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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Survival Comparison and Clinical Characteristics of Sunitinib and Pazopanib in the Treatment of Metastatic Renal Cell Cancer, Single Center Real-Life Data

Metastatik Renal Hücreli Kanser Tedavisinde Sunitinib ve Pazopanibin Sağkalım Karşılaştırılması ve Klinik Özellikleri, Tek Merkez Gerçek Yaşam Verileri

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ABSTRACT

Aim: *Renal cell cancer (RCC) is a tumor with increasing incidence and high morbidity and mortality. Our objective was to compare the progression-free survival (PFS) and overall survival (OS), as well as the clinical and demographic characteristics, of patients diagnosed with metastatic RCC at our center who received treatment with either sunitinib or pazopanib.*

Material and Methods: *The study included 39 patients retrospectively. Clinical and demographic characteristics were extracted from patient records and analyzed using IBM Statistical Package for Social Sciences (SPSS) program version 25. Progression-free survival and OS were analyzed using Kaplan-Meier curves.*

Results: *Among the patients, 30 (76.9%) had clear cell pathology, and 33 (84.6%) had undergone surgery, while 6 (15.4%) were diagnosed through biopsy. First-line treatment with sunitinib was initiated in 28 patients (71.8%), whereas pazopanib was administered to 11 patients (28.2%). The median PFS was 25.8 months, and the median OS was 84.3 months for patients who underwent surgery. In patients diagnosed by biopsy, median PFS was 4.2 months, and median OS was 4.7 months. Progression-free survival (p=0.004) and OS (p<0.001) were longer and statistically significant in operated patients. Patients who received sunitinib as first-line treatment had a median PFS of 25.4 months and a median OS of 50.3 months. In comparison, patients treated with pazopanib in the first-line setting had a median PFS of 24.7 months and a median OS of 56.6 months. There was no statistical difference between sunitinib and pazopanib for both PFS (p=0.767) and OS (p=0.684).*

Conclusion: *PFS and OS were longer in operated RCC patients. There was no difference in PFS and OS between sunitinib and pazopanib in RCC patients first-line treatment.*

Key words: *cancer; operation; overall survival*

ÖZET

Amaç: *Renal hücreli kanser (RHK) insidansı giderek artan, morbidite ve mortalitesi yüksek bir tümördür. Merkezimizde metastatik RHK tanısıyla, sunitinib veya pazopanib tedavisi verilen hastalarımızda progresyonsuz sağkalımı (PFS), genel sağkalımı (OS) ve klinik-demografik özelliklerini araştırmayı amaçladık.*

Materyal ve Metot: *Çalışmaya 39 hasta retrospektif olarak dâhil edildi. Hastaların klinik-demografik özellikleri hasta dosyalarından alındı. IBM Sosyal Bilimlerde İstatistik Paket Programı (SPSS) sürüm 25 kullanılarak analiz edildi. PFS ve OS Kaplan-Meier eğrileri kullanılarak analiz edildi.*

Bulgular: *Clear cell patolojisi olan 30 (%76,9) hastamız vardı. Otuz üç (%84,6) hasta opere olmuştu. Altı (%15,4) hasta biyopsi ile tanı almıştı. Birinci basamak sunitinib tedavisi 28 (%71,8) hastaya, pazopanib tedavisi 11 (%28,2) hastaya başlanmıştı. Cerrahi operasyon geçirenlerde median PFS 25,8 ay, median OS 84,3 ay idi. Biyopsi (bx) ile tanı konulan hastalarda median PFS 4,2 ay, median OS 4,7 ay idi. Opere olan hastalarda PFS (p=0,004) ve OS (p<0,001) daha uzundu ve istatiksel olarak anlamlıydı. Birinci basamakta sunitinib alan hastalarda median PFS 25,4 ay, medyan OS 50,3 aydı. Birinci basamakta pazopanib alan hastalarda median PFS 24,7 ay, medyan OS 56,6 ay idi. Hem PFS (p=0,767) hem OS (p=0,684) için sunitinib ve pazopanib arasında istatiksel fark bulunmadı.*

Sonuç: *Opere olan RHK'lı hastalarda PFS ve OS daha uzundu. Birinci basamakta RHK tedavisinde sunitinib ve pazopanib tercihlerinde PFS ve OS farkı yoktu.*

Anahtar kelimeler: *genel sağkalım; kanser; operasyon*

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Introduction

Renal cell carcinoma (RCC) constitutes approximately 3% of all reported cases of cancer worldwide. It is the eighth most prevalent form of cancer globally, with 30% of patients presenting with metastatic disease at the time of diagnosis[1,2]. The treatment of localized disease is surgical intervention. Approximately 50% of patients demonstrate recurrence within the first five years. The predominant histopathological diagnosis is clear cell, accounting for 80% of cases, followed by papillary, chromophobe, and other rare histopathologies[3,4].

According to Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic factors, RCC is classified into good, intermediate, and poor risk groups. In the good and intermediate risk clear cell RCC (ccRCC) group, sunitinib or pazopanib can be used in first-line treatment[5–7]. Nowadays, according to the International Metastatic RCC Database Consortium (IMDC), combinations with immunotherapy (axitinib plus pembrolizumab, axitinib plus avelumab, lenvatinib plus pembrolizumab, cabozantinib plus nivolumab or ipilimumab plus nivolumab) have gained priority in the patient group with moderate and poor disease[8].

Metastatic RCC demonstrates resistance to cytotoxic therapies. The response to interferon alpha, interleukin 2, and combined cytokine therapies is limited, with numerous side effects observed[9]. The employment of targeted therapies, incorporating VEGF receptor inhibitors such as sunitinib, sorafenib, pazopanib, axitinib, and cabozantinib, has yielded enhanced response rates and augmented survival outcomes[10]. Recent advancements in the field have led to a paradigm shift in treatment approaches, with the integration of immunotherapy and tyrosine kinase inhibitors (TKIs) becoming a prevailing strategy. Sunitinib and pazopanib have analogous mechanisms of action. A comparative analysis of the two drugs reveals that sunitinib primarily causes weakness, fatigue, and hematological problems, while pazopanib is associated with liver toxicity[11,12]. Studies have shown that sunitinib has a better overall survival (OS) contribution, and pazopanib is more selectable in terms of side effects[13].

The objective of this study was to compare the progression-free survival (PFS) and overall survival (OS) data of sunitinib and pazopanib in the initial treatment of patients with metastatic RCC. Additionally, the study sought to investigate the clinical parameters that affect PFS and OS.

Material and Method

The present study retrospectively included 39 patients with metastatic or subsequently metastatic RCC at the time of diagnosis who were admitted to our center between 2010 and 2021. The clinical-demographic characteristics of the patients were obtained from patient files and the hospital information system. Patients with missing data were excluded from the study. The analysis was conducted using IBM Statistical Package for Social Sciences (SPSS) program version 25 software. The primary outcomes of interest were progression-free survival (PFS) and overall survival (OS), which were analyzed using Kaplan-Meier curves. The significance level was set at $p < 0.05$ for all statistical analyses. The study was approved by the clinical research ethics committee (Date: 02/05/2023, Decision No: 2023/299).

Results

Table 1 presents the distribution of patients' clinical findings. As seen in Table 2, the overall median PFS (months) was 25.43 (95% CI: 8.81–42.25). While 2-year PFS was 53.6%, 5-year PFS was 23.5%.

Median PFS times (months) by gender were not statistically significant (p=0.937). While 2-year PFS was 60% in women, 5-year PFS was 21.7%. In men, 2-year PFS was 49.7%, and 5-year PFS was 27.2%.

Median PFS (months) by age groups was not statistically significant (p=0.196). In patients aged ≤65 years, 2-year PFS was 59.8%, and 5-year PFS was 24.6%. In patients aged >65 years, 2-year PFS was 33.3%, and 5-year PFS was 16.7%.

Median PFS times (months) by metastasis site were not statistically significant (p=0.685). The 2-year PFS was 47.4%, and the 5-year PFS was 27.1% in patients with lung metastases. In patients with bone metastases, 2-year PFS was 71.4%, and 5-year PFS was 17.9%. In patients with multiple metastases, 2-year PFS was 45.5%.

Median PFS times (months) by operation groups were statistically significant (p=0.004). The median PFS (months) was 4.26 (95% CI: 2.02–6.50) in the biopsy group and 25.83 (95% CI: 19.50–32.16) in the operated group. The 2-year PFS was 16.7% in the biopsy group. In the operation group, 2-year PFS was 60.3%, and 5-year PFS was 26%.

Median PFS times (months) by stage groups were not statistically significant (p=0.085). In non-metastatic

Table 1. *Distribution of patients' clinical findings (n=39)*

Variables		N	%
Sex	Female	15	38.5
	Male	24	61.5
Age	≤65	30	76.9
	>65	9	23.1
ECOG	0	2	5.1
	1	24	61.5
	2	13	33.3
Smoking	No	24	61.5
	Yes	15	38.5
Comorbidity	No	24	61.5
	HT	8	20.5
	DM	5	12.8
	Other	2	5.1
Operation	Biopsy	6	15.4
	Surgery	33	84.6
Drug	Sunitinib	28	71.8
	Pazopanip	11	28.2
Stage	Not metastatic	9	23.7
	Metastatic	29	76.3
Pathology	Unknown	4	10.3
	Clear	30	76.9
	Chromophobe	2	5.1
	Papillary	3	7.7
LVI	No	14	48.3
	Yes	15	51.7
Grade	I-II	12	40.0
	III-IV	18	60.0
Metastasis area	Lung	19	51.4
	Bone	7	18.9
	Multiple	11	29.7
Progression	No	12	30.8
	Yes	27	69.2
Mortality	Alive	17	43.6
	Ex	22	56.4
		Mean±SD	Median (IQR)
Age		57.54±10.70	55.00 (15.00)
Average follow-up time		44.22±44.08	28.60 (44.07)

Table 2. *PFS comparisons of patients*

PFS (months)	Median (%95 CI)	p
General	25.43 (8.61-42.25)	
Sex		
Female	25.83 (2.25-49.41)	0.937
Male	17.30 (0.00-35.88)	
Age		
≤65	29.30 (20.45-38.14)	0.196
>65	7.40 (0.68-14.12)	
Grade		
I-II	29.30 (0.00-67.74)	0.913
III-IV	25.83 (7.20-44.46)	
LVİ		
No	25.83 (0.00-54.13)	0.914
Yes	24.73 (4.08-45.38)	
Metastasis area		
Lung	11.70 (0.00-32.86)	0.685
Bone	34.46 (2.38-66.54)	
Multiple	17.30 (3.94-30.65)	
Operation		
Biopsy	4.26 (2.02-6.50)	0.004
Surgery	25.83 (19.05-32.16)	
Drug		
Sunitinib	25.43 (0.00-50.98)	0.767
Pazopanib	24.73 (0.38-49.08)	
Stage		
No metastatic	64.43 (-)	0.085
Metastatic	12.00 (0.45-23.54)	

Kaplan Meier curve, Long rank test

patients, 2-year PFS was 77.8%, and 5-year PFS was 77.8%. In metastatic patients, 2-year PFS was 44.8% and 5-year PFS was 17.5%.

As seen in Table 3, the overall median OS (months) was 56.63 (95% CI: 0.00–121.48). 2-year OS was 68.8%, while 5-year OS was 40.7%. Median OS duration (months) by gender was not statistically significant (p=0.864). In women, 2-year OS was 73%, and 5-year OS was 50%. In men, 2-year OS was 65.8%, and 5-year OS was 42.5%.

Median OS durations (months) by age groups were not statistically significant (p=0.281). In patients aged ≤65 years, 2-year OS was 76.1%, while 5-year OS was 43.9%. In those aged >65 years, 2-year OS was 44.4%, while 5-year OS was 29.6%.

Median OS times (months) by metastasis site were not statistically significant (p=0.487). In patients with lung metastases, 2-year OS was 68%, and 5-year OS was 49.5%. In patients with bone metastases, 2-year OS was 71.4%, and 5-year OS was 71.4%. In patients with multiple metastases, 2-year OS was 63.6%, and 5-year OS was 0%.

Table 3. *OS comparisons of patients*

OS (months)	Median (%95 CI)	P
General	56.63 (0.00-121.48)	
Sex		
Female	50.30 (0.00-132.29)	0.864
Male	56.63 (12.37-100.89)	
Age		
≤65	84.36 (1.58-167.17)	0.281
>65	12.56 (0.00-27.95)	
ECOG	84.36(-.-)	0.178
0	56.6(23.54-89.72)	
1	27.1(0.00-54.96)	
2		
Grade		
I-II	56.63 (41.37-71.89)	0.692
III-IV	96.36 (18.48-174.24)	
LVI		
No	96.36 (42.25-150.48)	0.105
Yes	27.10 (0.00-108.73)	
Metastasis area		
Lung	31.03 (0.00-119.19)	0.487
Bone	84.36 (19.83-148.90)	
Multiple	50.30 (12.04-88.55)	
Operation		
Biopsy	4.76 (1.16-8.36)	<0.001
Surgery	84.36 (36.39-132.33)	
Drug		
Sunitinib	50.30 (0.00-125.79)	0.684
Pazopanib	56.63 (0.00-118.64)	
Stage		
No metastatic	- (-)	0.040
Metastatic	30.93 (24.99-36.87)	

Kaplan Meier curve, Long rank test

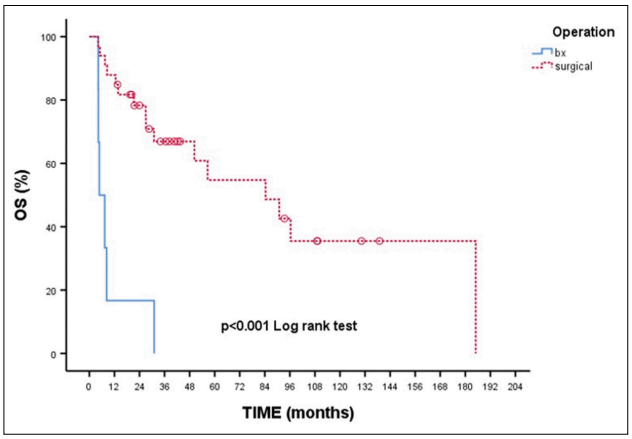

Figure 1. *Overall survival comparison for surgery and biopsy.*

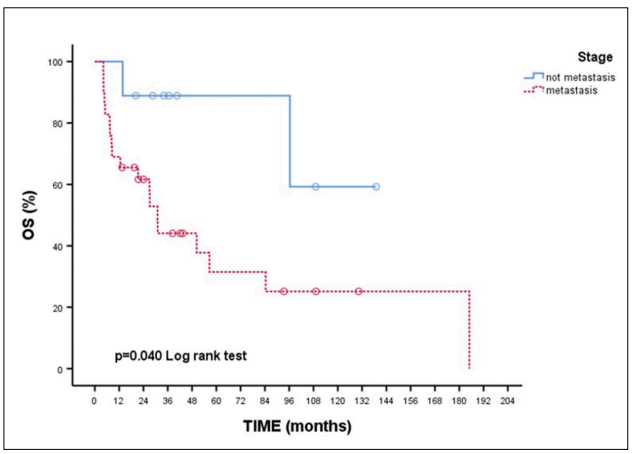

Figure 2. *Comparison of overall survival for patients with initial metastatic disease and those with subsequent metastatic disease.*

Median OS times (months) by operation groups were statistically significant (p<0.001). The median OS (months) was 4.76 (95% CI: 1.16–8.36) in the biopsy group and 84.36 (95% CI: 36.39–132.33) in the surgical group (Fig. 1). The 2-year OS was 16.7% in the biopsy group. In the operation group, 2-year OS was 78.3%, and 5-year OS was 54.7%.

Median OS times (months) by stage groups were statistically significant (p=0.040). Median OS months were not reached in non-metastatic patients (Fig. 2). In metastatic patients, the median OS (months) was 30.93 (95% CI: 24.90–36.87). In non-metastatic patients, 2-year OS was 88.9% and 5-year OS was 88.9%. In metastatic patients, 2-year OS was 61.7%, and 5-year OS was 31.5%.

Univariate analysis showed that operation and stage variables were statistically significant in terms of PFS (p<0.05). These variables, which were found to be significant in univariate analyses, were included in the multivariate Cox regression model, as shown in Table 4. Based on the results of the Multivariate Cox regression model, it was determined that having an operation (OR: 0.30; 95% CI: 0.10–0.87, p=0.026) increased PFS (p=0.009, -2 loglikelihood=142.96).

As a result of univariate analysis, operation and stage variables were found to be statistically significant in terms of mortality risk (p<0.05). As a result of univariate analyses, significant.

These variables were included in the multivariate Cox regression model, as shown in Table 5. The result of the Multivariate Cox regression model showed that

Table 4. *Multivariate Cox regression results for various clinical variables*

PFS	Multivariate	
Variables	HR (95%CI)	p
Operation (Ref:biopsy)	0.30 (0.10-0.87)	0.027
Stage (Ref:No metastatik)	2.33 (0.68-7.98)	0.176

p=0.009, -2 loglikelihood=141.96

Table 5. *Multivariate Cox regression results for various clinical variables*

OS	Multivariate	
Variables	HR (95%CI)	P
Operation (Ref:biopsy)	0.16 (0.05-0.46)	0.001
Stage (Ref:No metastatic)	3.09 (0.68-13.89)	0.141

p<0.001, -2 loglikelihood=108.95

having an operation (OR: 0.16; 95% CI: 0.05–0.46, p=0.001) decreased the risk of death (p<0.001, -2 loglikelihood=108.95).

Discussion

Renal cell cancer is the urinary tract tumor with the highest mortality. There are many different variables affecting prognosis. After interferon therapy, sunitinib and pazopanib, TKI therapies, have contributed to PFS and OS. The treatment of RCC has improved in the last decade with the combination of TKI and immunotherapy[14–17].

In many studies, RCC is seen at a higher rate in males than in females. In the study by Ko et al., the male/female ratio was 2/1[14]. In our study, the male/female ratio was 1.6/1, which was similar to the literature.

In the study by Rini et al., the median age was 60 years; in our study, it was 55 years. The median age in the study by Topal et al. was also 60 years. The younger patient group in our study may be attributable to risk factors such as hypertension[18,19].

The clear cell histopathology rate was 80.5% in the study by Leibovich et al. Similarly, the rate was 87.7% in the study by Patard et al. Likewise, 76.9% of the patients had clear cell histopathology in our study. The preponderance of clear cell histopathology in the extant literature is noteworthy[20,21].

Motzer et al. In the RECORD-1 study, a higher ECOG score was associated with shorter OS. Kim et al. found that a high ECOG score was associated with shorter OS in their study. In our study, no significant relationship was found between ECOG score and OS. This may be due to the small number of patients in our study[22,23].

McKay et al. found that bone and liver metastases were associated with shorter OS. In contrast, the present study found no such association between bone metastasis and OS. While the median OS was found to be numerically higher in patients with bone metastases compared to those with lung and multiple metastases, this difference was not statistically significant[24].

In Wood's study, nephrectomy was associated with prolonged survival. Flanigan et al. and Kassouf et al. recommended nephrectomy for specific metastatic patient groups before systemic immunotherapy and noted that nephrectomy was associated with prolonged survival. In our study, we observed a similar trend, with a longer OS observed in patients who underwent nephrectomy[25–27].

A comparison of sunitinib and pazopanib revealed no significant difference in PFS among patients with metastatic or subsequent metastatic disease. However, OS was found to be superior in patients with subsequent metastatic disease. This observation may be because the disease was not more aggressive in the post-metastatic patient group.

Motzer et al. found no difference in PFS and OS between sunitinib and pazopanib[22]. Consistent with the findings of our study, a lack of statistically significant variance in PFS and OS was observed among patients receiving sunitinib or pazopanib. These findings align with the existing literature on the subject.

The present study has certain limitations. These limitations include the retrospective nature of the study, the limited number of patients, and the absence of prognostic scoring (MSKCC/IMDC).

Conclusion

In the present study, no statistically significant difference in PFS and OS was observed between patients with RCC who received sunitinib as a first-line treatment compared to those who received pazopanib. These findings are consistent with the existing literature on the subject. The present study observed that survival was prolonged in patients who underwent surgery followed by metastasis. The investigation of these data with larger patient groups is expected to contribute to the literature.

Declaration of Interest

The authors declare that they have no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Investigation of Health Sciences Faculty Students' Knowledge About Postpartum Depression

Sağlık Bilimleri Fakültesi Öğrencilerinin Postpartum Depresyon Hakkında Bilgilerinin İncelenmesi

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ABSTRACT

Aim: *The research was conducted to investigate the knowledge of nursing and midwifery students studying at the faculty of health sciences of a university in the Eastern Anatolia Region of Türkiye about postpartum depression.*

Material and Methods: *Two hundred ninety students studying in the 3rd and 4th year nursing and midwifery departments in the 2019–2020 academic year who agreed to participate in the research constituted the sample of this descriptive study. A personal information form and a postpartum depression information form were used in data collection. The data were analyzed using the IBM Statistical Package for Social Sciences (SPSS) program version 22. Values, means, percentage frequency distributions, Kruskal-Wallis H test and the Mann-Whitney U test were used in data analysis.*

Results: *Of the study participants, 79.3% were nursing students, and 52.4% were studying in the 3rd year. Of the participants, 82.1% knew traditional practices related to postpartum depression, and 37.8% considered traditional practices correct. The average level of the participants' knowledge about postpartum depression was 4.70±2.39 points. The study revealed a statistically significant difference between the averages of the nursing and midwifery students' knowledge levels about postpartum depression and the total number of correct answers (p<0.05).*

Conclusion: *The awareness and correct knowledge levels of health sciences faculty students about postpartum depression were found to be inadequate. The average knowledge levels of students studying in two different departments were different. It is recommended that the education provided to students who are future healthcare professional candidates about postpartum depression be strengthened, and awareness-raising studies and practices be conducted.*

Key words: *knowledge; midwife; nurse; student; postpartum depression*

Özet

Amaç: *Türkiye'nin Doğu Anadolu Bölgesinde yer alan bir üniversitenin sağlık bilimleri fakültesinde öğrenim gören hemşirelik ve ebelik öğrencilerinin postpartum depresyon hakkında bilgilerini incelemek amacıyla yapılmıştır.*

Gereç ve Yöntemler: *Tanımlayıcı tipte yapılan bu araştırmanın örneklemini 2019–2020 yılında öğrenim gören 3. ve 4. sınıf hemşirelik ve ebelik bölümünde bulunan ve araştırmaya katılmayı kabul eden 290 öğrenci oluşturmuştur. Verilerin toplanmasında kişisel bilgi formu ve postpartum depresyon bilgi formu kullanılmıştır. Veriler, IBM Sosyal Bilimlerde İstatistik Paket Programı (SPSS) sürüm 22 ile analiz edilmiştir. Verilerin analizinde değerler, ortalamalar, yüzde frekans dağılımları, Kruskal-Wallis H testi ve Mann-Whitney U testi kullanılmıştır.*

Sonuçlar: *Katılımcıların %79,3'ünü hemşirelik bölümü öğrencisi ve %52,4'ü 3. sınıfta öğrenim görmektedir. Katılımcıların %82,1'inin postpartum depresyon ile ilgili geleneksel uygulamalar hakkında bilgisi olduğu ve %37,8'isinin geleneksel uygulamaları doğru bulduğu belirlenmiştir. Katılımcıların postpartum depresyon bilgi düzeyi ortalama olarak 4,70±2,39 puan elde edilmiştir. Araştırmada hemşirelik ve ebelik bölümündeki katılımcıların postpartum depresyon bilgi düzeyleri ve toplam doğru sayısı ortalamaları arasında istatistiksel olarak anlamlı düzeyde farklılık saptanmıştır (p<0,05).*

Sonuç: *Sağlık bilimleri fakültesi öğrencilerinin postpartum depresyon hakkında farkındalık ve doğru bilgi düzeylerinin yetersiz olduğu bulunmuştur. İki farklı bölümde öğrenim gören öğrencilerin bilgi düzeylerinin ortalamasının farklı olduğu belirlenmiştir. Geleceğin sağlık profesyoneli adayı olan öğrencilere postpartum depresyon hakkında verilen eğitimin güçlendirilmesi ve farkındalık artırıcı çalışmaların uygulamaların yapılması önerilmektedir.*

Anahtar kelimeler: *bilgi; ebe; hemşire; öğrenci; postpartum depresyon*

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Introduction

The moments experienced during pregnancy, childbirth, and the postpartum period are essential for women[1]. During the postpartum period, which is one of the said periods, women undergo biological, physiological, and psychological changes[2]. The postpartum period begins with the end of labor in women and covers the 6–8 weeks after childbirth. During the period in question, mothers have developmental and physical responsibilities, such as caring for their infants, communicating with them, creating a safe environment, and adapting to the changing family structure due to the inclusion of the infant in the family[3]. Additionally, women should assume these roles and responsibilities. Sometimes, the physiological changes and psychosocial challenges that occur in women's lives during this period can create a crisis environment[4]. In this case, women have mental disorders[5]. Biological, psychological, sociocultural, and economic factors have been reported to cause mental disorders[6]. Postpartum depression, one of the mental disorders after childbirth, adversely impacts mothers and is responsible for 20% of suicides after childbirth. The depression experienced also impacts the infant's behavioral, emotional, and cognitive development. The prevalence of postpartum depression is around 10–20% in general, and cultural changes and countries' income levels impact this rate[7]. Postpartum depression refers to a mood disorder occurring within the first six weeks to 1 year after childbirth[8,9]. Mothers experience symptoms such as loss of energy, fatigue, inability to show interest in the infant, poor memory, changes in appetite, sleep disturbances, and thoughts of suicide and harming the infant. Risk factors include low social support, low income, a history of depression during a previous pregnancy, becoming a mother at a young age, anxiety, perceived negative body image, breastfeeding problems, unwanted pregnancy, number of births, and smoking[9,10]. Moreover, a decreased social support level adversely impacts the quality of women's sleep and their physical and mental health[11]. Nowadays, behavioral and pharmacological treatment methods are applied in postpartum depression, and antidepressant drugs can pass from breast milk to the infant[12]. Therefore, women at risk should be identified, and precautions should be taken. The early diagnosis and treatment of the disease help to protect women against long-term problems, such as postpartum depression, by increasing mothers' quality of life[13]. In addition to the support provided to the mother by her family and environment during the postpartum period, the support provided by midwives and nurses is also essential[14]. Midwives and nurses evaluate mothers by making regular home visits during pregnancy and the postpartum period[15]. Few studies in the literature have determined levels of students' knowledge about postpartum depression. In this regard, it is aimed to determine the levels of understanding of midwifery and nursing students, who play an essential role in preventing postpartum depression, its early diagnosis and treatment, and who will serve the society as future healthcare personnel, about postpartum depression, to assess the levels of their awareness, and to contribute to the literature by determining the areas of deficiency and making the necessary arrangements in the curriculum.

Materials And Methods

Type of Research

The research was conducted as a descriptive study to investigate "health sciences faculty students' knowledge about postpartum depression."

Population and Sample of the Study

The study's population consisted of midwifery and nursing students studying at Kafkas University, Faculty of Health Sciences. Third and fourth-year nursing and midwifery students whose curriculum includes mental disorders in the postpartum period were included in the study's sample. In the study, the sample size was determined to be 246 students, calculated with a 5% alpha error level, 80% power, and an effect size of 0.8 using the program G-Power 3.1.9.7. Two hundred ninety students who continued their education in the 2019–2020 academic year and agreed to take part in the research were included in the study.

Research Questions

What are nursing and midwifery students' levels of knowledge about postpartum depression and the factors affecting it?

Do nursing and midwifery students' levels of knowledge about postpartum depression differ?

Is there a difference between the knowledge levels of 3rd- and 4th-grade students in the departments about postpartum depression?

Data Collection Instruments

Personal Information Form: This form includes 21 questions, prepared by the researchers as a result of the

literature review, about students' socio-demographic characteristics (age, grade, department, gender, etc.), and sources of information about postpartum depression (where they obtained the information, level of knowledge, practices they apply to individuals diagnosed with postpartum depression) and level of knowledge about traditional practices in postpartum depression, accuracy and examples of conventional practices[13,16,17].

Postpartum Depression Information Form: The researchers prepared the form by reviewing the literature and obtaining expert opinions to ensure content validity. It investigates nursing and midwifery students' knowledge about postpartum depression and includes a total of 40 questions. It includes items that contain information about the definition of postpartum depression, its frequency, symptoms, risk factors, treatment, impacts on maternal and child health, prevention, and the roles of nurses and midwives in early diagnosis. The form includes two questions about the definition and frequency of postpartum depression, 16 questions about risk factors, 10 questions about symptoms, seven questions about the role of nurses and midwives in prevention and early diagnosis, four questions about treatment, and 1 question about its impacts on maternal and child health. There are statements "true," "false," and "I don't know" against the items in the information form. With reference to the Karagöz 2011 study, the correct option in the information form is scored 1 point, the incorrect option is scored 0 points, and the don't know option is not scored[13]. A score between 0 and 40 points is obtained from the form[3,6,7,12,13,18–34].

Implementation of the Research

A survey form was applied to twenty 3rd and 4 th-year nursing and midwifery students to determine the comprehensibility and usability of the questions in the data collection form. The data of this pilot study were not included in the research analysis. The incomprehensible questions in the research form were examined, and necessary arrangements were made. The researcher applied the data collection forms to the 3rd and 4 th-year nursing and midwifery students of the Faculty of Health Sciences at Kafkas University between November and December 2019, using a face-to-face interview method lasting 15–20 minutes.

Data Evaluation

The data were analyzed using the "IBM Statistical Package for Social Sciences (SPSS) program version 22 for Windows" package program. Numbers, percentages, minimum and maximum values, mean and standard deviations, and statistical analyses were used in the data analysis. In the normality assumption of the data, skewness and kurtosis were based on -1.5 and +1.5 values[35]. Descriptive analyses were used in the evaluation of sociodemographic data. The Mann-Whitney U test was used to compare paired groups, and the Kruskal-Wallis H test was used for more than two group comparisons. Statistical significance was determined at a threshold of $p<0.05$.

Ethical Considerations of the Study

Before the study, ethics committee permission dated 02.10.2019 and numbered 81829502.903/85 was obtained from the Non-Interventional Research Ethics Committee of Kafkas University, Faculty of Health Sciences. Institutional permission was received from Kafkas University Faculty of Health Sciences Dean's Office. Participants were informed about the study's purpose, and a voluntary informed consent form was obtained. The research was conducted following the ethical standards in the Declaration of Helsinki.

Results

Of the study participants, 69% were female, 2.4% were married, 79.3% were nursing students, 52.4% were studying in the 3rd year, and 60% had income equal to their expenses. Of the participants, 89.7% knew about major depression, 14.8% had been diagnosed with major depression at some point in their lives, and 100% knew about postpartum depression. Of the participants, 58.3% learned about postpartum depression from the university, 27.6% had encountered an individual diagnosed with postpartum depression, and the majority (48.8%) had talked to an individual diagnosed with postpartum depression and helped them relax when they encountered such an individual. Of the participants, 82.1% were knowledgeable about traditional practices related to postpartum depression, and 37.8% considered traditional practices correct. Whereas the most well-known conventional practice applied in postpartum depression was "The postpartum mother should not leave the house for the first 40 days," to which 63.9% answered "I know," the least known traditional practice was "A man should be with the postpartum mother," to which 84.9% answered "I don't know." Of the participants, 31.7% most frequently gave a score of 5 points, and 71.3% showed a score between 1 and 5 points when scoring their levels

of knowledge about postpartum depression. The participants' mean age was 21.66±1.17, ranging from 19 to 25. The levels of participants' knowledge about postpartum depression varied between 1 and 10 points. The 8th item in the risk factors in the postpartum depression information form was answered correctly by 87.9% of the participants. The 38th item regarding the role of nurses and midwives in the prevention and early diagnosis of PPD is the one to which participants gave the most incorrect answers, with a rate of 38.6%. The highest number of "don't know" answers was in the 34th item in the treatment section of the form, with a rate of 44.5%. The participants' average level of knowledge about postpartum depression was 4.70±2.39. According to the participants' answers to information about postpartum depression, the average number of correct responses was 24.88±5.56, the average number of incorrect responses was 7.84±3.74, and the average number of "I don't know"responses was 7.30±4.69.

Table 1 examines the participants' average test results according to their department and grade levels. When the level of knowledge about postpartum depression was asked subjectively, it was revealed that the group with the highest score was the 4 th-year midwifery students. Considering the total number of correct answers, 4 th-year midwifery students scored the highest, while 4 th-grade nursing students gave the highest number of incorrect answers.

Table 2 shows a statistically significant difference between nursing and midwifery students' levels of knowledge about depression and total correct answer averages ($p<0.05$). No significant difference was identified between the groups in terms of the incorrect answer averages ($p>0.05$).

A statistically significant difference was found between 3rd and 4 th-year students in terms of the average level of knowledge about postpartum depression, the

Table 1. *Participants' average test results according to their department and grade levels*

	Level of knowledge about postpartum depression (mean ± SD)	Average of correct answers (mean ± SD)	Average of incorrect answers (mean ± SD)
All participants	4.70±2.39	24.88±5.56	7.84±3.74
Nursing	4.40±2.36	24.48±5.63	7.81±3.90
Midwifery	5.86±2.18	26.45±5.04	7.95±3.05
Midwifery 3rd year	4.96±2.17	26.23±4.93	7.53±2.45
Midwifery 4th year	6.76±1.83	26.66±5.23	8.36±3.54
Nursing 3rd year	3.65±2.13	26.06±4.88	6.17±3.37
Nursing 4th year	5.24±2.33	22.69±5.90	9.66±3.63

SD: Standard Deviation

Table 2. *Comparison of participants' mean scores on the postpartum depression information form in terms of their department and grade characteristics*

		Average level of knowledge about postpartum depression (mean ± SD)	Average of correct answers (mean ± SD)	Average of incorrect answers (mean ± SD)
Department	Nursing	4.40±2.36	24.48±5.63	7.81±3.90
	Midwifery	5.86±2.18	26.45±5.04	7.95±3.05
	Test and p– p-value	U: 4482.500 Z: -4259 p: 0.000	U: 5544.000 Z: -2.348 p: 0.019	U: 6465.000 Z: -0.755 p: 0.450
Midwifery Department	3rd year	4.96±2.17	26.23±4.93	7.53±2.45
	4th year	6.76±1.83	26.66±5.23	8.36±3.54
	Test and p– p-value	U: 242.000 Z: -3.217 p<0.001	U: 411.000 Z: -0.578 p: 0.563	U: 389.500 Z: 0.578 p: 0.368
Nursing Department	3rd year	3.65±2.13	26.06±4.88	6.17±3.37
	4th year	5.24±2.33	22.69±5.90	9.66±3.63
	Test and p– p-value	U: 3986.500 Z: -5.248 p: 0.000	U: 4417.000 Z: -4319 p: 0.000	U: 3036.500 Z: -7.079 p: 0.000

SD: Standard Deviation, U: Mann-Whitney U Test, Z: Standard Score, p<0.05

Table 3. *3rd- and 4th-year students' postpartum depression knowledge level, correct answer, and incorrect answer averages*

3rd-4th year (mean ± SD)	Average level of knowledge about postpartum depression (3rd year: 3.91±2.19 4th year: 5.57±2.32)	Average of correct answers (3rd year: 26.09±4.87 4th year: 23.55±5.97)	Average of incorrect answers (3rd year: 6.44±3.25 4th year: 9.38±3.64)
Mann-Whitney U	6223.500	7967.500	5694.000
Z	-6.094	-3.541	-6.748
p	0.000	0.000	0.000

SD: Standard Deviation, Z: Standard Score, p<0.05

Table 4. *Comparison of participants' mean scores on the postpartum depression information form according to their sociodemographic characteristics and knowledge about postpartum depression*

		Correct (mean ± SD)	Incorrect (mean ± SD)	I don't know (mean ± SD)
Sex	Female	25.69±5.30	7.46±3.42	6.83±4.72
	Male	23.10±5.75	8.67±4.25	8.34±4.49
	Test and p-value	U: 6515 p<0.001	U: 7335 p: 0.011	U: 6994.500 p: 0.002
Income status	Income <Exp.	24.58±4.70	8.06±4.14	7.46±4.12
	Income: Exp.	25.01±5.92	7.71±3.51	7.26±5.01
	Income >Exp.	25.23±6.28	7.85±3.79	6.90±4.51
	Test and p-value	H: 1.281 p: 0.527	H: 0.324 p: 0.850	H: 0.439 p: 0.850
Status of knowledge about depression	Yes	24.93±5.49	7.90±3.74	7.19±4.71
	No	24.50±6.22	7.26±3.75	8.23±4.53
	Test and p-value	U: 3809.500 p: 0.835	U: 3517.500 p: 0.377	U: 3307.500 p: 0.172
Status of being diagnosed with depression	Yes	24.83±5.25	7.13±3.04	8.02±4.49
	No	24.89±5.62	7.96±3.84	7.17±4.72
	Test and p-value	U: 5166 p: 0.775	U: 4777.500 p: 0.292	U: 4661 p: 0.200
Encountering someone diagnosed with PPD	Yes	24.51±5.25	8.62±3.68	6.86±4.37
	No	25.03±5.68	7.54±3.72	7.47±4.80
	Test and p-value	U: 7741 p: 0.301	U: 6897 p: 0.018	U: 7912.500 p: 0.444
Status of knowledge about traditional practices in PPD	Yes	25.27±5.31	7.85±3.61	6.91±4.59
	No	23.11±6.36	7.78±4.31	9.09±4.78
	Test and p-value	U: 4870 p: 0.016	U: 5998.500 p: 0.728	U: 4545.500 p: 0.003
Status of finding traditional practices correct	Yes	24.52±5.45	7.97±3.51	7.50±4.57
	No	25.73±5.18	7.77±3.67	6.55±4.58
	Test and p-value	U: 5564.500 p: 0.033	U: 6320.500 p: 0.508	U: 5718.500 p: 0.067

SD: Standard Deviation, U: Mann-Whitney U Test, H: Kruskal-Wallis H Test, p<0.05

average of correct answers, and the average of incorrect answers in Table 3 (p<0.05). A statistically significant difference was found between the 3rd-grade nursing and 4 th-grade nursing students in terms of PPD knowledge level, mean number of correct and mean number of incorrect (p<0.05). A statistically significant difference was found between the 3rd and 4th year midwifery students in terms of PPD knowledge level (p=0.001). Still, no significant difference was found in terms of the mean number of correct and the mean number of incorrect (p>0.05).

As seen in Table 4, women had a significantly higher average number of correct answers, a considerably lower

average number of incorrect answers, and a significantly lower average number of "I don't know" answers than men ($p<0.05$). Individuals who knew traditional practices in terms of PPD had a significantly higher average number of correct answers and a considerably lower average number of "I don't know" answers than those without such knowledge ($p<0.05$). The average number of correct answers was significantly higher in the group that stated they did not find traditional practices correct compared to the group that indicated they found such practices correct ($p<0.05$).

Discussion

Since it is thought that acquiring information about postpartum depression during midwifery and nursing education will also positively affect professional life, the current study investigated the cultural and medical knowledge levels of midwifery and nursing students about postpartum depression.

When asked to group their knowledge levels about postpartum depression, most participants stated that they knew about it. However, when asked to score their knowledge levels, the majority chose a score between 1 and 5, revealing that they perceived their knowledge as low to medium and considered themselves inadequate. A study conducted with midwives in Ireland and a survey conducted with midwives and nurses in Türkiye found that almost all of the participants knew about postpartum depression[36,37]. In the study by Işik et al.[36], participants indicated that they had moderate knowledge about postpartum depression. In the study performed by Mivsek et al.[38] in Slovenia and in the study carried out by Junior et al.[39] in Brazil, midwives and nurses stated that their knowledge levels about postpartum depression were inadequate. The fact that midwives and nurses who are active in their professional lives or students during their undergraduate education do not have accurate and adequate knowledge about postpartum depression indicates the inadequacy of the education provided. In this regard, knowledge deficiency should be eliminated through courses and training during or after the education period, and healthcare professionals should be more equipped.

The present study determined that most participants acquired their knowledge about postpartum depression during their undergraduate education. The results of the studies from Türkiye support our research, and the majority of the study participants indicated that they learned about postpartum depression during their undergraduate education[36,40]. A study from Saudi Arabia found that most midwives and nurses learned about postpartum depression during their university/college education[41]. We believe that knowledge and skills about postpartum depression should be prioritized during university education, and that more accurate and sufficient information will be provided by enhancing the quality of education.

The prevalence of postpartum depression is reported between 0.5–60.8% worldwide and between 3.5–63.3% in Asian countries[42]. The incidence of postpartum depression varies according to societies' characteristics[43]. Studies from Türkiye found the incidence of postpartum depression to be between 14.2–19.90%[44,45]. In this study, most midwifery and nursing students receiving undergraduate education, almost 3 out of every 4 participants, reported that they had not encountered an individual diagnosed with postpartum depression. A study conducted in the family health and community health center found that the majority of midwives and nurses had not encountered an individual diagnosed with postpartum depression[13]. The study results support our research, showing that the prevalence of postpartum depression is not very high. In this regard, it is recommended that simulation or case-based education be incorporated into undergraduate programs to teach physicians, nurses, and midwives their roles and responsibilities in preventing, diagnosing, referring, and providing care for postpartum depression.

The study found that students who encountered women diagnosed with postpartum depression mostly tried to comfort patients by talking to them and referred patients to a psychiatrist. In the study by Işik et al.[36], most participants stated that they would refer patients to a psychiatrist. Another study indicated that the nurse group mostly referred women for support and counseling, while the midwife group mainly directed women to meet with postpartum women[46]. Midwifery and nursing students indicated behaviors, such as referring women to a psychiatrist, supportive attitudes, and providing psychoeducation to the patient's family and relatives, which are essential in terms of postpartum depression (PPD) treatment. In this respect, it can be stated that the student group in our research focused on evidence-based treatment options for PPD.

The majority of our study participants indicated that they knew about traditional practices but did not consider them correct. Concerning traditional practices, not leaving home for forty days, keeping the Quran

and an amulet, and ensuring that a woman and her infant are not left alone for 40 days postpartum were the practices that the participants knew the most. In a study, the practices of not going home for forty days and keeping the Quran and an amulet were known[47]. The results of our research are similar to the results of the study. However, no study on the accuracy of traditional practices has been found in the literature.

In the postpartum depression information form, the participants' risk factors and clinical characteristics were at a medium-high level, and the treatment options were at a low-medium level. A study revealed that midwives and nurses had low levels of knowledge about PPD risk factors and moderate levels of knowledge about PPD symptoms and clinical manifestation[36]. The current study found that participants had a medium-high level of expertise from the postpartum depression information form. Kurtçu et al.[40] determined that midwives and nurses had a medium-high level of knowledge about postpartum depression, and Jones et al.[48] revealed that midwives in Australia had a medium-high level of knowledge about postpartum depression. The results of our study are consistent with the findings in the literature and show similar deficiencies in knowledge levels. The low levels of participants' knowledge about PPD indicate that they did not have an adequate understanding.

In the present study, women had a significantly higher average number of correct answers, a considerably lower average number of incorrect answers, and a significantly lower average number of "I don't know" answers compared to men ($p<0.05$). A study stated that men knew the symptoms experienced by women during postpartum depression less than women did[49]. The fact that men live in a patriarchal society and regard PPD as a problem influencing only women adversely impacts their ability to obtain adequate information about PPD.

The study revealed that the average number of correct answers was higher in individuals who knew traditional practices in terms of PPD than in those without such knowledge. Additionally, the group stating that they did not find traditional practices correct had a lower average than the group saying they did. Studies have found that most women know traditional practices[47,50]. It is thought that participants learn about conventional practices since traditional practices still exist nowadays. Yeşilçinar et al.[51] determined that women believed traditional practices were wrong after increasing their knowledge about the postpartum period. Increasing knowledge about the postpartum period hinders the implementation of wrong conventional practices.

In the current study, midwifery students scored higher than nursing students, and 3rd-grade students scored higher than 4 th-grade students on the postpartum depression information form. A study in the literature investigating midwives' and nurses' knowledge and approaches regarding postpartum depression determined that midwives scored higher than nurses in all correct answer averages[40]. This study, supporting our research, interpreted that midwives taking more practical and theoretical courses on pregnancy, childbirth, and the postpartum period during their education, along with encountering more women in the prepartum and postpartum periods, may have affected this situation.

Limitations of the Study

The research was conducted at a university in the east of Türkiye. Students studying at other universities in Türkiye may give different responses.

Conclusion

The early diagnosis and treatment of postpartum depression, which is one of the mental disorders in the postpartum period and adversely impacts the health of the mother and infant, are essential. Midwives and nurses, who communicate with women and take a significant part in the early diagnosis and treatment of the disease, should know about postpartum depression to provide adequate and quality care. The present study found that midwifery and nursing students, who are the healthcare personnel of the future, had inadequate knowledge about postpartum depression; female students had more knowledge than male students, midwifery students were more knowledgeable than nursing students, and students in both departments thought they had knowledge about postpartum depression but had incorrect or incomplete knowledge. Furthermore, it was determined that students had knowledge about traditional practices applied to prevent postpartum depression, which is widespread in Türkiye, and they described them as incorrect. This demonstrates the deficiency or inadequacy of the education curriculum, and necessary arrangements should be made to ensure that midwifery and nursing students, who will serve society, have adequate knowledge to provide quality and individualized care. Training should be organized to increase the awareness of male students about

postpartum depression. Additionally, a standard curriculum should be used, and quality education should be provided to prevent differences in knowledge levels between departments and grade levels.

Conflict of Interest

There is no conflict of interest related to this study

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Strong Ion Difference: A Promising Biomarker for Differential Diagnosis of Hypertensive Disorders in Pregnancy

Güçlü İyon Farkı: Gebelikte Hipertansif Bozuklukların Ayırıcı Tanısında Umut Vadeden Bir Biyobelirteç

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ABSTRACT

Aim: *Hypertensive disorders of pregnancy (HDP), including gestational hypertension (GHT) and preeclampsia, are significant causes of maternal and neonatal morbidity. Early differentiation is crucial, especially in severe cases. This study evaluated venous blood gas parameters, specifically Strong Ion Difference (SID) and Apparent Strong Ion Difference (SIDa), to distinguish GHT from preeclampsia and severe preeclampsia.*

Material and Method: *This retrospective, single-center study analyzed 94 pregnant patients with hypertension of unknown origin beyond 20 weeks' gestation (October 2021–2022). Patients were categorized as GHT (n=39) or preeclampsia spectrum (n=55), with subgroup analysis in 74 patients without chronic diseases. Proteinuria was assessed via 24-hour urine collection or protein/creatinine ratio. Statistical methods included t-tests, chi-square, Mann-Whitney U, Kappa, and ROC analysis.*

Results: *Significant differences were found between GHT and preeclampsia groups in dipstick protein ≥2+, protein/creatinine ratio, SID, and SIDa (p<0.001). In the subgroup analysis, significant differences were noted for dipstick protein ≥1+ and ≥2+, protein/creatinine ratio, SID, and SIDa (p=0.001, p<0.001, p<0.001, p=0.015, p=0.012). Kappa analysis showed poor agreement between SID and proteinuria in the total cohort (κ=-0.166, p=0.092) and slight agreement in the subgroup analysis (κ=0.190, p=0.020), suggesting a weak concordance between these two parameters. SID showed moderate discriminatory power (AUC: 0.672 overall, 0.668 in the subgroup).*

Conclusion: *SID and SIDa are promising biomarkers for distinguishing GHT from preeclampsia. Further extensive cohort studies are needed to establish accurate cut-off values for routine clinical use.*

Key words: *gestational hypertension, preeclampsia, severe preeclampsia, SID, strong ion difference*

ÖZET

Amaç: *Gestasyonel hipertansiyon (GHT) ve preeklampsi dâhil olmak üzere gebeliğin hipertansif bozuklukları (HDP), maternal ve neonatal morbiditenin başlıca nedenlerindendir. Özellikle ağır vakalarda, erken ayırt edilmesi hayati önem taşımaktadır. Bu çalışma, GHT'yi preeklampsiden ve ağır preeklampsiden ayırt etmek amacıyla venöz kan gazı parametrelerini, özellikle Güçlü İyon Farkı (SID) ve Görünür Güçlü İyon Farkı'nı (SIDa) değerlendirmiştir.*

Materyal ve Metot: *Bu retrospektif, tek merkezli çalışmada, 20. gebelik haftasını geçmiş ve nedeni bilinmeyen hipertansiyonu olan 94 gebe hasta (Ekim 2021–2022) analiz edilmiştir. Hastalar GHT (n=39) ve preeklampsi spektrumu (n=55) olarak sınıflandırılmıştır. Kronik hastalığı olmayan 74 hasta üzerinde alt grup analizi yapılmıştır. Proteinüri, 24 saatlik idrar toplama veya protein/kreatinin oranı ile değerlendirilmiştir. İstatistiksel yöntemler arasında t-testi, ki-kare, Mann-Whitney U, Kappa ve ROC analizi yer almıştır.*

Bulgular: *GHT ve preeklampsi grupları arasında idrar çubuğunda protein ≥2+, protein/kreatinin oranı, SID ve SIDa açısından anlamlı farklılıklar saptanmıştır (p<0,001). Alt grup analizinde, idrar çubuğunda protein ≥1+ ve ≥2+, protein/kreatinin oranı, SID ve SIDa açısından anlamlı farklılıklar tespit edilmiştir (p=0,001, p<0,001, p<0,001, p=0,015, p=0,012). Kappa analizi, toplam kohortta SID ile proteinüri arasında zayıf bir uyum olduğunu (κ=-0,166, p=0,092) ve alt grup analizinde hafif bir uyum bulunduğunu (κ=0,190, p=0,020) göstermiştir. Bu durum, bu iki parametre arasında zayıf bir korelasyon olduğunu düşündürmektedir. SID, orta düzeyde ayırt edici güce sahip bulunmuştur (AUC: 0,672 genel kohort, 0,668 alt grup).*

Sonuç: *SID ve SIDa, GHT'yi preeklampsiden ayırt etmede umut vadeden biyobelirteçlerdir. Rutin klinik kullanım için kesin eşik değerlerin belirlenmesi amacıyla daha geniş kohort çalışmalarına ihtiyaç vardır.*

Anahtar kelimeler: *gestasyonel hipertansiyon; preeklampsi; ağır preeklampsi; SID; güçlü iyon farkı*

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Introduction

Background

Hypertensive disorders of pregnancy (HDP), despite significant scientific advancements, remain a leading cause of maternal mortality and morbidity. Hypertensive disorders of pregnancy accounts for approximately 16% of maternal deaths in developing countries and 25% in developed countries, complicating 2–8% of pregnancies worldwide[1,2]. The differential diagnosis of new-onset hypertension after 20 weeks of gestation includes gestational hypertension (GHT), preeclampsia, superimposed preeclampsia, and preeclampsia with severe features. Gestational hypertension is defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or both, measured on at least two occasions four hours apart, arising after 20 weeks of gestation in women without prior hypertension and without proteinuria.

