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ORIGINAL ARTICLE

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Diagnostic Yield and Prognostic Value of Emergency Neuroimaging in Older Adults: Role of the Glasgow Coma Scale

Yaşlı Hastalarda Acil Nörogörüntülemenin Tanısal Getirisi ve Prognostik Değeri: Glasgow Koma Skalasının Rolü

Nisa BAŞPINAR, Pervin SÖNMEZ, İsmail SALK

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ABSTRACT

Aim: Emergency neuroimaging is increasingly used in older adults with neurological symptoms; however, evidence on diagnostic yield and outcomes in this population remains limited. This study evaluated the diagnostic performance of computed tomography (CT) and magnetic resonance imaging (MRI) in older adult emergency patients and assessed the prognostic significance of Glasgow Coma scale (GCS) combined with imaging findings.

Materials and Methods: This retrospective study included 743 patients aged ≥65 years who presented to a tertiary emergency department between January and March 2025 with non-traumatic neurological symptoms requiring brain imaging. Demographics, symptoms, GCS scores, imaging findings, hospital disposition, and mortality were analyzed. Logistic regression identified predictors of abnormal imaging and clinical outcomes.

Results: The cohort (mean age 77.1±7.7 years; 52.8% male) had abnormal CT findings in 20.7% of patients and MRI abnormalities in 36.1%. Cerebrovascular accidents were most common (CT: 12.0%, MRI: 26.7%). Abnormal GCS (<15) was associated with abnormal imaging (CT: 28.5% vs. 17.8%; MRI: 46.7% vs. 33.1%). Mortality was 1.3%, exclusively in patients with abnormal GCS. Among those with altered consciousness, mortality varied by imaging: CT abnormal (8.8%), MRI abnormal (14.0%), CT normal (3.5%), MRI normal (2.0%). Abnormal imaging was associated with substantially higher hospitalization rates (CT: 79.9% vs. 20.9%; MRI: 87.3% vs. 24.5%) and increased odds of mortality [CT: odds ratio (OR)=3.9, 95% confidence interval (CI): 1.1-13.8; MRI: OR= 11.0, 95% CI: 1.3-92.4].

Conclusion: MRI demonstrated higher diagnostic yield than CT in older adults with neurological emergencies. A normal GCS was a strong negative predictor of short-term mortality. Combining GCS with neuroimaging findings enables effective risk stratification and supports clinical decision-making in emergency care. In patients with altered consciousness (GCS <15), neuroimaging provided additive prognostic value, with mortality risk increasing stepwise from normal to abnormal imaging findings, highest in those with abnormal MRI.

Keywords: Emergency department, older adults, neuroimaging, Glasgow Coma scale, mortality

ÖZ

Amaç: Nörolojik semptomlarla başvuran yaşlı hastalarda acil nörogörüntüleme giderek daha sık kullanılmaktadır; ancak bu popülasyonda tanısal verim ve klinik sonuçlara ilişkin kanıtlar sınırlıdır. Bu çalışmada, yaşlı acil servis hastalarında bilgisayarlı tomografi (BT) ve manyetik rezonans görüntülemenin (MRG) tanısal performansı değerlendirilmiş, ayrıca görüntüleme bulguları ile birlikte Glasgow Koma skalası (GKS) skorunun prognostik önemi araştırılmıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya, Ocak-Mart 2025 tarihleri arasında üçüncü basamak bir acil servise travma dışı nörolojik semptomlarla başvuran ve beyin görüntülemesi yapılan, 65 yaş ve üzerindeki 743 hasta dahil edildi. Demografik özellikler, başvuru semptomları, GKS skorları, görüntüleme bulguları, hastaneye yatış durumu ve mortalite verileri analiz edildi. Anormal görüntüleme bulgularını ve klinik sonuçları öngören faktörler lojistik regresyon analizi ile değerlendirildi.

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Bulgular: Çalışma grubunun ortalama yaşı 77,1±7,7 yıl olup hastaların %52,8'i erkekti. BT'de hastaların %20,7'sinde, MRG'de ise %36,1'inde anormal bulgu saptandı. En sık görülen patoloji serebrovasküler olaydı (BT: %12,0; MRG: %26,7). Anormal GKS (<15), anormal görüntüleme bulguları ile ilişkiliydi (BT: %28,5'e karşı %17,8; MRG: %46,7'ye karşı %33,1). Mortalitenin %1,3 olduğu ve yalnızca GKS'si anormal olan hastalarda görüldüğü belirlendi. Bilinç değişikliği bulunan hastalarda mortalite oranları görüntüleme bulgularına göre farklılık gösterdi: BT anormal %8,8, MRG anormal %14,0, BT normal %3,5 ve MRG normal %2,0. Anormal görüntüleme bulguları, belirgin derecede daha yüksek hastaneye yatış oranları (BT: %79,9'a karşı %20,9; MRG: %87,3'e karşı %24,5) ve artmış mortalite olasılığı ile ilişkili bulundu [BT: olasılık oranı (OR)=3,9, %95 güven aralığı (GA): 1,1-13,8; MRG: OR=11,0, %95 GA: 1,3-92,4].

Sonuç: MRG, nörolojik acillerle başvuran yaşlı hastalarda BT'ye göre daha yüksek tanısal verim sağlamıştır. Normal GKS, kısa dönem mortalite açısından güçlü bir negatif öngörücü olarak bulunmuştur. GKS'nin nörogörüntüleme bulguları ile birlikte değerlendirilmesi, etkili risk sınıflandırması yapılmasına olanak sağlamakta ve acil serviste klinik karar verme sürecini desteklemektedir. Bilinç değişikliği olan (GKS <15) hastalarda nörogörüntüleme ek prognostik değer sağlamış; mortalite riski normal görüntülemeden anormal görüntülemeye doğru kademeli olarak artmış ve en yüksek risk anormal MRG bulgusu olan hastalarda gözlenmiştir.

Anahtar Kelimeler: Acil servis, yaşlı erişkinler, nörogörüntüleme, Glasgow Koma skalası, mortalite

INTRODUCTION

Emergency neuroimaging represents a critical component of acute care for older adults' patients presenting with neurological symptoms or altered mental status. Non-traumatic brain emergencies are the leading cause of morbidity and mortality in this population, driven by widespread age-related physiological changes and increased comorbidities[1]. The growing older adult population, combined with the higher incidence of emergent neurological conditions, necessitates rapid and reliable neuroimaging for accurate diagnosis and appropriate treatment decisions in this vulnerable age group[2].

Computed tomography (CT) remains the most utilized first-line neuroimaging modality in emergency departments due to its widespread availability, rapid acquisition, and cost-effectiveness[3]. The number of emergency department visits and neuroimaging examinations has increased significantly, with neuroimaging utilization in emergency departments growing considerably between 2007 and 2017[4]. CT is the most commonly used imaging modality for the assessment of patients with suspected stroke, owing to its widespread availability, rapid acquisition, and lower cost compared with magnetic resonance imaging (MRI)[5]. However, the diagnostic limitations of CT in detecting acute ischemic changes and subtle parenchymal abnormalities have led to increased utilization of MRI in emergency settings.

MRI is widely considered superior to CT for detecting acute stroke. However, this assumption has not been conclusively validated across the entire spectrum of patients in whom acute stroke is suspected[6]. Recent comparative studies have demonstrated significant differences in diagnostic yield between these modalities. MRI identified acute ischemic stroke in 164 of 356 individuals [46%; 95% confidence interval (CI: 41-51%], whereas CT detected it in only 35 of 356 patients (10%; 95% CI, 7-14%). When compared with the final clinical diagnosis, the sensitivity of MRI for detecting any acute stroke was 83% (181/217; 95% CI, 78-88%), while CT demonstrated a sensitivity of just 26% (56/217; 95% CI, 20-32%)[6].

The decision to perform neuroimaging in older adults patients requires careful consideration of clinical factors, as indiscriminate use of imaging studies can lead to increased costs and unnecessary radiation exposure[7]. When the etiology is uncertain and intracranial pathology cannot be safely excluded, neuroimaging should be performed during the first assessment of acute changes in mental status. Imaging is especially recommended for patients with trauma, anticoagulation therapy, hypertension or hypertensive emergencies, headache, gastrointestinal symptoms such as nausea or vomiting, suspected infection, new seizures, neurological deficits, a cancer history, older age, or pre-existing intracranial conditions[8].

The needs of older adults in acute care are unique, but little is known about the potential benefits of imaging in frail populations[9]. Older adults aren't typically included in clinical studies that examine the utility and efficacy of medical imaging procedures, and it's difficult to generalize study results to older groups[9]. According to a systematic review, CT scans revealed abnormal results in 15.6% of elderly emergency patients presenting with confusion or altered mental status, with focal neurological deficits showing a strong association with acute intracranial pathology[10]. This knowledge gap underscores the importance of studying diagnostic yields and clinical outcomes specifically in older adults.

Glasgow coma scale (GCS) serves as a fundamental neurological assessment tool that has demonstrated strong prognostic value across various clinical contexts[11]. A relationship between assessments of the GCS and outcome was shown clearly, demonstrating the existence of a continuous, progressive association between increasing mortality after a head injury and decreases in GCS score from 15 to 3[11]. The prognostic utility of GCS extends beyond traumatic brain injury to various neurological emergencies in older patients.

Recent studies utilizing machine learning approaches have demonstrated that key predictive factors for mortality include metabolic syndrome, NEWS2 score, GCS, surgical status, bowel movement status, potassium level, and aspartate transaminase level[12]. This evidence supports the integration of GCS with neuroimaging findings for comprehensive risk stratification in elderly patients.

The present study aims to evaluate the diagnostic yield of brain imaging modalities (CT and MRI) in older adults (≥65 years) presenting to the emergency department with non-traumatic neurological symptoms, and to assess the prognostic significance of neuroimaging findings in relation to GCS scores and short-term clinical outcomes.

MATERIALS AND METHODS

This retrospective, observational study was conducted at a tertiary care hospital emergency department. The study protocol was approved by the institutional ethics committee, and patient consent was waived due to the retrospective nature of the study. This study was approved by the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (approval no: 2025-06/18, date: 12.06.2025). All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

All patients aged 65 years and older who presented to the emergency department between January 1, 2025, and March 1, 2025, and required brain imaging were included in the study. All patients underwent non-contrast head CT as the initial imaging modality. Subsequent MRI was performed only in patients for whom additional imaging was deemed clinically necessary based on CT findings and/or persistent clinical suspicion, in accordance with routine emergency department practice. Inclusion criteria were age ≥65 years, emergency department presentation during the study period, and brain imaging (CT and/or MRI) performed during the emergency department visit. Exclusion criteria included age <65 years, history of trauma, and brain imaging with technical inadequacy or severe motion artifacts preventing proper evaluation. The patient selection process and imaging pathway are summarized in Figure 1.

Non-contrast brain CT was performed using a GE Revolution Evo scanner (GE Healthcare, USA) standard axial acquisition parameters with thin-section reconstruction, according to institutional emergency imaging protocols. MRI examinations were performed using a 1.5-T system (Siemens Magnetom Aera, Siemens Healthineers, Erlangen, Germany) and included mandatory sequences for acute neurological assessment: axial T1-weighted, T2-weighted, fluid-attenuated inversion recovery, diffusion-weighted imaging with corresponding apparent diffusion coefficient maps, and susceptibility-weighted imaging, when available. MRI was used to assess acute ischemia, intracranial hemorrhage, mass lesions, and other parenchymal abnormalities.

Patient data were retrospectively collected from the hospital information management system. Demographics including age, gender, and preliminary diagnoses recorded at emergency department presentation were extracted. Brain CT images were reviewed through the picture archiving and communication system. Acute pathologies (e.g., ischemic stroke, hemorrhage) and incidental findings (e.g., masses, aneurysms, calcifications) were separately documented. For patients who underwent MRI, imaging findings and reported diagnoses were similarly evaluated and recorded. Clinical outcomes and emergency department dispositions were categorized as discharged home, death, admission to neurology or neurosurgery services, or admission to other services for non-neurological diagnoses. The term "general disorder" was used to describe non-specific clinical presentations commonly observed in elderly emergency patients, including generalized weakness, malaise, functional decline, or nonspecific clinical deterioration.

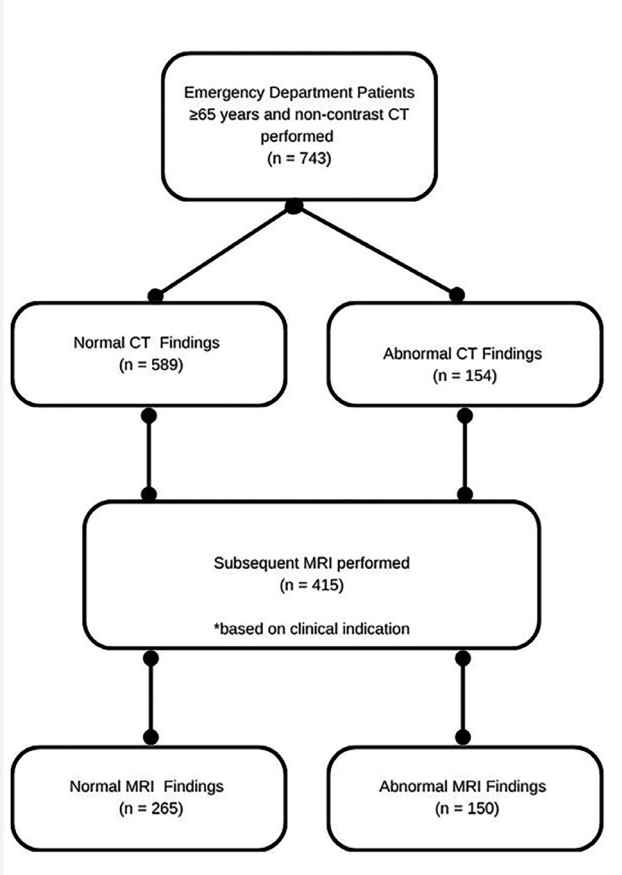

Figure 1. Patient flow diagram of emergency neuroimaging pathway in older adults

CT: Computed tomography, MRI: Magnetic resonance imaging

The GCS score was recorded at the time of initial emergency department admission, prior to neuroimaging. Patients were categorized as having normal consciousness (GCS=15) or altered consciousness (GCS<15), with further subcategorization into mild (GCS)[13-14], moderate (GCS)[9-12], and severe (GCS)[3-8] impairment.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 23.0. Descriptive statistics included mean ± standard deviation, median, minimum and maximum values for continuous variables, and frequencies with percentages for categorical variables. The chi-square test or Fisher's exact test (when appropriate) was used to evaluate associations between categorical variables. Normality of continuous variables was assessed using the Kolmogorov-Smirnov or Shapiro-Wilk tests. Independent sample t-tests were used for normally distributed data, while Mann-Whitney U tests were applied for non-parametric comparisons between two groups. For multiple group comparisons, one-way ANOVA was used for parametric data and Kruskal-Wallis test for non-parametric data. Logistic regression analysis was performed to evaluate the relationship between imaging findings and clinical outcomes (hospitalization, mortality). Variables found to be significant in univariate analysis were included in the multivariate model to assess their independent effects on hospital admission or mortality. A p-value<0.05 was considered statistically significant for all analyses.

RESULTS

A total of 743 older adult patients with a mean age of 77.1±7.7 years were included in this study, with 52.8% being male and 47.2% female (Table 1). The majority of patients (72.7%) presented with normal GCS scores of 15, while 26.9% had abnormal scores below 15 (GCS was not recorded in 3 patients, 0.4%)[15]. The most common presenting symptoms were general disorder (22.3%), dizziness (11.4%), and headache (9.4%).

Neuroimaging findings revealed significant differences between CT and MRI diagnostic capabilities (Table 2). CT imaging demonstrated abnormal findings in 20.7% of patients (154/743). MRI, which was performed in a clinically selected subset of patients following initial CT evaluation (n=415), demonstrated a substantially higher diagnostic yield of 36.1% (150/415, p<0.001). Cerebrovascular accident was the most frequently identified pathology, detected in 12.0% of CT scans and 26.7% of MRI examinations. Mass lesions were identified in 2.8% of CT and 4.3% of MRI studies, while intraparenchymal hemorrhage was found in 2.6% of CT and 1.9% of MRI cases.

Analysis of factors associated with abnormal brain imaging revealed that age and gender were not significantly associated with abnormal findings on either CT or MRI (Table 3). However, GCS status emerged as a strong predictor of abnormal neuroimaging results. Patients with abnormal GCS (<15) demonstrated significantly higher rates of abnormal CT findings (28.5% vs. 17.8%, p<0.001) and abnormal MRI findings (46.7% vs. 33.1%, p=0.017) compared to patients with normal GCS scores.

Overall mortality was low at 1.3% (10 of 743 patients), but

Table 1. Baseline characteristics and clinical presentation

Characteristic	Total (n=743)
Age (years)	
Mean ± SD	77.1±7.7
Median (IQR)	76
Age groups, n (%)	
65-74 years	293 (39.4%)
75-84 years	318 (42.8%)
≥85 years	132 (17.7%)
Gender, n (%)	
Male	392 (52.8%)
Female	351 (47.2%)
Glasgow Coma scale, n (%)	
Normal (15)	540 (72.7%)
Mild (13-14)	62 (8.3%)
Moderate (9-12)	96 (12.9%)
Severe (3-8)	42 (5.7%)
Most common symptoms, n (%)	
General disorder	166 (22.3%)
Dizziness	85 (11.4%)
Headache	70 (9.4%)
Speech disorder	66 (8.9%)
Fatigue	57 (7.7%)
Confusion	55 (7.4%)

SD: Standard deviation, IQR: Interquartile range

Table 2. Imaging findings and diagnostic yield

Findings	CT (n=743)	MRI (n=415)
Normal, n (%)	589 (79.3%)	265 (63.9%)
Abnormal, n (%)	154 (20.7%)	150 (36.1%)
Specific pathologies, n (%)		
Cerebrovascular accident	89 (12.0%)	111 (26.7%)
Mass lesion	21 (2.8%)	18 (4.3%)
Intraparenchymal hemorrhage	19 (2.6%)	8 (1.9%)
Subdural/epidural hemorrhage	16 (2.2%)	7 (1.7%)
Meningioma	9 (1.2%)	6 (1.4%)
Diagnostic Yield (%)	20.7	36.1*

*p<0.001 vs. CT (chi-square test), MRI: Magnetic resonance imaging, CT: Computed tomography

Table 3. Association between patient characteristics and CT/MRI abnormalities

Variable	CT abnormal n (%)	CT normal n (%)	CT p-value	CT adjusted OR (95% CI)	MRI abnormal n (%)	MRI normal n (%)	MRI p-value	MRI adjusted OR (95% CI)
Age groups								
65-74 years	63 (21.5%)	230 (78.5%)	0.912	1.00	59 (35.1%)	109 (64.9%)	0.892	1.00
75-84 years	65 (20.4%)	253 (79.6%)		0.90 (0.61-1.34)	66 (36.3%)	116 (63.7%)		1.07 (0.68-1.66)
≥85 years	26 (19.8%)	106 (80.3%)		0.78 (0.46-1.33)	25 (38.5%)	40 (61.5%)		1.06 (0.58-1.94)
Gender								
Male	83 (21.2%)	309 (78.8%)	0.751	1.00	78 (36.8%)	134 (63.2%)	0.779	1.00
Female	71 (20.2%)	280 (79.8%)		1.05 (0.73-1.50)	72 (35.5%)	131 (64.5%)		1.06 (0.70-1.59)
Glasgow Coma scale								
Normal (GCS=15)	96 (17.8%)	444 (82.2%)	<0.001*	1.00	106 (33.1%)	214 (66.9%)	0.017*	1.00
Abnormal (GCS<15)	57 (28.5%)	143 (71.5%)		1.91 (1.30-2.80)*	43 (46.7%)	49 (53.3%)		1.77 (1.10-2.86)*
Detailed GCS categories								
Normal (GCS=15)	96 (17.8%)	444 (82.2%)	0.009*	1.00	106 (33.1%)	214 (66.9%)	0.048*	1.00
Mild (GCS 13-14)	15 (24.2%)	47 (75.8%)		1.48 (0.79-2.75)	14 (37.8%)	23 (62.2%)		1.23 (0.61-2.49)
Moderate (GCS 9-12)	31 (32.3%)	65 (67.7%)		2.21 (1.36-3.57)*	26 (54.2%)	22 (45.8%)		2.39 (1.29-4.41)*
Severe (GCS 3-8)	11 (26.2%)	31 (73.8%)		1.64 (0.80-3.38)	3 (42.9%)	4 (57.1%)		1.51 (0.33-6.89)
Presenting symptoms								
General disorder	24 (14.5%)	142 (85.5%)	<0.001*	0.47 (0.29-0.76)*	20 (35.1%)	37 (64.9%)	<0.001*	1.00
Headache	13 (18.6%)	57 (81.4%)		0.63 (0.33-1.20)	9 (29%)	22 (71%)		0.76 (0.31-1.87)
Dizziness	5 (5.9%)	80 (94.1%)		0.17 (0.07-0.44)*	4 (8%)	46 (92%)		0.16 (0.05-0.49)*
Other symptoms	112 (26.5%)	310 (73.5%)		1.00	117 (42.2%)	160 (57.8%)		1.35 (0.75-2.43)

*p<0.05, statistically significant

CT: Computed tomography, MRI: Magnetic resonance imaging, GCS: Glasgow Coma scale, OR: Odds ratio, CI: Confidence interval, adjusted OR calculated using multivariable logistic regression including age group, gender, and GCS

demonstrated a critical pattern based on GCS status (Figure 1). All observed mortality occurred exclusively in patients presenting with an abnormal GCS score (<15), whereas no fatalities were recorded among those with a normal GCS (15) regardless of imaging findings. Among patients with abnormal GCS, mortality risk varied by imaging results: 3.5% for normal CT, 8.8% for abnormal CT, (p=0.152), 2.0% for normal MRI, and 14.0% for abnormal MRI (p=0.048). The highest mortality risk was observed in patients with both abnormal GCS and abnormal MRI findings (14.0%). Accordingly, a normal GCS demonstrated a 100% negative predictive value for in-hospital mortality (0/540 deaths). Mortality rates stratified by GCS status and neuroimaging findings are illustrated in Figure 2.

Clinical outcomes analysis demonstrated that patients with abnormal neuroimaging had dramatically different hospital dispositions (Table 4, Figure 3). Among patients with abnormal CT findings, 79.9% required hospitalization compared to only 20.9% of patients with normal CT (p<0.001). Similarly, 87.3% of patients with abnormal MRI findings required hospitalization versus 24.5% with normal MRI (p<0.001). As illustrated in Figure 3, discharge rates were correspondingly lower in patients with abnormal

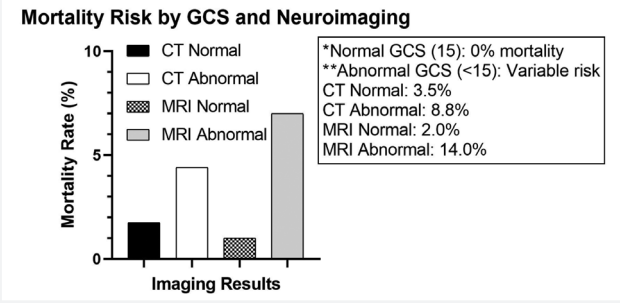

Figure 2. Mortality rates stratified by Glasgow Coma scale (GCS) status and neuroimaging results in geriatric patients (n=743). Patients with normal GCS (15) demonstrated 0% mortality regardless of CT or MRI findings. In contrast, patients with abnormal GCS (<15) showed variable mortality risk depending on imaging results: CT normal (3.5%), MRI normal (2.0%), CT abnormal (8.8%), and MRI abnormal (14.0%). The highest mortality risk was observed in patients with both abnormal GCS and abnormal MRI findings. Black bars represent normal GCS patients; patterned/gray bars represent abnormal GCS patients. Statistical significance was achieved for GCS groups (p<0.001).

MRI: Magnetic resonance imaging, CT: Computed tomography

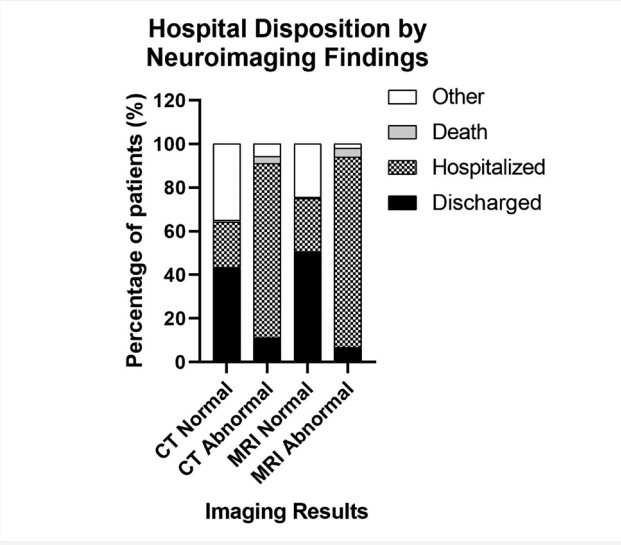

Figure 3. Distribution of hospital disposition outcomes stratified by neuroimaging results in geriatric patients (n=743). Stacked bar chart demonstrates the percentage distribution of patient outcomes: discharged (bottom, white), hospitalized (middle, gray), death (black), and other dispositions (top, striped). Patients with abnormal neuroimaging showed dramatically higher hospitalization rates compared to normal imaging: CT abnormal (79.9% vs. 20.9% for CT normal, p<0.001) and MRI abnormal (87.3% vs. 24.5% for MRI normal, p<0.001). Conversely, discharge rates were significantly lower in abnormal imaging groups: CT abnormal (11.0% vs. 43.3%) and MRI abnormal (6.7% vs. 50.6%). Mortality rates, while low overall, were consistently higher in abnormal imaging groups. Each bar represents 100% of patients in that imaging category.

MRI: Magnetic resonance imaging, CT: Computed tomography

imaging: 11.0% for abnormal CT versus 43.3% for normal CT, and 6.7% for abnormal MRI versus 50.6% for normal MRI.

Abnormal neuroimaging was associated with significantly elevated overall mortality rates. Patients with abnormal CT findings had higher odds of mortality [odds ratio (OR)=3.9,

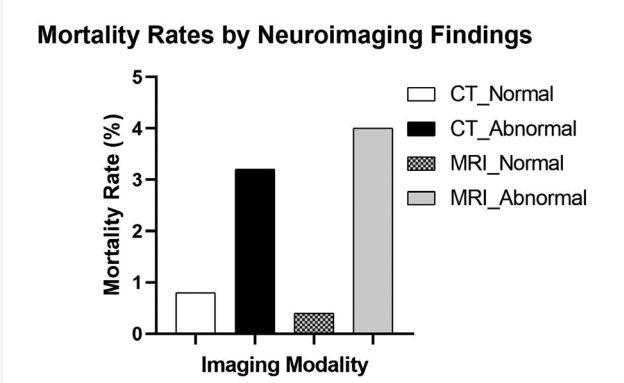

Figure 4. Comparison of mortality rates across different neuroimaging categories in geriatric patients (n=743). Bar chart displays mortality percentages for each imaging group: CT normal (0.8%), CT abnormal (3.2%), MRI normal (0.4%), and MRI abnormal (4.0%). Abnormal neuroimaging findings were associated with significantly higher mortality rates compared to normal findings: 3,9-fold increase for CT (p=0.021) and 11-fold increase for MRI (p=0.006). MRI abnormal patients demonstrated the highest mortality risk at 4.0%, while MRI normal patients had the lowest risk at 0.4%. These findings highlight the prognostic value of neuroimaging in geriatric patients and support risk stratification for clinical decision-making.

MRI: Magnetic resonance imaging, CT: Computed tomography

Table 4. Clinical outcomes and mortality analysis by imaging modality

Outcome	CT imaging (n=743)			p-value	MRI imaging (n=415)			p-value*
	Total n (%)	Normal n (%)	Abnormal n (%)		Total n (%)	Normal n (%)	Abnormal n (%)	
Hospital disposition								
Discharged	272 (36.6%)	255 (43.3%)	**17 (11.0%)**	**<0.001**	144 (34.7%)	134 (50.6%)	**10 (6.7%)**	**<0.001**
Hospitalized	246 (33.1%)	123 (20.9%)	**123 (79.9%)**	**<0.001**	196 (47.2%)	65 (24.5%)	**131 (87.3%)**	**<0.001**
Death	10 (1.3%)	5 (0.8%)	**5 (3.2%)**	**0.021**	7 (1.7%)	1 (0.4%)	**6 (4.0%)**	**0.006**
Other	215 (28.9%)	206 (35.0%)	9 (5.8%)	**<0.001**	68 (16.4%)	65 (24.5%)	3 (2.0%)	**<0.001**
Mortality by GCS status								
Normal GCS (15)	**540 (72.7%)**	**444 (75.4%)**	**96 (62.3%)**	---	**320 (77.1%)**	**214 (80.8%)**	**106 (70.7%)**	---
Death in normal GCS	0/540 (0.0%)	0/444 (0.0%)	0/96 (0.0%)	**<0.001**	0/320 (0.0%)	0/214 (0.0%)	0/106 (0.0%)	**<0.001**
Abnormal GCS (<15)	**200 (26.9%)**	**143 (24.3%)**	**57 (37.0%)**	---	**92 (22.2%)**	**49(18.5%)**	**43 (28.7%)**	---
Death in abnormal GCS	10/200 (5%)	5/143 (3.5%)	**5/57 (8.8%)**	**0.152**	7/92 (7.6%)	1/49 (2.0%)	**6/43 (14.0%)**	**0.048**
Overall mortality								
Total deaths	10 (1.3%)	5 (0.8%)	**5 (3.2%)**	**0.021**	7 (1.7%)	1 (0.4%)	**6 (4.0%)**	**0.006**

CT: Computed tomography, MRI: Magnetic resonance imaging, GCS: Glasgow Coma scale

95% CI: 1.1-13.8, p=0.021], while abnormal MRI findings were associated with markedly higher odds of mortality (OR=11.0, 95% CI: 1.3-92.4, *p=0.006). A comparative overview of mortality rates across different neuroimaging categories is presented in Figure 4.

DISCUSSION

This study provides comprehensive evidence regarding the diagnostic utility and prognostic significance of neuroimaging in older adults presenting to the emergency department with non-traumatic neurological symptoms. Our findings demonstrate substantial differences between CT and MRI diagnostic capabilities, with important implications for clinical decision-making and patient outcomes in this vulnerable population.

Previous studies have consistently reported that MRI has superior diagnostic sensitivity compared to CT in older patients with acute neurological presentations. For example, Kabra et al.[13]. found that MRI identified clinically significant findings in 37% of cases, whereas CT detected abnormalities in only 16%[14]. Similarly, Machner et al.[15] highlighted MRI's ability to detect small ischemic lesions and microbleeds that are often missed on CT scans in older populations.

Our findings are in agreement with these studies. The superior diagnostic yield of MRI compared to CT (36.1% vs. 20.7%, p<0.001) observed in our study reinforces the enhanced sensitivity of MRI for detecting acute neurological pathology. MRI is superior to CT in identifying acute ischemia and can detect both acute and chronic hemorrhage; therefore, it should be the preferred modality for accurate diagnosis in patients with suspected acute stroke[5,6]. Our findings extend this evidence to encompass a broader spectrum of non-traumatic neurological presentations in older adults, suggesting that MRI's superior tissue contrast resolution and sensitivity to subtle parenchymal changes provide significant clinical advantages. Despite its superior diagnostic sensitivity, the routine use of MRI in the emergency setting—particularly among older adults—may be limited by several practical factors. Prolonged acquisition times, increased susceptibility to motion artifacts, reduced patient cooperation, and clinical instability such as respiratory distress can restrict the feasibility of MRI in acutely ill elderly patients. These limitations underscore the continued importance of CT as a rapid and widely available first-line imaging modality in emergency care, while MRI may be reserved for selected patients in whom clinical stability and logistical conditions allow. It should be emphasized that the primary focus of this study was not to compare identical pathologies detected by CT and MRI, but to evaluate their overall diagnostic yield and prognostic contribution within real-world emergency department practice. While MRI provides superior tissue characterization and prognostic stratification in clinically stable patients, the limited feasibility of MRI in unstable older adults underscores the continued role of CT as the primary first-line imaging modality in emergency settings.

The identification of cerebrovascular accidents as the most common pathology (12.0% on CT, 26.7% on MRI) reflects both the high prevalence of stroke in older populations and the superior sensitivity of MRI for detecting acute ischemic changes. This finding has important implications for treatment decisions, particularly regarding thrombolytic therapy and secondary stroke prevention measures, where early and accurate diagnosis is crucial for optimal outcomes. These results align with Masood et al.[16], who reported cerebrovascular accident detection rates of 11.8% with CT and 25.9% with MRI in older patients. Early ischemic changes on non-contrast CT may be subtle or indirect, particularly in elderly patients, which limits CT sensitivity in the hyperacute phase. This limitation reflects inherent modality characteristics rather than under-evaluation and underscores the complementary role of MRI in the detection of acute cerebral ischemia.

Our study demonstrates that GCS status serves as a powerful predictor of both abnormal neuroimaging findings and clinical outcomes. Navi et al.[17] observed that older patients with GCS <15 had a 2.5-fold increased likelihood of positive findings on CT or MRI. Furthermore, Felfela et al.[18] conducted a meta-analysis showing a strong association between declining GCS scores and mortality in older populations. Importantly, GCS was assessed at the time of emergency department presentation, prior to neuroimaging, and was analyzed as a clinical predictor of imaging findings and outcomes; the reverse relationship was not evaluated.

These findings are consistent with our results, where abnormal GCS (<15) was associated with increased rates of abnormal imaging findings (28.5% vs. 17.8% for CT, 46.7% vs. 33.1% for MRI) and higher mortality. This supports the integration of neurological assessment with imaging decisions. Although it is one of the most powerful clinical prognostic features, neither the GCS score nor any single feature alone should be used to predict an individual patient's outcome, as the prognostic implications of the score are influenced by several factors[11,14]. In elderly patients, the assessment of GCS may also be influenced by pre-existing dementia, sensory impairment, or baseline cognitive dysfunction, which should be considered when interpreting GCS scores despite their strong prognostic value.

