserver variability. Although the methods used in this study are known to have high reliability, the integration of automated measurement software in future research could provide methodological improvement.

In conclusion, this study provides normative reference values for key brainstem angular measurements (IPA, PMA, and pontomedullary angle) in a healthy adult population and highlights their variation with age. IPA showed a significant age-related increase, while PMA and pontomedullary angles remained relatively stable. No significant sex-based differences were observed. These findings provide valuable diagnostic benchmarks to identify pathological alterations and aid in clinical assessments of neurological and neurosurgical conditions such as spontaneous intracranial hypotension.

Conflicts of Interest

The authors declare they have no conflicts of interest.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Committee Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Cukurova University Non-Interventional Clinical Research Ethics Committee (Date: 05.11.2021, Decision No: 2021/116-60).

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author, [N.K.Ş.].

Author Contributions: Concept – N.K.Ş., Design- N.K.Ş., H.E. and Y.K.A., Supervision – N.K.Ş., N.B. and Ö.O., Data collection and/or processing - S.T., H.E. and YKA, Analysis and/or interpretation - , Writing – N.K.Ş., Y.K.A., H.E., D.A. and Z.K.B. Critical review- H.E., Y.K.A., S.T., Z.KB., D.A., N.B., and Ö.O. All authors read and approved the final version of the manuscript.

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Research Article

Effectiveness of albumin-bilirubin score in predicting mortality in intensive care patients

Yoğun bakım hastalarında mortaliteyi tahmin etmede albumin-bilirubin skorunun etkinliği

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Abstract

Aim: The Albumin-Bilirubin (ALBI) score, originally developed to assess liver function in patients with hepatocellular carcinoma, has recently gained attention as a prognostic marker in critically ill patients. This study aimed to evaluate the effectiveness of the ALBI score in predicting mortality among intensive care unit (ICU) patients.

Material and Methods: This retrospective study included 157 adult patients admitted to the ICU diverse clinical conditions, including sepsis, respiratory failure, trauma, acute neurological events, and post-cardiac arrest, between November 2023 and November 2024. Clinical data, laboratory parameters, ALBI, SOFA, and APACHE II scores were assessed at ICU admission. The ALBI score is calculated as follows: (log10 bilirubin [µmol/L] × 0.66) + (albumin [g/L] × −0.085).

Results: Among the study participants (mean age: 71.7 ± 18.6 years; 55.4% male), 42.7% had diabetes mellitus, 21.7% chronic kidney disease (CKD), 38.9% chronic obstructive pulmonary disease, 73.9% cardiovascular disease, and 19.7% malignancies. The overall mortality rate was 42.7%. Multivariable Cox regression analysis revealed that CKD (HR: 1.90; 95% CI: 1.07–3.39; p = 0.029), higher ALBI scores (HR: 1.65; 95% CI: 1.03–2.65; p = 0.038) and higher APACHE II scores (HR: 1.04; 95% CI: 1.00–1.08; p = 0.031) were independent predictors of mortality.

Conclusion: The ALBI score is an independent predictor of mortality among critically ill patients with heterogeneous clinical conditions in general ICU settings. By integrating hepatic dysfunction, nutritional status, and systemic inflammation, ALBI complements traditional prognostic tools and may enhance clinical decision-making and risk stratification.

Keywords: ALBI score, intensive care, mortality, prognostic score, APACHE II, SOFA, albumin, bilirubin

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Öz

Amaç: Hepatoselüler karsinomlu hastalarda karaciğer fonksiyonunu değerlendirmek için geliştirilen Albümin-Bilirubin (ALBI) skoru, yakın dönemde kritik hastalarda prognostik belirteç olarak ilgi görmüştür. Bu çalışmada, yoğun bakım ünitesi (YBÜ) hastalarında ALBI skorunun mortaliteyi öngörmedeki etkinliğinin değerlendirilmesi amaçlandı.

Gereç ve Yöntemler: Bu retrospektif gözlemsel çalışmaya, Kasım 2023 ve Kasım 2024 tarihleri arasında, sepsis, solunum yetmezliği, travma, akut nörolojik olaylar ve kardiyak arrest sonrası gibi çeşitli klinik nedenlerle YBÜ'ye kabul edilen 157 erişkin hasta dahil edildi. Klinik veriler, laboratuvar parametreleri ile ALBI, SOFA ve APACHE II skorları YBÜ'ye kabulde değerlendirildi. ALBI skoru, (log10 bilirubin [µmol/L] × 0,66) + (albumin [g/L] × -0,085) formülü ile hesaplandı.

Bulgular: Hastaların yaş ortalaması 71,7 ± 18,6 yıl olup, %55,4'ü erkekti. Hastaların %42,7'sinde diabetes mellitus, %21,7'sinde kronik böbrek hastalığı (KBH), %38,9'unda kronik obstrüktif akciğer hastalığı, %73,9'unda kardiyovasküler hastalık ve %19,7'sinde malignite mevcuttu. Genel mortalite oranı %42,7 bulundu. Çok değişkenli Cox regresyon analizinde KBH varlığı (HR: 1,90; %95 GA: 1,07–3,39; p = 0,029), yüksek ALBI skoru (HR: 1,65; %95 GA: 1,03–2,65; p = 0,038) ve yüksek APACHE II skoru (HR: 1,04; %95 GA: 1,00–1,08; p = 0,031) mortalitenin bağımsız prediktörleri olarak saptandı.

Sonuç: ALBI skoru, farklı klinik nedenlerle yoğun bakıma yatırılan hastalarda mortalitenin bağımsız bir belirleyicisidir. ALBI skoru, karaciğer fonksiyonu, beslenme durumu ve sistemik inflamasyonu birlikte yansıtarak geleneksel prognostik araçları tamamlamakta ve klinik karar verme süreçlerini destekleyici bir araç olarak kullanılabilir.

Anahtar Kelimeler: ALBI skoru, yoğun bakım, mortalite, prognostik skor, APACHE II, SOFA, albumin, bilirubin

Introduction

Critically ill patients admitted to intensive care units (ICUs) – including those with sepsis, acute respiratory failure, severe trauma, acute neurological events, or post-cardiac arrest – face high mortality rates, often exceeding 15–50% in severe cases (1-4). To stratify risk and guide clinical management in such patients, clinicians frequently rely on established severity scoring systems like the Sequential Organ Failure Assessment (SOFA) and the Acute Physiology and Chronic Health Evaluation II (APACHE II). These scoring tools are widely used to predict ICU outcomes, but they involve complex calculations and require extensive clinical data, which can hinder rapid decision-making (5). This limitation has spurred interest in additional prognostic markers that might complement existing scores in critical care.

One emerging tool is the Albumin–Bilirubin (ALBI) score, originally developed as an objective measure of liver function to predict prognosis in patients with hepatocellular carcinoma (HCC) (6). The ALBI score is calculated solely from serum albumin and bilirubin levels, offering a simplified assessment of hepatic reserve compared to traditional liver scores. Notably, the ALBI score's applicability has extended beyond its initial use in HCC; it has shown prognostic value in broader contexts, suggesting potential utility outside of hepatology (7). Recent studies have indeed explored the ALBI score in ICU cohorts. An elevated ALBI score has been independently associated with higher mortality in septic ICU patients (8), and similar findings have been reported in patients with severe trauma in the ICU (9). Likewise, in acute cardiac critical illness, such as ICU patients with heart failure, a higher ALBI score correlated with increased risk of all-cause mortality (10). Moreover, the ALBI score was demonstrated to be a superior predictor of in-hospital mortality compared to established prognostic scoring systems like SOFA and APACHE II in acute pancreatitis patients (11). These observations suggest that the ALBI score captures important prognostic information in diverse critical illnesses, possibly reflecting the impact of systemic inflammation and liver dysfunction on patient outcomes.

Despite its promising performance in various critically ill patient populations, the predictive utility of the ALBI score remains understudied in general intensive care settings. Moreover, current literature includes only limited investigations evaluating the ALBI score specifically within heterogeneous ICU cohorts comprising conditions such as sepsis, respiratory failure, trauma, acute neurological events, and post-cardiac arrest. Given this gap, we hypothesized that the ALBI score could serve as an effective prognostic tool to predict mortality among critically ill ICU patients. Thus, the primary objective of this study was to evaluate the effectiveness of the ALBI score in predicting mortality in this diverse ICU population.

Material And Methods

This retrospective study was conducted between November 2023 to November 2024 on adult patients admitted to the tertiary-level reanimation ICU of Ordu State Hospital. The study was approved by the Ordu University Non-Interventional Clinical Research

Ethics Committee (Date: 20.12.2024, Approval No: 2024/207) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision). The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

During the study period, a total of 214 patients admitted to the tertiary-level reanimation ICU of the hospital were screened for eligibility. Adult patients aged 18 years or older, regardless of sex, were eligible for inclusion. Patients were included if they were either directly admitted to the ICU or transferred from another healthcare facility or department within the same institution. In patients with multiple ICU admissions, only the first admission was considered. Exclusion criteria were age under 18 years (n = 2), ICU admission following elective surgery (n = 25), ICU stays shorter than 24 hours (n = 22), and missing data (n = 8). After exclusion criteria, 157 patients were included in the final analysis.

The hospital's electronic information system and patient files were used to gather demographic and clinical data. Laboratory parameters were recorded at two time points: (1) Admission: upon ICU entry, and (2) Last available: for survivors, the value closest to the time of ICU discharge; for non-survivors, the last measurement obtained within 24 hours prior to death. In accordance with the ICU's standard treatment protocol during the study period, patients with serum albumin levels below 2.5 g/dL had been administered 200 mL of a 20% albumin solution intravenously. Patients with anuric chronic kidney disease (CKD), oliguric acute kidney injury (AKI), or anuria were not administered albumin due to the risk of fluid overload.

Definitions

The ALBI score is an evidence-based, objective, and easily applicable scoring system developed to assess liver function. It is calculated using only two basic biochemical parameters—serum albumin and total bilirubin—and does not include any subjective components. The ALBI score is calculated as follows: (log10 bilirubin [µmol/L] × 0.66) + (albumin [g/L] × −0.085). According to this score, patients are categorized into three prognostic grades: Grade 1 for scores ≤ −2.60, Grade 2 for scores > −2.60 to ≤ −1.39, and Grade 3 for scores > −1.39. Lower ALBI scores indicate better liver function, while higher scores reflect hepatic dysfunction and increased mortality risk [4].

The SOFA score is a widely used tool for mortality prediction and assessment of multiple organ failure in ICU patients, particularly those with sepsis. It evaluates six organ systems—respiratory, cardiovascular, central nervous, renal, coagulation, and hepatic—on a scale from 0 to 4. Higher scores are associated with increased mortality risk. For example, a SOFA score ≥14 is linked to mortality rates exceeding 95%, while a mean score > 5.1 corresponds to a mortality rate of up to 84.4% [12,13].

The APACHE II score estimates mortality risk in ICU patients by integrating age, chronic health status, and 12 physiological parameters (e.g., body temperature, mean arterial pressure, arterial pH, serum sodium and potassium, creatinine, hematocrit, white blood cell count, and Glasgow Coma Scale score). Scores range from 0 to 71, with higher scores indicating a worse prognosis. For instance, mortality rates are approximately 40% for scores of 20–24 and 73% for scores of 30–34 [14].

Statistical analysis

All analyses were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium) software. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Data exhibiting a normal distribution were presented as mean ± standard deviation (SD), and comparisons between groups were made using the Student's T-test. Non-normally distributed data were displayed as median (interquartile range (IQR): 25-75 percentiles) and comparisons between groups were conducted using the Mann-Whitney U test. Cox proportional hazards regression was used to determine the impact of demographic, clinical and laboratory parameters on mortality during the observation period. Multivariable Cox regression analysis with the backward method was subsequently performed to identify any possible independent predictors of mortality. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of the ALBI and APACHE II scores in predicting in-ICU mortality. Area Under the Curve (AUC) values are reported as AUC ± standard error (SE) with 95% confidence intervals (CI). Optimal cutoff values were determined by Youden's index. Changes in laboratory findings between admission and discharge were evaluated using a mixed model analysis for repeated measures. Value of $P < 0.05$ were considered statistically significant.

Results

The patients had a mean age of 71.7 ± 18.6 years, and the majority were male (55.4%). Among the patients, 42.7% had diabetes mellitus, 21.7% had CKD, 38.9% had chronic obstructive pulmonary disease (COPD), 73.9% had cardiovascular disease, and 19.7% had malignant conditions. The most common reason for admission to the intensive care unit was respiratory failure (52.2%), followed by sepsis (21.0%), acute neurological events (10.8%), cardiovascular arrest (9.6%), and trauma (6.4%). Invasive mechanical ventilation (IMV) was required in 58.6% of the patients, while 16.6% needed non-invasive mechanical ventilation (NIMV). Additionally, 45.6% required vasopressors, and 25.5% underwent hemodialysis. The median duration of ICU hospitalization was 9 days (range: 2–68), with a mortality rate of 42.7% (n = 67).

A 2.68-fold (95% CI = 1.58-4.57, p < 0.001) increase in mortality risk was observed in patients with CKD compared to those without. Admission due to acute neurological events was associated with lower mortality relative to sepsis (HR = 0.35, 95% CI = 0.13-0.98, p = 0.045). Patients who required IMV had a higher risk of mortality than those who did not (HR = 2.35, 95% CI = 1.07-5.87, p = 0.038). Likewise, patients with vasopressor requirements or those requiring hemodialysis demonstrated a significantly increased risk of mortality. Other demographic and clinical characteristics were not associated with mortality (Table 1).

At ICU admission, lower serum albumin levels were significantly associated with increased mortality risk (HR: 0.94; 95% CI: 0.91–0.98; p = 0.004). Similarly, higher ALBI score was associated with higher mortality (HR: 1.85; 95% CI: 1.19–2.87; p = 0.007). SOFA (HR: 1.12; 95% CI: 1.05–1.20; p = 0.001) and APACHE II scores (HR: 1.05; 95% CI: 1.02–1.09; p = 0.003) were associated with increased mortality risk. In contrast, admission levels of bilirubin, CRP, and procalcitonin were not significantly associated with mortality (p > 0.05) (Table 2).

All variables found to be significantly associated with mortality in univariable analysis (Table 1 and 2) were considered for inclusion in the multivariable regression analysis. However, the components of the ALBI, SOFA, and APACHE II scores were excluded due to potential multicollinearity with their respective composite scores. In the multivariable Cox regression analysis, CKD (HR: 1.90; 95% CI: 1.07–3.39; p = 0.029), higher admission ALBI score (HR: 1.65; 95% CI: 1.03–2.65; p = 0.038), and higher APACHE II score at ICU admission (HR: 1.04; 95% CI: 1.00–1.08; p = 0.031) were identified as independent predictors of mortality (Table 3).

The optimal cut-off point for the ALBI score in predicting mortality was found to be > -2.3, yielding a sensitivity of 79.1% and specificity of 61.1% (AUC ± SE: 0.774 ± 0.04; 95% CI: 0.700–0.837; p < 0.001). For the APACHE II score, the threshold was >13, with sensitivity and specificity values of 82.1% and 63.3%, respectively (AUC ± SE: 0.780 ± 0.04; 95% CI: 0.707–0.842; p < 0.001). No statistically significant difference was found between the two scores in terms of diagnostic performance (ΔAUC ± SE: 0.006 ± 0.05; 95% CI: 0.095–0.107; p = 0.900) (Figure 1).

Changes in laboratory parameters were more pronounced in non-survivors compared to survivors. In particular, the ALBI score showed a greater increase in non-survivors than in survivors (Table 4).

Table 1. Association between patients' demographic and clinical characteristics and mortality.

Variables	Intensive Care Discharge		Univariable Regression	
	Survivor n = 90	Deceased n = 67	HR (95% CI)	p
Age, years	68.2 ± 20.5	76.0 ± 15.9	1.02 (0.98-1.03)	0.093
Gender, n (%)				
Female	38 (42.2)	32 (47.8)	ref	
Male	52 (57.8)	35 (52.2)	0.75 (0.46-1.22)	0.243
Comorbidity, n (%)				
Diabetes mellitus	39 (43.3)	28 (41.8)	1.28 (0.78-2.11)	0.324
Chronic kidney disease	11 (12.2)	23 (34.3)	2.68 (1.58-4.57)	<0.001*
COPD	31 (34.4)	30 (44.8)	0.65 (0.39-1.09)	0.101
Cardiovascular disease	63 (70.0)	53 (79.1)	1.11 (0.61-2.01)	0.733
Malignancy	13 (14.4)	18 (26.9)	1.38 (0.79-2.40)	0.253
Reason for ICU admission, n (%)				
Sepsis	18 (20.0)	15 (22.4)	ref	
Respiratory failure	46 (51.1)	36 (53.7)	1.14 (0.70-1.85)	0.606
Trauma	10 (11.1)	-	0.50 (0.10-11.60)	0.995
Acute neurological event	12 (13.3)	5 (7.5)	0.35 (0.13-0.98)	0.045*
Cardiovascular arrest	4 (4.4)	11 (16.4)	1.17 (0.61-2.27)	0.635
Ventilator requirement, n (%)				
No	38 (42.2)	1 (1.5)	ref	
NIVM	21 (23.3)	5 (7.5)	1.15 (0.45-2.98)	0.770
IMV	31 (34.4)	61 (91.0)	2.35 (1.07-5.87)	0.038*
Vasopressor requirement, n (%)				
No	49 (54.4)	2 (3.0)	ref	
Low	26 (28.9)	33 (49.3)	1.37 (0.84-2.22)	0.210
High	15 (16.7)	32 (47.8)	1.58 (1.08-2.67)	0.033*
Need for hemodialysis, n (%)	10 (11.1)	30 (44.8)	2.02 (1.24-3.30)	0.005*
Length of ICU stay, days	8.0 (4.0-12.0)	10.0 (6.0-22.5)	-	-

The data are expressed as the mean ± SD or median (IQR) or number (%). * P-value <0.05 shows statistical significance. CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; ICU, intensive care unit; IMV, invasive mechanical ventilation; NIVM, non-invasive mechanical ventilation.

Table 2. Association of laboratory and clinical severity parameters with mortality.

Variables	Intensive Care Discharge		Univariable Regression	
	Survivor n = 90	Deceased n = 67	HR (95% CI)	p
Albumin, g/dL	34.6 ± 6.0	31.7 ± 5.8	0.94 (0.91-0.98)	0.004*
Bilirubin, mg/dL	0.4 (0.3-0.7)	0.5 (0.3-0.8)	1.04 (0.65-1.68)	0.864
CRP, mg/ dL	81.0 (28.6-134.0)	63.7 (23.4-144.4)	0.98 (0.96-1.01)	0.216
Procalcitonin, ng/mL	0.3 (0.1-1.2)	0.7 (0.2-2.5)	0.99 (0.97-1.01)	0.113
ALBI score	-2.4 ± 0.6	-2.1 ± 0.5	1.85 (1.19-2.87)	0.006*
SOFA score	5.0 (3.0-7.8)	8.0 (6.0-10.0)	1.12 (1.05-1.20)	0.001*
APACHE II score	11.0 (8.0-16.0)	19.0 (14.0-24.0)	1.05 (1.02-1.09)	0.003*

The data are expressed as the mean ± SD or median (IQR) or number (%). * P-value <0.05 shows statistical significance. ALBI, albumin–bilirubin score; APACHE, acute physiology and chronic health evaluation; CI, confidence interval; CRP, C-reactive protein; HR, hazard ratio; ICU, intensive care unit; SOFA, sequential organ failure assessment.

Table 3. Independent risk factors associated with mortality.

Variables	HR	95% CI		p
		Lower	Upper	
Chronic kidney disease	1.90	1.07	3.39	0.029*
ALBI score	1.65	1.03	2.65	0.038*
APACHE II score	1.04	1.00	1.08	0.031*
	-2Log Likelihood = 501.7; p < 0.001			

* P-value <0.05 shows statistical significance. ALBI, albumin–bilirubin score; APACHE, acute physiology and chronic health evaluation; CI, confidence interval; HR, hazard ratio.

Table 4. Changes in laboratory parameters at admission and discharge in deceased and surviving patients.

Variables	Survivor		p	Deceased		p	Δp
	Admission	Last available		Admission	Last available		
Albumin, g/dL	34.6 ± 6.0	30.6 ± 4.7	<0.001*	31.7 ± 5.8	24.1 ± 5.0	<0.001*	<0.001*
Bilirubin, mg/dL	0.4 (0.3-0.7)	0.4 (0.3-0.6)	0.213	0.5 (0.3-0.8)	0.8 (0.4-1.3)	<0.001*	<0.001*
CRP, mg/ dL	81.0 (28.6-134.0)	52.0 (26.0-92.2)	0.005*	63.7 (23.4-144.4)	170.0 (100.3-238.0)	<0.001*	<0.001*
Procalcitonin, ng/mL	0.3 (0.1-1.2)	0.2 (0.1-0.5)	<0.001*	0.7 (0.2-2.5)	2.6 (1.0-9.1)	<0.001*	<0.001*
ALBI score	-2.4 ± 0.6	-2.0 ± 0.4	<0.001*	-2.1 ± 0.5	-1.3 ± 0.5	<0.001*	<0.001*
SOFA score	5.0 (3.0-7.8)	4.0 (2.0-6.0)	0.002*	8.0 (6.0-10.0)	13.0 (11.0-15.0)	<0.001*	<0.001*
APACHE II score	11.0 (8.0-16.0)	10.5 (8.0-14.0)	0.008*	19.0 (14.0-24.0)	32.0 (26.0-36.0)	<0.001*	<0.001*

The data are expressed as the mean ± SD or median (IQR) or number (%). * P-value <0.05 shows statistical significance. Δp reflects the between-group difference in the change of laboratory parameters from admission to discharge between patients who survived and those who did not. ALBI, albumin–bilirubin score; APACHE, acute physiology and chronic health evaluation; CRP, C-reactive protein; ICU, intensive care unit; SOFA, sequential organ failure assessment.