Preeclampsia, typically occurring after 20 weeks and often near term, involves new-onset hypertension with proteinuria, defined as >300 mg/dL protein in a 24-hour urine collection or a protein/creatinine ratio >0.3[3,4]. When quantitative methods are unavailable or rapid decisions are needed, spot urine protein testing is acceptable. However, dipstick urinalysis may overdiagnose proteinuria in 53% and 23% of cases with 1+ and 2+ results, respectively, with accuracies of 70% and 82% compared to gold-standard methods[5].

Recent cadaver studies and case series using electron microscopy have revealed that chronic inflammation and secondary endothelial dysfunction are fundamental to the microangiopathy seen in preeclampsia. This microangiopathy contributes to a range of complications, including edema, end-organ damage, and, notably, proteinuria[6,7]. The pathogenesis of preeclampsia is closely linked to abnormal placentation, where inadequate trophoblastic invasion into the spiral arterioles of the decidua basalis leads to defective myometrial invasion[8]. A variety of factors are implicated in this abnormal process, including maternal and environmental factors such as defective trophoblast differentiation, placental hypoperfusion, hypoxia, ischemia, exaggerated inflammatory response, excessive complement activation and genetic predispositions[9]. Regardless of the cause, these factors converge on a common pathway of microangiopathy, endothelial dysfunction, and the diverse end-organ damage that defines the severity of clinical spectrums of preeclampsia[10,11].

Blood gas analysis is a widely used and rapid method for evaluating complex metabolic conditions in critically ill patients, such as those with sepsis, trauma, or major surgery. Various approaches for interpreting blood gas results are described in the literature. Unlike the classical approach for acid-base analysis, Stewart's theory, published in 1983, mathematically formulates acid-base balance based on the principles of mass conservation, dissociation curves, and the conservation of electrical neutrality in fluids. Maintaining normal membrane function is critical for preserving this balance, which can be disrupted in pathological conditions like microangiopathy[12]. According to Stewart's theory, the independent variables determining acid-base status are the partial pressure of carbon dioxide (PaCO2) in arterial blood, the total concentration of non-volatile weak acids in plasma (Atot), and the strong ion difference (SID) between the concentrations of fully dissociated cations and anions in plasma. Typically, membranes separating body fluids are impermeable to proteins, making Atot interactions negligible. However, in pathological conditions, alterations in Atot can significantly impact pH balance. SID, defined as the difference between the concentrations of strong cations (Na+, K+, Ca2+, Mg2+) and strong anions (Cl-, lactate-, SO42-, and other strong anions), is a key concept in Stewart's theory. SID, simplified as [(Na+) – (Cl-)], directly influences blood pH; a high SID is associated with alkalosis, while a low SID is associated with acidosis[13]. Changes in SID provide insights into acid-base disorders that traditional bicarbonate analysis might miss, allowing clinicians to conduct a more comprehensive assessment of acid-base balance in complex clinical scenarios[14].

Objectives

This study aims to retrospectively evaluate blood gas parameters at initial presentation in patients with HDP. The primary objective is to compare SID values between patients diagnosed with GHT, preeclampsia and preeclampsia with severe features. The secondary aim is to investigate whether SID values in blood gas analyses can serve as an additional biomarker in the diagnosis of HDP.

Material and Method

Study Design

This retrospective, single-center observational study aimed to analyze venous blood gas (VBG) parameters in pregnant individuals beyond 20 weeks of gestation who presented with hypertension of unknown origin. Demographic data, including age, gravidity, parity, and

number of abortions, gestational age week at initial presentation, recorded highest systolic and diastolic blood pressure at presentation, laboratory findings, presence of additional chronic diseases, and VBG results, were collected and analyzed (Additional file 1). According to our clinical protocol, the 24-hour urine collection was accepted as the gold standard for proteinuria diagnosis, and in cases where it was available, its results were prioritized. Otherwise, the protein/creatinine ratio was used as the diagnostic test. These parameters were evaluated in relation to the final diagnosis, which was determined based on clinical findings, laboratory, and quantitative urinalysis results.

Setting and Participants

A total of 232 pregnant patients admitted to our tertiary referral hospital's Obstetrics and Gynecology Emergency Department and undergoing VBG analysis from October 1, 2021, to October 1, 2022, were initially considered. Of these, 103 were excluded for non-hypertensive indications, 27 for pre-gestational chronic hypertension, and 7 for VBG analysis post-magnesium sulfate therapy. This left a study cohort of 94 patients. Proteinuria was assessed by 24-hour urine collection in 23 patients, while all 94 had protein/creatinine ratios and dipstick tests. Within the cohort, 39 had GHT, and 55 had preeclampsia-related conditions: 42 with preeclampsia, 9 with severe preeclampsia, and 4 with superimposed preeclampsia (Fig. 1, Table 1).

Variables

The parameters analyzed in this study included calculated SID [(Na+ – Cl-)] and apparent SID (SIDa) [(Na+) – (Cl– + Lac-)] from VBG analysis (Table 2). Urinalysis parameters included dipstick urinalysis protein readings, spot urine protein/creatinine ratio, and 24-hour urine protein excretion rate. Additionally, the presence of chronic diseases that could potentially cause electrolyte imbalances was meticulously assessed and treated as confounding variables. To address this, a subgroup analysis was performed on a cohort without these additional chronic conditions (n=74).

Data sources/Measurement

The accuracy of these parameters in differentiating diagnostic outcomes across HDP groups and within the subgroup analysis without additional chronic conditions (n=74) is detailed in Table 2, offering insights into their relevance to diagnostic efficacy.

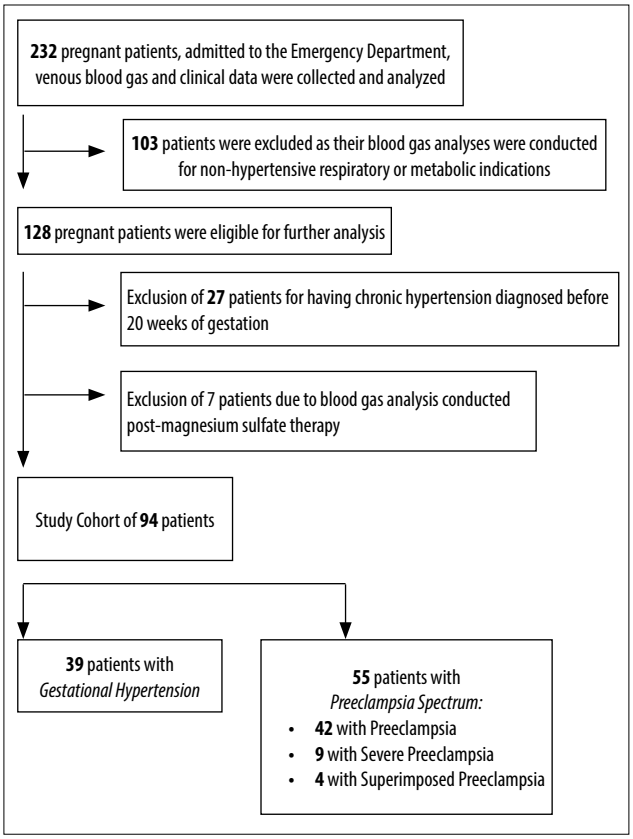

Figure 1. *Flowchart of patient exclusion criteria and formation of the total study cohort (AUC: Area Under the ROC Curve; Sensitivity, and Specificity at Optimized Cutoff Point for Predicting Differential Diagnosis of Hypertensive Disorders in Pregnancy; Total Study Cohort).*

Bias

Bias was minimized by excluding patients whose blood gas analysis was conducted after magnesium sulfate therapy and by conducting thorough assessments of all variables through subgroup analysis. Additionally, deliberate efforts were made to identify and mitigate any inherent biases in the study design and analytical processes.

Study Size

The sample size for this study was calculated based on prior research that identified significant hyperchloremic acidosis differences between healthy pregnancies and those diagnosed with severe preeclampsia[15]. Using the G*Power program, and assuming an alpha level of 0.05 and an effect size of 0.8, we aimed for a minimum power of 80%[16]. This calculation indicated that a sample size of 26 participants per group was required to ensure the study's ability to detect meaningful effects with statistical reliability.

Quantitative Variables

Proteinuria was quantified according to standard definitions, with a threshold set at 300 mg/dL of protein or more in a 24-hour urine collection, or a protein/creatinine ratio of 0.3 or higher[1]. The SID is measured, with a normal value defined as 38 mEq/L[13].

Ethical Considerations

This retrospective observational study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Institutional Clinical Research Ethics Committee on December 14, 2022 (approval number: 2022.12.400). Written informed consent specific to this study was not obtained as the data were collected retrospectively from patients' medical records. However, all patients had previously provided general written consent during their clinical admission, agreeing to the use of their anonymized data for scientific research, as approved by the ethics committee.

Statistical Methods

Statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS) program version 26.0. The Kolmogorov-Smirnov test was employed to assess the normality of continuous variables. Data that followed a normal distribution are presented as mean ± standard deviation, with comparisons made using the independent t-test. For data not normally distributed, results are presented as median (25th–75th percentile) and analyzed using the Mann-Whitney U test. Categorical variables are reported as numbers and percentages, with statistical significance determined by the chi-square test. The receiver-operating characteristic (ROC) curve was utilized to evaluate the sensitivity and specificity of diagnostic tests based on optimized cutoff points. Kappa statistics were used to assess the agreement between SID and proteinuria in both the total study cohort and the subgroup without additional diseases affecting electrolyte balance. Statistical significance was set at $p < 0.05$.

Results

Participants

The study included 94 pregnant individuals diagnosed with hypertensive disorders of pregnancy (HDP), divided into two groups: 39 with GHT and 55 with a spectrum of preeclampsia-related conditions. The subgroup study cohort without additional chronic diseases for electrolyte imbalance (n=74) consists of 31 GHT patients and 43 patients with preeclampsia spectrum of diseases (Table 1).

Descriptive Data

Demographically, there were no statistically significant differences between the two groups in terms of age, gravidity, parity, abortion numbers, or gestational week at the time of diagnosis. Additionally, there was no significant difference in the prevalence of chronic diseases that could contribute to electrolyte imbalance (p=0.88). The preeclampsia group demonstrated statistically significant but clinically insignificant elevations in creatinine (p=0.03) and AST levels (p=0.04) compared to the GHT group, while ALT levels were comparable between the groups (p=0.41). Blood pressure measurements revealed significant differences, with the preeclampsia spectrum group showing higher systolic and diastolic pressures (p<0.001 and p=0.02, respectively). In a subgroup analysis excluding patients with additional chronic conditions that could influence electrolyte balance (n=74), similar trends persisted. The preeclampsia spectrum group (n=43) continued to exhibit significantly higher systolic and diastolic blood pressure levels (p=0.001 and p=0.004, respectively) compared to the GHT group (n=31). Kappa analysis revealed poor agreement between SID and proteinuria in the total cohort (κ=-0.166, p=0.092). In contrast, a slight but statistically significant agreement was observed in the subgroup without electrolyte-altering conditions (κ=0.190, p=0.020). These findings suggest that while SID and proteinuria are both associated with preeclampsia, they may reflect different pathophysiological mechanisms.

Outcome Data

Blood gas and electrolyte parameters were analyzed between the GHT and preeclampsia spectrum groups; the comparison showed no statistically significant differences in pH, lactate, Na+, K+, and base excess values across both the study cohort (n=94) and subgroup cohort without additional electrolyte imbalance (n=74) (p>0.05 for all). However, a statistically significant difference was observed in the HCO_3- levels (p=0.03), and Ca+ levels (p=0.04), with the GHT group presenting higher levels compared to the preeclampsia spectrum group in the whole study cohort; while Cl- levels were marginally higher in the preeclampsia group (p=0.06) in the study cohort without additional chronic diseases for electrolyte imbalance (n=74). By implying Stewart approach and calculating SID [(Na+) – (Cl-)], a remarkable hyperchloremic acidosis can be observed in all 4 study cohorts (SID ≤38 mEq/L)[13].

In the total study cohort, there was no statistically significant difference in dipstick urinalysis protein readings ≥1+ between GHT and preeclampsia spectrum

patients (p=0.78). However, for dipstick urinalysis protein reading ≥2+, spot urine protein/creatinine ratio, SID, and SIDa measurements, statistically significant results were observed between the two groups (p<0.001, p<0.001, p=0.005, and p=0.005, respectively). In the study cohort without additional chronic diseases for electrolyte imbalance, both GHT and preeclampsia spectrum groups had statistically significant differences for dipstick urinalysis protein reading ≥1+ and ≥2+, spot urine protein/creatinine ratio, SID, and SIDa measurements (p=0.001, p<0.001, p<0.001, p=0.015, and p=0.012, respectively) (Table 2).

Table 1. *Comparative analysis of clinical findings and demographic data between patients diagnosed with gestational hypertension and preeclampsia spectrum with and without additional chronic diseases for electrolyte imbalance*

Parameter	Study cohort (n=94)			Study cohort without additional chronic diseases for electrolyte imbalance (n=74)		
	Gestational hypertension (n=39)	Preeclampsia spectrum (n=55)	P value	Gestational hypertension (n=31)	Preeclampsia spectrum (n=43)	P value
Age (years)	29.26±5.98	31.65±7.05	0.12	28.71±5.84	30.35±7.18	0.29
Gravidity (n)	2.49 (1,00–3,00)	2.65 (1,00–3,00)	0.12	1.00 (1,00–4,00)	2.37 (1,00–3,00)	0.54
Parity (n)	0.85 (0,00–2,00)	1.13 (0,00–2,00)	0.13	0.00 (0,00–2,00)	1.00 (0,00–2,00)	0.32
Abortus (n)	0.62 (0,00–1,00)	0.53 (0,00–1,00)	0.94	0.55 (0,00–1,00)	0.37 (0,00–0,00)	0.47
Gestation (weeks)	34.82 (34,00–38,00)	34.64 (34,00–37,00)	0.24	34.71±5.20	34.84±3.33	0.24
Systolic b. p. (mmHg)	141.28 (138,00–150,00)	152.36 (144,00–159,00)	<0.001	142.19±13.41	152.26±12.54	0.001
Diastolic b. p. (mmHg)	84.59±10.02	90.35±10.80	0.02	83.68±10.64	90.84±9.83	0.004
Platelets (x 1.000/mm$^{3)}$	269±78	247±87	0.18	276±79	245±87	0.12
Creatinine (mg/dl)	0.53 (0,49–0,62)	0.59 (0,53–0,77)	0.03	0.55 (0,48–0,62)	0.58 (0,50–0,67)	0.16
ALT (IU/l)	12.0 (9,0–14,0)	12.0 (9,0–19,0)	0.41	13.26±8.78	22.35±30.90	0.07
AST (IU/l)	18.00 (16,00–24,00)	22.00 (17,00–32,00)	0.04	21.35±9.18	31.35±42.01	0.19
Add. Chr. Renal D. (n)	0 (0%)	3 (5.45%)	0.88	0 (0%)	0 (0%)	-
Add. Chr. Diabetes (n)	2 (5.12%)	8 (14.54%)		0 (0%)	0 (0%)	
Add_Chr. Thyroid D. (n)	6 (15.38%)	1 (1.81%)		0 (0%)	0 (0%)	

Results were presented as mean (SD) for normally distributed data, median (25–75 percentile) was used for non-normally distributed data, and number (percentage) for categorical variables. To compare independent categorical variables, the chi-square test was applied, and the results were reported as numbers and percentages. b. p.: Blood pressure; Add. Chr.: Additional chronic; d.: Disease; n.: Number

Table 2. *Comparative analysis of urinalysis and venous blood gas analysis between patients diagnosed with gestational hypertension and preeclampsia spectrum with and without additional chronic diseases for electrolyte imbalance*

Parameter	Study cohort (n=94)			Study cohort without additional chronic diseases for electrolyte imbalance (n=74)		
	Gestational hypertension (n=39)	Preeclampsia spectrum (n=55)	P value	Gestational hypertension (n=31)	Preeclampsia spectrum (n=43)	P value
pH	7.38±0.03	7.39±0.03	0.89	7.39±0.03	7.39±0.02	0.87
HCO3	23.31±1.76	22.5±1.79	0.03	23.23±1.93	22.5±1.85	0.10
Lactate	1.28±0.55	1.29±0.52	0.93	1.26±0.56	1.30±0.55	0.73
Na	138.38±1.74	137.76±2.26	0.15	138.39±1.80	137.91±2.22	0.32
K	4.10±0.39	4.12±0.44	0.84	4.13±0.42	4.09±0.48	0.73
Ca	1.19±0.05	1.15±0.08	0.04	1.18±0.06	1.15±0.09	0.11
Cl	106.46±2.11	107.27±2.01	0.06	106.52±2.18	107.56±1.81	0.02
Base access	-1.58±1.9	-2.38±1.8	0.03	-1.64±2.10	-2.35±1.86	0.13
Dipstick Ur. Prot. ≥1+ (n)	23 (59.0%)	34 (61.8%)	0.78	9 (29.0%)	29 (67.4%)	0.001
Dipstick Ur. Prot. ≥2+ (n)	0 (0%)	20 (36.4%)	<0.001	0 ((0.00%)	14 (32.6%)	<0.001
Sp. Ur. Prot/Cre Ratio	0 (0%)	53 (96.4%)	<0.001	0 (0.00%)	41 (95.3%)	<0.001
SID (Na-Cl)	31.92±1.99	30.49±2.65	0.005	31.87±2.17	30.35±2.84	0.015
SIDa (Na-Cl-Lactate)	30.64±2.02	29.20±2.63	0.005	30.60±2.18	29.04±2.84	0.012

Results were presented as mean (SD) for normally distributed data, and number (percentage) for categorical variables. To compare independent categorical variables, the chi-square test was applied, and the results were reported as numbers and percentages. Dipstick Ur. Prot.: Dipstick Urinalysis Protein Reading; Sp. Ur. Prot/Cre Ratio: Spote Urine Protein/Creatinine Ratio; SID: Strong Ion Difference; SIDa: Apparent Strong Ion Difference

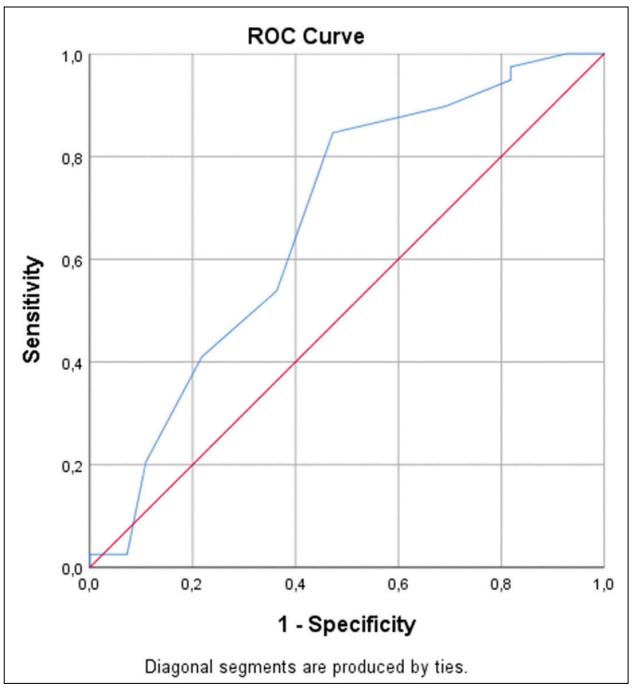

Figure 2. *Area under the receiver operating characteristic (ROC) analysis (total study cohort) (AUC: Area Under the ROC Curve; Sensitivity, and Specificity at Optimized Cutoff Point for Predicting Differential Diagnosis of Hypertensive Disorders in Pregnancy; Study cohort without additional chronic diseases for electrolyte imbalance).*

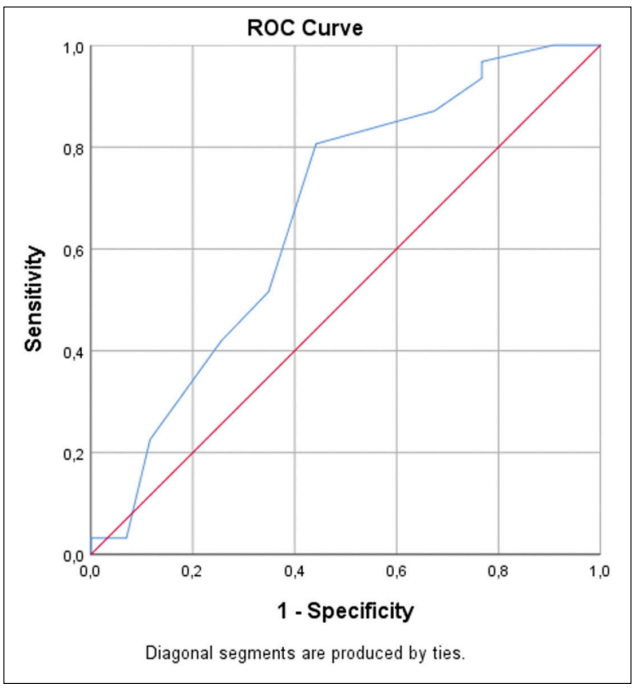

Figure 3. *Area under the receiver operating characteristic (ROC) analysis (study cohort without additional chronic diseases for electrolyte imbalance). Results were presented as median (25–75 percentile) was used for non-normally distributed data.*

Table 3. *Strong ion difference and predictive performance metrics for differential diagnosis of hypertensive disorders in pregnancy*

Study cohort (n=94)				
AUC (95% CI)	Cutoff according to Youden index	Sensitivity (%)	Specificity (%)	p value
0.672 (0.564 – 0.781)	31.5	53.8	46.2	0.005
	32.5	41.0	59.0	0.005
	33.5	20.5	79.5	0.005
Study cohort without additional chronic diseases for electrolyte imbalance (n=74)				
AUC (% 95% CI)	Cutoff according to Youden Index	Sensitivity (%)	Specificity (%)	p value
0.668 (0.545–0.791)	31.5	51.6	65.1	0.014
	32.5	41.9	74.4	0.014
	33.5	22.6	88.4	0.014

CI: Confidence Interval; AUC: Area Under Curve

Main Results

Analyzing the acid-base imbalance by Stewart approach that differs from the traditional bicarbonate-centered approach, SID and SIDa were evaluated for their diagnostic performance in distinguishing between hypertensive disorders in pregnancy. The SID values demonstrated moderate discriminative power with an AUC of 0.672 (95% CI: 0.564–0.781) for the overall study cohort (n=94) and an AUC of 0.668 (95% CI: 0.545–0.791) for the subgroup excluding chronic diseases (n=74) (Table 3, Fig. 2, Fig. 3). The most balanced cutoff values according to the Youden Index were 31.5 for both cohorts, with sensitivity and specificity reflecting moderate accuracy.

When comparing SID and SIDa between the pre-eclampsia group and those with severe features, no statistically significant differences were found (p=0.178 and p=0.190 respectively), suggesting that these

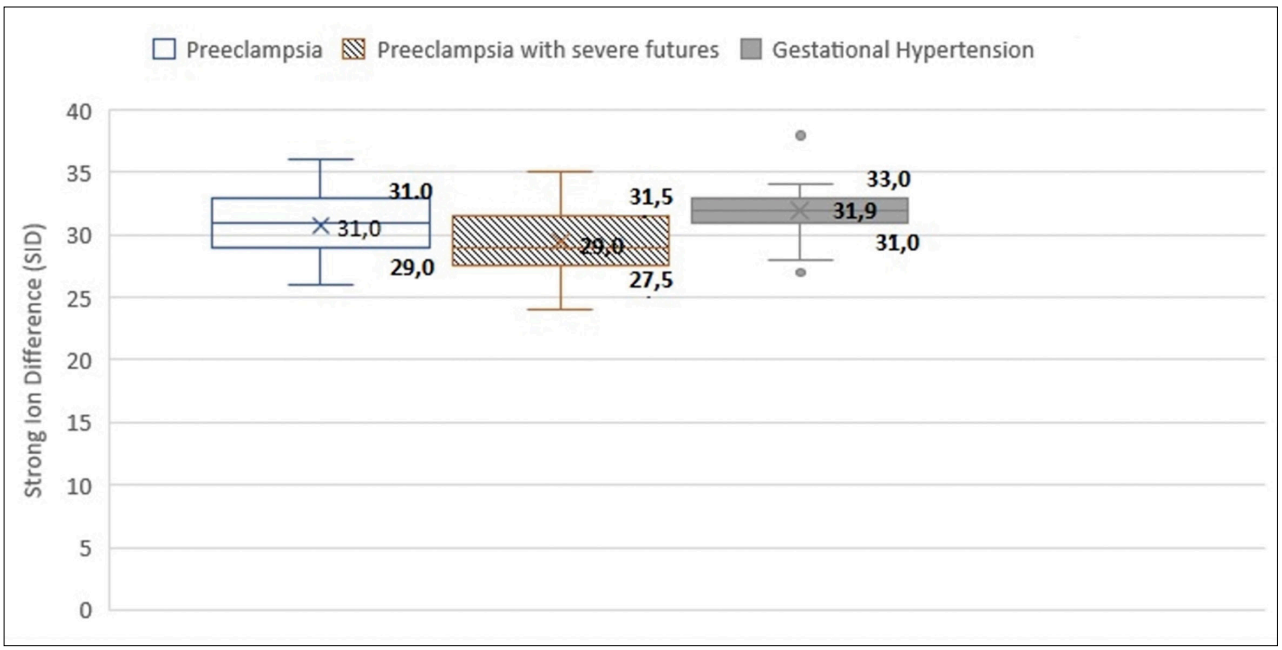

Figure 4. *Graphical illustration of SID between gestational hypertension group and preeclampsia patients and preeclampsia patients with severe futures in preeclampsia spectrum.*

Table 4. *Comparative analysis of strong ion difference and apparent strong ion difference between the preeclampsia group and the preeclampsia with severe features group*

	Patient cohort (n=51)		
Parameter	Preeclampsia (n=42)	Preeclampsia with severe features (n=9)	P value
SID	31.00 (29,00–31,00)	29.00 (27,50–31,50)	0.178
SIDa	29.60 (28,12–31,32)	28.10 (26,35–30,50)	0.190

Results were presented as median (25–75 percentile), which was used for non-normally distributed data.

parameters may not vary significantly between different severities within the preeclampsia spectrum. However, the SID and SIDa were slightly lower in the severe preeclampsia (Table 4, Fig. 4).

Discussion

This study suggests that SID provides additional diagnostic information independent of proteinuria, reinforcing its potential role in evaluating hypertensive disorders of pregnancy.

Principle Findings

Dipstick urinalysis (protein ≥1+) did not significantly differentiate between GHT and preeclampsia in the total cohort (p=0.78; sensitivity 59.6%, specificity 43.2%). In contrast, significance improved in patients without confounding electrolyte-affecting conditions (p=0.001; sensitivity 76.3%, specificity 61.1%). SID, with a cutoff of 31.5, showed statistically significant diagnostic value in both groups (p<0.001), and remained moderately accurate regardless of comorbidities. Kappa analysis revealed poor concordance between SID and proteinuria overall, and only slight agreement in patients without chronic disease.

Severe preeclampsia, a more critical form within the preeclampsia spectrum, may occur with or without proteinuria and is characterized by end-organ damage. It can manifest through thrombocytopenia, elevated liver enzymes, right upper quadrant pain from liver capsule distension, new-onset renal insufficiency, pulmonary edema, persistent headaches unresponsive to acetaminophen, and visual disturbances[1,17]. Although the definitions of these conditions are clear, in a clinical setting, symptoms often overlap, complicating accurate diagnosis, especially in emergent cases and patients with additional chronic diseases. Moreover, routine laboratory findings do not

always reflect the severity of the disease. For instance, right upper quadrant pain due to hepatic cell edema, parenchymal necrosis, and distention of Glisson's capsule, or headaches resulting from endothelial cell instability and periventricular edema, are non-specific symptoms. Therefore, in patient management algorithms, the sensitivity, specificity, and rapid turnaround of diagnostic tests are crucial for timely and accurate diagnosis[18–21].

Results

Despite various studies on blood gas analysis in HDP, classical approaches have limited clinical adoption, highlighting the value of the Stewart method[22–25]. Ortner et al.[15], found no significant SID differences post-magnesium sulfate, initially viewed as a limitation. However, aligned with our findings, this suggests that SID may serve not only as a diagnostic marker but also as a tool to monitor treatment efficacy.

Clinical İmplications

An ideal biomarker should be affordable, accessible, accurate, and yield rapid results. Venous blood gas analysis offers a reliable and practical alternative to arterial blood gas testing for electrolyte assessment[26,27]. Additionally, calculating the SID from VBG results is straightforward, further enhancing its utility in managing complex clinical conditions.

Although Stewart's theory and SID may initially seem unrelated to the preeclampsia spectrum of diseases, understanding the physiology of normal membrane function –impermeable to proteins– is crucial for maintaining quantitative acid-base balance in Stewart's world[28]. SID, as an independent variable, is notably affected in conditions like sepsis, where normal membrane functions are compromised is well-documented in the literature[29,30]. Recognizing the shared pathophysiological mechanisms underlying both sepsis and preeclampsia –including endothelial dysfunction, coagulation abnormalities, microcirculatory dysfunction, and end-organ damage– underpins our methodology. Thus, while the etiologies of sepsis and preeclampsia differ, it can be expected that the metabolic alterations in blood gas parameters and electrolyte concentrations result in comparable changes in SID.

Research İmplications

Larger prospective studies are needed to validate SID cut-off values and confirm its clinical utility. Future research should compare SIDa values across the HDP spectrum to refine its diagnostic and monitoring roles.

Strengths and Limitations

This study highlights SID's diagnostic potential in distinguishing preeclampsia from gestational hypertension and its role in monitoring severe cases. Its retrospective design and small sample size limit causal inference and statistical power, especially between preeclampsia subgroups. Nonetheless, the findings suggest clinical value, warranting further investigation.

Conclusion

In conclusion, traditional bicarbonate-based analyses may not fully capture the complexities of acid-base disturbances observed in hypertensive disorders of pregnancy. Stewart's theory, incorporating SID and SIDa, offers a more comprehensive approach to understanding these imbalances. By integrating these advanced diagnostic methods, clinicians can achieve a more precise assessment of the patient's acid-base status, leading to more effective treatment strategies. This study contributes valuable insights by retrospectively analyzing blood gas parameters alongside clinical data, based on microangiopathy and its role in the preeclampsia spectrum of diseases. Identifying novel biomarkers such as SID may enhance risk stratification, enable early detection, and support personalized management approaches, ultimately reducing maternal morbidity and mortality. While this study lays a solid foundation, further research is necessary to address its limitations and expand upon these findings.

Declarations

Funding

None.

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None.

Conflict of İnterest

The authors declare no conflict of interest.

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Microbial Foodborne Poisoning-Related Deaths: A 10-Year Retrospective Autopsy-Based Study

Mikrobiyal Gıda Zehirlenmesine Bağlı Ölümler: 10 Yıllık Otopsi Temelli Retrospektif Bir Çalışma

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ABSTRACT

Aim: *This study aims to evaluate foodborne death cases from a forensic medical perspective and to conduct a retrospective analysis based on autopsy findings.*

Material and Method: *A total of 36 cases reported to the Council of Forensic Medicine between 2014 and 2024, in which the cause of death was determined to be foodborne illness, were included. Sociodemographic data, clinical history, autopsy findings, microbiological analyses, and toxicological reports were reviewed. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) program with the Chi-square test used for categorical data comparisons ($p<0.05$ considered statistically significant).*

Results: *Most deaths occurred in summer months and following the consumption of poultry, particularly chicken. In 58.3% of cases, no microbiological analysis of food samples was conducted. Among the analyzed samples, the most frequently detected pathogens were Staphylococcus aureus, Salmonella spp., and Bacillus cereus. Significant associations were found between hospital admission and histopathological enteritis ($p=0.031$), presence of food analysis in mass poisoning events ($p=0.022$), and consistency of pathogens with Ministry of Agriculture reports ($p=0.0005$).*

Conclusion: *The findings highlight the importance of ensuring food safety, conducting comprehensive forensic autopsies, and enhancing inter-institutional coordination to protect public health.*

Key words: *foodborne diseases; forensic autopsy; microbiological analysis; bacillus cereus; public health*

ÖZET

Amaç: *Bu çalışma, gıda kaynaklı ölüm vakalarının adli tıp bakış açısıyla değerlendirilmesini ve otopsi bulgularına dayalı retrospektif bir analiz yapılmasını amaçlamaktadır.*

Gereç ve Yöntem: *Adli Tıp Kurumu'na 2014–2024 yılları arasında bildirilen ve ölüm nedeni gıda kaynaklı hastalık olarak belirlenen toplam 36 olgu çalışmaya dâhil edilmiştir. Olguların sosyodemografik verileri, klinik öyküleri, otopsi bulguları, mikrobiyolojik analizleri ve toksikolojik raporları incelenmiştir. İstatistiksel analizler IBM Sosyal Bilimlerde İstatistik Paket Programı (SPSS) kullanılarak yapılmış; kategorik verilerin karşılaştırılmasında Ki-kare testi uygulanmış, $p<0,05$ istatistiksel olarak anlamlı kabul edilmiştir.*

Bulgular: *Ölümlerin büyük çoğunluğu yaz aylarında ve özellikle tavuk eti tüketimini takiben meydana gelmiştir. Olguların %58,3'ünde gıda örneklerine yönelik herhangi bir mikrobiyolojik analiz yapılmamıştır. Analiz edilen örneklerde en sık tespit edilen patojenler Staphylococcus aureus, Salmonella spp. ve Bacillus cereus olmuştur. Hastane başvurusu ile histopatolojik enterit varlığı arasında ($p=0,031$), kitlesel zehirlenme vakalarında gıda analizi yapılmış olması ile zehirlenmenin doğrulanması arasında ($p=0,022$) ve tespit edilen patojenlerin Tarım Bakanlığı raporları ile uyumu arasında ($p=0,0005$) anlamlı ilişkiler saptanmıştır.*

Sonuç: *Elde edilen bulgular; gıda güvenliğinin sağlanmasının, kapsamlı adli otopsilerin gerçekleştirilmesinin ve kurumlar arası koordinasyonun güçlendirilmesinin halk sağlığının korunması açısından kritik öneme sahip olduğunu göstermektedir.*

Anahtar kelimeler: *gıda kaynaklı hastalıklar; adli otopsi; mikrobiyolojik analiz; bacillus cereus; halk sağlığı*

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Introduction

Foodborne illnesses refer to diseases that arise from the consumption of contaminated food –either through microorganisms (such as bacteria, viruses, or parasites) or toxic substances– at any stage of production, processing, distribution, or consumption. These diseases may present with mild gastrointestinal symptoms or escalate to life-threatening systemic conditions[1]. According to the World Health Organization (WHO), nearly 600 million people worldwide suffer from foodborne illnesses annually, resulting in approximately 420.000 deaths and the loss of 33 million healthy life years (DALYs). Children under the age of five and individuals living in developing countries are particularly vulnerable; around 125.000 children die from foodborne diseases each year[2]. In a study conducted in Türkiye, 1.702 deaths due to food poisoning were reported between 1993 and 2002. However, because foodborne illnesses are often underreported, the actual numbers are likely much higher; the recorded cases represent only "the tip of the iceberg"[3]. A 1999 study by Mead et al. in the United States found that bacteria accounted for 72% of food-related deaths, parasites for 21%, and viruses for 7%. Over 90% of the fatalities were attributed to five key pathogens: Salmonella (31%), Listeria (28%), Toxoplasma (21%), Norwalk-like viruses (7%), Campylobacter (5%), and E. coli O157:H7 (3%)[4]. In cases of fatal foodborne illness, forensic autopsies play a critical role, particularly those that include microbiological analysis aimed at identifying specific pathogens. These procedures are essential for investigating medico-legal concerns such as exposure to infectious agents, the nature and composition of the food involved, and potential negligence[5]. For example, in a study by Devers & Nine, an autopsy revealed diffuse muscular atrophy in the upper and lower extremities due to exposure to botulinum toxin produced by Clostridium botulinum[6]. In another study by Takabe & Oya, gross gastrointestinal findings were observed following exposure to Bacillus cereus, which were supported by histopathological examination of intestinal tissues[7]. Schreiber et al. further documented the possibility of Bacillus cereus-related acute liver failure in fatal cases[8]. In the absence of such pathological findings, microbiological studies can be crucial in confirming the diagnosis[9].

In addition, foodborne poisonings are of legal significance in forensic cases. Under Article 186 of the Turkish Penal Code, supplying spoiled food that endangers human life is punishable by up to five years of imprisonment[10]. Therefore, it is a legal obligation to report suspected food poisoning cases to judicial authorities, and comprehensive forensic evaluations are essential for identifying potential negligence or criminal liability[3]. Clinical presentation from medical records or witness statements, in addition to autopsy findings, significantly contributes to determining the cause and mechanism of death[11]. Reports from the Ministry of Agriculture and Forestry regarding microbiological analyses of the suspected food items are also considered crucial pieces of evidence in forensic case files[12,13].

This study aims to retrospectively analyze foodborne death cases referred to the Council of Forensic Medicine using forensic data such as autopsy reports, microbiological and laboratory findings, and scene investigation results. By examining demographic characteristics, causes of death, detected pathogens, and pathological findings of these cases in light of national and international literature, we seek to highlight the increased incidence of poisonings during the summer months and in communal dining settings. The findings are intended to guide forensic pathologists in similar cases and contribute to preventive strategies for public health.

Material and Method

Study Design

This study was designed as a retrospective cross-sectional analysis. Forensic case files submitted to the First Specialization Board of the Council of Forensic Medicine between July 5, 2014, and April 5, 2024, by courts or prosecutors for the determination of the exact cause of death were reviewed. The National Judiciary Informatics System (UYAP) was searched for expert opinions containing the phrases "...death due to food poisoning..." or "...death due to foodborne illness...". Cases in which the cause of death was determined to be food poisoning through forensic evaluation were included in the study. Initially, 51 cases were identified; however, 15 cases involving non-microbial causes such as toxic plants, mushrooms, or fish poisoning were excluded. A total of 36 cases were ultimately evaluated.

Data Collection

Expert reports and forensic files of the cases were thoroughly examined. Data were collected on

sociodemographic information (age, gender, occupation, etc.), incident history and clinical course (hospital admission, other affected individuals), autopsy findings (macroscopic and histopathological results), microbiological culture and toxicological analyses. All information was recorded on a standardized data form. Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) program. Descriptive statistics included means, standard deviations, minimum-maximum values, and percentages. The Chi-square test was used to compare categorical variables, with $p<0.05$ considered statistically significant.

Ethical Approval

This study was conducted with appropriate permissions in accordance with the scientific research procedures of the Council of Forensic Medicine (Approval Date: 06/08/2024; Approval Number: 21589509/2024/930). All data used in the study were anonymized, and confidentiality of personal information was maintained.

Results

A total of 36 cases were evaluated in which the cause of death was determined to be foodborne illness. The mean age of the cases was 42.4±24.8 years; 58.3% (n=21) were male, and 41.7% (n=15) were female. In 80.6% of the cases (n=29), other individuals who had consumed the same food also presented to hospitals with similar symptoms, and four of them were later reported to have died. Additionally, 66.7% of the cases involved two or more co-affected individuals, and 13.9% had one accompanying person.

Regarding the preparation sites of the food causing the poisoning, 38.9% of the meals were prepared at home, 27.8% in mass consumption environments (such as nursing homes, military units, or ceremonies), 8.3% were ordered or consumed at restaurants or similar establishments, and in 2.8% of cases, the source could not be identified.

The most common food category linked to poisoning was white meat (44.4%), particularly chicken (13 cases), followed by fish (2 cases), and Türkiye (1 case). In 58.3% of the cases, no laboratory analysis was performed on the suspected food item. Among the 15 cases with available food analysis, pathogen growth was detected in 11 (30.6% of total cases), while in 4 cases (11.1%), the food complied with the Turkish Food Codex, and no pathogens were detected. Detected pathogens included coagulase-positive staphylococci (4 cases), Salmonella spp. (4 cases), Listeria monocytogenes (1 case), Bacillus cereus (1 case), and a combination of Campylobacter spp. + Bacillus cereus (1 case).

Autopsy findings showed that in 58.3% of cases, no intestinal samples were taken. Histopathological examination revealed signs of enteritis in 22.2% of cases; no specific pathological findings were observed in 16.7%, and 2.8% of the autopsies were reported as incomplete.

While 91.7% of the individuals had hospital admissions before death, 8.3% were found dead without any prior medical contact. Among those who were admitted, 61.1% were hospitalized, whereas 38.9% were treated on an outpatient basis and later discharged. Moreover, 66.7% of the deaths occurred in hospitals, 22.2% in public settings, and 11.1% at home.

No statistically significant association was found between gender and the type of food causing the poisoning ($p=0.5378$), gender and the food source ($p=0.7130$), presence of co-affected individuals and compliance with the Turkish Food Codex ($p=0.5807$), season and place of death ($p=0.8955$), or history of chronic illness and place of death ($p=0.9999$). However, a statistically significant relationship was found between a history of hospitalization and histopathological findings ($p=0.031$), with enteritis findings more frequently observed in hospitalized cases. Additionally, a significant association was found between mortality in co-affected individuals and whether food analysis had been conducted ($p=0.022$). A highly significant correlation was observed between the microbiological findings of the consumed food and the agricultural inspection reports issued by the Ministry of Agriculture and Forestry ($p=0.0005$).

Discussion

The average age of the cases in our study was found to be 42 years, indicating that most fatalities occurred in the middle-aged population. Although foodborne illnesses can affect individuals of all ages, they tend to present more mildly in healthy young adults. However, vulnerable populations such as children and older people are at higher risk of severe outcomes and mortality. Indeed, WHO data show that a significant proportion of deaths from foodborne illnesses occur among children under the age of five[2]. Although our study included only one pediatric case (a 5-year-old),

it is noteworthy that this child died from a severe Salmonella infection despite having no underlying medical conditions.

An analysis of the adult cases revealed that most resided in rural areas and prepared their own food. This finding suggests an increased risk in environments where hygiene and food storage conditions may be inadequate. In rural communities, low levels of education and limited economic resources often prevent the implementation of proper food handling and storage techniques, especially during the summer months, thereby increasing the likelihood of outbreaks[14]. A significant portion of the cases occurred during June, July, and August, which aligns with previous literature indicating that food spoilage and contamination are more common during warmer months[15].

The male predominance (~58%) in our cases may suggest that men are more likely to consume food in riskier environments or outside the home. Similarly, a study by Başaran analyzing foodborne illness cases in Türkiye between 2016 and 2020 reported that students and employed individuals were the most commonly affected groups[15]. These demographics typically consume food in communal or institutional settings. In our study, 28% of the cases involved food prepared in mass consumption areas such as cafeterias or military barracks. It is well known that foodborne illnesses are more common in communal events such as schools, dormitories, or weddings. For instance, in a study by Urazel et al. evaluating food poisoning cases presenting to the emergency department, 82.8% of the patients were students, and most cases were linked to chicken-based meals[16]. Our findings also support that the majority of cases involved outbreaks affecting multiple individuals. In such scenarios, outbreak investigations, along with forensic autopsies, are vital for identifying the responsible food item, determining liability, and ensuring the timely withdrawal of contaminated products from circulation.

The distribution of food sources in our study was consistent with the literature. Chicken meat was the most frequently implicated food in fatal cases. Similarly, a study by Kumagai et al. (2020) in Japan found that chicken was the leading cause of microbial food poisoning[17]. Urazel et al. also reported chicken products as the most common culprit, followed by red meat products[16]. Chicken is particularly susceptible to contamination by pathogens such as Campylobacter and Salmonella if not stored or appropriately cooked[18,19]. In our study, nearly half of the cases were associated with chicken consumption, emphasizing the need for strict cold chain maintenance. Two additional fatalities occurred after fish consumption, possibly linked to bacterial growth (e.g., Vibrio spp. or histamine-producing flora) in improperly stored fish during the summer.

Additionally, approximately one-third of the food items causing poisoning in our cases were obtained from outside the home (e.g., restaurants, catering services). With the increasing trend of dining out, such cases have gained importance. Foodborne outbreaks associated with restaurants in tourist regions during the summer are frequently reported. In 80.6% of the cases (n=29), it was documented that other individuals who consumed the same food experienced similar symptoms and sought medical attention. This indicates that the majority of cases occurred as part of an outbreak involving multiple individuals. Food safety inspections in restaurants and cafeterias must therefore be carried out with rigor and continuity.

However, food prepared at home was responsible for 38.9% of the deaths, which shows that food safety is not solely the responsibility of food service establishments. Domestic food handling practices are equally important. Simple hygiene measures and proper storage and cooking methods can prevent many cases. The WHO's "Five Keys to Safer Food" initiative emphasizes keeping food clean, separating raw and cooked foods, cooking thoroughly, keeping food at safe temperatures, and using safe water and raw materials as essential measures to prevent foodborne illnesses[20].

One of the most striking findings of our study was the absence of microbiological reports on the consumed food in 58.3% of forensic files. This may have been due to the inability to collect food samples post-incident or a lack of coordination between institutions. However, in such cases, laboratory analyses from the Ministry of Agriculture and Forestry should be included in the forensic files without exception. In our study, a statistically significant relationship was found between the microorganisms identified in consumed food and the agricultural inspection reports from the Ministry ($p=0.0005$). In 11 of the 15 cases with microbiological analysis, specific pathogens were detected, suggesting a strong correlation between pathogen identification and official inspection processes.

The most commonly isolated pathogens were Staphylococcus aureus and Salmonella spp. . While S. aureus typically causes mild and self-limiting

symptoms, all four S. aureus-positive cases in our study involved elderly individuals or those with underlying health conditions. In such patients, staphylococcal enterotoxins may lead to severe dehydration and electrolyte imbalance, potentially resulting in death[3,21]. Salmonella is a more invasive pathogen and may cause sepsis and multi-organ failure, especially in immunocompromised individuals[4]. Another important pathogen was Listeria monocytogenes, known for causing meningitis and sepsis in pregnant women, neonates, and the elderly[22]. The Listeria-positive case in our study involved a 70-year-old male who died of meningoencephalitis. Additionally, Bacillus cereus was identified in food samples from two cases, both of which showed fulminant clinical progression. One of these cases also presented with severe liver enzyme elevation, indicative of acute liver failure. Although B. cereus is often associated with mild food poisoning, toxigenic strains can be fatal. Literature has reported sudden deaths caused by cereulide toxin produced by B. cereus[9,11].

Other spore-forming bacteria, such as Clostridium perfringens and Clostridium botulinum, can also proliferate under improper conditions and result in fatal poisonings. Although rare, botulism cases related to home-canned foods have been reported in Turkiye[6]. In these instances, autopsy findings may be nonspecific, making laboratory analysis essential for diagnosis. Thus, toxicological and microbiological investigations should never be overlooked in suspected foodborne deaths.