The finding that all mortality occurred exclusively in patients with abnormal GCS scores provides crucial insight for clinical practice. This observation suggests that normal consciousness level (GCS=15) may serve as a powerful negative predictor for short-term mortality, regardless of neuroimaging findings. Among patients with altered consciousness, the combination

of abnormal GCS and abnormal neuroimaging, particularly MRI, identified the highest-risk group with 14.0% mortality. This finding is consistent with recent evidence showing that decreasing GCS is strongly associated with higher incidence of mortality over time[14,19].

The dramatic differences in hospital disposition patterns based on neuroimaging results have significant implications for healthcare resource allocation and capacity planning. The finding that 87.3% of patients with abnormal MRI findings required hospitalization versus 24.5% with normal MRI represents a substantial impact on hospital resources and patient flow. In the chaotic environment of the emergency departments; complex, frail older adults with complex conditions are sometimes subjected to prolonged lengths of stay, excessive tests and iatrogenic complications[20]. These findings support the development of evidence-based imaging protocols that can optimize resource utilization while ensuring appropriate care for high-risk patients.

The low discharge rates in patients with abnormal imaging findings (11.0% for CT: 6.7% for MRI) demonstrate the clinical significance of positive findings and support the value of advanced neuroimaging in emergency decision-making. This aligns with systematic evidence that appropriate imaging improves diagnostic accuracy and guides management decisions effectively[21].

The increased odds of mortality associated with abnormal CT (OR=3.9) and MRI findings (OR=11.0) highlight the prognostic value of neuroimaging beyond its diagnostic role. Our study extends this concept to non-traumatic neurological presentations, showing that the combination of consciousness level and imaging findings provides powerful prognostic information. The variation in mortality risk among patients with abnormal GCS (ranging from 2.0% in MRI normal to 14.0% in MRI abnormal) demonstrates the additive prognostic value of advanced neuroimaging. This stratification capability has important implications for family counseling, treatment intensity decisions, and goals-of-care discussions in older adults.

Previous research has shown that older patients had significantly higher GCS scores than younger patients in traumatic brain injury contexts, suggesting that age-related factors may influence neurological presentation patterns[19]. Additionally, because many older adults have mobility difficulties, simply getting them to the radiology department to conduct a scan can be problematic, with image quality frequently being lower and inadequate for diagnosis[9]. These practical considerations highlight the importance of optimizing imaging protocols for older adults and ensuring adequate support for safe and effective scan acquisition.

Our findings support the development of risk stratification algorithms that incorporate both clinical assessment (particularly GCS) and imaging findings to guide decision-making in older adults with neurological presentations. The superior diagnostic yield and prognostic value of MRI suggest that broader access to emergency MRI services could improve outcomes in selected high-risk older patients, particularly those with altered consciousness. Neuroimaging should be performed in patients who did not previously receive imaging and in whom initial therapy has failed. In patients with new-onset delirium, imaging should be considered if there is no other obvious precipitating cause[8]. This evidence-based approach to imaging utilization, combined with our findings regarding the prognostic significance of neuroimaging results, supports the development of more precise clinical pathways for older patients.

Study Limitations

This study has several limitations. First, the retrospective study design may introduce selection bias, limits the ability to establish causality, and resulted in non-standardized documentation of focal neurological examination findings, which were therefore not included in the analysis. Second, the study population consisted of patients who had already been selected for brain imaging in the emergency department, which may have resulted in a higher pretest probability of abnormal findings compared to the general emergency population. Third, critically ill patients who were unable to undergo MRI were not included, which could potentially underestimate the diagnostic yield of MRI in the sickest subgroup Fourth, our analysis did not distinguish between clinically significant and incidental imaging findings, nor did it fully account for morbidity outcomes such as functional impairment, changes in functional independence, or neurological sequelae. Fifth, comorbid conditions, medications, and other confounding factors that might influence neuroimaging findings and outcomes were not fully controlled. Because CT and MRI were not uniformly applied to all patients and MRI was performed selectively based on clinical indication following initial CT evaluation, direct comparison of diagnostic yields between imaging modalities is subject to selection bias. The observed perfect negative predictive value of normal GCS for in-hospital mortality should be interpreted with caution, as it reflects short-term outcomes in a selectively imaged cohort and may not be generalizable to longer follow-up periods or unselected emergency populations. Finally, as this was a single-center study, the generalizability of our findings to other healthcare settings may be limited.

CONCLUSION

In conclusion, neuroimaging provides substantial diagnostic and prognostic value in older adults presenting with non-traumatic

neurological symptoms. The integration of GCS assessment and advanced neuroimaging, particularly MRI, enables effective risk stratification and supports critical clinical decisions regarding hospitalization, treatment intensity, intensive monitoring, and prognosis. These findings reinforce the importance of implementing evidence-based clinical pathways that combine clinical and imaging parameters to optimize the management of older adults in emergency settings.

Ethics

Ethics Committee Approval: This study was approved by the Sivas Cumhuriyet University Non-Interventional Clinical Research Ethics Committee (approval no: 2025-06/18, date:12.06.2025). All procedures were conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments.

Informed Consent: This retrospective, observational study was conducted at a tertiary care hospital emergency department.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.B., İ.S., Concept: N.B., İ.S., Design: N.B., P.S., İ.S., Data Collection or Processing: N.B., P.S., Analysis or Interpretation: N.B., P.S., İ.S., Literature Search: N.B., P.S., İ.S., Writing: N.B., İ.S.

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ORIGINAL ARTICLE

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Inability to Perform the Chair Stand Test Identifies a High-risk Geriatric Phenotype Associated with Frailty and Nutritional Impairment

Sandalyeden Kalkma Testini Yapamama: Frailty ve Beslenme Bozukluğu ile İlişkili Yüksek Riskli Geriatrik Fenotip

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ABSTRACT

Aim: Inability to perform the Five-Times Chair Stand test is frequently observed in very old adults but is often excluded from analyses, leading to an underestimation of advanced geriatric vulnerability. This study aimed to investigate whether inability to perform the Chair Stand test represents a clinically meaningful high-risk functional phenotype and to compare the associations of clinical and biochemical nutritional indices with this phenotype.

Materials and Methods: This retrospective cross-sectional study included 417 geriatric outpatients who underwent comprehensive geriatric assessment. Chair Stand performance was categorized as ≤15 s, >15 s, or unable to perform. Nutritional status was assessed using the Mini Nutritional Assessment-Short Form (MNA-SF), prognostic nutritional index (PNI), and controlling nutritional status (CONUT). Associations with frailty, functional dependence, and physical performance were examined using correlation analyses and multivariable logistic regression.

Results: Overall, 39.1% of participants were unable to perform the Chair Stand test. These individuals had significantly higher frailty and activities of daily living/instrumental activities of daily living dependency rates and poorer nutritional status. In adjusted models, higher MNA-SF and PNI scores were independently associated with lower odds of inability to perform the test, whereas CONUT was not.

Conclusion: Inability to perform the Chair Stand test reflects a distinct state of advanced functional vulnerability closely linked to frailty and nutritional impairment. Inability to perform the Chair Stand test identifies a clinically relevant high-risk geriatric phenotype and should be recognized as an integral component of geriatric assessment rather than excluded from analyses.

Keywords: Geriatrics, frailty, malnutrition, geriatric assessment, functional dependence

ÖZ

Amaç: Five-Times Chair Stand testini tamamlayamama, çok ileri yaştaki bireylerde sık görülmesine rağmen çoğu zaman analizlerin dışında bırakılmakta ve bu durum ileri düzey geriatrik kırılganlığın olduğundan düşük tahmin edilmesine yol açmaktadır. Bu çalışmanın amacı, Sandalyeden Kalkma testini tamamlayamamanın klinik açıdan anlamlı yüksek riskli bir fonksiyonel fenotipi temsil edip etmediğini araştırmak ve bu fenotip ile klinik ve biyokimyasal beslenme göstergeleri arasındaki ilişkiyi karşılaştırmaktır.

Gereç ve Yöntem: Bu retrospektif kesitsel çalışmaya kapsamlı geriatrik değerlendirmeden geçirilen 417 geriatrik poliklinik hastası dahil edildi. Chair Stand testi performansı ≤15 saniye, >15 saniye ve testi tamamlayamayanlar olarak sınıflandırıldı. Beslenme durumu Mini Nütrisyonel Değerlendirme-Kısa Formu (MNA-SF), prognostik nütrisyonel indeks (PNI) ve kontrol edici nütrisyonel durum (CONUT) skorları kullanılarak değerlendirildi. Kırılganlık, fonksiyonel bağımlılık ve fiziksel performans ile ilişkiler korelasyon analizleri ve çok değişkenli lojistik regresyon analizleri ile incelendi.

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Bulgular: Katılımcıların %39,1'i Chair Stand testini tamamlayamadı. Bu bireylerde kırılganlık ile günlük yaşam aktiviteleri ve enstrümantal günlük yaşam aktiviteleri bağımlılık oranları anlamlı derecede daha yüksek, beslenme durumu ise daha kötüydü. Düzeltilmiş modellerde, daha yüksek MNA-SF ve PNI skorları testi tamamlayamama olasılığının bağımsız olarak daha düşük olmasıyla ilişkili bulunurken, CONUT skoru ile anlamlı bir ilişki saptanmadı.

Sonuç: Chair Stand testini tamamlayamama, kırılganlık ve beslenme bozukluğu ile yakından ilişkili, ileri düzey fonksiyonel kırılganlığı yansıtan ayrı bir klinik durumu temsil etmektedir. Chair Stand testini tamamlayamama, klinik açıdan önemli, yüksek riskli bir geriatrik fenotipi tanımlamakta olup analizlerden dışlanmak yerine geriatrik değerlendirmenin ayrılmaz bir bileşeni olarak kabul edilmelidir.

Anahtar Kelimeler: Geriatri, kırılganlık, malnütrisyon, geriatrik değerlendirme, fonksiyonel bağımlılık

INTRODUCTION

Physical performance measures are essential elements of geriatric assessment, offering pragmatic insights into mobility, functional capacity, and overall health status in older adults. The Chair Stand test has become especially important among these measures because it is a simple, equipment-free way to measure lower extremity strength and functional reserve. It has also been linked to disability, falls, institutionalization, and death in older adults[1]. Historically, physical performance has been assessed on a quantitative continuum, where extended completion times signify inferior functional status. In the short physical performance battery (SPPB), which has a repeated chair stand part, longer completion times have been linked to worse clinical outcomes in older adults, such as functional decline, institutionalization, and death[2].

Nonetheless, a crucial yet frequently neglected facet of physical performance assessment in older adults is the condition of being unable to complete the test. In the majority of studies, individuals unable to complete physical performance tasks are excluded from analyses, either regarded as missing data or eliminated due to methodological limitations. This practice consistently excludes the functionally weakest segment of the geriatric population, leading to an underestimation of actual functional vulnerability and potentially skewing observed correlations with clinical outcomes[1,3]. Emerging evidence indicates that the inability to execute a physical test is not merely an outlier on a performance spectrum but signifies a unique clinical condition correlated with expedited functional deterioration, heightened care dependency, and increased mortality[3,4].

From a clinical standpoint, the inability to execute the Chair Stand test due to physical factors such as osteoarthritis, muscle weakness, balance impairment, and mobility limitation may indicate a qualitative threshold in geriatric health rather than merely a quantitative decline in performance. Crossing this threshold probably means that several geriatric syndromes, such as frailty, functional dependency, and decreased physiological reserve, are coming together. Although its clinical plausibility is evident, the inability to execute the Chair Stand test has seldom been investigated as a distinct functional phenotype, and its broader ramifications for geriatric vulnerability remain inadequately defined.

Malnutrition and the risk of malnutrition are significant public health issues among older adults, with epidemiological studies indicating prevalence rates of 20-45% among individuals aged 65 years and older in both community and clinical settings[5,6]. Age-related factors, including anorexia of aging, sensory decline, oral and dental issues, decreased physical activity, polypharmacy, and the progressive loss of functional capacity, significantly contribute to the deterioration of nutritional status as individuals age[7]. Malnutrition has significant repercussions that transcend weight loss, impacting muscle strength, immune function, wound healing, cognitive performance, mortality, and overall quality of life[8].

In geriatric practice, nutritional status is evaluated through both clinically oriented instruments and laboratory-based indices. The Mini Nutritional Assessment-Short Form (MNA-SF) was specifically designed for older adults and includes functional aspects pertaining to mobility and activities of daily living (ADL), facilitating a multidimensional assessment that closely correlates with geriatric syndromes[9]. Conversely, biochemical indices like the prognostic nutritional index (PNI) and the controlling nutritional status (CONUT) score were initially developed as prognostic indicators in surgical and oncological cohorts[10,11]. These laboratory-based indices, while responsive to metabolic stress and immunological changes, may only partially reflect the long-term functional effects of chronic malnutrition in older adults[12]. It has been underscored that dependence solely on biochemical parameters may inadequately represent the functional aspect of nutritional deficiency in geriatric cohorts[13].

Malnutrition is intricately linked to fundamental geriatric syndromes. Nutritional inadequacy has been linked to cognitive decline, likely through mechanisms involving protein-energy deficiency and micronutrient insufficiency. Epidemiological studies indicate a heightened risk of cognitive impairment in malnourished older adults[14]. Malnutrition exacerbates muscle weakness and increases dependency by reducing muscle mass and strength, thereby impairing performance in basic and instrumental ADL[15,16]. Polypharmacy complicates

this relationship by both contributing to malnutrition—by impairing appetite, taste perception, and gastrointestinal tolerance—and resulting from nutritional deterioration due to heightened disease burden and treatment demands[17].

Even though there are well-known links between nutritional status and functional outcomes, most studies so far have only looked at people who could pass physical performance tests. This means that they have assumed that there is a direct link between poor nutrition and poor function. The clinical importance of the incapacity to execute a basic physical task, along with the various nutritional assessment methodologies that illustrate this elevated-risk functional condition, has not been thoroughly investigated. Combining clinically relevant and laboratory-derived nutritional indices, while explicitly including individuals who cannot undergo physical performance assessments, may yield a more thorough comprehension of advanced geriatric vulnerability.

This study seeks to determine if the inability to complete the Chair Stand test in elderly individuals serves as a clinical marker of advanced geriatric frailty. Additionally, it aims to compare the efficacy of clinical Mini Nutritional Assessment-Short Form (MNA-SF) and biochemical (PNI and CONUT) nutritional indices in distinguishing this high-risk functional phenotype concerning frailty, functional dependence, cognitive performance, and physical performance impairment.

Aim

The aim of this study is to investigate whether the inability to perform the Chair Stand test in elderly individuals represents a clinically meaningful high-risk functional phenotype, that is frequently encountered in practice but commonly excluded from research analyses, and to comparatively evaluate the relationship between clinical (MNA-SF) and biochemical (PNI and CONUT) nutritional indices and this high-risk functional phenotype.

Hypothesis

We hypothesize that elderly individuals who are unable to perform the Chair Stand test have a substantially higher burden of frailty and functional dependency, and that this clinically vulnerable phenotype is more consistently reflected by the MNA-SF, which incorporates functional components, compared with biochemical nutritional indices.

MATERIALS AND METHODS

Study Design and Sample

This study was designed as a retrospective observational study with a cross-sectional analytical approach. Data were obtained from older adults who presented to the geriatric outpatient clinic of our hospital between 1 November 2024 and 1 November 2025. During this period, 417 consecutive individuals who underwent a comprehensive geriatric assessment (CGA) performed by a geriatric specialist were included in the study.

Demographic characteristics, clinical measurements, functional assessments, cognitive screening results, and nutritional indices were retrospectively extracted from the hospital information management system and standardized outpatient clinic record forms. For inclusion in the final sample, patients were required to have complete clinical assessments and laboratory data necessary for the calculation of nutritional indices.

To minimize the confounding effects of acute illness and inflammation on nutritional biomarkers, individuals with C-reactive protein (CRP) levels >5 mg/L, clinical evidence of active infection, or acute medical conditions at the time of assessment were excluded. Only patients who had been evaluated during periods of clinical stability, with CRP values below the predefined threshold, were included in the analysis.

During the study period, a total of 680 older adults were screened in the geriatric outpatient clinic. Of these, 38 individuals were excluded due to evidence of acute infection or elevated CRP levels at the time of assessment, and 125 individuals were excluded because of missing laboratory data required for the calculation of nutritional indices. In addition, 27 patients were unable to reliably complete the physical performance tests due to insufficient understanding of the assessment instructions, and 73 patients were excluded because of incomplete components of the CGA. After these exclusions, 417 patients with complete clinical and laboratory evaluations were included in the final analysis. No missing data were present for the variables analyzed in the study.

Laboratory Data

For the assessment of nutritional indices, laboratory parameters including serum albumin, total cholesterol, and lymphocyte count were extracted from fasting blood samples (≥8 hours) obtained during the geriatric outpatient visit or from laboratory tests carried out concurrently with the comprehensive clinical assessment.

For each patient, laboratory values closest to the date of the CGA were used to ensure temporal consistency between nutritional and clinical evaluations. The presence of normal CRP levels across the study population allowed variations in albumin and lymphocyte counts to be interpreted as reflecting chronic nutritional status rather than acute inflammatory or infectious processes.

Nutritional Assessment

MNA-SF

MNA-SF scores were retrieved from standardized CGA records, with total scores ranging from 0 to 14. Nutritional status was classified as normal (≥12 points), at risk of malnutrition (8–11 points), or malnourished (≤7 points). For statistical analyses, MNA-SF was evaluated both as a continuous variable and as a categorical measure.

PNI

PNI was calculated according to the established formula: PNI=10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (/mm^3). Based on conventional cut-off values, PNI scores were categorized as normal (≥50), moderate nutritional risk (45–49), or high nutritional risk (<45), and were analyzed as both continuous and categorical variables.

CONUT Score

The CONUT score was derived from serum albumin concentration, total cholesterol level, and peripheral lymphocyte count, in accordance with the established scoring criteria reported in previous studies. Based on total score values, nutritional status was categorized as normal (0-1 points), mild impairment (2-4 points), or moderate to severe malnutrition (≥5 points). For statistical analyses, the CONUT score was treated both as a continuous variable and as a categorical classification.

Frailty and Functional Assessment

Frailty status was assessed using the Clinical Frailty scale (CFS), which ranges from 1 to 9. Participants with CFS ≥5 were classified as frail.

Basic ADL were assessed using the Katz index, and participants with scores below 6 were classified as dependent in ADL instrumental activities of daily living (IADL) were evaluated with the Lawton IADL scale, with scores less than 8 indicating dependency in instrumental activities.

Mini-mental state examination (MMSE) was used for descriptive and group comparisons and was additionally included as a covariate in multivariable regression models.

Physical Performance Assessment

Physical performance was evaluated using the Five-Times Chair Stand test. Participants were instructed to rise from a standardized chair and sit down five consecutive times as quickly as possible without using their arms. Chair Stand performance was categorized into three groups: ≤15 s, >15 s, and unable to perform. The 15-second cut-off was selected based on previously established geriatric performance thresholds associated with impaired lower extremity strength, frailty, and increased risk of disability, rather than a data-driven quartile approach. A fixed, clinically meaningful time threshold was preferred to enhance interpretability and consistency with prior geriatric literature. In line with the conceptual framework of the SPPB, inability to perform the Chair Stand test was considered the poorest performance category rather than missing data[2]. Time-based measurements were available only for participants who completed the test (n=254). For analyses incorporating the full cohort, Chair Stand performance was treated as an ordinal variable (≤15 s, >15 s, unable to perform), allowing inclusion of individuals without time-based measurements; Spearman's rank correlation coefficient was used for correlation analyses in the entire sample (n=417).

Statistical Analysis

Statistical analyses were conducted utilizing IBM SPSS Statistics version 28. Continuous variables are displayed as either the mean with standard deviation or the median with interquartile range, depending on the distribution of the data. Categorical variables are represented as frequencies and percentages. We used the Kolmogorov-Smirnov test and graphical methods to assess the distributional characteristics.

We used Welch's t-test for continuous variables that were normally distributed and the Mann-Whitney U test for non-normal distributions to compare groups of participants who could and could not complete the Five-Times Chair Stand test. The chi-square test or Fisher's exact test was used to compare categorical variables, depending on what was needed.

Correlation analyses were conducted to examine the relationships between nutritional indices (MNA-SF, PNI, and CONUT score) and critical geriatric outcomes, including frailty status as defined by the CFS dependency in basic and IADL, and Chair Stand performance category. Due to the ordinal characteristics of certain variables, Spearman's rank correlation coefficient was utilized.

To ascertain independent associations between nutritional indices and functional outcomes, multivariable logistic regression models were developed. The primary model characterized the inability to complete the Five-Times Chair Stand test as a binary outcome. Separate regression models were also created for frailty (CFS ≥5), dependence in basic ADL (Katz index <6), and dependence in IADL (Lawton IADL score <8).

In every regression analysis, the MNA-SF, PNI, and CONUT score were incorporated as independent variables, with adjustments made for age, sex, body mass index, and cognitive performance evaluated through the MMSE. We used variance inflation factor values to check for multicollinearity, and all of them were less

than 2.0. Odds ratios with 95% confidence intervals are used to report effect estimates. A two-sided p-value below 0.05 was used to define statistical significance.

This study received ethical clearance from the Scientific Research Ethics Committee of Sancaktepe Martyr Prof. Dr. İlhan Varank Training and Research Hospital (approval no: 2025/413, date: 14.11.2025) and was conducted in line with internationally accepted ethical principles, including those of the Declaration of Helsinki.

RESULTS

The study population consisted of 417 older adults with a mean age of 82.9±4.9 years, of whom 65.7% were female. According to the MNA-SF, 66.2% of participants had normal nutritional status, while 29.7% were at risk of malnutrition and 4.1% were malnourished. Based on functional assessments, 69.3% of participants were classified as frail (CFS ≥5), 58.3% had ADL dependency, and 58.0% had IADL dependency. Regarding physical performance, 39.1% of the study population were unable to perform the Chair Stand test, highlighting a substantial burden of functional impairment in this geriatric outpatient cohort. In addition, 30.0% of participants had depressive symptoms based on a Geriatric Depression Scale-Short Form score ≥5, and 54.9% were exposed to polypharmacy, defined as the use of five or more medications (Table 1).

When participants were grouped according to their ability to perform the Chair Stand test, 254 (60.9%) were classified as able to perform, whereas 163 (39.1%) were unable to complete the test. Compared with those able to perform, individuals unable to perform the Chair Stand were significantly older and demonstrated a markedly worse geriatric profile, with substantially higher rates of frailty, ADL dependency, and IADL dependency (all $p<0.001$). Nutritional status was also poorer in the unable group, reflected by lower MNA-SF scores, lower PNI values, and higher CONUT scores. Body mass index did not differ significantly between groups, while cognitive performance assessed by MMSE was significantly lower among participants unable to perform the Chair Stand test (Table 2).

Correlation analyses demonstrated that MNA-SF showed the strongest associations with functional outcomes, displaying a moderate-to-strong negative correlation with frailty and positive correlations with both ADL and IADL scores. MNA-SF was also moderately correlated with Chair Stand performance when inability to perform the test was classified as the poorest category. In contrast, PNI and CONUT exhibited weaker correlations across functional domains, particularly in relation to Chair Stand performance (Table 3).

In multivariable logistic regression analysis, higher MNA-SF scores were independently associated with significantly lower

Table 1. Baseline clinical, nutritional, and functional characteristics of the study population (n=417)

Variable	Presentation format	Value
Age (years)	Mean ± SD	82.9±4.9
BMI (kg/m²)	Mean ± SD	27.9±5.8
MNA-SF	Median (IQR)	12 (10-13)
PNI	Mean ± SD	51.7±5.8
CONUT	Median (IQR)	1 (0-2)
CFS	Median (IQR)	5 (4-6)
MMSE	Mean ± SD	24.4±4.4
ADL (Katz)	Median (IQR)	5 (4-6)
IADL (Lawton)	Median (IQR)	6 (4-8)
Categorical variables (n, %)		
Variable	**n**	**%**
Sex		
Male	143	34.3
Female	274	65.7
MNA-SF categories		
Normal (12-14)	276	66.2
At risk of malnutrition (8-11)	124	29.7
Malnutrition (≤7)	17	4.1
PNI categories		
Normal (≥50)	274	65.7
Moderate risk (45-49)	100	24.0
High risk (<45)	43	10.3
CONUT categories		
Normal (0-1)	303	72.7
Mild (2-4)	106	25.4
Moderate-severe (≥5)	8	1.9
Frailty (CFS ≥5)	289	69.3
ADL dependency (Katz < 6)	243	58.3
IADL dependency (Lawton <8)	242	58.0
Depression (GDS-SF ≥5)	125	30.0
Polypharmacy (≥5 medications)	229	54.9
Chair Stand categories		
≤15 seconds	89	21.3
>15 seconds	165	39.6
Unable to perform	163	39.1

Continuous variables are presented as mean ± standard deviation (SD) for normally distributed variables and as median (interquartile range, IQR) for non-normally distributed variables. Categorical variables are presented as number (n) and percentage (%). Chair Stand performance was categorized as ≤15 seconds, >15 seconds, and inability to perform the test. BMI: Body mass index, MNA-SF: Mini Nutritional Assessment-Short Form, PNI: Prognostic Nutritional index; CONUT: Controlling nutritional status, CFS: Clinical frailty scale, MMSE: Mini-mental state examination, ADL: Activities of daily living, IADL: Instrumental activities of daily living, GDS-SF: Geriatric Depression Scale-Short Form

Table 2. Comparison of nutritional and functional characteristics between older adults able and unable to perform the Chair Stand test

Variable	Able to perform (n=254)	Unable to perform (n=163)	p-value
Age (years)	82.1±4.8	84.3±4.8	<0.001
BMI (kg/m^2)	27.6±5.1	28.4±6.8	0.187
MNA-SF	13 (12-14)	11 (10-13)	<0.001
PNI	52.7±5.3	50.1±6.1	<0.001
CONUT	1 (0-1)	1 (0-2)	0.005
Frailty (CFS ≥5), n (%)	138 (54.3%)	151 (92.6%)	<0.001
ADL dependency (Katz <6), n (%)	120 (47.2%)	123 (75.5%)	<0.001
IADL dependency (Lawton<8), n (%)	103 (40.6%)	139 (85.3%)	<0.001
MMSE	25.3±3.7	22.9±5.1	<0.001

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range, IQR), as appropriate. Categorical variables are presented as number (n) and percentage (%). Group comparisons were performed using Welch's t-test for continuous variables presented as mean ± SD, Mann-Whitney U test for non-normally distributed variables, and chi-square test for categorical variables. Inability to perform was defined as inability to complete the Five-Times Chair Stand test within the standardized assessment protocol, CFS: Clinical frailty scale, MMSE: Mini-mental state examination, ADL: Activities of daily living, IADL: Instrumental activities of daily living, MNA-SF: Mini Nutritional Assessment-Short Form

Table 3. Correlations between nutritional indices and functional outcomes, with inability to perform the chair stand classified as the poorest performance category

Nutritional index	Frailty (CFS)	ADL score (Katz)	IADL score (Lawton)	Chair Stand category
MNA-SF	–0.48*	+0.40*	+0.50*	–0.33*
PNI	–0.25*	+0.25*	+0.24*	–0.22*
CONUT	+0.16*	–0.20*	–0.22*	+0.16*

Values are Spearman's rank correlation coefficients. *p<0.05. Frailty (Clinical Frailty scale, CFS) and Chair Stand performance were coded such that higher values indicate worse functional status, with inability to perform the Chair Stand test classified as the poorest performance category. ADL (Katz index) and IADL (Lawton scale) scores were coded such that higher scores indicate better functional independence. Accordingly, negative correlation coefficients indicate better nutritional status associated with lower frailty or better, Chair Stand performance, whereas positive coefficients indicate better nutritional status associated with higher ADL and IADL scores (greater functional independence). MNA-SF: Mini Nutritional Assessment-Short Form, PNI: Prognostic nutritional index, CONUT: Controlling nutritional status, CFS: Clinical frailty scale, ADL: Activities of daily living, IADL: Instrumental activities of daily living

odds of inability to perform the Five-Times Chair Stand test [odds ratio (OR) 0.79, p<0.001]. PNI also showed an independent but more modest association with Chair Stand inability (OR: 0.94, p=0.017), whereas CONUT was not independently associated with the outcome. Increasing age (OR: 1.08 per year, p=0.002) and higher body mass index (BMI) (OR: 1.06 per kg/m^2, p=0.005) were independently associated with increased odds of inability to perform the Chair Stand test. Cognitive performance, assessed by MMSE, was not independently associated with Chair Stand inability after full adjustment (p=0.057). Sex was not a significant predictor (Table 4).

Table 4. Independent associations of nutritional indices and cognitive performance with inability to perform the Five-Times Chair Stand test

Variable	OR	95% CI	p-value
MNA-SF	0.79	0.71-0.89	<0.001
PNI	0.94	0.89-0.99	0.017
CONUT	0.94	0.75-1.17	0.568
Age (per year)	1.08	1.03-1.13	0.002
BMI (kg/m^2)	1.06	1.02-1.10	0.005
Sex (female)	1.45	0.89-2.31	0.129
MMSE	0.95	0.90-1.00	0.057

Results are derived from a fully adjusted multivariable logistic regression model in which Mini Nutritional Assessment-Short Form (MNA-SF), Prognostic Nutritional index (PNI), and controlling nutritional status (CONUT) score were entered simultaneously and adjusted for age, sex, body mass index (BMI), and cognitive performance assessed by the mini-mental state examination (MMSE). Inability to perform the Five-Times Chair Stand test was used as the binary outcome. Odds ratios (ORs) are presented with 95% confidence intervals (CIs). ORs <1 indicate lower odds of inability to perform the test, whereas ORs >1 indicate higher odds

DISCUSSION

This study examined the clinical significance of inability to perform the Chair Stand test in very elderly individuals and its associations with frailty, functional dependency, cognitive performance, and nutritional status. Our findings indicate that inability to complete the Chair Stand test represents a distinct and clinically identifiable functional phenotype reflecting advanced geriatric frailty.

The Chair Stand test is a key measure of lower extremity muscle strength and functional reserve and constitutes a core component of composite assessments such as the SPPB. In the original SPPB framework, individuals unable to perform the Chair Stand task are classified within the lowest performance category, a status consistently associated with increased risks

of disability, functional decline, and mortality[2]. Accordingly, failure to perform the Chair Stand test should be interpreted not merely as a quantitative extension of prolonged completion time, but as a qualitative threshold indicating advanced functional impairment.

Conversely, the current literature primarily assesses Chair Stand performance through time-based metrics or composite scores, often excluding individuals unable to complete the test from analyses or omitting it for methodological reasons[18]. This practice results in the oversight of the subgroup representing the most significant functional impairment within the geriatric population.

In our study, individuals unable to perform the Chair Stand test demonstrated an exceedingly high prevalence of frailty, markedly elevated rates of ADL and IADL dependency, and poorer cognitive performance in group comparisons, indicating that this cohort represents the segment of the geriatric population with the most severe functional impairment. Together, these findings underscore the central role of lower extremity function in maintaining functional independence in advanced age. These results are consistent with earlier evidence identifying lower extremity performance as a major determinant of disability and dependency[2,19].

Importantly, the inability to complete the Chair Stand test in our study was not attributable to insufficient cognitive cooperation but rather to genuine physical limitations, including reduced muscle strength, balance impairment, mobility restriction, and fear of falling. This observation reinforces the interpretation that the "unable to perform" category reflects a clinically meaningful loss of physical capacity rather than a methodological artifact[18,19].

In addition, nutritional status was closely associated with Chair Stand performance. Individuals unable to execute the test exhibited lower MNA-SF and PNI scores and higher CONUT scores, supporting existing literature that links advanced functional impairment with nutritional deficiency[20-22].

However, given the cross-sectional design of the present study, the observed associations between nutritional status and functional impairment should be interpreted as potentially bidirectional rather than causal. While nutritional impairment may contribute to muscle weakness, reduced physical performance, and increased functional dependency, advanced functional limitation may in turn exacerbate nutritional deterioration through reduced mobility, impaired access to food, decreased appetite, and greater care dependency. Consequently, nutritional impairment and functional decline likely interact in a reciprocal cycle, particularly among older adults with advanced geriatric vulnerability.

Among the nutritional indices examined, MNA-SF showed the most consistent association with inability to complete the Chair Stand test. A likely explanation is that MNA-SF incorporates functional elements, including mobility and daily activities, in addition to nutritional parameters. Although this feature may allow MNA-SF to better capture advanced geriatric frailty, some of the observed associations may partly reflect overlapping measurement domains. Therefore, MNA-SF should be interpreted not solely as a nutritional assessment tool but as a composite indicator of overall geriatric vulnerability encompassing nutritional, functional, and health-related dimensions.

In contrast, the purely biochemical indices PNI and CONUT showed weaker correlations with Chair Stand performance. Inflammatory states, chronic disease burden, and pharmacological effects can influence parameters such as serum albumin and total cholesterol, limiting the ability of these indices to accurately reflect functional capacity in older adults[23,24]. Indeed, previous studies have demonstrated weak associations between biochemical markers, including serum albumin, and functional performance outcomes[25].

Age was independently associated with inability to complete the Chair Stand test in multivariable analyses, consistent with prior evidence that cumulative age-related declines in neuromuscular function, balance, and physiological reserve substantially impair lower extremity performance. Even in advanced age, chronological age remains a marker of increased biological burden, particularly for mobility tasks requiring muscle strength, coordination, and postural control. Accordingly, inability to perform the Chair Stand test may be viewed as a phenotype reflecting advanced-stage functional frailty associated with age-related loss of reserve[26].

Likewise, although BMI did not differ significantly in unadjusted group comparisons, it emerged as an independent correlate of Chair Stand inability after multivariable adjustment. This apparent discrepancy likely reflects confounding and suppression effects revealed after adjustment for age, frailty, and other geriatric covariates. In advanced age, BMI is a limited proxy for body composition; higher BMI values may reflect increased fat mass rather than preserved muscle mass and may coexist with sarcopenia or sarcopenic obesity[27]. These phenotypes adversely affect lower extremity muscle strength and physical performance. Therefore, the observed association of BMI should be interpreted as an indirect marker of unfavorable body composition rather than nutritional adequacy.

Although individuals unable to perform the Chair Stand test exhibited poorer cognitive performance, those who failed to complete the test due to insufficient cognitive cooperation

were excluded at the assessment stage. In line with this classification, MMSE did not remain an independent predictor in multivariable models, indicating that inability to perform the test predominantly reflects physical rather than cognitive limitations.