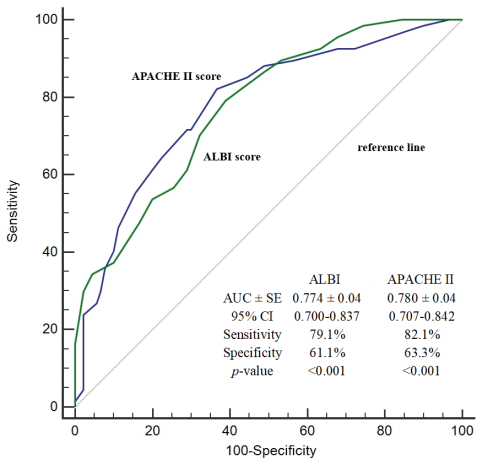

Figure 1. Diagnostic performance of ALBI and APACHE II scores in predicting mortality.

Discussion

The current study provides significant evidence supporting the prognostic value of the ALBI score in predicting mortality among patients admitted to the ICU for various clinical reasons. While the ALBI score has predominantly been evaluated within hepatology-focused populations, our findings highlight its effectiveness as a predictive tool across a diverse ICU cohort, including patients hospitalized due to respiratory failure, sepsis, trauma, acute neurological events, and post-cardiac arrest conditions. Specifically, we demonstrated that higher ALBI scores at ICU admission independently predict increased mortality risk, along with CKD and higher APACHE II scores. These findings emphasize the broader clinical relevance of the ALBI score, suggesting it can be effectively utilized in ICU settings as a simple, objective, and valuable tool for risk stratification.

Our study highlighted several clinical factors associated with increased mortality risk, including CKD, IMV, and vasopressor requirement. However, in addition to ALBI and APACHE II, only CKD remained an independent predictor after multivariable adjustment. One large sepsis study reported CKD approximately doubled 90-day mortality risk (HR ~2.3), independent of APACHE II and SOFA scores (12). The immunologic and metabolic derangements associated with CKD—such as uremic immune dysfunction and accumulation of inflammatory mediators—likely heighten vulnerability to critical illness, thereby explaining this association (12). In contrast, although IMV and vasopressor use were associated with mortality in univariate analyses, they were not independently predictive in multivariable models, likely due to their close relationship with the acute severity of illness already captured by scoring systems such as APACHE II and SOFA. Mechanical ventilation requirement is a recognized indicator of severe respiratory failure or profound neurological impairment, correlating with mortality rates ranging from approximately one-third in high-resource settings to two-thirds in resource-limited settings (13). Similarly, vasopressor use typically denotes significant hemodynamic instability, such as septic or cardiogenic shock, which inherently carries high acute mortality risks (14). Thus, our findings emphasize that both chronic conditions, such as CKD, and acute physiological disturbances captured by SOFA and APACHE II scores collectively contribute to the overall mortality risk in ICU patients.

The present study supports the finding that higher APACHE II scores are independently associated with mortality, in line with numerous studies conducted in ICU populations (15-19). As a defined component of the SOFA score, bilirubin plays a key role in assessing hepatic function. It can signify ischemic hepatopathy ("shock liver"), hemolysis, or resorptive bilirubinemia from extensive tissue injury, all of which portend a worse prognosis. Hyperbilirubinemia, which occurs in nearly 40% of critically ill ICU patients, is linked to higher organ failure rates and mortality (20, 21). Although this highlights the relevance of SOFA, previous studies have demonstrated that it shows diagnostic performance comparable to that of APACHE II (22). On the other hand, the SOFA score was significant in univariate analysis but lost its significance in the multivariate model, possibly due to acute physiology and liver dysfunction being accounted for by APACHE II and ALBI.

Hypoalbuminemia is a well-recognized marker of severe illness, poor nutritional reserve, and systemic inflammation. A substantial reduction in serum albumin levels is commonly observed in critically ill patients (23). In one ICU study, patients with profoundly low admission albumin (<~18.5 g/L) had more than double the mortality rate of those with higher albumin (52% vs 31%) (24). Yet albumin is not included in SOFA and APACHE II, meaning those scores may underweight the prognostic impact of chronic malnutrition or ongoing inflammatory burden. The ALBI score uniquely combines bilirubin with albumin, thus providing a more comprehensive assessment of liver function, metabolic stress, and inflammatory status. This integrative characteristic likely explains ALBI's superior predictive value for mortality observed in our adjusted multivariable model, consistent with prior evidence in heterogeneous ICU populations (8-11). Furthermore, in critically ill acute pancreatitis patients, ALBI demonstrated superior discrimination for in-hospital mortality (AUC: 0.86) compared to SOFA (0.72) or APACHE II (0.83) and was an independent risk factor for poor outcome (11). Likewise, recent large cohort analyses in sepsis have shown a near-linear relationship between higher ALBI values and increased death risk (adjusted HR ~1.5 per ALBI point) (8). The present study extends these observations across diverse ICU admission diagnoses – including sepsis, respiratory failure, trauma, acute neurological events, and cardiac arrest – indicating that ALBI's prognostic value is broadly applicable. Also, the diagnostic performance of the ALBI score was similar to that of the APACHE II score in the overall ICU cohort. The threshold values of the ALBI score vary across different ICU cohorts. In cardiac surgery intensive care unit patients, the ALBI cut-off for predicting mortality was reported as -2.44, while in heart failure cohorts, thresholds ranged between -2.19 and -1.92 (25-27). In sepsis cohorts, ALBI scores greater than -1.39 have been associated with an increased risk of mortality (8). The cut-off value identified in our study (> -2.3) is consistent with these findings and supports the overall applicability of the ALBI score across various intensive care settings.

The current study had several notable limitations. First, the retrospective retrieval of data from the hospital information management system carries the risk that some clinical parameters may have been missing or recorded inconsistently, which could introduce information bias into the interpretation of our findings. Second, the single-center design limits the generalizability of the results to all ICU patient populations. Third, the serum albumin and bilirubin levels used to calculate the ALBI score can be influenced by factors such as the patient's hydration status, nutritional state, and ongoing treatments. Finally, the causes of

death were not classified in detail, preventing a granular analysis of the specific factors leading to mortality. Future prospective, multicenter studies with larger and more diverse ICU cohorts are warranted to validate these findings, assess the temporal dynamics of the ALBI score, and explore causal mechanisms driving mortality in critically ill patients.

Conclusion

This study demonstrated that the ALBI score at ICU admission independently predicts mortality among critically ill adult patients admitted with diverse diagnoses, including sepsis, respiratory failure, trauma, acute neurological events, and cardiovascular arrest. Given that ALBI uniquely incorporates serum albumin, which is absent from widely used ICU prognostic scores such as SOFA and APACHE II, it provides additional prognostic value by capturing nutritional and inflammatory status alongside acute hepatic dysfunction. Therefore, ALBI may be beneficial for risk stratification and clinical decision-making in general ICU settings.

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Conflicts of Interest

The authors declare they have no conflicts of interest.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Ordu University Non-Interventional Clinical Research Ethics Committee (Date: 20.12.2024, Approval No: 2024/207).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

Authors' contribution

Concept – E.K., Design- E.K., Data collection and/or processing – E.K., S.E., and E.U., Analysis and/or interpretation - E.K., S.E., and E.U., Writing – E.K., Critical review- S.E., and E.U. All authors read and approved the final version of the manuscript.

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Research Article

Clinical profile and treatment outcomes of patients with urinary tract ınfections caused by raoultella planticola

Raoultella planticola kaynaklı idrar yolu enfeksiyonu olan hastaların klinik profili ve tedavi sonuçları

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Abstract

Aim: This study aimed to evaluate the clinical characteristics, treatment approaches, and outcomes in patients diagnosed with urinary tract infections (UTIs) caused by Raoultella planticola.

Material and Methods: This retrospective study included 25 adult patients with culture-confirmed Raoultella planticola UTIs admitted between January 2010 to January 2021. Clinical data such as demographics, presenting symptoms, comorbidities, laboratory findings, antibiotic treatments, and patient outcomes were retrospectively analyzed.

Results: The mean patient age was 67.8 ± 16.8 years. The most frequent comorbidities included diabetes mellitus (28%), chronic heart failure (24%) and chronic renal failure (24%). Anemia (64%), bacteriuria (60%), arthritis (56%), and altered sensorium (52%) were the most common clinical presentations. Bacteremia was identified in all patients. Acute cystitis was diagnosed in 80% of cases, while sepsis was identified in 20%. Ceftriaxone (32%) and ciprofloxacin (24%) were the most frequently administered antibiotics. The median hospital stay was 5 days (IQR: 3-14). Two patients died during hospitalization (8% mortality); both had bacteremia without sepsis criteria, and one had underlying pancreatic cancer.

Conclusion: Raoultella planticola UTIs predominantly affect older adults with significant comorbidities. While generally responsive to standard antimicrobial therapy, mortality may occur, particularly in patients with bacteremia and severe underlying diseases.

Keywords: Raoultella planticola, urinary tract infections, bacteremia, antibiotic therapy, clinical outcomes, mortality

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Öz

Amaç: Bu çalışmanın amacı, Raoultella planticola kaynaklı idrar yolu enfeksiyonu (İYE) tanısı alan hastaların klinik özelliklerini, uygulanan tedavi yöntemlerini ve tedavi sonuçlarını değerlendirmektir.

Gereç ve Yöntemler: Ocak 2010 ile Ocak 2021 tarihleri arasında, kültür ile doğrulanmış Raoultella planticola kaynaklı İYE tanısı ile yatırılan 25 erişkin hasta retrospektif olarak incelendi. Hastalara ait demografik veriler, başvuru semptomları, eşlik eden hastalıklar, laboratuvar bulguları, uygulanan antibiyotik tedavileri ve klinik sonuçlar değerlendirildi.

Bulgular: Hastaların ortalama yaşı 67,8 ± 16,8 yıldı. En sık görülen eşlik eden hastalıklar diyabetes mellitus (%28), kronik kalp yetmezliği (%24) ve kronik böbrek yetmezliği (%24) idi. Başvuruda en sık gözlenen klinik bulgular anemi (%64), bakteriüri (%60), artrit (%56) ve bilinç değişikliği (%52) idi. Tüm hastalarda bakteremi tespit edildi. Hastaların %80'inde akut sistit tanısı konurken, %20'sinde sepsis saptandı. En sık uygulanan antibiyotikler seftriakson (%32) ve siprofloksasin (%24) idi. Medyan hastanede kalış süresi 5 gün olarak bulundu (IQR: 3-14). Hastane yatışı sırasında iki hasta (%8) hayatını kaybetti; her iki hastada da bakteremi mevcuttu ancak sepsis kriterlerini karşılamıyorlardı ve bir hastada altta yatan pankreas kanseri vardı.

Sonuç: Raoultella planticola kaynaklı idrar yolu enfeksiyonları çoğunlukla ileri yaşta ve ek hastalığı olan bireyleri etkilemektedir. Bu enfeksiyonlar genellikle standart antibiyotik tedavisine iyi yanıt verse de, özellikle bakteremi ve ağır komorbiditeleri olan hastalarda mortalite görülebilmektedir.

Anahtar kelimeler: Raoultella planticola, idrar yolu enfeksiyonları, bakteremi, antibiyotik tedavisi, klinik sonuçlar, mortalite

Introduction

Raoultella (R.) planticola, previously known as Klebsiella planticola, is a gram-negative, aerobic, non-motile bacterium that belongs to the Enterobacteriaceae family (1, 2). Initially considered innocuous, it is commonly found in soil and aqueous environments. However, in recent years, there has been an increasing number of reports highlighting severe infections associated with R. planticola (3, 4). Despite being known as a pathogen for several decades, the management of R. planticola infections continues to pose challenges for clinicians due to limited published data, similar to the predicament faced with other rare pathogen infections (4).

Though R. planticola has rarely been implicated in urinary tract infections (UTIs) (5, 6), it has caused a range of opportunistic infections in humans, including cases of bacteremia, pneumonia, hepatobiliary infections, and UTIs (7, 8). Most reported patients have had underlying immunosuppression, comorbid illnesses, or recent invasive procedures, suggesting that R. planticola primarily causes infection in vulnerable hosts (6). These features raise concerns about missed identification and appropriate management of this unusual pathogen. The main concern for the physicians lies beneath carbapenem-resistant nosocomial R. planticola infections, thus originating from a resistant strain of genes (9, 10).

To date, published data consist mainly of individual case reports and small case series, highlighting a substantial knowledge gap. A recent 5-year review from a single center identified only 37 cases of R. planticola bacteriuria, u nderscoring the rarity of this infection even in large hospitals (11). Research on R. planticola urinary tract infections in Turkey primarily comprises case reports (12-14), and detailed demographic and clinical profiling of affected patients remains insufficiently studied.

We hypothesized that UTIs caused by R. planticola, though rare, have distinct clinical characteristics and outcomes that have not been fully described in the literature. In light of the gaps in current knowledge, the aim of the present study was to investigate the clinical profile and treatment outcomes of UTI patients with R. planticola in Turkey. By characterizing these cases, we seek to provide the first detailed account of the patient demographics, risk factors, clinical course, and responses to therapy for this unusual uropathogen in our region.

Material and Methods

A retrospective study was conducted on patients who were diagnosed with UTIs and whose urine cultures were positive for R. planticola, in the Internal Medicine Department of Maltepe University Faculty of Medicine from January 2010 to January 2021. The study was approved by the Maltepe University Clinical Research Ethics Committee (Date: 02.05.2023, Approval No: 2023/900/26) and was carried out in accordance with the relevant ethical guidelines and the Helsinki Declaration (2013 Brazil revision). The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

During the study period, patients diagnosed with UTIs were retrospectively evaluated. Inclusion criteria included patients over 18 years of age with confirmed R. planticola in urine cultures and complete demographic and clinical data. Patients younger than 18 years, those without bacterial growth, and cases with incomplete data were excluded. Twenty-five patients meeting the defined inclusion and exclusion criteria were selected for the analysis.

Data Collection

The hospital's electronic information system and patient files were used to gather demographic and clinical data at both the admission and discharge periods. Demographic data collected included age, gender, body mass index (BMI), and comorbidities. Patients' clinical symptoms were documented as bacteremia, anemia, bacteriuria, arthritis, altered sensation, fatigue, fever, dysuria, increased urination frequency, and flank pain. Clinical data comprised blood parameters such as white blood cell (WBC) count, platelet count, and creatinine levels, antibiotic types, duration of hospitalization, presence or absence of sepsis, and survival outcomes.

Diagnosis

Identification of the isolate as R. planticola was achieved by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) using the VITEK MS system (bioMérieux, Marcy l'Étoile, France). Antimicrobial susceptibility testing was conducted with the VITEK-2 Compact System. The VITEK 2 GN card (REF 21341) was used for identification, and the VITEK 2 AST-N420 card (REF 424039) was employed to determine antimicrobial susceptibility, including testing for carbapenem sensitivity. The microorganism was isolated from both blood and urine cultures. Interpretation of susceptibility results was based on the criteria defined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Statistical Analysis

The SPSS 26.0 (IBM Corporation, Armonk, New York, United States) program was used to analyze the variables. The conformity of the data to the normal distribution was evaluated with the Shapiro-Wilk test. Quantitative variables were summarized as mean ± standard deviation (SD) and categorical variables as frequency and percentage. Data exhibiting a normal distribution were presented as mean ± standard deviation, and comparisons between groups were made using the Student's T-test. Non-normally distributed data were displayed as median (interquartile range (IQR): 25-75 percentiles) and comparisons between groups were conducted using the Mann-Whitney U test. A p-value below 0.05 was considered statistically significant.

Results

The mean age of the patients was 67.8 ± 16.8 years (range: 26 – 91 years). The mean BMI was 26.6 ± 2.7 kg/m^2 (range: 18.1–37.2 kg/m^2). None of the subjects were alcohol users, and only six of them (24%) were former or current smokers. The most frequent comorbidities included diabetes mellitus (28%), chronic heart failure (24%) and chronic renal failure (24%) (Table 1). Additionally, one patient (a 76-year-old male) was using steroids and undergoing chemotherapy.

Table 1. Demographic profile of patients.

Variables	All population n = 25
Age, years	67.8 ± 16.8
Female gender, n (%)	9 (36.0)
BMI, kg/m2	26.6 ± 2.7
Smoking, n (%)	6 (24.0)
Comorbidities, n (%)	
No	3 (12.0)
Yes	22 (88.0)
Diabetes mellitus	7 (28.0)
Chronic heart failure	6 (24.0)
Chronic renal failure	5 (20.0)
Chronic obstructive pulmonary disease	4 (16.0)
Rheumatoid arthritis	3 (12.0)
Asthma	2 (8.0)
Dementia	1 (4.0)
Lymphoma	1 (4.0)
Paraplegia	1 (4.0)
Pancreatic cancer	1 (4.0)

The data are expressed as the mean ± SD, median (IQR), or frequency (%).

Clinical symptoms and laboratory findings of the 25 patients are summarized in Table 1. Anemia (64%), bacteriuria (60%), arthritis (56%), and altered sensorium (52%) were the most commonly observed clinical symptoms, with fatigue and fever noted less frequently (each 40%). Dysuria and increased urinary frequency occurred in 20% of cases, while flank pain was rare (8%). At hospital admission, 24% (n=6) of patients had a glomerular filtration rate (GFR) below 50 mL/min, and 4% (n=1) had a GFR below 10 mL/min. Bacteremia was identified in all patients. Acute cystitis was diagnosed in 80% of cases, while sepsis was identified in 20%. It is important to note that these percentages indicate overlapping diagnoses, as patients often presented simultaneously with multiple clinical conditions (e.g., bacteremia with acute cystitis or sepsis) (Table 2).

Table 2. Clinical symptoms, laboratory findings and diagnosis of patients.	
Variables	All population n = 25
Clinical symptoms, n (%)	
Anemia	16 (64.0)
Bacteriuria	15 (60.0)
Arthritis	14 (56.0)
Altered sensorium	13 (52.0)
Fatigue	10 (40.0)
Fever	10 (40.0)
Dysuria	5 (20.0)
Increased urinary frequency	5 (20.0)
Flank pain	2 (8.0)
Laboratory findings	
HgA1C, %	6.1 ± 1.1
GFR	70.0 ± 24.9
< 50 mL/min	7 (28.0)
WBC, ×103/uL	9.8 (9.0-11.2)
Platelets, ×103/uL	255.0 (189.0-325.0)
Creatinine, mg/dL	1.0 (0.9-1.2)
Lactic acid, mmol/L	1.6 ± 0.3
Diagnosis, n (%)	
Bacteremia	25 (100.0)
Acute cystitis	20 (80.0)
Sepsis	5 (20.0)
The data are expressed as the mean ± SD, median (IQR), or frequency (%).	

The primary treatment options administered were ceftriaxone in 32% of cases, followed by ciprofloxacin in 24%, ertapenem in 16%, levofloxacin in 12%, and meropenem in 12%. Five subjects (20%) received combination therapy. The median length of hospital stay (LOS) was 5 days, ranging from 1 to 40 days (IQR: 3-14). Treatment outcomes resulted in 92% of patients being discharged from the hospital, with an overall mortality rate of 8% (Table 3).

Table 3. Treatment and patient outcome.	
Variables	All population n = 25
Antibiotic, n (%)	
None	3 (12.0)
Ceftriaxone	8 (32.0)
Ciprofloxacin	6 (24.0)
Levofloxacin	3 (12.0)
Ertapenem	4 (16.0)
Meropenem	3 (12.0)
Combination therapy, n (%)	5 (20.0)
Length of hospital stay, days	5 (3-14)
Mortality, n (%)	2 (8.0)
The data are expressed as the median (IQR) or frequency (%).	

Discussion

In the current literature, data regarding urinary tract infections associated with R. planticola prior to 2021 is notably limited. However, in 2021, Alampoondi Venkataramanan identified a total of 37 R. planticola isolates over a 5-year study period (11). Our series of 25 patients thus represents one of the largest clinical cohorts to date, enabling a more robust characterization of the infection's features. Overall, our findings confirm that R. planticola UTIs tend to occur in older adults with significant comorbidities, and they generally respond well to appropriate antimicrobial therapy, in line with the scattered case reports and small series available for comparison.