Our study also highlighted some deficiencies in forensic procedures. In 58% of cases, no intestinal tissue samples were collected for histopathological examination, suggesting possible oversight during autopsy. However, acute infectious colitis can be identified microscopically and may support the diagnosis. In bacterial colitis, microscopic findings may include intact crypt architecture with neutrophilic infiltration of the lamina propria and occasional crypt abscesses. During the healing phase, these findings may become nonspecific[23,24]. Among the cases in our study where intestinal samples were collected, histological signs of enteritis were found in half of the cases. This indicates that proper tissue sampling during autopsy can significantly contribute to diagnostic accuracy.

As emphasized by Kattamreddy et al. (2022) in a report on a suspected food poisoning death, forensic autopsies in such cases require multidisciplinary attention and precision. Timely and proper sample collection, appropriate transport to laboratories, and the performance of all necessary analyses are vital for successful outcomes[14]. In our experience, these procedures were not consistently followed. For instance, some cases included food samples, but the corresponding lab reports were missing from the forensic files, reflecting a lack of inter-institutional coordination. This underscores the need for improved communication between forensic pathologists and public health or food safety authorities.

A further concern lies in the insufficient awareness among healthcare professionals regarding the medico-legal implications of foodborne illnesses. In a study published in the Dicle Medical Journal, 34.9% of emergency physicians failed to issue forensic reports for suspected food poisoning cases, and only 2% of the issued reports met proper legal standards[16]. This indicates the urgent need for training programs to raise awareness among healthcare providers about recognizing and managing such cases as medico-legal incidents.

In conclusion, our study revealed that foodborne deaths in Türkiye tend to cluster around specific pathogens and often result from preventable conditions. The increased incidence during the summer months and in large-scale catering events reflects the influence of climate and hygiene practices, consistent with trends reported in the literature[15]. Deaths related to food poisoning are not only a public health issue but also constitute forensic cases. Therefore, investigating such deaths provides critical information both for determining legal responsibility and for preventing similar future incidents.

Our findings reaffirm the importance of conducting comprehensive forensic autopsies supported by laboratory investigations. They also highlight the necessity of maintaining the cold chain for high-risk foods such as poultry and enforcing hygiene protocols in mass consumption settings. These insights can significantly guide both public health interventions and legislative measures aimed at preventing future foodborne fatalities.

Conclusion

Deaths due to foodborne illnesses are largely preventable and represent a shared concern for both public health and forensic medicine. A significant portion of fatal cases in our study stemmed from improper storage and cooking conditions. Therefore, strengthening food safety practices is essential.

Strict adherence to the World Health Organization's recommended food safety principles –including cleanliness, separation of raw and cooked foods, thorough cooking, safe temperature storage, and the use of clean water and raw materials– should be maintained in both households and food service establishments. During the summer months, in particular, when the risk of bacterial growth increases, preserving the cold chain becomes even more critical.

It is also recommended that hygiene inspections be conducted at every stage –from the sourcing of food materials to final service– before mass catering events.

Public education plays a crucial role in preventing foodborne illnesses. Simple but life-saving hygiene practices should be widely taught. In particular, children in rural areas and school-age populations should be educated on safe food preparation and storage techniques. Public awareness should be enhanced through media campaigns and healthcare personnel training about the symptoms of food poisoning and the initial steps to take.

All suspected cases of food poisoning should be promptly and thoroughly reported to judicial authorities. Physicians in emergency departments and primary healthcare settings should be aware that such cases fall under the category of forensic incidents and must issue medico-legal reports without delay. Greater emphasis should also be placed on the analyses conducted by agricultural and food control laboratories during forensic investigations. Protocols must be established to ensure that samples from suspect food items are promptly delivered to relevant laboratories and that the results are incorporated into the forensic file.

Each forensic food poisoning case should be managed as a multidisciplinary crisis, requiring coordinated efforts among forensic pathologists, public health experts, food safety professionals, and, when necessary, law enforcement authorities. Comprehensive forensic autopsies are imperative for all suspected foodborne deaths. During autopsy, samples should be collected from the stomach, intestines, and other relevant organs, and preserved appropriately for microbiological and toxicological analyses. As our findings show, the absence of such sampling may hinder diagnostic clarity. Forensic specialists should always consider the possibility of foodborne illness and conduct thorough internal examinations, planning every necessary laboratory investigation.

Advanced testing capabilities –such as special toxin assays for *Clostridium botulinum* and specific tests for *Bacillus cereus*– should also be developed.

Legal regulations regarding food safety must be enforced without interruption. Routine inspections of food businesses should be intensified, especially during the summer months. Sanctions should be imposed on establishments that violate hygiene standards or operate under illegal conditions. A national database to track foodborne poisoning cases is recommended to identify high-risk food items or regions and implement proactive measures.

In conclusion, reducing foodborne deaths requires a coordinated approach across prevention, detection, and intervention stages. Ensuring safe food production, raising public awareness, and conducting effective forensic evaluations can significantly reduce mortality. Our study provides national data at the intersection of forensic medicine and public health, serving as a foundation for future research and policy development. Continued multidisciplinary efforts in this field will contribute to enhancing food safety and ultimately protecting public health.

Limitations

Due to the retrospective design of this study, certain limitations were encountered regarding the availability and completeness of data. In many autopsy reports, intestinal samples were not collected, and histopathological examinations were not conducted according to a standardized protocol. This limited the evaluation of some pathological findings.

In 58.3% of cases, no microbiological analysis of the consumed food was performed, which restricted the ability to determine the cause of poisoning definitively. Moreover, the relatively limited sample size may have affected the statistical power and prevented some comparisons from reaching significance.

Another limitation is that all data were obtained solely from the Council of Forensic Medicine, which may limit the generalizability of the findings to the broader population. Finally, detailed information regarding the clinical course and treatment of the patients was not available, hindering a comprehensive evaluation of factors influencing prognosis.

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Consent

All procedures followed were in accordance with the ethical standards stated in the Helsinki Declaration of 1975 (in its most recently amended version). This study was conducted as a retrospective autopsy-based analysis of deceased individuals. No living participants were involved, and no personally identifiable information was disclosed. As such, the requirement for informed consent was waived. Ethical approval for the study was obtained from the Council of Forensic Medicine, Education and Scientific Research Committee (Approval no: 21589509/2024/930, Date: 06/08/2024).

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Right Ventricular Functions Using Noninvasive Methods in Patients Followed in the Cardiology Clinic with Inferior Myocardial Infarction

Kardiyoloji Kliniğinde Takip Edilen İnferior Miyokard İnfarktüsü Olan Hastalarda Sağ Ventrikül Fonksiyonlarının Noninvaziv Yöntemlerle Değerlendirilmesi

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ABSTRACT

Aim: *Coronary artery disease (CAD) continues to be one of the leading causes of morbidity and mortality in developed and developing countries. In this study, the right ventricular functions of patients with inferior myocardial infarction (inferior MI) were investigated.*

Material and Method: *In this prospective study, patients who were followed up with inferior MI between January 2023 and June 2023, along with a healthy control group, were included. Transthoracic echocardiography was performed on all patients under appropriate conditions and recorded.*

Results: *A total of 103 patients (68 males, average age: 51±12 years) were included in the study. The patients were divided into two groups: patients (n=50) and healthy controls (n=53). In single and multiple regression analyses between groups, age, glucose, tricuspid annular plane systolic excursion (TAPSE), and TAPSE/pulmonary arterial systolic pressure (SPAP) were shown to be independent risk factors for inferior myocardial infarction.*

Conclusion: *TAPSE and TAPSE/SPAP are independent risk factors for inferior myocardial infarction.*

Key words: *inferior myocardial infarction; tricuspid annular plane systolic movement; echocardiography*

ÖZET

Amaç: *Koroner arter hastalığı (KAH) gelişmiş ve gelişmekte olan ülkelerde morbidite ve mortalitenin en önde gelen nedenlerinden biri olmaya devam etmektedir. Bu çalışmada inferior miyokart infarktüsü (İnferior MI) ile takip edilen hastaların sağ ventrikül fonksiyonlarının araştırılması gerçekleştirilmiştir.*

Gereç ve Yöntem: *İleriye yönelik olarak yapılan çalışmada, Ocak 2023 ile Haziran 2023 tarihleri arasında İnferior MI ile takip edilen ve sağlıklı kontrol grubundan oluşan hastalar dâhil edilmiştir. Bütün hastalara uygun koşullarda transtorasik ekokardiyografi yapılıp kayıt altına alınmıştır.*

Bulgular: *Çalışmaya toplam 103 hasta (68 erkek, ortalama yaş: 51±12) alındı. Hastalar (n=50) ve sağlıklı kontrol grubu (n=53) olmak üzere ikiye ayrıldı. Gruplar arasında tekli ve çoklu regresyon analizlerinde yaş, glukoz, triküspit anüler düzlem sistolik hareketi (TAPSE), TAPSE/SPAP, inferior miyokart infarktüsü açısından bağımsız risk faktörü olarak gösterilmiştir.*

Sonuç: *TAPSE, TAPSE/SPAP inferior miyokart infarktüsü için bağımsız risk faktörü olarak gösterilmiştir.*

Anahtar Kelimeler: *inferior miyokart infarktüsü; triküspit anüler düzlem sistolik hareketi; ekokardiyografi*

Introduction

Coronary artery disease (CAD) is frequently seen in developed and developing countries. It is one of the most important causes of mortality and morbidity. It is stated that approximately 16 million people in the United States (USA) have CAD, and the majority of them are asymptomatic[1,2]. According to the data of the World Health Organization, it is predicted that deaths due to CAD will increase by 120% in women and 137% in men in the next twenty years[3]. Coronary artery disease poses both a severe economic burden and a social problem with its adverse effects on the quality of life. According to US data, one-fourth of all inpatient treatment expenses are caused by CAD with 71.2 billion dollars[4].

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The term acute coronary syndrome describes clinical conditions that occur as a result of impaired myocardial blood flow and are usually accompanied by acute chest pain or other symptoms of myocardial ischemia and electrocardiographic changes due to myocardial ischemia. Unstable angina pectoris (USAP) refers to a series of events that occur due to thrombotic coronary artery disease, including non-ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI), and sudden cardiac death[5]. It also occurs in patients with STEMI or NSTEMI. Mortality is extremely high, with in-hospital mortality of 7% in NSTEMI and 6.5–7% in STEMI[6]. Survivors of acute myocardial infarction (AMI) suffer from chronic heart failure due to heart failure, angina pectoris, and functional limitations due to myocardial damage. It faces the risk of morbidity[7]. The pathogenesis of acute coronary syndromes is common. Almost all of them have an underlying atherosclerotic plaque, which does not necessarily narrow the coronary artery to a critical level, but can be easily complicated[8]. Acute myocardial infarction is often caused by an unstable atherosclerotic plaque, which can be caused by high-intensity physical activity, emotional stress, sexual activity, cocaine/amphetamine use, extreme cold, and acute infections. It occurs due to damage to the vascular endothelial wall as a result of rupture or erosion due to triggers, intracoronary thrombus formation and ultimately coronary blood flow occlusion[9]. Many parameters in acute myocardial infarction have been investigated for use in defining the prognosis of the patient. Some of these parameters can also be detected with the help of echocardiography. Echocardiography is widely used in clinical practice as a noninvasive and easily applicable imaging method that can be performed at the bedside. Determination of cardiac functions in AMI patients will provide important information about the patient's mortality and morbidity, and can be easily determined by echocardiography[10].

The right ventricle (RV) is difficult to evaluate on echocardiography due to the irregularity of the endocardial surface, its unusual shape, and its complex contraction mechanism. Right ventricle has a complex geometry and physiology that differs from the left ventricle[11]. Advances in invasive and noninvasive assessments, combined with epidemiological analyses, have contributed to understanding RV pathophysiology across the spectrum of health and disease[12]. In addition to these factors, the fact that the RV is anatomically directly behind the sternum makes echocardiography even more difficult[13]. Right ventricle functions in STEMI patients have been examined in some studies. However, in these studies, the evaluation of RV functions was made using only routine parameters of echocardiography.

Our aim in this study is to examine the effects of inferior myocardial infarction on right ventricular functions in STEMI patients using advanced echocardiographic methods, compared to the control group, and to conduct more intensive follow-up and treatment for patients visiting the cardiology outpatient clinic.

Materials and Methods

Patient Selection

The flow diagram of the study is displayed in Fig. 1. Patients aged 18–90 years who had inferior myocardial infarction in the cardiology clinic were included in this single-center, case-controlled study. This study was conducted on 50 patients followed in the cardiology unit of our hospital. Echocardiographic examination was done on all patients within the first 24 to 72 hours. In addition to routine echocardiographic measurements, right ventricular tissue Doppler, right ventricular ejection fraction (RVEF), myocardial performance index (MPI) and tricuspid annular plane systolic excursion (TAPSE) measurements were taken. The diagnosis of Inferior MI is: According to the 4th Universal Myocardial infarction definition published by the European Society of Cardiology, acute myocardial infarction is defined as an increase and/or decrease in troponin and at least one troponin value >99. is above the perisantile URL and is accompanied by

- Myocardial ischemia symptoms;
- Novel ischemic ECG changes;
- Formation of pathological Q wave;
- New wall motion abnormality or new myocardial loss compatible with ischemic etiology in imaging methods;
- Angiography, intracoronary imaging or autopsy.

It was defined as being accompanied by at least one of the following conditions: intracoronary thrombus[14].

Fifty healthy individuals were taken as the control group. Participants were knowledgeable about the study protocol, and their written consent was received. Transthoracic echocardiography was performed by a single physician on the patient and the healthy control group. Biochemical parameters recorded in the system

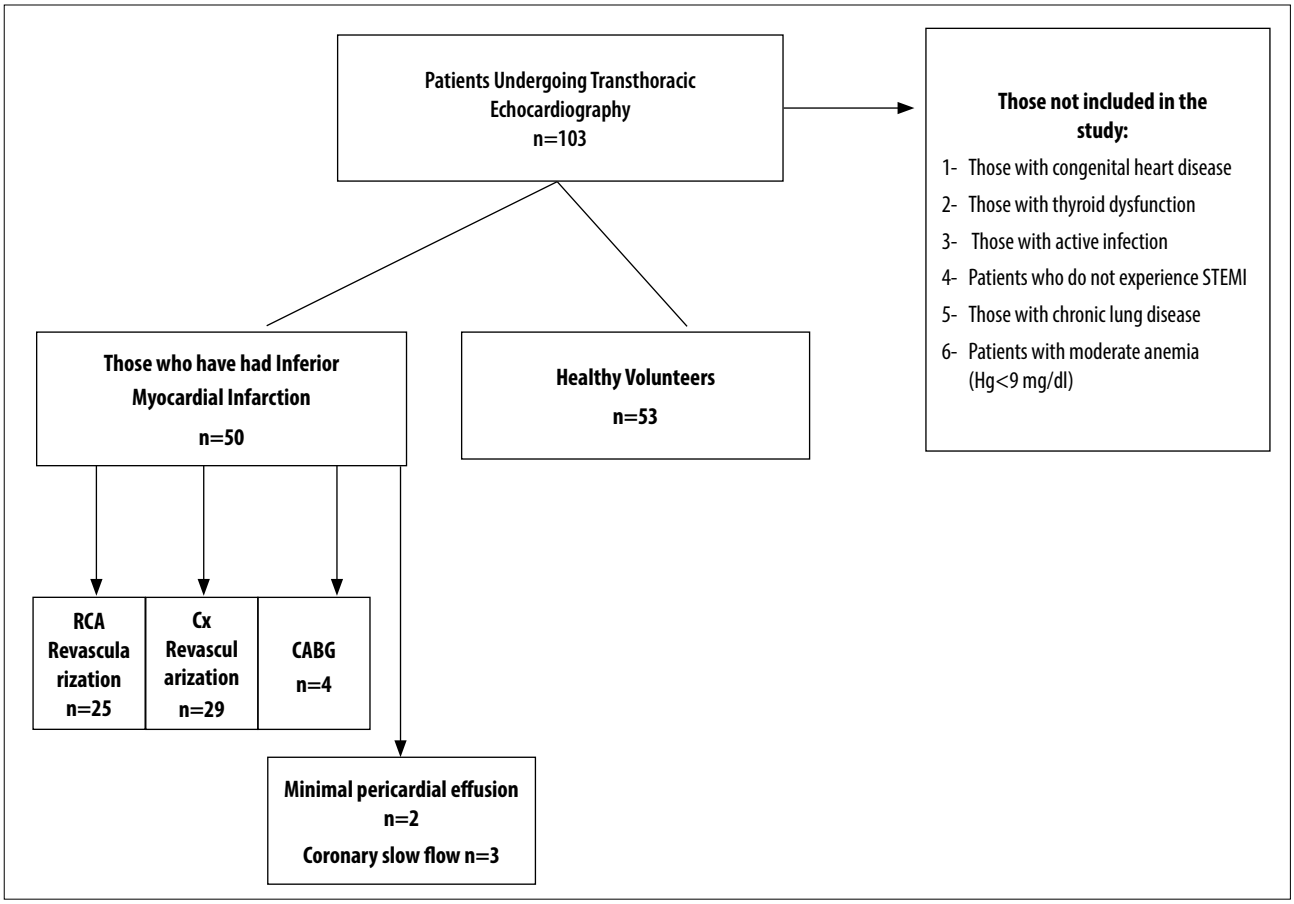

Figure 1. *Flow diagram (RCA: right coronary artery; Cx: circumflex artery; CABG: coronary artery bypass grafting; Hg: hemoglobin).*

were taken. Patients who were not registered in the system and did not have laboratory parameters were excluded from the study. Patients with thyroid dysfunction, active infection, without STEMI, with chronic lung disease, or with moderate anemia (Hgb <9 mg/dL) were not included. Transthoracic echocardiography was performed on all participants, and their measurements were recorded.

Echocardiographic examination: Echocardiographic measurements were performed on all patients and healthy volunteers who applied to the cardiology outpatient clinic within the first 24–72 hours using a Philips Epic 7 echocardiography device with a 2.5 mHz transducer. All Doppler measurements were saved at the end of expiration, while the patient was prevented from breathing. This ensured that the flow samples were not impacted by respiration and were more stable. The average of three consecutive measurements was then taken. Pulsed wave tissue Doppler velocities were measured with the echocardiography device's gain and filter settings at their lowest, compression and rejection settings at their highest, speed setting generally between -30 and +30 cm/sec, and a sampling volume width of 5 mm. All measurements were made in accordance with the recommendations of the American Heart Association[15]. As an indicator of RV systolic function; for right ventricular ejection fraction (RVEF), TAPSE and tricuspid Sm, diastolic function; premature and late diastolic velocities of tricuspid flow and their ratio (E/A) and tricuspid annular diastolic pulsed wave tissue doppler velocities and their ratio (Em/Am), also for global function; RV myocardial performance index (MPI) was taken. End-diastolic and end-systolic volumes calculated according to the 'ellipsoidal shell' model were used to measure RVEF. [EF=(Vdiast-Vsist) × 100/ Vdias]. Tricuspid annular plane systolic excursion was measured by M-mode echocardiographic measurement by placing the cursor lateral to the tricuspid annulus, and the movement of the lateral tricuspid valve annulus from the apical four chambers to the apex during the systole of the right ventricle was measured in mm[16]. By using pulsed wave Doppler sample volume in apical four-chamber

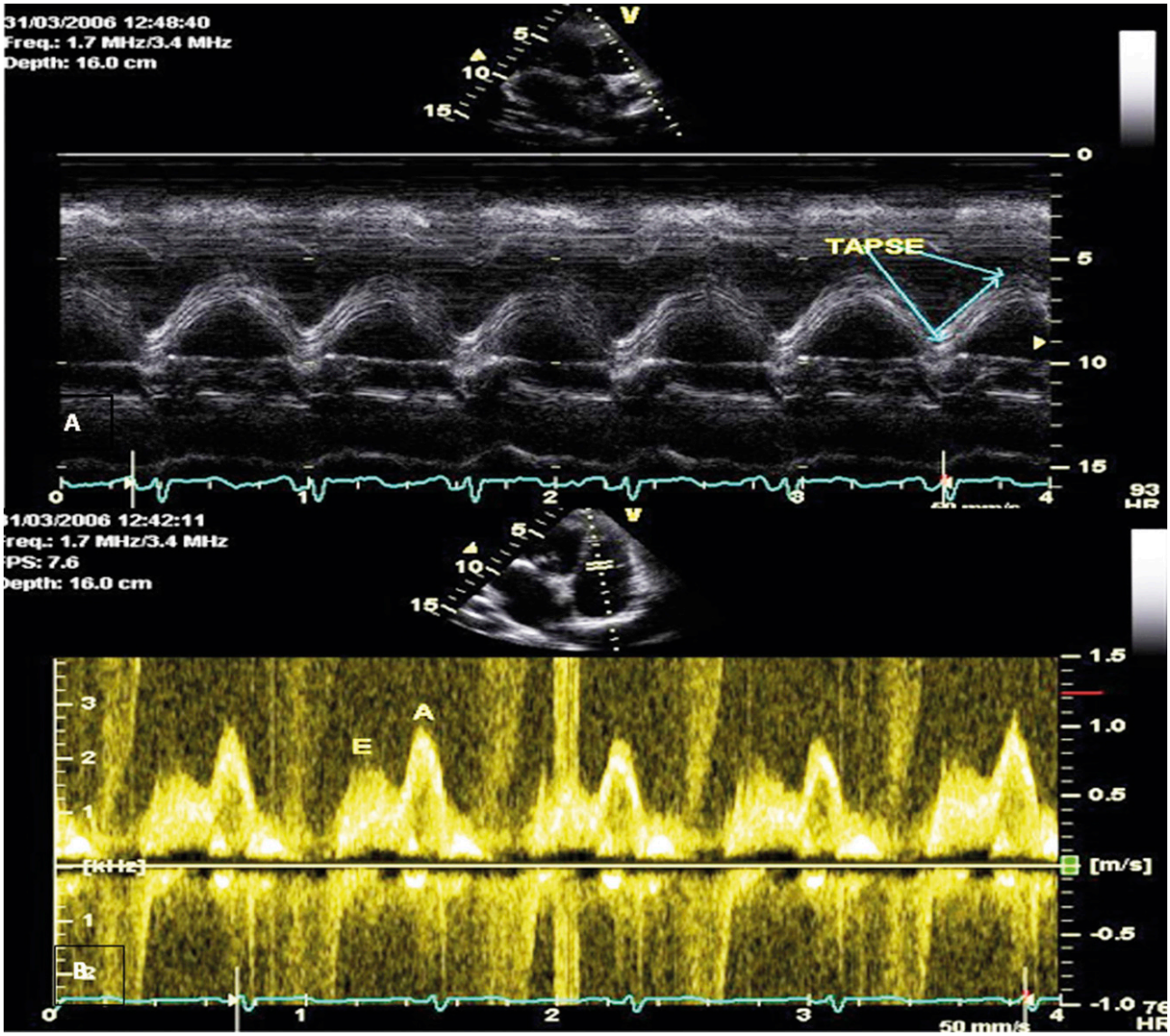

Figure 2. *a, b. Measurement of tricuspid annular plane systolic movements (TAPSE) (a). Tricuspid annular pulsed wave (PW) filling parameters (b).*

images, as previously described, the Early diastolic flow rate (E), the late diastolic flow rate (A), and the E/A ratio of the right ventricle were measured. In apical four-chamber images, pulsed wave tissue Doppler sample volume was placed at the right ventricular free wall-tricuspid annulus junction, and early diastolic (Em), late diastolic (Am), isovolumetric contraction time (IVCZ), and systolic wave (Sm) velocities were obtained (Fig. 2).

The tricuspid inflow velocity pattern was saved by placing a pulsed wave Doppler sample volume between the tricuspid valve tips from the apical-4 space. A pulsed wave Doppler was placed below the pulmonary valve to assess the right ventricular outflow pattern and was enrolled from the parasternal short axis. Doppler measurements were calculated as the average of three successive cardiac cycles. Doppler time intervals were measured from tricuspid inflow and right ventricular outflow velocity time intervals. The "a" interval is the time from the end to the start of tricuspid inflow, and the "a" interval is equal to the sum of isovolumetric contraction time, ejection time and isovolumetric relaxation time. Right ventricular ejection time "b" is the right ventricular outflow velocity profile time. The combined index of right ventricular systolic and diastolic functions (right ventricular MPI) (the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time) was calculated as "ab / b" (Fig. 2)

Ethical Approval

This study was conducted in accordance with the Declaration of Helsinki. Informed consent forms were obtained from patients and healthy volunteers, and an ethics committee application was received from the local ethics committee (2022/17-167) along with written informed consent acknowledgment from the patients.

Statistical Analysis

Those with normal distribution were expressed as mean ± standard deviation, and those without normal distribution were expressed as median (25%-75%). Mann-Whitney U and Student's t tests were used to compare continuous variables. Categorical variables were shown as numbers and percentages and analyzed with the chi-square test. Independent variables were determined to predict the presence of inferior MI by performing multiple regression analysis on the data, with only significant changes observed in the study. Statistical analysis was performed using IBM Statistical Package for Social Sciences (SPSS) program version 27.0 for Windows. A p-value of <0.05 was considered statistically significant.

Results

A total of 103 patients (68 male, mean age: 51±12) were involved in the study. They were divided into patients (n=50) and control groups (n=53). The basic characteristics of patients and healthy volunteers are displayed in Table 1. The mean age of the patients was higher than that of the healthy ones. Considering the laboratory characteristics of the patients, hemoglobin (Hb), albumin, and platelet (PLT) values were lower, and C-Reactive Protein (CRP), glucose, and low density lipoprotein (LDL) values were higher in the patient group.

The comparison of echocardiographic right ventricular functions between the groups is shown in Table 2. While Right VEF, TAPSE, and TAPSE/SPAP were lower in the patient group (p<0.05), the Pmax value measured over the tricuspid was higher in the patients (p<0.05). While right ventricular early diastolic flow rate (E) did not create a statistical difference between the groups (p>0.05), late diastolic flow rate (A) (p=0.015) and their ratio (E/A) (p=0.005) did show a statistical difference between the groups. Made a difference.

Table 1. *The relationship between demographic characteristics of the groups and laboratory parameters*

	Patients (n=50)	Control group (n=53)	p
Age, years	49±10	44±10	<0.001
Male n (%)	41 (82)	27(50.9)	<0.001
HT n (%)	38 (76)	0	<0.001
DM n (%)	16 (32)	0	<0.001
Cigarette n (%)	32 (64)	0	<0.001
Hg (g/L)	14.1±2.5	14.7±1.9	0.129
PLT (10^9/L)	258±76	292±72	0.025
CRP (mg/L)	20.1±5	4.2±4	0.011
Glucose (mg/dL)	138 ±69	90±16	<0.001
Creatinine (mg/dL)	0.9± 0.5	0.7±0.1	0.020
Albumin (g/L)	42±4	44±3.3	0.004
Uric Acid (mg/dL)	5.4±1.6	4.8±1.2	0.052
LDL (mg/dL)	140±53	120±33	0.023
HDL (mg/dL)	33±10	42±13	<0.001

HT: hypertension; DM: diabetes mellitus; Hb: hemoglobin; PLT: platelet; CRP: C-reactive protein; LDL: low density lipoprotein; HDL: high density lipoprotein.

Table 2. *Comparison of echocardiographic parameters of the groups*

	Patients (n=50)	Control group (n=53)	p
RVEF (%)	46±7	55±7	<0.001
LA mm	3.6±0.1	3.7 ±0.1	0.450
RA mm	3.7±0.2	3.6±0.2	0.540
Tricuspid E, cm/s	75.1±16.7	80.6±13.6	0.065
Tricuspid A, cm/s	75.2±23.4	65.2±12.1	0.015
Y/N	1.07±0.3	1.2 ±0.1	0.005
Pmax mmHG	27.7±12	18.5±1.8	0.009
Right ventricle free wall			
Sm,cm/s	12±3	17±5	<0.001
Em, cm/s	14±3	14±4	0.780
Am, cm/s	25±7	21±4	0.990
Em/Am	0.6±0.2	0.6±0.3	0.580
RightVDD, cm	3.7±0.4	3.6±0.3	0.450
RightVSD, cm	2.8±0.5	2.6±0.4	0.050
Right ventricular MPI	0.76±0.14	0.52±0.1	0.010
TAPSE cm	2.2±0.4	2.8±0.3	<0.001
TAPSE/SPAP	0.09±0.04	0.18±0.02	<0.001

RVEF: right ventricular ejection fraction; LA: left atrium; RA: right atrium; Tricuspid E: early diastolic velocity of tricuspid flow; Tricuspid A: late diastolic velocities of tricuspid flow; Sm: systolic wave; Em: early diastolic; Am: late diastolic; IVKZ: Isovolumetric contraction time; RVDD: right ventricular end-diastolic diameter; RVSD: Right ventricular end-systolic diameter; MPI: myocardial performance index; TAPSE: tricuspid annular plane systolic movements.

Table 3. *Effects of different variables on myocardial infarction in univariate and multivariate logistic regression analyses*

	Univariate			Multivariate		
	R.O.	95% CI	p	R.O.	95% CI	p
Age	1,131	(1.077-1.188)	<0.001	1,111	(1.033-1.194)	0.004
CRP	1,117	(1.023-1.218)	0.013	0.984	(0.899-1.077)	0.720
glucose	1,046	(1.022-1.070)	<0.001	1,048	(1.015-1.081)	0.004
Albumin	0.848	(0.754-0.954)	0.006	0.825	(0.623-1.090)	0.170
LDL	1,011	(1.001-1.021)	0.029	1,025	(0.994-1.056)	0.110
RVEF (%)	0.808	(0.691-0.944)	0.007	0.663	(0.384-1.145)	0.140
E/A	0.061	0.01-0.389	0.003	0.020	(0.01-1.795)	0.070
TAPSE	0.009	0.001-0.052	<0.001	0.011	(0.001-0.103)	<0.001
TAPSE/SPAP	1.12	(1.001-1.34)	<0.001	0.030	(0.01-0.059)	0.040

RR: risk ratio; CI: safe interval; CRP: C-reactive protein; LDL: low density lipoprotein; RVEF: right ventricular ejection fraction; E/A: right ventricular early diastolic flow rate/late diastolic flow rate, TAPSE: tricuspid annular plane systolic movements.

In the patient group, Sm was lower (p<0.05) and IVKT was higher (p=0.04). No significant difference was observed between Em, Am and Em/Am groups (p>0.05). Right ventricular MPI was observed to be higher in patients (p=0.01).

In single and multiple regression analysis, age (RR=1.111 95%, CI=1.033–1.194, p=0.004), glucose (RR=1.048 95%, CI=1.015–1.081, p=0.004), TAPSE (RR=0.011 95%), CI=0.001–0.103, <0.001), TAPSE/SPAP (RR=0.03 95%, CI=0.01–0.059, p=0.04) have been indicated to be independent risk factors for inferior myocardial infarction (Table– 3).

Discussion

In our study, significant statistical differences were observed in systolic and diastolic functions in transthoracic echocardiography performed in patients with inferior myocardial infarction compared to the control group.

A study has shown that TAPSE can be used to evaluate right ventricular systolic function[17]. In another study, it has been reported that TAPSE can be a physiological indicator of RV systolic function, as determined by M-mode echocardiography based on RVEF using the thermodilution method[18]. In another study, tricuspid annular motion (TAPSE and tricuspid annular Sm) has been observed to be strongly associated with radionuclide RVEF. It is a good indicator in distinguishing those with normal and impaired right ventricular functions[19]. Tricuspid annular motion is easy to use, reproducible, and inexpensive compared to the radionuclide technique. It has been shown that its sensitivity (80% and 80%, respectively) and specificity (75% and 85%, respectively) are recommended for clinical use[19]. In another study, TAPSE was associated with irritable bowel syndrome[20]. Our study also supports similar studies. Tricuspid annular plane systolic excursion was observed to be meaningfully lower than the control group. A study found that the Sm and Em peak rates from the RV free wall of patients with inferior myocardial infarction involving the RV were significantly lower than those without RV involvement and control patients. Additionally, the Em/Am ratio was similar[21]. In our study, the Sm peak rate was meaningfully lower than that of the control group. We observed that the Em/Am ratio was very low, the Em/Am ratio was similar to previous studies, and the Em peak velocity was not significantly different. In another study, they found that the tricuspid annulus Sm peak velocity, which indicates systolic function, measured in the first two days after the onset of symptoms, was lower in cases with RV involvement and inferior MI compared to those without right ventricular involvement. It has been reported that this decrease in the tricuspid annulus Sm peak velocity can be used in the diagnosis of MI with RV involvement[22]. In our study, it was shown that the tricuspid annulus Sm peak velocity of the patients in the inferior MI group was meaningfully lower than that of the control group.

In RV MI, right ventricular functions are impaired, although hemodynamic deterioration is not always present[23]. Myocardial performance index is a method that evaluates systolic and diastolic functions together[24]. It has been reported that right ventricular MPI increases in those with primary pulmonary hypertension, right

ventricular failure and Ebstein anomaly, and those who have had AMI[25]. In our study, MPI risen significantly in the patient group. In another study, it was reported that right ventricular MPI improved until the third month after acute MI and reached the values in healthy individuals at the end of the third month[26]. Although it has been reported that the right ventricular diastolic function, which was impaired on the first day of acute myocardial infarction, improved in the third month, it is not known when this improvement started and how it progressed[27].

Limitations of the study

The fact that the study was conducted in a single center and the number of patients was small may be considered a limitation. The fact that the patients were evaluated in a single visit may have relatively limited our study data.

Conclusion

As a result of this study, the use of advanced echocardiographic methods together with routine echocardiographic evaluation may provide more accurate information about RV functions in terms of directing STEMI treatment. A more intensive treatment can be performed using echocardiographic parameters on patients who come to the outpatient clinic for control.

Acknowledgements

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Impact of Clinical and Electrophysiological Features of Carpal Tunnel Syndrome on Sleep Disturbances

Karpal Tünel Sendromunda Klinik ve Elektrofizyolojik Bulguların Uyku Bozuklukları ile İlişkisi

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ABSTRACT

Aim: *This study investigates the relationship between clinical and electrophysiological severity of carpal tunnel syndrome (CTS) and sleep disturbances. While CTS is known to cause nocturnal symptoms, the extent to which these disturbances correlate with clinical and electrophysiological findings remains unclear.*

Material and Method: *This retrospective analysis was conducted on 48 patients with electrophysiologically confirmed CTS. Clinical severity was classified into five stages, and electrophysiological severity was determined through nerve conduction studies. Sleep disturbances were assessed using the Jenkins Sleep Scale (JSS). The Kruskal-Wallis and Mann-Whitney U tests were used to compare JSS scores across severity groups, while Spearman's correlation analysis evaluated associations between JSS scores and other parameters.*

Results: *JSS scores significantly correlated with clinical severity of CTS (Spearman's rho=0.46, p=0.001). Pairwise comparisons showed that patients with moderate (p=0.03) and severe (p=0.031) CTS symptoms had significantly higher JSS scores compared to those with very mild symptoms. However, no significant correlation was found between JSS scores and electrophysiological parameters (p >0.05).*

Conclusion: *Our findings indicate that sleep disturbances in CTS are more closely related to clinical symptom severity, particularly in patients with moderate to severe clinical findings. In contrast, electrophysiological parameters do not appear to correlate with sleep impairment, suggesting that central sensitization, pain perception, and nocturnal symptom fluctuations may play a more prominent role in sleep disturbances among CTS patients.*

Key words: *Carpal tunnel syndrome, electrophysiology, electromyography, sleep*

ÖZET

Amaç: *Bu çalışma, karpal tünel sendromu (KTS) olan hastalarda klinik ve elektrofizyolojik bulgular ile uyku bozuklukları arasındaki ilişkiyi incelemektedir. KTS'nin gece semptomlarına yol açtığı bilinmekle birlikte, bu bozuklukların klinik ve elektrofizyolojik bulgularla ne ölçüde ilişkilendiği netlik kazanmamıştır.*

Gereç ve Yöntem: *Elektrofizyolojik olarak tanısı KTS doğrulanmış olan 48 hasta üzerinde retrospektif bir analiz yapılmıştır. Semptomların şiddeti beş aşamada sınıflandırılmış ve elektrofizyolojik dereceleme sinir iletim çalışmaları ile belirlenmiştir. Uyku bozuklukları Jenkins Uyku Ölçeği (JSS) kullanılarak değerlendirilmiştir. Gruplar arasında JSS puanları Kruskal-Wallis ve Mann-Whitney U testleri ile karşılaştırılmış, klinik ve elektrofizyolojik bulgularla korelasyon Spearman analizi ile incelenmiştir.*

Bulgular: *JSS puanları, KTS'nin klinik şiddeti ile anlamlı bir korelasyon göstermiştir (Spearman's rho=0,46, p=0,001). Gruplar arası ikili karşılaştırmalar, orta (p=0,03) ve şiddetli (p=0,031) semptomları olan KTS'li hastaların, çok hafif semptomları olanlara kıyasla anlamlı şekilde daha yüksek JSS puanlarına sahip olduklarını göstermiştir. Ancak, JSS puanları ile elektrofizyolojik parametreler arasında anlamlı bir korelasyon bulunmamıştır (p >0,05).*

Sonuç: *Bulgularımız, KTS'deki uyku bozukluklarının daha çok klinik semptom şiddeti ile ilişkilendiğini ve özellikle orta ile şiddetli klinik bulguları olan hastalarda bu ilişkinin daha belirgin olduğunu göstermektedir. Elektrofizyolojik parametrelerin uyku bozukluğu ile ilişkili olmaması nedeniyle merkezi sensitizasyon, ağrı algısı ve gece semptomları dalgalanmalarının KTS hastalarında uyku bozukluklarında daha belirgin bir rol oynayabileceği düşünülmektedir.*

Anahtar kelimeler: *Karpal tünel sendromu, elektrofizyoloji, elektromiyografi, uyku*

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Introduction

Entrapment neuropathies are focal neuropathies that develop due to the compression of peripheral nerves by surrounding anatomical structures. Carpal tunnel syndrome (CTS) is a neuropathy resulting from the compression of the median nerve as it passes through the carpal tunnel at the wrist[1]. The estimated prevalence of CTS in the general population ranges from 1% to 5%[2]. Several risk factors have been identified, including systemic conditions such as diabetes mellitus, thyroid dysfunction, rheumatoid arthritis, pregnancy, obesity, repetitive wrist movements, occupational factors, and female sex[3].

The hallmark symptoms in CTS patients are paresthesia (numbness and tingling) and pain in the distribution of the median nerve, which typically worsen at night or are triggered by repetitive, strenuous hand movements. These symptoms are often relieved by shaking the hand or changing its position[1].

In patients with typical clinical findings, the diagnosis can be confirmed using electrophysiological methods. Electrophysiological examinations allow for the detection of sensory and motor conduction abnormalities in the median nerve, facilitating the classification of the disease into different severity stages[4,5]. Electrodiagnostic tests have been reported as the most definitive diagnostic tools for CTS across all disease stages, particularly in early diagnosis[1]. However, despite their diagnostic and classification value, electrophysiological findings do not always directly correlate with symptom severity[1,6].

Several studies have demonstrated a relationship between nocturnal symptoms caused by CTS and sleep disturbances[7–11]. This study aims to evaluate the relationship between electrophysiological findings and sleep disturbances by assessing sleep disturbances in CTS patients across different electrophysiological severity stages.

Methods

This retrospective study was conducted with the approval of the Clinical Research Ethics Committee of the University of Health Sciences, Adana City Training and Research Hospital (Registration number: 406/06.03.2025).

We reviewed the data of patients referred to our Clinical Neurophysiology Laboratory with an electrophysiologically confirmed diagnosis of carpal tunnel syndrome between April and December 2023. Age, gender, weight, height, body mass index (BMI), chronic diseases, symptom characteristics and duration (in months), neurological examination findings, and electrophysiological parameters are routinely recorded in the patient files of all individuals evaluated in our laboratory.

Patients aged over 18 with clinical and electrophysiological features consistent with CTS were included in this study. Clinically, patients were considered to have CTS if they exhibited at least one of the following[1]: 1) Paresthesia in the first three fingers; 2) Hypoesthesia in the first three fingers or weakness in hand muscles innervated by the median nerve on neurological examination.

The exclusion criteria were as follows: 1) Presence of diseases such as diabetes mellitus that may cause polyneuropathy; 2) Clinical, electrodiagnostic, or imaging findings suggestive of cervical radiculopathy or brachial plexopathy; 3) Presence of a neurodegenerative disease; 4) Coexisting mononeuropathy (e.g., ulnar or radial neuropathy); 5) History of upper extremity surgery for CTS or any other reason; 6) Pregnancy at the time of admission; 7) Presence of any additional rheumatologic or orthopedic disorders, or any cervical, shoulder, elbow, hand, or wrist problems; 8) A known sleep disorder, particularly obstructive sleep apnea; 9) A body mass index (BMI) above 40.

The clinical severity of CTS was classified as follows[12,13]: 1) Very mild: Nocturnal paresthesia in the first, second, or third fingers, 2) Mild: Diurnal paresthesia in the first, second, or third fingers, 3) Moderate: Sensory abnormalities in the first, second, or third fingers on neurological examination, 4) Severe: Weakness or atrophy in hand muscles innervated by the median nerve on neurological examination, 5) Very Severe: Plegia in hand muscles innervated by the median nerve on neurological examination.

Electrophysiological evaluations were conducted with the Cadwell Sierra Summit EMG unit (Cadwell Laboratories, Kennewick, Washington, USA) following previously suggested protocols and reference values for nerve conduction studies[14–17]. Nerve conduction studies were performed only if the extremity temperature was above 32°C. Surface electrodes were used for both stimulation and recording. The high- and low-pass filter settings were 20 Hz–10 kHz for motor nerve conduction studies and 20 Hz–2 kHz

for sensory nerve conduction studies. Peak-to-peak amplitudes of the compound muscle action potential (CMAP) and compound nerve action potential (CNAP) were recorded. Median and ulnar sensory nerve conduction studies were conducted using the antidromic technique. Median sensory nerve conduction velocity (NCV) was calculated based on peak latency. The electrophysiological classification of CTS was defined as follows[12,18]: 1) Mild CTS: Slowing of median sensory nerve conduction velocity (NCV) in the second finger-to-wrist segment (NCV <40.9 m/s); 2) Moderate CTS: In addition to mild CTS criteria, prolonged median nerve distal CMAP latency (CMAP latency >3.7 ms); 3) Severe CTS: Prolonged median nerve distal CMAP latency accompanied by an absent median nerve CNAP; 4) Very severe CTS: Absence of both median nerve CNAP and CMAP. For patients with bilateral CTS, analysis was conducted based on the side that is more clinically and electrophysiologically affected.

Sleep disturbances were assessed using the Jenkins Sleep Scale (JSS), a validated tool designed to determine the frequency and severity of sleep disturbances in various conditions[10,19,20]. JSS is a simple, self-reported, and time-efficient scale, making it useful for both clinical practice and research. Also, its validity and reliability have been demonstrated in Turkish[21]. Patients were asked four questions regarding their sleep problems over the past month and instructed to mark the most appropriate response. Responses were scored on a scale from 0 to 5 for each question. Higher scores indicate poorer sleep quality.

Statistical analysis was conducted using SPSS version 20 (IBM, Armonk, New York). Categorical variables were presented as frequencies and percentages, while numerical variables were expressed as mean ± standard deviation or median (minimum-maximum). The Shapiro-Wilk test was used to assess data distribution. As most variables were non-parametric, group comparisons were performed using the Mann-Whitney U and Kruskal-Wallis tests, while correlations were evaluated with Spearman's rank correlation test. A p-value <0.05 was considered statistically significant.

Results

A total of 48 patients (35 female, 13 male) were included in the study. Table 1 summarizes the demographic characteristics of the patients. The median duration of symptoms was 24 months (range: 2–240 months). Electrophysiological evaluations revealed bilateral CTS in 30 patients (62.5%), right-sided CTS in 12 patients (25%), and left-sided CTS in 6 patients (12.5%). Among those with bilateral CTS, all but two patients exhibited more severe clinical findings on the right side. Therefore, electrophysiological data from the right side were used for analysis in these patients.

Table 1. *The demographic characteristics of the patients*

Parameters	Mean ± standard deviation (median)
Age (years)	55.3±15.5 (59)
Sex (male/female)	13/35
Weight (kilograms)	72.1±11.6 (70)
Height (centimeters)	160.6±6.1 (160)
Body mass index	27.9±4.3 (27)
Symptom duration (months)	66±79.7 (24)
Side of carpal tunnel syndrome (right / left / bilateral)	12/6/30

Table 2. *Distribution of patients based on clinical severity and electrophysiological classifications*

Clinical severity grading	Number of patients
Very mild	15
Mild	24
Moderate	4
Severe	5
Very severe	-
Electrophysiological grading	**Number of patients**
Mild	11
Moderate	28
Severe	4
Very severe	5

Table 3. *Jenkins sleep scale scores of patients based on clinical and electrophysiological classifications*

Clinical severity grading	Jenkins sleep scale score median (min-max)
Very mild	7 (1–10)
Mild	9 (1–17)
Moderate	11.5 (9–14)
Severe	13 (5–16)
Very severe	-
Electrophysiological grading	**Jenkins sleep scale score median (min-max)**
Mild	3 (1–17)
Moderate	9 (1–14)
Severe	12 (1–16)
Very severe	7 (5–9)

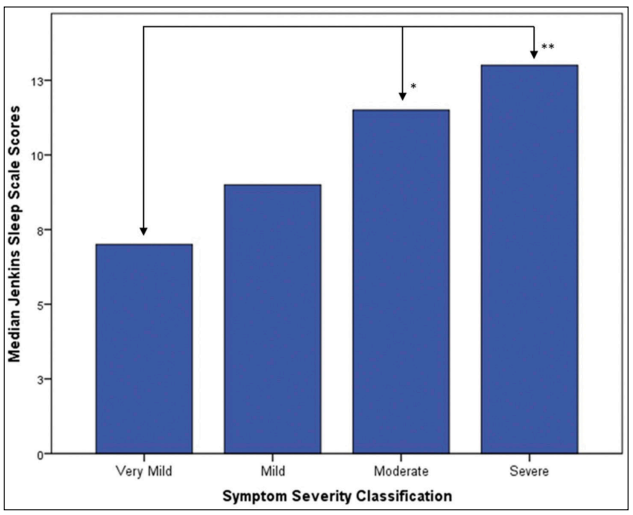

Figure 1. *Demonstration of median Jenkins Sleep Scale scores according to symptom severity classification. Significant differences between patients with mild symptoms and those with moderate (p=0.03) and severe symptoms (p=0.031) are indicated with asterisks (*).*

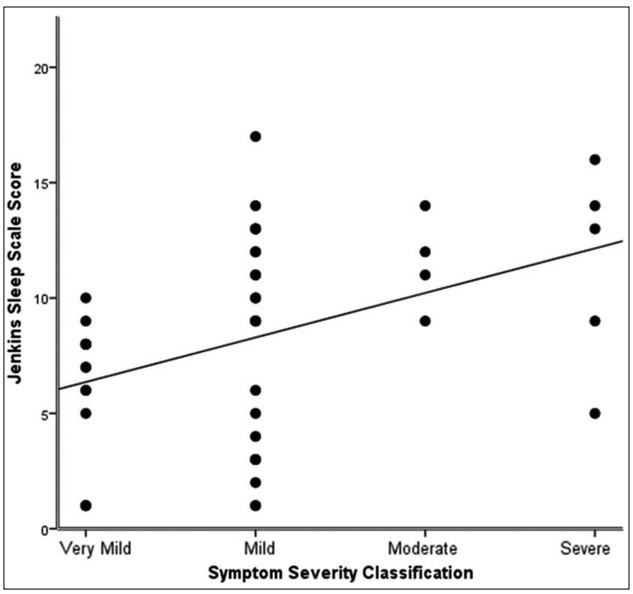

Figure 2. *Demonstration of positive correlation between clinical severity classification and Jenkins sleep scale scores (Spearman's rho=0.46, p=0.001).*

The distribution of patients according to symptom severity and electrophysiological classifications is summarized in Table 2. The median JSS score was 9 (range: 1–17), and Table 3 presents the median JSS scores of CTS patients based on clinical and electrophysiological classifications. The Kruskal-Wallis test revealed a significant difference in JSS scores among patients classified by symptom severity (p=0.017). Pairwise comparisons using the Mann-Whitney U test revealed a significant difference in JSS scores between CTS patients with very mild symptoms and those with moderate (p=0.03) or severe symptoms (p=0.031) (Fig. 1).

Spearman's analysis demonstrated a significant positive correlation between clinical severity classification and JSS scores (Spearman's rho = 0.46, p=0.001), while no correlation was observed with electrophysiological parameters. Fig. 2 illustrates the correlation between JSS scores and clinical severity classification.