A key methodological strength of this study is that individuals unable to perform the Chair Stand test were not excluded from analyses but were instead treated as a distinct clinical category representing the most severe functional impairment. This approach minimized sample attrition and enabled a more realistic assessment of the relationship between nutrition and function in the geriatric population[18].

From a clinical perspective, inability to perform the Chair Stand test should be regarded as a strong indicator of advanced geriatric frailty and care dependency, warranting CGA encompassing physical performance, nutritional status, functional dependency, and cognitive function.

Study Limitations

This study has several limitations that should be acknowledged. First, the single-center design may limit the generalizability of the findings, as patient characteristics, referral patterns, and clinical practices may differ across institutions. Therefore, the observed associations—particularly those related to advanced functional vulnerability—may partly reflect the profile of a tertiary academic geriatric outpatient clinic.

Second, the retrospective and cross-sectional nature of the study precludes causal inference. The observed relationships between nutritional status, functional impairment, and inability to perform the Chair Stand test can only be interpreted as associations. The directionality of these relationships—whether nutritional impairment precedes functional decline or vice versa—cannot be determined.

Third, laboratory parameters used to calculate PNI and CONUT were obtained within a limited time window around the clinical assessment and may not fully capture longitudinal changes in nutritional or inflammatory status. Although exclusion criteria were applied to minimize the effects of acute inflammatory states by removing individuals with acute infection or CRP levels >5 mg/L, the possibility that chronic disease–related factors may have influenced the results cannot be fully dismissed. In addition, the MNA-SF includes functional components such as mobility and ADL. Consequently, part of the strong association observed between MNA-SF and frailty or functional outcomes may reflect overlapping measurement constructs rather than purely biological nutritional effects. Nevertheless, this overlap mirrors real-world geriatric assessment, in which nutritional, functional, and frailty domains are inherently interconnected rather than independent. Importantly, the absence of significant multicollinearity among MNA-SF, PNI, and CONUT supports the interpretation that these indices provide independent contributions within multivariable models. However, the persistence of MNA-SF as an independent predictor after simultaneous adjustment for purely biochemical indices supports its clinical—not merely methodological—relevance.

The use of cholesterol-lowering medications was not evaluated separately in this study. As total cholesterol is a component of the CONUT score, pharmacological lowering of cholesterol may have influenced CONUT values in some participants, potentially leading to an overestimation of malnutrition prevalence. Nevertheless, even under these conditions, CONUT showed the weakest associations with geriatric outcomes. Therefore, it is unlikely that adjustment for lipid-lowering therapy would have materially altered the main conclusions.

Finally, although inability to perform the Chair Stand test was carefully evaluated and attributed primarily to physical limitations rather than cognitive non-cooperation, the categorization of physical performance remains dependent on clinical judgment and may be influenced by contextual factors such as fear of falling or temporary functional fluctuations.

Despite these limitations, the study is strengthened by its relatively large sample size, minimal missing data, CGA, and—most importantly—the deliberate inclusion of individuals unable to perform the Chair Stand test rather than excluding them from analysis. This methodological choice enhances clinical relevance and reduces selection bias. Future prospective, multicenter studies are needed to validate these findings and to explore the longitudinal implications of inability to perform simple physical performance tests in older adults, particularly to assess the predictive validity of the “unable to perform” phenotype for adverse clinical outcomes.

CONCLUSION

This study demonstrates that inability to perform the Chair Stand test represents a clinically meaningful marker of advanced functional vulnerability in older adults, characterized by a high burden of frailty, functional dependency, cognitive impairment, and nutritional risk. Treating “unable to perform” as a valid functional category—rather than excluding these individuals—provides a more realistic and clinically relevant understanding of geriatric vulnerability.

Among the nutritional indices examined, MNA-SF showed the most consistent associations with this high-risk functional phenotype, whereas laboratory-based indices such as PNI and CONUT demonstrated weaker and less stable relationships. These findings suggest that nutritional tools incorporating clinical and functional components are better aligned with advanced geriatric vulnerability than indices based solely on biochemical parameters.

From a clinical perspective, the results support the integration of simple physical performance assessments and functional nutritional screening into routine geriatric evaluation. In particular, inability to perform the Chair Stand test should be recognized as a red flag indicating severe functional compromise, warranting comprehensive geriatric and nutritional assessment rather than being dismissed as missing or unmeasurable data.

Ethics

Ethics Committee Approval: This study received ethical clearance from the Scientific Research Ethics Committee of Sancaktepe Martyr Prof. Dr. İlhan Varank Training and Research Hospital (approval no: 2025/413, date: 14.11.2025) and was conducted in line with internationally accepted ethical principles, including those of the Declaration of Helsinki.

Informed Consent: The requirement for informed consent was waived due to the retrospective design of the study.

Footnotes

Authorship Contributions

Concept: İ.K.U., Design: İ.K.U., Data Collection or Processing: İ.K.U., N.M.Ç., Analysis or Interpretation: İ.K.U., N.M.Ç., Literature Search: İ.K.U., N.M.Ç., Writing: İ.K.U.

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ORIGINAL ARTICLE

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Predictive Value of Laboratory, Radiological, and Non-invasive Tests for Liver Biopsy Findings in Treatment-naive, HBeAg-negative Chronic Hepatitis B Patients

Tedavi Naif HBeAg-negatif Kronik Hepatit B Hastalarında Karaciğer Biyopsi Bulgularının Öngörülmesinde Laboratuvar, Radyolojik ve Non-invaziv Testlerin Değeri

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ABSTRACT

Aim: Chronic hepatitis B (CHB) remains a major cause of liver-related morbidity and mortality worldwide. Liver biopsy is considered the reference standard for assessing significant histopathological abnormality (SHA); however, its invasive nature and potential complications limit routine use. This study aimed to evaluate the diagnostic performance of laboratory, radiological, and non-invasive indices in predicting significant histopathological abnormalities in treatment-naïve, HBeAg-negative CHB patients.

Materials and Methods: In this retrospective single-center study, adult HBeAg-negative, treatment-naïve CHB patients who underwent liver biopsy between 2010 and 2024 were evaluated. Liver histology was assessed using the Ishak fibrosis score and Knodell histological activity index (HAI). Significant histological activity was defined as HAI ≥6 and/or fibrosis stage ≥2. Several non-invasive indices were calculated. Multivariable logistic regression analyses were performed to identify independent predictors of high HAI and significant fibrosis. Diagnostic performance was assessed using ROC curve analysis.

Results: A total of 148 patients were included. Higher hepatitis B virus DNA levels were independently associated with both high HAI [odds ratio (OR): 1.7 per $\log_{10}$ increase, p=0.002] and significant fibrosis (OR: 1.3 per $\log_{10}$ increase, p=0.044). Lower serum albumin levels were independently associated with high HAI (p=0.025). Among non-invasive markers, aspartate aminotransferase to platelet ratio index (APRI), showed the highest accuracy for predicting high HAI [area under the curve (AUC): 0.785; sensitivity 68.2%, specificity 85.0% at a cut-off >0.35]. The KING score demonstrated the best performance for predicting significant fibrosis (AUC: 0.768; sensitivity 61.5%, specificity 87.8%). GUCI and Fibrosis-4 index also showed good discriminatory ability.

Conclusion: Simple, routinely available non-invasive indices particularly APRI and KING scores demonstrate good diagnostic performance in identifying SHA in HBeAg-negative CHB patients. These tools may help reduce the need for liver biopsy in selected patients and support clinical decision-making, especially in settings where biopsy access is limited.

Keywords: APRI, chronic hepatitis B, KING score, liver biopsy, non-invasive markers

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ÖZ

Amaç: Kronik hepatit B (KHB), dünya genelinde karaciğer ilişkili morbidite ve mortalitenin başlıca nedenlerinden biri olmaya devam etmektedir. Karaciğer biyopsisi, anlamlı histopatolojik anormalliğin (SHA) değerlendirilmesinde referans standart olarak kabul edilmekle birlikte, invaziv yapısı ve olası komplikasyonları nedeniyle rutin kullanımını sınırlamaktadır. Bu çalışmada, tedavi almamış, hepatit B e antijeni negatif KHB hastalarında anlamlı histopatolojik anormalliğin öngörülmesinde laboratuvar, radyolojik ve non-invaziv indekslerin tanısal performansının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif, tek merkezli çalışmada, 2010-2024 yılları arasında karaciğer biyopsisi yapılan erişkin, HBeAg-negatif, tedavi almamış KHB hastaları değerlendirildi. Karaciğer histolojisi, Ishak fibrozis skoru ve Knodell histolojik aktivite indeksi (HAI) kullanılarak değerlendirildi. Anlamlı histolojik aktivite HAI ≥6 ve/veya fibrozis evresi ≥2 olarak tanımlandı. Çeşitli non-invaziv indeksler hesaplandı. Yüksek HAI ve anlamlı fibrozisin bağımsız belirleyicilerini saptamak amacıyla çok değişkenli lojistik regresyon analizleri yapıldı. Tanısal performans ROC eğrisi analizi ile değerlendirildi.

Bulgular: Toplam 148 hasta çalışmaya dahil edildi. Daha yüksek hepatit B virüs (HBV) DNA düzeyleri, hem yüksek HAI [olasılık oranı (OR): $\log_{10}$ artış başına 1,7; p=0,002] hem de anlamlı fibrozis (OR: $\log_{10}$ artış başına 1,3; p=0,044) ile bağımsız olarak ilişkili bulundu. Daha düşük serum albümin düzeyleri yüksek HAI ile bağımsız olarak ilişkiliydi (p=0,025). Non-invaziv belirteçler arasında aspartate aminotransferaz/trombosit oranı indeksi (APRI), yüksek HAI'yi öngörmede en yüksek doğruluğu gösterdi [eğri altında kalan alan (AUC): 0,785; >0,35 kesim değerinde duyarlılık %68,2, özgüllük %85,0]. KING skoru ise anlamlı fibrozisi öngörmede en iyi performansı gösterdi (AUC: 0,768; duyarlılık %61,5, özgüllük %87,8). GUCI ve FIB-4 de iyi ayırt edici performans sergiledi.

Sonuç: Özellikle APRI ve KING skoru olmak üzere, kolay uygulanabilen ve rutin olarak kullanılabilen non-invaziv indeksler, HBeAg-negatif KHB hastalarında anlamlı histopatolojik anormalliklerin belirlenmesinde iyi tanısal performans göstermektedir. Bu araçlar, uygun hastalarda karaciğer biyopsisi gereksinimini azaltmaya yardımcı olabilir ve özellikle biyopsiye erişimin kısıtlı olduğu merkezlerde klinik karar verme sürecini destekleyebilir.

Anahtar Kelimeler: APRI, kronik hepatit B, KING skoru, karaciğer biyopsisi, non-invaziv belirteçler

INTRODUCTION

Hepatitis B virus (HBV) infection remains a major global public health challenge. As reported by the World Health Organization in its latest update from July 2025, an estimated 254 million people were living with chronic hepatitis B (CHB) worldwide in 2022. Additionally, HBV-related complications, including cirrhosis and hepatocellular carcinoma (HCC), accounted for approximately 1.1 million deaths during the same year[1]. In Türkiye according to Viral Hepatitis Prevention and Control Program for 2018-2023, there have been approximately 3.3 million patients with CHB infection[2].

Chronic HBV infection is classified into five distinct clinical phases based on a combination of serological markers, liver function tests, HBV DNA levels, and liver biopsy findings. The decision to initiate antiviral therapy is primarily guided by serum alanine aminotransferase (ALT) levels and HBV DNA concentrations. In cases where these criteria are not clearly met, liver biopsy is recommended to assess the degree of hepatic inflammation and fibrosis[3].

Percutaneous liver biopsy is widely regarded as the gold standard for assessing the extent of liver injury. However, its application is limited due to its invasive nature and the risk of serious complications, including bleeding, pneumothorax, hemothorax, organ perforation, bile peritonitis, infections such as bacteremia, abscess formation, or sepsis, as well as hemobilia and neuralgia[4].

In Türkiye, antiviral treatment is covered by national health insurance for patients with evidence of cirrhosis or those with contraindications to liver biopsy, such as coagulopathy. In most other cases histopathological evaluation through liver biopsy is required to access reimbursed HBV treatment. The aim of this retrospective study is to evaluate the effectiveness of non-invasive methods in assessing liver damage, with the ultimate goal of reducing the need for liver biopsy.

MATERIALS AND METHODS

Study Setting and Patients

Patients who presented to the infectious diseases and clinical microbiology outpatient clinic between June 1, 2010, and June 1, 2024, were retrospectively evaluated. Adult patients (≥18 years) who were hepatitis B surface antigen (HBsAg) positive, hepatitis B e antigen (HBeAg) negative, treatment-naïve, and who had undergone liver biopsy were eligible for inclusion. During the study period, a total of 435 HBsAg positive patients were identified.

Patients were excluded if they had hepatitis C virus co-infection (n=3), human immunodeficiency virus co-infection (n=4), malignancy (n=4), insufficient clinical or laboratory data (n=45), HBeAg positivity (n=31), unavailable HBeAg records (n=41), or follow-up without liver biopsy (n=159). After applying these exclusion criteria, the final study cohort consisted of 148 treatment-naïve adult patients with HBeAg-negative CHB infection who underwent liver biopsy after a minimum follow-up period of one year.

Demographic characteristics (age and sex), laboratory parameters [hemoglobin, platelet count, aspartate aminotransferase (AST), ALT, total bilirubin, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), international normalized ratio

(INR), alpha-fetoprotein (AFP) and albumin], virological data (HBV-DNA levels), and histopathological findings were obtained from patients' medical records. At the hospital where the study was conducted, the upper limit of normal for AST and ALT was defined as 40 IU/L.

Liver biopsy specimens were evaluated using the Ishak fibrosis score and the Knodell histological activity index (HAI) to assess fibrosis and necroinflammation[5]. Under the regulations of the Turkish Social Security Institution Healthcare Implementation Communiqué, histopathological criteria constitute a valid indication for initiating antiviral therapy in Türkiye. Patients meeting the definition of significant histological activity (fibrosis stage ≥2 and/or necroinflammatory activity grade ≥6) are considered eligible for treatment.

This study was approved by the Ethics Committee for Non-interventional Research of Tekirdağ Namık Kemal University by (decision no: 2025.215.11.12, date: 25.11.2025) in accordance with the Declaration of Helsinki.

Non-invasive İndices of Liver Fibrosis

- AST to platelet ratio index (APRI) = [(AST/AST upper limit of normal (U/L)/platelet count (10^9/L)] × 100,
- AST-ALT ratio = (AAR): AST (U/L)/ALT(U/L),
- Age-GGT-AST-platelet score AGAP) = [AST (U/L) x GGT (U/L)] × [age/platelet count^2 (10^9/L)],
- Fibrosis-4 index (FIB-4) = [age × AST (U/L)]/[platelet count (10^9/L) × √ALT (U/L)],
- Fibro alpha =1.35 + [AFP (μg/L) × 0.009584] + [AST (U/L)/ALT (U/L) × 0.243] - [platelet count (10^9/L) × 0.001624],
- Fibro Q = [(10 × age × AST (U/L) × INR)/(platelet count (10^9/L)] × ALT (U/L),
- Fibrosis-cirrhosis index (FCI) = [(ALP (U/L) × bilirubin (mg/dL)/[(albümin (g/dL) × platelet count (10^9/L)],
- DOHA score = 8.5 - [0.2 × albümin (g/dL) + [0.01× (AST (U/L)] - [0.02 ×platelet count (10^9/L)],
- GUCI = Normalized AST (U/L) x INR x 100/platelet count (10^9/L),
- KING's score = age x AST (U/L) x INR/platelet count (10^9/L)

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for MacOS, version 30.0 (IBM Corp., Armonk, NY, USA). Categorical variables were presented as numbers and percentages [n (%)], while continuous variables were summarized as median and interquartile range [median (IQR)]. Group comparisons were performed using the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, where appropriate. Multivariable logistic regression analyses were conducted to identify factors associated with high HAI (HAI ≥6) and fibrosis (fibrosis ≥2). Variables that were clinically relevant and found to be significant in univariable analyses were included in the multivariable models. To avoid collinearity, the AST/ALT ratio was used instead of AST and ALT individually, and HBV DNA levels were log-transformed ($\log_{10}$ HBV DNA) to represent viral replication better. Platelet count was included as a marker of portal hypertension, and serum albumin level was included as an indicator of hepatic functional reserve. To evaluate the diagnostic performance of non-invasive tests, widely used biochemical indices in CHB, including APRI, FIB-4, GUCI, KING, AGAP, DOHA, and Fibro-Q scores, were assessed using ROC curve analysis. The area under the curve (AUC), optimal cut-off values, sensitivity, and specificity were calculated for each score. A p-value <0.05 was considered statistically significant.

RESULTS

The distribution of demographic and clinical characteristics of patients according to low (HAI<6) and high (HAI ≥6) HAI scores is presented in Table 1. Patients in the high HAI group had significantly higher HBV DNA levels compared with those in the low HAI group (p<0.001). Markers of hepatocellular injury, including AST and ALT were also significantly elevated in the high HAI group (p<0.001). Furthermore, categorical analysis of ALT levels demonstrated that higher ALT strata were markedly more frequent among patients with high HAI scores (p<0.001). Although platelet counts tended to be lower in the high HAI group, this difference did not reach statistical significance (p=0.066). Serum albumin levels were significantly higher in the low HAI group (p=0.007), suggesting a relative preservation of hepatic functional reserve in patients with less severe histological inflammation. With regard to non-invasive liver injury indices, APRI, KING, GUCI, and AGAP scores were all significantly higher in patients with high HAI scores (p<0.001).

The demographic and clinical characteristics of patients with low (F<2) and high fibrosis (≥F2) scores are summarized in Table 2. Patients with high fibrosis had significantly higher HBV DNA levels(age and sex). Platelet counts were significantly lower in the high fibrosis group (p=0.010). Among the non-invasive tests, FIB-4, APRI, Fibro Q, KING, GUCI, DOHA and AGAP scores were significantly higher in patients with high fibrosis (p<0.001).

Each 1 $\log_{10}$ increase in HBV DNA levels was associated with an approximately 1.7-fold higher risk of having a high HAI score (≥6) (p=0.002). Patients with an AST/ALT ratio ≥1 had a nearly 60% lower likelihood of high HAI compared with those with an AST/ALT ratio <1 (OR: 0.4; p=0.034). Each 1 g/dL decrease in serum albumin level was associated with a significantly lower likelihood of high HAI (OR: 0.2; p=0.025) (Table 3).

Table 1. Comparison of laboratory and radiological findings of patients with HAI <6 and HAI ≥6

Parameters (n=148)	**HAI<6 (n=60)**	**HAI≥6 (n=88)**	**p-value**
	n (%) or median (IQR)	**n (%) or median (IQR)**	
Gender			**0.018**
Male	30 (50)	61 (69.3)	
Female	30 (50)	27 (30.7)	
Age (years)	45.5 (36.5-52)	46 (38.5-56.5)	0.228
HBV DNA (IU/L)	13126 (4372,5-55377)	293024 (12372-8189502)	**<0.001**
Fibrosis score			**<0.001**
<2	53 (88.3)	24 (27.3)	
≥2	7 (11.7)	64 (72.7)	
Hemoglobin (g/dL)	13.7 (12.9-15)	14.8 (13.3-15.3)	**0.032**
Platelet count (mm^3)	212 (178-251)	198 (164-235)	0.066
AST (IU/L)	21 (17-25.9)	35 (24-58)	**<0.001**
ALT (IU/L)	21 (16-30)	49.5 (28.5-100.1)	**<0.001**
<40	49 (81.7)	32 (36,4)	**<0.001**
40-80	7 (11.7)	26 (29.5)	
>80	4 (6.7)	30 (34.1)	
AST/ALT ratio			**<0.001**
<1	31 (51.7)	72 (81.8)	
≥1	29 (48.3)	16 (18.2)	
ALP (IU/L)	70.5 (53.5-88)	77 (63-95.5)	0.120
GGT (IU/L)	17 (12-23)	17.5 (12-27)	0.542
AFP (μg/L)	2.4 (1.6-3.7)	2.7 (1.7-4.2)	0.327
INR	1 (0.9-1.1)	1 (0.9-1.1)	0.496
Total bilirubin (mg/dL)	0.5 (0.3-0.7)	0.5 (0.3-0.8)	0.480
Albumin (g/L)	4.6 (4.4-4.8)	4.5 (4.2-4.6)	**0.007**
Ultrasonography			**0.006**
Normal	39 (65)	57 (64.8)	
Hepatic steatosis 1-2	20 (33.3)	15 (17)	
Hepatic steatosis 3-4	1 (1.7)	10 (11.4)	
Irregularity in liver contours	0 (0)	6 (6.8)	
Non-invasive tests			
FIB-4	0.9 (0.6-1.2)	1.1 (0.7-1.7)	**0.005**
APRI	0.2 (0.2-0.3)	0.5 (0.3-0.8)	**<0.001**
Fibro Q	1.5 (1-1.9)	1.8 (1.1-2.6)	0.106
AAR	1 (0.7-1.1)	0.7 (0.6-0.8)	**<0.001**
DOHA	3.6 (2.7-4.3)	4 (3.5-5)	**0.006**
Fibro alpha	1.3 (1.2-1.3)	1.2 (1.2-1.3)	0.202
FCI	0.04 (0.02-0.05)	0.05 (0.02-0.09)	**0.027**
GUCI	0.37 (0.27-0.49)	0.74 (0.44-0.12)	**<0.001**
KING	4.1 (2.7-6)	7.7 (4.6-16.3)	**<0.001**
AGAP	0.3 (0.2-0.8)	0.9 (0.4-2.2)	**<0.001**

AFP: Alpha-fetoprotein, AGAP, age-GGT-AST-platelet score, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, APRI: Aspartate aminotransferase to platelet ratio index, AST: Aspartate aminotransferase, AAR, AST/ALT ratio, FCI: Fibrosis-cirrhosis index, GGT: Gamma-glutamyl transferase, HBV: Hepatitis B virus, FIB-4: Fibrosis-4 index, INR: International normalized ratio, IQR: Interquartile range, significance set at p<0.05

Table 2. Comparison of laboratory and radiological findings of patients with fibrosis <2 and fibrosis ≥2

Parameters (n=148)	Fibrosis <2 (n=77)	Fibrosis ≥2 (n=71)	p-value
	n (%) or median (IQR)	n (%) or median (IQR)	
Gender			**0.013**
Male	40 (51.9)	51 (71.8)	
Female	37 (48.1)	20 (28.2)	
Age (years)	45 (35-53)	47 (39-57)	0.095
HBV DNA (IU/L)	16879 (5688-124233)	188239 (12372-8189502)	**<0.001**
HAI			**<0.001**
<6	53 (68.8)	7 (9.9)	
≥6	24 (31.2)	64 (90.1)	
Hemoglobin (g/dL)	13.8 (12.8-15)	14.9 (13.9-15.4)	**0.009**
Platelet count (mm^3)	213 (182-250)	193 (157-233)	**0.010**
AST (IU/L)	22 (18.3-32)	34 (24-65)	**<0.001**
ALT (IU/L)	24 (18-42)	49 (27-108)	**<0.001**
<40	56 (72.7)	25 (35.2)	**<0.001**
40-80	13 (16.9)	20 (28.2)	
>80	8 (10.4)	26 (36.6)	
AST/ALT ratio			**0.007**
<1	46 (59.7)	57 (80.3)	
≥1	31 (40.3)	14 (19.7)	
ALP (IU/L)	74 (54-90)	76 (61-96)	0.189
GGT (IU/L)	17 (12-22)	18 (12-30)	0.181
AFP (µg/L)	2.5 (1.6-3.7)	2.7 (1.7-4.6)	0.323
INR	1 (1-1.1)	1 (0.9-1.1)	0.286
Total bilirubin (mg/dL)	0.5 (0.3-0.7)	0.6 (0.3-0.7)	0.450
Albumin (g/L)	4.5 (4.4-4.7)	4.5 (4.3-4.6)	0.168
Ultrasonography			0.060
Normal	51 (66.2)	45 (63.4)	
Hepatic steatosis 1-2	22 (28.6)	13 (18.3)	
Hepatic steatosis 3-4	3 (3.9)	8 (11.3)	
Irregularity in liver contours	1 (1.3)	5 (7)	
Non-invasive tests			
FIB-4	0.9 (0.6-1.2)	1.2 (0.8-1.8)	**<0.001**
APRI	0.3 (0.2-0.4)	0.5 (0.3-0.8)	**<0.001**
Fibro Q	1.4 (0.9-1.8)	2.1 (1.4-3.2)	**<0.001**
AAR	0.9 (0.7-1.1)	0.7 (0.6-0.9)	**0.006**
DOHA	3.6 (2.8-4.3)	4.2 (3.5-5.1)	**0.001**
Fibro alpha	1.2 (1.2-1.3)	1.2 (1.2-1.3)	0.533
FCI	0.03 (0.02-0.06)	0.05 (0.03-0.08)	**0.029**
GUCI	0.43 (0.30-0.61)	0.75 (0.41-1.40)	**<0.001**
KING	4.5 (3.2-6.4)	8.2 (4.5-17.3)	**<0.001**
AGAP	0.4 (0.2-0.8)	0.9 (0.4-2.3)	**<0.001**

AFP: Alpha-fetoprotein, AGAP, age-GGT-AST-platelet score, ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, APRI: Aspartate aminotransferase to platelet ratio index, AST: Aspartate aminotransferase, AAR, AST/ALT ratio, FIB-4: Fibrosis-4 index, GGT: Gamma-glutamyl transferase, HAI: Histological activity index, HBV: Hepatitis B virüs, INR: International normalized ratio, IQR: Interquartile range, significance set at p<0.05

Each 1 log₁₀ IU/mL increase in HBV DNA levels was independently associated with an approximately 1.3-fold increased risk of advanced fibrosis (p=0.044) (Table 4).

Among the non-invasive markers, the APRI score demonstrated the highest discriminatory ability for predicting high HAI scores, with an AUC of 0.785 (95% CI: 0.710-0.860). Using a cut-off value of >0.350 for APRI, the sensitivity and specificity were 68.2% and 85.0%, respectively. GUCI and KING scores also showed good discriminatory performance, with AUC values of 0.753 (95% CI: (0.673-0.833) and 0.740 (95% CI: 0.659-0.820), respectively (Figure 1). The KING score demonstrated the highest discriminatory ability for predicting advanced fibrosis, with an AUC of 0.768 (95% CI: 0.667-0.869). Using a cut-off value of >6.995, the sensitivity and specificity were 61.5% and 87.8%, respectively. The APRI [AUC: 0.756; (95% CI: 0.654-0.857); sensitivity: 66.7%, specificity: 75.5%] and FIB-4 [AUC: 0.747; (95% CI: 0.640-0.854); sensitivity: 69.2%, specificity: 79.6%] scores also showed comparably good performance in distinguishing fibrosis (Figure 2).

Table 3. Multivariable logistic regression analysis for HAI ≥6

Variables	OR (95% CI)	p-value
Gender		
Female	Reference	-
Male	2.0 (0.8-4.7)	0.118
HBV DNA (log)	1.7 (1.2-2.4)	**0.002**
AST/ALT ratio		
<1	Reference	
≥1	0.4 (0.2-0.9)	**0.034**
Platelet count (mm³)	1.0 (0.9-1.1)	0.812
Albumin (g/dL)	0.2 (0.1-0.8)	**0.025**
KING	1.0 (0.9-1.1)	0.933

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBV: Hepatitis B virus, HAI: Histological activity index, OR: Odds ratio, CI: Confidence interval, significance set at p<0.05

Table 4. Multivariable logistic regression analysis for fibrosis ≥2

Variables	OR (95% CI)	p-value
Gender		
Female	Reference	-
Male	1.8 (0.8-4.0)	0.118
HBV DNA (log)	1.3 (1.1-1.8)	**0.044**
AST/ALT ratio		
<1	Reference	
≥1	0.6 (0.3-1.5)	0.304
Platelet count (mm³)	1.0 (0.9-1.1)	0.477
Albumin (g/dL)	0.2 (0.1-0.8)	0.449
KING	1.0 (0.9-1.1)	0.394

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HBV: Hepatitis B virus, HAI: Histological activity index, OR: Odds ratio, CI: Confidence interval, significance set at p<0.05

DISCUSSION

In this study, the demographic, laboratory, radiological, and non-invasive test characteristics of 148 patients diagnosed with CHB who underwent liver biopsy were evaluated. We aimed to retrospectively investigate the predictive factors for liver fibrosis or/and high HAI referred to as significant histopathological abnormality (SHA), in order to indicate the need for treatment. Multivariate analysis identified HBV-DNA as a significant predictor for detecting SHA in CHB infection. Additionally, ROC analysis showed that the APRI score demonstrated the highest discriminatory power for predicting significant histological activity, while the KING score was the most effective in identifying advanced fibrosis. GUCI score also exhibited good overall performance.

CHB represents a dynamic disease state resulting from the complex and evolving interaction between HBV replication and the host immune response[3]. Patients receiving antiviral therapy have been shown to experience a 40-60% reduction in the risk of developing HCC compared with untreated individuals[6]. Liver biopsy remains the gold standard for assessing the degree of hepatic fibrosis in patients with CHB; however, its invasive nature, potential for serious complications, high cost, and limitations related to the heterogeneous distribution of histopathological changes within the liver parenchyma have prompted the search for alternative assessment methods. Given the critical role of liver fibrosis in guiding treatment decisions and predicting complications in CHB, non-invasive, simple, and cost-effective scoring systems have been developed to facilitate fibrosis evaluation without the need for biopsy.

When our results were compared with those of Abdo et al.[7], who investigated predictors of highfibrosis (≥F2), notable similarities were observed. In both studies, advanced age, elevated AST levels, and reduced serum albumin and platelet counts emerged as independent predictors of significant fibrosis. In addition, Ozdemir et al.[8] demonstrated significant correlations between HAI scores and AST, ALT, and HBV DNA levels. Diktas et al.[9] reported significant correlations between HAI scores and AST, ALT, and HBV DNA levels in HBeAg-negative patients with CHB. In this study, several of these associations were corroborated. Higher AST and ALT levels, elevated HBV DNA, and particularly an AST/ALT ratio <1 were identified as predictors of significant histological activity in univariate analysis. In multivariate analysis, HBV DNA emerged as the main independent predictive factor. Previous studies have demonstrated a negative correlation between platelet count and the degree of fibrosis[10-12]. Consistent with these findings, our study showed lower platelet counts in patients with higher fibrosis scores (p=0.01). In addition, several studies have reported that reduced serum albumin levels are significant determinants in predicting the extent of liver damage[13,14]. In

Variables	AUC (95% CI)	p-value	Cut-off	Sensitivity (%)	Specificity (%)
AGAP	0.702 (0.616-0.789)	<0.001	>0.499	68.2	71.7
APRI	0.785 (0.710-0.860)	<0.001	>0.350	68.2	85.0
DOHA	0.633 (0.541-0.724)	0.004	>3.645	68.2	56.7
FIB-4	0.636 (0.546-0.726)	0.003	>1.265	40.9	86.7
GUCI	0.753 (0.673-0.833)	<0.001	>0.574	64.8	83.3
King	0.740 (0.659-0.820)	<0.001	>6.958	58.0	85.0

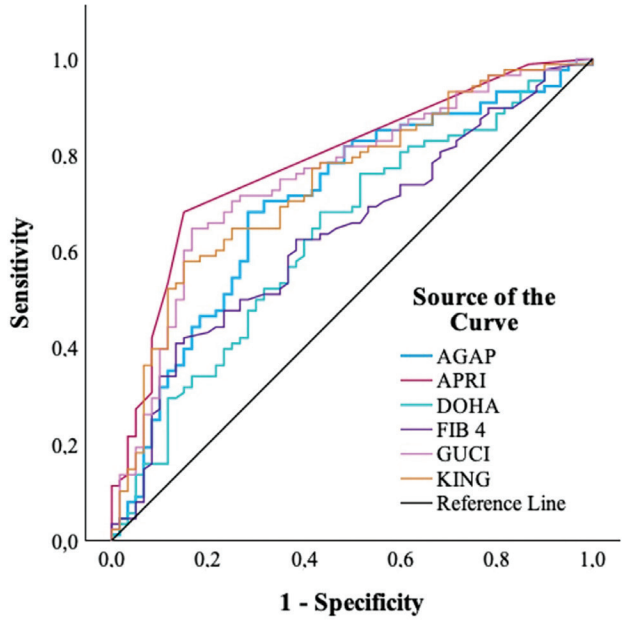

Figure 1. ROC curves of non-invasive scores for predicting high histological activity (HAI ≥6)

AGAP, age-GGT-AST-platelet score, AUC: Area under the curve, CI: Confidence interval, APRI: Aspartate aminotransferase to platelet ratio index, GGT: Gamma-glutamyl transferase, CI: Confidence interval, FIB-4: Fibrosis-4 index, HAI: Histological activity index, AST: Aspartate aminotransferase, GUCI: Gothenburg University Cirrhosis index, significance set at p<0.05

this study, serum albumin levels were found to be significantly lower in patients with HAI ≥6 in multivariate analysis (p=0.025).

Previous studies have reported that the AUC values of APRI for predicting significant fibrosis range from 0.61 to 0.787, with cut-off values varying between 0.47 and 1[15-18]. In this study, the cut-off value for significant fibrosis was determined to be 0.35, which is lower than those reported in the literature. In a study conducted by Lee et al.[14], APRI and FIB-4 scores were shown to have performance comparable to liver biopsy in risk stratification for liver-related morbidity and mortality among patients with non-alcoholic fatty liver disease. In a multicenter study conducted by Korkmaz et al.[15] in patients with CHB, APRI and FIB-4 were identified as the non-invasive models with the highest diagnostic accuracy for fibrosis staging. In the present study, APRI was found to have a particularly strong predictive value for identifying SHA.