The demographic profile in our cohort reinforce that R. planticola UTIs tend to occur opportunistically in vulnerable hosts – typically elderly individuals with comorbid conditions – rather than healthy populations. Risk factors such as older age, cancer, diabetes mellitus, immunosuppression, and impaired kidney function were identified as significant for R. planticola UTIs, consistent with risk factors for UTIs from other organisms (15-17). Alampoondi Venkataramanan et al., in their five-year retrospective review of R. planticola infections, reported a mean patient age of 77 years, highlighting a notable prevalence of diabetes mellitus and chronic kidney disease among these cases (11). Most literature cases likewise describe hosts with significant comorbidity or immune compromise. The first ever reported UTI due to R. planticola occurred in an 89-year-old man with multiple chronic conditions – including heart failure, chronic kidney disease, coronary artery disease, anemia, and other ailments (6) – illustrating the typical complexity of such patients. In a similar manner, many of our patients exhibited comorbidities, including diabetes, older age, and diseases potentially causing immunosuppression such as rheumatoid arthritis, asthma, pancreatic cancer, and lymphoma. These conditions align with known risk factors for R. planticola infection in general, such as immunosuppression, end-stage renal disease (especially dialysis dependence), malignancy, and recent medical interventions (6). Additionally, our series included a 76-year-old male patient who was receiving steroid therapy and chemotherapy. This observation echoes the findings of Venkataramanan et al., who noted that overt immunosuppressive therapy (e.g. chronic steroid use) was present in only 3 of 37 R. planticola UTI cases (11).

The clinical manifestations of R. planticola UTI in our series were largely similar to those of UTIs caused by more common gram-negative organisms, with some nuances due to patient age and comorbid status. The majority of patients presented with lower urinary tract symptoms such as dysuria, urinary frequency, and fever, often indistinguishable from routine UTI caused by

organisms like E. coli (18, 19). Notably, a substantial proportion of our patients – especially the very elderly – exhibited altered sensorium or confusion at presentation. This finding is in line with the report by Venkataramanan et al., where altered mental status was the most common presenting complaint among UTI patients with R. planticola, followed by fever (11).

In our cohort, sepsis developed in one-fifth of the patients. According to the study by Venkataramanan et al., 2 of 37 patients developed urosepsis, and another 2 progressed to septic shock (11). Previous studies have shown that approximately 10% to 30% of all sepsis cases could be attributed to UTIs (20-22). Although R. planticola has been historically viewed as a low-virulence environmental organism, our data and published cases make it clear that it can cause clinically significant illness, including frank sepsis, when host defenses are sufficiently compromised. Fager and Yurteri-Kaplan noted that R. planticola cystitis often occurred in immunocompromised or post-operative settings, and they identified cystitis as the single most common infection type associated with this organism (23).

R. planticola demonstrates inherent resistance to ampicillin through chromosomally encoded overexpression of class-A β-lactamase (24, 25). The pathogen's antimicrobial susceptibility pattern mirrors that of other Enterobacteriaceae such as Klebsiella. R. planticola isolates are generally susceptible to aminoglycosides, most cephalosporins, fluoroquinolones, and carbapenems (6, 14, 26). The treatment outcomes in our series were generally favorable. All patients received targeted antimicrobial therapy once R. planticola was identified, and the infection was cleared in the vast majority of cases. This is consistent with many cases reported in the literature (6, 9, 11, 22). However, mortality occurred in two patients. Both patients who died had concurrent R. planticola bacteremia, although notably neither met clinical criteria for sepsis at the time. One of these cases involved a patient with advanced pancreatic cancer, a serious comorbidity likely contributing to the poor outcome. This parallels case reports in high-risk patients: for instance, a fatal R. planticola sepsis was reported in an immunocompromised patient with pancreatic cancer (27). Moreover, evidence from R. planticola bacteremia studies supports the role of host factors in determining mortality. Chun et al. reviewed 20 cases of R. planticola bacteremia and found that 85% of patients had underlying malignancies; all infections that were monomicrobial responded to antibiotics with recovery, whereas the only fatalities occurred in polymicrobial or complicated cases (5).

This study has several limitations inherent to its design. First, the retrospective nature of the study introduces potential biases, particularly concerning data completeness and accuracy, as patient information was gathered from electronic records and clinical files. Some clinical details or patient outcomes might have been inadequately documented, potentially influencing the study's reliability. Second, the small sample size limits the generalizability of our findings due to the rare occurrence of Raoultella planticola infections. Third, being a single-center study further restricts the external validity, as the findings may not represent the clinical and microbiological characteristics seen in different geographic regions or healthcare settings. Lastly, due to the retrospective design, long-term follow-up and recurrence rates could not be evaluated, which are critical aspects for understanding the clinical course of infections caused by this rare pathogen. Future prospective, multicenter studies with larger cohorts and long-term follow-up are warranted to validate and expand upon these preliminary findings.

Conclusion

Our findings indicate that urinary tract infections caused by R. planticola typically occur in elderly patients with significant comorbidities, such as diabetes mellitus, chronic heart failure, and chronic renal failure. Although the clinical outcomes are generally favorable with appropriate antimicrobial therapy, the frequent association with bacteremia and potential for severe systemic complications, including sepsis, necessitate heightened clinical vigilance. The variable antimicrobial resistance patterns observed underline the importance of timely microbiological identification and susceptibility testing for optimal therapeutic management. Given the rarity and limited clinical awareness of R. planticola, clinicians should maintain a high index of suspicion in vulnerable patient groups, recognizing the potential severity and ensuring early initiation of targeted treatment.

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Conflicts of Interest

The author declare they have no conflicts of interest.

Ethics Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Maltepe University Clinical Research Ethics Committee (Date: 02.05.2023, Approval No: 2023/900/26).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author.

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Derleme

Sabit implant destekli protezlerde implant abutment sınıflamaları ve mikro-hareketlilik: kavramsal çerçeve ve klinik yansımalar üzerine derleme

Classıfıcatıons of ımplant abutments and mıcromovement ın fixed ımplant-supported prostheses: a conceptual framework and clınıcal ımplıcatıons-a revıew

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Öz

İmplant abutmentları, sabit implant destekli protezlerde kritik bileşenler olup, implant gövdesi ile nihai protez restorasyonu arasında bir ara yüz işlevi görür. Sınıflandırmaları, bağlantı tipi, malzeme bileşimi, tasarım, tutuculuk mekanizması ve üretim yöntemi gibi faktörlere dayanır. Uygun bir abutment seçimi, protez gereksinimleri, oklüzal kuvvetler, peri-implant doku durumu ve hasta spesifik anatomik özelliklere bağlıdır. Bu sınıflamaların anlaşılması, mekanik stabilite, fonksiyonel uzun ömür ve estetik sonuçların optimize edilmesi için hayati öneme sahiptir, çünkü yanlış abutment seçimi biyomekanik sorunlara, periimplantitis veya protez başarısızlığına yol açabilmektedir. Malzeme ve dijital iş akışlarındaki gelişmeler, implant abutmentlarının hassasiyetini ve uzun vadeli başarısını artırmaya devam etmektedir. İmplant ile abutment arasındaki mikro-hareketlilik, fonksiyonel yükleme sırasında ara yüzeyde meydana gelen küçük rölatif hareket anlamına gelmektedir. Bu hareket, implant-abutment bağlantı tipi, malzeme özellikleri ve mekanik uyumdan etkilenmekle beraber aşırı mikro-hareketlilik, vida gevşemesi, bağlantı alanında aşınma, mikrobiyal infiltrasyon ve nihayetinde protez başarısızlığına yol açabilmektedir. İnternal bağlantılar, özellikle konik veya Morse taper tasarımları, genellikle daha az mikro-hareketlilik sergilemekte ve eksternal bağlantılara göre daha fazla stabilite sunmaktadır. CAD/CAM teknolojisi ve abutment tasarımındaki gelişmeler, implant-abutment arasındaki bu hareketi minimalize etmeyi ve klinik sonuçları iyileştirmeyi amaçlamaktadır. Bununla birlikte implant destekli sabit protezlerin biyolojik entegrasyonunu geliştirmeyi de hedeflemektedir. Keza, mikro- hareketliliğin etkin bir şekilde yönetilmesi, implant destekli sabit protezlerin uzun vadeli başarısının sağlanması ve klinik performansının sürdürülebilirliği açısından kritik bir faktördür.

Anahtar Kelimeler: diş dayanakları, dental implant-dayanak tasarımı, diş implantları, diş protezi, implant destekli

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Abstract

Aim: Implant abutments are crucial components in fixed implant-supported Prostheses, serving as the interface between the implant body and the final prosthetic restoration. Their classification is determined by factors such as connection type, material composition, design, retention mechanism, and manufacturing method. The choice of an appropriate abutment depends on prosthetic requirements, occlusal forces, peri-implant tissue considerations, and patient-specific anatomical features. Understanding these classifications is vital for optimizing the mechanical stability, functional longevity, and aesthetic outcomes, as incorrect abutment selection can lead to biomechanical issues, peri-implantitis, or prosthetic failure. Ongoing advancements in materials and digital workflows continue to enhance the precision and long-term success of implant abutments. Micromovement between the implant and abutment refers to the small relative motion that occurs at the interface during functional loading. This movement is influenced by the implant-abutment connection type, material properties, and mechanical fit. Excessive micromovement can result in complications such as screw loosening, wear at the connection site, microbial infiltration, and eventual prosthetic failure. Internal connections, especially conical or Morse taper designs, typically exhibit less micromovement and offer greater stability compared to external connections. Advances in CAD/CAM technology and implant design have contributed to reducing micromovement, improving clinical outcomes, and enhancing the longevity and biological integration of implant-supported restorations. Managing micromovement effectively is essential for ensuring the long-term success of implant- supported prostheses.

Keywords: dental abutment, dental ımplant-abutment design, dental ımplants, dental prosthesis, ımplant-supported

Giriş

Dental implantların diş hekimliği alanına başarılı bir şekilde entegre edilmesi, tam ve parsiyel dişsizlik durumlarında çiğneme fonksiyonu ve estetik açıdan etkili bir restoratif alternatif sunmuştur. 60 yılı aşkın süredir devam eden kullanımları, çeşitli klinik senaryoların yönetimine yönelik farklı sistem ve yöntemlerin geliştirilmesine öncülük etmiştir. Günümüzde, 80'den fazla implant üreticisinin bulunması ve her bir üreticinin kendine özgü materyal ve tasarım çeşitliliği sunması, diş hekimlerine geniş bir tedavi yelpazesi sağlamaktadır. Bununla birlikte, özellikle karmaşık klinik vakalarda uygun abutment seçimi, diş hekimlerini karar verme sürecinde zorluklarla karşı karşıya bırakmakta ve kapsamlı araştırmalar yapmalarını gerektirebilmektedir [1]. Abutment, implant gövdesine vidalanarak doğal bir dişin prepare edilmiş hali gibi işlev gören ve temel görevi protetik üst yapıya retansiyon sağlamak olan bir implant bileşenidir. Taban kısmı, implant gövdesi ile sağlam bir bağlantı oluştururken, baş kısmı ağız içinde dışarı doğru uzanarak retansiyon fonksiyonunu yerine getirir. Boyun kısmı ise baş ve taban bölümlerini birbirine bağlayarak diş eti seviyesinde konumlanır ve biyolojik uyumu destekler [2]. Bu şekilde, abutmentlar final restorasyonlar için retansiyon, dayanıklılık, stabilite ve optimal konumlandırma işlevlerini yerine getirerek protezin uzun vadeli başarısını ve biyomekanik uyumunu sağlamış olur [3]. Günümüzde, fonksiyonun yanı sıra özellikle anterior bölgedeki estetik kaygılar kullanılacak olan abutment materyali ve sisteminin seçimini, ideal bir çıkış profili sağlanması için ise doğru transmukozal yükseklik ve alanın oluşturulmasını öncelikli kılmaktadır [4]. Fonksiyonel bir bütünlük sağlayan peri-implant yumuşak dokunun uygun abutment materyali ile yönetimi, bakteriyel penetrasyonu ve sitotoksisiteyi ve buna bağlı oluşan peri-implantitisi önlemekte, implant-abutment bağlantısının başarılı bir şekilde yalıtımını sağlamaktadır. Bu çok faktörlü mekanizmadaki eksiklikler kısa veya uzun vadede peri-implantitis oluşumunu kaçınılmaz kılmaktadır. İmplant çevresindeki sızdırmazlığın azalmasının sonuçlarını inceleyen 47 çalışmanın değerlendirildiği bir meta-analiz, bireylerin %19,83'ünde ve implant sahalarının %9,25'inde peri-implantitis geliştiğini göstermiş; bu nedenle, peri-implant yumuşak dokunun etkili bir bariyer oluşturmasının komplikasyon riskini önemli ölçüde azalttığını ortaya koymuştur [5]. Protetik yüklemenin tipi, implant- abutment bağlantı şekli, kemik-implant arayüzü, implant yüzey özellikleri, protetik restorasyonun kalitesi ve kemiğin yapısı implant başarısını belirleyen biyomekanik faktörlerin başında gelmektedir. Bu faktörleri en iyi şekilde organize etmek için en temel elemanlardan biri olarak abutment konusunda uygulayıcı hekimlerin donanımlı olması tedavide başarıya ulaşmak için temel bir zorunluluktur [6].

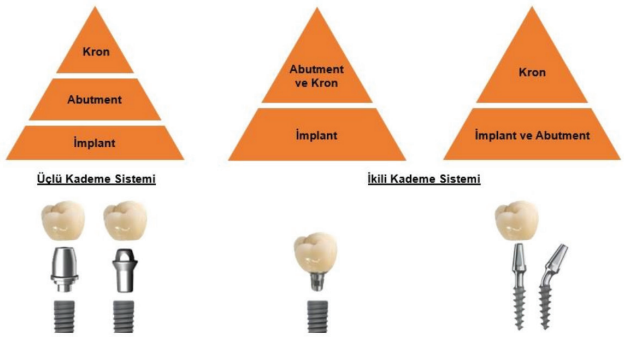
İmplant Sistemlerinin Sınıflandırılması

İmplant üstü protezlerin yapımı için temel bir eleman olan abutmentlar farklı araştırmacılar tarafından farklı yönlerinin değerlendirildiği benzer sınıflamalara sahiptirler:

Kademeye Göre Sınıflama

Abutmentlar, implant platformuna vida ile tutunur. Protetik restorasyon vida ile abutment üzerine bağlanabilir veya simante

edilerek bu işlem sağlanabilir. Bu tarz sistemlere 3'lü kademe sistemler denilmektedir. Bunun yanı sıra abutment ve kron bir bütün olarak üretilerek abutment üzerine vidalanabilir. Bunun yanı sıra, monoblok implant sistemleri ve abutmentın implant gövdesi içine sürtünme veya kilitlenme yoluyla oturduğu sistemler de yaygın olarak kullanılmaktadır [3] (Şekil 1).

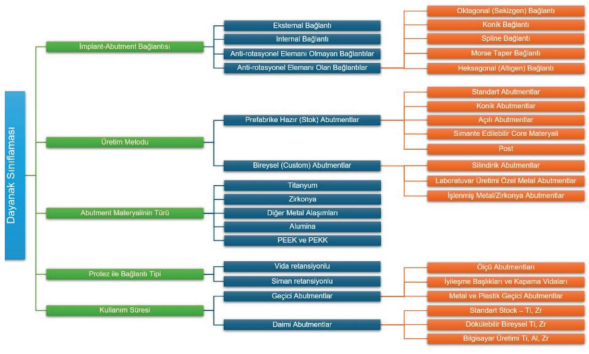


Şekil 1. Kademeye Göre Sınıflama.

Şekil 1. Kademeye Göre Sınıflama.

Genel Sınıflama

Yapılan derleme şeklindeki bu sınıflama birçok farklı açıdan implant-abutment bağlantı tiplerini sınıflamış olup; implant gövdesine bağlanma tipi, materyal çeşidi, protetik restorasyon için tutucu mekanizması ve üretim metodu gibi kritik komponentleri içermektedir [1] (Şekil 2).



Şekil 2. Genel Sınıflama.

Kullanım Süresine Göre Abutmentlar

Geçici Abutmentlar

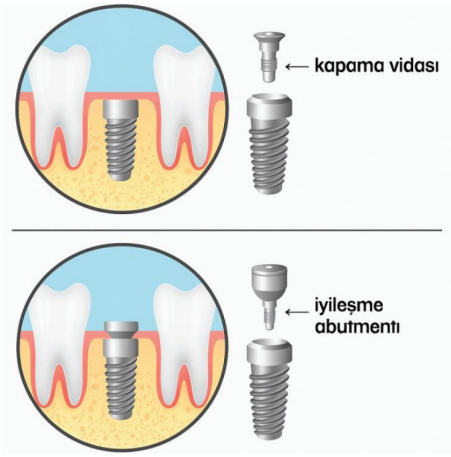
Kullanımı belli aşama ve/veya süreyle sınırlı olan abutment türleridir.

Ölçü Abutmentları

Geleneksel olarak 2 çeşit implant seviyesinde ölçü tekniği bulunur. Bunlar açık kaşık (pick-up) ve kapalı kaşık (transfer) ölçü tekniklerdir. Kapalı kaşık ölçü tekniği 3 veya daha az ardışık implant ölçülerinde önerilir. Ölçü postları alınan ölçünün içinde değil, implantlara vidalı bir şekilde ağızda kalır ve hekimin bu parçaları oradan sökmesi, implant analogları ile bağlaması ve alınan ölçünün içine yerleştirmesi gerekir. Açık ölçü tekniğinde ise ölçü kaşığının içinden nispeten uzun ölçü parçalarının vida deliklerine ulaşılır ve implant ve ölçü parçası bağlantısı açılır. Ölçü abutmentları alınan ölçünün içinde ağızdan çıkartılır ve analogları ile bağlanır. Ardışık implant sayısı 4 veya daha fazla ise tercih edilir.[7] (Şekil 3) Dijital sistemler ise 3 farklı yolla ölçü alınımına olanak sunmaktadır. Bunlardan ilki alınan ölçünün ana modelinin geleneksel yolla elde edilmesi ve bu modelin bir optik tarayıcı ile taranmasıdır. Daha sonrasında anatomik abutment veya daimî restorasyonların CAD/CAM ile üretimi için dijital platformda tasarımlarına başlanır. Bir diğer yöntem ise üzerinde özel kodlar içeren iyileşme başlıklarının kullanımıdır (Encode; Biomet 3i, Palm Beach Gardens, Fla). Bu sayede hekim, dijital veya geleneksel yöntemlerle iyileşme abutmentlarının üzerinden ölçü alabilir. Son olarak, ağız içi tarama parçaları (scan body) sayesinde intraoral tarayıcılar aracılığıyla ağız içi dijital ölçü, elektronik ortama aktarılabilir. Bu dijital veriler, tasarımcı tarafından ilgili implant firmasının kütüphanesinden alınan dijital implant analogları kullanılarak, dijital ortamda ana model üzerinde tasarım yapılmasına olanak tanır [7] (Şekil 4).

Şekil 3. Ölçü Abutmentları. Soldan Sağa: Kapalı Ölçü Postu, Kısa-açık Ölçü Postu ve Uzun-açık Ölçü Postu.

Şekil 4. Oklüzal yüzeyinde özel kodlar içeren iyileşme başlıkları (Encode; Biomet 3i, Palm Beach Gardens, Fla).



Şekil 5. Üst: Tek aşamalı yöntem ile kapama vidasının uygulanması. Alt: Çift aşamalı yöntem ve iyileşme abutmentının uygulanması.

İyileşme Abutmentları

İmplant yerleştirildikten ve osseoentegrasyon tamamlandıktan veya immediat olarak yerleştirilebilen, implant fikstürü girişinin kemik ve yumuşak doku ile kapanmasını önlemek amacıyla üretilmiş geçici abutmentlardır. Tek aşamalı veya çift aşamalı protokol ile uygulanabilmektedir. Tek aşamalı yöntemde iyileşme başlığı, implant cerrahisi sonrası evrede ağızda bulunur. Bu sayede hekim ikinci bir cerrahi işlem uygulamadan direkt olarak implant gövdesine erişebilir. Özellikle çekim sonrası immediat implantasyon uygulamalarında ve eş zamanlı diş eti şekillendirmesiyle çıkış profilinin oluşturulmasının hedeflendiği durumlarda tercih edilmektedir. Çift aşamalı yöntemde ise kapama vidası kullanılır ve implant cerrahisi sonrasında implantın üstü mukozayla örtülerek kapatılır. Bu protokolde, osseointegrasyon süreci boyunca implantın ağız ortamından izole edilmesi sağlanır. Böylece, erken yükleme veya dışsal kontaminasyon riskleri en aza indirilmiş olur. İyileşme tamamlandıktan sonra ikinci bir cerrahi işlemle mukoza açılır ve iyileşme başlığı takılarak protetik faza geçiş yapılır [3] (Şekil 5). Bireysel iyileşme abutmentları için kullanılan PEEK, PMMA, zirkonya, reçine kompozit ve titanyum gibi malzeme türlerini ve her bir malzemenin mekanik ve biyolojik özelliklerini inceleyen bir araştırma, tüm bu malzemelerin osseointegrasyon sürecinde ağız ortamında kalmak için yeterli özelliklere sahip olduğunu ve peri-implant yumuşak ve sert doku koruma faydaları sağladığını göstermiştir.[8] Son zamanlarda PEEK, implant diş hekimliğinde iyileşme abutmentı ve geçici implant restorasyonu olarak sıkça kullanılmaktadır. Enfeksiyon ve inflamasyon peri-implant dokusunda meydana geldiğinde, plak birikimi ve biyofilm oluşumu önemli sorunlar haline gelmektedir. Bununla beraber PEEK yüzeyinde biyofilm oluşumu ile ilgili çok az sayıda çalışma yapılmıştır. PEEK iyileşme abutmentı yüzeyindeki plak birikimi, geleneksel Ti iyileşme abutment malzemeleriyle benzer bulunmuştur. Bu nedenle hem PEEK hem de Ti iyileşme abutmentları, implant diş hekimliğinde protez gereksinimlerine göre iyileşme abutmentı biyomalzemesi olarak kullanılabilmektedir [9] (Şekil 6).