Discussion

In this study, we investigated the impact of CTS on sleep using the Jenkins Sleep Scale (JSS). Our findings demonstrated a significant correlation between CTS symptoms and sleep disturbances. However, despite their diagnostic significance, electrophysiological parameters did not exhibit a significant association with sleep disturbances.

Previous studies have established that CTS can contribute to sleep disturbances due to nocturnal paresthesia and pain, which can frequently awaken patients and disrupt sleep continuity[7–10]. The relationship between symptom severity and sleep impairment observed in our study aligns with these findings. Patients with more severe clinical symptoms reported higher JSS scores, suggesting that subjective symptom burden plays a critical role in sleep quality deterioration. The significant difference in JSS scores between patients with very mild and moderate or severe symptoms further supports the impact of symptom intensity on sleep disturbances.

Differing from previous studies examining the relationship between carpal tunnel syndrome (CTS) and sleep disturbances, this study assessed sleep disturbances using the Jenkins Sleep Scale (JSS). Previously, Akcay et al. demonstrated that JSS scores correlated with symptom severity in patients with mild to moderate CTS[10]. In our study, JSS was evaluated across all CTS severity levels, and our findings confirmed the correlation between clinical symptom severity and JSS scores.

Electrophysiological classifications did not correlate with sleep disturbances in our cohort. This finding is consistent with previous studies reporting a weak or inconsistent relationship between electrophysiological severity and patient-reported symptoms[1,6]. One possible explanation is that electrophysiological measures primarily assess nerve conduction abnormalities, whereas symptom severity, particularly pain and nocturnal discomfort, may be influenced by central

sensitization, inflammatory responses, or individual pain perception mechanisms that are not directly reflected in nerve conduction studies[18,22]. Additionally, nocturnal symptoms, which are a primary cause of sleep disruption in CTS, may not be strictly dependent on the degree of median nerve conduction impairment but rather on factors such as increased intracarpal pressure fluctuations during sleep, impaired microcirculation, or altered pain processing pathways[23,24].

The findings of this study emphasize the need for a multidimensional approach to CTS evaluation. While electrophysiological assessments remain the gold standard for diagnosis and staging, they may not fully capture the functional impact of CTS on patients' quality of life, particularly regarding sleep disturbances. The incorporation of patient-reported outcome measures, such as JSS or other sleep assessment tools, into routine clinical evaluations may provide a more comprehensive understanding of disease burden and help guide symptom-focused management strategies.

This study has several limitations. First, the retrospective design may introduce selection bias, and the relatively small sample size may limit the generalizability of the findings. Second, sleep disturbances were assessed using the JSS, a subjective self-reported scale. Future studies incorporating objective sleep assessments, such as polysomnography or actigraphy, could provide more definitive insights into the nature of sleep disturbances in CTS. Lastly, additional factors influencing sleep quality, such as anxiety, depression, or medication use, were not systematically evaluated in this study. Addressing these variables in future research may help further elucidate the mechanisms underlying sleep impairment in CTS.

Conclusion

Our study highlights the significant association between CTS symptom severity and sleep disturbances, while electrophysiological findings did not correlate with sleep impairment. These results suggest that patient-reported symptoms play a crucial role in sleep quality, underscoring the importance of incorporating subjective assessment tools in CTS management.

Conflict of Interest

The authors declared no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Prognostic Role of Blood Parameters in Subarachnoid Hemorrhage: A Retrospective Study

Subaraknoid Kanamada Kan Parametrelerinin Prognozu Belirleyici Rolü: Retrospektif Bir Çalışma

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ABSTRACT

Aim: *Subarachnoid hemorrhage (SAH) occurs when cerebral arteries rupture and bleed into the subarachnoid space. It occurs in approximately 2–22 per 10 000 people per year and is fatal. Abnormalities in hemogram and biochemical parameters are poor prognosis criteria in patients with SAH, and our study aimed to determine the importance of blood parameters in predicting 30-day mortality in patients diagnosed with SAH.*

Method: *The data of patients admitted to the emergency department of our hospital between January 2024 and January 2025 with a diagnosis of SAH and admitted to our hospital were retrospectively analyzed. The importance of 30-day mortality and the prediction of prognosis using blood parameters was determined.*

Results: *A total of 62 patient data were obtained, and 51 patients who met the inclusion and exclusion criteria were included in our study. The mean age of our patients was 59 years (19(37.3%) female and 32 (62.7%) male). Five of our patients (9.8%) were deceased. The correlation between parametric blood parameters (Hb; Htc; Plt; MCV; Neu%; PCO_2) and mortality was (0.09; 0.068; 0.154, 0.548, 0.632, 0.953), respectively.*

The relationship between nonparametrically distributed blood parameters (age; WBC; Ure; Kre; Ast; Alt; Glu; Alb) and mortality is (0.692; 0.486; 0.8; 0.849; 0.739; 0.739; 0.669; 0.447; 0.215), respectively.

Conclusion: *We think that different results may be obtained after classifying SAH patients as traumatic, nontraumatic, adult, pediatric and geriatric rather than as a single group and evaluating inflammatory markers accordingly.*

Key words: *subarachnoid hemorrhage; blood parameters; emergency medicine; prognostic role*

ÖZET

Amaç: *Subaraknoid kanama (SAK), serebral arterlerdeki rüptür sonucu subaraknoid boşluğa kanama ile oluşur. Yılda yaklaşık 10000 kişide 2–22 oranında görülür ve ölümcüldür. Subaraknoid kanama hastalarında hemogram ve biyokimyasal parametrelerdeki anormallikler kötü prognoz kriterleri olup çalışmamızın amacı SAK tanısı alan hastalarda kan parametrelerinin 30 günlük mortalite tahminindeki önemini belirlemektir.*

Yöntem: *Hastanemiz acil servisine Ocak 2024 – Ocak 2025 tarihleri arasında SAK tanısıyla başvuran ve hastanemize yatışı yapılan hastaların verileri retrospektif olarak incelenmiştir. Otuz günlük mortalite ve prognoz tahmininde kan parametrelerinin önemi belirlenmek istenmiştir.*

Bulgular: *Toplamda 62 hasta datasına ulaşılmış olup dâhil etme ve dışlama kriterlerini sağlayan 51 hasta verileri ile çalışmamız yapılmıştır. Hastalarımızın yaş ortalaması 59 (hastaların 19 (%37,3) kadın cinsiyet, 32(%62,7) erkek cinsiyet idi. Hastalarımızın 5 tanesi (%9,8) vefat etti. Parametrik dağılım gösteren kan parametreleri (Hb; Htc; Plt; MCV; Neu%; PCO_2) ile mortalite arasındaki ileşiki sırasıyla (0,09; 0,068; 0,154, 0,548, 0,632, 0,953) şeklidedir.*

Nonparametrik dağılım gösteren kan parametreleri (yaş; WBC; Ure; Kre; Ast; Alt; Glu; Alb) ile mortalite arasındaki ilişki sırasıyla (0,692; 0,486; 0,8; 0,849; 0,739; 0,669; 0,447; 0,215) şeklindedir

Sonuç: *Subaraknoid kanama hastalarını tek bir grup olarak değil de travmatik, nontravmatik; erişkin, pediatrik ve geriatrik olarak sınıflandırıp enflamatuvar belirteçlerin ona göre değerlendirilmesi sonrası daha farklı sonuçlar çıkabileceğini düşünmekteyiz.*

Anahtar kelimeler: *subaracnoid kanama; kan parametereleri; acil servis; prognostik rol*

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Introduction

Subarachnoid hemorrhage (SAH) is a devastating condition with an incidence of 2–22 per 10.000 people per year. Early detection is important due to a high mortality rate of 10–25% and a 30% rate of permanent sequelae as a result of poor and delayed treatment. Rupture of the cerebral arteries results in hemorrhage into the subarachnoid space, which can cause damage and even death by compressing the brain tissue. The accumulation of blood in the subarachnoid space stimulates local and systemic inflammatory processes. Acute damage to the brain causes the release of proinflammatory cytokines, and the stress reaction increases the level of catecholamines, which also promote immune activation. Therefore, elevation of inflammatory markers in blood and cerebrospinal fluid is observed both early and late in SAH[1]. Since SAH causes an inflammatory response, many researchers have analyzed the effect of elevated inflammatory markers on mortality and morbidity[2,3]. There are also studies on the effect of elevated leukocyte count on the prediction of mortality and morbidity after SAH[1,4]. Our study aimed to determine the importance of blood parameters in predicting 30-day mortality in patients diagnosed with SAH.

Material and Methods

Ethical Approval and Study Design

The study was initiated after the approval of the non-interventional ethics committee of Malatya Turgut Ozal University Faculty of Medicine, dated 13.03.2025, and numbered 2025000042-4. The data of patients admitted to the emergency department of hospital between January 2024 and January 2025 with the diagnosis of SAH and hospitalized in our hospital were retrospectively analyzed. 30-day mortality and prognosis prediction of blood parameters [Leukocyte 10%/uL (WBC), hemoglobin g/dL (Hb), hematocrit % (Htc), platelet 10%uL (Plt), mean erythrocyte volume fL (MCV), neutrophil percentage (%Neu); urea mg/dL, creatinine mg/dL (Cre), aspartate aminotransferase U/L (AST), alanine aminotransferase U/L (ALT), albumin g/dL (alb), glucose mg/dL (Glu), sodium mmol/L (Na), potassium mmol/L (K), chlorine mmol/L (Cl), calcium mg/dL (Ca), PCO_2 mmHg, PO_2 mmHg, lactate, pH, carboxyhemoglobin % (FCoHb)]. Biochemical markers were measured in the About Device in the biochemistry laboratory of our hospital using urea, creatinine, AST, ALT, alb, glo, Na, K, Cl and Ca kits. Hemogram parameters were measured using Cell pack DST, DCL, WNR, WDF and SLS Lysercell kits on the SYSMEX XN-1000 h device in the biochemistry laboratory of our hospital.

Inclusion Criteria

Patients diagnosed with SAH. Patients who presented to the emergency department with any complaint and were admitted to the hospital and diagnosed with SAH without any additional disease. Patients admitted to the hospital between January 2024 and January 2025 had their complete data retrospectively obtained from the hospital information system.

Exclusion Criteria

Patients whose data cannot be fully accessed in the hospital data system. All patients on anticoagulant and coagulant therapy. Patients who were transferred from the emergency department to other hospitals or left the hospital voluntarily by refusing hospitalization

Statistical Analysis

While evaluating the findings obtained in the study, IBM Statistical Package for Social Sciences (SPSS) program version 27 was used for statistical analysis. The conformity of the parameters to normal distribution was evaluated with the Kolmogorov-Smirnov test. Descriptive statistical methods were used to evaluate the study data: mean, median, standard deviation, percentage (25–75% (Inter Quantile Range-IQR) and frequency. When comparing quantitative data, the Student's t-test was used for normally distributed parameters between two groups, and the Mann-Whitney U test was used for non-normally distributed parameters between two groups. $p<0.05$ was considered statistically significant. Our study was planned retrospectively, and all patients who met the inclusion and exclusion criteria were included.

Results

In total, data from 62 patients were obtained, and our study was conducted with the data of 51 patients who met the inclusion and exclusion criteria. The mean age of our patients was 59 [19 (37.3%) were female and 32 (62.7%) were male]. Five of our patients (9.8%) were deceased. Parametric blood parameters of the patients are given as mean and SD, shown in Table 1.

Table 1. *Blood parameters with parametric distribution in patients with SAH*

	n	mean	± SD
Hb (g/dL)	51	13.5	1.7
Htc (%)	51	39.7	4.9
Plt (103/uL)	51	256.8	94.9
Mcv (fL)	51	86.4	6.5
Neu (%)	51	64.1	19.6
PCO_2 (mmHg)	51	38.1	10.5

Table 2. *Blood with a nonparametric distribution in patients with SAH*

			IQR	
	n	median	25%	75%
WBC (103/uL)	51	13.4	9.4	16
Urea (mg/dL)	51	37.1	27.1	45.3
Creatinine (mg/dL)	51	0.9	0.72	1
AST (U/L)	51	34	26	51
ALT (U/L)	51	24	19	31
Glucose (mg/dL)	51	156	131	201
FcoHb (g/dL)	51	1.2	0.8	2
Lactate (mmol/L)	51	2.8	1.6	3.9
PO_2 (mmHg)	51	43.4	32.8	40.4
Ph	51	7.36	7.32	7.41
Ca (mg/dL)	51	9	8.6	9.4
Cl (mmol/L)	51	111	107	115
Na (mmol/L)	51	139	136	140
Albumin (g/dL)	51	4	3.7	4.1

Table 3. *Relationship between mortality and parametric blood values*

	Mortality rate	n	P
Hgb (g/dL)	Discharged	46	0.095
	Exitus	5	
Htc (%)	Discharged	46	0.068
	Exitus	5	
Plt (103/uL)	Discharged	46	0.154
	Exitus	5	
Mcv (fL)	Discharged	46	0.548
	Exitus	5	
Neu (%)	Discharged	46	0.632
	Exitus	5	
PCO_2 (mmHg)	Discharged	46	0.953
	Exitus	5	

Table 4. *Association between nonparametrically distributed blood values and mortality*

	Mortality	n	p
Age (year)	Discharged	46	0.692
	Exitus	5	
WBC (103/uL)	Discharged	46	0.486
	Exitus	5	
Urea (mg/dL)	Discharged	46	0.8
	Exitus	5	
Creatinine (mg/dL)	Discharged	46	0.849
	Exitus	5	
AST (U/L)	Discharged	46	0.739
	Exitus	5	
ALT (U/L)	Discharged	46	0.669
	Exitus	5	
Glucose (mg/dL)	Discharged	46	0.447
	Exitus	5	
Albumin (g/dL)	Discharged	46	0.214
	Exitus	5	
Na (mmol/L)	Discharged	46	0.425
	Exitus	5	
K (mmol/L)	Discharged	46	0.776
	Exitus	5	
Ca (mg/dL)	Discharged	46	0.799
	Exitus	5	
Cl (mmol/L)	Discharged	46	0.132
	Exitus	5	
ph	Discharged	46	0.267
	Exitus	5	
PO_2 (mmHg)	Discharged	46	0.872
	Exitus	5	
Lactate (mmol/L)	Discharged	46	0.912
	Exitus	5	
FcoHb (g/dL)	Discharged	46	0.173
	Exitus	5	

SAH: subarachnoid hemorrhage; n: sample size; mean: average; SD: standard deviation; median: median value; IQR: interquartile range; Hb (Hgb): hemoglobin; Htc: hematocrit; Plt: platelets; MCV: mean corpuscular volume; Neu: neutrophils; WBC: white blood cells; AST: aspartate aminotransferase; ALT: alanine aminotransferase; FCOHb: carboxyhemoglobin fraction; Na: sodium; K: potassium; Ca: calcium; Cl: chloride; PCO_2:partial pressure of carbon dioxide; PO_2: partial pressure of oxygen; pH: hydrogen ion concentration; P (p): p-value.

The nonparametric blood parameters of the patients are given as median and interquartile range in Table 2.

The relationship between parametrically distributed blood parameters (Hb: 0.09; Htc: 0.068; Plt:

0.154; MCV: 0.548; Neu%: 0.632; PCO_2:0.953) and mortality is given in Table 3.

Age: 0.692; WBC: 0.486; Ure: 0.8; Kre: 0.849; AST: 0.739; ALT: 0.669; Glu: 0.447; Alb: 0.215, and the relationship between nonparametrically distributed blood values and mortality is given in Table 4. On the other hand, there was no significant correlation between the lymphocyte/albumin ratio and mortality ($p<0.480$).

Discussion

Subarachnoid hemorrhage is a ruptured cerebral artery that causes bleeding into the subarachnoid space. This bleeding can put pressure on brain tissue, causing damage and even death. The accumulation of blood in the subarachnoid space stimulates local and systemic inflammatory processes. Acute damage to the brain causes the release of proinflammatory cytokines, and the stress reaction increases the level of catecholamines, which also promote immune activation. Therefore, elevated levels of inflammatory markers in the blood and cerebrospinal fluid are observed both early and late in SAH[1].

In our study, we investigated the predictive power of early inflammatory markers for mortality in patients admitted to the emergency department with traumatic and non-traumatic SAH without comorbidities. Diagnosis of myocardial infarction in emergency departments by checking cardiac marker levels in the blood is a convenience for both patients and clinicians[5]. Again, markers such as amylase and lipase in acute pancreatitis and creatinine in renal failure are important in the diagnosis[6,7]. However, a blood marker that can diagnose SAH or be used as an early warning has not yet been used in routine practice. Several biomarkers, such as S100B protein and neuron-specific enolase (NSE), have been proposed for clinical application in studies on this subject[8].

Previous studies have shown that high serum glucose levels increase vasospasm and negatively affect the prognosis in SAH[9,10]. Although the mean glucose level (156 mg/dL) was high in our study, no statistically significant result was obtained (p=0.447). The multiplicity of factors affecting the increased glucose level due to stress factors, along with the rapid initiation of blood glucose regulation in the emergency department, may change the blood glucose results after blood sampling. This is due to high fingerstick blood glucose levels before blood sampling.

In another study, elevated serum leukocyte levels were thought to be a prognostic marker in cases of SAH[11]. In our study, although the mean leukocyte count (13.4×103 u/L) was high, its relation with mortality was not statistically significant. With this result in our study, we think that the elevated leukocyte level in the first blood drawn in the emergency department affects the treatment process of SAH patients. We believe that administering anti-inflammatory agents after hospitalization to reduce inflammation in patients with elevated leukocyte counts has a positive effect on mortality.

Another study provides preliminary evidence that high albumin levels in blood tests performed within the first 72 hours after diagnosis may be associated with a favorable outcome in patients with SAH[12]. In our study, we did not find a significant correlation between albumin levels and mortality. We think that a significant correlation may be found by re-evaluating the albumin levels in the first six hours after the onset of symptoms in patients admitted to the emergency department.

Studies have shown that blood electrolyte disturbances are associated with mortality in SAH. In another study, blood inflammatory parameters were found to be a predictor of poor prognosis in SAH. Other studies have shown that blood parameters such as urea, cre, AST, and ALT elevation are associated with poor prognosis[13–18]. In our study, we analyzed the WBC, Hb, Htc, PIt, MCV, urea, creatinine, AST, ALT, Na, K, Cl, and Ca values of early inflammatory markers examined in the first 6 hours in SAH patients individually. However, we could not reach a result in these parameters that we think may have a determinant effect on prognosis or mortality in patients with SAH. Following up on some of these inflammatory markers, not in the early period but in the following days, may yield meaningful results once the clinic is fully established. The role of blood parameters in predicting the prognosis of subarachnoid hemorrhage is limited[19–20].

Conclusion

We think that different results may be obtained by classifying SAH patients as traumatic, nontraumatic, adult, pediatric and geriatric rather than as a single group and evaluating inflammatory markers accordingly. The number of patients in our study was not sufficient to classify SAH patients as traumatic, nontraumatic, adult, pediatric and geriatric. Studies with a larger sample size are needed for this purpose.

Limitations

We believe that the absence of a significant marker for determining prognosis in our study's findings is due to certain limitations. The first of these is the small number of patients in the sample. Another limitation is that the study was conducted in a single center. The absence of a study on certain parameters prevented us from making comparisons with our own study.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Management Strategies for Synchronous Primary Lung Tumors: A Retrospective Two-Centre Study

Senkron Primer Akciğer Tümörlerinde Tedavi Stratejileri: Retrospektif İki Merkezli Çalışma

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ABSTRACT

Aim: *Synchronous primary lung tumors are uncommon and diverse clinical entities. Distinguishing them from intrapulmonary metastases is essential for accurate staging, prognosis evaluation, and selecting the right treatment. This study seeks to describe the clinical, radiological, and histopathological features of synchronous primary lung tumors and to aid in the diagnostic and treatment decision-making process.*

Material and Methods: *Between January 2023 and January 2025, patients diagnosed with synchronous primary lung tumors and evaluated at two tertiary centers were retrospectively analyzed. Clinical, radiological, and histopathological data were reviewed, including smoking history, occupational or environmental exposures, and TNM staging. Treatment strategies and follow-up outcomes were recorded.*

Results: *Out of 250 patients undergoing diagnostic or therapeutic interventions for lung cancer during the study period, four patients (1.6%) met the criteria for synchronous primary lung tumors. Detailed case-based analyses highlighted the heterogeneity in histologic subtypes, anatomical locations, and treatment approaches.*

Conclusion: *Synchronous primary lung tumors are rare but clinically significant. Comprehensive clinical evaluation, detailed histopathologic assessment, and individualized management strategies are essential to optimize outcomes.*

Key words: *synchronous lung tumors; multiple primary lung cancers; surgical management; personalized therapy; thoracic oncology*

ÖZET

Amaç: *Senkron primer akciğer tümörleri, nadir görülen ve heterojen özellikler gösteren bir klinik tablodur. Bu tümörlerin intrapulmoner metastazlardan ayırt edilmesi, doğru evreleme, prognozun öngörülmesi ve uygun tedavi stratejisinin belirlenmesi açısından kritik öneme sahiptir. Bu çalışma, senkron primer akciğer tümörlerinin klinik, radyolojik ve histopatolojik özelliklerini sunarak tanı ve tedavi sürecine katkı sağlamayı amaçlamaktadır.*

Gereç ve Yöntem: *Ocak 2023 ile Ocak 2025 tarihleri arasında senkron primer akciğer tümörü tanısı alan ve iki üçüncü basamak merkezde değerlendirilen hastalar retrospektif olarak analiz edildi. Klinik, radyolojik ve histopatolojik veriler; sigara öyküsü, mesleki veya çevresel maruziyetler ve TNM evrelemesi dâhil edilerek incelendi. Uygulanan tedavi stratejileri ve takip sonuçları kaydedildi.*

Bulgular: *Çalışma döneminde akciğer kanseri nedeniyle tanısal veya terapötik girişim uygulanan 250 hastadan dört hasta (%1,6) senkron primer akciğer tümörü kriterlerini karşıladı. Olgu bazlı ayrıntılı analizler; histolojik alt tipler, anatomik lokalizasyonlar ve tedavi yaklaşımlarındaki heterojenliği ortaya koydu.*

Sonuç: *Senkron primer akciğer tümörleri nadir ancak klinik açıdan önemli bir durumdur. Optimal sonuçlar için kapsamlı klinik değerlendirme, ayrıntılı histopatolojik inceleme ve bireyselleştirilmiş tedavi stratejileri esastır.*

Anahtar kelimeler: *senkron akciğer tümörleri; çoklu primer akciğer kanserleri; cerrahi tedavi; kişiselleştirilmiş tedavi; torasik onkoloji*

Introduction

Synchronous lung tumors represent a rare and heterogeneous group of neoplasms that present significant diagnostic and therapeutic challenges. Accurate differentiation between multiple primary lung cancers (MPLCs) and intrapulmonary metastases is essential, as it directly influences staging, prognosis, and the overall treatment strategy[1–3]. This distinction can be complicated due to overlapping radiologic and histopathologic features, necessitating a multidisciplinary approach that integrates clinical findings, histology, and increasingly, molecular profiling. Current guidelines emphasize individualized management plans, often involving combinations of surgical resection,

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systemic chemotherapy, immunotherapy, and targeted therapies guided by tumor histopathology and genetic alterations[4,5].

In this study, we present four illustrative cases of synchronous lung tumors, each highlighting the variability in clinical presentation, histologic patterns, and therapeutic decision-making, with a focus on practical considerations in real-world thoracic oncology practice.

Material and Methods

Between January 2023 and January 2025, patients who underwent diagnostic or therapeutic interventions for a preliminary diagnosis of lung cancer at two tertiary centers were retrospectively reviewed.

Inclusion Criteria

Only patients diagnosed with synchronous primary lung tumors, defined according to Martini–Melamed criteria and subsequent modifications, were included. The diagnosis required distinct histological types or, in cases of similar histology, anatomical separation without evidence of systemic or lymphatic spread.

Data Collection

For each patient, the following variables were systematically analyzed:

- Demographics: age, sex
- Smoking history (expressed in pack-years)
- Occupational and environmental exposure history, including asbestos or uranium (if available)
- Radiological and bronchoscopic findings
- Histopathology of all lesions
- Tumor size, TNM staging, and nodal involvement

Treatment and Follow-up

Therapeutic strategies, including surgical interventions, adjuvant or definitive chemoradiotherapy, and perioperative management, were recorded. Postoperative outcomes, recurrence, and survival were assessed based on follow-up visits. For cases with missing data, the lack of information was attributed to incomplete patient records.

Results

A total of 250 patients who underwent diagnostic or therapeutic interventions for suspected lung cancer between January 2023 and January 2025 were retrospectively reviewed. Among them, four patients (1.6%) fulfilled the criteria for synchronous primary lung tumors. Detailed clinical, radiological, and histopathological characteristics, as well as treatment and follow-up data, are summarized below.

The first patient was a 71-year-old male with a 65 pack-year smoking history and chronic obstructive pulmonary disease (COPD). There was no recorded occupational or environmental carcinogen exposure. Imaging revealed a spiculated mass in the left lower lobe and an irregular lesion with satellite nodules in the right upper lobe (Fig. 1). PET-CT demonstrated high FDG uptake in the left lesion and mild uptake in the right. Histopathological examination confirmed squamous cell carcinoma in the left lower lobe (T2bN0M0) and adenocarcinoma in the right upper lobe (T1cN0M0). A left lower lobectomy with mediastinal lymph node dissection was performed, followed by wedge resection of the right upper lobe lesion. The postoperative course was uneventful, and no adjuvant therapy was required. At 14 months of follow-up, no recurrence was observed.

The second patient was a 68-year-old male with a 40-pack-year smoking history and a past occupational history in construction, where asbestos exposure was likely but not definitively documented. Thoracic CT revealed a centrally located mass in the left upper lobe causing partial atelectasis and minimal pleural effusion (Fig. 2), and bronchoscopy incidentally identified an endobronchial lesion in the right upper lobe. Pathology confirmed adenocarcinoma in the left upper lobe (T3N2M0) and squamous carcinoma in situ (Tis) in the right upper lobe. The right-sided lesion was excised bronchoscopically, while the left-sided tumor was treated with definitive concurrent chemoradiotherapy due to limited pulmonary reserve. The patient remained clinically stable with no evidence of progression at the 12-month follow-up.

The third patient was a 64-year-old female, a nonsmoker with no known occupational or environmental exposure. A right upper lobe mass and an additional endobronchial lesion in the right lower lobe bronchus were detected radiologically (Fig. 3). Histopathology revealed adenocarcinoma in the

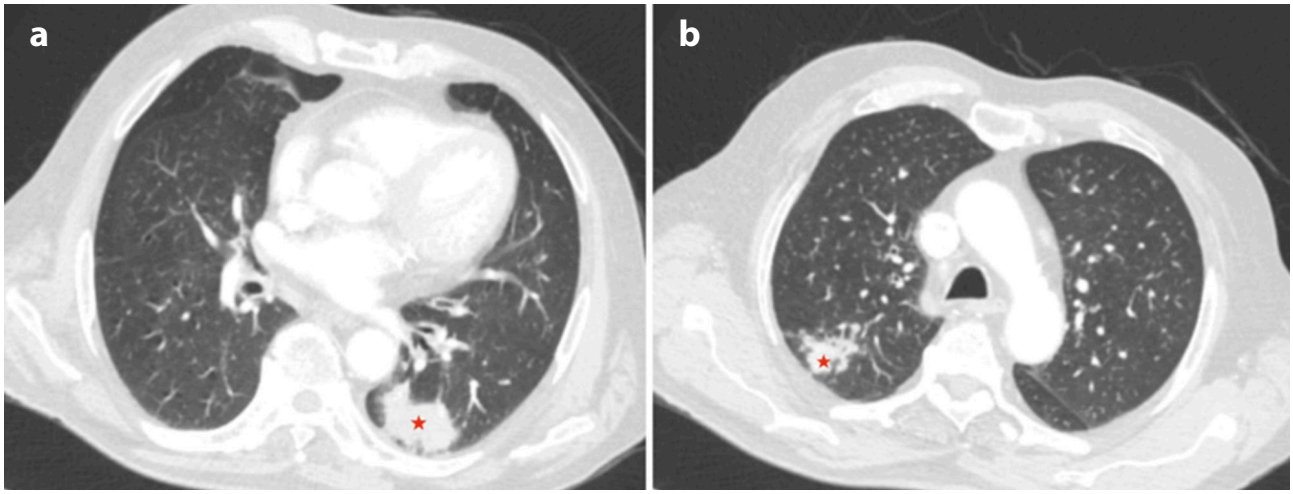

Figure 1. *Synchronous tumors located in the right upper lobe and left lower lobe are marked with arrows on thoracic CT images*

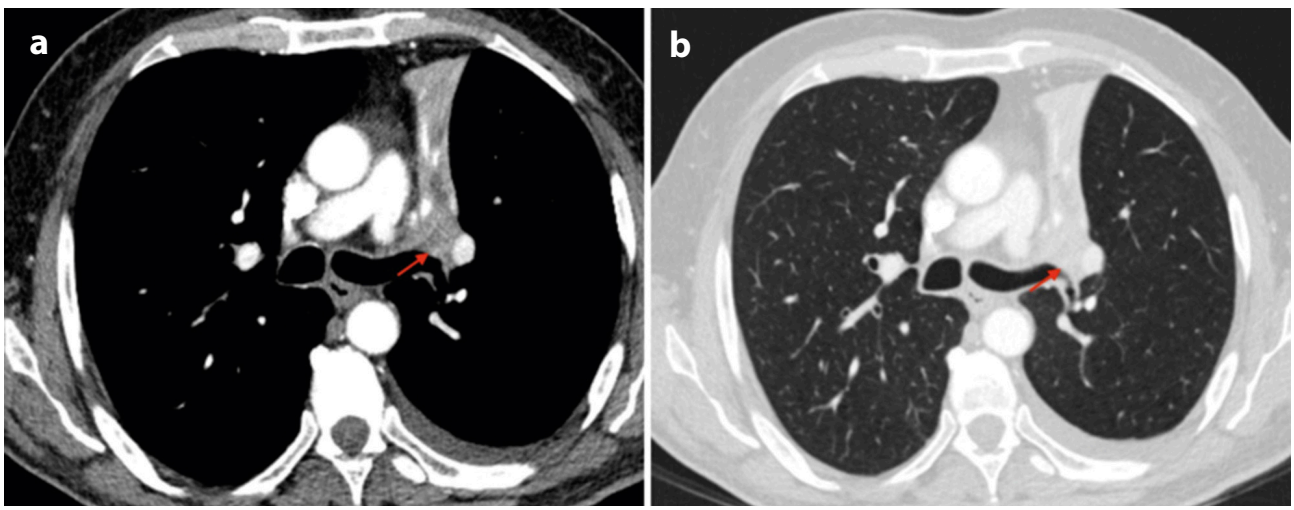

Figure 2. *Thoracic CT images showing a centrally located tumor in the left lung causing complete atelectasis of the upper lobe. The arrow indicates the centrally located mass.*

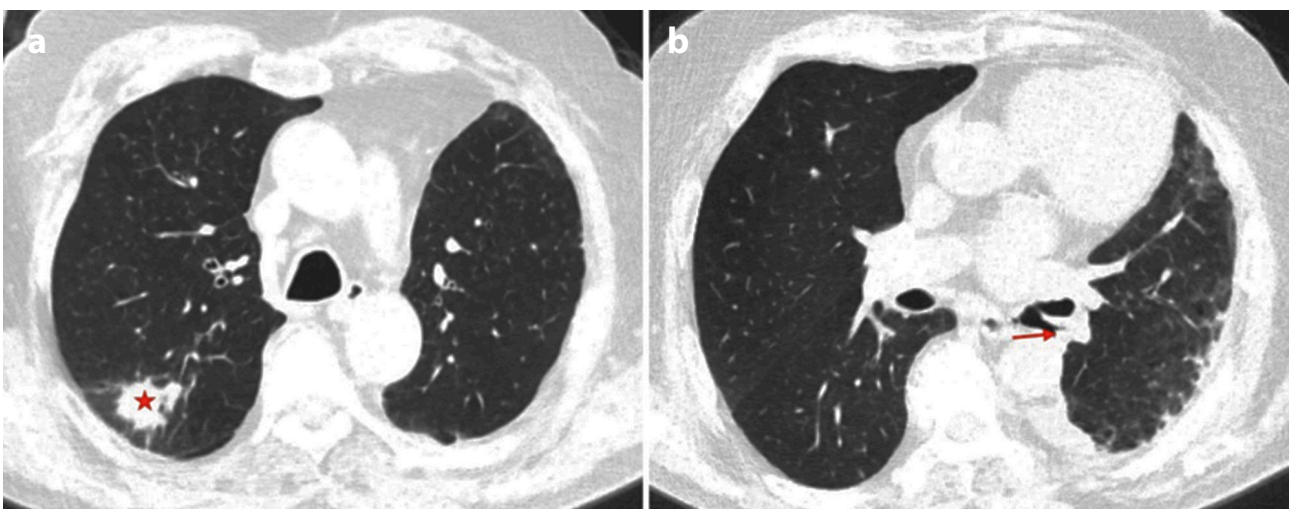

Figure 3. *Thoracic CT sections demonstrating synchronous tumors located in the periphery of the right upper lobe (asterisk) and within the left lower lobe bronchus (arrow).*

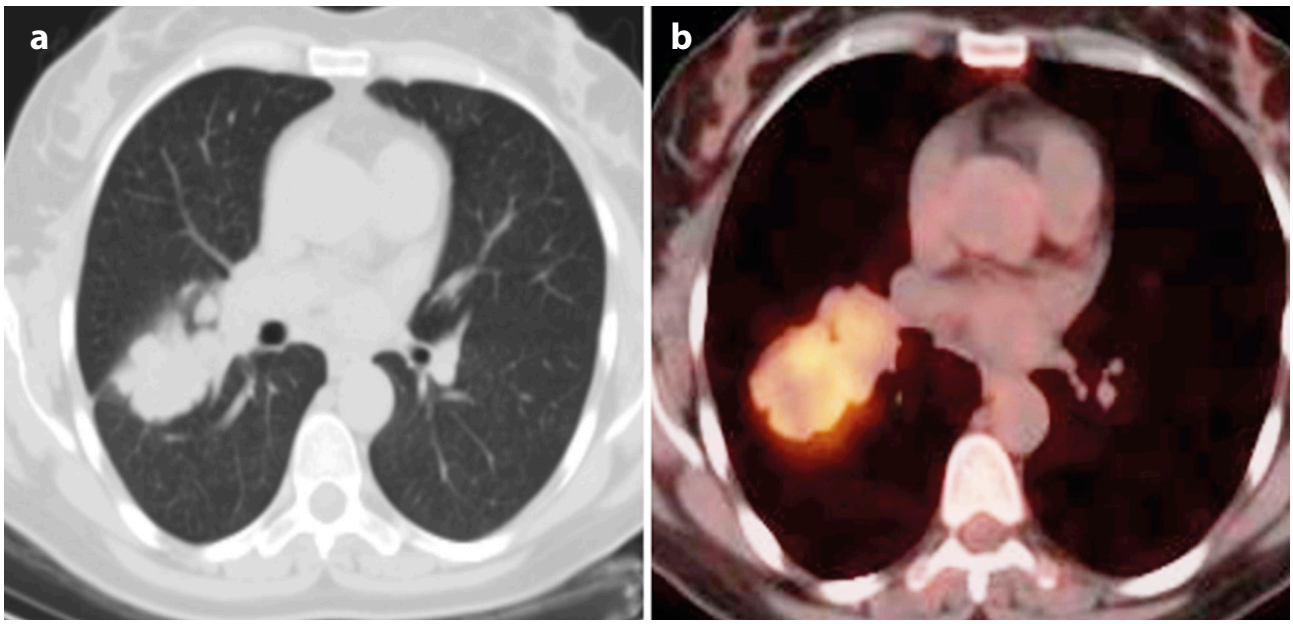

Figure 4. a, b. *Axial thoracic CT scan showing a cavitary mass lesion in the right lower lobe* ***(a)****. PET-CT scan demonstrating increased FDG uptake in the right lower lobe mass, consistent with malignancy* ***(b)****.*

right upper lobe (T2aN0M0) and squamous carcinoma in situ (Tis) in the right lower lobe bronchus. The patient underwent right upper lobectomy; additional surgical intervention was not deemed necessary. No adjuvant therapy was administered, and the patient remained recurrence-free after 10 months of follow-up.

The fourth patient was a 73-year-old female with a 55 pack-year smoking history and a past occupational history in agriculture, without documented asbestos exposure. Radiologic evaluation revealed a mass lesion in the right lower lobe and bronchiectatic changes in the adjacent right middle lobe (Fig. 4). Due to the proximity of the lower lobe mass to the middle lobe and the presence of bronchiectatic changes, a VATS right lower and middle bilobectomy was performed. Histopathological examination confirmed squamous cell carcinoma in the right lower lobe (T2bN0M0), while adenocarcinoma in situ was incidentally detected in the bronchiectatic middle lobe. Postoperative recovery was uneventful, and the patient remained disease-free at the six-month follow-up.

These four cases demonstrate the heterogeneity of synchronous primary lung tumors in terms of histologic subtypes, anatomical distribution, and treatment strategies, emphasizing the importance of a multidisciplinary and individualized approach.

Discussion

The management of synchronous primary lung tumors remains a clinical challenge, mainly due to the lack of standardized diagnostic criteria and treatment algorithms. Although the Martini-Melamed criteria and subsequent refinements have provided some guidance in differentiating MPLCs from intrapulmonary metastases, overlap in radiological, histopathological, and even molecular features continues to pose significant diagnostic uncertainty[6,7]. This distinction is crucial, as it directly influences staging, prognosis, and therapeutic decision-making.

In our series, except for the case of carcinoma in situ, all patients presented with combined histological subtypes, most commonly adenocarcinoma and squamous cell carcinoma, supporting the likelihood of distinct primary origins. Surgical intervention was feasible in three of the four cases, whereas one patient required definitive concurrent chemoradiotherapy due to poor pulmonary reserve. The incidence of synchronous primary lung tumors in our cohort was 1.6% (4/250 patients), which is consistent with the reported range of 0.5–2% in the literature. Early postoperative outcomes were favorable, with no recurrence observed during a median follow-up of 10.5 months. These findings emphasize the importance of individualized, multidisciplinary decision-making to achieve satisfactory oncological outcomes in this rare but clinically significant entity.

Surgical resection is generally considered the mainstay of treatment for patients with synchronous lung tumors when anatomically and functionally feasible. However, the extent of resection remains a topic of ongoing debate[1,4,8]. In cases where tumors are localized and resectable, lobectomy or even pneumonectomy may be required to achieve oncologic control. Yet, in select patients –particularly those with limited cardiopulmonary reserve or multifocal disease– sublobar resection (e.g., segmentectomy or wedge resection) may offer an acceptable compromise between oncologic efficacy and preservation of lung function. Several studies have suggested that sublobar resections can provide comparable outcomes to lobectomy in carefully selected patients, particularly when lesions are small, peripheral, and biologically indolent.

For patients who are poor surgical candidates or present with bilateral or centrally located lesions, definitive chemoradiotherapy serves as a viable alternative[9–11]. The use of advanced imaging modalities, bronchoscopic techniques, and multidisciplinary evaluation is essential in treatment planning, especially when deciding between surgical and non-surgical approaches.

An additional layer of complexity arises when different histological subtypes are present in the same patient, as seen in our series, where combinations of squamous cell carcinoma, adenocarcinoma, and carcinoma in situ coexisted. These cases underscore the heterogeneity of synchronous tumors and highlight the importance of individualized treatment strategies based on histopathological characteristics, anatomical distribution, and functional assessment.

Moreover, the evolving role of molecular and genomic profiling may further enhance our ability to distinguish synchronous primaries from metastases. Recent studies have demonstrated that next-generation sequencing (NGS) can reveal distinct mutational profiles in anatomically separate lesions, supporting the diagnosis of multiple primaries[12,13]. Incorporating such technologies into routine diagnostic workflows may improve staging accuracy and enable more tailored therapeutic decisions in the near future.

In summary, the management of synchronous lung tumors requires a personalized, multidisciplinary approach. These cases emphasize the necessity of integrating clinical judgment, pathological confirmation, and, where available, molecular diagnostics to guide treatment. Further prospective studies with larger patient cohorts and molecular analyses are needed to refine diagnostic criteria and optimize therapeutic strategies for this complex patient population.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

In Silico Analysis of Structural and Functional Impacts of Missense SNPs of SNCA Gene in Parkinson's Disease

SNCA Geninde Yanlış Anlamlı SNP'lerin Yapısal ve İşlevsel Etkilerinin in silico Analizi

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ABSTRACT

Aim: *Synuclein alpha (SNCA), the first gene identified as genetically associated with Parkinson's disease (PD), encodes the α-synuclein protein, which plays a role in synaptic function. Parkinson's disease is a progressive neurodegenerative disorder characterized by the abnormal accumulation and aggregation of α-synuclein and clinically presents with motor dysfunction such as tremor, bradykinesia, rigidity, and postural instability. Structural alterations in SNCA are thought to contribute to disease pathogenesis by promoting the misfolding of the α-synuclein protein, disrupting its stability, and leading to the formation of pathological aggregates.*

Material and Method: *In this study, the structural and functional effects of missense single nucleotide polymorphisms (SNPs) in SNCA were evaluated through comprehensive in silico analyses. First, gene–gene and protein–protein interaction networks were analyzed to identify functional partners of SNCA, and the evolutionary conservation of amino acid positions was assessed. A total of 245 missense SNPs were analyzed using SIFT, PANTHER, PolyPhen-2, and PredictProtein, and 25 SNPs were predicted to be potentially deleterious. Further analysis with machine learning-based tools, including PhD-SNP and SNPs&GO, revealed 14 disease-related SNPs, among which nine were consistently predicted as deleterious across all tools. Protein stability was evaluated using I-Mutant2.0, MUpro, and Meta-SNP, identifying 5 SNPs as potentially pathogenic.*

Results: *These five variants were located within the functionally and evolutionarily conserved N-terminal region of α-synuclein, and structural analyses suggested that they may impair protein stability and promote aggregation.*

Conclusion: *Overall, these findings highlight the pathogenic potential of missense SNPs in SNCA and provide strong candidates for future functional validation studies.*

Key words: *SNCA, alpha synuclein, Parkinson's disease, single nucleotide polymorphism (SNP), in silico*

ÖZET

Amaç: *Synuclein alpha, sinaptik işlevlerde rol alan α-sinüklein proteinini kodlayan ve Parkinson hastalığında genetik yatkınlıkla en erken ilişkilendirilen genlerden biridir. α-sinüklein proteininin anormal birikimi ve agregasyonu ile karakterize edilen ilerleyici bir nörodejeneratif hastalık olan Parkinson hastalığı, motor fonksiyonların bozulmasıyla seyretmekte olup, tremor, bradikinezi, rijidite ve postüral instabilite gibi semptomlarla klinik olarak ortaya çıkar. Synuclein alpha geninde meydana gelen yapısal değişikliklerin, α-sinüklein proteininin yanlış katlanmasına, stabilitesinin bozulmasına ve patolojik agregat oluşumuna neden olarak hastalığın patogenezinde önemli bir rol oynadığı düşünülmektedir.*

Gereç ve Yöntem: *Bu çalışmada, SNCA genindeki yanlış anlamlı tek nükleotid polimorfizmlerinin (SNP) yapısal ve fonksiyonel etkileri kapsamlı in silico analizlerle değerlendirildi. İlk olarak, gen-gen ve protein-protein etkileşim analizleriyle SNCA'nın fonksiyonel ortakları belirlendi ve amino asit pozisyonlarının evrimsel korunmuşluğu değerlendirildi. Toplam 245 missense SNP, SIFT, PANTHER, PolyPhen-2 ve PredictProtein araçlarıyla analiz edilerek 25 SNP'nin zararlı olabileceği öngörüldü. Daha sonra, PhD-SNP ve SNPs&GO gibi makine öğrenimi temelli araçlarla yapılan analizlerde 14 SNP'nin hastalıkla ilişkili olduğu belirlendi ve bu SNP'lerden 9'u tüm analizlerde ortak olarak zararlı bulundu. Protein stabilitesi üzerindeki etkiler I-Mutant2,0, MUpro ve Meta-SNP ile değerlendirildi ve 5 SNP'nin potansiyel olarak hastalıkla ilişkili olduğu saptandı.*

Bulgular: *Bu beş SNP'nin, α-sinüklein proteininin fonksiyonel ve evrimsel olarak korunmuş N-terminal bölgesinde yer aldığı görüldü ve yapısal analizler, bu varyantların protein stabilitesini bozabileceğini ve agregasyon eğilimini artırabileceğini gösterdi.*

Sonuç: *Sonuçlar, yanlış anlamlı SNCA SNP'lerinin patojen potansiyelini ortaya koymakta ve ileride yapılacak fonksiyonel doğrulama çalışmaları için güçlü adaylar sunmaktadır.*

Anahtar kelimeler: *SNCA, alfa sinüklein, Parkinson hastalığı, tek nükleotid polimorfizmi (SNP), in silico*

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Introduction

Synuclein alpha (*SNCA*), which encodes the α-synuclein protein, plays a significant role in neuronal physiology and is the first gene identified as associated with a progressive neurodegenerative disorder, Parkinson's disease (PD). Parkinson's disease is one of the most common neurodegenerative disorders, affecting 1–2% of the population above the age of 65 and 4–5% above the age of 85[1]. The disease is characterized by the loss of dopaminergic neurons in the pars compacta of the substantia nigra[2]. Moreover, the constitutional loss of dopaminergic neurons leads to dopamine deficiency within the basal ganglia, resulting in motor dysfunction, including tremors, rigidity, bradykinesia, and postural instability in patients[3]. Synuclein alpha is considered a major component of Lewy bodies and Lewy neurites, which are composed of abnormal α-synuclein aggregates and play a significant role in the development and progression of PD by leading to the characteristic motor and non-motor symptoms of the disorder[4]. Therefore, *SNCA* may serve as a key molecular marker for understanding PD pathogenesis. The major challenge related to PD is the lack of early diagnostic tests, which could hinder the progression of the disease and improve patient outcomes[5]. Identifying accurate biomarkers, including pathogenic missense mutations in the *SNCA* gene, may contribute to early diagnosis and targeted therapeutic strategies, ultimately improving disease management and patient outcomes.

The *SNCA* gene (OMIM 163890), located on chromosome 4q22.1, encodes a 140-amino acid-long α-synuclein protein and is primarily expressed in the central nervous system[6]. While the expression is particularly at the presynaptic terminals of neurons, α-synuclein plays a significant role in neurotransmitter release and synaptic vesicle trafficking[7]. Structural regions of the α-synuclein protein are N-terminal (residues 1–60), Non-Amyloid Component (NAC) (61–95), and C-terminal (96–140). The N-terminal forms amphipathic α-helixes involved in protein-protein interactions and membrane binding, thereby contributing to the protein's dynamic role at the synapse[4]. The NAC region forms β-sheet-rich structures, and due to its hydrophobic nature, the area is highly prone to aggregation. The C-terminal region extensively undergoes post-translational modifications, is involved in protein-protein interactions, and significantly impacts the stability, aggregation potency, and interaction of α-synuclein with other cellular components.

Single-nucleotide polymorphisms (SNPs) are among the most common forms of genetic variation in the human genome and may contribute to increased susceptibility to one or more diseases, making them valuable biomarkers[8]. SNPs occur in both coding and non-coding regions of DNA, while those located in coding regions have the potential to alter protein structure and function. Many SNPs may not affect protein structure and function due to the codon redundancy or conservative amino acid substitution in missense SNPs. On the other hand, some SNPs may result in significant functional and structural changes in protein structure due to the substitution of an amino acid that has different physicochemical properties[9]. Numerous missense SNPs are related to protein aggregation or misfolding, contributing to the pathogenesis of neurodegenerative diseases. Therefore, analyzing SNPs is crucial for identifying genetic risk factors and developing targeted therapeutic strategies. For this aim, in silico analyses are valuable for predicting the deleterious effects of SNPs –particularly in missense variants that cause amino acid substitution– prioritizing those that increase disease susceptibility and enabling researchers to focus on the most promising candidates for therapeutic development and experimental validation.

In this study, we aimed to identify potentially deleterious missense SNPs in the *SNCA* gene and evaluate their effects on the stability of α-synuclein protein. To achieve this aim, we first assessed gene-gene and protein-protein interactions to identify closely related partners and then investigated the evolutionary conservation of amino acid positions. Then, we classified SNPs as neutral or deleterious using in silico tools that focused on evolutionary conservation and functional annotation. Protein sequences of the SNPs that were predicted to be harmful were further analyzed to assess their impact on protein stability. Finally, SNPs that were consistently predicted to be deleterious were examined based on sequence features and predicted structural properties.