In the study by Karacaer et al.[19] 277 patients were divided into two groups according to the Ishak fibrosis score: the first group included patients with mild fibrosis (0-2), and the second group comprised those with advanced fibrosis (3-6). In that study, GUCI, KING, APRI, and FIB-4 scores were found to be statistically significant in differentiating between the two groups. In a study conducted by Dong et al.[20] KING score was found to be the most successful scores in distinguishing significant fibrosis in patients with CHB. According to thisstudy, GUCI and KING scores were effective in differentiating advanced significant fibrosis from mild HAI in patients with CHB, with AUROC values of 0.731 and 0.768, respectively. In previous studies, both GUCI and KING scores also demonstrated significant discriminative ability, as reflected by their AUROC values, in distinguishing patients with advanced fibrosis from those with no or low-grade fibrosis[18,19]. In our study, ROC analysis demonstrated that the KING score was significantly effective in predicting fibrosis stage ≥2, with

Variables	AUC (95% CI)	p-value	Cut-off	Sensitivity (%)	Specificity (%)
AGAP	0.739 (0.633-0.846)	<0.001	>0.499	71.8	73.5
APRI	0.756 (0.654-0.857)	<0.001	>0.350	66.7	75.5
FIB-4	0.747 (0.640-0.854)	<0.001	>0.995	69.2	79.6
FIBRO-Q	0.706 (0.594-0.819)	<0.001	>1.825	61.5	77.6
GUCI	0.731 (0.624-0.838)	<0.001	>0.587	61.5	79.6
KING	0.768 (0.667-0.869)	<0.001	>6.995	61.5	87.8

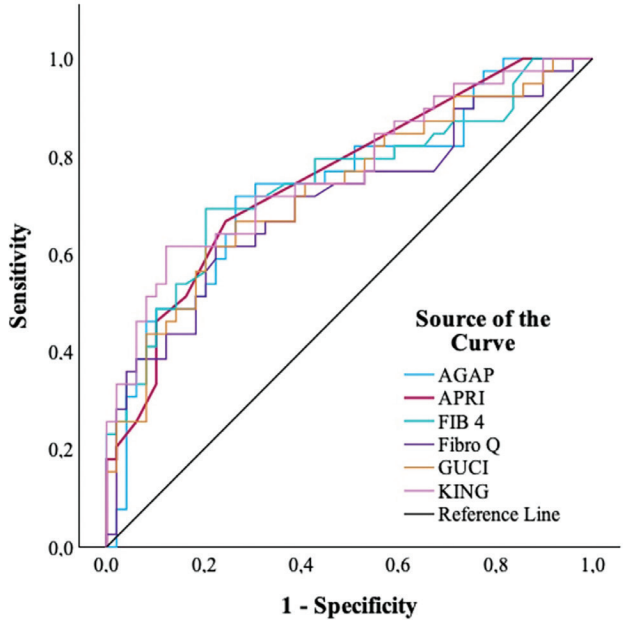

Figure 2. ROC curves of non-invasive scores for predicting significant fibrosis (fibrosis ≥2)

AGAP, age-GGT-AST-platelet score; AUC: Area under the curve, CI: Confidence interval, APRI: Aspartate aminotransferase to platelet ratio index, GGT: Gamma-glutamyl transferase, CI: Confidence interval, FIB-4: Fibrosis-4 index, AST: Aspartate aminotransferase, GUCI: Gothenburg University Cirrhosis index, significance set at p<0.05

an AUC of 0.768, and HAI ≥6, with an AUC of 0.740. Similarly, the GUCI score showed significant discriminative ability for both fibrosis stage ≥2 and HAI ≥6, yielding high AUC values of 0.731 and 0.758, respectively. In a study conducted by Xiao-Qiu Dong in treatment-naive patients, the Fibro-Q test demonstrated an AUC of 0.720 for predicting ≥F3 fibrosis and an AUC of 0.810 for predicting ≥F5 fibrosis[19]. In this study, the diagnostic performance of the Fibro-Q score for predicting SHA was found to be lower than that of other non-invasive tests.

Study Limitations

This study has several limitations. First, its single-center and retrospective design represents the most important limitation, which may restrict the generalizability of the findings. In addition, the inability to apply non-invasive methods across large and diverse patient populations, the use of different fibrosis scoring systems, variability in histopathological assessment by pathologists with differing levels of expertise, and heterogeneity in patient ethnicity and viral genotypes have hindered the standardization of any single non-invasive marker.

CONCLUSION

In conclusion, although the number of studies investigating non-invasive methods as alternatives to liver biopsy has increased in recent years, an adequate level of diagnostic accuracy has not yet been achieved. In addition to APRI, we believe that the King score is particularly valuable for providing insight into significant histological activity of the liver and may serve as a useful adjunct in the non-invasive assessment of disease severity. These findings suggest that simple, APRI and KING scores may serve as valuable tools in the clinical evaluation of CHB patients, potentially reducing unnecessary liver biopsy in selected patients.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee for Non-interventional Research of Tekirdağ Namık Kemal University by (decision no: 2025.215.11.12, date: 25.11.2025) in accordance with the Declaration of Helsinki.

Informed Consent: The study is a retrospective study.

Footnotes

Authorshıp Contribution

Concept: M.N.Ö., N.T., İ.E., Design M.N.Ö., N.T., İ.E., S.B., Data Collection or Processing: B.E., B.S.S., M.Ö., A.Ç., İ.E. Analysis or Interpretation: B.E., B.S.S., M.Ö., A.Ç., İ.E., Literature Search: M.N.Ö., N.T., S.B., İ.E., Writing: M.N.Ö., İ.E.

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Three-dimensional Morphometric Analysis of the Zygomatic Arch and Temporozygomatic Suture: Implications for Asymmetry and Sexual Dimorphism

Arcus Zygomaticusun ve Sutura Temporozygomatica'nın Üç Boyutlu Morfometrik Analizi: Asimetri ve Cinsel Dimorfizm Açısından Değerlendirme

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ABSTRACT

Aim: The zygomatic arch (arcus zygomaticus) forms a critical anatomical bridge between the viscerocranium and neurocranium, contributing to facial width, aesthetics and masticatory biomechanics. The temporozygomatic suture, which connects the temporal and zygomatic components of the arch, plays an important role in midfacial stability and is frequently involved in surgical interventions. Despite its clinical relevance, detailed three-dimensional morphometric data regarding the localization and variability of this suture remain limited. The aim of this study was to evaluate the three-dimensional morphometric localization of the temporozygomatic suture along the zygomatic arch and to determine side- and sex-related differences.

Materials and Methods: This retrospective study was conducted using computed tomography–based three-dimensional reconstructions. Standardized orientation protocols were applied, and morphometric measurements were obtained to assess the localization of the temporozygomatic suture along the zygomatic arch. Analyses were performed with respect to side-related asymmetry and sex-related differences.

Results: The findings revealed significant sexual dimorphism in several projection-related parameters of the zygomatic arch. A consistent left-sided predominance was observed in the localization of the temporozygomatic suture and in measurements related to the temporal process of the zygomatic bone, whereas the zygomatic process of the temporal bone demonstrated relative stability across sexes and sides.

Conclusion: The results indicate that variability of the zygomatic arch is segment-specific and influenced by both sex and laterality. Recognition of these three-dimensional anatomical patterns may improve surgical planning, radiological interpretation, and forensic assessments involving the zygomatic and temporal regions.

Keywords: Zygomatic arch, zygoma, cephalometry, facial asymmetry

ÖZ

Amaç: Zigomatik ark (arcus zygomaticus), visserokranium ile nörokranium arasında kritik bir anatomik köprü oluşturarak yüz genişliği, estetik görünüm ve çiğneme biyomekaniğine katkıda bulunur. Zigomatik arkın temporal ve zigomatik bileşenlerini birleştiren temporozigomatik sütür, orta yüz stabilitesinde önemli bir rol oynar ve cerrahi girişimlerde sıklıkla yer alır. Klinik önemine rağmen, bu sütürün lokalizasyonu ve değişkenliğine ilişkin ayrıntılı üç boyutlu morfometrik veriler sınırlıdır. Bu çalışmanın amacı, temporozigomatik sütürün zigomatik ark boyunca üç boyutlu morfometrik lokalizasyonunu değerlendirmek ve taraf ile cinsiyete bağlı farklılıkları belirlemektir.

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Gereç ve Yöntemler: Bu retrospektif çalışma, bilgisayarlı tomografi temelli üç boyutlu rekonstrüksiyonlar kullanılarak gerçekleştirildi. Standartlaştırılmış oryantasyon protokolleri uygulandı ve temporozigomatik sütürün zigomatik ark boyunca lokalizasyonunu değerlendirmek amacıyla morfometrik ölçümler yapıldı. Analizler, taraflar arası asimetri ve cinsiyete bağlı farklılıklar açısından gerçekleştirildi.

Bulgular: Bulgular, zigomatik arkın projeksiyonuna ilişkin çeşitli parametrelerde belirgin cinsiyet farklılıkları olduğunu gösterdi. Temporozigomatik sütürün lokalizasyonunda ve zigomatik kemiğin temporal çıkıntısına ilişkin ölçümlerde tutarlı bir sol taraf baskınlığı saptanırken, temporal kemiğin zigomatik çıkıntısı cinsiyetler ve taraflar arasında göreceli olarak daha stabil bulundu.

Sonuç: Bulgular, zigomatik arkın değişkenliğinin segmente özgü olduğunu ve hem cinsiyet hem de taraf farklılıklarından etkilendiğini göstermektedir. Bu üç boyutlu anatomik paternlerin tanınması, zigomatik ve temporal bölgeleri ilgilendiren cerrahi planlamanın, radyolojik değerlendirmelerin ve adli tıp incelemelerinin geliştirilmesine katkı sağlayabilir.

Anahtar Kelimeler: Zigomatik ark, zigoma, sefalometri, yüz asimetrisi

INTRODUCTION

The zygomatic arch (arcus zygomaticus) is a prominent anatomical bridge connecting the viscerocranium to the neurocranium and plays a pivotal role in the structural integrity and transverse dimension of the facial skeleton[1-3]. Composed of the temporal process of the zygomatic bone (Z) and the zygomatic process of the temporal bone (TE), the arch contributes significantly to facial width and cheek prominence, rendering it a key structure in both facial aesthetics and reconstructive procedures such as reduction malarplasty[4,5]. Functionally, it serves as the primary origin site of the masseter muscle, transmitting substantial masticatory forces through the midface and thereby influencing regional bone morphology and cortical architecture[3,6,7].

The junction between the zygomatic and temporal components forms the temporozygomatic (zygomaticotemporal) suture, a laterally projecting articulation that is particularly vulnerable to traumatic injury[4,8]. Accurate knowledge of the topographic anatomy of this region is therefore essential for minimizing complications during maxillofacial surgical procedures, including zygomatic implant placement and osteotomies performed for facial reconstruction[4,9]. Despite its clinical importance, the temporozygomatic suture has received comparatively limited attention in morphometric research, particularly when contrasted with more extensively studied craniofacial sutures.

Advances in 3D imaging techniques, including computed tomography (CT) and cone-CT (CBCT), have markedly improved the precision of craniofacial morphometric analyses[10,11]. Previous three-dimensional imaging studies have demonstrated that craniofacial structures exhibit considerable age- and sex-related morphometric variability, particularly in anatomically complex regions, underscoring the necessity of precise three-dimensional localization[12,13]. Unlike traditional two-dimensional radiography, 3D reconstruction enables detailed visualization of sutural maturation and measurement of specific anatomical landmarks without distortion caused by superimposition[14,15]. These techniques have been facilitated the classification of zygomatic arch shapes and the assessment of symmetry in the midfacial region[3,15].

However, despite growing interest in the zygomatic complex, quantitative data regarding the precise three-dimensional localization of the temporozygomatic suture along the zygomatic arch remain scarce. While the maturation and morphology of the zygomaticomaxillary suture have been widely categorized[14], the temporozygomatic suture is often simplified as a linear junction in biomechanical models, despite evidence demonstrating its complex interdigitated structure and age-related morphological changes[6]. Although this suture is known to remain patent into late adulthood, frequently not fusing until the seventh decade of life, its positional variability within adult populations has not been sufficiently documented[5,8]. This lack of precise morphometric localization limits both biomechanical modeling and the reliability of surgical landmarks in the temporal fossa region.

Therefore, the aim of this study was to quantitatively evaluate the three-dimensional localization of the temporozygomatic suture along the zygomatic arch using CT-based reconstruction methods, with particular emphasis on side-related asymmetry and sex-related differences. By providing detailed morphometric data, this study seeks to enhance anatomical accuracy in forensic anthropology, improve preoperative planning in maxillofacial surgery, and contribute to the development of safer surgical approaches involving the temporal and zygomatic regions.

MATERIALS AND METHODS

Study Design and Sample Selection

This retrospective study was performed on cranial CT images. An a priori power analysis for the primary mixed-design model (F test, repeated measures within–between interaction) indicated a required total sample size of 34 ($f=0.25$, $\alpha=0.05$, power=0.80); the study included 50 subjects (27 males, 23 females) aged 18-77 years (43.93±13.48 in males, 40.57±16.19 years in females) who underwent CT examinations for various clinical indications at the Department of Radiology, Zonguldak Bülent Ecevit University Faculty of Medicine. CT datasets with adequate image

quality and complete visualization of the zygomatic arch were included in the analysis. Subjects with a history of craniofacial trauma, congenital craniofacial anomalies, pathological bone lesions or prior surgical interventions involving the zygomatic or temporal region were excluded.

Ethical approval for the study was obtained from the Zonguldak Bülent Ecevit University Non-Interventional Clinical Research Ethics Committee (decision no: 2020/16-14, date: 05.08.2020), and the study protocol complied with the principles of the Declaration of Helsinki.

Image Processing and Three-Dimensional Reconstruction

All CT datasets were transferred to Horos software (version 4.0.0; open-source medical image viewer), where 3D reconstructions were generated using standardized thresholding protocols. To ensure consistency across measurements, all reconstructed skull models were reoriented prior to analysis. The Frankfort horizontal plane was used as the primary reference plane, and the median sagittal plane was established as the midline reference.

Measurements involving mediolateral distances relative to the midline were performed on the norma frontalis, whereas parameters related to the length and segmentation of the zygomatic arch were obtained on the norma lateralis, following optimal visualization of the arch contours and sutural landmarks.

Morphometric Measurements

For segmental measurements of the zygomatic arch, the sutura temporozygomatica was used as the anatomical junction separating the temporal process of the Z and the zygomatic process of the TE. For the Z measurement, the anterior endpoint was defined as the origin of the temporal process on the Z, and the posterior endpoint as the temporozygomatic suture. For the TE measurement, the anterior endpoint corresponded to the temporozygomatic suture, and the posterior endpoint to the root of the zygomatic process of the TE.

The temporozygomatic suture was identified on 3D reconstructions based on the anatomical junction between the temporal process of the Z and the zygomatic process of the TE. Localization was performed by examining the suture line on multiplanar reconstructions and confirming it on 3D surface renderings.

The following parameters were defined and measured bilaterally (R: right, L: left): the distance between the midline and the projection of the most prominent point of the zygomatic arch on the norma frontalis (R-MZ and L-MZ); the distance between the midline and the most medial point of the outer border of the zygomatic process of the frontal bone (R-MF and L-MF); the total length of the zygomatic arch (RT and L-T); the length of the zygomatic process of the temporal bone (R-TE and L-TE); and the length of the temporal process of the zygomatic bone (R-Z and L-Z).

All measurements were performed as linear (straight-line) distances between predefined anatomical landmarks using the measurement tools embedded within the Horos software environment and recorded in millimeters.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism version 10.6.1 (GraphPad Software, San Diego, CA, USA). The normality of data distribution was assessed using the Shapiro–Wilk test. Because the right and left anatomical measurements were obtained from the same individuals, these data were evaluated as paired samples. Accordingly, normally distributed paired data were analyzed using the paired t-test and are presented as mean ± standard deviation (mean ± SD), whereas non-normally distributed paired data were analyzed using the Wilcoxon signed-rank test and are presented as median (25^{th}-75^{th} percentile).

Comparisons between male and female groups, which consisted of independent samples, were performed according to data distribution. Normally distributed data were analyzed using the unpaired t-test with Welch's correction and are presented as mean ± SD. Non-normally distributed data were analyzed using the Mann-Whitney U test and are reported as median (25^{th}-75^{th} percentile). When data distributions differed between groups, non-parametric tests were preferred.

Age comparisons between male and female participants were performed using the independent samples t-test after confirming normality. A p-value of less than 0.05 was considered statistically significant.

All measurements were performed by a single experienced observer under blinded conditions with respect to the patients' sex and age. To assess intraobserver reliability, the same observer repeated the measurements on a randomly selected subset corresponding to approximately 20% of the sample after an interval of two weeks. The intraclass correlation coefficient, based on a two-way mixed-effects model with absolute agreement, was 0.991, demonstrating excellent measurement consistency. Interobserver reliability was not evaluated in this study.

RESULTS

The study population consisted of adult male and female subjects, and morphometric measurements of the zygomatic arch and its components were evaluated with respect to side-related asymmetry and sex-related differences. The mean age of the women was 40.57±16.19 years, whereas the mean age of the men was 43.93±13.48 years, with no statistically significant difference between the groups (p=0.4269).

Analysis of mediolateral projection parameters demonstrated a consistent left-sided predominance of the zygomatic arch in both sexes. In female subjects, the distance from the median line to the most prominent point of the zygomatic arch (L-MZ: 64.92±2.687) was significantly greater than the corresponding right-side measurement (R-MZ: 62.46±3.43) (p=0.001). A similar pattern was observed in males, with L-MZ values [70.30 (67.00-71.80)] exceeding R-MZ values [68.80 (65.30-70.40)] (p=0.0276). When sex-based comparisons were performed, both R-MZ and L-MZ values were significantly greater in males than in females (both p<0.001), indicating a more laterally prominent zygomatic arch configuration in males (Figure 1).

A comparable left-sided predominance was identified for the distances from the median line to the most medial point of the outer border of the frontal zygomatic process. In females, L-MF (48.57±2.191) was significantly greater than R-MF (47.23±2.523) (p=0.0012). In males, L-MF 50.99±2.167 was likewise significantly greater than R-MF 50.07±2.089 (p=0.0194). Furthermore, both R-MF and L-MF values were significantly greater in males compared with females (p<0.0001 and p<0.0003, respectively), further supporting the presence of sex-related differences in lateral facial projection (Figure 1 and Table 1).

In contrast to these projection-related parameters, no statistically significant side-related differences were detected in the total length of the zygomatic arch in either sex. In females, R-T (44.20±4.252) and L-T (44.38±5.190) values were comparable, and a similar bilateral symmetry was observed in males, with no significant difference between R-T [49.10

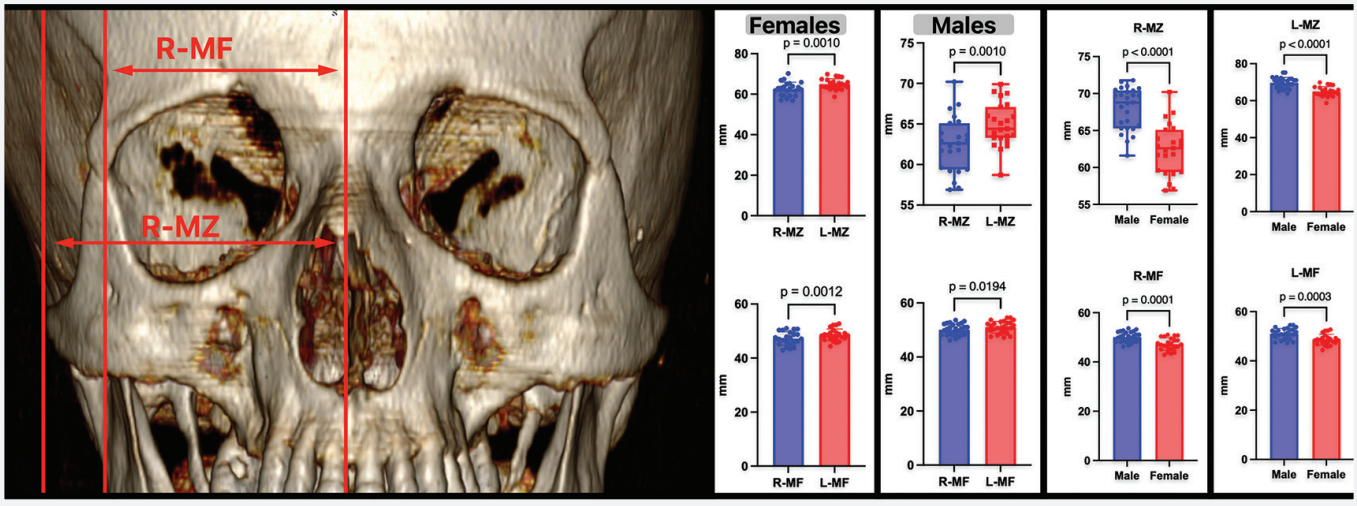

Figure 1. Assessment of mediolateral projection of the zygomatic arch and sex-based comparisons

R-MZ: Right midline-to-zygomatic bone distance, L-MZ: Left midline-to-zygomatic bone distance, R-MF: Right midline-to-frontal bone zygomatic process distance, L-MF: Left midline-to-frontal bone zygomatic process distance

Table 1. Comparison of morphometric parameters according to side (right vs. left) and sex

	Female	Female p (R-L)	Male	Male p (R-L)	p (Female-Male)
R-MZ	62.46±3.432	**0.0010**	68.80 (65.30-70.40)	**0.0276**	**<0.0001**
L-MZ	64.92±2.687		70.3 (67.0-71.80)		**<0.0001**
R-MF	47.23±2.523	**0.0012**	50.07±2.089	**0.0194**	**<0.0001**
L-MF	48.57±2.191		50.99±2.167		**0.0003**
R-T	44.20±4.252	0.8003	49.10 (46.10-49.80)	0.3895	**0.0017**
L-T	44.38±5.190		48.10 (45.10-51.30)		**0.0318**
R-TE	35.91±4.063	0.7867	38.10 (36.40-41.40)	**0.0001**	0.1299
L-TE	36.10±3.934		36.20 (31.10-38.80)		0.6960
R-Z	8.296±1.774	0.9773	8.50 (7.40-12.10)	**0.0003**	0.1386
L-Z	8.283±2.401		10.50 (8.30-14.50)		**0.0039**

Data are presented as mean ± standard deviation or median (25^{th}-75^{th} percentile), depending on data distribution. Paired comparisons were performed using paired t-test or Wilcoxon signed-rank test. Between-group comparisons were performed using unpaired t-test or Mann-Whitney U test, as appropriate, R-MZ: Right midline-to-zygomatic bone distance, L-MZ: Left midline-to-zygomatic bone distance, R-MF: Right midline-to-frontal bone zygomatic process distance, L-MF: Left midline-to-frontal bone zygomatic process distance

(46.10-49.80)] and L-T [48.10 (45.10-51.30)]. However, sex-based comparisons revealed that total arch length was significantly greater in males than in females on both sides (p=0.0017 and p=0.0318, respectively) (Figure 2 and Table 1).

Evaluation of the length of the zygomatic process of the TE demonstrated no significant side-related differences in either sex. In females, R-TE (35.91±4.063) and L-TE (36.10±3.934) values did not differ significantly, and a similar finding was obtained in males, in whom R-TE [38.10 (36.40-41.40)] and L-TE [36.20 (31.10-38.80)] were comparable. In addition, no statistically significant differences were observed between males and females for either R-TE or L-TE (Figure 2 and Table 1).

In contrast, analysis of the temporal process of the Z revealed a distinct pattern. While no significant difference was observed between R-Z (8.296±1.774) and L-Z (8.283±2.401) in females, male subjects exhibited a significantly greater L-Z [10.50 (8.30-14.50)] length than R-Z [(8.50 (7.40-12.10)] (p=0.0003), indicating a left-sided predominance specific to the male group. When sex-based comparisons were performed, no significant difference was observed for R-Z values; however, L-Z values were significantly greater in males than in females (p=0.0039) (Figure 2 and Table 1).

Overall, the results indicate that side-related asymmetry of the zygomatic arch was observed primarily in projection-related parameters and the temporal process of the Z, with a pronounced left-sided dominance, particularly in males. In contrast, the zygomatic process of the TE exhibited relative symmetry and did not show significant sex-related variation.

DISCUSSION

The morphological architecture of the zygomatic complex plays a pivotal role in facial esthetics and biomechanics, serving as a primary buttress for masticatory loads and a key determinant of facial width. Our morphometric study provides a detailed three-dimensional morphometric evaluation of the zygomatic arch and the temporozygomatic suture, revealing distinct patterns of sexual dimorphism and side-related asymmetry. By analyzing both projection-related parameters and the individual components of the zygomatic arch, our findings extend existing knowledge beyond traditional linear craniofacial measurements and offer anatomically meaningful insights with direct clinical relevance.

Sex-related differences constituted a prominent feature of our results. Measurements reflecting the mediolateral projection of the zygomatic arch were consistently greater in males than in females, supporting previous reports that identify the zygomatic region as one of the most sexually dimorphic areas of the craniofacial skeleton[3,7,10]. While earlier studies have largely focused on global indices such as bizygomatic width, the present analysis demonstrates that this dimorphism is not uniformly distributed across the arch. Specifically, elongation of the temporal process of the Z, rather than the zygomatic

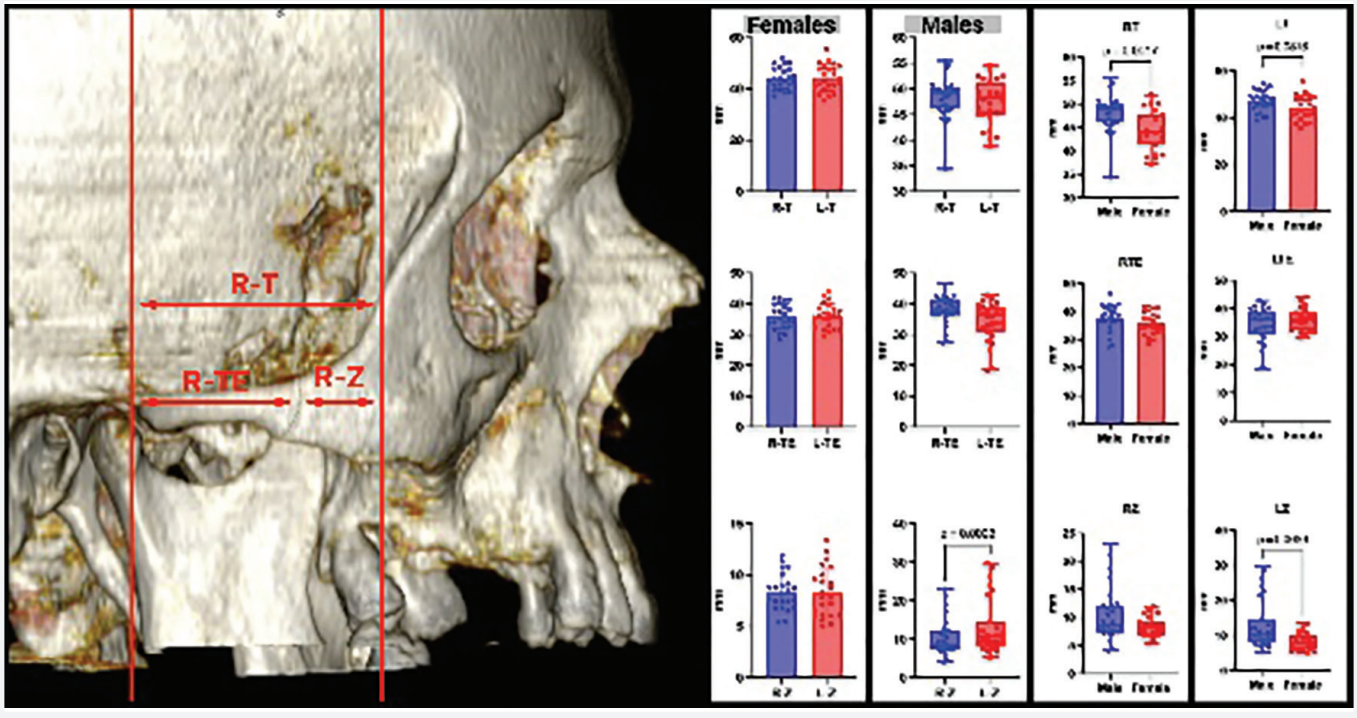

Figure 2. Morphometric analysis of zygomatic arch length and its components according to side and sex

process of the TE, appears to contribute more substantially to the observed sex differences. This finding aligns with geometric morphometric evidence suggesting that sexual dimorphism in the zygomatic region is expressed through complex surface remodeling rather than simple linear expansion[7].

A notable finding of this study is the consistent left-sided predominance observed in projection-related measurements and, in males, in the temporal process of the Z. Facial asymmetry is a well-recognized biological phenomenon, and perfect bilateral symmetry is rare in the human craniofacial skeleton[16,17]. Supporting this notion, Özen et al.[5] demonstrated significant side-related differences in the localization of the temporozygomatic suture, with a tendency toward a more anterior positioning on the left side of the zygomatic arch. Such asymmetrical sutural localization may contribute to differential segmental growth or remodeling of the arch components observed in the present study. In contrast, some cadaveric and radiological investigations have reported relatively symmetrical configurations of the zygomatic arch[4], suggesting that patterns of asymmetry may be population-specific and highly dependent on the anatomical landmarks and measurement strategies employed.

The asymmetrical elongation of the temporal process of the Z observed predominantly in males warrants particular consideration. The temporozygomatic suture is known to exhibit increasing interdigitation complexity with age and to respond dynamically to biomechanical forces transmitted by the masseter muscle and temporal fascia[6]. In this context, three-dimensional analyses have demonstrated that the morphology of the zygomatic arch is closely related to the functional demands of the masticatory system, particularly the orientation and force vectors of the masseter muscle[3]. Given that the Z serves as a primary attachment site for the masseter muscle, differential masticatory loading may preferentially influence remodeling of this component rather than the TE. Additionally, variability in the number and fusion patterns of zygomatic ossification centers may contribute to individual and side-related differences in adult morphology[18].

From a clinical perspective, the present findings have important implications for maxillofacial surgery, radiological assessment, and forensic analysis. In reconstructive procedures involving the zygomatic arch, the contralateral side is frequently used as a template for restoration. Our results suggest that such an approach may lead to underestimation of projection or segment length, particularly in male patients with pronounced left-sided dominance. This observation is consistent with recent recommendations emphasizing the need for sex-specific and side-aware planning in craniofacial surgery[11].

Furthermore, the stability of the zygomatic process of the TE across sexes and sides makes it a potentially more reliable surgical landmark than the variable zygomatic component. This is pertinent for procedures involving the zygomatic arch, where precise osteotomies are required to avoid complications such as trismus or facial asymmetry[4]. The structural variability of the Z also has implications for zygomatic implant placement, where understanding the specific dimensions of the zygomaticomaxillary complex is crucial to avoid injury to the orbit or infratemporal fossa[9].

Study Limitations

The present study is subject to certain limitations. The retrospective and cross-sectional design precludes evaluation of longitudinal changes in zygomatic arch asymmetry across different developmental stages. In addition, functional factors such as dental status, occlusal patterns, and habitual masticatory side preference were not assessed and may influence regional bone remodeling. In addition, a normalized positional index was not calculated; therefore, size-independent comparisons between individuals could not be performed. Future studies incorporating larger, population-diverse cohorts and advanced approaches such as dense surface morphometrics, normalization techniques, and finite element modeling may further elucidate the biomechanical mechanisms underlying the asymmetry patterns identified in this study.

CONCLUSION

This study provides a comprehensive three-dimensional morphometric analysis of the zygomatic arch, demonstrating clear patterns of sexual dimorphism and side-related asymmetry, particularly in projection-related parameters. The preferential involvement of the temporal process of the Z, contrasted with the relative stability of the zygomatic process of the TE, highlights the segment-specific nature of zygomatic arch variability. These findings underscore the importance of sex- and side-aware evaluation in surgical planning, forensic assessment, and radiological interpretation of the zygomatic region. A refined understanding of these anatomical characteristics may contribute to improved accuracy and safety in procedures involving the zygomatic arch.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Zonguldak Bülent Ecevit University Non-Interventional Clinical Research Ethics Committee (decision no: 2020/16-14, date: 05.08.2020), and the study protocol complied with the principles of the Declaration of Helsinki.

Informed Consent: This is a retrospective study. Declaration on the Use of Artificial Intelligence.

AI-Assisted Technologies: During the preparation of this manuscript, the authors made limited use of the OpenAI ChatGPT language model to improve linguistic clarity, academic phrasing, and grammatical accuracy of the text. All AI-generated suggestions were critically reviewed and validated by the authors prior to inclusion. The authors take full responsibility for the scientific content, data analysis, interpretation of results, and the final version of the manuscript. The use of artificial intelligence did not influence the study data, analyses, or conclusions.

Footnotes

Authorship Contributions

Concept: K.A., Design: C.M.Ö., N.K., Data Collection or Processing: K.A., A.Z.Y.K., N.K., Analysis or Interpretation: C.M.Ö., A.Z.Y.K., Literature Search: C.M.Ö., N.K., Writing: K.A., A.Z.Y.K.

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ORIGINAL ARTICLE

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GLIM Defined Malnutrition in Community Dwelling Older Adults: Prevalence, Predictors, Functional Impact, and Comparison with MNA and GNRI Introduction

Toplumda Yaşayan Yaşlı Bireylerde Nütrisyon Tarama Araçları Arasındaki Uyum: Erken Tanı ve Önleme Açısından Çıkarımlar

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ABSTRACT

Aim: Malnutrition remains a major global health challenge, particularly among older adults, where it contributes to frailty, sarcopenia, and chronic diseases. The Global Leadership Initiative on Malnutrition (GLIM) provides standardized diagnostic criteria to improve early detection. This study aimed to determine the prevalence of malnutrition among community-dwelling older adults using the GLIM criteria and to compare its diagnostic agreement with Mini Nutritional Assessment (MNA) and Geriatric Nutritional Risk index (GNRI).

Materials and Methods: This cross-sectional study included 251 older adults aged 65 years or older from a university hospital's geriatric outpatient clinic. Nutritional status was assessed using GLIM, MNA, and GNRI. Anthropometric measures, body composition (as determined by bioelectrical impedance analysis), handgrip strength, and laboratory markers were evaluated. Cognitive and functional assessments were also conducted. Concordance among tools was analyzed using kappa statistics.