Şekil 6. Straumann marka Anatomic Healing Abutment, PEEK materyalinden üretilmiş olup molar diş bölgesinde çıkış profilinin (emergence profile) optimal şekillenmesini sağlar ve immediat soket koruma fonksiyonu ile alveoler dokunun korunmasına katkıda bulunur. Osseointegrasyon sonrası, dijital protetik uygulamalarda tarama bayrağı (scan body) olarak kullanılabilir.

Metal/Plastik Geçici Abutmentlar

Daimî restorasyon yapılmadan önce form, renk, yumuşak doku profili ve oklüzyon düzenlemesinde kullanılmaktadırlar. Metal, titanyum, zirkonya veya PEEK materyalinden üretilebilmektedirler. Laboratuvar çalışanları veya hekimler tarafından modifiye edilebilmektedirler. Plastik olanların kullanım ömrü ortalama olarak 180 gündür [3].

Daimî Abutmentlar

Daimî abutmentlar, final restorasyonu için kullanılmakta ve daimî restorasyon yapımıyla beraber yerlerine sabitlenmektedirler. Diş hekimi bu aşamada, standart stok abutment, dökümle yapılan kişiye özel abutment veya bilgisayar destekli üretimle yapılan kişiye özel abutment seçeneklerinden birini tercih edebilir. Bu seçim, klinik vaka, klinisyenin deneyimi ve hastanın tercihleri doğrultusunda değişiklik gösterebilmektedir.[6] İmplant cerrahisi sırasında implant platformu ile alveolar kemik tepesi arasındaki radyografik mesafe, kesin restorasyon için abutment yüksekliğinin seçiminde önemli bir parametre olarak hizmet edebilmektedir.[10] Doğru daimî abutment seçimi, mukoza ve periodontal dokular üzerinde hem kısa hem de uzun

vadeli takiplerde büyük bir öneme sahiptir. Mevcut kanıtlar, implantların transmukozal arayüzünün seçimlerinin peri-implant mukozal entegrasyonu etkileyebileceğini ve sonuç olarak yaşamın ilerleyen dönemlerinde peri-implant hastalık geliştirme riskini belirleyebileceğini göstermektedir [11].

Üretim Metoduna Göre Abutmentlar

Prefabrike (Stok) Abutmentlar

Stok abutmentlar, diş hekimi ya da teknisyen tarafından modifiye edilebilen abutmentlardır. Son zamanlarda implant üreticileri, abutmentın preparasyon süresini kısaltmak için kronun doğal konturlarına uygun olarak şekillendirilmiş abutmentlar üretmektedirler ve bunları estetik abutment olarak adlandırmaktadırlar. Ek olarak, bu abutmentlar; implant yerleşimindeki pozisyonel sapmaları telafi edebilmek için çeşitli açılanmalarda ve seviyelerde, ayrıca implantların protetik bitim sınırlarını belirlemeye yönelik olarak farklı diş eti yüksekliği opsiyonlarıyla tasarlanmaktadır [12].

Standart Abutmentlar

Kullanımı genelde çok üyeli restorasyonlarla ve özellikle estetik gerektirmeyen bölgelerle sınırlıdır. Marjinleri supragingivaldir ve iyi bir çıkış profili elde etmek güçtür. Marjin tespiti ve hasta için temizlenebilirliği kolaydır [2]. Bununla beraber Ti- base (Titanium Base) abutment tasarımı günümüzde hem tek hem de çok üyeli restorasyonlar için mevcuttur. Özellikle posterior (estetik gerektirmeyen) bölgede kullanımı uygun görülen ve monolitik zirkonya üst yapının simantasyonuyla kullanılan bir tasarımdır. Çok üyeli restorasyonlar için olan Ti-base tasarımı konik şekilde, daha dışbükey duvarlara ve daha az bonding yüzeyine sahip olmakla birlikte anti-rotasyonel implant bağlantısına sahip değildir. Bu spesifik tasarım vida gevşemesi veya desimantasyon gibi teknik komplikasyonlara neden olabilmektedir [13].

Konik Abutmentlar

Multi-unit abutment ya da çok üniteli abutment olarak da bilir. Estetiğin önemli olduğu bölgelerde tek veya çok üyeli restorasyonlarda kullanılabilir. Restorasyon subgingival 2-3 mm'de bitirilebildiği için başarılı bir çıkış profili ve estetik sağlar. Boyun yüksekliğinin çevresel olarak uniform olması ve gingival marjinin doğal konturunu takip etmemesi dezavantajıdır. Bundan dolayı interproksimal alanda dişeti kollapsına neden olabilir.[2] Multi-unit abutmentlar, sabit protetik restorasyonları implantlara bağlamak için altın standart olarak kabul edilmekte olup, özellikle tam çene restorasyonlarında hâlâ yaygın olarak kullanılmaktadır. Multi-unit abutmentların büyük avantajı, farklı implant açılarını düzeltebilme imkânı sayesinde pasif uyum sağlaması ve vida retansiyonlu sabit restorasyonların gerektiğinde rahatça çıkarılabilmesidir. Ancak, yaygın bir teknik komplikasyon olarak abutment vidasının gevşemesi görülebilmektedir [14] (Şekil 7).

Şekil 7. Farklı açı ve diş eti yüksekliği seçeneklerini temsil eden konik abutment tasarımları.

Açılı Abutmentlar

Konik abutmenta benzer, açı ve pozisyonlandırmadaki tutarsızlıkları 15-35 derece arasında kompanse edebilir. Açılı abutmentın implant yüzeyi internal olarak 12 kenarlı olabildiği gibi altıgen, sekizgen gibi farklı profillerde olabilir. 12 kenarlı şekil, abutment konumlandırmasını basitleştirmek için altıgen implanta 12 farklı şekilde yerleştirme sağlar [2].

Simante Edilebilir Çekirdek (Core) Abutmentlar

CeraOne sistem olarak bilinir. Abutment üzerine simante edilecek olan protez, altın alaşım veya seramikten üretilen bir çekirdek (core) materyali üzerinde üretilmektedir. Estetiğin önemli olduğu anterior tek üye restorasyonlarda kullanımı tercih edilmektedir. Genellikle 1-5 mm arasında abutment dişeti yüksekliği seçeneği mevcuttur [1].

Post Abutmentlar

Tek aşamada yapılan COC (Cement-on-Crown), çift aşamada yapılanlar CerAdapt olarak bilinmektedir. Tamamen seramikten üretilir, implant üzerine vidalanır ve doğal diş şeklinde prepare edilir. CerAdapt sistemde seramik post, laboratuvarda prepare edilmekte ve implanta altın alaşım vida ile sabitlenmektedir. Hazırlanan post ağızda tekrar uyumlanabilir ve daha sonrasında kron, çekirdek üzerine simante edilir [1].

Bireysel (Custom) Abutmentlar

Kişiye özel abutmentlar ekseri, olağandışı açılanma problemlerini kompanse etme, implantüstü sabit protetik restorasyon tasarımına uygun altyapı elde etmek, bireysel, transgingival ve periodonsiyuma uygun çıkış profili sağlamak amacı ile kullanılmaktadırlar. Bu abutmentlar, pasif yerleşmeyi ve doğru konturları elde edebilmek adına hassas bir modelaja ve işçiliğe ihtiyaç duymaktadırlar. Üretimleri detaylı ve dolayısıyla masraflı laboratuvar işlemleri gerektirmektedir. Bireysel abutment kullanımını gerektiren durumlardan bazıları, yetersiz interoklüzal mesafe, 15 dereceden fazla açılanma problemleri, implant üreticisinin en fazla boyun yüksekliğine sahip abutmentından en az 1 mm daha yüksek boyun yüksekliğine sahip abutment gerektiren durumlar, ideal bir

çıkış profili sağlamak için, dişlerin ve yumuşak dokunun orijinal kesitsel profillerinin taklit edilmesini gerektiren durumlar, 3 ya da daha fazla implantın splinte edilmesini gerektiren vakalar ve interproksimal aralığın hijyen sağlanması bakımından yeterli olmadığı durumlar olarak sıralanabilir [6]. Bununla birlikte yapılan araştırmalar, klinik duruma göre kusursuz anatomik şekillerde üretilmiş bireysel abutmentların, çiğneme sırasında oluşan stresi azalttığını ve uzun dönem estetik ve fonksiyonel başarıyı arttırdığını gösterilmişlerdir [15]. Benakatti ve ark. tarafından yapılan bir çalışmada özellikle siman retansiyonlu restorasyonlarda bireysel abutment kullanımının vakaya özel siman marjin hattı oluşumu ile daha iyi yumuşak doku yanıtı sağladığı ve temizlenemeyen siman artığı kalma riskini azalttığı gösterilmiştir [16] (Şekil 8).

Şekil 8. Bireysel (Custom) Abutment tasarımları.

Şekil 9. UCLA Abutment tasarımı.

Diğer Bireysel Abutmentlar

Kişinin eksik dişlerinin olduğu bölgedeki spesifik duruma özel çıkış profili sağlanabilmekte; dişeti altına az bir miktar alınan abutment kenarı dişeti kenarı konturunu birebir takip etmeyi sağlamaktadır. Frezeleme (copy-milling) veya CAD/CAM teknikleriyle üretilebilirler. İki teknikte de teknisyen tarafından rezin veya dental mum materyalinden ana model üzerinde bir ön-abutment (prospective abutment – kısaca pro-abutment) tasarlanır. Bu tasarıma göre blok(ingot), abutment üretimi için freze makinesine alınır. CAD/CAM sistemlerde pro-abutment bir tarama cihazı tarafından taranır ve dijitalize edilir. CAD/CAM sistemlerinin sağladığı bir diğer seçenek ise, bireysel abutmentların doğrudan sanal tasarım programlarında tasarlanabilmesi ve sonrasında pro-abutmentın dijital haliyle doğrudan freze cihazında işlenebilmesidir [17].

Nobel Procera (Nobel Biocare USA, LLC, Yorba Linda, CA)

Abutmentları, titanyum, zirkonyum veya aluminyumdan elde eden bir sistemdir. Ana model elde edildikten sonra abutment 2 türlü üretilebilir. İlk sistemde model taranır ve abutment 3 boyutlu yazılım programıyla tasarlanır. İkinci sistem ise prepare edilmiş bir silindirin modele yerleştirilmesine ve modelajına izin verir. Bu modelaj tarayıcıya aktarılır.

Straumann CARES (Straumann, USA, Andover, MA)

Zirkonyum dioksit ve titanyumdan abutment üretilmektedir. Bireysel abutment üretimi için bilgisayar destekli tasarım ve dijital modeller Straumann üretim merkezine gönderilir.

Atlantis (Dentsply, International, York, PA)

Abutmentlar; titanyum, altın nitrat kaplanmış titanyum ve zirkonya olarak üretilebilmektedir. Altın kaplama titanyum abutmentlar, titanyumun gümüş rengini kapatmakta ve estetik katkı sağlamaktadır. Bu sistem ile birçok implant sistemi ile uyumlu olarak o sistemler için abutment üretilebilmektedir. Ölçü, tanı modeli ve ana modelin taranması ile abutmentlar; sanal destekli tasarım (Virtual Assisted Design) ile tasarlanmakta, işleme alınmakta ve üretilmektedir. İnternal bağlantıya sahip implantlara direkt bir şekilde yekpare bir ünite olarak yerleştirilen abutmentsız (abutment-free) sabit protetik restorasyonlar güncel araştırma konularındandır. Schäfer ve ark. tarafından yapılan güncel bir in-vitro çalışmada, bireysel olarak tasarlanmış 3 üniteli implant destekli sabit restorasyonların üretimine olanak tanıyan bir implant-abutment bağlantısına sahip sabit protetik restorasyonların kırılma yükü ve kırılma modu test edilmiş, sonuçlar monolitik zirkonya ve titanyum CAD-CAM protezler için prefabrike abutmentların kullanıldığı geleneksel Ti-Base ve multi-unit implant-abutment arayüzleri ile karşılaştırılmıştır. Sonuç olarak abutmentsız monolitik zirkonya CAD-CAM restorasyonlar, diğer zirkonya gruplarıyla karşılaştırıldığında benzer kırılma yükleri ve kırılma tipleri gösterirken, titanyum grupları üstün kırılma dayanımı sergilemiştir. Farklı implant-abutment bağlantılarının, kırılma yükleri veya tiplerini etkilemediği gösterilmiştir [14].

Protez İle Bağlantı Tipine Göre Abutmentlar

Vida retansiyonlu restorasyonlar, protetik restorasyonun

abutment üzerine laboratuvar ortamında simante edildiği ve hekimin abutment ve restorasyon kompleksini direkt olarak implant gövdesine vida ile sabitlediği restorasyon tipleridir. Avantajları yerinden sökümlerinin (Retrievel) kolay olması, interoklüzal mesafenin limitli olduğu durumlarda kullanılabilmeleri ve periodontal olarak siman retansiyonlu tipleri göre daha sağlıklı ve doku yanıtının daha iyi olması şeklinde sıralanabilir. Dezavantajları ise ideal implant pozisyonlandırması gerektirmeleri, restorasyonun vida üzerinde fazla stres oluşmaması için pasif oturmasının gerekli olması, genelde tek seansta tamamlandıklarından oklüzal interferans oluşma ihtimali ve vida gevşemesi veya kırılması ihtimalinin simante restorasyonlardan fazla olmasıdır. Ayrıca göreceli olarak kullanılan parçalar sebebiyle siman retansiyonlu restorasyon tiplerine göre üretimleri daha maliyetlidir. Siman retansiyonlu restorasyonlar, abutmentın implant fikstürü üzerine vida yordamıyla sabitlenmesinin ardından restorasyonun abutment üzerine simante edildiği restorasyonlar olarak tanımlanabilir. Avantajları, esnek implant pozisyonlandırmasının mümkün oluşu, oklüzyonun detaylı ve ince kontrolünün yapılabilmesi, göreceli olarak daha az maliyetli oluşu ve geçici protez yapımının kolay olmasıdır. Dezavantajları ise istendiğinde protez sökümünün rölatif zor oluşu, minimum 4 mm abutment simantasyon yüzey yüksekliğinin gerekmesi ve siman artıklarının sebep olduğu kötü doku yanıtı ve periimplantitis gelişme riskidir [18-21].

Üretildiği Materyale Göre Abutment Tipleri

Titanyum

İmplanta en yakın mekanik özellikler gösteren materyal türüdür. Mükemmel biyo-uyum göstermektedir. Bireysel ve prefabrik abutment yapımında en çok tercih edilen materyaldir. Halim ve ark. çalışmalarında titanyum abutmentların mekanik dirençlerinin zirkonya abutmentlardan daha iyi olduğunu ve estetiğin abutment materyalinden çok, yumuşak doku kalınlığıyla (>3 mm) ilgili olduğunu iddia etmişlerdir [22]. Başka bir araştırmacı ise titanyum abutmentların anterior estetik restorasyonlarda kullanılabileceğini savunmuş; ilave olarak perimukozal dokulardan gri renk yansımasını engellemek adına anodizasyon işlemi yapılmasını önermiştir [23]. Bunun yanı sıra titanyum nitrit (TiN) bireysel abutmentlar nitrit kaplamaya sahip olmayan titanyum alaşımlara göre aşınmaya daha yüksek direnç, daha düşük sürtünme katsayısı ve kimyasal inertlik göstermişlerdir.[24] Bu tarz abutmentların dezavantajları, kemik defektlerinde ve gingival resesyonların varlığında metalin gözükür duruma gelmesi ve ince peri-implant yumuşak doku varlığında doku içerisinden gözükerek estetiği bozabilmesi olarak belirtilebilir [25].

Zirkonya

Zirkonya, monoklinik, kübik ve tetragonal olmak üzere üç kristalin faza sahip yüksek mukavemetli bir seramiktir. Tetragonal faz, oda sıcaklığında MgO, CaO ve Y2O3 veya CeO2 gibi metal oksitlerle karıştırılarak stabilize edilir. Sinterleme ve soğutma sırasında kristal fazın dönüşümü ile yüksek mukavemet ve aşınma direnci sağlayarak restorasyonlarda çatlak oluşumu önlenir. Abutment materyali olarak zirkonyanın en önemli avantajı, titanyuma göre daha estetik, doğal ve beyaz bir renge sahip olma özelliğidir. Dolayısıyla zirkonya abutmentlar, anterior bölge restorasyonlarında ve ince dişeti biyotipine sahip durumlarda özellikle önerilmektedirler. Fibroblast canlılığı, adezyonu ve proliferasyonu, titanyum ve diğer malzemelere göre zirkonya üzerinde daha üstün bulunmuştur, bu da daha güçlü mukozal sızdırmazlık, çevredeki yumuşak dokuların daha iyi iyileşmesi ve daha yüksek yumuşak doku bütünlüğü ile sonuçlanmaktadır. Yumuşak dokuların enflamatuar infiltrasyonu, titanyum dayanakların etrafındakinden daha düşüktür ve peri-implantitise neden olan Porphyromonas gingivalis ve Clostridium nucleatum biyofilmleri önemli ölçüde azalmaktadır [5]. Ayrıca zirkonya abutmentlar, altın ve titanyum abutmentlara göre marjinal kemiği korumada daha başarılı bir etki göstermişlerdir [26] Dens ve dayanım gücü çok yüksektir. Dayanıklılığı alümina materyalinden daha iyi olduğu için alümina abutment kullanımında oluşan mekanik başarısızlıklar daha az görülmektedir. Zr02 ve Y2O3, sinterize edilmiş zirkonyum- dioksiti oluşturur ve böylelikle zirkonyum elementinin abutment için kullanılabilecek formu elde edilmiş olur. CAD/CAM sistemlerle üretimi sağlanır. Cut-back tasarımına sahip monolitik zirkonya restorasyonları üzerindeki porselende bağlantının zayıflığından dolayı chipping görülebilmesi en büyük dezavantajlarından biridir. Ayrıca, titanyum ve zirkonya arasındaki mekanik farklılıklar ve zirkonyanın titanyuma göre daha yüksek olan elastik modülü ve sertliği, implant-abutment arayüzünün aşınmasına ve özellikle internal hekzagon bağlantılarda bu bağlantının bozulmasına neden olabilmektedir [25]. Yine de Pesce ve ark. tarafından yapılan literatür derlemesinde genel olarak zirkonya abutmentların titanyum abutment kullanımına güvenilir bir alternatif olduğu öne sürülmüştür [27]. Bakteriyel adezyona karşı direnç göz önüne alındığında, klinisyenlerin abutment yüzeyinin kimyasal bileşimi yerine yüzey pürüzlülüğüne daha fazla odaklanması gerektiği sonucuna varılmıştır [28] .

Alumina

1993'te titanyuma alternatif olarak estetik kaygıları gidermek amacıyla kullanımına başlanmıştır. Düşük kırılma dayanımı ve buna bağlı olarak görülen sık dayanak kırıkları sebebiyle kullanımı terk edilmiştir [29].