Material and Methods

Data Mining

To access missense SNPs in *SNCA* (NCBI Gene ID: 6622)[10], the NCBI dbSNP database was used in January 2024[11]. The primary sequence of α-synuclein (UniProt accession number: P37840), encoded by *SNCA,* was retrieved from the UniProt database[12].

Gene-Gene Interactions

Gene-gene interaction networks were analyzed using GeneMANIA, which includes both known and predicted gene interactions, and incorporates data from gene co-expression, colocalization, and shared protein domains[13].

Protein-Protein Associations

The STRING database was utilized to predict the protein–protein interaction network. The resulting network includes both physical and functional interactions, as all publicly accessible data on protein–protein interactions are collected, scored, and integrated by STRING. The top twenty proteins with the highest interaction scores were included in the analysis[14].

Prediction of Evolutionary Conservation Profiles

The evolutionary conservation profiles of the α-synuclein protein were predicted using the ConSurf server[15]. The conservation score was calculated and visualized by the tool. A score of 1 indicates high variability and is probably functionally not important, while a score of 9 means the substitution is evolutionarily critical and often functionally or structurally important. ConSurf also predicts whether a residue is "exposed" (surface-accessible) or "buried" (hidden inside the protein structure) and "functional" (e.g., active/binding site) or "structural" (important for maintaining protein fold).

Prediction of the Pathogenic Effects of SNPs

Sorting Intolerant from Tolerant (SIFT), Protein Analysis Through Evolutionary Relationships (PANTHER), Polymorphism Phenotyping-2 (PolyPhen-2), and PredictProtein were used to determine the pathogenic effects of the missense SNPs in *SNCA*. Briefly, SIFT classifies SNPs as tolerated (≥0.05) or deleterious (<0.05), based on evolutionary conservation, sequence similarity, and the physical features of amino acids[16]. Protein analysis through evolutionary relationships predicts the functional impact of SNPs by analyzing evolutionary conservation and protein family relationships[17]. PolyPhen-2 evaluates the potential effect of amino acid substitutions according to homology and assigns each SNP a score between 0 and 1[18]. Two models of PolyPhen-2, Human Diversity (HumDiv) and Human Variation (HumVar), were utilized. HumVar examines broader genetic variations to distinguish disease-causing mutations from neutral polymorphisms in population-based contexts, whereas HumDiv calculates the possible impact of rare, pathogenic mutations by defining them from common benign variants. PredictProtein classifies the SNPs as either effect or neutral, indicating whether the mutation probably alters the protein's structural or functional characteristics[19].

Prediction of Disease-Related SNPs

The Predictor of Human Deleterious Single-Nucleotide Polymorphisms (PhD-SNP) and Predicting Human Disease-Related Mutations in Proteins with Functional Annotations (SNPs & GO) were used to analyze missense SNPs and determine whether they are disease-related or neutral. PhD-SNP, which uses Support Vector Machines (SVMs) to categorize SNPs as neutral or deleterious[20], while SNPs & GO combines protein functional annotation with machine learning algorithms, and integrates Gene Ontology (GO) terms, sequence conservation, and mutational data to classify each variant as disease-related or neutral[21].

Prediction of Protein Stability Alterations Caused by SNPs From the Protein Sequence

To evaluate the structural impact of SNPs on protein stability, we selected those variants that were consistently predicted to be pathogenic by all prediction tools in the previous analysis steps.

I-Mutant 2.0, Meta-SNP, and MUpro were utilized to predict protein stability changes caused by missense SNPs in the α-synuclein protein. I-Mutant 2.0, an SVM-based server, was used for the prediction of the effects of single substitutions on the stability of α-synuclein[22]. pH 7.0 and 25°C temperature were the input parameters, and an estimate of prediction confidence was provided by the output, including reliability index scores ranging from 0 (unreliable) to 10 (reliable). Meta-SNP, which predicts the pathogenicity of SNPs by integrating multiple computational tools, including PhD-SNP, SNPs&GO, MutPred, and PANTHER, evaluates the potential deleterious effects of amino acid substitutions on protein function and stability[23]. This ensemble approach allows for a comprehensive evaluation of the mutational effects on protein function and stability. MUpro, which utilizes both SVM and neural network-based models, was used to predict protein stability[24]. By estimating the free energy change (ΔΔG) upon amino acid substitution, increases or decreases in protein stability were predicted. A negative ΔΔG value indicates a decrease in protein stability, while a positive ΔΔG value suggests an increase in stability.

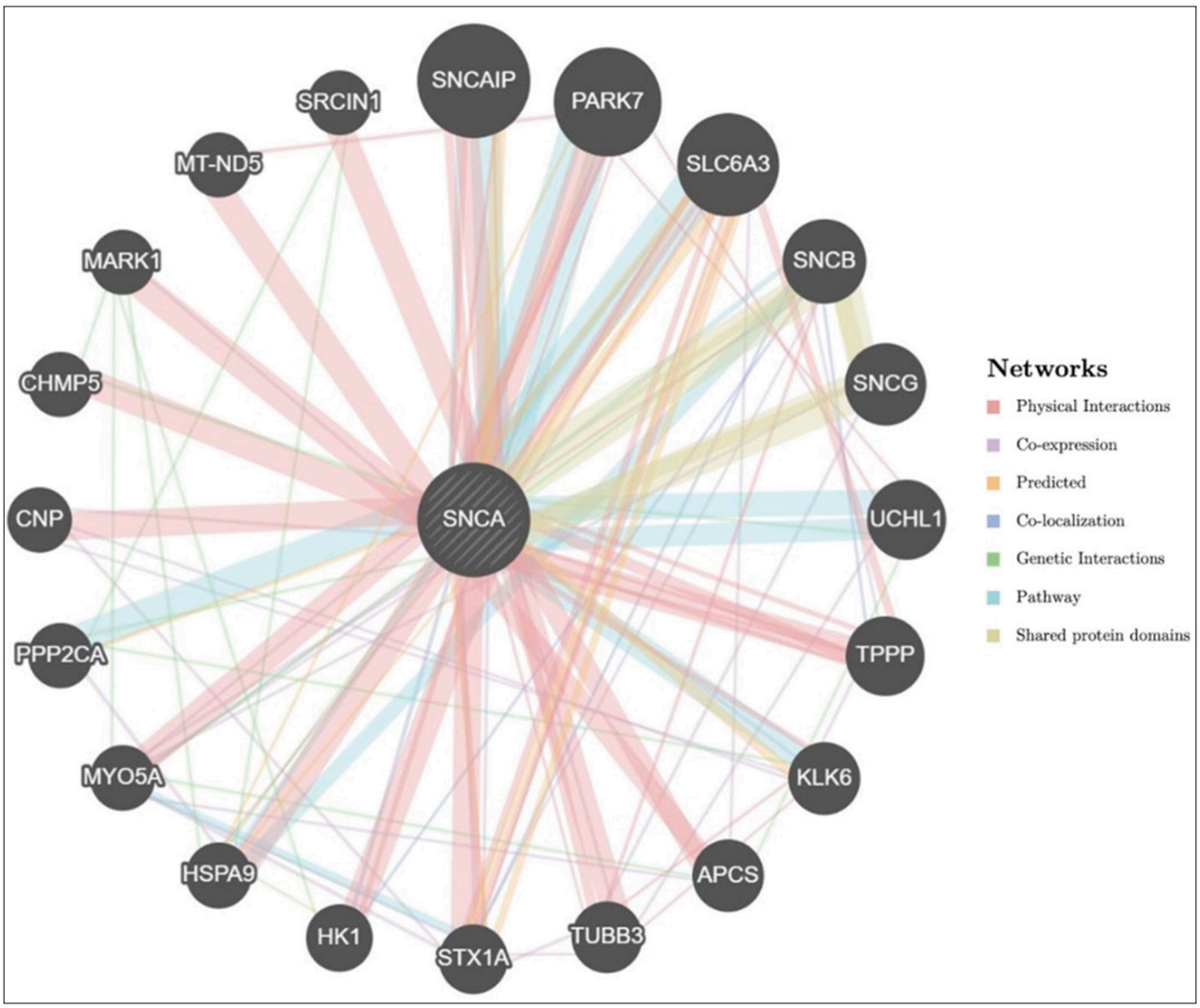


Figure 1. *Gene-gene interaction network of the SNCA gene and its top 20 functionally associated genes, generated using GeneMANIA.*

Visualization and Assessment of the Structural Impact of SNPs

The structural effects of the pathogenic SNPs in *SNCA* were analyzed using the ProjectHOPE tool, which predicts the functional and structural effects of mutations on proteins by integrating data from UniProt annotations and secondary structure predictions using Reprof[25]. Missense3D was employed to generate structural models and assess local changes caused by missense mutations, using predicted or homologous structural templates available from UniProt[26].

Results

Gene-Gene Interaction Network of SNCA

The gene-gene interaction network of *SNCA* was analyzed by GeneMANIA software and presented in Fig. 1. The interaction network includes 20 genes that are directly linked with *SNCA*. These genes include *SNCAIP* (synuclein alpha interacting protein), *PARK7* (Parkinsonism-associated deglycase), *SLC6A3* (dopamine transporter), *SNCB* and *SNCG* (beta and gamma synucleins), *UCHL1* (ubiquitin C-terminal hydrolase L1), and *TPPP* (tubulin polymerization promoting protein), which signify the genes most functionally and physically linked to *SNCA*.

Determination of Protein-Protein Interactions

According to the protein-protein interaction data generated by STRING, α-synuclein has numerous functional partners based on physical interaction, co-expression, and pathway co-involvement (Fig. 2). Although the visualization was limited to the top

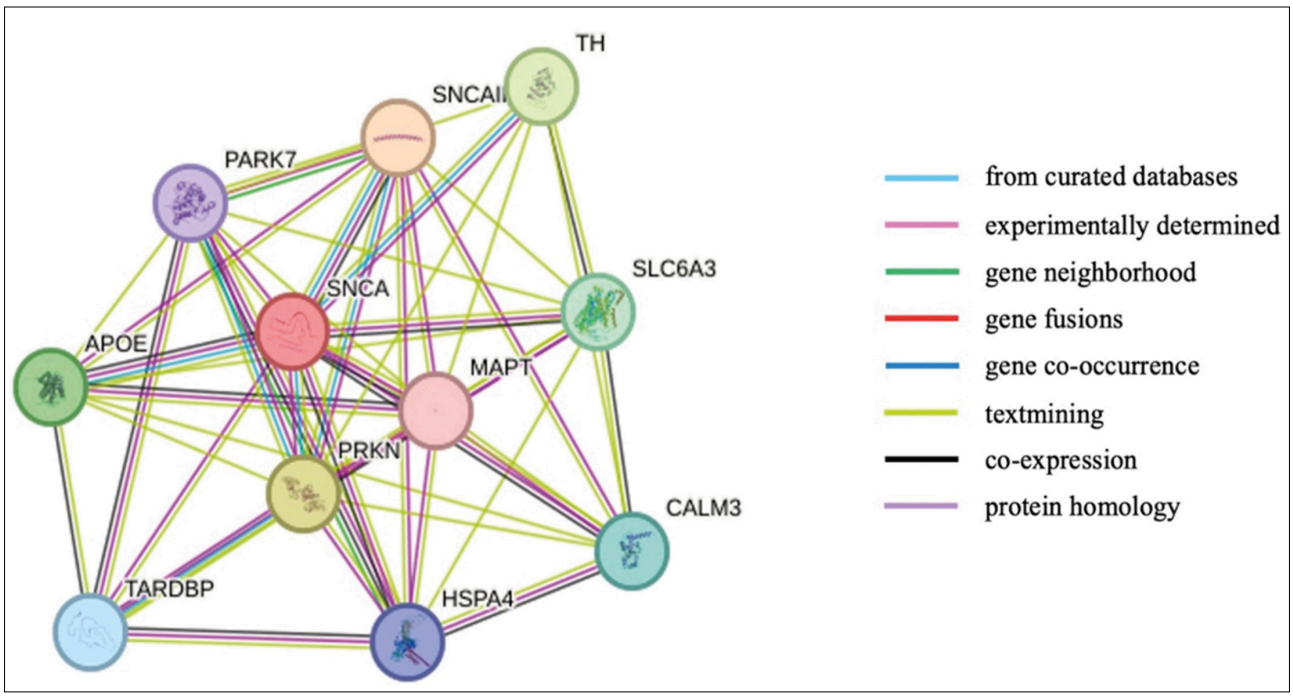


Figure 2. *Protein-protein interaction network of SNCA and its functional partners generated by STRING.*

interactions for clarity, the most prominent interactors included Synphilin-1 (SNCAIP), Parkin RBR E3 Ubiquitin Protein Ligase (PRKN), Tyrosine Hydroxylase (TH), Apolipoprotein E (APOE), Solute Carrier Family 6 Member 3/ Dopamine Transporter (SLC6A3), Calmodulin-3 (CALM3), TAR DNA-Binding Protein 43 (TARDBP), Heat Shock Protein Family A Member 4 (HSPA4), Protein/Nucleic Acid Deglycase DJ-1 (PARK7), and Microtubule-Associated Protein Tau (MAPT), with interaction scores ranging from 0.994 to 0.999, suggesting a high confidence in their association.

Prediction of Pathogenic Effects of SNCA SNPs on α-Synuclein Structure

Data obtained from the NCBI dbSNP database showed that a total of 44.612 SNPs were identified in the *SNCA* gene, 245 of which were classified as missense SNPs. These SNPs were analyzed by SIFT, PANTHER, PolyPhen-2 model HumVar and HumDiv, and PredictProtein (Table S1). The SIFT database provided a result of "Not Found" for 91.02% of the analyzed SNPs. Since the SIFT database predicts the effects of SNPs on protein function based on evolutionary conservation and sequence similarity, the result "Not Found" may be given when there is insufficient homologous sequence data (typically requiring at least 20 sequences), a lack of evolutionary conservation at the mutation site, or missing or outdated database entries. Therefore, due to the high percentage of "Not Found" results, SIFT analysis was excluded. Pathogenicity assessment using PANTHER showed that 38 of the SNPs were "probably damaging" and 2 of them were "possibly damaging", indicating that a total of 40 SNPs were predicted to be deleterious. Moreover, 60 SNPs were probably damaging, 12 SNPs were possibly harmful, and 44 SNPs were benign, according to the PolyPhen-2 HumVar analysis. Similarly, PolyPhen-2 HumDiv analysis showed that 64 SNPs were probably damaging, 12 SNPs were possibly harmful, and 40 SNPs were benign. Based on the results of PredictProtein, 47 SNPs were classified as "effect", indicating the SNPs are likely to alter the protein's structure and function. In comparison, 68 SNPs were classified as "neutral", suggesting that the impact of the SNPs on the protein is not predicted. According to the findings of PANTHER, PolyPhen-2 model HumVar and HumDiv, and PredictProtein analyses, 25 of 245 SNPs were consistently predicted to be damaging across all tools, and results were presented in Table 1.

Table 1. *Pathogenicity predictions of missense SNPs in the SNCA gene using multiple in silico tools*

SNP ID	Amino acid	PANTHER (preservation time)	PolyPhen2 HumDiv (score)	PolyPhen2 HumVar (score)	Predict Protein (score)	PhD-SNP (RI)	SNPs&GO (RI)
rs104893875	E46K	Probably damaging (0.57)	Probably damaging (0.959)	Probably damaging (0.603)	Effect (54)	Disease (4)	Disease (9)
rs104893878	A30P	Probably damaging (0.57)	Probably damaging (0.996)	Probably damaging (0.994)	Effect (79)	Disease (6)	Disease (9)
rs1168809349	V3E	Probably damaging (0.57)	Probably damaging (0.972)	Possibly damaging (0.903)	Effect (50)	Disease (4)	Neutral (2)
rs1188720061	K6N	Probably damaging (0.57)	Probably damaging (1000)	Probably damaging (0.999)	Effect (52)	Disease (1)	Neutral (6)
rs1219278381	A11S	Probably damaging (0.57)	Possibly damaging (0.887)	Probably damaging (0.979)	Effect (63)	Disease (0)	Disease (2)
rs1239518140	V52A	Probably damaging (0.57)	Probably damaging (1000)	Probably damaging (1000)	Effect (56)	Neutral (1)	Neutral (2)
rs1261243630	K80E	Probably damaging (0.57)	Probably damaging (0.960)	Possibly damaging (0.591)	Effect (61)	Neutral (2)	Disease (2)
rs1273319141	T22I	Probably damaging (0.57)	Probably damaging (0.999)	Probably damaging (0.996)	Effect (57)	Neutral (2)	Disease (6)
rs1289807114	K97N	Probably damaging (0.57)	Probably damaging (0.997)	Possibly damaging (0.904)	Effect (32)	Disease (1)	Disease (5)
rs1319839593	V82A	Probably damaging (0.57)	Probably damaging (0.999)	Probably damaging (0.999)	Effect (61)	Neutral (4)	Neutral (8)
rs1330229174	K34E	Probably damaging (0.57)	Probably damaging (0.960)	Possibly damaging (0.591)	Effect (69)	Disease (3)	Disease (3)
rs1342686707	G36R	Probably damaging (0.57)	Probably damaging (1.000)	Probably damaging (1.000)	Effect (73)	Disease (3)	Disease (4)
rs1342686707	G36S	Probably damaging (0.57)	Probably damaging (0.999)	Probably damaging (0.999)	Effect (55)	Disease (5)	Disease (1)
rs1433622151	G25S	Probably damaging (0.57)	Probably damaging (0.999)	Probably damaging (0.999)	Effect (62)	Disease (2)	Neutral (3)
rs1482689946	G25C	Probably damaging (0.57)	Probably damaging (1.000)	Probably damaging (1.000)	Effect (59)	Neutral (6)	Disease (1)
rs1739239286	G14R	Probably damaging (0.57)	Probably damaging (1.000)	Probably damaging (1.000)	Effect (84)	Neutral (1)	Disease (2)
rs2110218111	M1V	Probably damaging (0.57)	Probably damaging (1.000)	Probably Damaging (1.000)	Effect (70)	Neutral (6)	Disease (9)
rs533442704	M1K	Probably damaging (0.57)	Probably damaging (0.968)	Probably Damaging (0.969)	Effect (88)	Neutral (0)	Disease (9)
rs750512067	G41D	Probably damaging (0.57)	Probably damaging (0.998)	Probably Damaging (0.914)	Effect (73)	Disease (6)	Disease (9)
rs750745088	V37F	Probably damaging (0.57)	Possibly damaging (0.949)	Possibly Damaging (0.747)	Effect (72)	Disease (3)	Disease (4)
rs752472160	A18G	Probably damaging (0.57)	Probably damaging (0.998)	Probably Damaging (0.993)	Effect (64)	Neutral (2)	Neutral (1)
rs753674628	V26M	Probably damaging (0.57)	Probably damaging (0.996)	Probably Damaging (0.991)	Effect (53)	Neutral (3)	Disease (1)
rs774113587	G73S	Probably damaging (0.57)	Probably damaging (1000)	Probably Damaging (0.999)	Effect (52)	Neutral (5)	Disease (1)
rs777070190	V71A	Probably damaging (0.57)	Probably damaging (1000)	Probably Damaging (1000)	Effect (56)	Neutral (6)	Neutral (8)
rs778867145	E20G	Probably damaging (0.57)	Probably damaging (1000)	Probably Damaging (0.999)	Effect (71)	Neutral (6)	Disease (1)

Table 2. *Protein stability and pathogenicity of selected SNCA missense SNPs using Meta-SNP, I-Mutant 2.0, and MUpro*

SNP ID	Amino Acid	Meta-SNP (score)	I-Mutant 2.0 (RI)	MUpro (ΔΔ)
rs104893875	E46K	Disease (0)	Decrease (6)	Decrease (-0.86491132)
rs104893878	A30P	Disease (3)	Decrease (0)	Decrease (-15082158)
rs750512067	G41D	Disease (5)	Decrease (3)	Decrease (-78916257)
rs1342686707	G36R	Disease (3)	Decrease (6)	Increase (-44433528)
rs1330229174	K34E	Disease (4)	Increase (1)	Decrease (-18349697)
rs1219278381	A11S	Neutral (1)	Decrease (9)	Decrease (-1.4006632)
rs1289807114	K97N	Neutral (2)	Decrease (0)	Decrease (-0.5986704)
rs1342686707	G36S	Neutral (0)	Decrease (6)	Decrease (-0.66713422)
rs750745088	V37F	Neutral (0)	Decrease (7)	Decrease (-10089218)

Identification of Disease-Associated Missense Variants in SNCA

The SVM-based tools, PhD-SNP and SNP&GO, were utilized for the in silico analysis of disease-associated SNPs in *SNCA,* and the results were provided in Table S1. Both tools classify SNPs as "disease" and "neutral", indicating whether the mutation has the potential to cause disease or is likely to be functionally benign. Based on the results of the PhD-SNP analysis, 20 SNPs were classified as "disease", while 97 SNPs were classified as "neutral". SNP&GO analysis showed that 34 of the SNPs were identified as "disease", and 82 SNPs were identified as "neutral". Among the SNPs analyzed, 14 SNPs were commonly classified as "disease" by PhD-SNP and SNP&GO (Table 1).

Among the 245 SNPs analyzed by the six tools (PANTHER, PolyPhen-2 HumVar and HumDiv, PredictProtein, PhD-SNP, and SNP&GO), a total of 9 SNPs were consistently predicted to be deleterious/disease-related across all tools: rs750745088, rs104893878, rs750512067, rs1342686707, rs1342686707, rs104893875, rs1219278381, rs1330229174, and rs1289807114 (Table 1). These overlapping nine SNPs were selected for further analysis to predict protein stability alterations using I-Mutant2.0, MUpro, and Meta-SNP.

Impact of Deleterious SNPs on α-Synuclein Stability

MUpro, Meta-SNP, and I-Mutant2.0 were utilized to predict protein stability changes in the α-synuclein protein, and the results were presented in Table 2. I-Mutant2.0

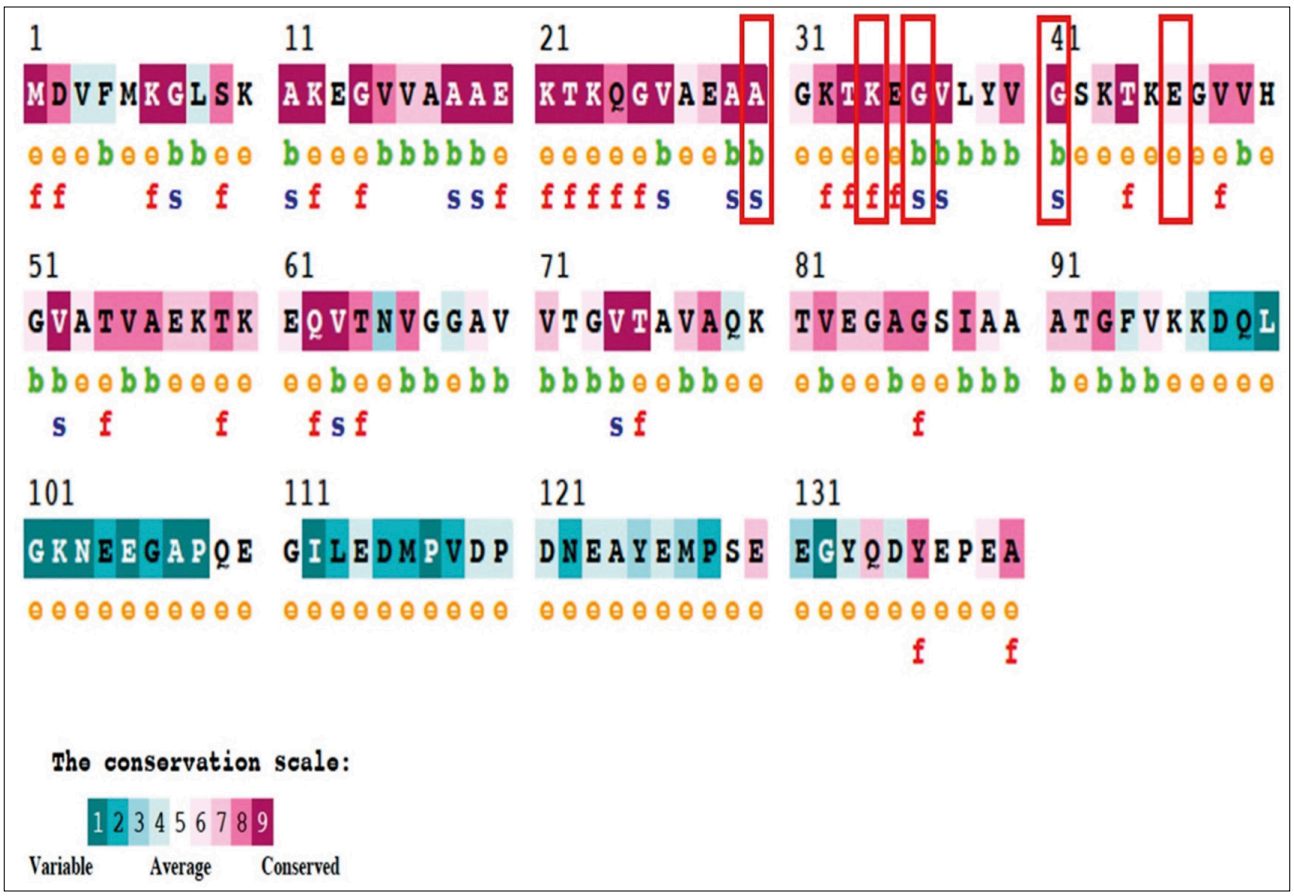


Figure 3. *Conservation profile of α-synuclein generated by the ConSurf server. The top row represents the amino acid sequence of α-synuclein (residues 1–140). The second row indicates predicted residue exposure, where "b" denotes buried and "e" denotes exposed residues. The third row shows predicted residue importance: "s" for structurally important and "f" for functionally important positions. Red boxes highlight the locations of the five SNPs prioritized for structural analysis.*

analysis showed that only 1 SNP (rs1330229174) was predicted to increase stability, while the remaining eight were predicted to decrease the stability of the protein. MUpro analysis also showed that 8 of the 9 SNPs were predicted to decrease in stability, while 1 SNP (rs1342686707) showed an increase in the stability of the protein. Increased stability may also be harmful in aggregation-prone proteins like α-synuclein by promoting misfolding or disrupting normal dynamics. Then, we utilized Meta-SNP, an ensemble tool that integrates multiple computational methods to predict the pathogenicity of SNPs and assess their effects on protein stability and function. Among the 9 SNPs, Meta-SNP identified 5 SNPs as "disease" and 4 SNPs as "neutral". The SNPs that are categorized as "disease" are as follows: rs104893875, rs104893878, rs1330229174, rs750512067, and rs1342686707. Therefore, the five SNPs identified as disease-related by Meta-SNP were selected for subsequent analysis, regardless of their predicted impact on protein stability.

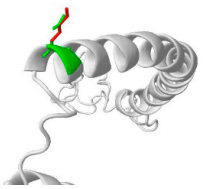
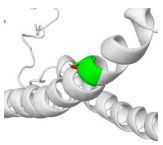
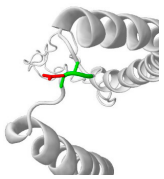
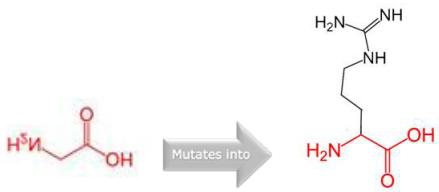
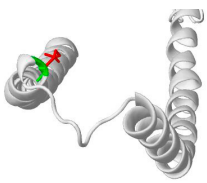
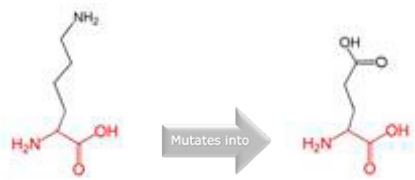
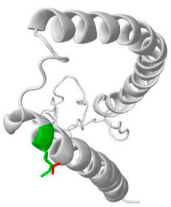
Evolutionary Conversation Analysis

Conserved regions, exposed/buried and functional/structural residues were estimated by the ConSurf server and are given in Fig. 3. The ConSurf data revealed that 26 residues were predicted to be functional and 13 to be structural in α-synuclein. The affected regions of five SNPs, consistently predicted to be deleterious, also include conserved sites. Among them, A30P, G36R, and G41D (rs104893875, rs1342686707, and rs750512067, respectively) were located in highly conserved regions (conservation scores: 9), while K34E and E46K (rs1330229174 and rs104893875, respectively) were located in relatively conserved regions (conservation scores: 7 and 6, respectively) in α-synuclein.

Structural Modeling and Functional Impact of Deleterious SNPs on α-Synuclein

The five SNPs consistently predicted to be deleterious by both gene-based and protein-level prediction tools

Table 3. *Amino acid substitutions and structural impact of selected SNCA SNPs on α-synuclein protein based on ProjectHope and Missense3D analysis*

SNP ID	Amino Acid Substitution	Protein
rs104893875	E46K 	
rs104893875	A30P 	
rs750512067	G41D 	
rs1342686707	G36R 	
rs1330229174	K34E 	

were selected for structural and functional analysis using the ProjectHOPE and Missense3D tools. Using annotations from the UniProt database and predictions from the Reprof software, HOPE evaluated the structural effects, while the Missense3D tool visualized the substitutions. The structural and functional consequences of these five SNPs, as predicted by Project HOPE and Missense3D, are summarized in Table 3.

The rs104893875 SNP resulted in the E46K substitution, the replacement of glutamic acid (E) with lysine (K) at position 46. Glutamic acid is a negatively charged amino acid and significantly differs in size compared to lysine. Since the substituted amino acid (lysine) is positively charged and larger in size, this substitution may lead to repulsion with other residues in the protein or ligands. It may cause steric clashes or structural distortion in the protein structure. The presence of lysine in homologous proteins suggests that this substitution may be tolerated in some structural contexts; however, the difference in physicochemical properties still indicates a potential functional effect that should be further investigated.

The rs104893875 SNP leads to an A30P substitution, replacing alanine (A) with proline (P) at position 30. Proline is larger than alanine, which potentially leads to structural incompatibility or disruption. Because the 30th amino acid position is within residues annotated in the UniProt database as a special tandem repeating region, differences in amino acid properties can disrupt this region and may alter protein function. This region also forms an α-helix. The substitution of proline within the helix leads to disruption of helix

structure. Furthermore, the MetaRNN score of this variant was reported as 0.97442156, indicating that the substitution is more likely to be pathogenic.

The rs750512067 SNP results in a G41D substitution, replacing the 41st amino acid glycine with aspartic acid. Glycine and aspartic acid are significantly different in size, charge, and hydrophobicity, indicating that substituting one for the other may result in significant changes in protein structure. Aspartic acid is more hydrophobic and larger than glycine. Also, aspartic acid is a negatively charged amino acid, while glycine is neutral. Substitution with a negatively charged amino acid leads to repulsion of ligands or other residues with the same charge, and larger amino acids disrupt the protein structure. Furthermore, glycine is the most flexible amino acid, responsible for making the torsion angles in this protein, and this flexibility may be necessary for the protein's function. Substitution of glycine for any other residue will force the local backbone into an incorrect conformation, disrupt the regional structure, and abolish this function. Therefore, this mutation is probably damaging to the protein.

The rs1342686707 SNP leads to G36R substitution, the replacement of glycine (A) with arginine (P) at position 30. Glycine and arginine differ in size, charge, and hydrophobicity. The substituted amino acid is larger and less hydrophobic compared to the wild type. Furthermore, arginine is positively charged, while glycine is neutral. Due to the flexibility of glycine, substitution with arginine probably alters the protein's function.

The rs1330229174 SNP results in K34E substitution, which replaces lysine (K) with glutamic acid (E) at position 34. Lysine is positively charged, while glutamic acid is negatively charged and smaller than lysine. The charge difference of the replaced amino acid may lead to repulsion with other residues in the protein or ligands. Furthermore, substitution with a smaller amino acid may lead to the loss of interactions.

Discussion

Alterations in the *SNCA* gene have been frequently linked to structural instability, abnormal protein interactions, and increased aggregation tendency of α-synuclein, leading to the development of PD. Along with its aggregation-prone nature, α-synuclein is also involved in a complex protein interaction network that plays a critical role in the pathogenesis of PD. Therefore, amino acid substitutions in α-synuclein resulting from missense mutations may not only lead to aggregation but also disrupt its functional interactions. Gene-gene and protein-protein interactions revealed that *SNCA* is closely interacting with *PRKN, PARK7, MAPT*, and *SNCAIP*, which are directly involved in PD-related pathways.

Determination of SNPs in PD would play an essential role in new treatments and personalized medicine. In this study, 25 of 245 SNPs identified by five widely accepted in silico tools, which rely on multiple sequence– and function-based features, were consistently predicted to be damaging, indicating a high likelihood of functional disruption. To further evaluate these SNPs' clinical relevance, two machine learning-based in silico tools, PhD-SNP and SNP&GO, were utilized. With this analysis, 14 of them were predicted to be disease-related, indicating their potential pathogenicity. Remarkably, nine of them overlapped across sequence-based and SVM-based tools and represented high-confidence variants selected for downstream structural and stability evaluation.

The stability of α-synuclein is essential in PD development, because destabilization significantly impacts the formation of Lewy bodies by promoting misfolding and aggregation of the protein. I-Mutant2.0 and MUpro tools showed that these SNPs changed the protein stability, which may affect both the aggregation of α-synuclein and interactions with other proteins within the interaction network. Meta-SNP data also identified five of them –rs104893875, rs104893878, rs1330229174, rs750512067, and rs1342686707– as disease-related, which may indicate their potential in PD development. Furthermore, all five SNPs were located in regions above-average evolutionarily conserved, with conservation scores exceeding 6, suggesting their potential structural or functional importance and a higher likelihood of contributing to pathogenicity.

Notably, these five variants are located within the N-terminal region of the α-synuclein protein, the most reported region for harboring disease-related mutations or polymorphisms. The polymorphism rs10489387, which leads to E46K substitution, was first identified in a multinational Spanish family and was shown to induce α-synuclein fibril formation and aggregation, accelerate Lewy body formation, promote protein aggregation, and contribute to Parkinsonism and dementia[27]. By accelerating aggregation, the E46K substitution was previously shown to lead to Lewy body pathology in both cortical and subcortical regions in mice[28]. Given its essential link

to familial PD, the E46K variant emphasizes its clinical relevance, and our *in silico* findings further support its pathogenic potential.

The A30P substitution, which resulted from the rs104893878 SNP, is another well-characterized familial PD variant and is known for its helix-destabilizing properties. Pathological examination of postmortem brain tissue from PD patients with the rs104893878 SNP demonstrated cortical hypometabolism, particularly in the frontal, parietal, and left temporal lobes, suggesting that this variant may play a significant role in disease progression[29]. Furthermore, experimental findings demonstrate that A30P alters the fibrillation pathway and leads to modified fibril formation compared to the wild type[30]. The α-synuclein protein has a conserved fibrillation core (residues 38–95), which is essential for amyloid formation. Although this core region remains preserved in A30P, the substitution induces subtle changes that influence fibril morphology and accelerate aggregation, probably due to altered oligomerization dynamics[31]. Consistent with these experimental data, we consistently predicted this SNP to be destabilizing by in silico analyses. Based on this experimental data and our findings, A30P substitution contributes to α-synuclein pathogenicity by altering its conformation and aggregation kinetics.

Three of the SNPs, K34E (rs1330229174), G36R (rs750512067), and G41D (rs1342686707), are all located within the conserved KTKEGV repeat motifs of α-synuclein's N-terminal region, which are critical for helical stability and membrane interaction. Although these variants have not yet been linked to any clinical or experimental studies, they share a common feature of introducing charge alterations or replacing flexible glycine residues, potentially disrupting local structure and dynamic behavior. Due to the major role of the glycine residue in the flexibility of α-synuclein, the substitution probably alters the dynamic behavior of the protein[32]. While no clinical or experimental data have yet been linked to these SNPs, only a single *in silico* study has examined their potential impact[33]. Despite this limited background, our findings suggest that they emerge as strong candidates for further functional validation. Their predicted involvement in early conformational rearrangements and impaired membrane interactions indicates a plausible role in α-synuclein misfolding and aggregation, consistent with the pathogenic mechanisms described for other familial PD mutations in this region.

Previous in silico studies investigating *SNCA* variants, such as those by da Silva et al. and Elnageeb et al., have provided valuable insights into the structural effects of a limited number of known α-synuclein mutations, often with a focus on post-translational modifications or generalized synucleinopathies[33,34]. da Silva et al. primarily examined a few selected variants and PTMs using molecular dynamics simulations to explore their influence on protein flexibility and aggregation[34]. At the same time, Elnageeb et al. focused on disease associations of selected variants without evaluating broader mutational landscapes or structural consequences[33]. In contrast, our study adopts a more comprehensive and systematic approach by analyzing 245 missense SNPs retrieved from the NCBI dbSNP database and integrating multiple bioinformatics tools to assess pathogenicity, protein stability, disease relevance, structural impact, conservation, and interaction networks. Furthermore, our focus on Parkinson's disease specifically –combined with the identification of three novel deleterious variants not reported in prior work– provides an expanded and disease-centered understanding of *SNCA* genetic alterations, strengthening the foundation for future experimental validation and therapeutic exploration.

Conclusion

This study comprehensively analyzed the structural and functional impacts of missense SNPs in the *SNCA* gene, which plays a major role in PD pathogenesis. By integrating multiple in silico tools, we identified five high-confidence SNPs that are potentially disease-related and located within evolutionarily conserved and functionally critical regions of α-synuclein. Notably, while two of the SNPs have previously been associated with familial PD, the remaining three SNPs represent novel risk candidates. This analysis highlights the importance of specific *SNCA* variants in PD pathogenesis and provides a basis for future studies for the development of new therapies.

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Declaration of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table S1. *Comprehensive in silico analysis results for missense SNPs in the SNCA gene*

SNP ID	Amino acid	SIFT (score)	PANTHER (preservation time)	PolyPhen2 HumDiv (score)	PolyPhen2 HumVar (score)	Predict Protein (score)	PhD-SNP (RI)	SNPs&GO (RI)
rs10014396	H16R	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs10014396	H165P	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1013203939	R4C	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1013203939	R4G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1024288001	P120L	Not found	Probably benign (0.19)	Probably damaging (0.999)	Probably damaging (0.995)	Neutral (30)	Neutral (5)	Neutral (9)
rs1024288001	P72L	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1025381692	R23G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1030827990	K45R	Not found	Probably damaging (0.57)	Benign (0.024)	Benign (0.015)	Neutral (34)	Neutral (5)	Neutral (5)
rs1041143368	V117M	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1047173234	P109A	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs104893875	E46K	Tolerated (0.125)	Probably damaging (0.57)	Probably damaging (0.959)	Probably damaging (0.603)	Effect (54)	Disease (4)	Disease (9)
rs104893877	A53T	Tolerated (1)	Probably benign (0.19)	Benign (0.000)	Benign (0.000)	Neutral (-16)	neutral (8)	Neutral (6)
rs104893878	A30P	Deleterious (0.005)	Probably damaging (0.57)	Probably damaging (0.996)	Probably damaging (0.994)	Effect (79)	Disease (6)	Disease (9)
rs1157296904	R163S	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1159163387	R23I	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1159163387	R23K	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1165791954	L38P	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (0.994)	Effect (64)	Disease (5)	Disease (7)
rs1168809349	V3E	Not found	Probably damaging (0.57)	Probably damaging (0.972)	Possibly damaging (0.903)	Effect (50)	Disease (4)	Neutral (2)
rs1170926072	T37S	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1170926072	T37N	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1188720061	K6N	Not found	Probably damaging (0.57)	Probably damaging (1000)	Probably damaging (0.999)	Effect (52)	Disease (1)	Neutral (6)
rs1200583867	F137Y	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1219278381	A11S	Not found	Probably damaging (0.57)	Possibly damaging (0.887)	Probably damaging (0.979)	Effect (63)	Disease (0)	Disease (2)
rs1232916562	F128L	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1239518140	V52A	Not found	Probably damaging (0.57)	Probably damaging (1000)	Probably damaging (1000)	Effect (56)	Neutral (1)	Neutral (2)
rs1246005408	G31R	Not found	Probably benign (0.19)	Possibly damaging (0.930)	Possibly damaging (0.764)	Effect (67)	Neutral (5)	Neutral (3)
rs1261243630	K80E	Not found	Probably damaging (0.57)	Probably damaging (0.960)	Possibly damaging (0.591)	Effect (61)	Neutral (2)	Disease (2)
rs1261306303	N122D	Not found	Probably benign (0.19)	Benign (0.000)	Benign (0.001)	Neutral (9)	Neutral (9)	Neutral (9)
rs1261306303	N74D	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1261963254	G73V	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (1000)	Effect (71)	Neutral (1)	Disease (7)
rs1268270588	S51T	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1273319141	T22I	Not found	Probably damaging (0.57)	Probably damaging (0.999)	Probably damaging (0.996)	Effect (57)	Neutral (2)	Disease (6)
rs1280602243	Q122R	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1288210687	G106R	Not found	Probably benign (0.19)	Benign (0.107)	Benign (0.049)	Neutral (39)	Neutral (8)	Neutral (8)
rs1288210687	G58R	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1289802008	V16A	Not found	Probably damaging (0.57)	Probably damaging (1000)	Probably damaging (0.999)	Neutral (37)	Neutral (5)	Neutral (7)
rs1289807114	K97N	Not found	Probably damaging (0.57)	Probably damaging (0.997)	Possibly damaging (0.904)	Effect (32)	Disease (1)	Disease (5)
rs1300600312	R153W	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1308138426	M127T	Not found	Probably benign (0.19)	Probably damaging (0.968)	Probably damaging (0.932)	Neutral (27)	Neutral (8)	Neutral (8)
rs1308138426	M79T	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1311370693	D121E	Not found	Probably benign (0.19)	Benign (0.000)	Benign (0.000)	Neutral (-32)	Neutral (9)	Neutral (9)
rs1311370693	D73E	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1319839593	V82A	Not found	Probably damaging (0.57)	Probably damaging (0.999)	Probably damaging (0.999)	Effect (61)	Neutral (4)	Neutral (8)
rs1330229174	K34E	Not found	Probably damaging (0.57)	Probably damaging (0.960)	Possibly damaging (0.591)	Effect (69)	Disease (3)	Disease (3)
rs1336508566	W152C	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1341543771	C127W	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1342686707	G36R	Not found	Probably damaging (0.57)	Probably damaging (1.000)	Probably damaging (1.000)	Effect (73)	Disease (3)	Disease (4)
rs1342686707	G36S	Not found	Probably damaging (0.57)	Probably damaging (0.999)	Probably damaging (0.999)	Effect (55)	Disease (5)	Disease (1)
rs1342971994	V70M	Not found	Probably benign (0.27)	Probably damaging (0.999)	Probably damaging (0.996)	Effect (52)	Neutral (6)	Neutral (2)
rs1350883078	C169G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found

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SNP ID	Amino acid	SIFT (score)	PANTHER (preservation time)	PolyPhen2 HumDiv (score)	PolyPhen2 HumVar (score)	Predict Protein (score)	PhD-SNP (RI)	SNPs&GO (RI)
rs1350883078	C169R	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1353659879	D119G	Not found	Probably benign (0.19)	Benign (0.076)	Benign (0.085)	Neutral (23)	Neutral (6)	Neutral (8)
rs1353659879	D71G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1356365361	A90P	Not found	Probably benign (0.19)	Probably damaging (0.996)	Probably damaging (0.994)	Effect (69)	Disease (2)	Disease (2)
rs1358566725	A124S	Not found	Probably benign (0.19)	Benign (0.022)	Benign (0.065)	Neutral (20)	Neutral (6)	Neutral (9)
rs1358566725	A124T	Not found	Probably benign (0.19)	Benign (0.000)	Benign (0.003)	Neutral (23)	Neutral (8)	Neutral (9)
rs1358566725	A76S	Not found	Probably benign (0.19)	Probably damaging (0.958)	Probably damaging (0.989)	Neutral (24)	Neutral (3)	Neutral (7)
rs1358566725	A76T	Not found	Probably benign (0.19)	Probably damaging (0.995)	Probably damaging (0.990)	Neutral (-2)	Neutral (8)	Neutral (5)
rs1378041201	M116I	Not found	Probably benign (0.19)	Benign (0.000)	Benign (0.000)	Neutral (30)	Neutral (9)	Neutral (8)
rs1378041201	M68I	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1386226420	S154G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs138969470	L100V	Tolerated (1)	Possibly damaging (0.5)	Benign (0.000)	Benign (0.001)	Neutral (6)	Neutral (7)	Neutral (8)
rs1390433251	Q7K	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1390941715	K8R	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1391033968	E33D	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1418203843	G67R	Not found	Probably benign (0.19)	Probably damaging (0.992)	Probably damaging (0.947)	Effect (67)	Neutral (2)	Disease (6)
rs1418816543	E123V	Not found	Probably benign (0.19)	Probably damaging (0.999)	Probably damaging (0.995)	Neutral (45)	Neutral (7)	Neutral (8)
rs1418816543	E75V	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1422143532	I17V	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1422143532	I17L	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1430517226	F141I	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1432393907	F144L	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1433622151	G25S	Not found	Probably damaging (0.57)	Probably damaging (0.999)	Probably damaging (0.999)	Effect (62)	Disease (2)	Neutral (3)
rs1437489851	A39S	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1437489851	A39T	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1439048770	N55S	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1439048770	N130S	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1450032325	P157T	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs145138372	P117T	Tolerated (0.146)	Probably benign (0.19)	Benign (0.049)	Benign (0.057)	Neutral (41)	Neutral (6)	Neutral (9)
rs145138372	P117S	Tolerated (0.146)	Probably benign (0.19)	Benign (0.025)	Benign (0.038)	Neutral (29)	Neutral (5)	Neutral (9)
rs145138372	P69S	Tolerated (0.146)	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs145138372	P69T	Tolerated (0.146)	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1453729005	E110G	Not found	Probably benign (0.19)	Benign (0.002)	Benign (0.002)	Neutral (32)	Neutral (8)	Neutral (9)
rs1453729005	E62G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1457882398	Q99E	Not found	Probably benign (0.19)	Benign (0.006)	Benign (0.007)	Neutral (-18)	Neutral (9)	Neutral (9)
rs1457882398	Q99K	Not found	Probably benign (0.19)	Benign (0.002)	Benign (0.003)	Neutral (14)	Neutral (7)	Neutral (9)
rs1461467439	K102E	Not found	Probably benign (0.19)	Possibly damaging (0.779)	Possibly damaging (0.527)	Neutral (7)	Neutral (7)	Neutral (8)
rs1465127736	V40I	Not found	Probably damaging (0.57)	Benign (0.125)	Benign (0.101)	Neutral (46)	Neutral (5)	Neutral (3)
rs1477642198	L8F	Not found	Probably benign (0.19)	Benign (0.018)	Benign (0.012)	Neutral (10)	Neutral (9)	Neutral (5)
rs1479114032	F146S	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1482689946	G25C	Not found	Probably damaging (0.57)	Probably damaging (1.000)	Probably damaging (1.000)	Effect (59)	Neutral (6)	Disease (1)
rs149189004	Y156H	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1560486891	Q134H	Not found	Probably benign (0.19)	Possibly damaging (0.940)	Benign (0.360)	Neutral (44)	Neutral (6)	Neutral (9)
rs1560486891	Q86H	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1560486891	Q106H	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1560524266	R139K	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1578143026	A107V	Not found	Probably benign (0.19)	Benign (0.005)	Benign (0.009)	Neutral (-31)	Neutral (7)	Neutral (8)
rs1578143026	A107D	Not found	Probably benign (0.19)	Benign (0.022)	Benign (0.013)	Neutral (27)	Neutral (8)	Neutral (8)
rs1578143026	A59V	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1578143026	A59D	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1578295344	H104R	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1725233317	E82G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1725233317	E103G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1725233739	S129P	Not found	Probably benign (0.19)	Benign (0.000)	Benign (0.003)	Neutral (4)	Neutral (8)	Neutral (9)
rs1725233739	S81P	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found

Table S1. *Comprehensive in silico analysis results for missense SNPs in the SNCA gene*