Results: According to GLIM, 51.2% of participants were malnourished, compared to 42.4% with MNA and 7.1% with GNRI. GLIM identified malnutrition in 12.8% of patients with normal body mass index. Agreement between GLIM and MNA was moderate ($p<0.001$), while agreement between GLIM and GNRI was weak ($p=0.001$). Malnutrition was significantly associated with advanced age, female sex, cognitive impairment, and lower physical performance. GLIM showed greater sensitivity in identifying malnutrition and its clinical correlates.

Conclusion: GLIM criteria are more sensitive in detecting malnutrition compared to MNA and GNRI, particularly in identifying individuals with subtle nutritional deficits. A multidimensional approach integrating GLIM with cognitive, functional, and body composition assessments is essential for early diagnosis and prevention in geriatric populations.

Keywords: GLIM, malnutrition, elderly, nutritional assessment, community-dwelling, geriatric screening

ÖZ

Amaç: Yetersiz beslenme, özellikle yaşlı yetişkinlerde kırılganlık, sarkopeni ve kronik hastalık yükünü artırması nedeniyle küresel çapta önemli bir halk sağlığı sorunu olmaya devam etmektedir. Küresel Malnütrisyon Liderlik Girişimi (GLIM), erken tanıyı iyileştirmek amacıyla standardize edilmiş tanı kriterleri sunmaktadır. Bu çalışma, toplumda yaşayan yaşlı yetişkinlerde GLIM kriterlerine göre yetersiz beslenme yaygınlığını belirlemeyi ve GLIM'in tanısal uyumunu Mini Nutrisyon Değerlendirmesi (MNA) ve Geriatrik Beslenme Risk indeksi (GNRI) ile karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: Bu kesitsel çalışmaya, bir üniversite hastanesinin geriatrik polikliniğine başvuran 65 yaş ve üzeri 251 birey dâhil edilmiştir. Beslenme durumu GLIM, MNA ve GNRI kullanılarak değerlendirilmiştir. Antropometrik ölçümler, vücut kompozisyonu (biyoelektrik impedans analizi),

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el kavrama gücü ve laboratuvar parametreleri kaydedilmiştir. Ek olarak bilişsel ve işlevsel durum değerlendirmeleri yapılmıştır. Değerlendirme araçları arasındaki tanısal uyum kappa istatistikleri ile analiz edilmiştir

Bulgular: GLIM kriterlerine göre katılımcıların %51,2'si malnütrisyonlu bulunmuştur; bu oran MNA'da %42,4, GNRI'de ise %7,1 olarak saptanmıştır. GLIM, normal vücut kitle indeksine sahip bireylerin %12,8'inde malnütrisyonu tespit edebilmiştir. GLIM ile MNA arasındaki uyum orta düzeyde (p<<0,001), GLIM ile GNRI arasındaki uyum ise zayıf bulunmuştur (p=0,001). Malnütrisyon; ileri yaş, kadın cinsiyeti, bilişsel bozukluk ve düşük fiziksel performansla anlamlı şekilde ilişkiliydi. GLIM kriterleri malnütrisyonu ve klinik ilişkilerini tanımlamada daha yüksek duyarlılık göstermiştir.

Sonuç: GLIM kriterleri, özellikle hafif düzeyde beslenme yetersizliği olan bireyleri belirlemede, MNA ve GNRI'ye kıyasla daha duyarlıdır. GLIM'in bilişsel, işlevsel ve vücut kompozisyonu değerlendirmeleriyle bütünleştirilmesi, toplumda yaşayan yaşlı bireylerde erken tanı ve önleme stratejilerinin güçlendirilmesi açısından önem taşımaktadır.

Anahtar Kelimeler: GLIM, yetersiz beslenme, yaşlı yetişkin, beslenme değerlendirmesi, toplumda yaşayan yaşlılar, geriatrik tarama

INTRODUCTION

Malnutrition, driven by factors such as disease, poverty, hunger, conflict, and natural disasters, continues to affect a significant proportion of the global population. Despite advances in agriculture, healthcare, industry, and living standards, nutrition-related disorders remain a persistent global challenge[1] . Among vulnerable populations, older adults are particularly at risk. Nutrition plays a vital role in promoting health, functionality, and quality of life in older adults. Consequently, nutritional status should be a primary focus in the care and management of aging individuals. Malnutrition—including both undernutrition and obesity—contributes to the progression of various chronic conditions such as cancer, cardiovascular disease, and dementia, and is also a major contributor to sarcopenia and frailty[2-4]. It is strongly linked to higher rates of morbidity and mortality, as well as greater healthcare expenditures. Identifying nutritional risk at an early stage and implementing suitable interventions can substantially enhance patient outcomes and lessen the strain on healthcare services[5].

Until recently, a universally endorsed definition or diagnostic standard for malnutrition had not been available. In response to this need, the Global Leadership Initiative on Malnutrition (GLIM) was formed in 2016 to provide a unified diagnostic framework for adults. The GLIM approach integrates phenotypic markers—such as unintentional weight loss, low body mass index (BMI), and diminished muscle mass—with etiologic components, including insufficient food intake, impaired nutrient assimilation, or the presence of inflammation. A diagnosis is made when at least one etiologic and one phenotypic criterion are present, after which the severity is categorized as stage 1 (moderate) or stage 2 (severe) (1).

With increasing life expectancy and the rising proportion of older adults worldwide, aging-related nutritional challenges are emerging as pressing public health issues[6,7]. Age-related declines in muscle strength, mobility, and balance further contribute to dependency on daily living activities[6,8]. In this context, early identification of malnutrition using reliable tools such as GLIM is critical.

This study aims to assess malnutrition prevalence among older adults using the GLIM criteria and to ascertain the correlation between nutritional status and age groups within a population of community-dwelling older adults.

MATERIALS AND METHODS

Study Design and Participants

In this cross-sectional analytical study, 251 community-dwelling older adults aged 65 years and above were retrospectively enrolled from the geriatric outpatient clinic of a university hospital as part of a healthy aging initiative. Initially, the medical records of 757 older adults were screened. However, participants with missing data necessary to apply the full GLIM criteria—such as anthropometric or etiologic indicators—were excluded. Consequently, 251 participants with complete GLIM-relevant data comprised the final sample. Since this was a retrospective analysis, the sample size was not determined by a priori power analysis but was based on data availability from routine clinical records. The study population included both functionally independent older individuals and those with geriatric syndromes, all of whom underwent comprehensive nutritional and functional assessments during routine health evaluations.

Exclusion criteria were: (i) age below 65 years, (ii) inability to obtain essential data required for the GLIM assessment (e.g., anthropometric, etiologic, or functional measures), and (iii) inability to perform handgrip strength testing or undergo body composition analysis via bioelectrical impedance analysis (BIA). In addition, individuals with acute illness (e.g., active infection, delirium, or recent unstable cerebrovascular events), active malignancy (e.g., ongoing oncologic treatment or cancer cachexia), or terminal conditions (e.g., end-stage organ failure with limited life expectancy requiring palliative care) were excluded from the study.

Prior to participation, written informed consent was obtained from all individuals. The study received approval from the Ege University Medical Faculty Hospital Institutional Research Ethics Committee (approval no: 20-5.1T/53, date: 28.05.2020)

and was conducted in conformity with the principles of the Declaration of Helsinki.

Data Collection and Clinical and Nutritional Assessment

Demographic characteristics, comorbidities, clinical and functional data, medication records, and laboratory parameters (hemoglobin, albumin, lymphocytes, platelets) were extracted (Figure 1). Medication use was summarized descriptively according to drug classes. Additional information on cognitive and functional status was recorded using standardized tools, including the Mini-Mental State Examination (MMSE), Katz Activities of Daily Living (ADL), and Lawton Instrumental Activities of Daily Living (IADL) scales. Nutritional parameters were obtained from assessments conducted by trained geriatricians and nurses.

In this study, clinical and nutritional evaluations were retrospectively conducted based on data collected from patients aged 65 years and older who visited the geriatric outpatient clinic. Anthropometric measurements, including BMI, calf circumference (CC), triceps skinfold thickness, and mid-arm circumference, were assessed using standardized protocols. Body composition was measured via BIA (Tanita Body Composition Analyzer), which provided a fat-free mass index, phase angle, body water percentage, visceral fat level, and skeletal muscle mass. Muscle strength was assessed using a handgrip dynamometer (EH101, CAMRY, China), recording the highest value of three attempts from the dominant hand.

Nutritional status was examined using three validated assessment methods: the GLIM framework, the Mini Nutritional Assessment (MNA) and the Geriatric Nutritional Risk index (GNRI). According to the GLIM approach, a diagnosis of malnutrition required at least one phenotypic indicator (such as unintentional weight loss, low BMI, or diminished muscle mass) together with one etiologic factor (including reduced food intake or absorption, or evidence of inflammation).

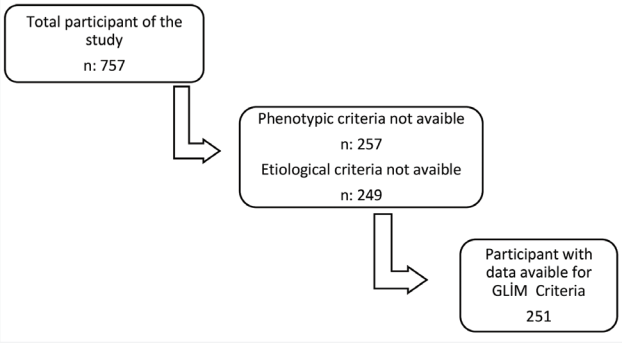

Figure 1. Study Flowchart

GLIM: Global Leadership Initiative on Malnutrition

Muscle mass reduction was identified using CC thresholds (<30 cm for men and <29 cm for women), consistent with criteria commonly applied in sarcopenia evaluation. Data regarding recent weight change and dietary intake were gathered from patient-reported information and medical documentation. Malnutrition severity was categorized as stage 1 (moderate) or stage 2 (severe) based on phenotypic measures. For the etiologic component of the GLIM criteria, reduced food intake or assimilation and inflammation were assessed retrospectively, in accordance with the GLIM consensus report. Reduced food intake or assimilation was defined based on patient self-reports and medical documentation indicating reduced oral intake, prolonged inadequate intake lasting more than two weeks, or the presence of gastrointestinal conditions adversely affecting food intake or absorption.

Inflammation was defined as disease burden–related inflammation and was assumed in patients with at least one documented chronic inflammatory condition (e.g., chronic heart failure, chronic kidney disease, chronic obstructive pulmonary disease, diabetes mellitus, or malignancy). Supportive laboratory markers, including C-reactive protein (CRP) and serum albumin levels, were reviewed as supportive proxy indicators of inflammation, in line with GLIM recommendations[9]. Elevated CRP (≥5 mg/L) and/or hypoalbuminemia (serum albumin <3.5 g/dL) measured at the time of nutritional assessment were considered indicative of systemic inflammation. Although parameters derived from BIA (e.g., lean mass index, skeletal muscle mass, and phase angle) were evaluated, CC was used as the primary indicator of reduced muscle mass for GLIM classification. This approach is consistent with the GLIM consensus, which recognizes anthropometric measurements such as CC as valid and clinically applicable alternatives, particularly in older adults and routine clinical practice. BIA-derived indices were therefore considered complementary measures to support body composition assessment.

The determination of malnutrition and its severity classification followed GLIM recommendations and is detailed in Tables 1 and 2. Laboratory findings included hemoglobin, serum albumin, platelet count and lymphocyte count, which were used to compute the HALP score (hemoglobin × albumin × lymphocytes / platelets). Additional clinical assessments incorporated the Charlson Comorbidity index (CCI), Katz ADL, Lawton IADL, the MMSE, and depressive symptom scores. All data were reviewed by trained geriatric nurses and physicians to ensure consistency and accuracy of GLIM assessments.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics software (version 24; IBM Corp., Armonk, NY, USA). In the context of the study, continuous variables were summarised using the

Table 1. Diagnostic criteria according to GLIM framework

Phenotypic criteria			Etiologic criteria	
Weight loss (%)	**Low body mass index (kg/m²)**	**Reduced muscle mass**	**Reduced food intake or assimilation**	**Inflammation**
>5% body weight loss within the past 6 months, or >10% if beyond 6 months	<20 kg/m² if <70 years, <22 kg/m² if ≥70 years	Reduced by validated body composition measuring techniques	50% of ER>1 week, or any reduction for>2 weeks, or any chronic GI condition that adversely impacts food assimilation or absorption	Acute disease/ injury, for chronic disease-related

Cederholm et al.[1], GI: Gastro-intestinal, ER: Energy requirements, GLIM: Global Leadership Initiative on Malnutrition

Table 2. Phenotypic severity grading of malnutrition based on GLIM

	Phenotypic criteria		
	Weight loss (%)	**Low body mass index (kg/m²)**	**Reduced muscle mass**
Stage 1/moderate malnutrition	5-10% within the past 6 mo, or 10-20% beyond 6 mo	<20 if <70 yr, <22 if >70 yr	Mild to moderate deficit (per validated assessment method see below)
Stage 2/severe malnutrition	>10% within the past 6 mo, or>20% beyond 6 mo	<18.5 if <70 yr, <20 if >70 yr	Severe deficit (per validated assessment method see below)

Cederholm et al.[1], GLIM: Global Leadership Initiative on Malnutrition

mean and standard deviation, while categorical variables were presented as numerical data accompanied by the relevant percentages. The Kolmogorov-Smirnov and Shapiro-Wilk tests were employed to analyse the variable distributions. Non-parametric Kruskal-Wallis H tests were conducted to compare functional (Katz ADL, Lawton IADL) and cognitive (MMSE, Clock Drawing test) performance across nutritional risk groups as defined by GLIM, MNA, and GNRI. Post-hoc pairwise comparisons were performed when appropriate. Subgroup analyses stratified by age (<74 years vs. ≥75 years) were also conducted to evaluate age-related variations in these associations. The agreement between the malnutrition classifications provided by GLIM and MNA was assessed using the McNemar test and cross-tabulation with chi-square analysis. Decision tree modeling via the chi-squared automatic interaction detection (CHAID) algorithm was applied to explore potential predictors of malnutrition based on each nutritional tool and to identify distinct risk profiles. HALP scores were analyzed across nutritional risk groups and relevant clinical variables using non-parametric statistical methods. Variables such as age, sex, educational status, and anthropometric measures were considered as independent predictors. For all statistical tests, a two-tailed p-value below 0.05 was regarded as indicative of statistical significance. Descriptive statistics were reported for MNA (n=243) and GNRI (n=227) scores. The difference in sample size is due to missing biochemical data required for GNRI calculation in 23 participants. As several secondary analyses were exploratory in nature, no formal multiple-comparison correction was applied. All reported p-values are unadjusted and should be interpreted cautiously.

RESULTS

Participants

The participants had a mean age of 76.75±7.3 years, and the sample was predominantly female (63.4%). More than half of the individuals were married (54.5%), and the most common living arrangements were cohabitation with a spouse (51.4%) or with another family member (21.5%), while 21.9% reported living alone (Table 3). The median MNA score was 24.5 interquartile range (IQR: 21.5-27.0) among 243 participants. The median GNRI score was 118.2 (IQR: 110.4-125.6) among 227 individuals. Antihypertensive agents were the most commonly used medications (67.9%), followed by other medications (73.3%) and antidiabetic agents (35.4%). Cardiac medications were used by 28.8% of participants, whereas dementia-related drugs (12.3%) and biological or antineoplastic agents (4.5%) were less frequently prescribed. A small proportion of participants (6.2%) reported no regular medication use.

Ordinal Logistic Regression Analysis: GLIM Stages and Predictors

Ordinal logistic regression was performed to evaluate the effects of sex and age group on malnutrition severity according to GLIM staging (normal, moderate, severe). The overall model demonstrated statistical significance ($\chi^2(2)=13.57$, $p=0.001$), and model fit indices were acceptable (Pearson $p=0.165$; deviance $p=0.207$). Sex and age group were both significant predictors. Specifically, males had higher odds of being in a more severe malnutrition category compared to females [odds ratio (OR)=1.77, 95% confidence interval (CI): 1.07-2.93,

Table 3. Sociodemographic characteristics and body composition parameters of the participants (n=251)

Variable	Category	n (%)/mean ± SD
Age (years)		76.75±7.3
Sex	Female Male	159 (63.4) 92 (36.6)
Body mass index (kg/m²)	Female Male	29.7±6.2 26.8±4.8
Age group	<75 years ≥75 years	112 (44.4) 139 (55.6)
Marital status	Marriage Single Widowed Divorced	137 (54.5) 7 (2.7) 98 (39.0) 9 (3.5)
Living arrangement	Lives with spouse Lives alone Nursing home Lives with other family members Lives with a caregiver	129 (51.4) 55 (21.9) 10 (3.9) 54 (21.5) 3 (1.2)
Educational level	Illiterate Literate Elementary school Middle school High school College/university	28 (11.1) 24 (9.5) 89 (35.6) 21 (8.4) 37 (14.7) 52 (20.7)
Fat-free mass index (kg/m²)	Female Male	18.5±2.3 19.5±3.4
Calf circumference (cm)	Female Male	37.6±5.0 36.54±4.07
Triceps skinfold thickness (cm)	Female Male	30.02±3.9 28.68±3.8
Handgrip strength (kg)	Female Male	17.4±6.3 27.41±8.7

SD: Standard deviation

p=0.025]. Participants aged <75 years had significantly lower odds of severe malnutrition compared to those aged ≥75 (OR=0.50, 95% CI: 0.31-0.82, p=0.006). Interaction effects were not included due to non-significant age × sex interaction in preliminary GLM analyses (Figures 2, 3).

Correlation between Nutritional Status and Functional/Cognitive Outcomes

Both the correlation analyses and the comparisons between groups revealed significant relationships between nutritional status and outcomes related to functional and cognitive performance. Spearman correlation analyses showed that GLIM-defined malnutrition (binary coded) was moderately and

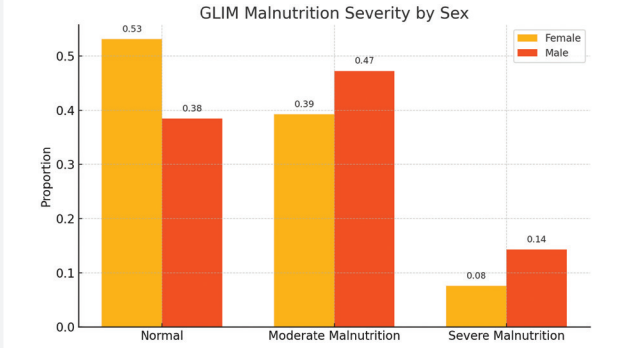

Figure 2. Distribution of GLIM-defined malnutrition severity by sex
GLIM: Global Leadership Initiative on Malnutrition

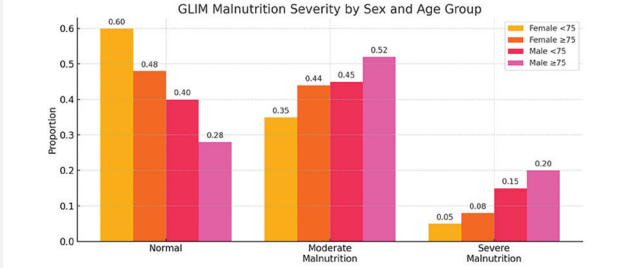

Figure 3. Distribution of GLIM-defined malnutrition severity by sex and age group Malnutrition was more prevalent in males and participants aged ≥75 years, particularly in the moderate and severe categories,
GLIM: Global Leadership Initiative on Malnutrition

negatively associated with MMSE scores (rho=–0.264, p<0.01), Katz ADL (rho=–0.225, p<0.01), and Lawton IADL scores (rho=–0.327, p<0.01). Kruskal-Wallis tests further revealed that functional and cognitive performance decreased progressively across GLIM and MNA nutritional categories (p<0.001 for all). Subgroup analyses indicated that these associations were particularly evident in participants aged ≥75 years, where MMSE and Lawton IADL scores were most affected by malnutrition severity.

Binary Logistic Regression: Predictors of GLIM-defined Malnutrition

Binary logistic regression model was constructed using GLIM-based malnutrition status as the outcome variable (0 =normal nutrition, 1=malnutrition). The model was statistically significant [$\chi^2(20)=55.41$, p<0.001] and achieved an overall classification accuracy of 68.0%. Significant predictors of malnutrition were older age (p<0.001), male sex (p=0.025), lower MMSE scores (p<0.001), lower educational attainment

(p=0.012), being single (p=0.043), and lower BMI (p=0.046). The model demonstrated a sensitivity of 66.4% and a specificity of 69.8% (Figure 4).

Group Comparisons Across GLIM and MNA Categories

CCI, CC, triceps skinfold thickness, and HALP scores (all p<0.05). Phase angle, edema percentage, and visceral fat levels did not significantly differ. Similarly, significant differences between MNA groups were found for CC (p<0.001), triceps skinfold (p<0.001), and HALP score (p=0.016), but not for phase angle, edema, visceral fat or CCI.

Participants with elevated CRP levels had significantly lower HALP scores than those with normal CRP levels (p=0.029).

Across GLIM stages, there were differences in objective physical and metabolic parameters, including disease burden and muscle/fat reserves, while MNA groups showed differences in nutritional risk factors related to appetite and the psychosocial domain (Figures 5, 6).

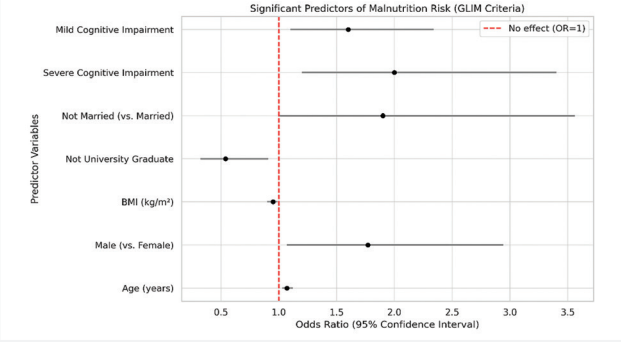

Figure 4. Predictors of GLIM-defined malnutrition
GLIM: Global Leadership Initiative on Malnutrition, BMI: Body mass index

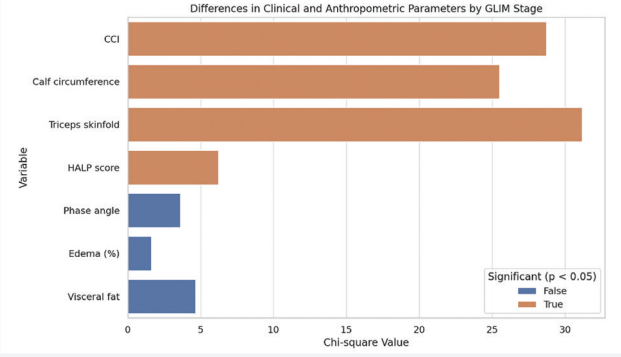

Figure 5. Differences in clinical and anthropometric parameters by GLIM stage
CCI: Charlson Comorbidity index, GLIM: Global Leadership Initiative on Malnutrition

Decision Tree Analyses (CHAID): GLIM, MNA, and GNRI Models

a. GLIM-based Model (Supplementary 1)

The GNRI decision tree identified BMI as the only significant predictor (χ^2=23.620, p<0.001), with a split value of 28.01 kg/m^2. Participants with BMI values above this threshold were predominantly classified as normal or low nutritional risk. However, due to the marked class imbalance in GNRI-defined malnutrition (7.1% at risk), the model failed to adequately identify individuals with mild, moderate, or severe nutritional risk. Consequently, the high overall classification accuracy [93.0%; risk estimate=0.070, standard error (SE)=0.017] primarily reflects prediction of the majority class rather than true discriminatory performance.

b. GNRI-based Model (Supplementary 2)

The GNRI decision tree included only BMI as a predictor (χ^2=23.620, p<0.001). Participants with a BMI>28.01 were classified as "normal or low risk" (100%). However, due to the marked class imbalance in GNRI-defined malnutrition, the model failed to adequately identify individuals at mild, moderate, or severe nutritional risk categories. Consequently, the high overall classification accuracy (93.0%) with a low risk estimate (0.070, SE=0.017) mainly reflects prediction of the majority class rather than true discriminatory performance.

c. MNA-based Model (Supplementary 3)

The CHAID model for MNA classification identified BMI and age group as the main predictors. A BMI>28.20 was associated with a higher probability of normal nutritional status, whereas individuals aged ≥75 years showed an increased likelihood of malnutrition. Although the model correctly classified all individuals with normal nutritional status (100%), its ability to distinguish malnourished or at-risk participants was limited (risk estimate =0.428, SE=0.032), suggesting reduced discriminatory performance across nutritional risk categories.

Comparative Model Performance

Figure 7 presents accuracy and risk estimates across the three decision tree models. The GNRI model showed the highest classification accuracy (93.0%) with the lowest error rate. The MNA and GLIM models demonstrated classification accuracies of 57.2% and 54.6%, respectively.

Concordance Between GLIM and MNA

A McNemar test revealed significant discordance between GLIM and MNA classifications (χ^2=8.862, p=0.003). GLIM identified more individuals as malnourished compared to MNA. Agreement between GLIM and MNA was moderate (Cohen's kappa κ =0.467, p<0.001). GLIM classified 128 individuals

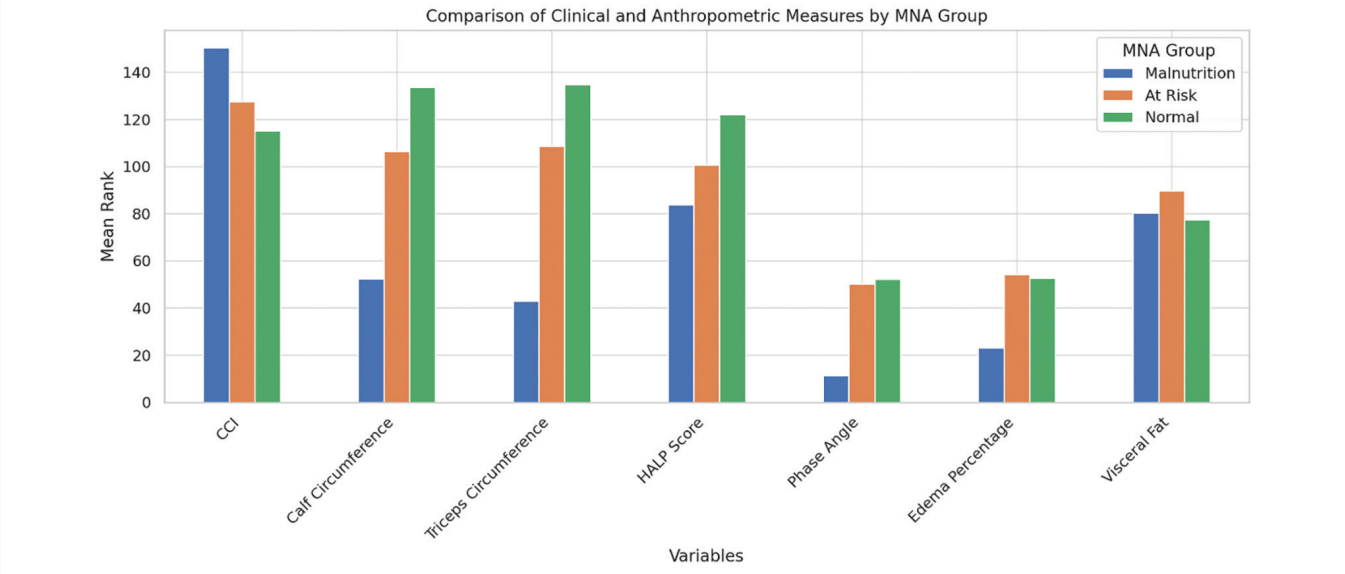

Figure 6. Differences in clinical and anthropometric parameters by MNA stage
MNA: Mini Nutritional Assessment, CCI: Charlson Comorbidity index

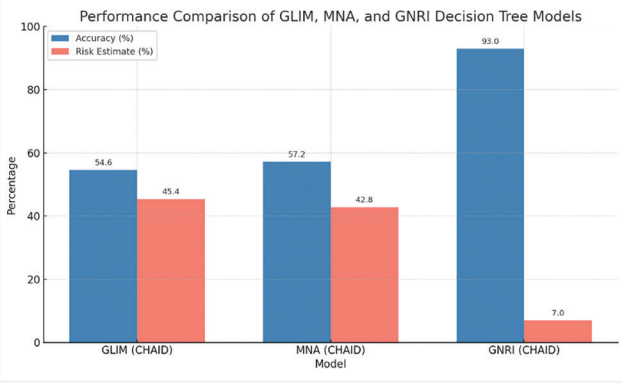

Figure 7. Comparison of accuracy and risk estimates across GLIM, MNA, and GNRI decision tree models
GLIM: Global Leadership Initiative on Malnutrition, MNA: Mini Nutritional Assessment, GNRI: Geriatric Nutritional Risk index, CHAID: Chi-Square Automatic Interaction Detection

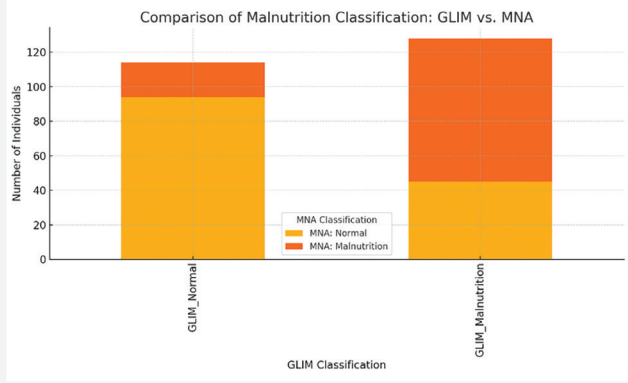

Figure 8. Comparison of malnutrition classification: GLIM and MNA
GLIM: Global Leadership Initiative on Malnutrition, MNA: Mini Nutritional ssessment

as malnourished, whereas MNA classified 103, with 45 cases detected by GLIM but not by MNA. Agreement between GLIM and GNRI varied by cut-off. With a GNRI threshold of 92, agreement was poor and not significant (Cohen's kappa κ =0.022, p=0.234). Using a cut-off of 98 improved statistical significance (Cohen's kappa κ =0.105, p=0.001), but agreement remained weak. GNRI classified 16 individuals as malnourished compared to 122 by GLIM (Figure 8).

Associations with Functional and Cognitive Status

GLIM and MNA classifications were significantly associated with functional and cognitive measures. Katz ADL, Lawton IADL, Clock Drawing test, and MMSE scores decreased progressively with increasing malnutrition severity (p<0.001 for all). In the <75 age group, all MNA-based comparisons were significant except MMSE in the GLIM model. In participants aged ≥75, significant associations were observed in Lawton IADL and

MMSE, particularly with MNA classification. Depressive symptoms were present in 15.9% of participants; however, no statistically significant association was observed between depressive symptom status and nutritional status as classified by either MNA or GLIM ($p>0.05$ for both).

Nutritional and Body Composition Differences by Age Group

Nutritional and body composition parameters were compared across age groups using Mann-Whitney U tests. GNRI scores significantly differed by age group ($p=0.019$), with individuals aged ≥75 years having lower values. Participants aged ≥75 years had significantly lower MNA scores than younger individuals ($p=0.044$). HALP scores did not reach statistical significance across age groups ($p=0.078$). BMI ($p=0.238$) and skeletal muscle index (SMI) ($p=0.593$) likewise showed no significant differences by age group.

Effects of Sex and Age Group on GLIM-based Malnutrition Severity

A two-way ANOVA examined the effects of sex and age group on GLIM-based malnutrition severity. The analysis revealed significant main effects of both sex ($p=0.015$) and age group ($p=0.025$), indicating that malnutrition severity was higher in specific sex and age categories. However, the interaction between sex and age group was not statistically significant ($p=0.437$), indicating that the effect of sex on malnutrition severity did not vary across age groups.

DISCUSSION

Our findings align with previous studies indicating the superior sensitivity of the GLIM criteria in detecting malnutrition among older adults. In our study, 51.2% of community-dwelling older individuals were classified as malnourished by GLIM, a figure consistent with hospital-based estimates reported in Asian populations (16%-78%) but significant given the non-hospitalized nature of our cohort[3]. Notably, 12.8% of individuals categorized as "normal" by BMI were identified as malnourished using GLIM, emphasizing its ability to detect subclinical malnutrition overlooked by traditional anthropometric measures.

Previous studies have demonstrated that GLIM criteria effectively identify malnutrition in geriatric populations[10]. Large nationwide cohort studies have reported a higher proportion of men among individuals with GLIM-defined malnutrition, although sex differences were not consistently significant across populations[11]. In our regression analysis, male sex emerged as an independent predictor of greater malnutrition severity. Furthermore, our findings echo the results of Galindo Martín et al.[12], who reported that GLIM-defined malnutrition was associated with higher mortality and poorer clinical outcomes. In their study, malnourished patients had significantly higher in-hospital mortality and unplanned transfers to critical care, and the odds of adverse outcomes increased progressively with malnutrition severity. Although our study did not assess prognosis, the strong association of malnutrition with cognitive decline and impaired ADL/IADL supports GLIM's multidimensional utility.

According to GLIM, 51.2% of participants were classified as malnourished, compared with 42.4% by MNA and 7.1% by GNRI. Notably, GLIM identified malnutrition in 12.8% of individuals with normal BMI, highlighting its ability to detect cases that may be overlooked by BMI-based assessments. Agreement between GLIM and MNA was moderate, whereas agreement with GNRI was weak. Malnutrition was significantly associated with advanced age, cognitive impairment, and lower physical performance. These findings are consistent with previous research demonstrating the greater sensitivity of GLIM in identifying malnutrition and its clinical correlates in older adults[13].

A study from New Zealand also reported that nutritional risk Mini Nutritional Assessment-Short Form (MNA-SF ≤11) was associated with increasing age, reduced gait speed, and dysphagia risk. Although the prevalence was lower (12%), likely due to the use of MNA-SF, these findings support the importance of incorporating functional parameters into nutritional assessment, consistent with the broader evaluation provided by GLIM[14].

In our study, HALP scores showed significant differences between GLIM and MNA categories but did not differ across age groups; this finding suggests that HALP may be considered a composite marker reflecting nutritional status and disease burden rather than chronological age. Although HALP has been reported to be associated with prognostic outcomes in the literature, the cross-sectional design of our study does not allow for prognostic inferences. Accordingly, and in line with previously reported associations between HALP, muscle mass, and mortality in NHANES data, HALP was interpreted in the present study solely as a composite marker of nutritional status and disease burden[15]. Consistent with population-based analyses demonstrating an inverse association between HALP and CRP levels, our findings showed significantly lower HALP scores in participants with elevated CRP, further supporting the interpretation of HALP as an integrated nutrition–inflammation marker, particularly relevant in older adults[16].