PEEK (Polietereterketon) ve PEKK (Polieterketonketon)

Polieterketonketon (PEKK) ve polietereterketon (PEEK), poliarileterketon (PAEK) ailesinin en bilinen iki üyesidir ve yüksek performanslı polimerler (HPP) olarak da bilinirler.[30,31] Çalışmalar, CAD-CAM ile üretilen implant abutmentları ve bireysel iyileşme abutmentları için PEEK materyalinin performansını değerlendirmiştir [32,33.] PEEK ve zirkonya bireysel abutmentlarını karşılaştıran bir sonlu eleman analizi, PEEK abutmentlarda daha yüksek gerilim değerleri ortaya koymuştur [33]. Beretta ve ark. tarafından yürütülen randomize klinik çalışma, istenilen çıkış profilinin oluşturulması amacıyla cerrahi aşamada yerleştirilen CAD-CAM ile üretilmiş bireysel iyileşme abutmentları ile standart iyileşme başlıklarının kullanımını kıyaslamıştır. 1 ila 3 ay süren iyileşme döneminin ardından, PEEK bireysel iyileşme abutmentları doğal bir gingival mimari oluşturmuş ve çıkış profilinin şekillendirilmesi için standart iyileşme dayanaklarına kıyasla daha az protetik aşama gerektirmiştir [32]. Ayrıca Mishra ve ark.'ın yaptığı sistematik derleme, PEEK yüzeyinde oluşan biyofilm tabakasının Ti veya zirkonya abutment materyalleriyle aynı seviyede veya daha düşük olduğunu, PEEK iyileşme abutmentlarının, başlangıç iyileşme dönemi boyunca marjinal kemik kaybı ve yumuşak doku çekilmesi riskini arttırmadığını göstermektedir [34] Bununla beraber, PEEK'in Ti'ye kıyasla daha düşük aşınma direncine sahip olduğunu ve PEEK abutmentların, protezin ağızda 1 ila 3 ay arasında kalması gereken sabit geçici restorasyonlar için önerildiğini belirtmektedir. Güçlendirilmiş PEEK ise, yumuşak doku stabilitesini, kemik yüksekliğini ve biyouyumluluğu korumada Ti abutmentlarına etkili bir alternatif olarak öne çıkmaktadır. Fakat, PEEK implant abutmentları, mikrosızıntı ve tork kaybı gibi biyomekanik gereksinimler açısından titanyum kalıcı abutmentlarla karşılaştırıldığında yeterli performansı göstermemekte ve 140 N'yi aşmayan hafif kuvvetleri 1,2 milyon döngü boyunca, yani yaklaşık 5 yıl süren çiğneme fonksiyonu kadar destekleyebilmektedirler [35]. PEEK abutmentlarının sınırlamaları arasında, titanyum abutmentlara göre daha fazla dikey yer değiştirme yapmaları ve abutment- implant arayüzünde plastik deformasyon oluşması yer almaktadır. Bu durum, yüksek tork kaybı ve mikrosızıntıya yol açabilmektedir. Bu sebeplerle, PEEK abutmentlar özellikle anterior bölgelerde ve parafonksiyonu olmayan hastalar için geçici abutment materyali olarak uygun olabilseler de tork kaybı ve mikrosızıntı gibi sorunlar göz önünde bulundurulmalıdır [35].

PEKK, metakrilat içermeyen, yüksek performanslı, gelişmekte olan yeni bir termoplastik malzemedir. İyi darbe emilimi ve kırılma direncine sahip elastik bir yapıya sahip olmakla beraber tüm termoplastik kompozitler arasında üstün mekanik dayanıklılık, kimyasal direnç ve yüksek termal stabilite ile ultra yüksek performans sergilemektedir. Bu sebeplerden dolayı sabit implantüstü protezlerde altyapı materyali ve abutment olarak kullanılabileceği gösterilmiştir.[30] Ayrıca PEKK'nin, PEEK'e kıyasla daha iyi uzun vadeli yorulma direnci ve daha yüksek basma dayanımı gibi üstün özellikler sunduğu bildirilmiştir [36]. Zol ve ark. tarafından yapılan bir materyal bilimi derlemesinde PEKK, 49 MPa ile yüksek darbe emilimi ve düşük gerilim konsantrasyonu sağlarken, PEEK'in protez tabanında 58 MPa'lık daha yüksek bir gerilim oluşturduğu belirtilmiştir. Aynı çalışma gerilim konsantrasyonunun azalmasıyla protezde oluşabilecek kırık riskinin de düştüğünü göstermiştir. Mükemmel fiziksel, mekanik ve biyolojik özelliklere sahip bir PAEK polimeri olan PEKK, diğer malzemelerle daha uyumlu olması nedeniyle implantlarda titanyuma güçlü bir alternatif olarak değerlendirilebilir. Ayrıca, titanyum ile birleştirildiğinde uzun ömürlü tutuculuk sağlar [31].

Diğer Metal Alaşımları

Altın alaşımları, paslanmaz çelik ve nikel-krom-kobalt alaşımı gibi çeşitli materyaller abutment olarak kullanılmıştır [37]. Ancak, farklı metaller arasındaki galvanik etkileşim nedeniyle elektrokimyasal korozyon, oksidasyon ve ağrı tetiklenmesi, özellikle değersiz metal alaşımlarında yaygın olarak gözlemlenmektedir [38]. Ayrıca değersiz metal alaşımlardan yapılan döküm abutmentların çevrelerindeki periodontal dokunun, daha biyoinert malzemelerle üretilen abutmentlara kıyasla daha sağlıksız olduğu izlenmiştir. Bu sebeple implant çevresi doku enflamasyonunu önlemek adına bu abutmentlar, implantların kısa olduğu ve derin yerleştirildiği durumlarda kullanılmamalıdır. Güncel bir çalışmada freze edilmiş titanyum ve lazerle sinterlenmiş Cr-Co abutmentlar, 160 adet internal (n = 80) ve eksternal (n = 80) bağlantıya sahip implanta, implant-abutment arayüzündeki dikey uyumsuzluğun değerlendirilmesi adına rastgele atanıp sabitlenmiş ve termal döngü testleri uygulanmıştır. Taramalı elektron mikroskobu ölçümlerinin sonuçları, freze edilmiş titanyum abutmentların en düşük uyumsuzluğu (<10 µm) gösterdiğini, internal bağlantılardaki lazerle sinterlenmiş abutmentların ise ortalama <12 µm olduğunu ve bağlantı tipinin, implant sistemleri arasında uyumsuzluğu önemli derecede etkilediğini göstermiştir [39].

İmplant-Abutment Bağlantı Tipine Göre Abutment Türleri

Eksternal Bağlantı

Birçok implant firması tarafından uzun süre üretimi sağlanmıştır. Bu üretim çokluğu, çok fazla çeşitte abutment seçeneğini de beraberinde getirdiğinden hekimler tarafından yıllarca tercih edilmiştir. Branemark'ın orijinal implant-

abutment arayüzü 0.7 mm ekternal hekzagondur ve bu bağlantı tipi bağdaşım(coupling) işlevinin yanı sıra tork transfer ünitesi olarak da çalışmıştır.[40] Sınırlı yüksekliğe sahip olması sebebiyle yüksek düzeyde aksiyel dışı kuvvetler karşısında yetersiz kalmıştır [41.] Tek diş eksikliklerinin tedavisinde ve sabit parsiyel protezlerde vida gevşemesi, abutment kırılmaları ve arayüzde mikro-hareketlilik görülmesi nedeniyle Branemark'ın orijinal hekzagon bağlantısının kullanımı terk edilmiş ve modifikasyonları kullanılmaya başlanmıştır [42]. Avantajları arasında uzun süreli takip verilerinin mevcut olması, gelişebilecek olası komplikasyonlarının çözümlerinin yaygın kullanımlarından ötürü literatürde yaygın olarak yer alması ve birçok implant sistemi ile uyumlu olması yer almaktadır. Dezavantajları ise, vida gevşeme prevalanslarının yüksek oluşu (%6-48 arası), düşük estetik sonuçlar, rotasyonel uyumsuzluk oranının yüksek oluşu ve mikrobiyal sızıntının fazla oluşudur. Tek bir diş restorasyonu için eksternal hex implant kullanıldığında, implant, abutment bağlantısı, vida ve kemik arasından en zayıf linkin vida olduğu gösterilmiştir. Bunun sebebi, bu tarz bağlantılarda sadece vidanın her türlü kuvvete karşılık abutmentı yerinde tutmasıdır [43]. Kama Bağlantı (Spline Connection) denilen eksternal bağlantı tipinde bulunan "spline" kelimesi İngilizcede şaft dişi, kama, yiv anlamına gelmektedir. Mühendislikte uzun ve başarılı bir geçmişi bulunan kanattan yive (fin-to-groove) denen anti-rotasyonel bağlantı konfigürasyonlarıdır. 1992 yılında Calcitek tarafında diş hekimliğinde ilk kez kullanılmıştır. İlk tasarım, implant gövdesinden dışarı doğru uzanan 6 adet dişe abutment üzerindeki 6 oluk denk gelecek şekilde yapılmıştır. Geleneksel eksternal bağlantı tiplerine göre daha az vida gevşemesi sorunu ve minimal rotasyonel hareket görülmektedir [44]. Wee ve ark. tarafından Ohio Eyalet Üniversitesi Diş Hekimliği Fakültesi'nde gerçekleştirilen çalışmada, öğrenciler ve asistanlar tarafından restore edilen spline dental implant sistemine bağlı protez komplikasyonları in vitro olarak incelenmiştir. Çalışma, protezlerin %95,75'inde herhangi bir komplikasyon görülmediğini ortaya koymuştur. Ayrıca, vida gevşemesine neden olan iyatrojenik faktörler tespit edilmiştir. Restorasyon sonrası 29 ila 59 ay süren klinik takipleri kapsayan bu kısa vadeli çalışmanın bulgularına göre, spline dental implantlar stabil ve güvenilir bir implant-protez bağlantısı sağlamıştır [45].

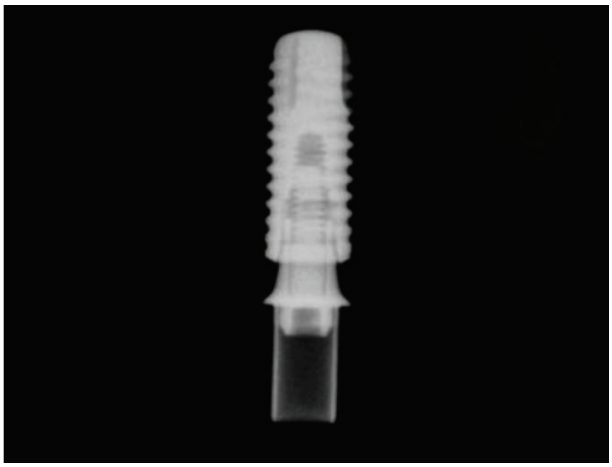
İnternal Bağlantı

Fonksiyon boyunca bağlantı stabilitesini arttırmak ve prosedürü kolaylaştırmak amaçlarıyla tasarlanmıştır. İlk tasarımlardan biri 1986 Niznick tarafından yapılmıştır. En başta gelen avantajlarından biri implant cerrahisi sonrası takılan kapama vidasının implant bağlantısı ile eşit seviyede olmasıdır [46]. Eksternal bağlantılı implantlarda kapama vidasının seviyesi implant fikstürünün seviye olarak üzerindedir. Uzun süre kullanımları daha iyi estetik sonuçlar, daha az vida gevşemesi (%3,5), iyi bir mikrobiyal yalıtım ve güçlü bağlantı dayanımı sağladıklarını göstermekle birlikte internal bağlantı tiplerinde platform-switching özelliğinin hekim tarafından tercih edilebilmesinden dolayı kullanımları yaygınlaşmıştır. In vitro çalışmalar, internal bağlantıların ve özellikle konik tiptekilerin, implant-abutment boşluğunu ve müteakip bakteri penetrasyonunu azalttığını bildirmiştir [47]. Bununla beraber tek parça seramik abutment kullanılan klinik durumlarda, internal bağlantının eksternal bağlantıya göre daha yüksek kırılma insidansıyla alakalı olabileceği görülmüştür [48]. Başka bir çalışmada ise, seramik abutmentların, bağlantı tipinin eksternal veya internal olması fark etmeksizin metal abutmentlara göre kırılma indeksinin daha yüksek olduğu bulunmuştur [49]. Yapılan çok merkezli, split-mouth kontrollü başka bir çalışmada, dış hexagonal bağlantıların ve iç hexagonal bağlantıların anında yükleme yapılan tam çene rehabilitasyonlarında başarı, kemik rezorpsiyonu ve peri-implant parametreleri üzerinde bir etkisi olup olmadığı değerlendirilmiş olup 72 ay süresince fonksiyonel kullanımın ardından, iki bağlantı tipi de iyi klinik sonuçlar sağlamış ve klinik sonuçlar herhangi bir anlamlı farkla ilişkilendirilmemiştir [50]. 12 Noktalı/Çift İnternal Hekzagon Bağlantı (12-Point Internal Hexagon), abutmentın implant üzerine her 30 derecede bir dönecek şekilde oturmasına izin vermektedir. Tang ve ark.'ın yaptığı bir çalışmaya göre çift hekzagon bağlantı diğer bağlantı tiplerine göre daha iyi stres dağılımı ve azalmış hareketlilik sağlamaktadır [51]. Örnek olarak Biomet 3i (Palm Beach Gardens, FL, USA) markasının Osseotite CERTAIN implantları verilebilir [46]. 3-Nokta İnternal Tripod Bağlantı (3-Point Internal Tripod/Trilobe) tipi üçgensel internal tasarıma sahiptir ve üçlü kanal (trichannel) tasarımı bulunmaktadır. En büyük dezavantajı üçgensel tasarımından ötürü abutmentın implant gövdesi üzerinde sadece 120 derecede bir hareketine izin vermesidir. Bunun yanında Saidin ve ark. tarafından yapılan bir çalışmada trilobe bağlantının, poligonal profilinden dolayı diğer implant- abutment bağlantı tiplerine kıyasla en az büyüklükte mikro-hareketlilik gösterdiği bulunmuştur [52]. Yine başka bir çalışmada bu bağlantı tipinin internal konik hex Morse Taper ve internal okta Morse Taper bağlantı tiplerine kıyasla farklı kuvvetler uygulandığında implantın gövde içinde ve çevresinde maksimum stres dağılımı sağladığı gösterilmiştir [53]. Camlog implant sistemi (CAMLOG Biotechnologies GmbH), internal tripod şeklinde bir implant-abutment bağlantısı sunmaktadır. İç bağlantı uzunluğu 5,4 mm olup tüp içinde tüp etkisi (tube-in-tube effect) oluşturduğu, implant ile abutment arasında

hassas ve mekanik olarak güvenli bir bağlantı kurarak anti-rotasyonel stabilite sağladığı ve buna bağlı olarak da vida gevşeme riskini düşürdüğü öne sürülmektedir (Şekil 10). Bu sayede oluşan derin ve sıkı bağlantı iyi bir antimikrobiyal bariyer sağlamaktadır [46]. 6-Bıçaklı Kilitli Bağlantı (6-Blade Connection-Lock), 3-Nokta İnternal Tripod bağlantının altı farklı şekilde rotasyonuna müsaade modifikasyonudur. İnternal Oktagon Bağlantı tipi sekizgen internal tasarıma sahiptir ve abutmentın 45 derece aralıklarla hareketine izin verir. Dairesel geometrisi minimal rotasyonel direnç sağlar ve fonksiyon esnasında lateral kuvvetlere karşı direnci düşüktür (Şekil 11). Morse-Taper (Konik) Bağlantı, konik form verilmiş bir abutmentın yine içbükey konik formdaki internal bağlantıya sahip implant gövdesine sürtünmesel uyum (friction-fit) veya soğuk kaynak (cold-welding) ile yerleştiği tasarımdır (Şekil 12). Konik arayüz lateral hareketler karşısında implantın devrilme ve mikro-hareketliliğini önler. Bu 8 derece Morse-Taper bağlantı tipi ITI grubu tarafından ilk kez İsviçre'de kullanıma girmiştir. Konik bağlantının stabil, güvenli ve kendini kitleyen bir arayüz oluşturması fikriyle tasarlanmıştır. Bu tarz bağlantıların daha uzun süre tork değerini koruduğu, vida gevşemesi/kırığı gibi mekanik komplikasyon risklerini azalttığı yapılan araştırmalarca gösterilmiştir [54]. Bu tasarım üzerine Wiskot ve Belser abutmentın farklı açılarla yön değiştirmesini sağlayabilmesi için internal hekzagon bağlantı eklemişlerdir. Ugurel ve ark. tarafından yapılan Vidasız Morse- Taper bağlantı tipinin internal hekzagonal bağlantı ve Straumann markasının Crossfit bağlantı tipine kıyaslamasında elde edilen sonuçlara göre, Straumann Crossfit bağlantıya sahip implantlar, internal hekzagonal ve VMT bağlantılara göre önemli bir farkla yükleme siklus testinde başarılı olmuşlardır. Biohorizons'a ait internal hekzagonal bağlantı, Xive'ın aynı bağlantı tipine ve Octo'nun VMT bağlantısına göre yükleme siklus testinde daha başarılı olmuştur ve daha yüksek kırılma/eğilme direnci göstermiştir. Octo'ya ait VMT bağlantı sistemi siklus testlerinde, Straumann ve Biohorizons implant sistemlerine göre çok daha düşük başarı ve düşük kırılma/eğilme direnci göstermiştir. Fakat, Xive internal hekzagonal bağlantı sistemiyle aralarında anlamlı fark bulunamamıştır [55]. Bagegni ve ark. tarafından yapılan bir araştırmada da vidasız Morse Taper bağlantı tipinin özellikle tek diş eksikliklerinin tedavisinde kabul edilebilir başarı gösterdiği ve ortalama oklüzal kuvvetler karşısında uzun süren periyotlarda bile dayanıklılık sağladığı belirtilmiştir [56]. Başka bir çalışmada konik bağlantı tipinin in vitro olarak diğer sistemlere göre bakteriyel sızdırmazlığının daha iyi olduğu, daha yüksek tork azalma direnci gösterdiği ve daha iyi stres dağılımı sağladığı; in vivo olarak da daha az marjinal kemik kaybına yol açtığı gösterilmiştir [57]. Alla ve ark. tarafından yapılan sistematik derleme, implant-abutment tasarımının peri-implant sağlığı ve kısa vadede kemik seviyelerinin korunması üzerindeki etkisini incelemiştir. Derlemede, konik bağlantı tasarımının iç ve dış hekzagonal tasarımlara kıyasla marjinal kemiğin daha etkili bir şekilde stabilizasyonunu sağladığı belirlenmiştir. Ancak, farklı konik açılar kıyaslandığında marjinal kemik stabilitesinde anlamlı bir fark tespit edilememiştir [58].

Şekil 10. CAMLOG implant sistemi ve internal tripod tasarımı.

Şekil 11. Solda internal ve sağda eksternal bağlantılı implant gövdeleri.



Şekil 12. Morse-taper (konik) implant-abutment bağlantısının izlendiği periapikal radyografik film.

İmplant-Abutment Bağlantı Ve Mikro-Hareketlilik

Mikro-hareketlilik kavramı implant gövdesi ile abutment arasında oluşan, özellikle abutment üzerine gelen lateral ve eksentrik kuvvetlerin yol açtığı hareketliliği ifade etmektedir. Bu hareketlilik sonucunda kuvvetin geldiği tarafta abutment ve implant gövdesi arasında mikro-boşluk (micro-gap) oluşurken kuvvete zıt tarafta implant gövdesi ve abutment arasında sıkışma kuvveti ve buna bağlı olarak metal yüzeylerde aşınmalar oluşmaktadır (Abrazyon). Bu oluşan abrazyon ile titanyum partikülleri serbestleşmekte ve canlı doku içerisine penetre olmaktadır. Jäger ve ark. tarafından yapılan bir araştırmada 10 mikrometreden daha küçük partiküllerin osteoklastlarca hücre içine alındığı ve güçlü hücresel yanıta yol açan enflamatuvar sitokinlerin salınımını indüklediği gösterilmiştir [59]. Titanyum in vitro olarak yüksek derece sitokompabilite gösterse de fagosite edilen Ti partiküllerinin fibroblastik dönüşümü uyardığı bu çalışmada öne sunulmuştur. Bu durum, implant boyun bölgesindeki osteoklastik ve nihayetinde fibroblastik dönüşümü açıklamaya yöneliktir. Mikro-boşluk oluşumunun olası nedenleri olarak üç ana faktör tanımlanmıştır: Fizyolojik fonksiyon sırasında oluşan oklüzal yük, üretim toleransı ve implant-abutment bağlantısı arasındaki mikro-hareketlilik.[52] Mikro-hareketlilik ve mikro-boşluğun neticelerinden biri de implant gövdesi içerine doğru oluşan mikro- pompa (micro-pump) etkisi ve mikrosızıntıdır. Bu durumun sonucunda oluşan enflamatuvar hücre akümülasyonunun ise mikro-boşluk oluşan bölgenin 1-1.5 mm yakın komşuluğunda oluştuğu gösterilmiştir [4]. Son yapılan çalışmalar en çok mikrosızıntının eksternal hekzagon bağlantılarda, daha sonrasında sırayla internal trilobe, internal hekzagon ve internal konik konfigürasyona sahip bağlantılarda olduğunu göstermiştir. İçerisinde Dr. Marco Degidi'nin de bulunduğu, Scarano ve ark. tarafından yapılan çalışmada da bu bilgiyle tutarlı sonuçlar bulunmuştur [60]. Mikro- hareketlilik ve mikrosızıntı kavramlarını olabildiğince azaltmak için araştırmacılar mekanik ve tasarımsal birtakım yenilikler yönelmişlerdir ve bu süreçte platform- switching (PLS) konseptinden faydalanılmıştır. PLS, implant boyun çapına kıyasla daha dar çapta abutment kullanımını ifade etmektedir. Bu sayede implant-abutment bağlantısı implant orta hattına yakınlaştırılmaktadır [4,11]. Sonuç olarak:

• Lazzara ve Porter tarafından gösterildiği üzere enflamatuvar hücre infiltrasyonu da implant merkezine çekildiğinden krestal kemik korunmuş olur [61].