SNP ID	Amino acid	SIFT (score)	PANTHER (preservation time)	PolyPhen2 HumDiv (score)	PolyPhen2 HumVar (score)	Predict Protein (score)	PhD-SNP (RI)	SNPs&GO (RI)
rs1725235754	E126Q	Not found	Probably benign (0.27)	Probably damaging (0.997)	Probably damaging (0.992)	Neutral (46)	Neutral (7)	Neutral (9)
rs1725235754	E78Q	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1725246888	A107T	Not found	Probably benign (0.19)	Benign (0.009)	Benign (0.017)	Neutral (-16)	Neutral (9)	Neutral (9)
rs1725246888	A59T	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730491175	S49N	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730491492	C48R	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730492057	L46V	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730492879	V42D	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730493151	V42I	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730494908	T34P	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730495830	G31V	Not found	Probably benign (0.19)	Probably damaging (0.964)	Possibly damaging (0.862)	Neutral (49)	Neutral (4)	Neutral (5)
rs1730496897	W28R	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730497167	N27H	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730499966	Y12C	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730500223	T10I	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1730504059	I3K	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733005636	R163M	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733006021	V161G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733006745	P157L	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733007496	Y156C	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733008179	Q155P	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733010215	F151C	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733010589	V148G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733012809	F145I	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733013769	F144L	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733015468	F140L	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733017378	S136P	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733019162	I126V	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733020766	L120P	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733021034	L120V	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733022595	Q113R	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733023185	R112G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733024573	S110P	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1733025440	K103E	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs1737221469	T92N	Not found	Probably benign (0.19)	Possibly damaging (0.937)	Probably damaging (0.957)	Effect (66)	Neutral (1)	Disease (6)
rs1737226139	A76T	Not found	Probably benign (0.19)	Probably damaging (0.995)	Probably damaging (0.990)	Neutral (-2)	Neutral (8)	Neutral (5)
rs1737231525	V63M	Not found	Probably benign (0.19)	Probably damaging (0.999)	Probably damaging (0.996)	Neutral (47)	Neutral (8)	Neutral (3)
rs1738096664	G47E	Not found	Probably benign (0.19)	Probably damaging (1.000)	Probably damaging (1.000)	Effect (71)	Disease (4)	Disease (7)
rs1739236610	Q24R	Not found	Probably damaging (0.57)	Probably damaging (0.962)	Probably damaging (0.978)	Neutral (58)	Neutral (6)	Disease (0)
rs1739238968	V15A	Not found	Probably damaging (0.57)	Probably damaging (1000)	Probably damaging (0.999)	Neutral (51)	Neutral (4)	Disease (1)
rs1739239286	G14R	Not found	Probably damaging (0.57)	Probably damaging (1.000)	Probably damaging (1.000)	Effect (84)	Neutral (1)	Disease (2)
rs191055637	M127I	Deleterious (0.029)	Probably benign (0.19)	Possibly damaging (0.925)	Probably damaging (0.932)	Neutral (33)	Neutral (9)	Neutral (9)
rs191055637	M79I	Deleterious (0.029)	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs200056149	E123K	Tolerated (0.052)	Probably benign (0.19)	Probably damaging (0.997)	Probably damaging (0.989)	Effect (59)	Neutral (7)	Neutral (8)
rs200056149	E75K	Tolerated (0.052)	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs201106962	H50Q	Tolerated (0.854)	Probably benign (0.19)	Possibly damaging (0.469)	Benign (0.090)	Neutral (27)	Neutral (7)	Disease (4)
rs2110065132	E131Q	Not found	Probably benign (0.27)	Possibly damaging (0.906)	Possibly damaging (0.478)	Neutral (14)	Neutral (7)	Neutral (9)
rs2110065132	E83Q	Not found	Probably damaging (0.57)	Probably damaging (0.984)	Probably damaging (0.963)	Neutral (34)	Neutral (2)	Neutral (5)
rs2110065132	E103Q	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs2110217613	P43L	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs2110217706	L35V	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs2110218111	M1V	Not found	Probably damaging (0.57)	Probably damaging (1.000)	Probably damaging (1.000)	Effect (70)	Neutral (6)	Disease (9)
rs2110296574	S154N	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found

Table S1. *Comprehensive in silico analysis results for missense SNPs in the SNCA gene*

SNP ID	Amino acid	SIFT (score)	PANTHER (preservation time)	PolyPhen2 HumDiv (score)	PolyPhen2 HumVar (score)	Predict Protein (score)	PhD-SNP (RI)	SNPs&GO (RI)
rs2110460289	F94S	Not found	Probably benign (0.19)	Possibly damaging (0.921)	Possibly damaging (0.801)	Not found	Neutral (4)	Disease (0)
rs2110460484	E83Q	Not found	Probably damaging (0.57)	Probably damaging (0.984)	Probably damaging (0.963)	Neutral (34)	Neutral (2)	Neutral (5)
rs2110525413	A30G	Not found	Probably damaging (0.57)	Probably damaging (0.989)	Probably damaging (0.985)	Neutral (48)	Disease (0)	Disease (0)
rs372101729	M116V	Tolerated (0.294)	Probably benign (0.19)	Benign (0.000)	Benign (0.000)	Neutral (23)	Neutral (7)	Neutral (8)
rs372101729	M68V	Tolerated (0.294)	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs374953392	T54A	Tolerated (0.211)	Probably benign (0.19)	Probably damaging (0.994)	Probably damaging (0.985)	Neutral (32)	Neutral (4)	Neutral (8)
rs375682339	P138S	Deleterious (0.043)	Probably benign (0.19)	Probably damaging (0.993)	Probably damaging (0.968)	Effect (50)	Neutral (6)	Neutral (9)
rs375682339	P90S	Deleterious (0.043)	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs375682339	P110S	Deleterious (0.043)	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs377006107	Y133C	Tolerated (0.168)	Probably benign (0.19)	Benign (0.002)	Benign (0.001)	Neutral (43)	Neutral (4)	Neutral (7)
rs377006107	Y85C	Tolerated (0.168)	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs377006107	Y105C	Tolerated (0.168)	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs386352363	G84E	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (0.999)	Effect (70)	Neutral (3)	Disease (6)
rs386352363	G84V	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (0.999)	Effect (54)	Neutral (1)	Neutral (2)
rs431905511	G51D	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (0.1000)	Effect (71)	Neutral (5)	Disease (9)
rs533442704	M1K	Not found	Probably damaging (0.57)	Probably damaging (0.968)	Probably damaging (0.969)	Effect (88)	Neutral (0)	Disease (9)
rs542171324	A53G	Not found	Probably benign (0.19)	Benign (0.028)	Benign (0.015)	Neutral (48)	Neutral (4)	Neutral (2)
rs542171324	A53V	Not found	Probably benign (0.19)	Benign (0.014)	Benign (0.006)	Neutral (25)	Neutral (7)	Neutral (4)
rs548523899	K96I	Not found	Probably benign (0.19)	Probably damaging (0.996)	Probably damaging (0.965)	Neutral (41)	Disease (4)	Neutral (9)
rs548523899	K96R	Not found	Probably benign (0.19)	Benign (0.001)	Benign (0.003)	Neutral (23)	Neutral (8)	Neutral (8)
rs557671924	M118I	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs563224784	L13F	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs568285340	F140V	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs745815563	A91D	Not found	Probably benign (0.19)	Probably damaging (0.971)	Possibly damaging (0.758)	Effect (73)	Disease (4)	Neutral (8)
rs746232417	P138H	Not found	Probably benign (0.19)	Probably damaging (0.999)	Probably damaging (0.990)	Effect (55)	Neutral (5)	Neutral (9)
rs746232417	P90H	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs746232417	P110H	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs748517599	K111N	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs749476922	N122I	Not found	Probably benign (0.19)	Benign (0.395)	Benign (0.151)	Neutral (13)	Neutral (7)	Neutral (9)
rs749476922	N122S	Not found	Probably benign (0.19)	Benign (0.000)	Benign (0.001)	Neutral (-15)	Neutral (9)	Neutral (10)
rs749476922	N122T	Not found	Probably benign (0.19)	Benign (0.037)	Benign (0.025)	Neutral (-7)	Neutral (8)	Neutral (9)
rs749476922	N74I	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs749476922	N74S	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs749476922	N74T	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs749526106	G84R	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (0.999)	Effect (79)	Disease (0)	Disease (2)
rs749526106	G84W	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (1000)	Effect (78)	Neutral (4)	Disease (1)
rs749526106	G132W	Not found	Probably benign (0.19)	Probably damaging (0.970)	Possibly damaging (0.722)	Effect (50)	Neutral (8)	Neutral (5)
rs749526106	G132R	Not found	Probably benign (0.19)	Benign (0.001)	Benign (0.007)	Neutral (4)	Neutral (8)	Neutral (7)
rs749526106	G104W	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs749526106	G104R	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs750512067	G41D	Not found	Probably damaging (0.57)	Probably damaging (0.998)	Probably damaging (0.914)	Effect (73)	Disease (6)	Disease (9)
rs750745088	V37F	Not found	Probably damaging (0.57)	Possibly damaging (0.949)	Possibly damaging (0.747)	Effect (72)	Disease (3)	Disease (4)
rs750745088	V37I	Not found	Probably damaging (0.57)	Benign (0.057)	Benign (0.077)	Effect (59)	Neutral (4)	Neutral (3)
rs750899874	P80T	Not found	invalid substitution	Not found	Not found	Not found	Neutral (2)	Not found

Table S1. *Comprehensive in silico analysis results for missense SNPs in the SNCA gene*

SNP ID	Amino acid	SIFT (score)	PANTHER (preservation time)	PolyPhen2 HumDiv (score)	PolyPhen2 HumVar (score)	Predict Protein (score)	PhD-SNP (RI)	SNPs&GO (RI)
rs750899874	P128T	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (0.998)	Neutral (5)	Neutral (8)	Neutral (7)
rs751833438	A56T	Not found	Probably damaging (0.57)	Probably damaging (0.995)	Probably damaging (0.990)	Neutral (49)	Disease (5)	Neutral (4)
rs752472160	A18G	Not found	Probably damaging (0.57)	Probably damaging (0.998)	Probably damaging (0.993)	Effect (64)	Neutral (2)	Neutral (1)
rs752981956	G68E	Not found	Probably benign (0.19)	Benign (0.000)	Benign (0.003)	Neutral (32)	Neutral (6)	Neutral (3)
rs753674628	V26M	Not found	Probably damaging (0.57)	Probably damaging (0.996)	Probably damaging (0.991)	Effect (53)	Neutral (3)	Disease (1)
rs757477802	Q99R	Not found	Probably benign (0.19)	Benign (0.003)	Benign (0.004)	Neutral (15)	Neutral (9)	Neutral (1)
rs760548842	M116T	Not found	Probably benign (0.19)	Benign (0.000)	Benign (0.000)	Neutral (37)	Neutral (8)	Neutral (8)
rs760548842	M68T	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs767026129	T72R	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (0.999)	Effect (50)	Neutral (5)	Neutral (3)
rs767026129	T72M	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (0.998)	Neutral (39)	Neutral (5)	Neutral (3)
rs768838511	D121G	Not found	Probably benign (0.19)	Benign (0.000)	Benign (0.000)	Neutral (35)	Neutral (8)	Neutral (8)
rs768838511	D73G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs769664191	A91T	Not found	Probably benign (0.19)	Possibly damaging (0.757)	Benign (0.343)	Neutral (41)	Neutral (8)	Neutral (8)
rs770296707	V3I	Not found	Probably damaging (0.57)	Benign (0.085)	Benign (0.054)	Neutral (14)	Neutral (8)	Neutral (7)
rs770804878	E114D	Not found	Probably benign (0.19)	Benign (0.037)	Benign (0.042)	Neutral (30)	Neutral (9)	Neutral (9)
rs770804878	E66D	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs774113587	G73C	Not found	Probably benign (0.19)	Probably damaging (1000)	Probably damaging (1000)	Effect (64)	Neutral (4)	Disease (4)
rs774113587	G73S	Not found	Probably damaging (0.57)	Probably damaging (1000)	Probably damaging (0.999)	Effect (52)	Neutral (5)	Disease (1)
rs774124882	E13D	Not found	Probably damaging (0.57)	Benign (0.015)	Benign (0.010)	Neutral (38)	Neutral (6)	Neutral (5)
rs776535649	E105A	Not found	Probably benign (0.19)	Benign (0.173)	Benign (0.052)	Neutral (18)	Neutral (8)	Neutral (9)
rs776535649	E57A	Not found	Possibly damaging (0.5)	Probably damaging (0.999)	Probably damaging (0.998)	Neutral (29)	Neutral (3)	Neutral (3)
rs777070190	V71A	Not found	Probably damaging (0.57)	Probably damaging (1000)	Probably damaging (1000)	Effect (56)	Neutral (6)	Neutral (8)
rs777339905	F4L	Not found	Probably damaging (0.57)	Probably damaging (0.993)	Probably damaging (0.981)	Neutral (14)	Neutral (7)	Neutral (7)
rs778867145	E20G	Not found	Probably damaging (0.57)	Probably damaging (1000)	Probably damaging (0.999)	Effect (71)	Neutral (6)	Disease (1)
rs779158137	P120T	Not found	Probably benign (0.19)	Probably damaging (0.999)	Probably damaging (0.995)	Neutral (10)	Neutral (3)	Neutral (8)
rs779158137	P72T	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs781595227	A140V	Not found	Probably benign (0.19)	Benign (0.437)	Benign (0.066)	Neutral (31)	Neutral (8)	Neutral (8)
rs781595227	A92V	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs781595227	A112V	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs918531737	E137K	Not found	Probably benign (0.19)	Possibly damaging (0.725)	Benign (0.039)	Effect (59)	Neutral (8)	Neutral (8)
rs918531737	E89K	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs918531737	E109K	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs927774368	H32L	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs927774368	H32P	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs931426378	S110F	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs931426378	S110C	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs951147810	R4H	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs967037290	Y167H	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs975274572	L138F	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found
rs980640378	C52G	Not found	invalid substitution	Not found	Not found	Not found	Not found	Not found

ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Injuries Related to Equestrian Sports: The Case of Javelin (Jereed) in Kars

Binicilik Sporlarıyla İlgili Yaralanmalar: Kars'ta Cirit Vakaları

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ABSTRACT

Aim: *Individuals engaged in equestrian sports are susceptible to injuries resulting from falling off a horse, being kicked by a horse, or other horse-related contact situations. This study aimed to examine injury cases associated with the javelin (jereed) game played on horseback and to compare our findings with those of previous studies conducted in this field.*

Materials and Methods: *The study was conducted prospectively over a three-month period during which equestrian jereed activities were most frequent. Patients who experienced injuries due to falling from a horse, being kicked by a horse, horse collisions, being crushed beneath a horse, or injuries caused by the jereed stick were included in the study. Data on patients' age, type of injury, injury location, and medical interventions performed were recorded.*

Results: *The study was completed with a total of 51 patients, the majority of whom were young individuals. According to the mechanism of trauma, the most common injuries (52.9%) were associated with falling from a horse. Regarding injury location, the upper extremities were the most frequently affected area, accounting for 33.3% of cases. In terms of medical procedures, wound debridement with dressing and splint applications were the most common interventions. Approximately one-third of the patients were hospitalized, while the remaining two-thirds were discharged after receiving treatment.*

Conclusion: *In the jereed game, life-threatening injuries may occur. Therefore, we believe that the use of protective equipment by riders and receiving proper training on injury prevention and management can significantly reduce the occurrence of such injuries.*

Key words: *equestrian sports; jereed; injury*

ÖZET

Amaç: *Binicilik sporlarıyla uğraşan bireyler, attan düşme, at tarafından tekmelenme veya atla ilgili diğer temas durumlarından kaynaklanan yaralanmalara karşı hassastır. Bu çalışma, at sırtında oynanan cirit oyunuyla ilişkili yaralanma vakalarını incelemeyi ve bulgularımızı bu alanda yapılmış önceki çalışmalarla karşılaştırmayı amaçlamaktadır.*

Gereç ve Yöntemler: *Çalışma, binicilik cirit aktivitelerinin en sık olduğu üç aylık bir süre boyunca prospektif olarak yürütülmüştür. Attan düşme, at tarafından tekmelenme, at çarpışmaları, atın altında ezilme veya cirit sopasının neden olduğu yaralanmalar nedeniyle yaralanma yaşayan hastalar çalışmaya dâhil edilmiştir. Hastaların yaşı, yaralanma türü, yaralanma yeri ve yapılan tıbbi müdahalelerle ilgili veriler kaydedilmiştir.*

Sonuçlar: *Çalışma, çoğunluğu genç bireylerden oluşan toplam 51 hasta ile tamamlanmıştır. Travma mekanizmasına göre en sık görülen yaralanmalar (%52,9) attan düşme ile ilişkiliydi. Yaralanma yeri açısından, vakaların %33,3'ünü oluşturan üst ekstremiteler en sık etkilenen bölgeydi. Tıbbi prosedürler açısından, pansuman ve atel uygulamaları ile yara debridmanı en yaygın müdahalelerdi. Hastaların yaklaşık üçte biri hastaneye yatırılırken, kalan üçte ikisi tedavi gördükten sonra taburcu edildi.*

Sonuç: *Cirit oyununda yaşamı tehdit eden yaralanmalar meydana gelebilir. Bu nedenle, biniciler tarafından koruyucu ekipman kullanılmasının ve yaralanma önleme ve yönetimi konusunda uygun eğitim alınmasının bu tür yaralanmaların oluşumunu önemli ölçüde azaltabileceğine inanıyoruz.*

Anahtar kelimeler: *binicilik sporları; cirit; yaralanma*

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Introduction

Throughout history, Turks have used horses primarily as a means of transportation[1]. Warrior men who spent long hours on horseback developed the equestrian sport of javelin (jereed) as a display of strength[1]. Although the need for horses as a mode of transportation has decreased in modern times, horses remain a significant part of daily life in our region. It is essential to recognize that interaction with horses can pose risks and may result in injuries[2]. Numerous studies have investigated injuries associated with horseback riding[3–5]. In the United States, horseback riding injuries affect an average of 36 individuals per 100,000 people annually[6]. Among these injuries, the most commonly affected body regions are the extremities (49.7%), head (24.5%), and torso (23.2%)[6,7]. Notably, falling from a horse has been identified as the most common injury mechanism, with the head being reported as the most frequently affected region[7].

Injuries associated with horses have also been reported following incidents such as being crushed beneath a horse, being kicked by a horse, or horse collisions[8]. Wearing personal protective equipment while engaging in equestrian sports may prevent many injuries and reduce morbidity[9]. Unfortunately, it was observed that insufficient attention is given to this precaution in the region where the study was conducted. On the other hand, it is known that the majority of patients with injuries (>85%) were discharged from emergency departments after receiving medical interventions[9]. This study aimed to investigate the types of injuries, injury locations, medical interventions performed, discharge outcomes, and hospitalization rates of patients with injuries resulting from horseback riding and equestrian sports (particularly the jereed game) in the Kars province. To our knowledge, this is the first study in the literature that specifically addresses injuries associated with the sport of jereed.

Materials and Methods

Study Design

Ethics Committee Approval: The ethical approval of this study was accepted as a result of the evaluation by the Kafkas University Faculty of Medicine Ethics Committee Presidency in session number 05, dated 2022, with the number 80576354-050-99/88.

Patients with injuries resulting from equestrian sports who presented to the emergency departments of two hospitals in Kars province were prospectively collected. The study period was selected to coincide with the three-month timeframe during which equestrian activities –primarily the jereed game– were most frequently performed. This period also included the peak season for jereed tournaments. During these three months, non-minor injuries occurring during equestrian sports activities were examined in the emergency departments. Minor injuries were defined as superficial abrasions and lacerations up to 5 cm in size, as well as small traumas that did not require medical intervention. Fractures were classified according to whether they affected the upper or lower extremities.

Patient Data Assessment

Information regarding the injured individuals was provided by local administrators in the regions where the jereed game was played. Hospital patient records were accessed using the names of these injured individuals, and additional information was obtained from on-duty emergency physicians. The mechanism of injury was evaluated separately for each category: falling from a horse, being kicked by a horse, being crushed beneath a horse, horse collisions, and jereed stick-related injuries. Cases where riders fell together with their horses were also classified under the "falling from a horse" category. The type of surface onto which the patients fell was the same across all cases. There were no additional factors that could alter the severity of the trauma. The inclusion criteria consisted of patients of all age groups who participated in jereed or engaged in amateur or professional horseback riding. Individuals without trauma-related lesions or those with minor injuries were excluded from the study. Additionally, since the number of patients who wore protective equipment (helmet, gloves, vest, boots) was very low (n=4), this factor was not specifically addressed in the study.

Statistical Analysis

Excel (Microsoft® Office Excel©) and SPSS version 25.0 (IBM, Chicago, IL) were used for statistical analysis. Numerical variables were expressed as mean ± standard deviation, while categorical variables were presented as percentages. The Chi-square test or Student's t-test was applied for categorical variables. A p-value of <0.05 was considered statistically significant in all analyses.

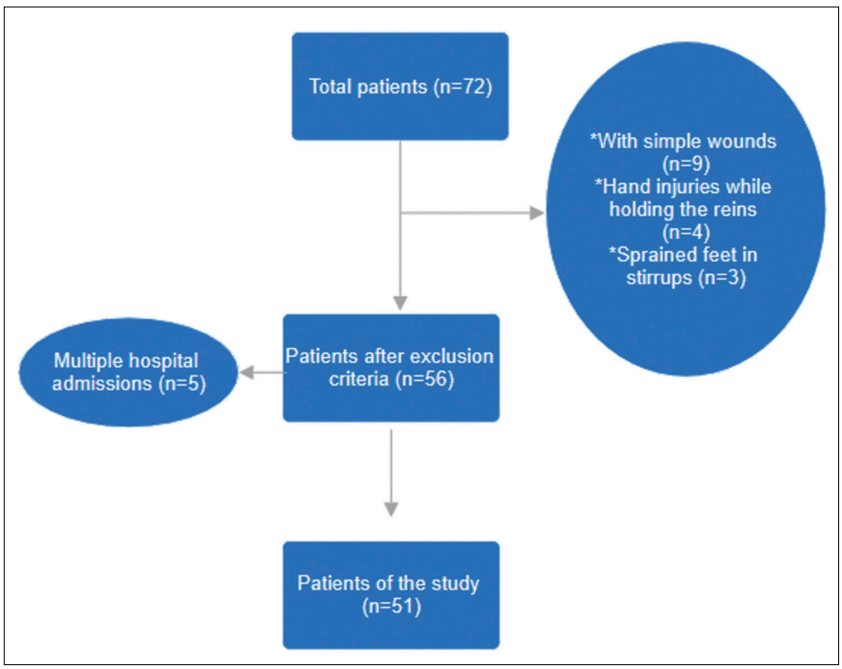

Figure 1. *Flowchart of the study.*

Table 1. *Distribution of injury mechanisms and injury locations among patients*

	Locations					
Trauma Mechanism	Upper Extremity	Lower Extremity	Head / Spinal	Thorax	Pelvis	Total
Falling from a horse	29.6% (n=8)	14.8% (n=4)	18.5% (n=5)	18.5% (n=5)	18.5% (n=5)	27
Being kicked by a horse	50% (n=6)	16.6% (n=2)	25% (n=3)	8.3% (n=1)	-	12
Being crushed by a horse	40% (n=2)	-	20% (n=1)	40% (n=2)	-	5
Horse collisions	75% (n=3)	-	25% (n=1)	-	-	4
Impact of a jereed stick	-	-	66.7% (n=2)	33.3% (n=1)	-	3

Results

Data from a total of 72 patients were recorded. However, patients with minor injuries, hand injuries sustained while holding the reins, injuries resulting from foot sprains in the stirrup, and duplicate entries from the same patient were subsequently excluded. The study was conducted with the remaining 51 patients (Fig. 1).

The mean age of the patients was 34.35 ± 16.61 years (min: 10, max: 79), and all patients were male. When examining the mechanisms of trauma, falling from a horse ranked first, accounting for 52.9% (n=27) of all cases. This was followed by being kicked by a horse at 23.5% (n=12), being crushed beneath a horse at 9.8% (n=5), injuries resulting from horse collisions at 7.8% (n=4), and finally, injuries caused by the impact of a jereed stick at 5.9% (n=3) (Table 1).

Among the injury locations, upper extremity injuries were the most common, observed in 33.3% (n=17) of cases. Injuries to the left and right upper extremities were equally distributed (50%/50%). Head and spinal injuries ranked second, accounting for 25.5% (n=13) of cases. Thoracic injuries were observed in 17.6% (n=9), lower extremity injuries in 13.7% (n=7), and pelvic injuries in 9.8% (n=5) of cases.

The distribution of trauma types was as follows, with abrasions ranking first at 29.4% (n=15), fractures of the upper and lower extremities at 27.5% (n=14), lacerations at 11.8% (n=6), shoulder dislocations at 7.8% (n=4), intracranial hemorrhages at 3.9% (n=2), rib fractures at 3.9% (n=2), pelvic fractures at 3.9% (n=2), vertebral fractures at 1.9% (n=1), skull base fractures at 3.9% (n=2), pneumothorax at 3.9% (n=2), and lung contusion at 1.9% (n=1).

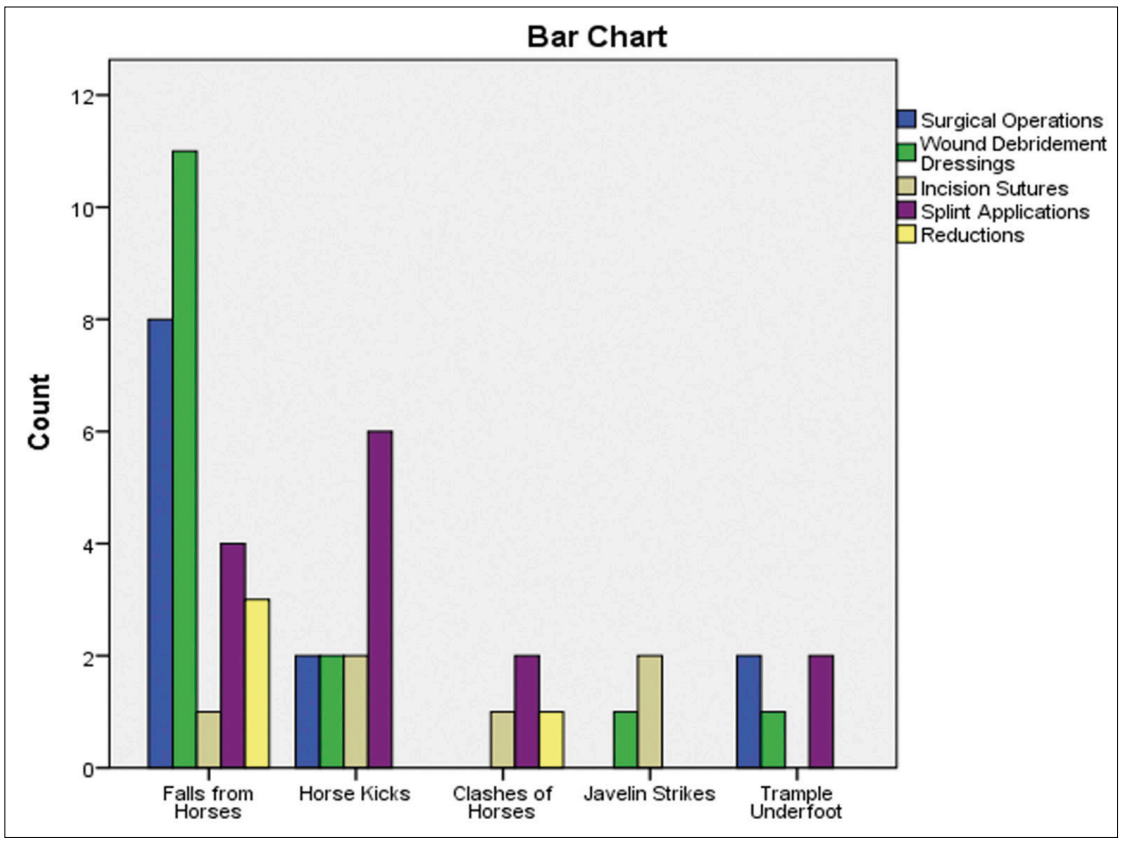

Figure 2. *Comparison of injury mechanisms with medical interventions (Bar chart based on chi-square test).*

The medical interventions performed were as follows: wound dressings with debridement were 29.4% (n=17), short and long splint applications were 27.5% (n=14), all interventional surgical procedures were 23.5% (n=10), laceration sutures were 11.8% (n=6), and shoulder/elbow reductions were 7.8% (n=4).

A comparative statistical Chi-square analysis was performed to evaluate the relationship between the mechanism of injury and the medical interventions performed. The higher frequency of splint applications following horse kicks was found to be statistically significant ($p < 0.05$) (Fig. 2). No statistically significant association was observed between the type of injury, trauma location, and outcome ($p > 0.05$). Similarly, no statistically significant relationship was found between age distribution and the type of injury, trauma location, and outcome ($p > 0.05$).

A total of 62.7% (n=32) of the patients were discharged from the emergency department, while 31.4% (n=16) were admitted to hospital wards, and 5.9% (n=3) were admitted to intensive care units. Given that 9 out of the 16 patients admitted to hospital wards underwent surgery, the association was statistically significant ($p < 0.05$).

Among the patients admitted to hospital wards, internal fixation was performed for extremity fractures in two patients, hip surgery was performed in one patient, thoracic tube placement was carried out in two patients, and two patients underwent surgery for vertebral fractures. For the patients admitted to intensive care units, thoracic tube placement was performed in one patient, hip surgery was performed in one patient, and one patient underwent surgery for intracranial hemorrhage.

A statistical analysis was conducted to evaluate the relationship between the mechanism of injury and patients' admission or discharge status. The higher rate of ward admissions among patients who fell from a horse was found to be statistically significant according to the T-test analysis ($p = 0.021$).

Discussion

The most common locations where horse-related injuries occur are horse farms and sports fields[10]. Although jereed is a sport played on horseback, it is performed on open fields used as sports arenas. During the game, players throw a stick called a jereed at their opponents

while riding at speed, aiming to hit their opponent without falling from the horse. This sport, unique to the Turkish culture, is currently practiced most actively in the cities of Kars, Ardahan, Erzurum, and Bayburt[11].

The force generated by a horse's kick is estimated to be around 400 joules. This high-energy impact can cause cranial fractures or intracranial hemorrhages in cases of head trauma[12]. In the United Kingdom, head injuries occur in more than one-third of horse-related accidents[13]. Serious head injuries resulting from falls from horses are attributed to the rider's head being positioned up to 4 meters above the ground and the horse's average running speed of approximately 65 km/h.

In the study conducted by Meredith et al., the age group of horse riders generally consisted of young adults under the age of 40[4]. Globally, horseback riding injuries are more commonly observed among women; however, jereed, as an equestrian sport, is exclusively performed by men[14]. In our study, all patients were male. A study by Chitnavis et al. reported that the most frequently injured individuals were amateur young female riders[15]. Similarly, a study conducted in rural Virginia showed that the injury rate among children was nearly twice that of adults[16]. Since adults predominantly practice this sport, the proportion of children in our study was low (11.7%). In the study by Neville E. K., although the majority of riders were young individuals under the age of 40, a significant portion of the injured population (90%) consisted of women[17]. However, since the jereed game is played exclusively by men, no female participants were included in our study, and thus, no comparison could be made.

Among injuries resulting from falls from horses, upper extremity injuries rank first, accounting for one-third of the cases[4,18]. While a decrease in head trauma has been observed with helmet use, the number and severity of upper extremity injuries tend to increase[18]. In our study, due to the absence of helmet use, head and neck injuries were observed in one out of every four patients. On the other hand, upper extremity injuries, accounting for 33.3%, ranked first among all injury types.

In a study examining horseback riding injuries, falls from horses accounted for 58.4% of injury mechanisms. The rate of head and neck injuries following horse kicks was reported as 44%. Cranial pathologies mostly (82%) occurred after falls from horses[4]. Head injuries are also frequently observed in accidents where the individual is not mounted, such as horse kicks[19]. In our study, cranial pathologies following falls from horses were observed at a rate of 18.5%, which was higher compared to other trauma mechanisms. In a study conducted by Thomas et al., abrasions and lacerations ranked first among injuries at 31.4%, followed by fractures at 25.2%[20].

Although serious injuries can occur in horse-related accidents, it is common for more than 80% of cases to be treated and discharged from the emergency department[21]. We believe that the slightly lower discharge rate in our study (62%) is due to severe injuries resulting from the lack of protective equipment. On the other hand, approximately 20% of the patients in our study underwent surgical procedures. Horseback riding is associated with a high rate of morbidity and mortality. When evaluated in terms of accident frequency, it is considered nearly 20 times more dangerous than motorcycle riding[22]. In a study analyzing US data, a review of medical reports on fatalities revealed that 217 deaths per year were associated with horseback riding[23]. However, in our study, no deaths were observed.

Limitations

There are several limitations in our study. Firstly, some riders did not seek hospital care after experiencing traumas such as falls or kicks, considering them insignificant. As a result, data for these cases could not be obtained. Additionally, the number of patients included in the study was insufficient to represent a general sample. Conducting similar studies with larger patient populations would provide more statistically significant results.

Conclusion

Horseback riding and jereed, among the most common sports activities in our region, lead to serious injuries due to the limited use of protective equipment. Our study is the first to specifically examine injuries occurring during the jereed game within the context of equestrian sports-related injuries. The likelihood of injuries progressing to life-threatening conditions can be reduced by wearing protective gear and providing more comprehensive training in horseback riding.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Examining Prediabetes Risks in COVID-19 Cases: What Insights Does the COVID Follow-up Clinic Provide?

COVID-19 Vakalarında Prediyabet Risklerinin İncelenmesi: COVID Takip Kliniği Hangi Bilgileri Sunuyor?

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ABSTRACT

Aim: *Given the potential metabolic impacts of COVID-19, understanding the relationship between post-COVID-19 health and prediabetes can provide insights into the long-term consequences of the disease. This study aims to evaluate the risk factors associated with the development of prediabetes in patients following COVID-19 infection.*

Materials and Methods: *This descriptive case series study included five patients diagnosed with new-onset prediabetes after COVID-19, who visited the COVID-19 Follow-up Clinic. Demographic data, medical history, and laboratory findings were collected retrospectively from the Health Management System. Risk factors such as physical activity levels, smoking, body mass index, and the use of corticosteroids were assessed concerning prediabetes development.*

Results: *Prediabetes was diagnosed in 4.2% of patients after COVID-19 disease. The findings revealed that 80% of the patients were male, with an average age of over 65 years. Several risk factors, including age, gender, low physical activity levels, and corticosteroid use during COVID-19 treatment, were associated with an increased likelihood of prediabetes. One patient was found to have high clinical frailty, which may further predispose them to metabolic imbalances.*

Conclusion: *COVID-19 may contribute not only to acute health issues but also to long-term metabolic risks such as prediabetes. Post-COVID-19 patients with prediabetes require close monitoring and lifestyle interventions to mitigate the risk of progression to diabetes mellitus. This study underscores the importance of assessing metabolic health in COVID-19 survivors and calls for further research with larger sample sizes to deepen our understanding of COVID-19's long-term effects on metabolic health.*

Key words: *prediabetic state; COVID-19; preventive health services; assessment of healthcare needs*

ÖZET

Amaç: *COVID-19'un potansiyel metabolik etkileri göz önüne alındığında, hastalık sonrası sağlık durumu ile prediyabet arasındaki ilişkinin anlaşılması, uzun vadeli sonuçlara dair önemli ipuçları sağlayabilir. Bu çalışma, COVID-19 enfeksiyonu sonrası prediyabet gelişimi ile ilişkili risk faktörlerini değerlendirmeyi amaçlamaktadır.*

Materyal ve Metot: *Bu tanımsal olgu serisi çalışması, COVID-19 Takip Kliniğine başvuran ve COVID-19 sonrası yeni başlamış prediyabet tanısı alan beş hastayı içermektedir. Hastaların demografik verileri, tıbbi özgeçmişleri ve laboratuvar bulguları, Sağlık Yönetim Sistemi'nden geriye dönük olarak toplanmıştır. Egzersiz öyküleri, sigara kullanımı, kilo değişimleri ve tedavide steroid kullanımı gibi risk faktörleri prediyabet gelişimi açısından incelenmiştir.*

Bulgular: *COVID-19 hastalığı sonrasında hastaların %4,2'sine prediyabet tanısı konulmuştur. Hastaların %80'inin erkek olduğu ve ortalama yaşın 65'in üzerinde olduğu belirlenmiştir. Egzersiz düzeyinin düşük olması ve COVID-19 tedavisi (kortikosteroid kullanımı) gibi risk faktörleri prediyabet gelişme olasılığını artırmaktadır. Ayrıca, bir hastada yüksek klinik kırılganlık tespit edilmiştir.*

Sonuç: *COVID-19 sadece kısa dönemde sağlık sorunlarına neden olmakla kalmamakta ve uzun vadeli metabolik risklere de yol açabilmektedir. Prediyabet tanısı alan COVID-19 sonrası hastaların, diyabetes mellitus gelişme riskini azaltmak için yakından izlenmesi ve yaşam tarzı değişiklikleri yapması gerekmektedir. Bu çalışma, COVID-19'dan kurtulan bireylerin metabolik sağlık durumunun değerlendirilmesinin önemini vurgulamakta ve uzun dönemde metabolik sağlığa etkilerini daha iyi anlamak için daha geniş örneklemli araştırmaların gerekliliğine dikkat çekmektedir.*

Anahtar kelimeler: *diyabet öncesi dönemler; COVID-19; koruyucu sağlık hizmetleri; sağlık bakım gereksinimlerinin değerlendirilmesi*

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Introduction

In 2019, in Wuhan province of China, an infectious disease was identified; the cause of this disease is unknown, and it progresses to lung failure[1]. Subsequent research identified the SARS-CoV-2 virus as the cause of this disease, which was officially named COVID-19[2]. Due to the rapid global transmission of COVID-19, the World Health Organization (WHO) declared it a pandemic on March 12, 2020[3]. Although COVID-19 is known to be acute and fatal, the potential to cause chronic diseases in the long term is being investigated by many studies[4,5]. One of these chronic diseases is Diabetes Mellitus (DM)[6]. It has been theorized that COVID-19 disease can prepare the ground for the development of DM, either directly or indirectly[7]. Patients with severe COVID-19 have a higher risk of developing insulin resistance, impaired beta cell function, glucose intolerance (prediabetes), and type 2 diabetes during long-term follow-up, compared to individuals who were not hospitalized or who did not have COVID-19. The most important of these theories is that the SARS-CoV-2 virus causes damage to these cells by binding to ACE-2 receptors in the beta cells of the pancreas, thereby reducing insulin release[8]. This has been based on studies that may increase the risk of developing DM in individuals undergoing COVID-19[6]. Also, the rise of new cases of prediabetes after COVID-19 is noteworthy[8].

Prediabetes is an intermediate stage with a 37% risk of developing DM if left untreated. However, in people diagnosed with prediabetes, the development of DM can be prevented mainly through effective lifestyle changes and interventions[9]. The risk factors involved in the development of DM are often examined in two main categories: Unmodifiable risks (age, gender, ethnicity, etc.) and modifiable risks (obesity, smoking, alcohol use, physical activity, etc.)[10].

In this study, individuals diagnosed with prediabetes after COVID-19 will be assessed how effective these risk factors are.

Materials and Methods

This cross-sectional study included all patients who applied to the COVID Follow-up Clinic affiliated with a training and research hospital between 01/12/2021 and 01/03/2022 and were newly diagnosed with prediabetes during this period. Ethical permission was obtained from the Bandırma Onyedi Eylül University, Faculty of Health Sciences Non-Interventional Research Ethics Committee for this study with date 13 September 2022 and number 2022-109. In the study, 118 patients who had not previously been diagnosed with prediabetes or DM were evaluated in the COVID Follow-up Clinic, and a total of five patients were newly diagnosed with prediabetes. Patient data were obtained through the file scanning method via the Public Health Management System. The data includes patients' sociodemographic information, medical history, applied test results, and laboratory findings.

COVID Follow-up Clinic

The COVID Follow-up Clinic, where the study was conducted, was established by the Ministry of Health in 2021 to monitor patients who had received inpatient treatment for COVID-19. The clinic is staffed by a multidisciplinary team comprising a specialist physician, a general physician, allied health personnel, and administrative support. Patients eligible for screening are identified by the Ministry of Health. Following a 28-day whole recovery period after completion of COVID-19 treatment, patients' information is entered into the Public Health Management System. Written and verbal informed consent was obtained from all participants, and the designated screening tests were subsequently administered.

In this study, the patients' demographic information (age, gender, marital status), medical history, chronic diseases before and after COVID-19, smoking and alcohol use, exercise habits, COVID-19 diagnosis period, presence of pneumonia, medications used due to COVID-19, history of intensive care admission, symptoms, and physical examination results were examined. In addition, laboratory tests (glucose, HbA1c) and functional assessment tests (Six-Minute Walking Test, Malnutrition Universal Screening Tool (MUST), Mini Nutritional Assessment short-form (MNA-SF), Mini-Mental Test Health-Related Quality of Life (EQ-5D), ECOG Performance Test, and Clinical Frailty Scale) were evaluated[11–17]. Prediabetes was diagnosed when the fasting blood sugar (FBS) level was 100-125 mg/dl or the HbA1c level was 5.7-6.4%. One of the diagnostic criteria, being within these limits, was considered sufficient to diagnose the patient with prediabetes.

Statistical Analysis

The data of all patients were systematically entered into an Excel file, and both dependent and independent

variables were analyzed using descriptive statistical methods, including frequency (n, %), mean ± standard deviation, median, and range (minimum and maximum values).

Results

The mean age of the 118 patients included in the screening was 58.48 ± 14.33 years, with 59.3% male and 40.7% female. Among these patients, five were newly diagnosed with prediabetes following COVID-19. The rate of newly diagnosed prediabetic patients was determined to be 4.2%. The mean age of this group was 66.6 ± 3.21 years, and 80% were male. The median time for patients to apply to the COVID Follow-up Clinic after a COVID-19 diagnosis was 10 (8-14) months. Three patients were married, and two patients were found to have lost their spouses due to COVID-19 and were living alone.

A history of smoking was detected in 40% of the patients, but they were not active smokers. None of the patients drank alcohol. When their exercise habits were examined, it was determined that three patients exercised irregularly (less than 20 minutes 3 days a week), and two did not exercise. Following the course of COVID-19, one patient reported experiencing weight loss exceeding 10% of their initial body weight.

Upon reviewing pre-existing chronic conditions before COVID-19, it was found that one patient suffered from both hypertension and asthma, another had coronary artery disease, and a third was diagnosed with chronic obstructive pulmonary disease (COPD). Only one patient was diagnosed with hypertension after COVID-19 and started treatment.

All patients were diagnosed with COVID-19 pneumonia, with four requiring monitoring in the intensive care unit (ICU), although none of them needed intubation. It was determined that all patients were started on favipiravir treatment and all patients were given methylprednisolone treatment during their hospitalization. It was determined that one patient was administered high-dose methylprednisolone (250 mg/day) and two patients were given high-dose vitamin C treatment. The patient's demographic data and medical information regarding COVID-19 disease are included in Table 1.

Table 1. *The patient's demographic data and medical information on COVID-19 disease*

Age (year), Mean ± SD	66.60±3.21
Women, N (%)	1 (20%)
Men, N (%)	4 (80%)
Body Weight, now (kg), Median (Min-Max)	81.7 (69,5–82,70)
Body Weight, before COVID-19 (kg), Median (Min-Max)	82 (70–85)
Body Weight, after COVID-19 (kg), Median (Min-Max)	80 (60–82)
Weight loss during COVID-19 (kg), Median (Min-Max)	3 (0–12)
COVID-19 Diagnosis Period (month), Median (Min-Max)	10 (8–14)
Pneumonia, N (%)	5 (100%)
Intensive Care, N (%)	4 (80%)
Intubation, N (%)	0 (0%)
Treatments	
Favipiravir, N (%)	5 (100%)
Corticosteroid, N (%)	1 (20%)
Vitamin-C, N (%)	1 (20%)

SD: standard deviation.

Physical Examination Results

During the physical examinations of the patients, tachycardia (pulse>120/min) was detected in one patient, and uncontrolled hypertension was detected in one patient. When the body mass indexes (BMI) were evaluated, it was determined that two patients were of normal weight, two were overweight, and one was classified as type 1 obesity. The physical examination results are included in Table 2.

Table 2. *The physical examination results*

Body Temperature (°C), Median (Min-Max)	36.2 (36–37)
Pulse (/minute), Median (Min-Max)	87 (66–127)
Systolic Blood Pressure (mmHg), Median (Min-Max)	120 (110–160)
Diastolic Blood Pressure (mmHg), Median (Min-Max)	70 (60–90)
Respiratory Rate (/minute), Median (Min-Max)	16 (14–24)
SpO^2 (%), Median (Min-Max)	97 (97–99)
Height (cm), Median (Min-Max)	175 (155–182)
Weight (kg), Median (Min-Max)	81.7 (69.5–82.7)
Body Mass Index (kg/m^2), Mean ± SD	26.3±4.69

SD: standard deviation.

Functional Assessment Tests

Analysis of the Six-Minute Walking Test revealed that three patients reported mild shortness of breath and fatigue following the walking exercise. The Malnutrition Test (MUST) results were normal, and the nutritional tests (MNA-SF) were also normal in all patients. Mini-Mental Test scores were between 28 and 30, and quality of life scores ranged between 95 and 100%. Based on the ECOG performance scale, four patients demonstrated full activity levels, while one patient exhibited minor limitations in physical functioning. In the Clinical Frailty Test, one patient was found to have a higher risk of frailty. The functional assessment tests are included in Table 3.

Table 3. *The functional assessment test results*

	Median (Min-Max)
MUST	0 (0–0)
MNA-SF	12 (10–12)
Mini-Mental Test	29 (28–30)
EQ-5D	100 (95–100)
ECOG Performance Test	0 (0–1)
Clinical Frailty Scale	0 (0–0)

MUST: Malnutrition Universal Screening Tool; MNA-SF: Mini Nutritional Assessment short-form; EQ-5D: Euroqol 5 Dimension Health-Related Quality of Life; ECOG: Eastern Cooperative Oncology Group.

Discussion

This study focuses on identifying risk factors in patients who developed prediabetes following COVID-19. The results indicate that most patients are male and aged over 65, with post-COVID-19 weight fluctuations, reduced physical activity, and pre-existing chronic conditions (particularly hypertension) being linked to prediabetes onset. Notably, corticosteroid therapy and intensive care admission were found to elevate the risk of prediabetes. Additionally, lifestyle factors, including physical inactivity, were identified as significant contributors to the development of prediabetes. Our study reveals that COVID-19 is not only an acute disease, but can also lead to long-term metabolic complications.

Among the risk factors for DM, an analysis of gender and age revealed that 80% of the participants were male, with an average age exceeding 65 years. It has been reported in previous studies that modifiable risk factors for prediabetes are more common in male individuals[9,10]. It is known that insulin resistance may increase physiologically with advanced age, and glucose metabolism may deteriorate[18]. These findings obtained in our study support that gender and age are important risk factors in the development of prediabetes. In addition, quarantine measures implemented during the COVID-19 pandemic have led to significant lifestyle changes, especially in the elderly population. Especially in elderly individuals living alone, the difficulty in accessing the necessary materials for proper nutrition has led to an increase in nutritional disorders and, therefore, metabolic risks[19].

When evaluated in terms of habits, although smoking was not actively continuing in our study, it was determined that two patients had smoked in the past. Previous studies have shown that smoking increases abdominal fat and triggers insulin resistance[10]. Therefore, smoking is considered a significant risk factor for prediabetes. When the patients' physical activity habits were examined, it was determined that two patients did not exercise at all, while the others had irregular exercise habits. Inadequate physical activity is a strong risk factor in the development of prediabetes and DM[9]. Studies conducted especially during the COVID-19 pandemic indicate that quarantine practices and a decrease in physical activity increase the risk of developing insulin resistance and DM[6].

Upon reviewing the patients' medical histories, it was found that one individual had both hypertension and asthma, another suffered from coronary artery disease, and a third was diagnosed with COPD. Additionally, one patient developed hypertension following COVID-19, and their blood pressure was noted to be poorly managed. There are similar risk factors associated with metabolic syndrome, such as smoking, insufficient physical activity, and obesity, for hypertension and prediabetes[18]. Therefore, it is important to screen patients diagnosed with hypertension for prediabetes and DM regularly. In addition, one patient did not have a diagnosis of hypertension, but his blood pressure was uncontrolled. Studies have observed an increase in systolic and diastolic blood pressures after COVID-19 disease, which increases the susceptibility to the development of hypertension[5]. For this reason, it is recommended that patients at risk of hypertension after COVID-19 be followed up regularly. COVID-19 pneumonia was detected in all patients, 80% of whom received intensive care treatment, but no patient was intubated. All patients received corticosteroid treatment, including high-dose methylprednisolone. Treatment for COVID-19 was administered in accordance with the guidelines set by the Turkish Ministry of Health, with favipiravir and corticosteroids being the preferred therapeutic options for

patients presenting with pneumonia. Metabolic changes after COVID-19 are influenced by the immune system's response to viral infection and the treatment protocols used (e.g., corticosteroids). Corticosteroids are known to increase insulin resistance and increase blood sugar levels. Previous studies have shown that the risk of developing prediabetes and DM increases in patients receiving corticosteroid treatment due to acute COPD attacks[20]. In light of these findings, patients receiving corticosteroid treatment due to COVID-19 pneumonia should have their blood sugar levels closely monitored after discharge. Physical examinations of patients applying to the COVID-19 Follow-up Clinic revealed that fever levels were within normal limits, and tachycardia was detected in one patient. In addition to the acute manifestations of COVID-19 infection, symptoms such as postural orthostatic tachycardia syndrome (POTS) have also been observed in some patients 4 weeks after infection[21]. Although the pathophysiology of POTS is not fully understood, it is thought to be associated with COVID-19.