Unlike studies conducted in hospitalized or institutionalized populations, our study highlights the burden of malnutrition among community-dwelling older adults. The prevalence observed in our cohort is comparable to rates reported in inpatient studies, such as those by Hiraike et al.[17] and Ohta et al.[18] (≈46%). These findings indicate that malnutrition is also

common in outpatient settings. Moreover, previous studies have shown that GNRI predicts mortality in hospitalized older adults, emphasizing the clinical importance of early nutritional assessment. Our inclusion of cognitive, functional, and body composition variables allowed a broader evaluation of nutritional risk. Previous studies indicate that the diagnostic performance of GNRI varies by clinical setting; while it may show stronger prognostic value in hospitalized populations, its discriminatory capacity appears limited in community-based settings, supporting its role primarily as a screening rather than a diagnostic tool[19,20].

Although prognostic outcomes such as mortality or hospitalization were not evaluated, the observed associations between malnutrition, age, sex, cognitive status, and physical performance highlight the importance of routine multidimensional nutritional screening. GLIM-based assessment, integrated with functional and cognitive evaluation, may support earlier identification of at-risk older adults in community settings. Future studies should explore the prognostic impact of GLIM-defined malnutrition and the potential benefits of community-based, nurse-led screening and intervention programs[21].

Study Limitations

Our study has several strengths, including its focus on community-dwelling older adults and the use of a comprehensive geriatric assessment incorporating functional, cognitive, anthropometric, and laboratory parameters. The application of the GLIM criteria in a real-world outpatient setting and the demonstration of associations between malnutrition and multidimensional outcomes enhance the clinical relevance of our findings. Nevertheless, certain limitations should be acknowledged. The cross-sectional design precludes causal inference, and the single-center setting may limit generalizability. Missing data in the MNA and GNRI assessments restricted some analyses to complete cases, introducing potential selection bias. In addition, the CHAID model for GNRI showed high overall accuracy driven by class imbalance, limiting its ability to identify individuals at nutritional risk. Finally, due to the exploratory nature of several analyses, no multiple-comparison correction was applied; therefore, findings should be interpreted cautiously and confirmed in future studies.

CONCLUSION

This study highlights the multidimensional nature of malnutrition in older adults and emphasizes the necessity of comprehensive nutritional assessment. The GLIM criteria demonstrated higher sensitivity in detecting malnutrition, while age and sex emerged as significant independent predictors of malnutrition severity. Conventional metrics such as BMI and SMI may overlook subtle nutritional impairments in older populations. Furthermore, the association between malnutrition and both cognitive and functional decline reinforces the need for integrated geriatric evaluations. A multidimensional approach encompassing anthropometric, functional, cognitive, and demographic parameters is essential for accurate and timely diagnosis of malnutrition in the older adults.

Ethics

Ethics Committee Approval: The study received approval from the Ege University Medical Faculty Hospital Institutional Research Ethics Committee (approval no: 20-5.1T/53, date: 28.05.2020) and was conducted in conformity with the principles of the Declaration of Helsinki.

Informed Consent: Prior to participation, written informed consent was obtained from all individuals.

Footnotes

Concept: Z.D., S.Ş., E.T., H.E.A., S.F.A., Design: Z.D., S.Ş., E.T., H.E.A., S.F.A., Data Collection or Processing: Z.D., E.T., Analysis or Interpretation: Z.D., S.Ş., S.F.A., Literature Search: Z.D., E.T., H.E.A., Writing: Z.D., S.Ş., S.F.A.

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

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Supplementary Link: https://d2v96fxpocvxx.cloudfront.net/bb2eeae3-0e60-42a4-acea-81e4a349912c/content-images/e35f8c6a-45e1-49be-a794-76fe4b0b2ba0.pdf

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ORIGINAL ARTICLE

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Serum Lactate Dehydrogenase Dynamics in Acute Ischemic and Hemorrhagic Stroke: A Marker of Prognosis but Not Diagnosis

Akut İskemik ve Hemorajik İnmede Serum Laktat Dehidrogenaz Dinamiği: Tanı Değil, Prognoz Belirteci

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ABSTRACT

Aim: Lactate dehydrogenase (LDH) is a marker of cellular damage, increasingly recognized for its prognostic value in stroke. However, its role in differentiating stroke types and in predicting outcomes remains incompletely defined.

Materials and Methods: In this retrospective, single-center study, 1,299 patients [1,185 acute ischemic stroke (AIS), 114 intracerebral hemorrhages (ICHs)] between 2018 and 2023 were analyzed. Admission and first-week LDH levels were compared across stroke types, etiologies, and outcomes. Functional status was assessed using the 3-month modified Rankin Scale (mRS). Multivariate stepwise linear regression was applied to determine factors independently associated with admission LDH.

Results: Mean admission LDH was 329.3±176.1 U/L in AIS and 342.4±174.9 U/L in ICH (p=0.45). First-week LDH levels were 276.2±148.1 U/L in AIS and 300.1±123 U/L in ICH (p=0.19). In AIS, higher admission LDH levels were associated with unfavorable outcomes (mRS 3-6; p=0.002) and were significantly elevated in total anterior circulation infarcts (total anterior circulation infarction: 354.1±165 U/L) compared to lacunar infarcts (lacunar infarction: 312.1±141 U/L; p=0.077). First-week LDH levels were significantly higher in cardioembolic strokes compared with large-artery atherosclerosis (cholesteryl ester: 302 U/L vs. LAA: 248 U/L; p=0.006). In ICH, higher first-week LDH levels were associated with unfavorable outcomes, particularly in deep hematomas. In multivariate analysis, chronic kidney disease (B=63.1, p=0.017), female sex (B=47.9, p=0.004), and unfavorable outcome (B=58.4, p=0.008) were independently associated with elevated admission LDH.

Conclusion: LDH levels alone do not distinguish between AIS and ICH, but higher admission values and sustained elevation are associated with poorer 3-month functional outcome, especially in ischemic stroke subtypes with larger infarcts or cardioembolic origin, and in deep ICH. LDH may be a marker that contributes to early risk stratification, yet the retrospective single-center design, small hemorrhagic subgroup, and exploratory multiple comparisons mean that these findings should be interpreted with caution and confirmed in prospective studies.

Keywords: Intracerebral hemorrhage, acute ischemic stroke, lactate dehydrogenase, prognosis, modified Rankin Scale

ÖZ

Amaç: Laktat dehidrogenaz (LDH), hücresel hasarın bir belirteci olup, inmede prognostik değeri giderek daha fazla kabul görmektedir. Bununla birlikte, farklı inme tiplerinin ayırt edilmesindeki ve klinik sonuçların öngörülmesindeki rolü henüz tam olarak açıklığa kavuşmamıştır.

Gereç ve Yöntem: Bu retrospektif, tek merkezli çalışmada 2018-2023 yılları arasında takip edilen 1,299 hasta [1,185 akut iskemik inme (Aİİ), 114 intraserebral hemoraji (İSH)] analiz edildi. Başvuru sırasında ve ilk hafta ölçülen LDH düzeyleri inme tipleri, etiyolojileri ve klinik sonuçlar açısından karşılaştırıldı. Fonksiyonel durum, 3. ay modifiye Rankin Ölçeği (mRS) ile değerlendirildi. Başvuru LDH düzeyi ile bağımsız ilişkili faktörleri belirlemek amacıyla çok değişkenli aşamalı doğrusal regresyon analizi kullanıldı.

Bulgular: Ortalama başvuru LDH düzeyi Aİİ grubunda 329,3±176,1 U/L, İSH grubunda ise 342,4±174,9 U/L idi (p=0,45). İlk hafta LDH düzeyleri sırasıyla Aİİ grubunda 276,2±148,1 U/L ve İSH grubunda 300,1±123 U/L olarak bulundu (p=0,19). Aİİ grubunda, yüksek başvuru LDH düzeyleri

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kötü fonksiyonel sonuç (mRS 3-6) ile ilişkiliydi (p=0,002) ve total anterior sirkülasyon infarktı (total anterior dolaşım infarktı: 354,1±165 U/L) olan hastalarda laküner infarkt (laküner infarct: 312,1±141 U/L) olanlara kıyasla daha yüksek saptandı (p=0,077). İlk hafta LDH düzeyleri kardiyoembolik inmelerde büyük arter aterosklerozuna (LAA) bağlı inmelere göre anlamlı derecede daha yüksekti (302 U/L'ye karşı 248 U/L; p=0,006). İSH grubunda ise ilk hafta LDH düzeylerinin yüksek olması, özellikle derin yerleşimli hematomlarda olmak üzere kötü fonksiyonel sonuçlarla ilişkili bulundu. Çok değişkenli analizde kronik böbrek hastalığı (B=63,1, p=0,017), kadın cinsiyet (B=47,9, p=0,004) ve kötü fonksiyonel sonuç (B=58,4, p=0,008), yüksek başvuru LDH düzeyleri ile bağımsız olarak ilişkiliydi.

Sonuç: LDH düzeyleri tek başına Aİİ ile İSH'yi ayırt etmede yeterli değildir. Ancak yüksek başvuru LDH düzeyleri ve ilk haftada devam eden yüksek seyir, özellikle daha geniş infarkt alanına veya kardiyoembolik kökene sahip iskemik inme alt tiplerinde ve derin yerleşimli İSH olgularında, 3. ayda daha kötü fonksiyonel sonuçlarla ilişkilidir. LDH, erken risk sınıflandırmasına katkı sağlayabilecek bir belirteç olabilir. Bununla birlikte, çalışmanın retrospektif ve tek merkezli tasarımı, hemorajik alt grubun küçük olması ve çoklu karşılaştırmaların keşifsel nitelikte yapılmış olması nedeniyle bulgular dikkatle yorumlanmalı ve ileriye dönük çalışmalarla doğrulanmalıdır.

Anahtar Kelimeler: İntraserebral kanama, akut iskemik inme, laktat dehidrogenaz, prognoz, modifiye Rankin ölçeği

INTRODUCTION

Stroke remains a leading cause of mortality and long-term disability worldwide[1]. Biomarkers that facilitate stroke subtype differentiation and prognostic stratification may improve clinical decision-making and patient outcomes. Lactate dehydrogenase (LDH) is a ubiquitous intracellular enzyme involved in glycolysis, catalyzing the conversion of pyruvate to lactate under anaerobic conditions[2,3]. It is released into the circulation following cellular membrane damage and has therefore been considered a potential biomarker of tissue injury. However, LDH is a non-specific marker and may be influenced by a wide range of systemic conditions, which should be taken into account when interpreting its clinical significance. Elevated LDH levels have been associated with poor outcomes in various clinical settings, including malignancies, cardiovascular diseases, sepsis, and hypoxic–ischemic events[4]. In recent years, interest in LDH as a prognostic biomarker in neurological disorders, particularly stroke, has increased[2,4].

In intracerebral hemorrhage (ICH), LDH has been associated with hematoma expansion and unfavorable outcomes, likely reflecting inflammatory processes and microvascular injury mechan isms[5]. Radiological markers, such as computed tomography (CT) angiography spot sign and non-contrast CT blend sign, can help predict hematoma growth; however, these findings may be subject to interobserver variability. In contrast, serum biomarkers such as LDH may provide a more objective and widely accessible approach for early risk stratification. Similarly, although evidence is more limited, LDH has also been associated with adverse outcomes in acute ischemic stroke (AIS)[2,4]. Inflammation, anaerobic metabolism, and cellular necrosis within the ischemic penumbra may contribute to elevated LDH levels in these patients.

Composite biomarkers, such as the LDH-to-albumin ratio (LAR), have emerged as indicators of systemic inflammation, nutritional status, and oxidative stress factors that may influence stroke outcomes[6]. Although an increasing number of studies have evaluated LDH or LAR in ischemic and hemorrhagic stroke, direct comparisons of LDH dynamics across both stroke types within a single cohort remain scarce. Previous studies have reported associations between higher LDH levels or LAR and adverse functional outcomes, mortality, early onset cognitive impairment, and post-stroke depression in both AIS and ICH[4-8].

This study aimed to investigate the association between serum LDH levels and stroke type, severity, localization, and short-term outcomes in patients with acute ischemic or hemorrhagic stroke. The primary objective was to evaluate whether admission and first week LDH levels are associated with third-month functional outcome, assessed by the modified Rankin Scale (mRS), in both AIS and ICH. Given the non-specific nature of LDH and the heterogeneity of stroke pathophysiology, we further aimed to determine whether LDH functions as a complementary biomarker reflecting tissue injury burden rather than a disease-specific diagnostic marker. Secondary exploratory objectives included evaluating the relationship between LDH levels and stroke localization (Bamford classification)[9], etiological subtypes (TOAST classification)[10], vascular risk factors, and laboratory parameters.

MATERIALS AND METHODS

This retrospective, observational study was conducted following approval by the Trakya University Non-Interventional Studies Ethical Committee (approval no: TÜTF-GOBAEK 2024/32, decision no: 13/12, date: 19.08.2024). Written informed consent for the use of clinical and laboratory data was obtained from all patients at the time of hospitalization. Due to the retrospective design, no additional informed consent was required. Previously recorded electronic and written data were analyzed. All procedures were performed in accordance with the Declaration of Helsinki and local ethical regulations.

Study Population

Patients with acute AIS or primary ICH who were hospitalized in the Neurology Service between January 2018 and December 2023 were consecutively enrolled. The diagnosis of AIS was confirmed according to World Health Organization criteria

and neuroimaging findings (brain CT or magnetic resonance imaging). ICH diagnosis was established by non-contrast CT performed within 24 hours of symptom onset.

Inclusion criteria were: age ≥18 years; symptom onset within 72 hours for AIS or within 24 hours for ICH; and availability of baseline clinical and laboratory data. Exclusion criteria included secondary causes of ICH (e.g., cerebral aneurysm, arteriovenous malformations, moyamoya disease, trauma, tumors, or hemorrhagic transformation of infarction), prior major surgery or infection within 90 days, history of malignancy, transient ischemic attacks, and treatment with intravenous thrombolysis or endovascular mechanical thrombectomy. Patients with recent major surgery, active infection, or known malignancy were excluded to minimize potential confounding effects on LDH levels. However, due to the retrospective design, other conditions that may influence LDH levels could not be systematically controlled. Patients requiring primary intensive care unit admission at stroke onset were not included in this neurology ward–based cohort, which should be considered when interpreting the ICH subgroup findings. The flow diagram of patient inclusion and exclusion is shown in Figure 1.

Data Collection and Methods

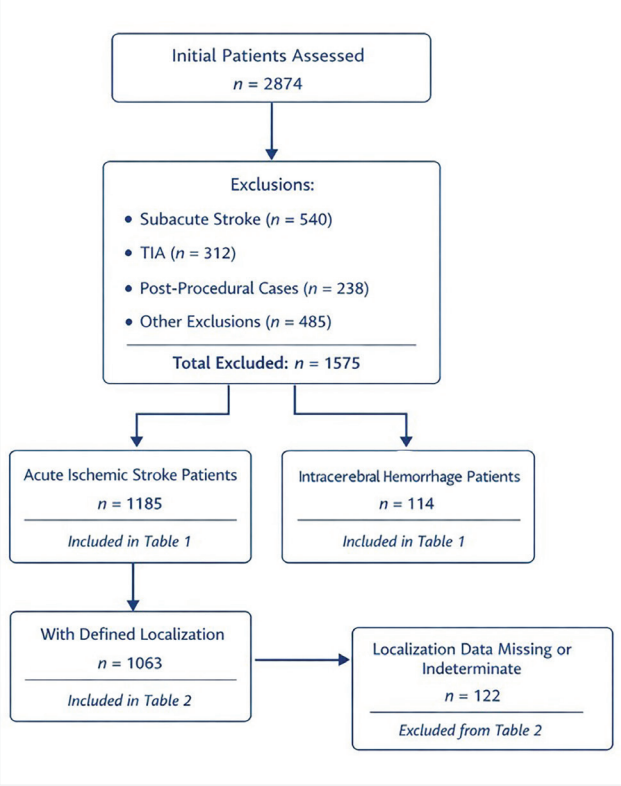

Figure 1. Flow diagram of patient selection and study inclusion

TIA: Transient ischemic attack

Comprehensive clinical data were extracted from inpatient electronic and written records by trained personnel. Demographic variables included age and sex (as recorded in official identity records). Medical history variables included hypertension (HT), diabetes mellitus (DM), dyslipidemia, heart failure (HF), coronary artery disease (CAD), chronic kidney disease (CKD), prior stroke, smoking status, alcohol use, atrial fibrillation (AF), and use of antiplatelet or anticoagulant agents, in accordance with previous literature[4,6]. Length of stay (LOS) was defined as the number of hospitalization days.

After classification into ischemic and hemorrhagic stroke groups, further sub-classification was performed. Hemorrhagic stroke was categorized as lobar or deep, and anatomical localization (basal ganglia, thalamus, cerebellum, brainstem, lobar) was recorded. AIS was classified according to localization using the Bamford classification [total anterior circulation infarction (TACI), partial anterior circulation infarction (PACI), posterior circulation infarction (POCI), lacunar infarction (LACI)] and according to etiology using the TOAST classification [cardioembolism (CE), large artery atherosclerosis (LAA), small vessel disease (SVD), unknown etiology (UE), and other determined etiology (OE)][9,10].

Stroke severity was assessed using the National Institutes of Health Stroke scale (NIHSS), and functional outcome was assessed using the third-month mRS[11,12]. NIHSS scores were obtained from hospitalization records, and mRS scores from third-month outpatient follow-up visits. An mRS score of 0-2 was defined as favorable outcome and ≥3 as unfavorable outcomes.

Laboratory parameters obtained from blood samples within 24 hours of admission included total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, urea, creatinine, LDH, white blood cell count (WBC), red blood cell count (RBC), hemoglobin (HGB), platelet count (PLT), mean corpuscular volume (MCV), hematocrit (HCT), neutrophil and lymphocyte percentages, neutrophil-to-lymphocyte ratio (NLR), and erythrocyte sedimentation rate. Follow-up LDH levels at one week were also recorded.

Demographic and laboratory variables were compared between ischemic and hemorrhagic stroke groups. In AIS, admission and first week LDH levels were analyzed according to localization, etiology, vascular risk factors, and outcomes. In ICH, LDH levels were evaluated according to localization, vascular risk factors, and outcome. The change in LDH between admission and the first week was categorized as an increase or decrease and analyzed in relation to outcomes. Correlations between admission LDH and clinical variables (stroke severity, NLR, LOS, and outcome) were assessed. A multivariable regression model was used to explore factors associated with admission LDH; in this model, admission LDH was treated as the dependent

variable, and clinical variables, including outcome measures, were included as independent variables to assess associations rather than imply causality.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation or median (interquartile range), and categorical variables as frequencies (percentages). Group comparisons were conducted using the χ^2 test or Fisher's exact test for categorical variables, and Student's t-test, one-way ANOVA, Mann-Whitney U test, or Kruskal-Wallis test for continuous variables, as appropriate. Pearson or Spearman correlation analyses were used depending on data distribution.

A multivariable stepwise linear regression model was used to explore factors associated with admission LDH. Variables included age, sex, AIS localization, AIS etiology, admission NIHSS, third-month mRS, NLR, HGB, urea, CKD, MCV, LOS, and anticoagulant use. Results are presented as unstandardized regression coefficients (B) with corresponding p-values. The multivariable model was constructed using a stepwise selection procedure; however, given the known limitations of stepwise methods, including potential instability and sensitivity to sample variation, the findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory.

Given the number of subgroup and correlation analyses performed, no formal adjustment for multiple comparisons was applied, and these analyses should be interpreted cautiously. All analyses were performed under the supervision of a biostatistician. A two-sided p-value <0.05 was considered statistically significant for primary analyses.

RESULTS

A total of 2.874 stroke hospitalizations between January 2018 and December 2023 were screened. After excluding subacute strokes, transient ischemic attacks, and patients hospitalized for interventional or diagnostic procedures, 1.185 patients with AIS and 114 patients with ICH were included in the final analysis.

Baseline demographic and clinical characteristics are summarized in Table 1. Vascular risk factors, including HT, DM, dyslipidemia, smoking, AF, and HF, were more frequent in AIS than in ICH. LOS was longer in patients with ICH (p=0.002). No significant differences were observed in admission or first week LDH levels between AIS and ICH groups. No clinically useful LDH cut-off value was identified for differentiating between stroke types.

In AIS, admission LDH levels showed a non-significant trend across localization subtypes (p=0.077), with higher values observed in TACI compared with other subtypes. Female sex and CKD were associated with higher LDH levels across all localization groups. Higher admission LDH levels were also associated with unfavorable outcomes. Admission LDH levels according to localization and their associations with vascular risk factors are presented in Table 2. For localization-based analyses, only patients with clearly defined ischemic stroke subtypes according to the Bamford classification were included; patients with missing or indeterminate localization data were excluded, which accounts for the difference in sample size (1132 vs. 1185) compared to Table 1.

First week LDH levels differed across ischemic stroke localizations, with higher levels in TACI (p=0.016): TACI LDH 321 (130-950), PACI 270 (110-977), POCI 280 (114-1914), LACI 262 (22-1914). Higher first week LDH levels were observed in women in all AIS localization groups (TACI 331 vs. 312; PACI 288 vs. 255; POCI 311 vs. 257; LACI 271 vs. 257; p=0.004). Other risk factors for higher first week LDH were CKD in PACI (288 vs. 269), POCI (357 vs. 268), LACI (322 vs. 257) (p=0.014); anticoagulant use in POCI (433 vs. 270) (p=0.038); and AF in all groups (TACI 356 vs. 300; PACI 296 vs. 262; POCI 345 vs. 269; LACI 295 vs. 254; p<0.001). Higher first week LDH levels were associated with unfavorable outcome in PACI (264 vs. 254), POCI (474 vs. 248), and LACI (303 vs. 261) (p=0.015). Given the number of subgroup comparisons, these associations should be interpreted as exploratory.

There was no significant association between admission LDH levels and etiological classification of AIS [cardioembolic (CE) 340, LAA 337, SVD 335, UE 319, Other 244; p=0.14]. Females had higher LDH levels than males in all etiological groups (CE 354 vs. 325; LAA 344 vs. 354; SVD 337 vs. 334; UE 348 vs. 301; Other 339 vs. 262; p=0.005). CKD was associated with higher LDH in CE (351 vs. 339), LAA (367 vs. 336), and UE (400 vs. 310) etiological groups (p=0.004). Anticoagulant use in CE (356 vs. 336) and UE (484 vs. 309) was associated with higher LDH levels (p=0.001). Unfavorable outcome was associated with higher admission LDH in LAA (387 vs. 302) and UE (428 vs. 301) AIS groups (p=0.002).

First week LDH levels differed significantly according to AIS etiology (p=0.006): CE 302, LAA 248, SVD 257, UE 279, Other 237. Higher first week LDH levels were associated with female sex in CE (325 vs. 278), LAA (258 vs. 243), UE (298 vs. 268), and Other (249 vs. 213) (p=0.004); CKD in CE (355 vs. 297), SVD (471 vs. 238), and UE (303 vs. 277) (p=0.014); anticoagulant use in UE (376 vs. 274) (p=0.038); and AF in CE (316 vs. 276) and UE (319 vs. 276) (p<0.001). Higher first week LDH levels were associated with unfavorable outcome in CE (349 vs. 293) and UE (358 vs. 257) groups (p=0.015).

The distribution of admission and first week LDH among AIS types is shown in Figure 2. Overall, LDH levels decreased

Table 1. Demographic data between ischemic and hemorrhagic strokes

	Ischemic stroke n=1185	Hemorrhagic stroke n=114	p
Female	505 (42.6%)	48 (42.1%)	0.91
Age	68.64 (SD 13.3)	68.24 (SD 13)	0.75
Hypertension	801 (67.6%)	60 (52.6%)	0.002
Diabetes mellitus	481 (40.6%)	34 (29.8%)	0.032
Dyslipidemia	333 (28.1%)	18 (15.8%)	0.007
CAD	279 (23.5%)	21 (18.4%)	0.24
Stroke history	49 (4.1%)	5 (4.4%)	0.8
CKD	117 (9.9%)	12 (10.5%)	0.82
HF	112 (10.3%)	4 (3.5%)	0.019
Smoking	279 (23.5%)	16 (14%)	0.019
Alcohol	112 (9.5%)	8 (7%)	0.49
Anti-aggregant	372 (31.4%)	26 (22.8%)	0.07
Anti-coagulant	112 (10.3%)	10 (8.8%)	0.74
AF	283 (23.9%)	9 (7.9%)	<0.001
LOS	11.57 (SD 8.2)	14.22 (SD 8.5)	0.002
Admission NIHSS	4.3 (SD 4.3)	4.8 (SD 4)	0.48
24-hour NIHSS	3.6 (SD 4.1)	4.2 (SD 4.1)	0.43
7-day NIHSS	3.1 (SD 3.7)	3.7 (SD 3.9)	0.41
Third-month mRS	1.05 (SD 1.5)	1.88 (SD 2.3)	0.037
WBC	9.4 (SD 3.3)	9.9 (SD 3.7)	0.12
RBC	4.55 (SD 0.6)	4.58 (SD 0.5)	0.57
PLT	256.8 (SD 95)	249 (SD 83)	0.41
Hemoglobin	13.2 (SD 1.9)	13.1 (SD 1.8)	0.62
MCV	86.6 (SD 7.1)	86.2 (SD 5.58)	0.53
HCT	39.5 (SD 5.4)	39.2 (SD 5.1)	0.53
NLR	4.76 (SD 6.2)	5.67 (SD 5.5)	0.13
Urea	43.2 (SD 19.8)	39.9 (SD 19.8)	0.08
Creatinine	0.99 (SD 0.7)	0.94 (SD 0.5)	0.45
Admission LDH	329.3 (SD 176.1)	342.4 (SD 174.9)	0.45
First week LDH	276.2 (SD 148.1)	300.1 (SD 123)	0.19
Total-C	189.2 (SD 50.2)	184.6 (SD 46.8)	0.4
LDL-C	125.4 (SD 39.4)	119.8 (SD 35.7)	0.19
HDL-C	40.5 (SD 10.8)	43.8 (SD 12.3)	0.005
TG	148.2 (SD 94.2)	124 (SD 67.3)	0.019

Values are presented as mean ± standard deviation or n (%). Units: WBC and PLT ($\times 10^3/\mu L$), RBC ($\times 10^6/\mu L$), hemoglobin (g/dL), urea (mg/dL), creatinine (mg/dL), LDH (U/L), total cholesterol (mg/dL), LDL-C (mg/dL), HDL-C (mg/dL), triglycerides (mg/dL). CAD: Coronary artery disease, CKD: Chronic kidney disease, HF: Heart failure, AF: Atrial fibrillation, LOS: Length of stay in days, NIHSS: National Institutes of Health Stroke scale, mRS: modified Rankin Scale, NLR: Neutrophil-to-lymphocyte ratio, SD: Standard deviation, WBC: White blood cell, RBC: Red blood cell, PLT: Platelet, MCV: Mean corpuscular volume, HCT: Hematocrit, LDH: Lactate dehydrogenase, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, TG: Triglycerides, p-values were calculated using the χ^2 test or Fisher's exact test for categorical variables and Student's t-test or ANOVA for continuous variables

by the first week in most AIS subtypes. The magnitude of change did not significantly differ by localization [TACI mean ± standard deviation (SD) LDH difference –35±202, PACI –77 ± 201, POCI –41±189, LACI –47±176; p=0.108], but differed across etiological subtypes (CE –33±204, LAA –103±231, SVD –69±146, UE –45±164, OE +6±113; p=0.003), with smaller reductions observed in cardioembolic stroke. An increase in LDH was associated with unfavorable outcome, particularly in TACI and POCI subtypes.

In hemorrhagic stroke, admission LDH levels did not differ significantly according to anatomical localization (basal

Table 2. Admission LDH levels according to AIS localization and vascular risk factors

		TACI n=130 LDH mean (SD)	PACI n=474 LDH mean (SD)	POCI n=226 LDH mean (SD)	LACI n=302 LDH mean (SD)	Total n=1132 LDH mean (SD)	p
Sex	Female	362 (153)	348 (174)	354 (313)	327 (165)	346 (199)	0.005
	Male	345 (171)	327 (177)	303 (120)	301 (139)	316 (155)	
HT	Yes	344 (151)	329 (149)	316 (127)	305 (142)	322 (143)	0.061
	No	379 (189)	354 (221)	332 (327)	323 (164)	343 (230)	
DM	Yes	344 (132)	329 (152)	304 (120)	317 (165)	323 (148)	0.33
	No	361 (182)	342 (190)	333 (256)	308 (139)	333 (193)	
Dyslipidemia	Yes	374 (163)	323 (130)	325 (134)	305 (132)	324 (136)	0.538
	No	347 (162)	342 (190)	319 (235)	314 (100)	331 (189)	
CAD	Yes	377 (162)	344 (237)	282 (100)	318 (155)	331 (190)	0.829
	No	345 (162)	335 (152)	330 (228)	309 (148)	328 (171)	
Prior stroke	Yes	449 (158)	326 (152)	330 (177)	284 (103)	328 (152)	0.985
	No	351 (162)	337 (177)	321 (212)	313 (151)	329 (177)	
HF	Yes	370 (150)	363 (156)	278 (114)	376 (208)	354 (165)	0.11
	No	151 (164)	333 (177)	325 (217)	305 (141)	326 (177)	
CKD	Yes	417 (190)	361 (152)	414 (482)	331 (169)	375 (284)	0.004
	No	347 (158)	334 (178)	307 (124)	310 (150)	324 (159)	
Alcohol	Yes	393 (230)	320 (185)	310 (154)	326 (130)	328 (169)	0.976
	No	350 (154)	338 (175)	322 (216)	310 (152)	329 (176)	
Smoking	Yes	341 (168)	358 (282)	301 (109)	301 (131)	326 (201)	0.731
	No	356 (161)	331 (134)	328 (234)	312 (150)	330 (167)	
Outcome	Favorable	326 (207)	314 (150)	314 (133)	302 (150)	310 (147)	0.002
	Unfavorable	385 (180)	353 (137)	515 (712)	250 (50)	379 (309)	
TOAST	CE	322 (143)	352 (285)	320 (129)	340 (172)	340 (169)	0.143
	LAA	368 (178)	355 (230)	318 (144)	290 (132)	337 (192)	
	SVD	-	328 (140)	317 (87)	348 (206)	335 (164)	
	Un-known	374 (164)	317 (127)	325 (274)	300 (125)	319 (174)	
	Other	-	278 (77)	243 (118)	224 (79)	244 (80)	

Values are presented as mean (standard deviation). LDH is expressed in U/L. TACI: Total anterior circulation infarction, PACI: Partial anterior circulation infarction, POCI: Posterior circulation infarction, LACI: Lacunar infarction, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, CKD: Chronic kidney disease, HF: Heart failure, AIS: Acute ischemic stroke, CE: Cardioembolic, LAA: Large-artery atherosclerosis, SVD: Small-vessel disease, TACI: Total anterior circulation infarction, SD: Standard deviation, LDH: Lactate dehydrogenase, p-values were calculated using one-way ANOVA. Some subgroups show wide SD due to small sample sizes and outlier values. Given the number of subgroup comparisons, these analyses should be interpreted as exploratory

ganglia, thalamus, cerebellum, brainstem, or lobar) (p=0.18). Similarly, first week LDH levels were not significantly different across localization groups (p=0.094). When categorized as deep vs. lobar hemorrhage, LDH levels were comparable both at admission (344±190 vs. 339±107; p=0.89) and at first week (291±130 vs. 318±108; p=0.38).

Admission LDH levels were not associated with outcome in either deep or lobar hematomas (p=0.36). However, at first week, elevated LDH levels were significantly associated with unfavorable outcome in deep hematomas (560 vs. 290; p=0.014), largely driven by high LDH levels in basal ganglia hemorrhages. Smoking was associated with higher admission LDH in deep compared with lobar hematomas (619 vs. 250; p=0.004). No other consistent associations between vascular risk factors and LDH levels were observed in the ICH subgroup.