• İmplant çevresi konnektif doku lateral olarak kalınlaştığından kan akımı da artmış olur.

• Enflamatuvar hücreler orta hatta yaklaştığı için biyolojik genişlik azalmamış olur, böylelikle de kemik remodelasyonu ve krestal kemik kaybı yaşanmaz.

Hürzeler-Zuhr grubunun yaptığı çalışmada final restorasyon konmuş PLS implantlarda 1 yıl sonra krestal kemik kaybı ortalama 0.22 mm bulunurken non-PLS implantlar için bu değer 2.02 mm bulunmuştur. Aynı zamanda abutmentın her bir taraftan 0.45 mm redüksiyonunu pre-implant kemik kaybını önlemek için yeterli bulmuşlardır [62].

Çalışmalar, mikro-boşluğun aslında tüm implant-abutment bağlantı tiplerinde oluştuğunu ve literatürde bu durumu azaltmaya yönelik birçok araştırma bulunduğunu göstermektedir [63]. Liu ve ark., implant-abutment arayüzünde mikro-boşluk ve mikro-hareketin neden olduğu kemik rezorpsiyonunu azaltmak için ilk ve en önemli şeyin, sadece bakteri ve endotoksinleri doğrudan azaltmakla kalmayan, aynı zamanda zararlı mikro ortamı arayüzden uzağa yani implant merkezine yakın bir noktaya aktaran uygun Morse Taper veya hibrit bağlantıya ve platform-switching özelliğine sahip bir abutment seçimi olduğunu belirtmişlerdir [64]. Kumar ve ark. yaptıkları çalışmada internal bağlantıların konik bağlantılı implantlara kıyasla bakteri infiltrasyonuna daha yatkın olduğunu, ancak konik bağlantının koniklik açısının, implant-abutment bağlantısının bakteriyel geçirgenliği üzerinde anlamlı bir etkisi bulunmadığını göstermişlerdir [65]. Alves ve ark. ise, Morse Taper bağlantı tipinin bakteriyel izolasyonu yalnızca komponentler arasında soğuk kaynak (cold-welding) özelliği gösteriyorsa sağlayacağını iddia etmişlerdir [66].

Sonuç

Yapılan çalışmalar konik (morse-taper) ve platform switching (PLS) bağlantı tiplerinin diğer implant-abutment bağlantı tiplerine göre üstünlüğünü ön plana koymuştur. Her ne kadar bu bağlantı tiplerinin üstünlükleri gösterilse de implant firmaları ve hekimler tarafından daha başarılı farklı bağlantı konfigürasyonları bulma çabaları ve halihazırda olan bağlantı tiplerinin beraber uygulanarak (ör; konik + trilobe) başarıyı arttırma istekleri devam etmektedir. Diş hekimliğinde son zamanlarda kullanıma giren yüksek performanslı polimerler doğru endikasyonda uygulandıklarında sabit implantüstü protezlerde abutment materyali olarak başarılı sonuçlar vermektedir ve titanyum abutmentlar yerine kullanımları günden güne yaygınlaşmaktadır. Mikro-hareketler sonucunda oluşan abrazyon ve mikro-aralık, hücrelere titanyum infiltrasyonu sonucu fibroblast ve osteoklast aktivitesini indükleyerek ve aynı zamanda implant gövdesine bakteri içerikli sıvının sürekli giriş- çıkış yaparak kronik bir enflamasyon oluşturmasıyla krestal kemikte yıkıcı sonuçlar doğurabilmektedir. Biyomekanik yönden bakıldığında da doğru bağlantı tipi seçilmediğinde vida gevşemesi ile başlayan vida kırıkları, implant kırıkları hatta implant kaybına kadar ilerleyen mekanik komplikasyonlar oluşabilmektedir. Bu nedenle hekim, implant-abutment bağlantı tipleri ve seçeneklerini çok iyi bilmeli, ilgili endikasyonda doğru implant sistemini seçerek hasta için en ideal tedaviyi sağlamayı ilke edinmelidir.

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Olgu Sunumu

Hiperglisemi ve paraneoplastik antikor pozitifliği etyolojili nadir bir hemikore olgusu

A rare case of hemichorea wıth hyperglycemia and paraneoplastic antibody positive etiology

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Öz

Kore bir çok nörolojik ve metabolik bozukluk sebebi ile ortaya çıkabilen etyolojisi çok geniş bir hareket bozukluğudur. Hiperglisemi esık gözüken metabolik sebep iken, paraneoplastik bozukluklar da nadir görülen sebeplerden bir tanesidir. Biz de bu olgu sunumu ile literatürde nadir görülen anti-Yo antikor pozitifliği ve hiperglisemi ile ilişkili bir hemikore olgusu sunmayı planladık.

1,5 ay önce kanşeker yüksekliği ile diabet tanısı alan, o dönemden itibaren sağ kol va bacakta istemsiz hareketleri olması nedeni ile başvuran yapılan incelemelerde etyolojide anti-Yo antikoru pozitifliği ile birlikte hiperglisemi tespit edilen, kranial görüntülemede hiperglisemik hemikore tanısı ile uyumlu olarak sol bazal ganglionda lezyon tespit edilen, 68 yaşında bir hasta sunduk.

Hemikore şikayeti ile başvuran hastalarda etyoloji araştırılırken öncelikle kanşekeri kontrolü yapılması önemlidir. Etyolojide farklı mekanizmaların da rol oynayabileceği, paraneoplastik kore açısından değerlendirme ve gerekirse malignite taraması yapılması da akılda tutulmalıdır.

Anahtar Kelimeler: kore, hiperglisemi, paraneoplastik

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Abstract

Chorea is a movement disorder with a very wide etiology that can occur due to many neurological and metabolic disorders. Hyperglycemia is a commonly observed metabolic cause, while paraneoplastic disorders are one of the rare causes. In this case presentation, we aim to present a rare case of hemichorea associated with anti-Yo antibody positivity and hyperglycemia, which has been rarely reported in the literature.

We presented a patient 68 year old that was diagnosed as diabetes with high blood sugar 1.5 months ago . He applied because of involuntary movements in the right arm and right leg since than 1.5 months. Hyperglycemia with anti-Yo antibody positivity in etiology. A lesion in the left basal ganglia that matches with the diagnosis of hyperglycemic hemichorea was detected in the cranial magnetic resonance.

It is important to check the blood sugar firstly when investigating the etiology in patients who applies with the complaint of hemichorea. Different mechanisms may play role in the etiology. Therefore, evaluation of the case in terms of paraneoplastic chorea and, if necessary, screening for malignancy should also be kept in mind.

Keywords: chorea,, hyperglycemia, paraneoplastic

Giriş

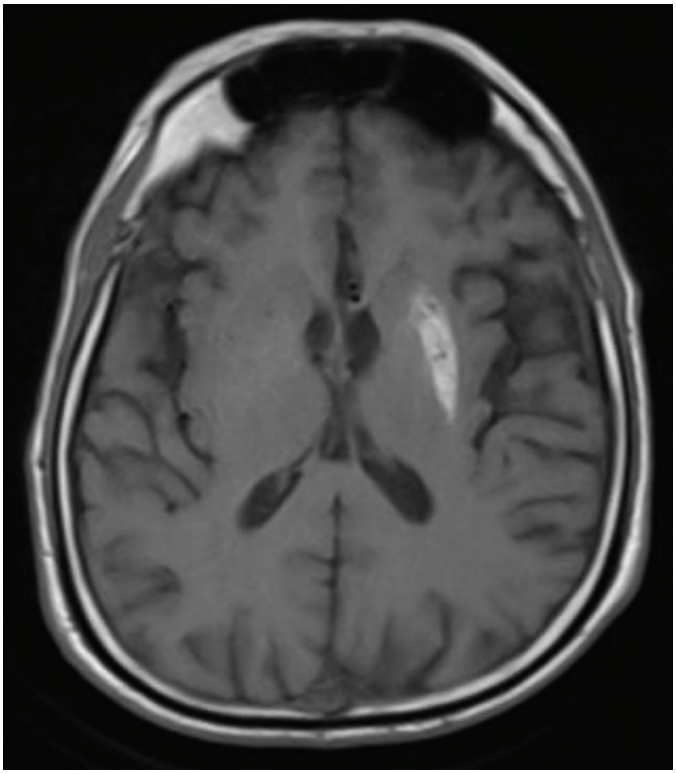
Kore özellikle ekstremite distallerinde görülen hızlı, istemsiz, anormal ve düzensiz hareketler ile karakterize hiperkinetik bir hareket bozukluğudur. Etyolojisinde öncelikle serebrovasküler hastalıklar olmak üzere, dejeneratif, metabolik, enfeksiyöz, paraneoplastik süreçler ve yer kaplayan lezyonlar yer alır. Bu hareketler genellikle tek taraflıdır ancak bilateral de seyredebilir (1). Hemikorenin altında yatan en önemli metabolik sebep hiperglisemidir. Kore hiperglisemin ilk klinik belirtisi olarak ortaya çıkabilir (2). Kore etyolojisinde nadir de olsa paraneoplastik mekanizmalar rol oynayabilir. Paraneoplastik korenin spesifik klinik özellikleri ve hastalığa özgü antikorları net olarak ortaya konulamamıştır. Ancak literatürde genellikle anti-CV2/CRMP5 ve anti-Hu antikorları suçlanmıştır (3). Biz de bu olgu sunumu ile literatürde nadir görülen, etyolojisinde anti-Yo antikor pozitifliği ve hiperglisemi birlikteliği olduğu düşünülen bir hemikore olgusu sunmayı planladık.

Olgu Sunumu

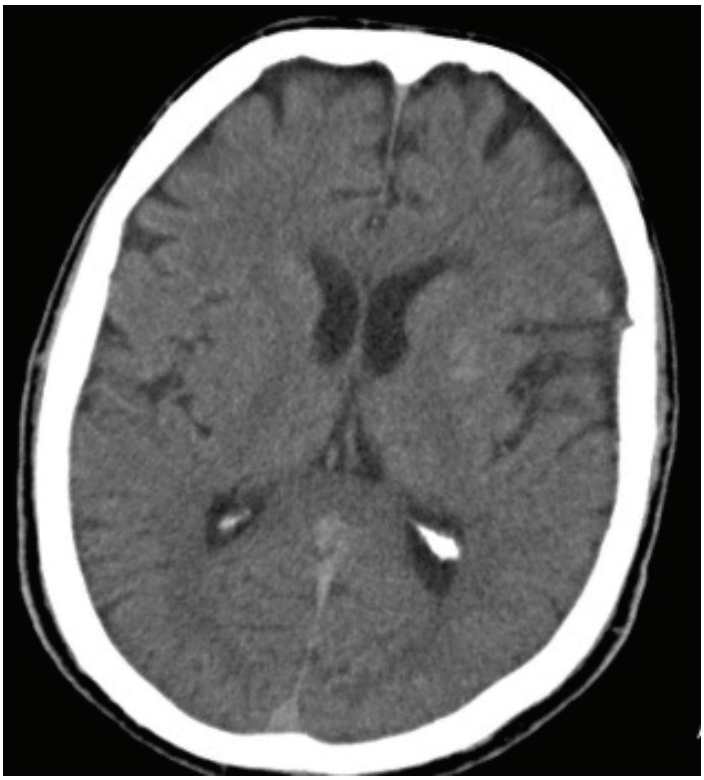
Sağ elini kullanan 60 yaşında erkek hasta, 1,5 aydır sağ kol ve bacak distallerinde belirgin olan istemsiz hareket şikayeti ile başvurdu. Koroner arter hastalığı tanısı olan ve 2019 yılında kardiak pil takılma öyküsü olan hastaya 1,5 ay önce kan şekeri 600 mg/dl olması nedeni ile diabetes mellitus tanısı konulmuş ve idrarda ketonu negatif tespit edilmiştir. Nörolojik muayenesinde sağ üst ve alt extremite distallerinde istemsiz, düşük amplitüdlü, düzensiz hareketler izlendi.

Laboratuar incelemesinde açlık kan şekeri 105 mg/dl (70-105 mg/dl) olup normal, Hba1c %8,7 (%4-6) olup yüksek, sodyum değeri 136 mmol/l (136-145 mmol/l) olup normal ve serum osmolaritesi 275 mOsm/kg (275-295 mOsm/kg) olup normaldi. Diğer biyokimyasal parametreler ve hemogram sonuçları normal olarak değerlendirildi. Kore etyolojisine yönelik yaptığımız diğer tetkiklerden biri olan paraneoplastik antikor testi sonucunda anti-Yo antikoru pozitif tespit edildi. Tarama amaçlı yapılan malignite testlerinde herhangi bir anormallik tespit edilmedi.

Kranial bilgisayarlı tomografide (BT) sol putamen lokalizasyonunda silik tarzda hafif hiperdensite izlendi (Şekil-1). DWI (Diffusion-Weighted- Imaging) -ADC (Apparent Diffusion Coefficient) ağırlıklı manyetik rezonans (MR) incelemesinde akut iskemi ile uyumlu bir lezyon izlenmedi. Bununla birlikte T1 ağırlıklı sekansta sol putamen lokalizasyonunda hiperintensite izlendi (Şekil-2). Hasta mevcut bulguları ile ''non-ketotik hiperglisemi ile ilişkili hemikore '' olarak değerlendirildi. Kanşekeri regülasyonu ile birlikte haloperidol ve olanzapin tedavisi ile şikayetleri gerileyen hastanın semptomları ilk şikayetinden 4 ay sonra düzeldi. Olgu ileride oluşabilecek maligniteler açısından rutin poliklinik kontrolüne alındı. Hastadan bilgilendirilmiş onam formu alınmıştır.



Şekil 1. Kontrastsız kranial BT



Şekil 2. T1 Ağırlıklı Kranial MR

Tartışma

Hiperglisemik hemikore ilk olarak 1960 yılında tanımlanmıştır (4). Genellikle 50-80 yaş arası, kan şeker düzensizliği olan diabet hastalarında görülür. Sıklıkla diyabet tanısı istemsiz hareketler ortaya çıktıktan sonra konulmaktadır (5). Literatürde en sık kötü kontrollü diabeti olan Asyalı hastalarda görüldüğü ve sıklıkla üst extremitelerin etkilendiği bildirilmiştir (6). Hiperglisemi ile indüklenen kore tablosu genellikle tek taraflıdır. Kontralateral bazal gangliaların özellikle putamen kısmında kranial manyetik rezonans (MR) T1 ağırlıklı sekanslarda hiperintensite izlenmektedir. Beyin tomografisinde (BT) ise aynı bölgelerde hiperdensite izlenmektedir (7). Bazı olgularda kranial MR incelemesinin normal olduğu da bildirilmiştir (8). Bizim olgumuzda da putaminal hiperintensite bulgusu tanıyı desteklemiştir.

Hiperglisemi ile ilişkili hemikore patofizyolojisi için öne sürülen mekanizmalar bazal gangliada meydana gelen peteşiyal kanamalar ya da gama-aminobütirik asit ve asetilkolin miktarında azalmaya neden olan serebral iskemi durumlarıdır (9). Etkilenen bazal gangliada serebral glukoz metabolizmasının bozulduğu FDG-PET incelemeleri ile gösterilmiştir (10). Hiperglisemi durumunda doku ödemine bağlı olarak vasküler direnç artar, viskosite fazlalaşır, beyin hücrelerinde metabolizma hızı azalır ve sonuç olarak kan beyin bariyeri hasarlanır. Bununla birlikte Krebs siklusu inaktive olur ve beyin enerji elde etmek için gama aminobütirik asit (GABA) kullanmaya başlar. Bazal ganglion nöronları arasında GABA inhibe edici, glutamat aktive edici, asetilkolin ise modülatör işlev görmektedir. Hiperglisemi nedeniyle bölgesel kan akımının azalması ve inhibitör bir nörotransmitter olan GABA'nın tükenmesinin patofizyolojide rol oynadığı düşünülmektedir (11).

Hiperglisemik hemikorenin tedavisinde en önemli ve ilk basamak hiperglisemiyi düzeltmektir (9). Çünkü bu genellikle diyabetin ilk belirtisi olabilir. Hiperglisemi tedavi edilmeden hastalığın seyri bilinmemektedir, ancak tedavi ile kore çoğu vakada iyileşir. Hemikorenin sadece kan şekeri regülasyonu ile bile günler ya da haftalar içinde düzeldiği, ancak hastaların %20 kadarında 3 aydan daha uzun süre devam ettiği bildirilmiştir (12). Eğer kore rahatsız edici veya kalıcı olursa, semptomatik tedavi başlanmalıdır. Hiperglisemik hemikore için standart bir tedavi yoktur ve tedaviye dair kontrollü veriler bulunmamaktadır. En yaygın tedaviler dopamin antagonistleri

olan haloperidol, benzodiazepin, valproat ve karbamazepindir. Şiddetli vakalarda tetrabenazin kullanılabilir. Medikal tedaviye dirençli vakalarda ise ventral lateral talamotomi uygulanabilir. Tedavi başlatıldıktan sonra doz azaltma ve tedavi kesilmesi periyodik olarak denenmelidir. Bizim vakamızda da kan şekeri regülasyonu yanı sıra ek tedavi ihtiyacı olmuştur.

Paraneoplastik kore ise paraneoplastik hareket bozukluklarından bir tanesidir. Malign neoplazmların nonmetastatik komplikasyonu olarak nadiren gelişir. Otoimmün aracılıklı mekanizmalarla meydana geldiği düşünülmektedir. Sendromlar genel olarak tümör tespitinden daha önce ve subakut olarak başlarlar. Tipik olarak 60 yaş erişkinlerde subakut başlangıçlı olarak izlenir. Kore fokal ya da jeneralize olabilirken, literatürde bir hastada unilateral olarak tarif edilmiştir. Genellikle anti- CRMP5 ve Anti-hu antikorları ile ilişkilidir. Küçük hücreli akciğer kanseri ve çeşitli adenokarsinomlar paraneoplastik kore ile en çok ilişkili malignitelerdir. Paraneoplastik kore tanılı hastaların kranial MR görüntülemeleri genellikle normal izlenmekle birlikte bazı olgularda bazal ganglionlarda hiperintensite gözlemlenebilmektedir (13). Anti-Yo antikoru, hedef proteini serebellar Purkinje hücrelerinin sitoplazmasında yüksek oranda bulunan bir intranöronal antikorlara karşı üretilen bir antikordur. Genellikle meme veya over kanseri ile ilişkili paraneoplastik serebellar dejenerasyon görülen kadınlarda bulunur (14). Literatürde anti-Yo antikor pozitif kore gelişen olgu bildirimleri az sayıdadır (15,16). Ren ve ark. anti-Yo ve anti-MOG antikor pozitifliği birlikte olan bir kore hastasını bildirmiştir (15). Goldstein ve ark ise sağ üst extremitesinde kore şikayetleri olan anti-Yo antikoru pozitif metastatik adenokarsinomlu bir hasta bildirmiştir (16). Olgumuzda paraneoplastik otoantikorlardan anti-Yo antikoru pozitifliği olması paraneoplastik kore sendromunu tanısının da akılda tutulması, malignite açısından dikkatli olunması ve rutin malignite taramasının yapılması gerektiğini de göstermiştir.

Sonuç olarak, hemikore şikayeti ile başvuran hastalarda etyoloji araştırılırken öncelikle erişilebilirliği kolay olan kan şekeri kontrolü yapılması hızlı bir şekilde tanıya yardımcı olacaktır. Diğer taraftan aynı anda farklı mekanizmaların rol oynayabileceği, hiperglisemenin yanı sıra paraneoplastik sendromların da kore, ballismus gibi hareket bozuklukları ile prezente olabileceği her zaman akılda tutulmalıdır.

Çıkar Çatışması

Bu çalışmada yazar ile herhangi bir kişi, kurum veya kuruluş arasında çıkar çatışması bulunmamaktadır. Çalışma, bilimsel etik kurallarına uygun, tarafsız ve bağımsız olarak gerçekleştirilmiştir. Ayrıca, yazım ve yayın sürecinde herhangi bir finansal destek veya bağış alınmamıştır.

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Letter to the Editor

The impact of patient consumerism in clinical laboratories

Klinik Laboratuvarda Hasta Tüketiminin Etkisi

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Dear Editor,

We are writing to highlight an important trend in modern healthcare —patient consumerism— and its implications for clinical laboratories. The increasing awareness among patients about their health and the widespread availability of medical information have led to a shift in their expectations from healthcare providers, including laboratory services. Patients today are more proactive, seeking direct access to laboratory tests, questioning test necessity, and comparing services based on cost, turnaround time, and perceived quality. While this shift can enhance patient engagement and health literacy, it also presents challenges. Self-requested testing, often without proper clinical guidance, may lead to unnecessary investigations, misinterpretation of results, and increased healthcare costs [1].