When the patients' BMI was evaluated, it was determined that one patient had type 1 obesity, two patients were overweight, and two patients were of normal weight. In our study, metabolic imbalances such as weight loss or excessive weight gain were observed in the patients. It was observed that one patient lost more than 10% of his body weight during the COVID-19 infection. Weight loss during the COVID-19 process has been associated with factors such as major inflammation, malnutrition, and muscle loss due to immobilization (sarcopenia)[22]. Other factors that may contribute to this weight loss include loss of appetite, taste disturbance, and renal and cardiac dysfunctions. Physical weakness and muscle loss that develop in individuals after COVID-19 can disrupt glycemic control. Therefore, it is recommended to place more importance on nutrition and rehabilitation in the treatment of patients. Rapid weight gain was detected in one patient after COVID-19. Previous studies have shown that obesity has increased rapidly during the pandemic period[22]. Therefore, it is recommended that policies and interventions considering BMI be included in future pandemic planning.

According to the patients' Six-Minute Walking Test results, symptoms (mild dyspnea and fatigue) were observed in three patients after walking. This test plays an important role in evaluating patients' cardiopulmonary functions and pulmonary capacities, providing information about the disease's prognosis. It was observed that the Six-Minute Walking Test distances were longer and the symptoms were less severe in individuals with mild COVID-19 infection compared to those with moderate and severe COVID-19 infection[23]. It is known that these symptoms cause restrictions in the patients' daily activities. In clinical frailty tests, it was determined that a patient was at risk of serious frailty. In individuals with clinical frailty, decreased physical activity, loss of muscle mass, poor nutritional status, and cognitive function losses, as well as metabolic disorders such as impaired glucose metabolism and increased insulin resistance, can accelerate the development of prediabetes[24]. In individuals diagnosed with prediabetes, frailty may increase the risk of transitioning to DM. In this context, the clinical frailty observed in our study should be considered as an additional risk factor in the monitoring of prediabetes patients.

Limitations of the Study

Limitations of the study include the small sample size and retrospective design. Therefore, the lack of important findings for prediabetes, such as waist circumference and biochemical markers like HDL, triglycerides, and uric acid, limited the ability to perform a comprehensive metabolic evaluation.

Conclusions

This study evaluated various risk factors in patients diagnosed with prediabetes after COVID-19 disease and presented important findings regarding the long-term metabolic effects of COVID-19. Our study observed that factors such as advanced age, male gender, low physical activity, and frailty were effective in the development of prediabetes. In particular, it was determined that corticosteroid treatment applied due to COVID-19 may increase insulin resistance and thus increase the risk of prediabetes.

It should be considered that COVID-19 can lead to not only acute but also chronic metabolic complications. Therefore, it is recommended that individuals diagnosed with prediabetes after COVID-19 be under close follow-up and make lifestyle changes to improve their metabolic health. This study highlights the need to assess the risk of prediabetes and DM in COVID-19 survivors and underscores the significance of conducting additional research with larger cohorts to explore this association further.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Effect of Meteorological Parameters on the Frequency of Acute Myocardial İnfarction Events: A Retrospective Study

Meteorolojik Parametrelerin Akut Miyokard Enfarktüsü Olaylarının Sıklığı Üzerindeki Etkisi: Retrospektif Bir Çalışma

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ABSTRACT

Aim: *Environmental factors, diet, exercise, smoking, and psychological and physical stress affect the frequency of acute myocardial infarction (AMI). Weather events also affect this frequency. This study aimed to investigate the effects of meteorological parameters in Amasya/Türkiye on AMI frequency.*

Material and Methods: *We evaluated the association of the frequency of AMI subtypes, such as unstable angina pectoris (USAP), non-ST-elevation myocardial infarction (NSTEMI), or ST-elevation myocardial infarction (STEMI), with meteorological parameters over 6 years.*

Results: *AMI frequency significantly increased in the winter. In summer, there was a significant positive relationship between the mean current pressure and the number of NSTEMI events. The STEMI risk was 1,174 times higher in summer than in winter and 1,214 times higher in summer than in spring. Non-ST-elevation myocardial infarction risk was 1,138 times higher in winter than in summer. The USAP risk was 1,350 times higher in winter than in summer. In summer, a significant positive relationship was observed between total precipitation and the number of USAP events. Among meteorological parameters, air temperature was closely associated with AMI risk.*

Conclusions: *We observed that AMI frequency increases, particularly in the winter, when the average temperature is low. Thus, establishing awareness of avoiding long-term exposure to cold weather can help reduce the risk of low-temperature-related AMI.*

Key words: *acute myocardial infarction; air temperature; atherosclerosis; cold weather*

ÖZET

Amaç: *Çevresel faktörler, diyet, egzersiz, sigara içme ve psikolojik ve fiziksel stresin akut miyokard enfarktüsü (AMI) sıklığını etkilediği gibi hava olayları da bu sıklığı etkiler. Bu çalışma, Amasya/Türkiye'de meteorolojik parametrelerin AMI sıklığı üzerindeki etkilerini araştırmayı amaçlamıştır.*

Gereç ve Yöntemler: *Kararsız angina pektoris (USAP), ST yükselmesiz miyokard enfarktüsü (NSTEMI) veya ST yükselmesiz miyokard enfarktüsü (STEMI) gibi AMI alt tiplerinin sıklığının meteorolojik parametrelerle ilişkisini altı yıllık bir periyotta değerlendirdik.*

Bulgular: *AMI sıklığı kışın önemli ölçüde arttı. Yaz aylarında, ortalama mevcut basınç ile NSTEMI olaylarının sayısı arasında önemli bir pozitif ilişki vardı. STEMI riski yaz aylarında kışa göre 1.174 kat ve yaz aylarında ilkbahara göre 1.214 kat daha yüksekti. NSTEMI riski kışın yaza göre 1.138 kat daha yüksekti. Kararsız angina pektoris riski kışın yaza göre 1.350 kat daha yüksekti. Yazın, toplam yağış ile USAP olaylarının sayısı arasında anlamlı bir pozitif ilişki gözlemlendi. Meteorolojik parametreler arasında, hava sıcaklığının AMI riski ile yakından ilişkili olduğu görüldü.*

Sonuç: *Akut miyokard enfarktüsü sıklığının, özellikle ortalama sıcaklığın düşük olduğu kış aylarında arttığını gözlemledik. Bu nedenle, soğuk havaya uzun süreli maruz kalmaktan kaçınma konusunda farkındalık oluşturmak, düşük sıcaklıkla ilişkili AMI riskini azaltmaya yardımcı olabilir.*

Anahtar kelimeler: *akut miyokard enfarktüsü; hava sıcaklığı; ateroskleroz; soğuk hava*

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Introduction

Health is a state of biological, psychological, and social well-being. Human health is affected by many factors, including the environment in which a person lives and weather conditions. Along with the changing seasons, changes in air temperature also have a significant impact on human health. Recent epidemiological studies have shown that chronobiological and environmental factors, such as air temperature, air pollution, relative humidity, precipitation, wind, and atmospheric pressure, affect the frequency of acute myocardial infarction (AMI)[1,2]. Decreases in temperature during the autumn and winter months significantly affect social life, human psychology, hormonal balance, and many systems in the human body. Blood pressure, glucose level, heart rate, blood fluidity, brain activity, skeletal system mobility, gastrointestinal habits, and skin tension are affected by air temperature[3–6].

The mechanisms related to the effects of meteorological parameters on AMI frequency are multifactorial. As a result of activation of the sympathetic nervous system in cold weather conditions, blood pressure, heart rate, left ventricular end-diastolic pressure, and myocardial oxygen demand increase with catecholamine overflow. Subsequently, the cardiac diastole period shortens, and coronary blood flow begins to deteriorate. The ischemia threshold decreases, and the coagulation cascade is activated[7–10]. Another mechanism is that, in cold weather, constriction occurs in the vascular bed to maintain the body's internal temperature at a certain level, which results in increased blood pressure. Total vasoconstriction increases arterial wall stress; therefore, this phenomenon is an important precursor of coronary plaque rupture and AMI[11–14].

Cold weather conditions are associated with pro-inflammatory and prothrombotic activation. Prothrombotic activation is associated with plaque rupture, which can lead to acute coronary syndrome[15,16]. Cold weather also increases the formation of new platelets, and tendency to clot. Consequently, as the viscosity and number of red blood cells increases, the amount of blood plasma decreases[17–19]. In cold weather, there is a relative increase in cholesterol levels owing to hemoconcentration, an increase in average daily calorie intake, and a decrease in physical activity. In addition, the incidence of upper respiratory tract infections increases during cold weather. Influenza is specifically associated with an increased risk of AMI[18–20].

To the best of our knowledge, no study has been conducted in Türkiye investigating the effects of weather changes on myocardial infarction. We believe that this is an important public health issue in our country, where dynamic weather changes are observed, and that studies conducted in this area are valuable for primary prevention measures. Therefore, we aimed to reveal the effect of meteorological parameters on the incidence of AMI in a group of patients who underwent invasive coronary angiography and percutaneous coronary intervention.

Material and Methods

Study Population and Definitions

Our department, the only third-level hospital in the province, is a high-intensity unit where primary percutaneous coronary intervention (PCI) is performed throughout the day. Approximately 1,000 patients apply to the emergency department of our hospital daily. Patients with a preliminary diagnosis of AMI were accepted from Amasya City Center, the districts, and the surrounding provinces.

We included 5,234 patients, aged >18 years, who were admitted to Amasya University Medical Faculty Education and Research Hospital with a diagnosis of AMI between 1 January 2018 and 1 January 2024 and underwent emergency coronary angiography. The authors had access to information that could identify individual participants during or after data collection. All the data, which has been used for research purposes, was accessed and collected between 15 June 2024 and 30 August 2024. All patients diagnosed with unstable angina pectoris (USAP), non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI), according to the Fourth Universal Definition of Myocardial Infarction, were included[21]. Clinical evidence of acute myocardial ischemia is accompanied by a rise and/or fall in cardiac troponin levels, with at least one value greater than the 99th percentile of the upper reference limit and at least one of the following: symptoms of myocardial ischemia; new ischemic electrocardiogram changes; pathological Q wave formations; imaging evidence of recent loss of viable myocardium or recent regional wall motion abnormalities consistent with ischemic etiology; and detection of a coronary thrombus by angiography or autopsy[22].

Ethics Statement

Due to the retrospective nature of the study, the requirement for obtaining informed consent from patients was waived by Amasya University Rectorate Non-Interventional Clinical Research Ethics Committee. The study was approved by the ethics committee of the Amasya University Rectorate Non-Interventional Clinical Research Ethics Committee (document date and number: 08.03.2024-184593; board decision number: E-76988455-050.04-184593). All experiments were performed in accordance with relevant guidelines and regulations.

The values of meteorological parameters for the relevant period were obtained with official permission from the Amasya Meteorology Directorate of the Republic of Türkiye.

Climate Characteristics

Amasya City is located in northern Türkiye, in the Central Black Sea Region. According to data from the General Directorate of State Meteorology, the climate is generally semi-arid and slightly humid, with mild winters and hot, dry summers. Amasya has a transitional climate between the humid Black Sea Climate and the semiarid and continental Central Anatolian climate. The annual average temperature in Amasya is approximately 13.5°C. The difference between the city's summer and winter temperatures is significant (21.3°C); the highest monthly average temperature is seen in August (23.8°C), and the lowest average temperature is seen in January (2.5°C)[23].

Although the city is affected by cold air currents in winter, it is a settlement where snowfall is low. The temperature does not drop significantly in winter, and the summer temperatures are relatively high. The average duration of monthly sunshine was 5.7 h. The average sunshine duration in Amasya is 9.1 hours in the summer months, with the highest duration in July (9.5 hours).

Meteorological data were obtained from the Amasya Meteorology Directorate of the Republic of Türkiye, the only meteorological unit in the city center of Amasya, and included daily, monthly, and annual data tables covering January 2018 to January 2024. Temperature values (°C), relative humidity (%), precipitation (mm), and atmospheric pressure (hpa) were collected. Seasons were defined as follows: Winter months: December, January and February; Spring months: March, April and May; Summer months: June, July and August; Autumn months: September, October and November.

Statistical Analysis

Data were analyzed using IBM Statistical Package for Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). The conformity of the data to a normal distribution was examined using Kolmogorov-Smirnov and Shapiro-Wilk tests. One-way analysis of variance was used to compare parameters that were normally distributed among the groups, and multiple comparisons were made using the Duncan and Tamhane Tests. The Kruskal-Wallis test was used to compare parameters that were not normally distributed according to the groups, and multiple comparisons were made using Dunn's test. To examine the relationship between the parameters, the Pearson correlation coefficient was used for data with a normal distribution, and Spearman's rho correlation coefficient was used for those without a normal distribution. Analysis results are presented as the mean ± standard deviation and median (minimum–maximum). The significance level was set at $p < 0.050$.

Results

Study Population

Of the 5,234 patients included in the study, 2,932 were diagnosed with non-ST-elevation myocardial infarction (NSTEMI; 56.01%), 1,423 with ST-elevation myocardial infarction (STEMI; 27.19%), and 879 with unstable angina pectoris (USAP; 16.80%).

Meteorological Data

Meteorological data were collected from Amasya City and its surroundings, where all patients resided. Between 2018 and 2024, maximum temperatures occurred in summer months, with an average of 38°C, whereas minimum temperatures were observed in winter months, with an average of 15°C. Large temperature variations were observed in the summer months, with an average of 23°C. Relative humidity values were highest in the winter months, averaging 99%. In contrast, the lowest values were recorded at 13% in the summer months. The maximum current pressure was observed in the winter months, averaging 982 hPa, while the average current pressure was also highest in the winter months, averaging 972 hPa. Total precipitation was

Table 1. *Number of annual events by season*

Year	Winter	Spring	Summer	Autumn
2018	187	135	154	153
2019	280	241	233	233
2020	244	158	141	151
2021	142	211	207	189
2022	168	208	233	260
2023	250	284	276	264
2024	232			
Total number of events	1503	1237	1244	1250
Total number of patients	5234 (STEMI-1423, NSTEMI-2932, USAP-879)			

STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; USAP: unstable angina pectoris.

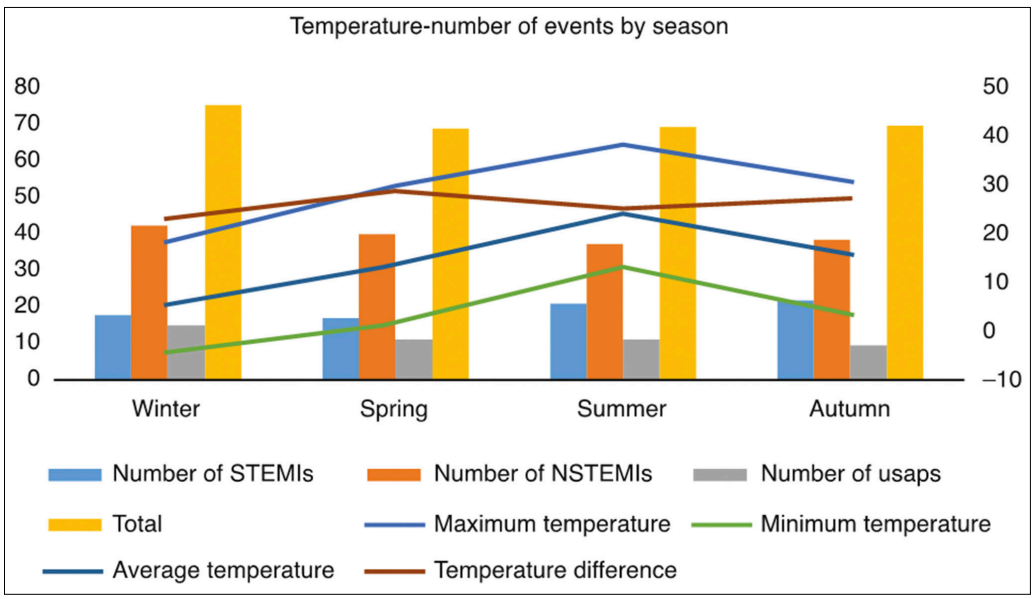

Figure 1. *Number of event–temperature relationships by season.*

highest in the spring months, averaging 50 mm, which corresponded with the highest number of rainy days, averaging 13 days.

Summer was the hottest season, with the highest rainfall occurring in spring, and the lowest temperatures observed in winter. Relative humidity was highest in winter, whereas the highest atmospheric pressure values were recorded in winter.

Effect of weather conditions on acute coronary syndromes

The total number of seasonal AMI events was 1,503 in winter, 1,237 in spring, 1,244 in summer, and 1,250 in autumn (Table 1). There was a significant increase in the frequency of AMI in winter, when the weather was significantly cold (p=0.003). In correlation analyses, a positive relationship was found between the minimum temperature and number of USAP events in winter (r=0.542; p=0.014), and a mild-to-moderate relationship (r=-0.459; p=0.042) between the temperature difference and number of USAP events (Fig. 1).

When the seasons were compared in terms of AMI subtypes (i. e., the summer season values were used as reference values for comparison), the risk of STEMI in summer was 1.174 (1/0.852) times higher than that in winter (p=0.030), and 1.214 (1/0.824) times higher than that in spring (p=0.012) (Table 2). The risk of NSTEMI in winter was 1.138 times higher than that in summer (p=0.012) (Table 2). When the risk of USAP was examined according to season, it was found that the risk in winter was 1.350 times higher than that

Table 2. *Analysis of ST-elevation and non-ST-elevation myocardial infarction risk by season*

	Season	ERR (95% CI)	p
STEMI	Summer (Reference season)	20,884 (18,878 – 23,104)	<0.001
	Winter	0.852 (0.737 – 0.985)	0.030
	Spring	0.824 (0.71 – 0.958)	0.012
	Autumn	1.013 (0.879 – 1.169)	0.856
NSTEMI	Summer (Reference season)	37,151 (34,467–40,085)	<0.001
	Winter	1.138 (1.028–1.26)	0.012
	Spring	1.078 (0.97–1.197)	0.163
	Autumn	1.035 (0.931–1.15)	0.533

STEMI: ST-elevation myocardial infarction; NSTEMI: non-ST-elevation myocardial infarction; CI: confidence interval; ERR: estimated relative risk. Bold text: statistically significant result.

Table 3. *Analysis of unstable angina pectoris and total myocardial infarction risk by season*

	Season	ERR (95% CI)	p
USAP	Summer (Reference season)	11,112 (9, 67–12,769)	<0.001
	Winter	1.35 (1.129–1.614)	0.001
	Spring	1.03 (0.848–1.251)	0.766
	Autumn	0.885 (0.723–1.083)	0.236
Total MI	Summer (Reference season)	69.2 (65,431–73,113)	<0.001
	Winter	1.085 (1.007–1.17)	0.032
	Spring	0.994 (0.919–1.075)	0.872
	Autumn	1.004 (0.929–1.085)	0.920

USAP, unstable angina pectoris; MI, myocardial infarction; CI, confidence interval; ERR, estimated relative risk. Bold text: statistically significant result.

in summer (p=0.001) (Table 3). When the total risk of myocardial infarction was examined by season, the risk in winter was 1.085 times higher than that in summer (p=0.032) (Table 3).

When examining the relationship between the maximum, minimum, and average relative humidity in the winter season and the number of STEMI, NSTEMI, USAP events, and the total number of events, no significant relationship was observed.

There was a significant relationship between the minimum relative humidity and the number of STEMI events (r=0.538) (p=0.021); however, we observed no significant association of the maximum and average relative humidity in spring with the number of STEMI, NSTEMI, and USAP events and total number of events, or that of the minimum relative humidity with the number of NSTEMI, USAP events, and total number of events.

The relationship between the minimum and average relative humidity in summer and the number of STEMI, NSTEMI, and USAP events, as well as the total number of events, was examined. Similarly, the relationship between the maximum relative humidity and the number of STEMI and NSTEMI events, as well as the total number of events, was examined, and there were no significant relationships. The relationship between the maximum relative humidity in the summer and the number of USAP events was significant (r=0.538) (p=0.021).

There was no significant relationship between the maximum, average, and minimum relative humidity in autumn and the number of STEMI, NSTEMI, and USAP events, as well as the total number of events examined (Fig. 2).

When the number of pressure events (measured in hPa) was evaluated according to the seasons, there was no significant relationship between the maximum, minimum, and average current pressures in winter and spring and the number of STEMI, NSTEMI, USAP events, and the total number of events.

In the summer season, there was no significant relationship between the maximum and minimum current pressures and the numbers of STEMI, NSTEMI, and USAP events, or between the mean current pressure and the numbers of STEMI and USAP events. However, there was a significant positive relationship

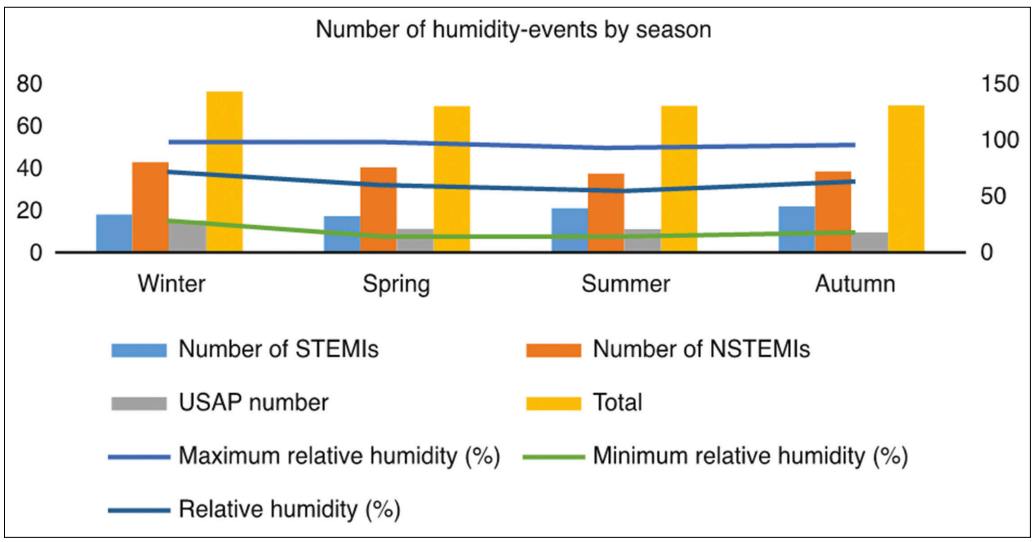

Figure 2. *Humidity rate and the number of acute myocardial infarction events by season.*

between the mean current pressure and the number of NSTEMI events (r=0.500; p=0.035).

When the relationship among the maximum, minimum, and mean actual pressures in autumn, as well as the numbers of STEMI, NSTEMI, and USAP events, and the total number of events, was examined, no significant relationship was observed. Also, there was no significant association between total rainfall, the number of rainy days in winter, and the number of STEMI, NSTEMI, USAP, and total myocardial infarctions.

When the relationship between total spring precipitation and the number of STEMI, NSTEMI, and USAP events, as well as the total number of events, and between the number of rainy days and the number of NSTEMI and USAP events, as well as the total number of events, was examined using Spearman correlation, no significant relationship was observed. The relationship between the number of rainy days and the number of STEMI events was significant (p=0.017, r=0.553).

There was no significant relationship between the total precipitation in summer and the number of STEMI and NSTEMI events, or the total number of events; nor between the number of rainy days and the number of STEMI, NSTEMI, and USAP events, or the total number of events. When the relationship between total precipitation and USAP number was examined using Spearman correlation, there was a significant and moderately positive relationship (r=0.591; p=0.010).

Discussion

The frequency of AMI was significantly higher in spring and autumn, and it was more pronounced in winter than in summer. When evaluating the effects of meteorological parameters on the frequency of AMI, the minimum and maximum relative humidity, average current pressure, number of rainy days, and total rainfall were associated with the frequency of acute coronary syndrome. The results of our study are consistent with those of previous studies conducted in this field[24] and in places with similar seasonal conditions as in our region[5,25–27].

Acute myocardial infarction is the main cause of mortality in ischemic heart disease. Acute myocardial infarction is an umbrella term that includes the diagnoses of USAP, NSTEMI, and STEMI. Epidemiological studies have shown that changes in air temperature (especially in cold weather) and certain meteorological parameters (such as relative humidity, the number of rainy/snowy days, atmospheric pressure, and maximum wind direction/speed) increase the risks of acute cardiovascular events and the associated mortality. Simultaneously, some studies have shown that extremely high and low air temperatures increase hospital admissions and AMI mortality[16,28–30]. In a study conducted in Innsbruck (Austria) comparing two winter seasons with a temperature difference of 7.5°C in two different years, a significant decrease was observed in the number of patients with acute coronary syndrome who underwent emergency coronary angiography during the warm winter period[6].

Given the severity of global warming, extreme changes in air temperature and climate instability are likely to become more intense and severe in the future[31]. The relationship between low air temperature and AMI is well-defined and is still being investigated. The mortality rate of cardiovascular events was found to be higher in cold weather, and the ratio of fatal to nonfatal cardiovascular events was higher than that in warm periods[6,32]. A study conducted in Lithuania, examining the associations between cold winter weather and AMI risk, found that each additional cold spell day in the week before AMI increased the risk of AMI by 5%[33].

Until recently, studies investigating the relationship between air temperature and AMI have been mostly conducted in developed countries[10]. The lack of access to long-term health data in underdeveloped and developing countries has prevented large-scale studies. In our country, the recent transition to an electronic health record system has made it possible to access reliable data. To date, no large-scale studies have investigated the relationship between weather conditions and coronary events in Türkiye. Similar to other studies in this field[34], we observed a decrease in the frequency of AMI, especially in the summer months, and an increase during periods of cold weather, when the perceived temperature decreased. We observed that the frequency of AMI increased on colder days when adaptation to the cold was more difficult.

Studies have shown that the effects of air temperature on AMI are delayed and U- or V-shaped[35,36]. In our study, the frequency of AMI increased with a decrease in temperature in October, remained high throughout winter, and decreased from May, when temperatures started to rise again. The relative increase in the frequency of AMI in April and May appears to be due to insufficient vascular adaptation when exposed to a sudden temperature increase for 6 hours, as determined by some authors in their studies[37]. However, we did not use the data from such a short period of time in our study.

Some large-scale studies have also shown a negative effect of relative humidity levels on heart disease[38]. In our study, we also found that changes in relative humidity values affected the frequency of AMIs. Especially in spring, the relationship between the minimum relative humidity and the number of STEMI events was statistically significant. In summer, the relationship between the maximum relative humidity and the number of USAP events was found to be significant. Previous studies indicated that relative humidity has no effect on coronary events, or that it can affect the frequency of AMI by affecting the central body temperature and *in vivo* water balance[39]. In addition, an increase in relative humidity leads to a rise in the amount of water-soluble air particles, and a higher concentration of fine particulate matter increases the frequency of AMI[40].

According to our research, atmospheric pressure is another meteorological parameter that affects the frequency of AMI. When the relationship between the average current pressure and the number of NSTEMI events in the summer season was examined, a significant and moderately positive relationship was observed. Important studies have been conducted on the effects of atmospheric pressure on the frequency of AMI[41,42].

When we examined the effect of the number of rainy days and total precipitation on AMI, we found a significant relationship between the number of rainy days in the spring and the number of STEMI events. There was also a significant positive relationship between total precipitation and the number of USAP events in summer. Although some previous studies found a relationship among the amount of rainfall, number of rainy days, and frequency of AMI[43,44], this relationship was not observed in other studies[45].

A limitation of our study is that we evaluated patients during a certain period of weather and climatic effects (January 2018 – January 2024). In addition, we investigated the effects of meteorological parameters on the frequency of AMI on a monthly and annual scale. Revealing the effects of weekly, daily, and hourly parameter changes on the frequency of AMI could have provided more quantitative data[38]. Another limitation is that we did not have data regarding the level of exposure to cold weather (outdoor activity and endogenous-exogenous factors) in patients presenting with AMI. If the coronary angiography results of patients could be evaluated on a patient-by-patient basis, incorporating current diagnoses such as myocardial infarction with non-obstructive coronary arteries, it could have provided new insights into identifying other possible mechanisms of AMI-meteorological parameter interactions that have not been defined. Ischemia without obstruction of the coronary arteries appears to be caused by processes acting alone or in combination[46]. We excluded patients who died outside the hospital or before angiography because of AMI. This may have

created a bias in evaluating possible meteorological parameters that have serious and fatal effects.

Another limitation is that we did not evaluate the effect of air pollution on the frequency of AMI. Air pollution, which increases periodically, especially during cold weather, is also associated with an increase in AMI frequency[47]. In addition, these results obtained in Amasya can only be generalized to countries with similar climatic characteristics and socioeconomic environments.

Conclusion

Among the meteorological parameters investigated in this study, air temperature was closely associated with the risk of AMI. The frequency of AMI increases, particularly in the winter months when the average temperature is low. Raising awareness about avoiding long-term exposure to cold weather would be extremely beneficial in reducing the risk of low-temperature-related AMI. It should also be emphasized that before attributing symptoms that may be related to heart disease (such as chest and arm pain, shortness of breath) to seasonal air temperature changes, it is important to seek medical attention and rule out cardiac disease. During periods when cardiovascular risk increases, patients should be thoroughly informed that they must follow the prescribed and protective recommendations to avoid a possible recurrence of the disease after acute treatment. Additional studies are needed to increase awareness in this area, reveal currently unknown pathophysiological mechanisms, and demonstrate the effects of meteorological parameters on AMI at daily and hourly periods.

Author Contributions

A. C. initiated and directed the study, and A. C. and O. K. were the principal investigators. A. C. and O. K. developed the study protocol. A. C. and O. K. collected data. A. C. and O. K. supervised the analysis of data and the writing of the manuscript. A. C. and O. K. performed statistical analyses. A. C. and O. K. drafted the manuscript. All authors read, contributed, and approved the final version of the manuscript.

Ethics Statement

The study was approved by the ethics committee of the Amasya University Rectorate Non-Interventional Clinical Research Ethics Committee (document date and number: 08.03.2024-184593; board decision number: E-76988455-050.04-184593). All experiments were performed in accordance with relevant guidelines and regulations.

Due to the retrospective nature of the study, the requirement for obtaining informed consent from patients was waived by Amasya University Rectorate Non-Interventional Clinical Research Ethics Committee.

Data Availability Statement

Data is provided within the manuscript or supplementary information files. If needed, the datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluating the Quality and Reliability of YouTube Videos on Acute Epididymitis: A Cross-Sectional Study

Akut Epididimit ile İlgili YouTube Videolarının Kalite ve Güvenilirliğinin Değerlendirilmesi: Kesitsel Bir Çalışma

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ABSTRACT

Aim: *This study aimed to evaluate the reliability, quality, and educational value of YouTube videos related to acute epididymitis, a common urological condition for which many individuals seek information online.*

Material And Methods: *On May 15, 2025, a cross-sectional search was conducted on YouTube using the terms "acute epididymitis," "epididymitis," and "epididymo-orchitis." To reduce algorithmic bias, the search was performed using incognito mode with a cleared history and a US-based VPN connection. The first 100 videos from each term were screened (total: 300). After applying exclusion criteria, 121 videos were included. Two reviewers independently assessed all videos. A third evaluator resolved disagreements. Video content was evaluated using three standardized tools: DISCERN, Global Quality Scale (GQS), and JAMA benchmark criteria. Videos were categorized as either applicable or deceptive based on scientific accuracy and completeness.*

Results: *Out of 121 videos, 85 (70.2%) were found to be useful. Videos uploaded by medical professionals and institutions had significantly higher quality scores across all evaluation tools. Helpful videos had a longer average duration compared to deceptive ones. Excellent inter-rater agreement was achieved for all scoring tools. No significant correlation was observed between the number of views or likes and the reliability of the video content.*

Conclusion: *YouTube hosts a substantial number of high-quality videos on acute epididymitis, especially those produced by medical professionals. However, the presence of misleading content highlights the need for greater involvement from healthcare providers in creating accurate, patient-centered educational material on digital platforms.*

Key words: *acute epididymitis; YouTube; video quality assessment*

Özet

Amaç: *Bu çalışma, birçok kişinin çevrim içi bilgi aradığı yaygın bir ürolojik hastalık olan akut epididimit ile ilgili YouTube videolarının güvenilirliğini, kalitesini ve eğitici değerini değerlendirmeyi amaçlamaktadır.*

Gereç ve Yöntemler: *15 Mayıs 2025 tarihinde YouTube'da "acute epididymitis", "epididymitis" ve "epididymo-orchitis" anahtar kelimeleri kullanılarak kesitsel bir tarama yapıldı. Algoritma kaynaklı yanlılığı azaltmak amacıyla aramalar gizli modda, geçmiş verileri silinmiş bir şekilde ve ABD merkezli bir VPN bağlantısı ile gerçekleştirildi. Her bir terim için ilk 100 video tarandı (toplam: 300 video). Dışlama kriterleri uygulandıktan sonra 121 video analize dâhil edildi. Videolar iki bağımsız araştırmacı tarafından değerlendirildi; görüş ayrılığı durumlarında üçüncü bir değerlendirici nihai kararı verdi. Video içerikleri, DISCERN, Global Quality Scale (GQS) ve JAMA kriterleri olmak üzere üç standart araçla değerlendirildi. Videolar bilimsel doğruluğu ve kapsamına göre "yararlı" veya "yanıltıcı" olarak sınıflandırıldı.*

Sonuçlar: *Analiz edilen 121 videonun 85'i (%70,2) yararlı olarak değerlendirildi. Sağlık profesyonelleri veya tıbbi kurumlar tarafından yüklenen videolar, tüm değerlendirme araçları açısından anlamlı derecede daha yüksek kalite puanlarına sahipti. Yararlı videoların ortalama süresi yanıltıcı olanlara göre daha uzundu. Tüm puanlama araçları için gözlemciler arası uyum mükemmel düzeydeydi. Video izlenme veya beğeni sayısı ile içerik güvenilirliği arasında anlamlı bir ilişki saptanmadı.*

Sonuç: *YouTube, özellikle sağlık profesyonelleri tarafından üretilen içerikler açısından akut epididimit hakkında yüksek kaliteli videolar barındırmaktadır. Ancak yanıltıcı içeriklerin varlığı, sağlık çalışanlarının doğru, hasta odaklı ve eğitici dijital materyaller üretme konusunda daha aktif rol üstlenmeleri gerektiğini göstermektedir.*

Anahtar kelimeler: *akut epididimit; YouTube; çevrim içi sağlık bilgisi*

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Introduction

Epididymitis is a significant urological condition characterized by acute or chronic inflammation of the epididymis, and it can affect males of all ages[1]. Acute epididymitis is characterized by unilateral pain, palpable swelling and increasing temperature of the epididymis over several days[1,3]. Testicles and scrotum can be affected, swelling and redness may occur. Pain is usually localized behind the affected testicle[5]. Acute epididymitis is generally caused by STI's (sexually transmitted epididymitis) or *Enterobacterales*[5,7]. Epididymitis comprises approximately 10–15% of all scrotal diseases in men[5–8]. The close association between the severity and duration of inflammation and prognosis is critically important for patients to receive a timely diagnosis and an appropriate treatment approach.

In recent years, online medical resources have increased significantly. It has been reported that seven out of ten adults search online for information on health issues, including diagnosis and treatment options[9]. This is even more prevalent with young men who feel shame about genital symptoms. With their cohort study on Australian men, Schlichthorst et al.[10] showed that men are not inclined to seek medical attention for genital symptoms. MacDonald et al.[11] performed a qualitative study with adolescents with acute testicular pain and indicated that shame was the main reason for delayed medical attention. YouTube is the leading free video platform with over a billion users worldwide and is considered the largest online multimedia library[12]. Over a billion hours of video content are being streamed and thousands of contents are being produced daily[12,13]. This platform is frequently used by patients who want to search for information about diseases, conduct preliminary research before going to the hospital, or try to resolve their complaints without going to the doctor. The popularity of YouTube can be both advantageous and worrying for disseminating correct and valuable information. Many studies have been conducted to assess the accuracy and quality of medical information on YouTube videos about subjects such as rheumatoid arthritis, heart failure, high blood pressure and coronavirus disease 2019 (COVID-19) pandemic[12,14]. Interestingly, 72% of people searching for medical information believe that most information is available online, and 69% believe that they've never seen wrong or deceitful information[15]. This situation shows how high the level of trust patients have in online health information, but it also has potential risks.

In this context, it is crucial to evaluate the quality of YouTube videos about urological emergencies such as acute epididymitis. This study aims to systematically assess the quality, reliability and educational value of YouTube videos about acute epididymitis and analyze the role of this platform in informing patients.

Materials And Methods

Video Search Strategy and Data Collection

In this cross-sectional study, on 15 May 2025, we conducted YouTube searches for the terms acute epididymitis, epididymitis, and epididymo-orchitis. To reduce the impact on search results and outputs, all search history was deleted before the search. In addition, to avoid user bias, all personal accounts were logged out of, "incognito mode" was enabled, and a connection was established using a proxy server in the United States of America via a free VPN software. Considering that more than 90% of internet users worldwide watch videos on the first three pages, 100 videos were chosen for the three keywords totaling 300 videos[16] To minimize bias in the evaluation process, all videos were independently assessed by two assistant professors (B. B. and N. A. K.). Reviewers were unaware of each other's evaluations. When there were inconsistencies, a third writer (a urology professor) made the final decision. For the 300 videos, the only inclusion criterion is the English language. From these, duplicate (n=98), non-English (n=36), off-topic (n=19), silent (n=2) and surgical (n=16) videos and videos longer than 40 minutes (n=8) were excluded, and 121 videos were studied (Fig. 1).

Video Parameters

The following variables were obtained for all videos included in the study: length of video (min), number of days on YouTube, number of likes, dislikes and comments. Videos were separated into five categories based on uploading source: 1) physicians/ medical institutions; 2) health information web pages; 3) non-profit physicians/healthcare providers; 4) medical advertisements; 5) other (patients, TV shows, news agencies, etc.). Videos were also divided into four categories based on the narrator: physician, healthcare professional other than physicians, patients and voice-over.

Video Quality and Reliability Assessment Tools

A five-point scale was used to assess the quality and reliability of the videos, similar to prior studies. Video

reliability was evaluated using the Modified Quality Criteria for Consumer Health Information (DISCERN) tool. DISCERN consists of 16 questions divided into three groups: reliability (questions 1–8), quality information on treatment options (questions 9–15) and general scores (16th question). The total DISCERN score was calculated by adding up the points of questions 1–15. Global Quality Scale (GQS) is a scale that rates the quality, flow, content and ease of use of the video on a scale of 1 to 5. JAMA comparison was used to assess the quality of internet information on healthcare services. For this, four criteria, including authorship, citation, explanation and validity, were evaluated. One point was awarded for each criterion met, with a maximum of 4 points for the highest quality[16].

For the accuracy and usability of videos, the European Association of Urology (EAU) guidelines were referenced[1], and based on this, videos were categorized as applicable and deceptive.

Useful –if the video contains any scientifically accurate information; if subjects on etiology, risk factors, clinical symptoms, diagnostic approaches and surgical complications are included in the content.

Deceptive –if the video contains information not proven scientifically (e.g., baseless claims about herbal treatment without any evidence in the literature, the claims that this disease is caused solely by sexual transmission, or that sexually active patients can be re-infected after treatment, etc.).

Ethics Committee Approval

There was no need for an ethics committee approval because YouTube is an open-access social platform, and there were no human or animal subjects.

Statistical Analysis

Data were analyzed with IBM Statistical Package for Social Sciences (SPSS) program for Windows version 27.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was evaluated using the Kolmogorov-Smirnov test. Descriptive statistics for non-normally distributed data were presented as the median

Table 1. *Analysis of videos based on reliability*

	Reliable information n: 85 (70%, 2)	Unreliable information n: 36 (29%, 8)	P value
Total views	19714.19±69259	286116.11±534715	<0.001
Video duration (min)	17.11±6.71	7.90±10.92	<0.001
Age of the video on YouTube (months)	32.1±66.5	39.4±40.2	0.426
Likes	1299±850	534±438	0.002
Dislikes	141±121	536±411	0.018
Comments	221±702	258±428	0.003
Reliability score	2.58±1.18	1.04±0.91	<0.001
DISCERN	40.6±12.4	29.6±20.4	<0.001
GQS score	2.15±1.12	0.81±0.61	0.002
JAMA Score	3.25±1.02	1.31±0.79	<0.001
Narrator, n			
Physician	59 (69%)	10 (29%)	0.001
Non-physician health provider	8(9.)	3 (8%)	0.123
Individual in the video	3 (4%)	12 (34%)	<0.001
External voice	15 (18%)	10 (29%)	0.178
Source of upload, n (%)			
Physician/medical institutions	39 (46%)	5(14%)	<0.001
Health information web sites	37 (45.3%)	15(42%)	<0.001
Non-profit physician/ healthcare provider	4(5%)	2 (6%)	<0.001
Medical advertisement	2 (2%)	5 (14%)	0.023
Other media	3 (2%)	9 (24%)	<0.001

Variables are presented as mean ± standard deviation, median, or frequency (%), and n: number. Values of P <0.05 were accepted as significant and marked in bold; GQS: global quality score; min: minute, JAMA: Journal of American Medical Association.

Table 2. *Detailed analysis of video features by uploading the source*

	Physicians/ medical institutions	Health information web sites	Non-profit physician/ healthcare provider	Medical advertisement	Other media	P value
Video number (n)	44	52	6	7	12	
Video duration (minutes)	9.72 (1.31–40) b	4.32 (0,42–19,36) b	7.89 (0,42–39) a	3.07 (0,31–40) b	4.17(1,07–40) a	<0.001
Average number of views (n)	2172 (30–62267) c	1892 (40–37217) c	921 (12–16557) c	9880 (25–358765) a	892 (40–6267) c	<0.001
Likes	24(0–194) a	55(0–7449) b	100 (0–6216) b	292 (1–24976) a	245.5(0–25814) a	<0.001 *
Dislikes	2 (0–35) b	5 (0–189) a	6 (0–199) a	37 (0–2550) b	17 (0–978) ab	<0.001 *
Comments	8 (0–226) c	6 (0–157) c	11 (1–257) c	155 (0–1673) a	85 (0–973) a	<0.001 *
Reliability score	4.35±0.85	3.10±1.25	2.86±1.60	1.56±0.90	2.53±1.40	0.001**
DISCERN	44.6±10.4	39.6±15.43	34.6±18.2	25.6±12.2	34.5±8.4	0.001**
GQS score	4.05±0.85	3.00±0.95	2.96±0.90	0.56±0.90	2.13±1.40	0.001**
JAMA Score	3.25±0.60	2.89±0.85	2.25±0.60	1.60±1.05	2.05±0.60	0.001**
Narrator (n)						0.274†
Physician	24	21	0	1	0	
Non-physician healthcare professional	12	15	2	2	2	
Individual in the video	5	6	1	0	4	
External voice	2	10	2	4	6	
Video Content, (n)						
Epidemiology,	39/44	44/52	2/6	0/7	3/12	0.001†
Etiyology	35/44	40/52	2/6	0/7	4/12	0.001†
Risk factors	41/44	48/52	3/6	1/7	5/12	0.021†
Clinical symptoms	44/44	45/52	4/6	2/7	4/12	0.001†
Diagnostic approach	35/44	35/52	1/6	0/7	2/12	0.001†
Medical and surgical treatment	41/44	46/52	2/6	2/7	4/12	0.04†
Complications	35/44	29/44	0/6	1/7	0/12	0.003†
Prevention	29/44	35/52	1/6	3/7	1/12	0.001†

Variables are presented as mean ± standard deviation, median, or frequency (%), and n: number. Values of P <0.05 were accepted as significant and marked in bold. GQS: Global Quality Score; min: minute, JAMA: Journal of the American Medical Association; *: Kruskal-Wallis Test; **: One-way ANOVA test; †: Fisher's exact test: a, b, c: for the median values specified with indices such as a, b, and c, those with the same index are the same, others are different, statistically.

(1st quartile–3rd quartile range), while categorical data were presented as numbers and percentages. The Kruskal-Wallis test was used to evaluate differences between three or more independent groups. Agreement between assessors was determined using Cohen's kappa score, and reliability between assessors was quantified by calculating the intraclass correlation coefficient. Student's t-test, Fisher's exact test, chi-squared test and ANOVA were used to compare categorical and numerical variables. A p-value of <0.05 was considered statistically significant.

Results

The agreement between assessors on categorizing the 121 videos, which met the inclusion criteria, as reliable or unreliable was evaluated as positive (kappa coefficient: 0.823). Moreover, the intraclass correlation coefficient was calculated as 0.973 for DISCERN, 0.972 for GQS and 0.976 for the JAMA score, and excellent agreement was achieved for all three tools. Eighty-five videos (70.2%) were useful, and 36 (29.8%) were deceptive. Median duration of helpful videos was 17.11±6.71 minutes. The mean duration of useful videos was shorter than that of deceptive videos (p<0.01). DISCERN, GQS and JAMA scores were statistically significantly higher in the functional group (respectively p<0.001, p=0.002 and p<0.001). Most of the videos were uploaded by health information web pages (42.9%), followed by physicians/medical institutions (36.3%). The number of views, reliability, and quality analysis of helpful and deceptive videos are summarized in Table 1.

Analysis based on uploading source revealed that videos uploaded by physicians/medical institutions had the highest reliability and DISCERN, GQS and JAMA scores, and medical advertisements had the lowest reliability ($p<0.001$). Median video duration was much higher with videos uploaded by physicians/medical institutions compared to all other upload sources ($p<0.001$). Detailed analysis of video characteristics based on the uploading source is shown in Table 2.

Discussion

Since 2005, YouTube has become the largest video sharing platform with billions of users worldwide and has emerged as an important resource in the search for medical information[13,16]. Over a billion hours of video are being watched and thousands of contents are uploaded on YouTube each day[12]. This platform has become a preferred resource for patients looking for information on sensitive subjects such as sexual health[12,13]. In our study, we planned to study the quality and reliability of videos on acute epididymitis on YouTube. To our knowledge, this is the first study analyzing acute epididymitis videos on YouTube. We established that the videos uploaded by physicians/medical institutions were the most reliable, and % 70.2% of cute epididymitis videos uploaded to YouTube had reliable information.

From studies conducted on the reliability of YouTube videos consulted for medical information, Ku et al.[17] reported % 70% reliability in their research on male infertility. Melchionna et al.[18] reported that % 68.4% of videos from their study on testicular pain contained reliable information. Similarly, in their research on renal stones, Sood et al.[19] found that % 58.3% of the videos were reliable. Our study showed that % 70.2% of the 121 videos on acute epididymitis (AE) contained reliable information. These similar findings suggest that urological videos on YouTube have the potential to be a reliable source of information.

In our study, we found that the mean duration of reliable videos was significantly longer (17.11±6.71 minutes). Sood et al.[19] found that helpful videos were longer than deceptive ones, even though the difference was statistically insignificant. Melchionna et al.[18] found that video duration and quality had a negative correlation; shorter videos had better quality, and Gul and Diri[12] reported a mean video duration of 7.11±2.71 minutes and found no association between video duration and reliability. All these studies demonstrate that the relation between video duration and quality can vary between different urological topics. An explanation for the longer duration of reliable videos found in our study might be that emergencies such as acute epididymitis require more detailed descriptions and thus longer times.

The analysis we performed based on video sources revealed that videos uploaded by physicians and medical institutions were the most reliable and had the highest DISCERN, GQS and JAMA scores. This finding of our study is consistent with Ku et al.[18] study on male infertility; they also reported that videos produced by medical institutions have the most intense information content. The most remarkable point is that in reliable videos, 69% of narrators are physicians, whereas this rate is only 29% in the unreliable group. Similarly, in Gul and Diri's[12] study on premature ejaculation, most of the unreliable information group consisted of medical advertisements and for-profit companies (% 51%) and personal users (% 41%). In their study on testicular pain, Melchionna et al.[19] reported that physicians produced 68.4% of videos, and 77.8% of the target audience for these videos were patients. These data reveal the critical role medical authorities hold in creating quality content on YouTube.

Another important finding of our study was that there was no meaningful difference in the number of views between reliable and unreliable videos. This shows that patients have a hard time differentiating quality content on YouTube. The study conducted by Bizpinar Munis et al.[20] on mild cognitive impairment also showed no correlation between the number of views and the quality of videos. Gul and Diri[12] also found no significant difference in daily video viewing rates of reliable and unreliable information groups. These findings suggest that YouTube determines popularity based on the number of views, likes and comments, not quality. As Ku et al. indicated, typical metrics on YouTube, such as the number of likes, dislikes and total views, can be deceiving in determining applicable content in medical topics[17]. This increases the risk of patients receiving inaccurate information and underscores the need for the medical community to play a more active role on YouTube.