Analyses of LDH change between admission and first week showed that an increase in LDH was more frequently related to unfavorable outcome in hemorrhagic stroke than in AIS (p=0.012). An increase in LDH was more frequently associated with HT in ischemic strokes than in hemorrhagic ones (p=0.02). No other vascular risk factors were consistently related to LDH difference between AIS and ICH. In AIS, both etiologic and localization classifications showed predominantly decreased LDH at first week (68.8% decrease vs. 31.2% increase), with

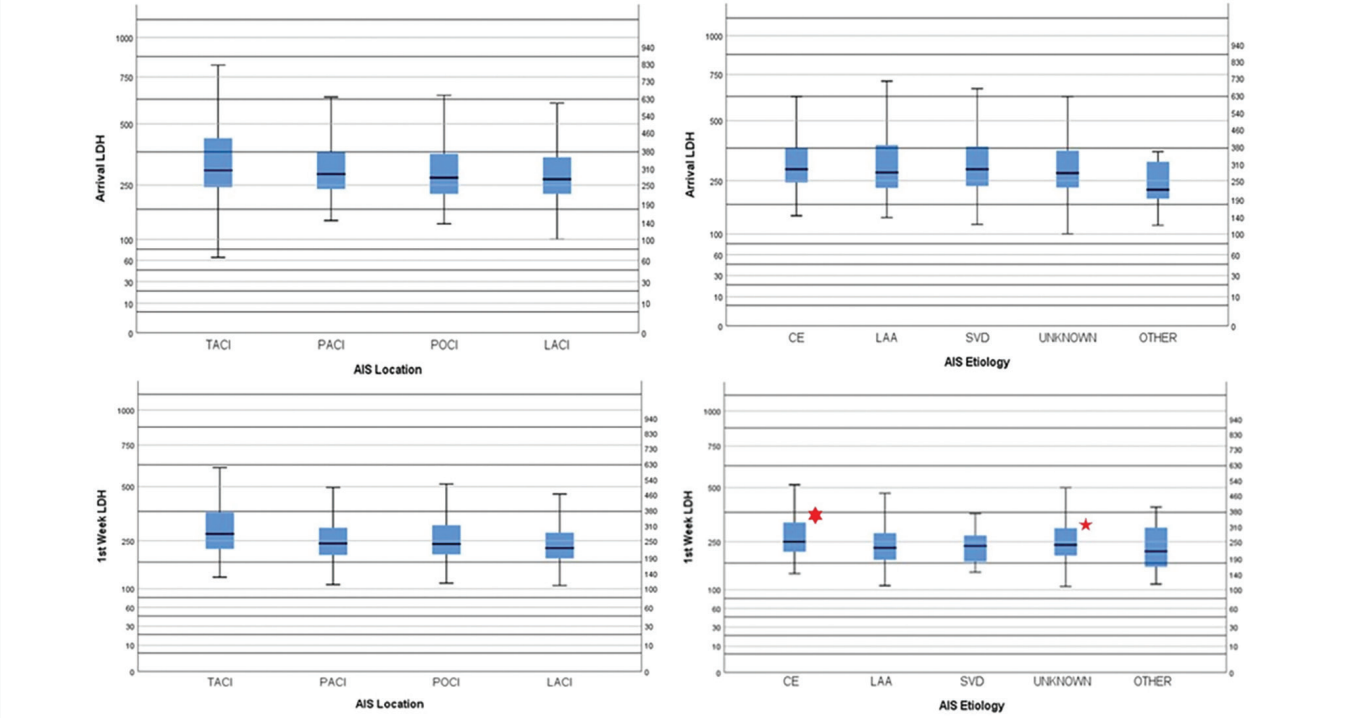

Figure 2. Admission and first week LDH levels among AIS types

*LDH was presented as U/L. Arrival LDH: admission LDH. Boxes represent interquartile ranges, horizontal lines indicate medians, and whiskers represent minimum and maximum values. *Persistent elevation of LDH at first week was observed particularly in TACI and in cardioembolic and undetermined etiology subgroups, AIS: Acute ischemic stroke, LDH: Lactate dehydrogenase, TACI: Total anterior circulation infarction, PACI: Partial anterior circulation infarction, POCI: Posterior circulation infarction, LACI: Lacunar infarction, CE: Cardioembolic, LAA: Large-artery atherosclerosis, SVD: Small-vessel disease*

a more pronounced but still non-significant difference for etiologic classification (p=0.059 vs. 0.095). CE and UE etiologies showed more LDH increases than LAA, SVD, and OE. TACI and POCI showed more LDH increases than PACI and LACI. CE and UE showed more LDH increases than LAA in the presence of smoking (p=0.04) and dyslipidemia (p=0.004). LDH increase was associated with unfavorable outcome particularly in TACI and POCI (p=0.003). In hemorrhagic strokes, female lobar hematomas more often showed LDH increases than deep hematomas (p=0.043). Although non-significant (p=0.071), female BG and thalamic hematomas also tended to show greater LDH increases than other localizations. No other risk factors were clearly associated with LDH difference in hemorrhagic strokes.

Correlation analyses were performed using Pearson correlation (r) for normally distributed variables and Spearman rank correlation (rho) for non-normally distributed or ordinal variables. Statistically significant but numerically weak associations were observed between LDH levels and several clinical and laboratory parameters. Admission LDH was associated at the p<0.05 level with admission NIHSS (r=0.061), first week NIHSS (r=0.077), third-month mRS (rho=0.110), HGB (rho=0.071), RBC (rho=0.072), AIS etiology (rho = 0.076), CKD (rho=–0.065), and AF (rho=–0.060), and at the p<0.01 level with WBC (r=0.097), MCV (r=0.096), NLR (r=0.092), urea (r=0.092), LOS (r=0.110), outcome (rho=0.121), sex (rho=0.090), AIS localization (rho=–0.119), and anticoagulant treatment (rho=–0.091). First week LDH was associated at the p<0.05 level with age (r=0.079), urea (r=0.081), MCV (r=0.076), alcohol consumption (rho=0.075), and anticoagulant use (rho=–0.073), and at the p<0.01 level with admission NIHSS (r=0.113), first week NIHSS (r=0.118), third-month mRS (rho=0.163), WBC (r=0.128), NLR (r=0.183), LOS (r=0.112), AIS localization (rho=–0.136), AF (rho=–0.129), sex (rho=0.100), and outcome (rho=0.167). These correlation coefficients (absolute values generally ≤0.18) indicate small effect sizes despite statistical significance, reflecting the large sample size and underscoring that the clinical impact of these associations is modest.

In multivariable regression analysis, CKD, female sex, unfavorable outcome, and higher MCV were independently associated with higher admission LDH levels (Table 3). Among these, CKD and unfavorable outcome showed the strongest associations. Age demonstrated a borderline negative association (p=0.051). However, the overall explanatory value

Table 3. Multivariable linear regression analysis for admission LDH

Factor	B	p
Length of stay	0.040	0.385
Admission NIHSS	0.002	0.976
Third-month mRS	0.022	0.808
AIS localization	0.031	0.496
AIS etiology	0.016	0.718
Age	-0.088	0.051
NLR	0.048	0.280
Hemoglobin	0.038	0.439
Urea	0.021	0.691
Unfavorable outcome	58.401	0.008
CKD	63.071	0.017
Female	47.914	0.004
MCV	2.842	0.012

Values represent unstandardized regression coefficients (B) with corresponding p-values. The model was constructed using a stepwise selection procedure. The overall model fit was low (adjusted R^2=0.048), AIS: Acute ischemic stroke, NLR: Neutrophil-to-lymphocyte ratio, LDH: Lactate dehydrogenase, CKD: Chronic kidney disease, MCV: Mean corpuscular volume, NIHSS: National Institutes of Health Stroke scale, mRS: modified Rankin Scale

of the model was limited (adjusted R^2=0.048), indicating that LDH levels are influenced by multiple interacting factors rather than a single dominant predictor. The model was constructed using a stepwise selection procedure given the exploratory nature of the analysis.

DISCUSSION

In this large, single-center retrospective cohort, we evaluated the relationship between serum LDH dynamics and clinical characteristics in patients with AIS and ICH. Although mean LDH levels were slightly higher in hemorrhagic strokes, LDH alone was not sufficient to reliably differentiate between ischemic and hemorrhagic stroke. In ischemic stroke, LDH levels appeared to be related to lesion volume as inferred from localization, with higher levels in TACI compared with PACI and POCI. In both ischemic and hemorrhagic stroke, female patients and those with CKD had higher LDH levels. Elevated admission LDH was modestly associated with unfavorable outcome in AIS, particularly in LAA. In cardioembolic strokes, higher first week LDH, rather than admission levels, was associated with AF and unfavorable outcome. In ICH, higher first week LDH was associated with unfavorable outcome in deep hematomas. Multivariable regression indicated that CKD, higher MCV, female sex, and unfavorable outcome were independently associated with admission LDH. However, the overall explanatory value of the model was limited (adjusted R^2=0.048), indicating that these variables account for only a small proportion of LDH variability. Importantly, most correlations were numerically weak, reflecting small effect sizes; therefore, these findings should be interpreted as modest associations rather than strong predictors. These results support the view that LDH reflects a global injury response rather than a disease-specific or high-precision prognostic marker.

To our knowledge, no studies have simultaneously compared LDH across both ischemic and hemorrhagic stroke within a single cohort. Prior work has linked LDH to hematoma expansion and prognosis in ICH and to etiology, prognosis, and response to revascularization therapy in AIS[2,4-6,13]. In our study, admission LDH tended to be higher in hemorrhagic than ischemic stroke; however, substantial overlap and wide distributions in both groups precluded identification of a clinically reliable cut-off. Therefore, LDH alone cannot be used to distinguish stroke type in the absence of imaging, further emphasizing its non-specific nature as a biomarker. Current stroke guidelines recommend different management strategies in acute stroke, including different blood pressure targets for ischemic and hemorrhagic stroke[14,15]. Serum LDH levels may provide supportive information regarding the extent of tissue injury; however, LDH should not be considered a substitute for neuroimaging or a determinant of acute management decisions. In resource-limited settings, markedly elevated LDH may reflect more severe brain injury; however, its clinical utility remains supportive rather than directive. Future studies may further explore whether LDH can complement imaging and clinical parameters in assessing overall injury burden.

In line with the concept that LDH reflects cellular damage, we excluded ischemic stroke patients treated with thrombolysis or thrombectomy, as these procedures may cause additional cellular breakdown and influence LDH levels while also modifying outcomes through reperfusion of the ischemic penumbra. By focusing on patients who did not receive reperfusion therapy, we aimed to better characterize the independent association between LDH and outcome in AIS. Previous studies have reported that elevated pre-thrombolysis LDH is associated with poor third-month outcomes and a higher risk of symptomatic ICH in patients treated with rt-PA, while other studies have demonstrated associations between LDH or LAR and mortality, poor functional outcome, post-stroke depression, or early cognitive impairment even in non-reperfused AIS cohorts[6,7,13,16,17]. Our findings support a similar association between LDH and outcome in patients who did not receive thrombolysis. Because LDH is related to the extent of tissue injury, additional damage such as hemorrhagic transformation may increase LDH levels and worsen prognosis. Although hemorrhagic transformation was not specifically evaluated in this study, higher first week LDH showed a stronger association with third-month mRS than admission LDH, suggesting that persistent or increasing LDH may reflect ongoing tissue injury. However, given the retrospective design, this interpretation should be considered exploratory.

Most prior studies examining LDH and prognosis in ischemic stroke have used the TOAST classification. Consistent with our findings, higher admission LDH has been associated with poorer outcomes in LAA and in broader AIS or TIA cohorts[2,4,13,16,17]. These studies often included a higher proportion of male patients, and sex-specific differences in LDH were not explored. In our cohort, LDH levels were significantly higher in women with both AIS and ICH. This may reflect hormonal, genetic, or behavioral factors; however, the underlying mechanisms remain unclear, and causality cannot be inferred from this observational study. Further studies evaluating sex-specific determinants of LDH, including estrogen levels and LDH isoenzyme patterns, are warranted. As expected, higher LDH levels were also observed in patients with CKD, consistent with previous studies, and LDH correlated with urea levels[4]. Impaired clearance of nephrotoxic or inflammatory molecules may contribute to increased tissue injury and LDH release in this context. Associations between LDH and hematologic parameters (MCV, HCT, HGB) and inflammatory markers (NLR) may similarly reflect the interplay among inflammatory burden, nutritional status, and comorbid conditions. These findings should be considered hypothesis-generating and require confirmation in targeted studies.

Given the half-life of LDH, a decline in serum levels would be expected if cellular breakdown ceases. We observed that persistently elevated LDH beyond the first week was associated with cardioembolic stroke, particularly in patients with AF, and with anticoagulant use. One possible explanation is ongoing thrombus-related processes; however, we did not systematically assess intracardiac thrombi or anticoagulation adequacy, and the observed correlations were modest. Therefore, this interpretation should be considered exploratory and interpreted with caution. In cryptogenic stroke, persistent LDH elevation at first week may support further evaluation for cardioembolic sources, such as prolonged cardiac monitoring for paroxysmal AF. Our finding of higher LDH levels in TACI and in patients with higher NIHSS scores is consistent with previous reports linking LDH to lesion volume and stroke severity, supporting the concept that LDH reflects the overall burden of tissue injury[13].

When outcome was assessed using the third-month mRS, higher admission LDH levels were associated with scores of 3-6, indicating an unfavorable prognosis. Consistent with previous studies, our findings support an association between elevated LDH and poorer clinical outcomes in ischemic stroke, particularly in LAA at admission and in cardioembolic stroke at first week[2,4,13,16,17]. We also observed that increases in LDH from admission to the first week were associated with unfavorable outcomes, with a more pronounced relationship in hemorrhagic stroke than in AIS. However, because LDH change was analyzed dichotomously (increase vs. decrease), the magnitude of change could not be assessed, which may have reduced the sensitivity of this analysis. Clinically, an unexpected rise or failure of LDH to decline during the first week after stroke onset may reflect ongoing tissue injury and a higher risk of poor outcome. However, given the retrospective design, small ICH sample size, and lack of adjustment for multiple comparisons, LDH dynamics should be considered supportive rather than a stand-alone prognostic tool. LDH levels were also associated with LOS, although this relationship was modest. Beyond mortality and disability, previous studies have linked elevated LDH to post-stroke depression and early cognitive decline after AIS, suggesting that LDH may reflect broader aspects of brain injury and systemic response[7,18].

For hemorrhagic stroke, we observed that elevated LDH levels were associated with longer LOS and, in line with previous studies, with unfavorable prognosis at third-month mRS. Prior reports have demonstrated associations between admission LDH and hematoma volume as well as short-term mortality, and have identified LDH ≥220 U/L as a predictor of early hematoma expansion and poor outcome in ICH[5,19,20]. In our study, LDH levels tended to be higher in deep hematomas than in lobar ones, consistent with previous reports, although we did not observe statistically significant differences according to localization[19]. Elevated first week LDH was more strongly associated with poor outcome in deep hematomas. The lack of statistical significance in some comparisons may reflect the relatively small number of ICH cases and the exclusion of patients requiring intensive care, and should therefore be interpreted cautiously given the limited statistical power. We were also unable to define a robust prognostic cut-off for LDH, reinforcing its limited clinical applicability as a stand-alone marker. Similar to previous studies, our ICH cohort was restricted to spontaneous ICH; however, elevated LDH has also been associated with adverse outcomes and mortality in aneurysmal subarachnoid hemorrhage[5,19,20]. Additional studies have shown that LDH predicts early hematoma expansion and poor outcome in ICH and is associated with poor neurological outcome and mortality after aneurysmal subarachnoid hemorrhage, further supporting its role as a marker of brain injury severity[5,21-23].

Our multiple regression analysis showed that CKD, female sex, unfavorable outcome, and higher MCV were independently associated with admission LDH in acute stroke patients. Although statistically significant, the coefficients indicate modest associations and a limited explanatory contribution of the model. Given that the model was constructed using a stepwise selection procedure, which is known to be sensitive to sample variability and may yield unstable variable selection, these findings should be interpreted with caution and considered hypothesis-generating rather than confirmatory. Future studies examining LDH as an outcome biomarker should adjust for renal function and sex and consider hematologic

parameters to more accurately evaluate LDH's independent contribution.

Study Limitations

This study has several limitations. First, it is a retrospective, single-center analysis, which may limit generalizability and introduce residual confounding despite multivariable adjustment. Second, the hemorrhagic stroke subgroup (n=114) was relatively small, providing limited power for detailed localization and subgroup analyses. Third, our cohort includes only patients admitted to the neurology ward; those with very severe strokes requiring primary intensive care admission were not captured, particularly in the ICH group, likely biasing the sample toward less severe hemorrhages. Fourth, we performed multiple subgroup and correlation analyses without formal adjustment for multiple testing; therefore, p-values from these exploratory analyses should be interpreted cautiously, and statistically significant findings with small effect sizes should not be viewed as definitive. In addition, the multivariable model was constructed using a stepwise selection procedure, which may be sensitive to sample variability and yield unstable variable selection. Fifth, LDH change was analyzed dichotomously (increase vs. decrease), which limited the ability to assess the magnitude of change and may have reduced analytical sensitivity. Finally, we did not systematically assess all conditions that may elevate LDH levels, such as medications, comorbid diseases, hemorrhagic transformation of AIS, intracardiac thrombus burden, or detailed measures of anticoagulation, which could have provided additional mechanistic insight.

Among the strengths of our study are the large AIS sample (>1,000 patients), uniform laboratory measurements from a single center, and evaluation of both admission and first week LDH, allowing us to characterize dynamic changes rather than relying on a single time point. The inclusion of both ischemic and hemorrhagic strokes within the same cohort provides a broader perspective on LDH in acute cerebrovascular disease and confirms, in a real-world setting, the modest but consistent association between higher LDH and poorer outcomes.

CONCLUSION

In conclusion, LDH levels alone cannot differentiate between ischemic and hemorrhagic stroke. Elevated admission LDH is associated with poorer prognosis in both AIS and ICH, and persistent elevation during the first week is particularly linked to cardioembolic ischemic stroke and unfavorable outcomes in deep ICH. Given the modest effect sizes, retrospective design, and exploratory nature of the analyses, LDH should be considered a complementary biomarker reflecting overall tissue injury rather than a stand-alone diagnostic or prognostic tool. Future prospective, multicenter studies with predefined statistical approaches are needed to validate the prognostic role of LDH dynamics and to determine whether integrating LDH with established clinical and imaging parameters can improve risk stratification in acute stroke.

Ethics

Ethics Committee Approval: This retrospective, observational study was conducted following approval by the Trakya University Non-Interventional Studies Ethical Committee (approval no: TÜTF-GOBAEK 2024/32, decision no: 13/12, date: 19.08.2024).

Informed Consent: Due to the retrospective design, no additional informed consent was required. Previously recorded electronic and written data were analyzed.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K., Concept: S.K., S.Ko, Design: S.K., S.Ko, Data Collection or Processing: S.K., S.Ko, Analysis or Interpretation: S.K., S.Ko, Literature Search: S.K., S.Ko, Writing: S.K.

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

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ORIGINAL ARTICLE

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The Effect of Using Surgical Safety Checklists on Team Communication: Systematic Review and Meta-analysis Study

Güvenli Cerrahi Kontrol Listelerinin Kullanımının Ekip İletişimi Üzerine Etkisi: Sistematik Derleme ve Meta-analiz Çalışması

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ABSTRACT

Aim: The aim of the study is to determine the effect of the use of safe surgery checklists on team communication using the meta-analysis method.

Materials and Methods: The study utilised Google Scholar, Medline, PubMed, the National Thesis Centre, ScienceDirect, and the Tekirdağ Namık Kemal University Library catalogue and databases. Research studies published between 2009 and 2023 in Turkish or English, including postgraduate theses, national or international peer-reviewed journals, and national books, were included in the study. The following keywords were used to search for studies: "safe surgery", "safe surgery checklist", "checklist", "team communication" in English and Turkish. According to the latest search conducted on 10 March 2023, a total of 172 research results were found. A meta-analysis was performed on 5 studies that met our research criteria.

Results: As a result of the meta-analysis of the five included articles, the studies were found to have a homogeneous structure. The five studies included in the meta-analysis, which evaluated the effect of using safe surgery checklists on team communication, were research articles published between 2011 and 2020. The mean effect size, expressed as the odds ratio, was positive (+1.806). The odds ratio for the effect of safe surgery checklists on team communication was 1.806 (95% confidence interval: 1.357-2.402; $p<0.001$), indicating a statistically significant effect.

Conclusion: It was found that surgical teams using safe surgery checklists could have 1.8 times more effective team communication compared to those not using them.

Keywords: Safe surgery, safe surgery checklist, checklist, surgical team communication, meta-analysis

ÖZ

Amaç: Çalışmanın amacı güvenli cerrahi kontrol listelerinin kullanımının ekip iletişimine etkisini meta-analiz yöntemi ile belirlemektir.

Gereç ve Yöntemler: Çalışmada Google Scholar, Medline, PubMed, Ulusal Tez Merkezi, ScienceDirect, Tekirdağ Namık Kemal Üniversitesi Kütüphanesi katalog ve veri tabanlarından yararlanıldı. Çalışmaya 2009-2023 yılları arasında Türkçe veya İngilizce dillerinde yayımlanmış, lisansüstü tezlerde, ulusal ya da uluslararası hakemli dergilerde ve ulusal kitaplarda yayın olmuş bilimsel makale niteliği taşıyan araştırmalar dahil edildi. Araştırmalar taranırken İngilizce "safe surgery", "safe surgery checklist", "checklist", "team communication" ve türkçe "güvenli cerrahi", "güvenli cerrahi kontrol listesi", "kontrol listesi", "ekip iletişimi" kelimeleri kullanıldı. 10 Mart 2023 tarihli yapılan son taramaya göre toplamda 172 araştırma sonucuna ulaşıldı. Araştırma kriterlerimize uyan 5 çalışma ile meta analiz gerçekleştirildi.

Bulgular: Analize dahil edilen 5 makalenin meta-analizi ile yapılan inceleme sonucunda araştırmaların homojen bir yapıda olduğu belirlendi. Meta-analize dahil edilen, güvenli cerrahi kontrol listelerinin kullanımının ekip iletişimine etkisinin değerlendirilen 5 çalışma 2011 ile 2020 arasında yayımlanmış araştırma makaleleridir. Çalışmada ortalama etki büyüklüğü değeri (olasılıklar oranı) (+1,806) pozitif bulundu. Güvenli cerrahi kontrol listelerinin ekip iletişimi üzerindeki etki büyüklüğünün 1,806 (95% güven aralığı: 1,357-2,402; p=0,000) olan Odds oranı, istatistiksel olarak anlamlı olduğunu gösterdi.

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Sonuç: Güvenli cerrahi kontrol listelerini kullanan cerrahi ekiplerde, kullanmayanlara göre ekip iletişiminin 1,8 kat daha fazla etkili olabileceği saptandı.

Anahtar Kelimeler: Güvenli cerrahi, güvenli cerrahi kontrol listesi, kontrol listesi, cerrahi ekip iletişimi, meta-analiz

INTRODUCTION

According to World Health Organization (WHO) data, 234 million surgical procedures are performed worldwide each year. Approximately 7 million patients are affected by complications related to surgical procedures each year. The WHO states that half of the complications arising from surgical procedures are preventable. The WHO has been put forward the "Safe Surgery Saves Lives" Project in 2008. The project aims to reduce the number of surgical deaths worldwide[1-3].

The checklist is a simple and useful tool designed to ensure that surgical teams act in a timely, consistent, and effective manner before, during, and after surgery. This tool aims to improve the performance of surgical teams to provide greater benefits to patients. Operating rooms are stressful environments where time is of the essence and complex procedures are performed. It is crucial that all members of the surgical team working in this complex environment coordinate their efforts. Safe surgery checklists are an important tool for ensuring this coordination, improving team communication, and preventing situations that may threaten patient safety. At this point, it is important to emphasize the team communication and awareness of the surgical team regarding the safe surgery checklist[4,5]. Surgical team communication is vital due to the complexity and risks of surgical procedures. Research shows that team communication directly affects surgical outcomes[6]. Transparent and effective communication among team members contributes to each individual clearly understanding their roles and responsibilities. This helps surgical operations to be coordinated more effectively and reduces the risk of errors. Furthermore, internal team communication is necessary for dealing with unexpected situations and making immediate decisions[7].

In this context, the study was conducted to determine the effect of the use of safe surgery checklists on team communication using the meta-analysis method.

MATERIALS AND METHOD

This study was analysed using meta-analysis methods, and a comprehensive and systematic literature review approach was adopted. Due to the use of a literature review format, no ethical committee approval was required for the study, as it did not involve any direct intervention, effect, or experiment on animals or humans.

Protocol and Registration

The study protocol is registered with PROSPERO (registration number: CRD42024518217). The study was reviewed in accordance with the PRISMA guideline for systematic reviews and meta-analyses.

Search Strategy

The study utilised Google Scholar, Medline, PubMed, the National Thesis Centre, ScienceDirect, and the Tekirdağ Namık Kemal University Library Catalogue and databases. The study included postgraduate theses published in English or Turkish between 2009 and 2023, articles published in national or international peer-reviewed journals, and studies related to the subject included in national books. The following keywords were used to search for studies: "safe surgery", "safe surgery checklist", "checklist", "team communication" in English and Turkish. According to the latest search conducted on 10 March 2023, a total of 172 research results were found. The total sample size of the studies examined in the meta-analysis is 1,507, with sample sizes ranging from 96 to 747. The average sample size was calculated as 301. A meta-analysis was performed with 5 studies that met our research criteria. The study included 1 study published in 2011, 1 study published in 2012, 1 study published in 2016, and 2 studies published in 2020.

Inclusion and Exclusion Criteria

Full-text studies published in English and Turkish between 2009 and 2023, employing quantitative research methodology and examining the effect of safe surgery checklists on team communication, were included.

Qualitative studies and reviews that did not contain quantitative data, as well as studies for which the statistical data required for meta-analysis could not be obtained, were excluded.

Study Selection

A total of 172 studies examining the impact of the use of Safe Surgery Checklists on team communication were identified. After removing duplicates (32), 58 studies for which full texts were not accessible, 56 studies lacking quantitative data on team communication, and 21 studies published in languages other than English and Turkish were evaluated by two independent reviewers according to the inclusion and exclusion criteria. The study was conducted with 5 research articles (Figure 1).

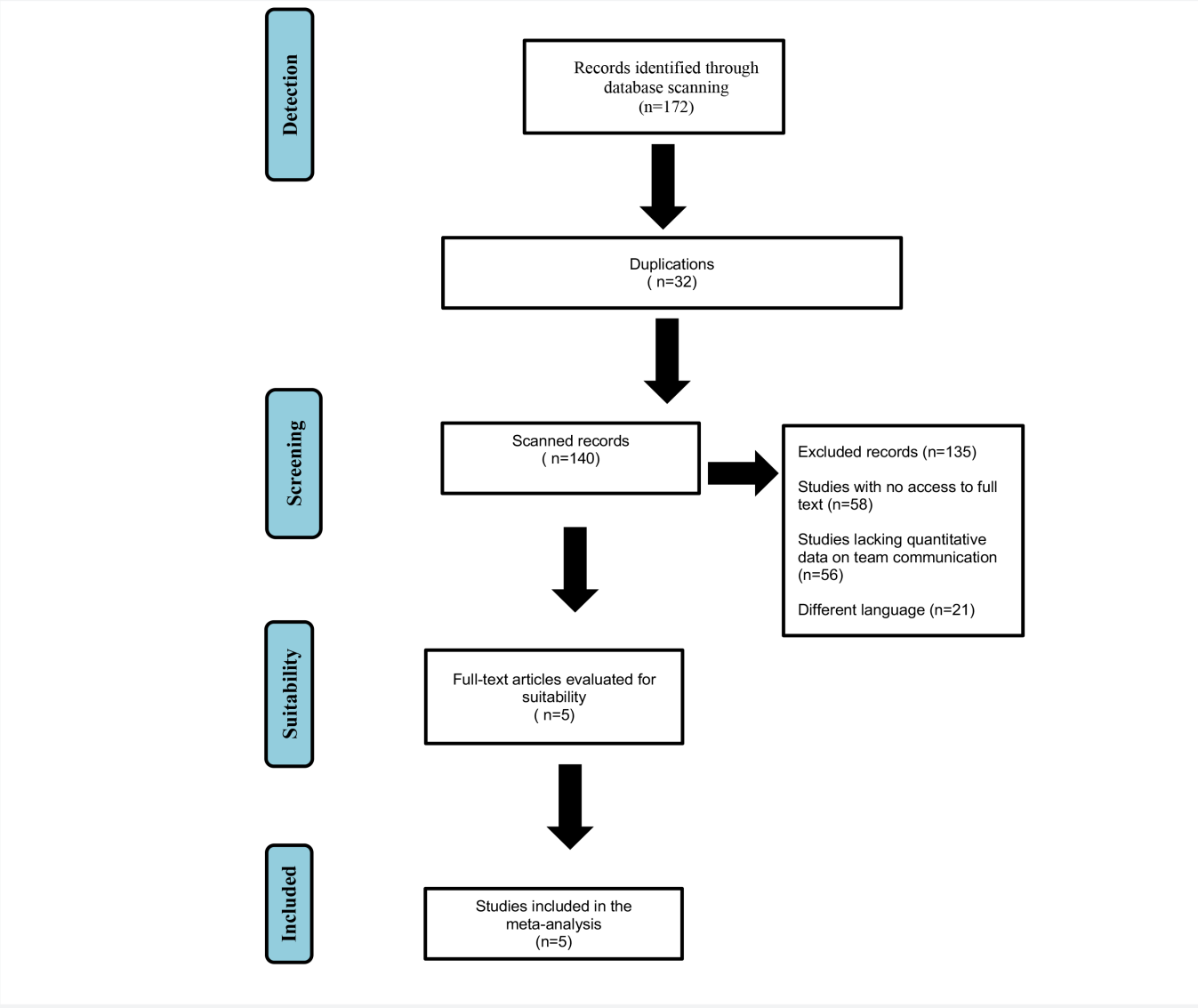

Figure 1. Flowchart of the meta-analysis

Methodological Quality Assessment

Following the review of the articles, the Joanna Briggs Institute MAStARI Critical Appraisal Tool was used for five publications adapted into Turkish by Nahcivan and Seçginli[8] for Descriptive/Case Series studies. This tool contains a total of 9 items. During the review of each study, the fulfilment of each of the 9 features found in these forms was evaluated in detail. Where the relevant feature was fulfilled, 1 point was awarded, and where it was not fulfilled, 0 points were awarded. All articles belonging to the subgroups included in the study were reviewed independently by two researchers, and articles scoring 6 or higher in the quality assessment were considered high quality. Inter-coder agreement was found to be 81% based on the quality assessment scores, indicating a very good level of agreement between coders.

Statistical Analysis

The licensed software "Comprehensive Meta Analysis Academic/Non-profit Pricing (version 3)" was used for data analysis. Data from all articles meeting the inclusion criteria and selected for inclusion in the study were entered into this software, and the heterogeneity of the articles was assessed. In the heterogeneity test, the random effects model was used for group analyses with $p<0.05$, while the fixed effects model was used for group analyses with $p>0.05$. The effect sizes, study weights, 95% confidence intervals (CIs), and overall effect size of all studies

were calculated. For analyses performed on binary data, the "risk ratio and odds ratio" values were used as the basis for evaluating the overall effect size. Cohen's d coefficient was used to compare means and calculate the overall effect size. A statistical significance threshold of $p<0.05$ was accepted for evaluating the overall effect. The kappa statistic was used in the SPSS programme to assess inter-rater reliability.

RESULTS

Each of the five studies included in the meta-analysis, which evaluated the effect of using safe surgery checklists on team communication, is a research article and has been published in peer-reviewed journals. The total sample size of the studies examined in the meta-analysis is 1.507, with sample sizes ranging from 96 to 747. The average sample size is 301. Three of the studies included in the research are descriptive, and two are retrospective research articles. The studies were published between 2011 and 2020.

Following the review of the articles, the Joanna Briggs Institute MAStARI Critical Appraisal Tool was used for the Descriptive/Case Series studies adapted into Turkish by Nahcivan and Seçginli[8] for the remaining five publications. All articles belonging to the subgroups included in the study were independently reviewed by two researchers, and articles scoring 6 or higher in the quality assessment were considered high quality. Inter-coder agreement was found to be 81% based on the quality assessment scores. The Kappa value was used to determine the degree of agreement. The Kappa value (0.81) indicated a very good level of agreement between coders (Table 1).

To assess potential publication bias, a funnel plot, Rosenthal's Safe N method, and Orwin's Safe N method were prepared. However, as the meta-analysis included only five studies, statistical evaluation of publication bias is limited. Therefore, publication bias could not be formally assessed, although a funnel plot was constructed for visual inspection (Figure 2).

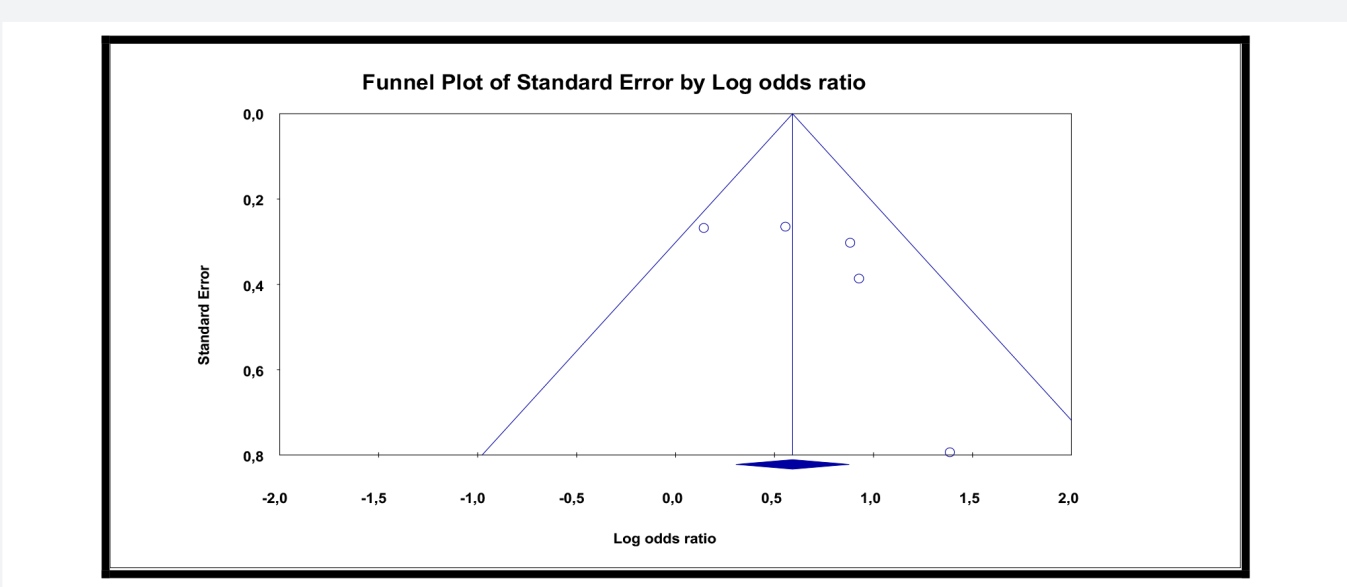

Figure 2. Funnel plot of five studies using the meta-analysis method to determine the effect of using safe surgery checklists on team communication

Table 1. Evaluation details of all studies subjected to quality assessment (n=5)

Score												Total score
No	Author name-date	Type	S1*	S2*	S3*	S4*	S5*	S6*	S7*	S8*	S9*	
1	Cabral[10]	Descriptive Semi-experimental	1/1	1/1	1/1	1/0	1/1	1/1	1/1	1/1	0/1	9/9
2	Govindappagari[16]	Retrospective	1/1	0/0	1/1	1/0	1/1	1/1	1/1	1/1	0/0	8/8
3	Helmiö[17]	Descriptive	1/1	0/0	1/1	1/1	1/1	1/1	1/1	1/1	1/1	8/8
4	Mohammed[18]	Retrospective	0/1	0/0	1/1	1/1	1/1	1/0	1/1	1/1	1/0	7/7
5	Solsky[19]	Descriptive	0/1	1/0	1/1	1/1	1/1	1/1	1/1	1/1	1/1	8/8

*S1…S9: S1-S9 represent the items of the Joanna Briggs Institute MAStARI Critical Appraisal Tool. Each item (S) assesses a specific aspect of methodological quality, such as randomization, blinding, completeness of outcome data, or appropriate statistical analysis. S1 corresponds to the first criterion, S2 to the second, and so on

When the Begg-Mazumdar and Egger tests were evaluated for the skewness indicators of the funnel plot, Kendall's tau value was found to be 0.300 and the p-value was 0.462 for the Begg-Mazumdar test. The analyses revealed no skewness. Rosenthal's fail-safe number data also supported the findings in the funnel plot (Table 2).