Additionally, the pressure to provide rapid results can sometimes compromise quality and accuracy, affecting clinical decision-making. Clinical laboratories must adapt by balancing patient expectations with ethical and scientific responsibilities. This includes enhancing communication between laboratory professionals and patients, implementing clearer guidelines for direct-access testing, and promoting awareness about the limitations of certain tests [2].

Furthermore, regulatory policies should evolve to ensure that consumer-driven testing aligns with medical necessity and clinical relevance [3]. We believe that patient consumerism in laboratory medicine is an area that warrants further discussion and research.

Conflict of interest

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Letter to the Editör

The psychiatric symptoms in covid-19 inpatients and 2-month follow-up: an exploration of the relationship with neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and D-dimer

Covid-19 sebebiyle yatışı olan hastaların psikiyatrik belirtiler açısından 2 aylık takibi ve psikiyatrik belirtilerin nötrofil-lenfosit oranı (NLR), trombosit-lenfosit oranı (PLR) ve D-dimer ile ilişkisinin incelenmesi

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Abstract

The study by Turan et al. [1] explores the relationship between psychiatric symptoms and inflammatory markers in COVID-19 inpatients over a 2-month follow-up period. The research highlights the importance of monitoring psychiatric symptoms such as anxiety, depression, and sleep quality during the COVID-19 process and their correlation with inflammatory parameters. The study found that patients with a history of psychiatric diagnosis had significantly higher platelet (PLT) and platelet-to-lymphocyte ratio (PLR) values. Additionally, hospitalization duration was positively correlated with NLR, PLR, Ferritin, D-Dimer, and CRP values, while negatively correlated with lymphocyte count. The study underscores the need for continuous psychiatric care during and after hospitalization for COVID-19 patients. However, the study has limitations, including a small sample size, lack of a control group, and short follow-up duration. Further research with larger sample sizes and longer follow-up periods is recommended to validate these findings.

Keywords: pandemic; anxiety; depression; sleep quality; COVID-19

Öz

Turan ve ark. [1] tarafından yapılan çalışma, COVID-19 nedeniyle hastanede yatan hastalarda psikiyatrik semptomlar ile inflamatuar belirteçler arasındaki ilişkiyi 2 aylık bir takip süresi boyunca incelemektedir. Araştırma, COVID-19 sürecinde anksiyete, depresyon ve uyku kalitesi gibi psikiyatrik semptomların izlenmesinin önemini ve bu semptomların inflamatuar parametrelerle olan ilişkisini vurgulamaktadır. Çalışmada, psikiyatrik tanı öyküsü olan hastalarda trombosit (PLT) ve trombosit-lenfosit oranı (PLR) değerlerinin anlamlı derecede yüksek olduğu bulunmuştur. Ayrıca, hastanede kalış süresi NLR, PLR, Ferritin, D-Dimer ve CRP değerleri ile pozitif, lenfosit sayısı ile negatif korelasyon göstermiştir. Çalışma, COVID-19 hastalarında hastanede yatış sırasında ve sonrasında sürekli psikiyatrik bakımın önemini vurgulamaktadır. Ancak, çalışmanın küçük örneklem büyüklüğü, kontrol grubunun olmaması ve kısa takip süresi gibi sınırlılıkları bulunmaktadır. Bu bulguları doğrulamak için daha geniş örneklemli ve uzun takip süreli çalışmalar önerilmektedir.

Anahtar Kelimeler: Pandemi; anksiyete; depresyon; uyku kalitesi; COVID-19

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Dear Editor,

The study titled "Psychiatric Symptoms in COVID-19 Inpatients and 2-Month Follow-Up: An Exploration of the Relationship with Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and D-Dimer" by Turan et al., published in your journal (Turk J ClinLab 2024; 4: 579-586) [1], provides a significant contribution by examining the relationship between psychiatric symptoms and inflammatory markers in COVID-19. The study stands out for its prospective design, addressing both the psychiatric profile of hospitalized individuals during the pandemic and its connection with hematological parameters. However, there are certain points that need to be evaluated in light of methodological limitations and controversial findings in the literature.

The study found that platelet (PLT) and PLR values were significantly higher in patients with a history of psychiatric diagnosis [1], which is consistent with previous studies supporting the role of inflammation in psychiatric disorders [2,3]. However, the specific impact of markers such as NLR and PLR in predicting the prognosis of psychiatric symptoms remains unclear. For instance, Kayhan et al. [4] reported that PLR is associated with the severity of major depression, but no significant correlation was found between HADS scores and PLR in this study [1]. This discrepancy may be explained by the heterogeneous nature of inflammatory markers and the multifactorial etiology of psychiatric symptoms.

The positive correlation between the length of hospital stay and NLR, PLR, D-Dimer, and CRP [1] highlights the impact of systemic inflammatory response on the clinical course of COVID-19. Similarly, Chan and Rout [5] suggested that NLR and PLR could serve as prognostic markers in predicting the severity of COVID-19. However, the lack of association between psychiatric symptoms and the length of hospital stay in the study indicates the need to differentiate between the psychiatric and immunological dimensions of pathophysiological mechanisms.

Among the most significant limitations of the study are the small sample size (n=110), the absence of a control group, and the lack of pre-COVID-19 blood parameter values. Additionally, the two-month follow-up period may be insufficient to assess the potential chronicity of psychiatric symptoms. In terms of recommendations, larger-scale, long-term follow-up studies and investigations into the relationship between inflammatory markers and treatment response would contribute significantly to the literature.

Additional studies cited support the prognostic role of inflammatory markers in different clinical conditions. For example, Vural et al. [6] determined that NLR and Systemic immune-inflammation index have high diagnostic power in multiple sclerosis relapses, emphasizing the role of inflammation in neuropsychiatric processes. Similarly, Duyan et al. [7] reported that MLR and Systemic immune-inflammation index predict mortality in acute aortic dissection. These findings provide an important framework for understanding the systemic effects of inflammatory markers in relation to the psychiatric complications of COVID-19.

In conclusion, this study is valuable for its integrated perspective on the psychiatric and immunological dimensions of COVID-19. However, more comprehensive research is needed to translate these findings into clinical practice.

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Araştırma Makalesi

The diagnostic performance of non-invasive fibrosis markers for predicting fibrosis in primary biliary cholangitis patients

Primer biliyer kolanjit hastalarında fibrozisi öngörmede invaziv olmayan fibrozis belirteçlerinin tanısal performansı

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Abstract

Aim: This study aimed to investigate the relationship between liver fibrosis measured by transient elastography and non-invasive fibrosis scoring systems, including Fibrosis-4 (FIB-4) and aspartate-aminotransferase (AST)-to-platelet ratio index (APRI), in patients with primary biliary cholangitis (PBC).

Material and Methods: A total of 45 PBC patients followed in the Gastroenterology Clinic were included in this retrospective study. Transient elastography was performed on all participants, and liver stiffness measurement (LSM) values were recorded in kilopascals (kPa). Fibrosis was defined as LSM ≥ 6.3 kPa, while advanced fibrosis was defined as LSM ≥ 10.5 kPa. To calculate the APRI score, the formula [(AST / upper normal limit × 100) / platelet count] was used, and for the FIB-4 score, the formula [(age × AST) / (platelet count × √alanine aminotransferase)] was applied.

Results: Liver fibrosis was identified in 71.1% (n = 32) of patients, with advanced fibrosis present in 40.0% (n = 18). Patients with fibrosis had higher APRI and FIB-4 scores compared to those without fibrosis. Also, the median APRI score (0.7 vs. 0.5, p < 0.001) and median FIB-4 score (2.4 vs. 1.6, p < 0.001) were higher in patients with advanced liver fibrosis than in those without. For detecting fibrosis, the AUROC values were 0.73 (95% CI: 0.58–0.89) for APRI and 0.84 (95% CI: 0.73–0.96) for FIB-4. FIB-4 also showed higher accuracy than APRI for identifying advanced fibrosis (AUROC: 0.78 vs. 0.70, p = 0.048).

Conclusion: Both APRI and FIB-4 are useful non-invasive tools for detecting and staging fibrosis in PBC. However, FIB-4 demonstrated superior diagnostic performance compared to APRI, particularly in predicting advanced fibrosis. Incorporating these markers into routine clinical practice may reduce the need for invasive liver biopsy and help optimize patient management.

Keywords: Primary biliary cholangitis, transient elastography, liver fibrosis, FIB-4 score, APRI score

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Öz

Amaç: Bu çalışma, primer bilyer kolanjit (PBC) hastalarında transient elastografi ile ölçülen karaciğer fibrozisi ile Fibrozis-4 (FIB-4) ve aspartat-aminotransferaz-trombosit oranı indeksi (APRI) gibi non-invaziv fibrozis skorlama sistemleri arasındaki ilişkiyi araştırmayı amaçladı.

Gereç ve Yöntemler: Gastroenteroloji Kliniğinde takip edilen toplam 45 PBC hastası bu retrospektif çalışmaya dahil edildi. Tüm katılımcılara transient elastografi uygulandı ve karaciğer sertliği ölçüm (LSM) değerleri kilopaskal (kPa) cinsinden kaydedildi. Fibrozis, LSM ≥ 6.3 kPa olarak tanımlanırken, ileri fibrozis LSM ≥ 10.5 kPa olarak kabul edildi. APRI skorunun hesaplanmasında [(AST / üst normal sınır × 100) / trombosit sayısı] formülü, FIB-4 skorunun hesaplanmasında ise [(yaş × AST) / (trombosit sayısı × √alanin aminotransferaz)] formülü uygulandı.

Bulgular: Hastaların %71.11'inde (n = 32) karaciğer fibrozisi, %40.0'ında (n = 18) ise ileri fibrozis saptandı. Fibrozisi olan hastalarda fibrozisi olmayan hastalara kıyasla APRI ve FIB-4 skorları daha yüksekti. İleri fibrozisi olan hastalarda ileri fibrozis olmayan hastalara kıyasla da APRI (9.7 vs. 0.5, p < 0.001) ve FIB-4 (2.4 vs. 1.6, p = 0.001) skorları daha yüksekti. Fibrozisin saptanmasında, AUROC değerleri APRI için 0.73 (%95 GA: 0.58–0.89) ve FIB-4 için 0.84 (%95 GA: 0.73–0.96) olarak bulundu. FIB-4, ileri fibrozisi belirlemede de APRI'ye göre daha yüksek doğruluk gösterdi (AUROC: 0.78 karşı 0.70, p = 0.048).

Sonuçlar: APRI ve FIB-4, PBC hastalarında fibrozis tespiti ve evrelemesi için değerli non-invaziv araçlardır. Bununla birlikte, FIB-4 özellikle ileri fibrozisi öngörmede APRI'ye kıyasla üstün tanısal performans sergilemiştir. Bu belirteçlerin rutin klinik uygulamalara dahil edilmesi, invaziv karaciğer biyopsilerinin sayısını azaltabilir ve hasta yönetimini optimize etmeye yardımcı olabilir.

Anahtar Kelimeler: Primer bilyer kolanjit, transient elastografi, karaciğer fibrozisi, FIB-4 skoru, APRI skoru

Introduction

Primary biliary cholangitis (PBC) is an autoimmune disease that causes gradual destruction of the intrahepatic bile ducts, increased inflammation in the portal area, and cholestasis (1, 2). It was previously known as primary biliary cirrhosis. Although genetic factors are blamed for the etiology of PBC, environmental factors are also thought to play a role (3, 4). It is frequently seen in women between the ages of 30 and 60. In the USA, the incidence of PBC is estimated to be 45 per million in women and 17 per million in men, and the prevalence is 65 per million in women and 121 per million in men (5-7). Untreated cholestasis associated with PBC can progress to cirrhosis and portal hypertension, underscoring the need for early fibrosis assessment (8).

Liver fibrosis, rather than bile duct loss, is considered a more reliable marker of histological progression in PBC. Liver biopsy is the gold standard for evaluating fibrosis, but its invasive nature, associated risks, and patient discomfort limit its routine use (9). non-invasive alternatives, such as the aspartate-aminotransferase-to-platelet ratio index (APRI), Fibrosis-4 (FIB-4) score, and imaging methods like transient elastography, have gained traction for diagnosing and monitoring fibrosis in PBC. Many studies have found that transient elastography provides a higher diagnostic performance in the differential diagnosis of fibrosis (10-14). However, transient elastography has limitations, including high cost and limited availability in many healthcare systems. In contrast, APRI and FIB-4 are cost-effective, easy-to-calculate, and widely applicable, offering a more accessible alternative for fibrosis evaluation (15, 16). Despite their lower diagnostic accuracy compared to transient elastography, their affordability and simplicity make them valuable tools in clinical practice.

The current literature provides limited findings on the diagnostic performance of these scoring systems in PBC patients. Therefore, this study aimed to investigate the relationship between liver fibrosis measured by transient elastography and non-invasive fibrosis scoring systems, including FIB-4 and APRI, in PBC patients.

Material and Methods

This retrospective study was conducted with PBC patients who admitted to the Gastroenterology Clinic of the Umraniye Training and Research Hospital. The present study adhered to the ethical regulations and principles as stipulated in the Declaration of Helsinki. The study received approval from the

Ethical Committee of the Umraniye Training and Research Hospital, Clinical Research Ethics Committee (Date: 02.11.2023, Decision No. B.10.1.TKH.4.34.H.GRUL01/412). The requirement for obtaining informed consent was exempted by the Ethics Committee, given the retrospective design of the study.

Study population

The study enrolled 45 patients diagnosed with PBC, monitored at the Liver Clinic from January 2016 to October 2021, and who had transient elastography performed. PBC was diagnosed in patients with elevated alkaline phosphatase (ALP) if one of the following criteria was met: positivity for antimitochondrial antibodies (AMA) or histopathological evidence of non-suppurative destructive cholangitis with interlobular bile duct damage [7]. Exclusion criteria comprised individuals under 18, those with decompensated cirrhosis confirmed clinically, radiologically, or through laboratory findings, patients with pacemakers, those with ascites, those with pregnant women, those with alcohol consumption, those with viral hepatitis, and those with missing transient elastography data or incomplete records. Data on demographic information (age, gender, waist circumference, height, weight, body mass index (BMI)), clinical characteristics (comorbidities, duration of PBC) and laboratory findings were retrieved from patient records.

Laboratory parameters

Blood samples for routine analyses, including complete blood count and biochemical parameters, were taken from the antecubital vein of all patients at the Liver Clinic following at least 8 hours of fasting. All analyses were performed in the same laboratory using consistent equipment. Non-invasive fibrosis scores are calculated using demographic and laboratory data obtained [7-19]:

$$APRI = \frac{AST\ (U/L)}{upper\ limit\ of\ normal\ AST\ (U/L)} \times 100 \div Platelets\ (x10^9/L)$$

$$FIB\text{-}4 = \frac{Age \times Aspartate\ aminotransferase\ (AST;\ U/L)}{\sqrt{Alanine\ aminotransferase\ (ALT;\ U/L)} \times Platelets\ (x10^9/L)}$$

Transient elastography

Transient elastography was conducted by a single operator using the FibroScan® Compact 530 device (Echosens SA, Paris, France). Participants were instructed to fast for at least 3 hours prior to the assessment. The procedure was performed with participants lying in the supine position, with their right arm fully abducted. The M probe was used for all examinations, and the XL probe was employed when indicated by the automatic probe selection tool. Only measurements with at least 10 valid readings and an interquartile range (IQR) to median ratio of <30% were considered reliable.

Liver stiffness measurement (LSM) values were recorded in kilopascals (kPa), while controlled attenuation parameter (CAP) values, obtained simultaneously, were measured using the second-generation CAP (CAP2) and expressed in dB/m. The procedure was continued until 10 valid measurements were achieved for 100% of measurements [20]. Fibrosis was considered present at LSM ≥ 6.3 kPa, while advanced fibrosis was defined as LSM ≥ 10.5 kPa [20].

Statistical analysis

All statistical analyses were conducted using STATA/MP v.16 software (StataCorp LLC, Texas, USA). Numerical data with a normal distribution, as determined by the Kolmogorov-Smirnov test, are presented as mean ± standard deviation, whereas non-normally distributed variables are expressed as median (25th-75th percentiles). Comparisons between two groups were performed using the Student t-test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. For comparisons involving more than two groups, the ANOVA test (post-hoc: Bonferroni) was used for normally distributed data, and the Kruskal-Wallis H test (post-hoc: Dunn's test) was used for non-normally distributed data. Categorical variables were summarized as numbers and percentages, with group comparisons performed using the Chi-square test or Fisher's exact test when applicable. A multivariable logistic regression analysis employing the backward Wald method was used to identify potential independent predictors of fibrosis. The diagnostic performance of non-invasive fibrosis scores was evaluated through receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC), standard error (SE), sensitivity, and specificity reported. The optimal cutoff values for predicting fibrosis were determined using the Youden Index method. A p-value of $P < 0.05$ was considered statistically significant for all analyses.

Results

The study population consisted of 45 patients with a mean age of 60.2 ± 9.4 years, the majority of whom were female. The mean disease duration was 5.4 ± 1.8 years. The demographic and clinical findings of the patients are detailed in Table 1. Liver fibrosis was detected in 71.1% of cases (n = 32), with advanced liver fibrosis present in 40.0% (n = 18). The ratio of hypertension was higher in patients with liver fibrosis than in

those without (59.4% vs. 15.4%, p= 0.009). Other demographic characteristics did not show significant differences between the groups with and without liver fibrosis. The median AST and ALT levels were similar in patients with and without liver fibrosis, but mean platelet levels were lower in those with fibrosis. The median APRI score (1.5 vs. 0.3, p = 0.015) and median FIB-4 score (1.9 vs. 1.0, p < 0.001) were higher in in patients with liver fibrosis than in those without (Table 1).

The demographic characteristics were comparable between patients with and without advanced fibrosis. While platelet and AST values did not differ significantly, the median AST level was higher in patients with advanced fibrosis. The median APRI score (1.7 vs. 0.5, p < 0.001) and median FIB-4 score (2.4 vs. 1.6, p < 0.001) were higher in patients with advanced liver fibrosis than in those without (Table 2).

The diagnostic performance of the APRI and FIB-4 scores in predicting fibrosis was evaluated using ROC curve analysis. The area under the ROC curve (AUROC) for APRI in detecting fibrosis was 0.73 (95% CI: 0.58-0.89), while for FIB-4, the AUROC was 0.84 (95% CI: 0.73-0.96). The FIB-4 score demonstrated superior diagnostic performance in predicting fibrosis compared to the APRI score (AUC: 0.84 vs. 0.73, p < 0.001) (Figure 1) (Table 3).

Table 1. The demographic and clinical findings of patients with primary biliary cholangitis.

Variables	All population n=45	Fibrosis		p
		No n=13	Yes n=32	
Age, years	60.2 ± 9.4	54.8 ± 10.0	62.3 ± 8.4	0.014*
Gender, n (%)				
Female	39 (86.7)	11 (84.6)	28 (87.5)	0.999
Male	6 (13.3)	2 (15.4)	4 (12.5)	
WC, cm	95.6 ± 12.4	90.1 ± 11.2	97.9 ± 12.3	0.054
BMI, kg/m2	29.3 ± 5.8	28.2 ± 5.7	29.8 ± 5.9	0.404
Hypertension, n (%)	21 (46.7)	2 (15.4)	19 (59.4)	0.009*
Diabetes mellitus, n (%)	10 (22.2)	2 (15.4)	8 (25.0)	0.698
Disease duration, years	5.4 ± 1.8	5.4 ± 1.8	5.3 ± 1.9	0.728
TE findings				
CAP score, dB/m	227.8 ± 49.9	216.2 ± 39.0	232.5 ± 53.6	0.328
Fibrosis score, kpa	8.6 (6.3-14.3)	5.7 (5.6-6.2)	11.8 (8.4-18.4)	<0.001*
Laboratory findings				
Glucose, mg/dL	94.0 (86.0-101.0)	92.0 (88.0-99.0)	94.5 (85.0-102.0)	0.688
Albumin, g/L	42.5 ± 3.6	43.2 ± 1.9	42.2 ± 4.1	0.405
Platelets, x109/L	216.2 ± 77.3	268.9 ± 55.4	194.7 ± 75.1	0.002*
HDL-C, mg/dL	54.0 (47.0-63.0)	54.0 (49.0-61.0)	54.5 (46.5-65.2)	0.634
LDL-C, mg/dL	118.9 ± 30.5	135.7 ± 34.0	112.1 ± 26.5	0.017*
Triglyceride, mg/dL	104.0 (76.0-136.0)	103.0 (91.0-136.0)	107.0 (74.5-134.2)	0.861
AST, U/L	24.0 (20.0-32.0)	25.0 (22.0-30.0)	23.5 (20.0-34.5)	0.661
ALT, U/L	20.0 (14.0-31.0)	20.0 (14.0-25.0)	21.5 (13.8-31.2)	0.725
IgG, g/L	13.9 (12.2-15.8)	12.2 (10.1-14.0)	14.1 (12.5-16.8)	0.082
IgM, g/L	1.8 (1.3-2.4)	1.8 (1.4-1.9)	1.7 (1.3-2.7)	0.745
GGT, U/L	51.0 (24.0-107.0)	51.0 (22.0-82.0)	50.0 (25.5-114.5)	0.698
Total bilirubin, mg/dL	0.6 ± 0.3	0.5 ± 0.2	0.6 ± 0.3	0.107
Sodium, mEq/L	140.5 ± 2.8	140.4 ± 2.2	140.6 ± 3.1	0.832
AFP, ng/mL	142.0 (114.0-179.0)	125.0 (114.0-144.0)	152.0 (119.5-181.2)	0.150
Creatinine, mg/dL	0.8 ± 0.2	0.7 ± 0.1	0.8 ± 0.2	0.100
CRP, mg/L	4.9 (2.1-6.3)	4.0 (1.8-5.4)	5.1 (3.0-8.8)	0.106
APRI score	0.4 (0.3-0.6)	0.3 (0.2-0.4)	0.5 (0.3-0.6)	<0.001*
FIB-4 score	1.8 (1.2-2.4)	1.0 (0.9-1.5)	1.9 (1.5-3.2)	<0.001*

Data are mean ± standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase, AST, aspartate aminotransferase, ALP, alkaline phosphatase; BMI, body mass index; CAP, controlled attenuation parameter; CRP, C-reactive protein; GGT, gamma glutamyl transferase; IgG, immunoglobulin G, IgM, immunoglobulin M; TE, transient elastography

Table 2. Demographic and clinical findings associated with advanced fibrosis.