The strengths of our study include the utilization of standard assessment tools and the analysis of two independent assessors. Cohen's kappa statistics are calculated as 0.823, indicating excellent agreement. Moreover, the intraclass correlation coefficients for

DISCERN, GQS, and JAMA scores were calculated as 0.973, 0.972, and 0.976, respectively, indicating excellent agreement. However, our study has weaknesses too. Firstly, there is no proven method in the literature for assessing videos on health problems. Nevertheless, in this study, we analyzed videos using methods previously identified and utilized for analyzing medical YouTube videos[12,13]. Secondly, only English videos were included, and videos in other languages were not evaluated. Finally, due to the dynamic structure of YouTube, content is constantly changing, and this can affect the generalizability of the results.

Conclusion

In conclusion, YouTube has the potential to be a valuable resource for information on acute epididymitis, but to realize this potential, it is critical to improve the quality of content and ensure patients are directed to the right sources. The medical community should utilize social media platforms such as YouTube as an effective tool in patient education and public health promotion, rather than ignoring them.

Additional Information

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ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Evaluation of Patient Satisfaction with the Use of Robotic Gait Devices in Stroke Patients

İnmeli Hastalarda Robotik Yürüme Cihazı Kullanımına Yönelik Memnuniyetin Değerlendirilmesi

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ABSTRACT

Aim: *The aim of this study was to evaluate the satisfaction of stroke patients using assistive technology in robot-assisted gait training and to identify the factors associated with their satisfaction.*

Material and Methods: *A total of 60 patients with stroke, including 30 females and 30 males, were included in the study. Motor recovery stages of the upper and lower extremities were assessed using the Brunnstrom Motor Recovery Staging System, cognitive performance was evaluated with the Mini-Mental State Examination, and satisfaction with assistive technology use was measured using the Quebec User Evaluation of Satisfaction with Assistive Technology scale.*

Results: *Female patients had lower levels of satisfaction with assistive technology, cognitive performance, and certain sociodemographic and physical characteristics (age, height, weight) compared to males (p<0.05); however, their body mass index (BMI) values were similar. Both genders had comparable stroke-related characteristics. Satisfaction with assistive technology use showed a significant negative correlation with age (r=-0.393) and BMI (r=-0.302), and a significant positive correlation with height (r=0.542) and cognitive performance (r=0.658).*

Conclusion: *This study demonstrated that factors, especially gender and cognitive performance, should be taken into account in the use of assistive technologies in the field of stroke rehabilitation.*

Key words: *assistive technology; patient satisfaction; stroke rehabilitation*

ÖZET

Amaç: *Bu çalışmanın amacı robotik yardımlı yürüme eğitimi alan inmeli hastaların yardımcı teknoloji kullanımı memnuniyetlerini ve memnuniyetleri ile ilişkili faktörleri değerlendirmekti.*

Gereç ve Yöntem: *Çalışmaya 30'u kadın ve 30'u erkek toplam 60 inmeli hasta dâhil edildi. Alt ve üst ekstremite motor iyileşme evresi Brunnstrom motor iyileşme evreleme sistemi ile, bilişsel performans mini mental durum testi ile, yardımcı teknoloji kullanımı memnuniyeti ise Quebec yardımcı teknoloji kullanıcı memnuniyeti ölçeği ile değerlendirildi.*

Bulgular: *Kadın katılımcıların erkeklere kıyasla yardımcı teknoloji kullanımı memnuniyeti, bilişsel performans ve bazı sosyodemografik ve fiziksel özellikleri (yaş, boy, kilo) daha düşüktü (p<0,05); ancak vücut kitle indeksi (VKİ) değerleri benzerdi. İki cinsiyet de benzer inme karakteristiğine sahipti. Yardımcı teknoloji kullanımı memnuniyeti yaş (r=-0,393) ve BKİ (r=-0,302) ile negatif, boy (r=0,542) ve bilişsel performans (r=0,658) ile pozitif yönde anlamlı ilişki gösterdi.*

Sonuç: *Bu çalışma inme rehabilitasyonu alanında yardımcı teknolojilerin kullanımında cinsiyet ve bilişsel performans gibi faktörlerin göz önünde bulundurulması gerektiğini gösterdi.*

Anahtar kelimeler: *yardımcı teknoloji; hasta memnuniyeti; inme rehabilitasyonu*

Introduction

Although stroke is characterized by widespread sensorimotor impairments from head to toe [1,2], it is also considered one of the main causes of gait disturbances[3]. While motor recovery following stroke is mostly completed before the chronic phase, gait disturbances persist in some patients even during the chronic period[4]. Persistent gait disturbances, reported in approximately one-third of patients with chronic stroke[5], often lead to significant limitations in activities of daily living[6]. Furthermore, walking difficulties increase patients' susceptibility to falls and subsequently elevate the risk of fall-related fractures[7].

The significant limitations in activities of daily living caused by post-stroke gait disturbances[6], the limited

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effectiveness of conventional therapist-guided rehabilitation on gait restoration[7], and the recognition of gait recovery as one of the primary goals of stroke rehabilitation[8] have collectively laid the groundwork for the development of technological approaches such as robot-assisted gait training devices[9].

Robot-assisted gait training devices represent a post-stroke rehabilitation approach that provides patients with the opportunity for active, high-repetition, and high-dose functional gait practice—key components for gait restoration after stroke[10,11]. These devices also stimulate neural reorganization and brain adaptation[12]. Although various commercially available robot-assisted gait systems exist today[13], body weight-supported treadmill training systems are the most commonly used[14]. With the widespread adoption of robot-assisted gait devices, questions have also been raised regarding their actual effectiveness[15].

Although there is a substantial body of research on robot-assisted gait training in patients with stroke, most of these studies have primarily focused on evaluating the effects of robot-assisted gait devices on walking and balance using quantitative assessment tools[4,6,9,15,16]. While such approaches are valuable in demonstrating the measurable impact of robot-assisted gait training devices on patients' gait and balance performance – thus contributing to the development of evidence-based treatment strategies[4,6,9,15,16]– studies addressing patients' perceived functional improvements or subjective recovery experiences remain extremely limited[9]. Existing research has often been conducted with small sample sizes, and satisfaction with robot-assisted gait training devices has generally been evaluated as a secondary or supportive measure, rather than being examined as a primary outcome[17–21]. As is well known, motivation and active participation are critical components robot-assisted gait training[14], yet such advanced technologies may also provoke skepticism or fear among patients[22]. Furthermore, gaining insight into patients' personal experiences with robot-assisted gait training may contribute to the improvement and refinement of these devices[22].

In this context, our study aims to evaluate the satisfaction of stroke patients with the use of robot-assisted gait training devices and to identify the factors associated with their satisfaction levels.

Materials and Methods

Population and Sample

This cross-sectional and analytical observational study was conducted at Izzet Baysal Physical Treatment and Rehabilitation Training and Research Hospital. Patients were verbally informed before the study and provided written informed consent. Patients with stroke aged 18 years and older in the subacute or chronic phase who underwent three sessions of robot-assisted gait training during one week were included, while those with cognitive dysfunction or any additional neurological or neurodegenerative diseases were excluded (Fig. 1).

Due to the lack of similar studies with comparable characteristics, a post hoc power analysis was performed using G*Power 3.1.9.5 software, based on the correlation coefficient between the Mini-Mental State Examination Test (MMSE) scores and the questionnaire scores (r=0.68), and the study power was found to be 99%. The study protocol received approval from the local ethics and research committee and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Data Collection Tools

To assess patients' satisfaction with robot-assisted gait training devices, patients participated in three sessions over one week, alongside a 40-minute conventional rehabilitation program aimed at improving gait and postural stability. The conventional program included

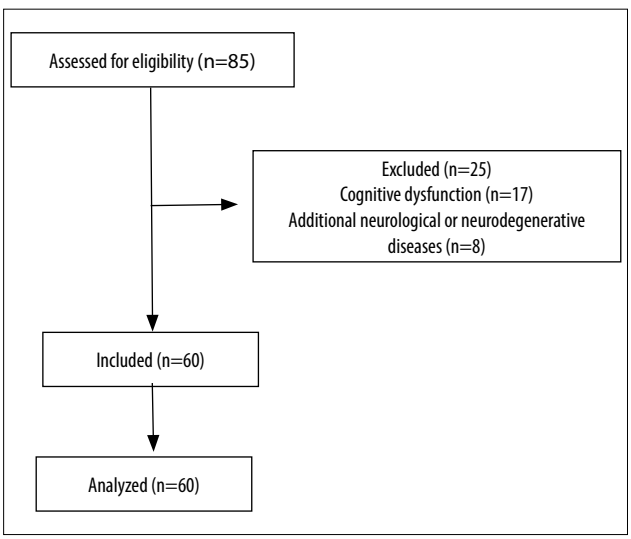

Figure 1. *Study flow chart.*

trunk positioning, manual-assisted overground training, and static and dynamic postural tasks[4].

Robot-assisted gait training was performed using the RoboGait® device (Bama Technology Middle East Technical University Teknokent, Ankara, Türkiye), with each session lasting 40 minutes. The device was adjusted to accommodate an appropriate lower extremity range of motion and to ensure symmetrical weight bearing, while compensatory movements were restricted. Training was conducted at a walking speed of 0.4 m/s with 50% body weight support[23]. During the session, patients engaged in a virtual reality game displayed on a 40-inch screen integrated into the device. In the game, patients were instructed to collect virtual coins while avoiding trees in a forest setting[24].

The motor recovery stages of the upper and lower extremities of the patients were evaluated using the Brunnstrom motor recovery staging system, which consists of six stages ranging from the flaccid stage to near-normal movement[25]. The Brunnstrom motor recovery stages demonstrated high inter-rater reliability, with coefficients ranging from 0.69 to 0.98. Strong agreement was noted for the upper extremity (r=0.89–0.98), hand (r=0.69–0.92), and lower extremity (r=0.80–0.95). In addition, overall consistency among raters was confirmed by Kendall's coefficient of concordance, which ranged between 0.89 and 0.95, all with statistically significant results[26]. The motor recovery stages of the upper and lower extremities were categorized for analysis as low recovery (Stages I–III) and high recovery (Stages IV–VI).

The cognitive performance of the patients was evaluated using the MMSE. The test consists of 11 items grouped under five main categories: orientation, registration, attention and calculation, recall, and language. The total score is 30 points, with each item scored on a one-point scale. The cutoff score for cognitive impairment is 23 points. Mini-mental state examination test has been shown to possess strong test-retest reliability (r=0.827–0.98) and consistent inter-rater reliability. Additionally, it exhibited satisfactory concurrent validity, with correlation coefficients ranging from 0.660 to 0.776[27].

Patients' satisfaction with assistive technology use was evaluated using the Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST 2.0) scale. The scale consists of 12 items: eight related to the characteristics of the assistive device and four related to the assistive technology services. The eight-item section assesses user satisfaction with the device's features, while the four-item section evaluates how users experience the services provided as part of assistive technology. Each item on the scale is scored from 1 to 5 points, with 1 point reflecting no satisfaction at all and 5 points reflecting a high level of satisfaction[28]. For the evaluation, eight items from the scale addressing the following aspects were used: comfort, safety, ease of use, user adaptability, effectiveness, follow-up and training services, service delivery, and overall satisfaction.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation or as median with minimum and maximum values, while categorical variables were summarized using frequencies and percentages. The assumption of normality was assessed using the Shapiro-Wilk test. Mann-Whitney U test, independent samples t-test, Fisher's exact test, and Chi-square test were used to compare sociodemographic, physical, stroke characteristics, and assistive technology satisfaction by gender, based on the variable type (continuous or categorical, nominal or ordinal) and whether the normality assumption was satisfied. Since the variables involved in the correlation analysis did not show a normal distribution, Spearman's rank correlation test was used. Statistical analysis was performed with the IBM Statistical Package for Social Sciences (SPSS) program version 27, and the significance level was adjusted as $p<0.05$.

Results

Among the patients, ischemic stroke was the most prominent type of stroke, and the middle cerebral artery was the most commonly affected. While more than half of the patients had a low level of motor recovery in the upper extremity, those with a low level of recovery in the lower extremity constituted more than three-quarters of the patients. All patients were in the chronic stage of the stroke (Table 1).

Female patients reported lower levels of satisfaction with assistive technology and cognitive performance, along with lower sociodemographic and physical characteristics such as age, height, and weight ($p<0.05$); however, their body mass index (BMI) values were similar to those of male patients. Both genders had similar stroke-related characteristics, including time

Table 1. *Sociodemographic, physical and stroke characteristics of the participants*

			Average	
Age (years)			58.53±12.58	
Height (cm)			164.41±11.02	
Body weight (kg)			78.50±13.74	
BMI (kg/cm^2)			29.00±4.20	
Brunnstrom stage of recovery			n	%
	I	Upper limb	-	-
		Lower limb	3	5
	II	Upper limb	10	17
		Lower limb	29	48
	III	Upper limb	27	45
		Lower limb	18	30
	IV	Upper limb	22	37
		Lower limb	10	17
	V	Upper limb	1	1
		Lower limb	-	-
Gender	Male		30	50
	Female		30	50
Time since stroke onset (month)			15.63±6.82	
Stroke type	Ischemic		49	82
	Hemorrhagic		11	18
Affected artery	MCA		53	88
	ACA		3	5
	PCA		4	7

BMI: body mass index; MCA: middle cerebral artery; ACA: anterior cerebral artery; PCA: posterior cerebral artery.

Table 2. *Comparison of sociodemographic, physical, stroke characteristics, and assistive technology satisfaction by gender*

	Male (n=30)		Female (n=30)			
	mean ± s. d.	Median (min-max)	mean ± s. d	Median (min-max)	z	p
QUEST score	39.76±0.50	40 (38–40)	37.53±1.59	37 (35–40)	5.566	<0.001*[a]
Age (years)	53.83±13.73	50 (30–79)	63.23±9.37	63 (46–79)	3.096	0.003*
Height (cm)	172.80±7.76	173 (158–186)	156.03±6.46	158 (144–169)	9.093	<0.001*
Body weight (kg)	84.16±13.73	84.5 (57–111)	72.83±11.35	73 (50–92)	3.483	<0.001*
BMI (kg/cm^2)	28.03±2.98	28.41 (20.68–32.83)	29.98±5.00	29.86 (22.03–42)	1.829	0.074
Time since stroke onset (month)	17.60±7.58	15.5 (7–32)	13.66±5.39	12.5 (6–26)	1.919	0.055[a]
Mini mental test score	28.30±1.29	28 (26–30)	26.63±1.40	26 (25–29)	4.040	<0.001*[a]
Brunnstrom stage of recovery	n	%	n	%		
Lower recovery stage for lower limb	24	80	26	87	0.480	0.488[c]
Higher recovery stage for lower limb	6	20	4	13		
Lower recovery stage for upper limb	16	53	21	70	1.763	0.184[c]
Higher recovery stage for upper limb	14	47	9	30		
Stroke type	n	%	n	%		
Ischemic	25	83	24	80	0.111	0.739[c]
Hemorrhagic	5	17	6	20		
Affected artery	n	%	n	%		
Middle cerebral artery	27	90	26	86	N. A.	1.000[b]
Anterior cerebral artery	1	3	2	7		
Posterior cerebral artery	2	7	2	7		

* p<0.05 statistical significance; independent sample t test; [a] Mann-Whitney U test; [b] Fisher's exact test; [c] Chi-square test; BMI: body mass index.

Table 3. *Correlation between outcome measures after talocrural joint manipulation and cavitation*

	Age		Height		Weight		BMI		MMSE score	
	r	p	r	p	r	p	r	p	r	p
QUEST score	-0.393**	0.002	0.542**	<0.001	0.072	0.584	-0.302*	0.019	0.628*	<0.001

* correlation is significant at the <0.05 level; ** correlation is significant at the <0.01; Spearman rank's correlation; BMI: body mass index; MMSE: mini-mental state examination.

Discussion

This study demonstrated that patients with stroke exhibit a very high level of satisfaction with robot-assisted gait training device technology, and that satisfaction levels are associated with gender, cognitive performance, and certain anthropometric variables.

Although previous studies have employed different robot-assisted gait training devices or protocols compared to our study, similar results have been reported[17–21]. Kim et al.[17] evaluated the usability of a robot-assisted gait training device in eight stroke patients, assessing four subdomains, including satisfaction, and found that patients reported very high levels of satisfaction. In a feasibility study conducted by Sung et al.[18], satisfaction with the use of a robot-assisted gait training device was assessed through a few questions among 13 predominantly chronic stroke patients (2 subacute, 11 chronic), and the results similarly indicated high levels of satisfaction. Another study by Fricke et al.[19], involving six patients with chronic stroke and four spinal cord injury patients, found that both groups were highly satisfied with the safety and comfort provided by the over-ground robot-assisted gait training device. In a study by Bortole et al.[20] involving three stroke patients, they expressed great excitement about using the over-ground robot-assisted gait training device. Similarly, Nilsson et al.[21] reported positive attitudes toward the over-ground robot-assisted gait training device among eight patients with stroke. While these studies demonstrated the safety and functional benefits of robot-assisted gait training with high levels of user satisfaction, the present study extends these findings by identifying how patient-specific factors –such as gender, cognitive performance, and anthropometric characteristics– are associated with satisfaction levels.

Considering that motivation and active participation are critical components in robot-assisted gait training[14], it can be suggested that these factors may have contributed to the high levels of satisfaction observed in our study.

Another factor influencing satisfaction with robot-assisted gait training devices is their standardized manufacturing design, which limits their use to individuals within certain anthropometric ranges (e.g., height: 150–170 cm; weight: ≤80 kg)[4,9,16,29]. This suggests that robot-assisted gait training devices may offer greater comfort for users whose anthropometric characteristics fall within these specifications. Consistent with this view, our study also found a correlation between certain anthropometric parameters, such as height and BMI, and satisfaction scores.

Another factor influencing satisfaction with robot-assisted gait training is the specific application protocol of the device[30]. In our study, a virtual reality component was integrated into the robot-assisted gait training sessions. Previous research has shown that the use of virtual reality in robot-assisted gait training enhances patients' active participation[30]. Given that active participation is largely influenced by patient motivation[31], it can be suggested that virtual reality contributes to improved motivation and engagement in robot-assisted gait training. In our study, the integration of virtual reality may have positively influenced patients' satisfaction with robot-assisted gait training.

Gait training with robot-assisted devices has been shown to require less energy expenditure and place less stress on the cardiorespiratory system[32]. These characteristic features of robot-assisted gait training devices may have contributed to the high levels of patient satisfaction observed in our study.

In our study, satisfaction levels with the robot-assisted gait training device differed according to gender. We believe this difference may be due to female patients being older than their male counterparts. This interpretation is supported by the well-established view that age is a significant factor contributing to poorer outcomes in patients with stroke[33]. Another study also reported that age is one of the key determinants of gains achieved through robot-assisted gait training[34]. Another study also reported that age is one of the factors influencing gait independence[35].

The lower satisfaction levels observed among female patients may also be partly explained by adverse events associated with the use of robot-assisted gait training devices. In body weight-supported robot-assisted gait training, the harness system may irritate areas such as the shoulders, armpits, and groin[36,37]. Although these adverse effects have been reported, the distribution of such events by gender was not specified[36,37]. Considering that musculoskeletal complaints are more prevalent in women than in men[38], that women tend to have lower pain thresholds and reduced tolerance to painful stimuli, and that female gonadal hormones are known to play a role in pain modulation[39], it is plausible that female patients were more sensitive to device-related discomfort. As a result, their satisfaction levels with robot-assisted gait training may have been negatively affected. To improve satisfaction, clinicians may consider individualized harness adjustments and proactive patient feedback, especially for those with higher sensitivity to discomfort. Device developers could address these issues by designing harness systems that are adjustable, size-inclusive, and gender-sensitive, using softer materials to reduce pressure-related complaints.

Lower satisfaction levels among female patients may also be partly attributed to their lower cognitive performance. Cognitive impairments can contribute to balance and gait difficulties[24] and are recognized as key factors in maintaining balance[40]. Although a harness supported patients during training, the influence of cognitive performance on balance control may still have affected their overall satisfaction with the use of the robot-assisted gait training device.

Another factor reported to influence the gains obtained from robot-assisted gait training is the Brunnstrom stage of motor recovery[34]. In our study, no significant difference was found between male and female patients in terms of their Brunnstrom motor recovery stages. This suggests that this factor did not play a role in the gender-based differences in satisfaction observed in our study and, at least indirectly, supports the findings of the previous study[34].

Limitations of the Study

Certain limitations of our study should be noted. The intervention duration in this study was relatively short, consisting of only three robot-assisted gait training sessions over one week, which may limit the understanding of long-term satisfaction and adherence. Future research should consider extended intervention durations and long-term follow-up assessments to evaluate these outcomes better. Additionally, the absence of a follow-up period restricts insights into whether the observed satisfaction levels were sustained over time or translated into functional improvements. The study relied solely on quantitative measures of satisfaction, lacking qualitative data that could have provided a deeper understanding of patients' subjective experiences. Potential response bias may have also influenced self-reported satisfaction, as patients might have responded favorably due to social desirability or expectations from clinicians. Future studies could incorporate qualitative interviews or open-ended survey items to capture these perspectives more comprehensively. Furthermore, the findings are device-specific, as only the RoboGait® system was utilized, limiting the generalizability of results to other robot-assisted gait training devices with different designs and features. Including multiple device types in future research would strengthen external validity. The cognitive assessment was limited and did not include a comprehensive neuropsychological evaluation, potentially overlooking subtle cognitive deficits that could affect satisfaction. Lastly, the absence of a control group receiving conventional gait training without robot assistance prevents a clear attribution of satisfaction effects solely to robot-assisted gait training.

Conclusion

Our study demonstrated that patients with stroke have a very high level of satisfaction with robot-assisted gait training devices assisting walking. That satisfaction is particularly associated with patients' cognitive performance and gender. In this context, considering individual factors such as gender and cognitive performance in the clinical setting of assistive technologies –specifically robot-assisted gait training devices– will contribute to the effective delivery of rehabilitation services in stroke rehabilitation.

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DERLEME / *REVIEW*

Biotinidase Deficiency as a Regional Problem and Solution Suggestions

Bölgesel Bir Sorun Olarak Biyotinidaz Eksikliği ve Çözüm Önerileri

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Abstract

Biotinidase enzyme is the enzyme that activates biotin, which is the cofactor of 4-carboxylase enzymes in our body. After its deficiency began to be treated in 1971, it was screened in the 1980 s. A local newborn study was conducted in our country under the leadership of the Istanbul Faculty of Medicine between 1991 and 2005, and the first data were obtained. As a result of this study, it was shown that biotinidase deficiency, which is known to occur in one in 60,000 people worldwide, is seen at a frequency of one in 11,000. Biotinidase newborn screening was added to the national screening program in our country in 2012, with a reported frequency of one in 5500. National screening data supported Istanbul University, revealing that the most common region was Northeastern Anatolia, with the provinces having the highest number of patients being Ardahan, Kars, and Iğdır. The number of centers that can perform metabolic follow-up of diagnosed patients in the region is insufficient. It was decided to write this article to highlight the need to establish a "Biotinidase Deficiency Research Institute" affiliated with Kafkas University in Kars, one of the provinces with the highest incidence of patients, to provide an on-site solution to the problem.

Key words: *biotinidase deficiency; newborn screening; hereditary deafness; hereditary blindness; demyelinating diseases; alopecia; sudden infant death syndrome; genetic diseases*

Özet

Biyotinidaz enzimi, vücudumuzda 4-karboksilaz enziminin kofaktörü olan biyotinin aktif hale getirilmesini sağlayan enzimdir. Eksikliği 1971'de tedavi edilmeye başlandıktan sonra, 1980'lerde taranmaya başlanmıştır. 1991–2005 yılları arasında ülkemizde İstanbul Tıp Fakültesi önderliğinde, lokal bir yenidoğan çalışması yapılarak ilk verilere ulaşılmıştır. Bu araştırmanın sonucunda Dünyada 60.000'de bir sıklıkta olduğu bilinen biyotinidaz eksikliğinin, 11,000'de bir sıklıkta görüldüğü gösterilmiştir. Ülkemizde biyotinidaz yenidoğan taraması 2012 yılında ulusal tarama programına eklenmiş ve sıklığın 5500'de bir olduğu bildirilmiştir. Ulusal tarama verileri İstanbul Üniversitesi'ni destekler bulgular vermiş, en sık görülen bölgenin Kuzeydoğu Anadolu ve en çok hastanın bulunduğu illerin Ardahan, Kars, Iğdır olduğu görülmüştür. Bölgenin tanı konan hastalarının metabolik takibini yapacak merkez sayısı yetersizdir. Sorunun yerinde çözümü için hastaların en sık olduğu illerin başında gelen Kars'ta bulunan Kafkas Üniversitesi'ne bağlı bir "Biyotinidaz Eksikliği Araştırma Enstitüsü" kurulması ihtiyacına dikkat çekebilmek için bu makalenin yazılmasına karar verilmiştir.

Anahtar kelimeler: *biyotinidaz eksikliği; yenidoğan tarama; kalıtsal sağırlık; kalıtsal körlük; demiyelinizan hastalıklar; alopesi; ani bebek ölüm sendromu; genetik hastalıklar*

Introduction

The primary function of the enzyme biotinidase is to separate biotin from biocytin. Biotin acts as a cofactor for four carboxylase enzymes involved in amino acid catabolism, fatty acid synthesis and gluconeogenesis[1]. Biotinidase deficiency (BD) is defined as partial deficiency (activity 10–30% of the mean normal value) and profound deficiency (activity less than 10% of the mean normal value) according to the activity level of the enzyme. However, in cases of partial deficiency, similar clinical signs of a profound deficiency may be observed under catabolic conditions such as infection and starvation[2]. Clinical findings are variable among BD patients. Suppose the patient has epilepsy refractory to conventional treatment, acidosis, dermatitis, unexplained hearing or visual loss, spastic paraparesis and growth retardation. In that case, biotinidase deficiency

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should be considered in the specific diagnosis along with these outcomes[3–10]. Biotinidase deficiency as one of the causes of sudden infant death has also been published[11].

Patients are usually recognised with lactic acidosis, hyperammonemia and characteristic organic aciduria. In urine organic acid analysis, lactic acid, 3-OH-isovaleric acid, methylcrotonyl glycine, and methyl citrate excretion are increased. Cerebral oedema, hypodense areas in the white matter, cerebral atrophy and ventricular enlargement are seen with cranial magnetic resonance imaging (MRI). An increase in lactic acid can be seen on magnetic resonance spectroscopy (MRS). Visual and auditory impairment can be demonstrated by electrophysiological evaluation. Visual evoked potential (VEP), electroretinography (ERG) and brainstem auditory stimulus response (BERA) are used for this purpose[7,9,12].

The treatment of BD with biotin was described for the first time in 1971[11,13]. Wolf et al. provided a detailed clinical description of biotinidase deficiency in the 1980s[1,14–16]. Biotinidase deficiency is an autosomal recessive inherited disease. The cytogenetic localisation of the gene responsible for the disease was identified as 3p25.1 and the genomic coordinates (GRCh38,hg38) were identified as Chr3:15.601.745–15.653.714 (ENST00000643237.3)[17–21]. An economical screening method was described by Heard et al. (1984)[14]. Nowadays, BD tests are screened in many countries. The prevalence is known to be 1 in 60,000 worldwide. However, in a local survey of Istanbul province conducted between 1991 and 2005 at Istanbul University, Istanbul Faculty of Medicine, the prevalence of definite biotinidase deficiency was found to be 1/11144[22,23]. Based on the results of this local screening, it was decided to include biotinidase deficiency in the national newborn screening programme. According to the 2012 national screening results, the prevalence of biotinidase deficiency was found to be ~1/5,500[24]. This value means that the frequency is the highest in the world. The province of Istanbul, where the local screening was conducted, has a population mix of people from all provinces of our country. The provinces from which the screened patients migrated are analyzed in detail, with the prominent ones being Ardahan, Kars, Sivas, and Iğdir, respectively (Fig. 1)[22]. As a result of the national screening programme in 2012, the region with the highest prevalence of biotinidase deficiency in Türkiye was found to be the Northeastern Anatolia region.

Discussion

Dermatological findings in biotinidase deficiency include alopecia and eczematous dermatitis, which are independent of enzyme levels and time of diagnosis, and are defined as the first findings to improve with treatment[5]. However, neurological findings do not respond as satisfactorily to treatment as dermatological findings. Pindolia et al (2010), in a 2010 update on BD mutations and clinical considerations, emphasised that there is a close relationship between the level of enzyme activity and the mutation, and that those with profound deficiency share the same genotype[20]. Also, Swango et al. (1998) also described that the c. 1330G >C mutation causes a 50% loss of enzyme activity[18] and behaves like the Duarte variant described in galactosemia. This mutation has been detected in a family in our province.

In Ankara, Genç et al. (2007) found a 55% frequency of deafness in 20 patients with late-diagnosed BD, and it was observed that hearing was affected in all patients whose diagnosis and treatment were initiated,

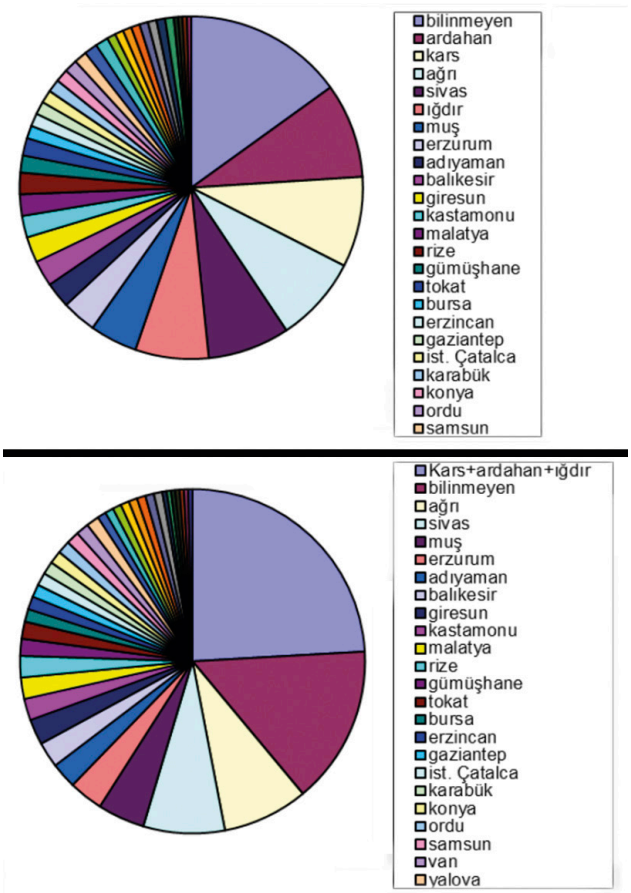

Figure 1. *Distribution of patients diagnosed with biotinidase deficiency according to familial geographical origin.*

particularly after 30 months. Molecular characteristics of these patients were not reported[9]. Sivri– Kalkanoğlu et al. (2007) defined the frequency of deafness as 76% in a group of 20 patients with late diagnosis[10]. Molecular genetic characteristics of these patients: c.98-104Del7ins3 (frameshift) in 4 patients, c.171T >G; p.(57Y >stop) in 4 patients, c.1612C >T; p.(538R >C) in 1 patient, c.194ins4 (frame, shift) in 1 patient, c.1493insT (frame-shift) in 1 patient was identified[10].

Over one year, 23 patients were admitted to the Paediatric Metabolism Clinic of Kafkas University after newborn screening, and 9 of them were diagnosed and followed up. While being followed up by family screening and other centres, 43 patients were included in a clinical follow-up for 1 year, including 20 patients who came to our hospital after the announcement of our department's opening. However, since we are still inadequate in terms of laboratory support in the follow-up of patients, we have to ask for assistance from external laboratories or for help from the facilities of other centres. Among the 10 families in which mutation analysis could be performed, the c.1330G >C mutation was found in 1 patient, the c.1270G >C mutation in 5 patients, and the p. (D242 H) mutation in 4 patients. Six of the patients had significant biotinidase deficiency. All patients who had started follow-up at other centres and continued to our department had been without follow-up and treatment history since the pandemic period.

All patients' families reported that they went to at least two different centres for clinical follow-up and that they were unable to supplement the old clinical follow-up information from the metabolic outpatient clinics, which were closed due to the departure of doctors at the end of the compulsory service period. Old patients had to be re-examined. The metabolic and genetic data of the patients could not be accessed from the electronic patient tracking system of the Ministry of Health of Türkiye. From the neonatal screening system using the mother's identification number, the patient's initial application data has been accessed for the last four months. It has been observed that VEP and BERA scores deteriorate during the period of the patient's loss to clinical follow-up. It was found that none of the families were screened. It was planned to screen and clinically evaluate family members born before the national screening programme began in 2012. However, as there is no genetic laboratory support in our hospital, we try to contribute to the follow-up of patients and their families by preparing projects.

When the geographical distribution and socio-cultural structure of the patients are evaluated, the fact that the screening has Azerbaijani origins in terms of population genetics and that patient information has been available for more than a century, especially in the provinces of Kars, Ardahan, and Iğdir, shows that a collaboration with Azerbaijan, Nakhchivan and Iran is needed. In 2013, the Azerbaijan government initiated screening for phenylketonuria, galactosemia, glucose-6-PO4 dehydrogenase, sickle cell anaemia, thalassaemia, and congenital hypothyroidism; however, it was noted that biotinidase deficiency was not included in the screening programme[25]. It is evident that collaborations should be carried out with neighbouring countries in this regard, and it is also essential for patients to reveal genetic diagnoses.

Conclusion

The number of Paediatric Metabolism doctors responsible for clinical follow-up and treatment in the provinces where the disease is most common is one after 2024, and the number of laboratories to perform confirmatory treatment is zero. If a disease is selected for screening, the screening is a means, a tool, not a goal in itself. The aim is to ensure that a health organisation capable of properly monitoring and treating the screened diseases is employed where necessary and that patients are treated without harm. The realistic, solution-oriented aim is to screen patient or carrier parents, therefore reducing the birth of new patients. Even if it is the prevention of the birth of new patients through preimplantation genetics, it raises ethical concerns. It would be a logical approach to establish a research centre that can achieve this 'Biotinidase Institute' , within Kafkas University, the largest university in the provinces where the disease is most common. Pediatric Metabolism,

Medical Genetics, Pediatric Neurology, Otorhinolaryngology, Ophthalmology, Biochemistry, Obstetrics and Gynaecology doctors should be on the Institute staff. This review has been written to make the situation more visible in its local dimension and to raise awareness of expectations.

Declaration of Interest

The authors declare no conflict of interest.

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OLGU SUNUMU / *CASE REPORT*

Fahr`s Syndrome Accompanied by Psychotic Symptoms and Memory Impairment

Psikotik Belirtiler ve Bellek Bozukluğu ile Birlikte Seyreden Fahr Sendromu

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ABSTRACT

This case report highlights the importance of considering Fahr's syndrome in the differential diagnosis of neuropsychiatric disorders and underscores the necessity of a comprehensive metabolic evaluation in affected patients. Fahr's syndrome, also known as Primary Familial Brain Calcification (PFBC), is a rare disorder characterized by bilateral, symmetric intracranial calcifications, neurodegenerative changes, and disturbances in calcium-phosphorus metabolism. A patient presenting with psychotic symptoms and cognitive impairment is described, with an unusual finding of elevated urinary copper levels despite normal blood calcium levels. The case demonstrated typical features of Fahr's syndrome, including bilateral intracranial calcifications and cognitive dysfunction, along with potential disturbances in copper metabolism. This finding highlights the complexity of metabolic abnormalities associated with the condition and the importance of a thorough diagnostic approach. The report emphasizes the need to consider Fahr's syndrome in patients with neuropsychiatric symptoms, particularly those with cognitive impairment and psychotic features. The presence of elevated urinary copper levels in the absence of blood calcium abnormalities suggests the necessity of a comprehensive metabolic assessment. Early recognition and appropriate diagnostic work-up are crucial for guiding treatment and management, as Fahr's syndrome is often overlooked in the presence of more common neuropsychiatric disorders.

Key words: *Fahr syndrome; primary familial brain calcification; neurodegeneration; calcium; psychosis; cognitive impairment*

ÖZET

Bu olgu sunumu, Fahr sendromunun nöropsikiyatrik bozuklukların ayırıcı tanısında dikkate alınmasının önemini vurgulamakta ve etkilenen hastalarda kapsamlı bir metabolik değerlendirme gerekliliğinin altını çizmektedir. Fahr sendromu (güncel literatürde Primary Familial Brain Calcification – PFBC olarak da adlandırılır), bilateral, simetrik intrakraniyal kalsifikasyonlar, nörodejeneratif değişiklikler ve kalsiyum-fosfor metabolizmasındaki bozukluklarla karakterize nadir bir hastalıktır. Psikotik semptomlar ve bilişsel bozukluklar gösteren bir hasta sunulmuş olup, bu vakada kan kalsiyum seviyeleri normal olmasına rağmen idrar bakır seviyelerinin yüksek olması dikkat çekici bir bulgudur. Olgu, Fahr sendromunun tipik özelliklerini, yani bilateral intrakraniyal kalsifikasyonlar ve bilişsel işlev bozukluğunu sergilemiş ve bakır metabolizmasındaki olası bozuklukları da ortaya koymuştur. Bu bulgu, hastalığa eşlik eden metabolik anormalliklerin karmaşıklığını ve kapsamlı bir tanısal yaklaşımın önemini vurgulamaktadır. Sunulan olgu, bilişsel bozukluk ve psikotik belirtiler gösteren hastalarda Fahr sendromunun ayırıcı tanıda göz önünde bulundurulması gerektiğini ortaya koymaktadır. Kan kalsiyum seviyelerinde herhangi bir anormallik olmaksızın idrar bakır seviyelerinin yüksek olması, kapsamlı bir metabolik değerlendirmenin gerekliliğini düşündürmektedir. Fahr sendromu, yaygın nöropsikiyatrik hastalıkların varlığında sıklıkla gözden kaçabileceğinden, erken tanı ve uygun tanısal değerlendirme, tedavi ve yönetimin yönlendirilmesi açısından büyük önem taşımaktadır.

Anahtar kelimeler: *Fahr sendromu; nörodejenerasyon; kalsiyum; psikoz; bilişsel bozukluk*

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Introduction

Fahr's syndrome is a rare neurodegenerative disorder characterized by bilateral, symmetric intracranial calcifications, particularly in the basal ganglia, thalamus, cerebellum, and subcortical white matter. It was first described in 1930, but its exact pathophysiology remains poorly understood. Fahr's syndrome is associated with several etiologies, including primary genetic mutations (particularly in the MYORG gene), metabolic disturbances (especially calcium-phosphorus imbalances), infections, and endocrine dysfunctions such as hypoparathyroidism. Clinical presentation varies greatly, ranging from asymptomatic calcifications detected incidentally to progressive neurological and psychiatric manifestations. Symptoms may include movement disorders, seizures, psychosis, cognitive decline, and mood disturbances. Neuropsychiatric symptoms can sometimes precede motor abnormalities, leading to frequent misdiagnoses[1–3].

The clinical manifestations of Fahr's syndrome are highly variable, with neuropsychiatric symptoms being among the most prominent. Patients often present with movement disorders, cognitive decline, and psychiatric disturbances, including psychosis, mood disorders, and personality changes. Psychotic symptoms such as hallucinations and delusions have been reported in cases where basal ganglia calcifications disrupt key neurotransmitter pathways, particularly those involving dopamine. Cognitive impairment is also common, with affected individuals exhibiting deficits in executive function, memory, and processing speed. These features can lead to misdiagnosis as schizophrenia or other primary psychiatric disorders[4,5].

Neuroimaging, particularly computed tomography (CT), is crucial in diagnosing Fahr's syndrome, as it reveals the characteristic bilateral calcifications. However, a thorough metabolic and genetic workup is necessary to differentiate idiopathic Fahr's syndrome from secondary causes linked to metabolic disturbances[5].

This case report describes a patient with Fahr's syndrome presenting with psychotic symptoms and cognitive impairment, adding to the literature on its neuropsychiatric manifestations and highlighting the importance of comprehensive diagnostic evaluations.

Case Report

A 55-year-old female presented with delusions of reference and persecution, a depressive mood, and memory impairment, which had developed over 1.5 months. The patient had no previous psychiatric history or significant medical conditions. She had a university degree and had worked as a teacher until retirement. There was no family history of psychiatric disorders or neurodegenerative diseases.



Figure 1. *Tomography of basal ganglia calcification.*

Her symptoms included fear of being harmed, poisoned, and followed, along with disorganized behavior, speech difficulties, anger management issues, and sleep disturbances. Given the acute onset of symptoms and their severity, an organic etiology was suspected. A neurology consultation was requested to rule out underlying structural or metabolic causes of her psychiatric symptoms. The neurological examination revealed mild bradykinesia and subtle gait abnormalities, warranting further neuroimaging.

Brain CT revealed extensive bilateral lentiform nucleus calcifications (Fig. 1), which were highly suggestive of Fahr's syndrome. Laboratory evaluations showed normal blood calcium, phosphate, and parathyroid hormone (PTH) levels, ruling out common metabolic causes of basal ganglia calcifications. However, a 24-hour urine analysis revealed elevated copper levels (113 μg, normal range: 2–60 μg), while blood copper levels remained within the normal range. Additional metabolic and genetic screenings were unremarkable.

Psychiatric evaluation was performed according to the Structured Clinical Interview for DSM-5 Disorders (SCID-5-TR), and a diagnosis of psychotic disorders was made based on DSM-5 TR (Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision) criteria. The Positive and Negative Syndrome Scale (PANSS) and neurocognitive assessments were administered. Due to her psychotic symptoms, olanzapine was prescribed at 10 mg/day, leading to significant symptom improvement after four weeks.

Neuropsychiatric Assessments

Pre-treatment PANSS Scores:

- PANSS Positive: 36
- PANSS Negative: 16
- PANSS General: 37
- PANSS Total: 89

Post-treatment PANSS Scores (week 4):

- PANSS Positive: 18
- PANSS Negative: 12
- PANSS General: 24
- PANSS Total: 54

The patient demonstrated a significant reduction in positive and general symptoms following olanzapine treatment, with mild improvements in negative symptoms.

Neurocognitive Assessment

The neuropsychological tests indicated deficits in multiple cognitive domains:

Montreal Cognitive Assessment (MOCA): The patient showed impairments in visual and spatial functions, attention, language, abstract thinking, and delayed recall, suggesting cognitive decline.

Audio-Visual Number Sequence Test: The score of 14 indicated difficulties in attention and short-term memory.

Benton Visual Retention Test: A total of 17 errors were observed, indicating significant visual memory impairment. Errors included distortions, misplacements, rotations, and perseverations, distributed across both visual fields.

Stroop Test: Prolonged response times in sections 3, 4, and 5 suggested deficits in attention control, response inhibition, and cognitive processing speed.

These findings highlight the presence of cognitive dysfunction in Fahr's syndrome, particularly in executive functioning, memory, and information processing.

Discussion

Fahr's syndrome is primarily associated with movement disorders; however, psychiatric symptoms, including psychosis and cognitive impairment, are increasingly recognized as significant components of the disease. This case contributes to the literature by emphasizing the importance of considering Fahr's syndrome in patients presenting with new-onset psychotic symptoms and cognitive dysfunction, even in the absence of metabolic abnormalities such as calcium disturbances.

To enhance diagnostic clarity, especially in cases presenting with overlapping neuropsychiatric symptoms, the use of proposed diagnostic criteria for Fahr's syndrome may be beneficial. According to Saleem et al.[1], these criteria include a) bilateral basal ganglia calcifications, b) progressive neurological dysfunction, c) absence of biochemical abnormalities or infectious/metabolic causes, and d) a positive family history or idiopathic presentation. In the presented case, bilateral calcifications and cognitive dysfunction were evident, while the metabolic workup was largely unremarkable except for elevated urinary copper. However, the lack of family history and the incomplete exclusion of differential diagnoses, such as Wilson's disease, represent limitations in applying these criteria comprehensively.

Several case reports in recent years have highlighted the diverse psychiatric manifestations of Fahr syndrome, including cases mimicking late-onset schizophrenia, catatonia, and treatment-resistant psychosis[6]. The current case adds to this growing body of literature by demonstrating a rare presentation of psychotic symptoms accompanied by elevated urinary copper levels. Wazir et al. (2023) and Haider et al. (2025) have emphasized the diagnostic complexity when psychiatric symptoms precede calcification-related motor signs, underscoring the importance of early imaging[7,8]. Notably, Sieffien et al. (2025) also reported psychosis as a primary presentation, emphasizing the need for neuroimaging in atypical psychotic disorders[9].

In contrast to the aforementioned cases, the present case uniquely highlights an atypical copper metabolism

profile without calcium-phosphorus imbalance. This metabolic anomaly, although not diagnostic of Wilson's disease, raises important questions regarding trace metal metabolism in PFBC patients. Although the patient demonstrated marked improvement after four weeks of 10 mg/day olanzapine, long-term follow-up data is limited. Follow-up evaluations revealed no significant extrapyramidal side effects or metabolic disturbances (e.g., weight gain, hyperlipidemia, or glucose dysregulation).

One of the unique aspects of this case is the presence of elevated urinary copper levels, which have not been widely reported in association with Fahr's syndrome. The role of altered metal metabolism in the pathogenesis of the disorder remains unclear. Still, this finding suggests that further research is warranted to investigate potential metabolic contributors beyond calcium and phosphorus disturbances[10].

This case report highlights the need for increased awareness among psychiatrists regarding Fahr's syndrome as a differential diagnosis for psychotic disorders. Misdiagnosis as schizophrenia or primary psychotic disorder can lead to inappropriate treatment and delayed recognition of the underlying neurodegenerative condition. Neuroimaging, particularly CT scans, should be considered in cases where atypical psychiatric symptoms emerge in middle-aged or elderly individuals with no prior psychiatric history[7].

Conclusion

Fahr's syndrome should be considered in the differential diagnoses for patients with unexplained neuropsychiatric symptoms. The presence of elevated urinary copper levels in this case suggests the need for further research into metabolic disruptions associated with Fahr's syndrome. Early recognition and appropriate psychiatric and neurological management are crucial for improving patient outcomes. Increased awareness of the psychiatric presentations of Fahr's syndrome will aid in timely diagnosis and intervention, ultimately improving patient prognosis.

Although the patient's elevated urinary copper levels raise suspicion for Wilson's disease, further diagnostic steps such as serum ceruloplasmin measurement or ophthalmologic evaluation for Kayser-Fleischer rings were not conducted. As copper accumulation can manifest neuropsychiatric symptoms similar to Fahr's syndrome, this represents a limitation in the differential diagnostic process. Future cases should consider a complete Wilson's disease workup when copper metabolism abnormalities are observed, even in the absence of typical hepatic or ocular findings.

Unlike most reported cases, this patient presented with psychosis as a first and predominant symptom, without motor symptoms or calcium-phosphorus abnormalities. The unusual presence of elevated urinary copper adds a novel biochemical finding not commonly reported in Fahr syndrome literature, raising the possibility of non-traditional metabolic contributors.

This case has several limitations. First, the short duration of follow-up limits conclusions regarding long-term psychiatric and neurological outcomes. Second, although elevated urinary copper was observed, comprehensive testing for Wilson's disease (such as serum ceruloplasmin levels or ophthalmological evaluation) was not performed. Third, genetic testing for known PFBC mutations was not available, precluding a definitive familial classification. Future studies should investigate the role of copper and other trace elements in the pathophysiology of PFBC. In addition, longitudinal case series with genetic and metabolic profiling could enhance our understanding of phenotypic variability and treatment response in Fahr syndrome.

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Conflict of Interest Statement

There are no conflicts of interest.

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Erratum: Publication Status of Postgraduate Theses Completed in Ankara University's Health Sciences Institute (1984-2023): A Biometric Study

Ankara Üniversitesi Sağlık Bilimleri Enstitüsü'nde Tamamlanan Lisansüstü Tezlerin Yayın Durumu (1984-2023): Biyometrik Bir Çalışma

The incorrects word in title information in the first page of the article with the title **"Publication Status of Postgraduate Theses Completed in Ankara University's Health Sciences Institute (1984-2023): A Biometric Study"** published in the **Kafkas J Med Sci 2025;15(2):260-269 (DOI: 10.5505/kjms.2025.06926)**, word in the title has been corrected. The corrected parts is as follows. We apologize to our readers.

Publication Status of Postgraduate Theses Completed in Ankara University's Health Sciences Institute (1984-2023): A Bibliometric Study

Ankara Üniversitesi Sağlık Bilimleri Enstitüsü'nde Tamamlanan Lisansüstü Tezlerin Yayın Durumu (1984-2023): Bibliyometrik Bir Çalışma

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