Variables	Fibrosis			p
	No n=13	No advanced n=14	Advanced n=18	
Age, years	54.8 ± 10.0	62.2 ± 5.7	62.4 ± 10.1	0.050*
Gender, n (%)				
Female	11 (84.6)	13 (92.9)	15 (83.3)	0.264
Male	2 (15.4)	1 (7.1)	3 (16.7)	
WC, cm	90.1 ± 11.2	94.4 ± 13.7	100.7 ± 10.7	0.060
BMI, kg/m2	28.2 ± 5.7	28.1 ± 5.4	31.1 ± 6.1	0.239
Hypertension, n (%)	2 (15.4)	7 (50.0)	12 (66.7)	0.018*
Diabetes mellitus, n (%)	2 (15.4)	3 (21.4)	5 (27.8)	0.712
Disease duration, years	5.5 ± 1.8	5.0 ± 1.7	5.5 ± 2.1	0.851
TE findings				
CAP score, dB/m	216.2 ± 39.0	236.5 ± 61.7	229.3 ± 48.0	0.576
Fibrosis score, kpa	5.8 ± 0.4	8.2 ± 1.2	23.3 ± 10.8	<0.001*
Laboratory findings				
Glucose, mg/dL	94.3 ± 11.1	94.6 ± 10.2	110.6 ± 34.5	0.210
Albumin, g/L	43.2 ± 1.9	43.3 ± 1.8	41.3 ± 5.1	0.206
Platelets, x109/L	268.9 ± 55.4	206.6 ± 58.6	185.5 ± 66.3	0.008*
HDL-C, mg/dL	54.0 (49.0-61.0)	60.5 (52.5-69.0)	49.0 (44.2-56.8)	0.131
LDL-C, mg/dL	135.7 ± 34.0	112.4 ± 31.6	111.8 ± 22.8	0.059
Triglyceride, mg/dL	103.0 (91.0-136.0)	114.5 (71.5-127.8)	104.0 (76.5-143.5)	0.921
AST, U/L	25.8 ± 10.0	23.2 ± 5.5	45.3 ± 10.8	0.025*
ALT, U/L	20.0 (14.0-25.0)	21.5 (13.2-24.0)	23.0 (14.2-50.5)	0.621
IgG, g/L	12.6 ± 4.1	12.9 ± 2.4	17.2 ± 4.5	0.016
IgM, g/L	1.8 (1.4-1.9)	1.8 (1.3-2.3)	1.7 (1.3-4.1)	0.845
GGT, U/L	51.0 (22.0-82.0)	39.5 (14.0-81.5)	67.5 (30.2-149.0)	0.219
Total bilirubin, mg/dL	0.5 ± 0.2	0.6 ± 0.2	0.7 ± 0.3	0.068
Sodium, mEq/L	140.4 ± 2.2	141.0 ± 2.1	140.2 ± 3.7	0.730
AFP, ng/mL	125.0 (114.0-144.0)	141.0 (108.5-166.8)	163.5 (136.2-249.5)	0.083
Creatinine, mg/dL	0.7 ± 0.1	0.8 ± 0.2	0.8 ± 0.2	0.246
CRP, mg/L	4.0 (1.8-5.4)	3.3 (2.1-6.2)	5.8 (3.9-9.0)	0.112
APRI score	0.3 (0.2-0.4)	0.5 (0.3-0.5)	0.7 (0.4-0.9)	<0.001*
FIB-4 score	1.0 (0.9-1.5)	1.6 (1.4-2.1)	2.4 (1.9-3.9)	<0.001*

Data are mean ± standard deviation or median (IQR), or number (%). *p<0.05 indicates statistical significance. Differences between groups are highlighted in bold characters. Abbreviations: AFP, alpha fetoprotein; ALT, alanine aminotransferase, AST, aspartate aminotransferase, ALP, alkaline phosphatase; BMI, body mass index; CAP, controlled attenuation parameter; CRP, C-reactive protein; GGT, gamma glutamyl transferase; IgG, immunoglobulin G, IgM, immunoglobulin M; TE, transient elastography.

Table 3. Diagnostic performance of the aspartate aminotransferase-to-platelet ratio index APRI), and fibrosis score 4 (FIB-4) for distinguishing fibrosis.

ROC curve findings	APRI	FIB-4
Fibrosis vs. no fibrosis		
AUC	0.73	0.84
Standard Error	0.08	0.06
95% CI	0.58-0.89	0.73-0.96
Sensitivity	53.0	88.0
Specificity	92.3	69.2
Cut-off value	0.45	1.33
Advanced fibrosis vs. no advanced fibrosis		
AUC	0.70	0.78
Standard Error	0.09	0.08
95% CI	0.53-0.86	0.58-0.89
Sensitivity	40.0	77.2
Specificity	100.0	72.4
Cut-off value	0.60	1.80

Abbreviations: APRI, aspartate aminotransferase to platelet ratio index; AUC, area under the curve; CI, confidence interval; FIB-4: fibrosis-4 score.

The area under the ROC curve (AUROC) for APRI in detecting advanced fibrosis was 0.70 (95% CI: 0.53-0.86), while for FIB-4, the AUROC was 0.78 (95% CI: 0.58-0.89), the FIB-4 score demonstrated superior diagnostic performance in predicting fibrosis compared to the APRI score (AUC: 0.78 vs. 0.70, p = 0.048) (Figure 1) (Table 3).

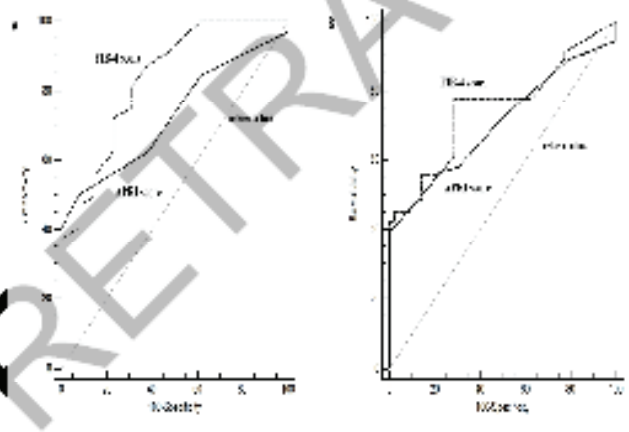

Figure 1. The diagnostic performance of the APRI and FIB-4 scores in predicting presence (A) and advanced (B) fibrosis.

Discussion

To the best of our knowledge, this study is among the few that investigate the correlation between fibrosis measured by transient elastography and non-invasive fibrosis scoring systems in in patients with PBC. In the present study, we evaluated the diagnostic accuracy of non-invasive fibrosis markers in patients with PBC. Our findings demonstrated that both APRI and FIB-4 scores were higher among patients with liver fibrosis, as well as in those with advanced fibrosis. Furthermore, FIB-4 showed a superior diagnostic performance compared to APRI for detecting both presence and advanced fibrosis.

PBC typically presents more frequently in women aged between 40 and 60 years, and patients are often diagnosed in middle to older age (21, 22). The mean age of our cohort and the predominance of women align with previously reported demographic profiles. The study identified a higher prevalence of hypertension in the fibrotic group. In a study examining cardiac function and morphology in non-cirrhotic PBC patients, it was reported that PBC, when compared to age-matched controls, is linked to higher blood pressure, heart remodeling, and functional abnormalities (23). While the precise mechanisms connecting hypertension to PBC-related fibrosis are not yet fully understood, systemic comorbidities like hypertension are frequently associated with chronic liver diseases and may indicate elevated vascular resistance or portal hypertension in advanced stages. However, further research is needed to determine whether hypertension arises directly from liver-related pathophysiological changes or shares common underlying risk factors.

In accordance with the literature, platelet levels were lower in patients with fibrosis, likely due to hypersplenism and increased platelet sequestration secondary to portal hypertension (24). Although AST and ALT levels did not differ significantly between those with and without fibrosis, we found that AST levels were higher among patients with advanced fibrosis, suggesting a more pronounced hepatocellular injury (25). Advanced fibrosis is associated with increased risk of complications such as portal hypertension and cirrhosis, emphasizing the importance of early and accurate fibrosis detection.

A study by Carpechot et al. showed that elastography outperformed non-invasive scores in identifying advanced fibrosis and cirrhosis, while APRI and FIB-4 exhibited comparable diagnostic performance (26). The challenges of elastography include its unavailability in many clinics, as well as the additional costs and time required. This underscores the importance of more affordable and easily accessible non-invasive fibrosis markers. Non-invasive tools such as APRI and FIB-4, which have been extensively validated in chronic viral hepatitis and non-alcoholic fatty liver disease, are increasingly being explored in cholestatic conditions like PBC (27, 28). In our study, both APRI and FIB-4 effectively predicted the presence and advanced

fibrosis. FIB-4 demonstrated higher AUROC values compared to APRI for identifying both fibrosis and advanced fibrosis. FIB-4 index integrates age, AST, ALT, and platelet count, capturing multiple components of fibrogenesis. This may explain its particular effectiveness in predicting advanced fibrosis. In contrast, APRI, which relies solely on AST levels and platelet counts, provides a more limited perspective—yet remains valuable due to its simplicity and low cost. However, the current literature contains conflicting findings regarding the diagnostic performance of these indices. A study by Li and colleagues on PBC patients demonstrated AUROC values of 0.65 for APRI and 0.72 for FIB-4 in predicting advanced fibrosis (28). A study involving 107 PBC patients identified erythrocyte distribution width, FIB-4, albumin, and platelet levels as fibrosis-associated markers, with FIB-4 demonstrating the greatest sensitivity and specificity for differentiating histological severity (26). In a study conducted by Ölmez et al. involving 40 PBC patients, APRI and FIB-4 scores were found to be higher in patients with early and advanced-stage fibrosis. However, While the APRI score had a higher AUROC value than the FIB-4 score, the difference was not statistically significant (0.75 vs. 0.69, respectively) (29). In a study conducted by Sayar et al. involving 53 PBC patients, APRI and FIB-4 scores were reported to show no differences between early and advanced fibrosis groups (16). Variations between studies could be attributed to differences in patient selection.

From a clinical standpoint, our results highlight the significant advantage of using these non-invasive indices to assess the stage of fibrosis without requiring a liver biopsy. The invasive nature of biopsy, along with the risk of complications such as bleeding and patient discomfort, increasingly drives the search for reliable non-invasive alternatives. The high sensitivity and specificity of FIB-4 make it a particularly valuable tool for guiding treatment decisions and monitoring disease progression in PBC. Identifying patients at higher risk of developing advanced fibrosis or cirrhosis at earlier stages can help clinicians tailor more intensive therapeutic strategies.

One major limitation of this study is the relatively small sample size, predominantly consisting of female patients, which may restrict the generalizability of our findings. Second, the cross-sectional design limits the ability to assess temporal changes in fibrosis markers or their prognostic value over time. Additionally, liver biopsy, the gold standard for diagnosing and staging fibrosis, was not utilized in this study. Lastly, the study did not account for all potential confounders, such as co-existing conditions (e.g. alcohol consumption, or viral hepatitis), which could influence fibrosis progression or the values of non-invasive markers. Future prospective studies with larger cohorts and multifaceted evaluations are needed to establish more comprehensive data in this field.

Conclusion

This study confirms the diagnostic utility of non-invasive markers such as APRI and FIB-4 for predicting both the presence and severity of fibrosis in patients with PBC. FIB-4, in particular, demonstrated superior performance and may reduce the need for invasive liver biopsy in routine practice. The integration of non-invasive approaches benefits clinicians by enabling earlier detection of fibrosis progression and helping guide timely therapeutic interventions. Hence, the use of tools like FIB-4 and APRI—either individually or in combination with other diagnostic modalities—retains critical importance in the early identification and management of PBC-related fibrosis.

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Ethics Committee Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Umraniye Training and Research Hospital, Clinical Research Ethics Committee (Date: [illegible].2023, Decision No. B.10.1.TKH.4.34.H.GP8.01/412).

Informed Consent

The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Conflicts of Interest

The authors declare they have no conflicts of interest.

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

Availability of Data and Material

The data that support the findings of this study are available on request from the corresponding author, [N.M.B.].

Author Contributions

Concept – N.M.B. and G.A., Design – N.M.B. and G.A., Supervision – G.A., Data collection and/or processing – N.M.B. and G.A., Analysis and/or Interpretation – N.M.B. and G.A., Writing – N.M.B., Critical review- G.A. All authors read and approved the final version of the manuscript.

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Etik kurallar: Klinik araştırmaların protokolü etik komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda, "Yöntem ve Gereçler" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın Helsinki İlkeler Deklerasyonuna (www.wma.net/e/policy/b3.htm) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm insanların bilgilendirilmiş onam formunu imzaladığı metin içinde belirtilmelidir. Turkish Journal of Clinics and Laboratory gönderilen yazıların Helsinki Deklarasyonuna uygun olarak yapıldığını, kurumsal etik ve yasal izinlerin alındığını varsayacak ve bu konuda sorumluluk kabul etmeyecektir.

Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntemler bölümünde Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) prensipleri doğrultusunda çalışmalarında hayvan haklarını koruduklarını ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır.

Teşekkür yazısı: Varsa kaynaklardan sonra yazılmalıdır.

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Kitaptan yapılan alıntı;

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Turkish Journal of Clinics and Laboratory - Türk Klinik ve Laboratuvar Dergisi

Tıp dergilerine gönderilecek makalelerin standart gereksinmeleri ile ilgili tüm bilgileri www.icmje.org internet adresinde bulabilirsiniz

Amaç ve kapsam: "Turkish Journal of Clinics and Laboratory", hakemli, açık erişimli ve periyodik olarak çıkan, DNT Ortadoğu Yayıncılık A.Ş. ye ait bir dergidir. Hedefimiz uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayınlamaktır. Yılda dört kez çıkan bir bilimsel bir tıp dergisidir. Hakemli bir dergi olarak gelen yazılar konsültanlar tarafından, öncelikle, biyomedikal makalelere ait Uluslararası Tıp Dergileri Editörleri Komitesi (www.icmje.org adresinden ulaşılabilir) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilir. Tıbbın her dalı ile ilgili retrospektif/prospektif klinik ve laboratuar çalışmalar, ilginç olgu sunumları, davet üzerine yazılan derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve cerrahi teknik yazılarıları yayımlayan bilimsel, uluslar arası hakemli bir dergidir. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez.

On-line makale gönderimi: Tüm yazışmalar ve yazı gönderimleri dergipark üzerinden http://dergipark.gov.tr/tjcl yapılmalıdır. Yazı gönderimi için detaylı bilgi bu internet adresinden edinilebilir. Gönderilen her yazı için özel bir numara verilecek ve yazının alındığı e-posta yolu ile teyid edilecektir. Makalelerin "full-text" pdf formuna http://dergipark.gov.tr/tjcl linkinden ulaşılabilir.

Açık erişim politikası: Turkish Journal of Clinics and Laboratory açık erişimi olan bir dergidir. Kullanıcı lar yazıların tam metnine ulaşabilir, kaynak gösterilerek tüm makaleler bilimsel çalışmalarda kullanılabilir.

Aşağıdaki rehber dergiye gönderilen makalelerde aranan standartları göstermektedir. Bu uluslararası format, makale değerlendirme ve basım aşamalarının hızla yapılmasını sağlayacaktır.

Yazarlara Bilgi: Yazıların tüm bilimsel sorumluluğunu yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayınlanan yazılar için herhangi bir sorumluluk kabul etmez.

Dergi adının kısaltması: Turk J Clin Lab

Yazışma adresi: Yazılar e-mail yoluyla sorumlu yazar tarafından, Dergipark ta yer alan Turkish Journal of Clinics and Laboratory linkine girip kayıt olduktan sonra gönderilmelidir.

Makale dili: Makale dili Türkçe ve İngilizcedir. İngilizce makaleler gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanı tarafından düzeltilebilir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu amaçla, Türk Dil Kurumu Sözlük ve Yazım Kılavuzu yazım dilinde esas alınmalıdır.

Makalenin başka bir yerde yayımlanmamıştır ibaresi: Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. 400 kelimeden az özetler kapsam dışıdır. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazarlara aittir.

Değerlendirme: Dergiye gönderilen yazılar format ve plagiarism açısından değerlendirilir. Formata uygun olmayan yazılar değerlendirilmeden sorumlu yazara geri gönderilir. Bu tarz bir zaman kaybının olmaması için yazım kuralları gözden geçirilmelidir. Basım için gönderilen tüm yazılar iki veya daha fazla yerli/yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayıma kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir. Makalenin dergiye gönderilmesi veya basıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

Basıma kabul edilmesi: Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak basım sırasına alınır. Her yazı için bir doi numarası alınır.

Yayın hakları devri: http:/www.dergipark.ulakbim.gov.tr/tjclinlab adresi üzerinden online olarak gönderilmelidir. 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

Makale genel yazım kuralları: Yazılar Microsoft Word programı (7.0 ve üst versiyon) ile çift satır aralıklı ve 12 punto olarak, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New roman olmalıdır. "System International" (SI) unitler kullanılmalıdır. Şekil tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Türkçe makalelerde %50 bitişik yazılmalı, aynı şekilde İngilizcelerde de 50% bitişik olmalıdır. Türkçede ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Derleme 4000, orijinal çalışma 2500, olgu sunumu 1200, editöre mektup 500 kelimeyi geçmemelidir. Özet sayfasından sonraki sayfalar numaralandırılmalıdır.

Yazının bölümleri

1. Sunum sayfası: Yazının Turkish Journal of Clinics and Laboratory 'de yayınlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, maddi destek ve çıkar ilişkisi durumu belirtmelidir.

2. Başlık sayfası: Sayfa başında gönderilen makalenin kategorisi belirtilmedir (Klinik analiz, orijinal çalışma, deneysel çalışma, olgu sunumu vs).

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir. Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, unvanları, çalıştıkları kurum, klinik ve şehir yazar isimleri altına eklenmelidir.

Bu sayfada "sorumlu yazar" belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir.

Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir.

3. Makale dosyası: (Yazar ve kurum isimleri bulunmamalıdır)

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemelidir. Türkçe ve İngilizce yazılmalı ve kısa başlık (runing title) Türkçe ve İngilizce olarak eklenmelidir.

Özet: Türkçe ve İngilizce yazılmalıdır. Orijinal çalışmalarda özetler, Amaç (Aim), Gereç ve Yöntemler (Material and Methods), Bulgular (Results) ve Sonuçlar (Conclusion) bölümlerine ayrılmalı ve 250 sözcüğü geçmemelidir. Olgu sunumları ve benzerlerinde özetler, kısa ve tek paragraflık olmalıdır (150 kelime), Derlemelerde 300 kelimeyi geçmemelidir.

Anahtar kelimeler: Türkçe ve İngilizce özetlerin sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce anahtar kelimeler "Medical Subject Headings (MESH)" e uygun olarak verilmelidir. (www.nlm.nih.gov/mesh/MBrowser.html). Türkçe anahtar kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda birebir Türkçe tercümesi verilmelidir.

Metin bölümleri: Orijinal makaleler; Giriş, Gereç ve Yöntemler, Bulgular, Tartışma olarak düzenlenmelidir. Olgu sunumları; Giriş, Olgu sunumu, Tartışma olarak düzenlenmelidir. Şekil, fotoğraf, tablo ve grafiklerin metin içinde geçtiği yerler ilgili cümlenin sonunda belirtilmeli metin içine yerleştirilmemelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Tablolar metin sonuna eklenmelidir. Resimler/fotoğraf kalitesi en az 300dpi olmalıdır.