Table 2. Graphical table showing publication bias in studies

Begg and Mazumdar rank collections	
Kendall's statistics (P-Q)	4,00000
Kendall's tau without continuity correction	
Tau	0,40000
z-value for tau	0,97980
P-value (1-tail)	0,16359
P-value (2-tail)	0,32719
Kendall's tau with continuity correction	
Tau	0,30000
z-value for tau	0,73485
P-value (1-tail)	0,23122
P-value (2-tail)	0,46243
Classic fail-safe N	
Z-value for observed studies	4,33289
P-value for observed studies	0,00001
Alpha	0,05000
Tails	2,00000
Z for alpha	1,95996
Number of observed studies	5,00000
Number of missing studies that would you bring p-value to> alpha	200,000
Orwins fail-safe N	
Odds ratio in observed studies	1,80568
Creterion for a "trivial" odds ratio	1,00000
Mean odds ratio in missing studies	1,00000
Criterion must fall between other values	

A heterogeneity test was applied to determine the effect of the use of safe surgery checklists on team communication in the articles included in the study. The p-value obtained from the heterogeneity test was greater than 0.05 (p=0.241>0.05) and the Q-value (0.548) was found to be less than the value corresponding to the degree of freedom [(df=4 for χ^2 (0.95)=0.711)]. These results indicate that the studies examined in the meta-analysis have a homogeneous structure. The Z-test calculations performed for statistical significance yielded a Z value of 3.493. The I2 statistic was calculated as 27.014%, indicating homogeneity. The effect size distribution was assessed according to the fixed-effects model (p>0.05) (Table 3).

Figure 3 shows the meta-analysis results of five studies included in the research examining the effect of using safe surgery checklists on team communication, presented as a forest plot. The mean effect size (odds ratio) was found to be (+1.806). According to this result, the effect size of the use of safe surgery checklists on team communication (G.A; 1.357-2.402; p= 0.000) was found to be statistically significant, as it exceeded the odds ratio value of +1. It was determined that surgical teams using safe surgery checklists were 1.8 times more likely to have better team communication than those not using them (95% CI).

DISCUSSION

In this systematic review and meta-analysis, data from five studies with a sample size of 1.507, in which safe surgical checklists were used, were evaluated, and the effects of using safe surgical checklists on team communication were discussed. Operating theatres are fast-paced, stressful work environments where multidisciplinary staff work, complex tasks are performed, and real-time information from patients, colleagues, and monitors must be responded to[9]. Effective surgical team communication is vital for establishing a reliable safety culture in operating theatres[10]. The use of the WHO safe surgery checklist is an established practice worldwide and contributes to patient safety and collaborative teamwork. It is also used as a standard tool for team communication during

Table 3. Results of the heterogeneity test for the effect of using safe surgical checklists on team communication

Effect size and 95% interval				
Model	**Number studies**	**Point estimate**	**Lower estimate**	**Upper limit**
Fixed	5	1.805	1.357	2.401
Random	5	1.857	1.312	2.628
Test of null (2-tail)				
Model	**Z-value**	**P-value**		
Fixed	3.493	0.001		
Random	7.258	0.000		
Heterogenity				
Model	**Q-value**	**Df (Q)**	**P-value**	**I-squared**
Fixed	0.548	4	0.241	27.014

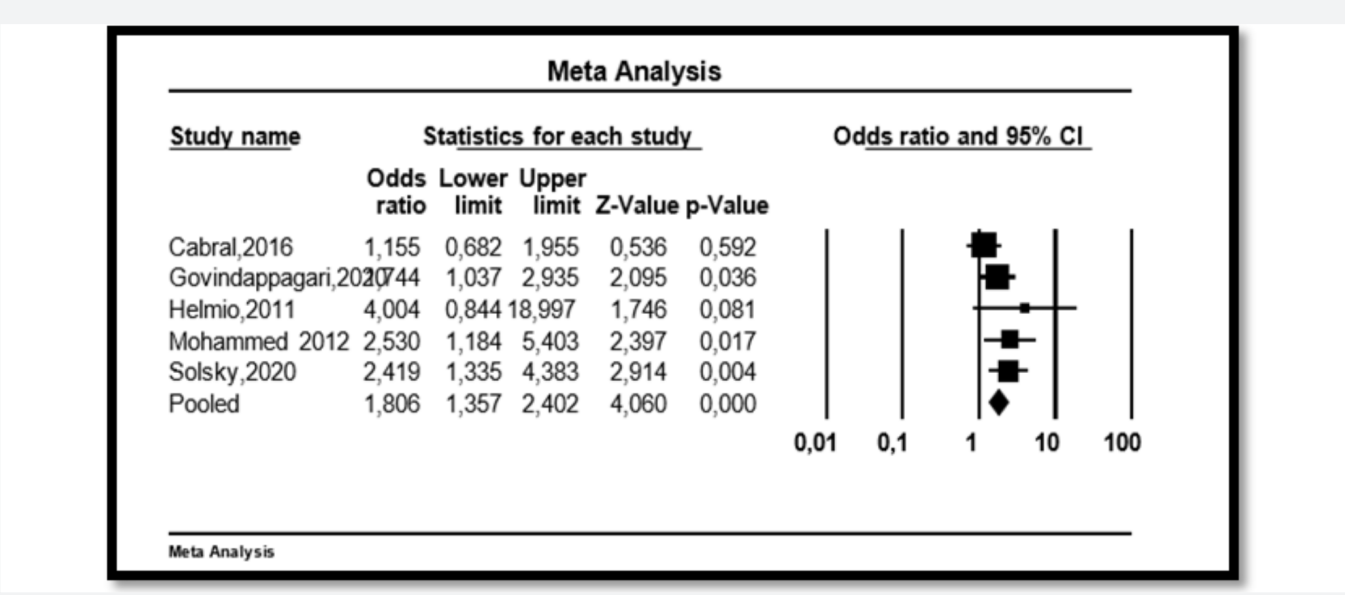

Figure 3. Forest plot of the effect of using surgical safety checklists on team communication

CI: Confidence interval

surgical procedures to encourage communication and reduce hierarchy. Challenges in communication and collaboration can arise within surgical teams; a hierarchical environment, team members not knowing each other, different communication patterns, and conflicting views on teamwork are some of the issues mentioned[11]. Cabral et al.[10] attempted to implement a programme for the use of a safe surgery checklist in their study, conducting the study with a pre-test and post-test. They found that 30% of the 114 surgical team members used the safe surgical checklist, that communication had the highest internal consistency, and that nurses' perception of communication increased the most from the pre-test to the post-test.

Another study evaluating whether the use of safe surgical checklists improves communication in the operating theatre investigated the benefits of preoperative briefings in cardiac surgery. It found that the number of miscommunication events in the briefing group was reduced by 50 per cent compared to the group that did not use the briefing tool[12,13].

A proven communication tool, safe surgical checklists incorporate a standardised surgical checklist to minimise human error. Communication of the checklist has been shown to reduce mortality rates by improving teamwork, the safety environment and surgical outcomes[1].

The WHO reports that surgical safety checklists significantly reduce morbidity, mortality and complication rates[1,14]. It is estimated that more than half of the complications occurring in hospital settings are related to surgical procedures. Therefore, safety in operating theatres is a major concern[13]. The surgical process is a complex procedure encompassing preoperative, intraoperative, and postoperative phases. Care is provided to the patient through multidisciplinary collaboration at every stage of the surgical process. In this multidisciplinary collaboration, team communication is paramount during transitions between surgical procedures[15]. Communication gaps are considered one of the main causes of preventable adverse outcomes in obstetrics. A study investigating whether the use of an obstetric safe surgery checklist, based on the WHO safe surgery checklist for caesarean sections, could improve communication found that the implementation of the safe surgery checklist did improve communication[16]. The use of surgical safety checklists in ear, nose, and throat (ENT) and head and neck surgery procedures has been found to positively contribute to the surgical workflow in ENT and head and neck surgery and to improve the sharing of patient-related medical information among team members[17]. A study examining the effect of the safe surgery checklist (WHO checklist) on perioperative communication between anesthesiologists and obstetricians concluded that the implementation of the safe surgery checklist positively improved communication[18]. The WHO also emphasizes that the checklist should not lose its ability to influence teamwork and communication. In a study conducted by Solsky et al.[19], 155 checklists were examined to investigate whether communication and teamwork were emphasized in surgical safety checklist modifications. This study concluded that increased team communication would lead to an improvement in safety culture.

As the roles of the surgical team during an operation are interdependent, effective communication between the team, including anaesthetists, nurses and surgeons, is crucial in preventing avoidable complications such as operating on the wrong area and inappropriate antibiotic use.

Study Limitations

This study aims to determine the effect of safe surgery checklists on team communication using the meta-analysis method. This meta-analysis has several limitations. First, the number of included studies is relatively small, which may limit the statistical power and generalizability of the findings. Second, despite clinical and methodological heterogeneity among the studies, a fixed-effect model was used in some subgroup analyses because the number of studies was small ($n \leq 5$) and heterogeneity tests were not statistically significant ($p > 0.05$). Inter-study variance could not be reliably estimated using a random-effects model, which may further limit generalizability. Third, due to the limited number of studies, although funnel plots and safe N methods were created for visual inspection, publication bias could not be formally assessed. In conclusion, the limited number of studies included in the study, the fact that they were only observational and descriptive studies, differences in the use of safe surgery checklists, the limited number of studies examining only the effect on communication, cultural and clinical differences in practice, and limited reporting in some studies may affect the interpretation of the results.

CONCLUSION

The complexity of the surgical environment can lead to communication errors. This study evaluated the effect of using the safe surgery checklist on team communication in hospitals, starting from the clinic where the checklist was first implemented, using a meta-analysis method. The study included surgeons, nurses, anaesthetists, anaesthesia technicians, and surgical teams working in the surgical field. According to the analysis results, it was found that team communication was 1.8 times higher in surgical teams using safe surgical checklists than in those not using them. However, the meta-analysis was conducted with only five studies included in the study, which creates limitations and cannot be generalised. It is recommended that different studies be conducted to determine the effect of variables affecting team communication in the use of safe surgical checklists.

Ethics

Ethics Committee Approval: This study was analysed using meta-analysis methods, and a comprehensive and systematic literature review approach was adopted. Due to the use of a literature review format, no ethical committee approval was required for the study, as it did not involve any direct intervention, effect, or experiment on animals or humans.

Informed Consent: These data were analyzed using meta-analytic methods.

Footnotes

Authorship Contributions

Concept: N.A., Design: T.Y., Data Collection or Processing: N.A., Analysis or Interpretation: T.Y., Literature Search: N.A., T.Y., Writing: N.A., T.Y.

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

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ORIGINAL ARTICLE

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Screening for Asthma- and Allergy-related Symptoms and Associated Factors in Children: A School-based Cross-sectional Study

Çocuklarda Astım ve Alerjiyle İlişkili Semptomlar ile İlişkili Faktörlerin Taranması: Okul Temelli Kesitsel Bir Çalışma

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ABSTRACT

Aim: This school-based cross-sectional study aimed to determine the proportion of school-age children who screened positive for asthma- and allergy-related symptoms and to identify associated child- and parent-level factors.

Materials and Methods: This cross-sectional study was conducted among children attending grades 2-7 at a single school in İstanbul. Data were collected using a structured Child and Parent Information Form and the School-Based Asthma and Allergy Screening Questionnaire (SBASQ), which comprises a parent/caregiver questionnaire (PQ) and a student questionnaire (SQ). SBASQ cut-off scores were used to identify screening-positive results for asthma- and allergy-related symptoms. A total of 379 children with complete questionnaires were included in the analysis.

Results: The mean age of participants was 10.09±1.97 (7-14) years, and 62.8% were aged 7-10 years. Based on the PQ, 27.7% of children screened positive for asthma-related symptoms and 68.1% for allergy-related symptoms; corresponding proportions based on the SQ were 25.3% and 63.6%, respectively. Antibiotic use during the first year of life and a history of respiratory disease before the age of two years were significantly associated with higher screening-positive rates for both asthma- and allergy-related symptoms across both PQ and SQ analyses ($p<0.05$ for all comparisons). Positive screening for asthma-related symptoms according to the PQ was more frequent among boys ($p=0.041$), children with low birth weight ($p=0.035$), and those with a history of hospitalization due to pneumonia ($p=0.018$). For allergy-related symptoms, positive screening according to the PQ was significantly associated with maternal asthma/allergy ($p=0.012$) and frequent consumption of packaged/processed foods ($p=0.017$).

Conclusion: This study demonstrated that a substantial proportion of school-age children screened positive for asthma- and allergy-related symptoms. Several child- and parent-level characteristics were associated with positive screening results. These findings suggest that symptom-based school screening may help identify children who could benefit from further clinical evaluation, without implying a clinical diagnosis.

Keywords: Asthma, allergy, children, school, screening

ÖZ

Amaç: Bu okul temelli kesitsel çalışma, okul çağı çocuklarında astım ve alerji ile ilişkili semptomlar açısından pozitif tarama sonucuna sahip olanların oranını belirlemeyi ve çocuk ve ebeveyn düzeyindeki ilişkili faktörleri tanımlamayı amaçlamıştır.

Gereç ve Yöntem: Bu kesitsel çalışma, İstanbul'da tek bir okulda 2-7. sınıflarda öğrenim gören çocuklar arasında yürütüldü. Veriler, yapılandırılmış Çocuk ve Ebeveyn Bilgi Formu ile ebeveyn/bakıcı anketi (EA) ve öğrenci anketinden (ÖA) oluşan Okul Temelli Astım ve Alerji Tarama Anketi (OTATA) kullanılarak toplandı. OTATA kesme puanları, astım ve alerji ile ilişkili semptomlar açısından pozitif tarama sonuçlarını belirlemek amacıyla kullanıldı. Anketleri eksiksiz dolduran toplam 379 çocuk analize dahil edildi.

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Bulgular: Katılımcıların yaş ortalaması 10,09±1,97 (7-14) yıl olup, %62,8'i 7-10 yaş grubundaydı. EA'ya göre çocukların %27,7'si astım ile ilişkili semptomlar, %68,1'i ise alerji ile ilişkili semptomlar açısından pozitif tarama sonucuna sahipti; ÖA'ya göre karşılık gelen oranlar sırasıyla %25,3 ve %63,6 olarak bulundu. Yaşamın ilk yılında antibiyotik kullanımı ve iki yaşından önce solunum yolu hastalığı öyküsü, hem EA hem de ÖA analizlerinde astım ve alerji ile ilişkili semptomlar açısından daha yüksek pozitif tarama oranları ile anlamlı düzeyde ilişkiliydi (tüm karşılaştırmalar için $p<0,05$). EA'ya göre astım ile ilişkili semptomlar açısından pozitif tarama; erkek çocuklarda ($p=0,041$), düşük doğum ağırlığı olanlarda ($p=0,035$) ve pnömoni nedeniyle hastaneye yatış öyküsü bulunanlarda ($p=0,018$) daha sık görüldü. Alerji ile ilişkili semptomlar açısından pozitif tarama ise EA'ya göre annede astım/alerji öyküsü ($p=0,012$) ve paketlenmiş/işlenmiş gıdaların sık tüketimi ($p=0,017$) ile anlamlı düzeyde ilişkili bulundu.

Sonuç: Bu çalışma, okul çağı çocuklarının önemli bir bölümünün astım ve alerjiyle ilişkili semptomlar açısından pozitif tarama sonucuna sahip olduğunu göstermiştir. Çocuklara ve ebeveynlere ait çeşitli özelliklerin pozitif tarama sonuçları ile ilişkili olduğu saptanmıştır. Bu bulgular, klinik tanı anlamına gelmemekle birlikte, daha ileri değerlendirmeden yarar görebilecek çocukların belirlenmesinde semptom temelli okul taramasının potansiyel değerini ortaya koymaktadır.

Anahtar Kelimeler: Alerji, astım, çocuk, okul, tarama

INTRODUCTION

Asthma and other allergic diseases, including allergic rhinitis (AR), atopic dermatitis (AD), and food allergies, represent a major public health concern in childhood[1]. According to the World Health Organization, approximately 300 million individuals worldwide are affected by asthma, and its burden continues to rise globally[2].

Data from the Global Asthma Network Phase I study, which included 14 countries, reported a prevalence of asthma of 9% among children aged 6-7 years and 11% among those aged 13-14 years[3]. Similarly, the prevalence of allergic diseases in children has increased markedly over recent decades[4]. The distribution of asthma and allergic conditions varies across regions and is influenced by multiple environmental and host-related factors, including urbanization, air pollution, exposure to tobacco smoke, respiratory infections, dietary habits, genetic predisposition, and perinatal characteristics[5].

In school-age children, asthma and allergic diseases may adversely affect school attendance, academic performance, and participation in daily and social activities, particularly when symptoms remain unrecognized or undiagnosed. Delayed recognition may contribute to ongoing symptom burden and potentially preventable morbidity. Early identification of children with asthma- and allergy-related symptoms is therefore critical to enable timely clinical assessment and appropriate management[6].

School-based screening approaches may offer a practical opportunity to detect children with previously unrecognized asthma- or allergy-related symptoms and to examine associated child- and parent-level characteristics within the community setting. Evidence from prior school-based initiatives supports the feasibility of such programs in identifying undiagnosed or poorly controlled asthma and facilitating care coordination[7]. At the same time, qualitative evidence from school-based health providers suggests that screening practices and the integration of contextual and social risk information may vary depending on available resources and implementation capacity[8].

This study aimed to determine the proportion of school-age children with positive screening results for asthma- and allergy-related symptoms and to examine associated child- and parent-level factors within a school-based cross-sectional framework.

MATERIALS AND METHODS

Study Design and Setting

This school-based cross-sectional study was conducted among primary and secondary school students aged 7-14 years attending grades 2-7 in a school located in the Gaziosmanpaşa district of İstanbul, Türkiye. The selected school was randomly chosen from schools in the district and was classified as representing a middle socioeconomic level based on available administrative indicators, including parental educational attainment, household income distribution, and neighborhood characteristics. This approach was intended to approximate the average urban population and to minimize potential confounding related to socioeconomic extremes, which are known to influence the prevalence and reporting of asthma and allergic diseases.

Sample size was determined pragmatically based on feasibility within the selected school. A total of 600 questionnaires were distributed (300 to primary school students in grades 2-5 and 300 to secondary school students in grades 6-7) to ensure balanced representation across age groups and school levels while anticipating a response rate of approximately 75-80%. This approach yielded sufficient participants for reliable prevalence estimation of asthma- and allergy-related symptoms in a school-based setting.

Inclusion and Exclusion Criteria

Children aged 7-14 years whose parents provided written informed consent and who were able to understand and respond to the study questionnaires were eligible. Children with communication barriers (including hearing or speech impairment and cognitive impairment) affecting themselves and/or their parents, as well as children whose parents were

illiterate, were excluded. Children whose parents did not provide written informed consent or whose questionnaires had missing data were excluded, as detailed in Figure 1.

Ethics approval was obtained from the University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital Ethics Committee (approval no: 398, date: 22.12.2021) and the İstanbul Governorship Provincial Directorate of National Education (24.02.2022, no: E-59090411). Parents were informed about the study objectives and procedures through written information sheets provided together with the questionnaires, and written informed consent was obtained prior to participation.

Data Collection Tools

Child and Parent Information Form

A structured form developed by the authors based on the relevant literature was used to collect data on sociodemographic characteristics (age, sex, grade level), early-life factors (maternal age at delivery, mode and timing of birth, birth weight,

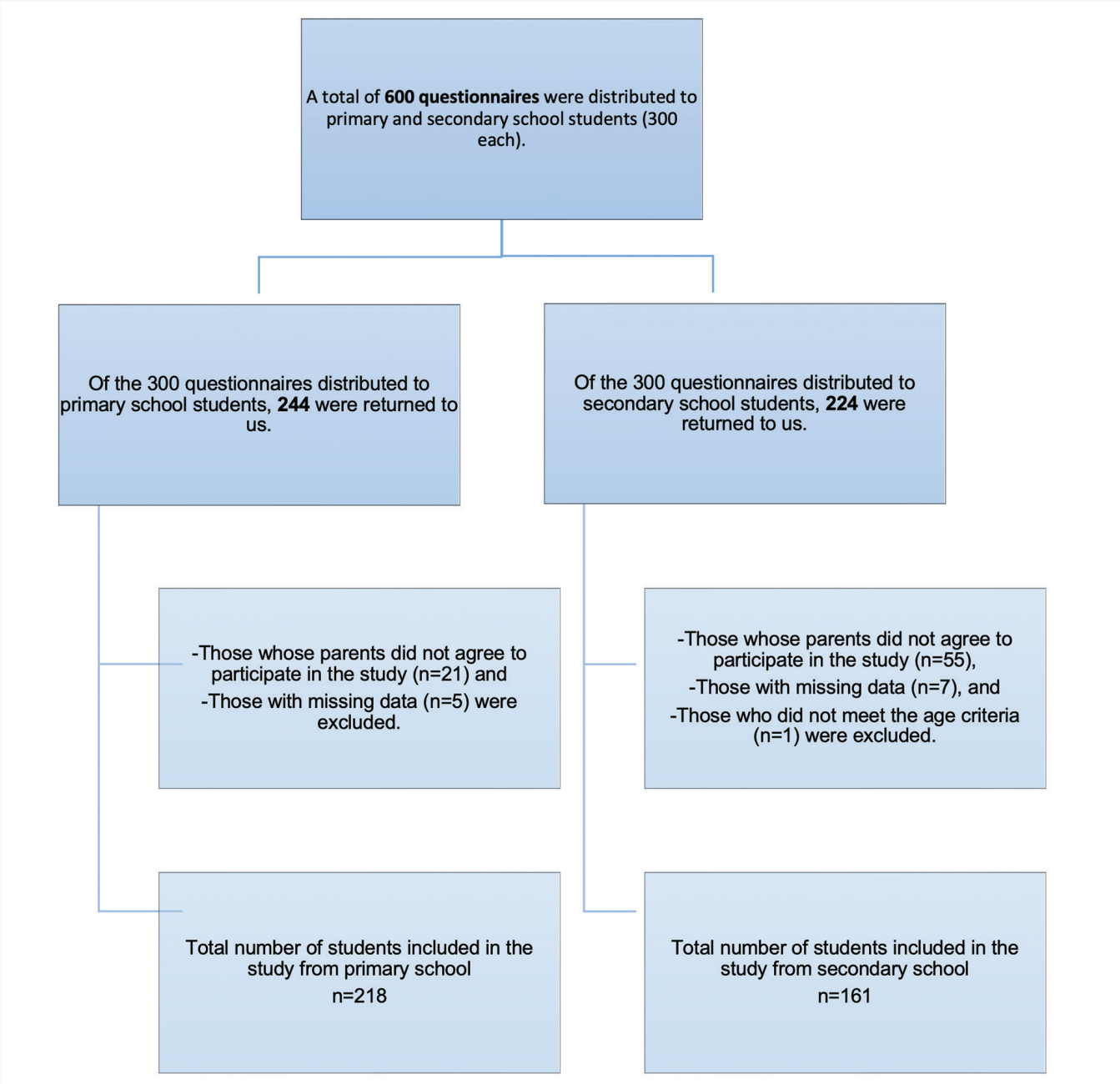

Figure 1. Study flowchart

breastfeeding history, antibiotic use during the first year of life, respiratory disease before age two, history of hospitalization due to pneumonia), dietary habits (packaged/processed food consumption), and known medical conditions. Parental sociodemographic and medical characteristics, including age, educational level, household income, asthma/allergy history, chronic disease status, and smoking status, were also recorded.

School-based Asthma and Allergy Screening Questionnaire

The School-based Asthma and Allergy Screening Questionnaire (SBASQ) was developed by Redline et al.[9] in 2004 to identify school-aged children who may be at increased risk for asthma and allergic conditions, particularly those who have not been previously diagnosed. The Turkish validity and reliability study was conducted by Kilic et al.[10]. The SBASQ consists of two components: a parent/caregiver questionnaire (PQ) and a student questionnaire (SQ). The final four items in both components, which relate to physician diagnosis and medication use, are excluded from scoring, as they are not part of the symptom-based screening score. According to the scoring system, a total score of ≥3 indicates asthma-related screening positivity, while a score of ≥1 indicates allergy-related screening positivity. In the present study, these cut-off values were operationally interpreted as indicating positive screening results rather than clinical diagnosis. The Turkish version demonstrated acceptable internal consistency, with Cronbach's alpha coefficients of 0.72 for the SQ and 0.80 for the PQ[10].

Study Procedure

Data collection was conducted between March 1 and April 5, 2022. Questionnaires were distributed to 600 students (300 primary school and 300 secondary school) via their teachers and completed at home by the children and their parents/caregivers. Of these, 468 questionnaires were returned (response rate: 78%). After excluding 76 cases due to parental non-consent and 13 cases with incomplete data or failure to meet age criteria, a total of 379 complete and eligible questionnaires were included in the final analysis (Figure 1).

Statistical Analysis

All statistical analyses were conducted using IBM SPSS Statistics version 22. The distributional properties of continuous variables were evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables were summarized as mean ± standard deviation, whereas categorical variables were expressed as frequencies and percentages. Associations between categorical variables were examined using the chi-square test. Yates' continuity correction was applied when appropriate, and Fisher's exact test was used when expected cell counts were low. All analyses were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

The study included 379 children aged 7-14 years, with a mean age of 10.09±1.97 years. The mean age of mothers was 36.9±5.5 years (range: 26-56), and the mean age of fathers was 41.3±5.2 years (range: 29-57). A physician-diagnosed history of asthma and/or allergy was reported in 89 children (23.5%). Among the 89 children (23.5%) with a physician-diagnosed respiratory/allergic condition, 70 (18.5%) had asthma (with or without allergy) and 56 (14.8%) had allergy (with or without asthma). The sociodemographic and clinical characteristics of the children and parents are summarized in Table 1 and Table 2, respectively.

According to the PQ, 27.7% of the children screened positive for asthma-related symptoms, and 68.1% screened positive for allergy-related symptoms. Based on the SQ, 25.3% of the children screened positive for asthma-related symptoms, and 63.6% screened positive for allergy-related symptoms (Table 3).

As shown in Table 4, children who had received antibiotics during the first year of life showed significantly higher positive screening rates for both asthma- and allergy-related symptoms according to both the PQ (34.1% and 73.2%, respectively; p=0.009 and p=0.043) and the SQ (30.2% and 71.5%, respectively; p=0.040 and p=0.002). Similarly, a history of respiratory disease before the age of two years was associated with markedly higher screening-positive rates in both the PQ (50.0% and 87.1%) and the SQ (44.3% and 82.9%) ($p<0.001$ for all comparisons). Positive screening for asthma-related symptoms based on the PQ was also more frequent among boys than girls (p=0.041).

As presented in Table 5, maternal history of asthma or allergy was associated with significantly higher positive screening rates for allergy-related symptoms according to both the PQ (84.3%) and the SQ (78.4%) (p=0.012 and p=0.027, respectively). Paternal history of asthma or allergy was associated with higher positive screening rates for asthma-related symptoms according to the PQ (47.8%) and for both asthma-related (47.8%) and allergy-related (87.0%) symptoms according to the SQ (p=0.047, p=0.021, and p=0.029, respectively).

DISCUSSION

In this school-based cross-sectional screening study, 27.7% of children screened positive for asthma-related symptoms and 68.1% for allergy-related symptoms according to parent reports, with similar proportions observed in the student component. These rates exceeded the prevalence of physician-diagnosed asthma and/or allergy in the study population, reflecting the broader symptom burden captured by screening-based assessment. Screening-positive results were associated with male sex, early-life respiratory morbidity and antibiotic

exposure, low birth weight, and parental history of asthma or allergy. Although screening positivity does not equate to clinical diagnosis, these findings highlight the presence of potentially unrecognized respiratory and allergic symptoms in school-age children and suggest a gap between symptom experience and formal diagnosis.

Large-scale international studies have consistently demonstrated wide cross-country variation in the prevalence of asthma symptoms and physician-diagnosed asthma, with rates differing markedly across regions and age groups[11-14]. National data from Türkiye similarly indicate considerable heterogeneity in asthma and allergic disease prevalence among school-age children[15,16]. Within this context, the proportion of physician-diagnosed asthma observed in the present study (18.5%) falls within previously reported ranges, whereas the higher screening-positive proportions are consistent with the broader symptom patterns typically identified through questionnaire-based assessment.

Discrepancies between symptom-based screening results and physician-diagnosed asthma have been reported in pediatric community populations, where questionnaire-based tools often identify children with unrecognized respiratory symptoms[17-19].

Table 1. Sociodemographic, clinical, and environmental characteristics of children

		n	%
Sociodemographic characteristics			
Gender	Female	191	50.4
	Male	188	49.6
Age (years)	7-10	238	62.8
	11-14	141	37.2
Number of siblings	None	28	7.4
	1-3	289	76.2
	4 and above	62	16.4
Clinical characteristics			
Physician-diagnosed asthma and/or allergy	Yes	89	23.5
	No	290	76.5
Perinatal and early-life characteristics			
Mode of delivery	Vaginal delivery	201	53.0
	Cesarean section	178	47.0
Time of birth	Term	326	86.0
	Preterm	34	9.0
	Postterm	19	5.0
Birth weight	Normal	337	88.9
	Low	35	9.2
	High	7	1.8
Breastfeeding history	Yes	366	96.6
	No	13	3.4
Antibiotic use during the first year of life	Yes	179	47.2
	No	200	52.8
Respiratory tract disease before the age of two	Yes	70	18.5
	No	309	81.5
History of hospitalization due to pneumonia	Yes	29	7.7
	No	350	92.3
Packaged/processed food consumption	Never/almost never	31	8.2
	Rarely	257	67.8
	Often	91	24
Household smoking exposure	Yes	182	48.0
	No	197	52.0

Data presented as number (%) of participants

Such differences are often attributed to under-recognition and variability in healthcare access. In this context, school-based screening may be viewed as a complementary strategy that enhances early detection of symptom burden rather than as a measure of confirmed disease prevalence.

Early-life biological vulnerability and familial predisposition are well-established determinants of susceptibility to asthma- and allergy-related symptoms[20,21]. Longitudinal evidence demonstrates that early respiratory infections, antibiotic exposure in infancy, and perinatal factors contribute to later

Table 2. Sociodemographic and clinical characteristics of parents

		n	%
Parental educational level			
Mother	Literate	20	5.3
	Primary school	145	38.3
	Middle school	95	25.1
	High school	93	24.5
	University	26	6.9
Father	Literate	10	2.6
	Primary school	141	37.2
	Middle school	97	25.6
	High school	103	27.2
	University	28	7.4
Parental smoking status			
Mother	Current smoker	93	24.5
	Former smoker	22	5.8
	Never smoker	264	69.7
Father	Current smoker	210	55.4
	Former smoker	57	15
	Never smoker	112	29.6
Parental asthma/allergy history			
Mother	Yes	51	13.5
Father	Yes	23	6.1
Household income level	Low	123	32.5
	Middle	225	59.4
	High	31	8.2

Data presented as number (%) of participants

Table 3. SBASQ score distribution and screening-positive results for asthma- and allergy-related symptoms

Distribution of SBASQ scores	**Min-max**	**Mean ± SD (median)**
Asthma (PQ)	0-8	1.8±2.1 (1)
Allergy (PQ)	0-2	0.9±0.7 (1)
Asthma (SQ)	0-7	1.6±1.8 (1)
Allergy (SQ)	0-2	0.8±0.7 (1)
Screening-positive results based on SBASQ cut-off scores	**n**	**%**
Asthma-related symptoms (PQ)	105	27.7
Allergy-related symptoms (PQ)	258	68.1
Asthma-related symptoms (SQ)	96	25.3
Allergy-related symptoms (SQ)	241	63.6

Data are presented as mean ± SD (median) and minimum-maximum values

Screening-positive results were defined according to SBASQ cut-off scores (≥3 for asthma-related symptoms and ≥1 for allergy-related symptoms)

PQ: Parent/caregiver questionnaire, SQ: Student questionnaire, SBASQ: School-Based Asthma and Allergy Screening Questionnaire, SD: Standard deviation

Table 4. Distribution of screening-positive results for asthma- and allergy-related symptoms according to child characteristics

		Asthma-related symptoms (PQ)	Allergy-related symptoms (PQ)	Asthma-related symptoms (SQ)	Allergy-related symptoms (SQ)
		n (%)	n (%)	n (%)	n (%)
Sociodemographic characteristics					
Gender	Female	44 (23%)	123 (64.4%)	41 (21.5%)	118 (61.8%)
	Male	61 (32.4%)	135 (71.8%)	55 (29.3%)	123 (65.4%)
	[1]p	**0.041***	0.122	0.081	0.461
Age	7-10	65 (27.3%)	164 (68.9%)	67 (28.2%)	155 (65.1%)
	11-14	40 (28.4%)	94 (66.7%)	29 (20.6%)	86 (61%)
	[1]p	0.824	0.651	0.101	0.419
Perinatal and early-life characteristics					
Mode of delivery	Vaginal	59 (29.4%)	134 (66.7%)	51 (25.4%)	126 (62.7%)
	C/S	46 (25.8%)	124 (69.7%)	45 (25.3%)	115 (64.6%)
	[1]p	0.446	0.532	0.984	0.698
Time of birth	Term	86 (26.4%)	223 (68.4%)	82 (25.2%)	205 (62.9%)
	Preterm	14 (41.2%)	26 (76.5%)	9 (26.5%)	26 (76.5%)
	Postterm	5 (26.3%)	9 (47.4%)	5 (26.3%)	10 (52.6%)
	[1]p	0.184	0.088	0.981	0.174
Birth weight	Normal	88 (26.1%)	226 (67.1%)	82 (24.3%)	211 (62.6%)
	Low	16 (45.7%)	29 (82.9%)	13 (37.1%)	26 (74.3%)
	High	1 (14.3%)	3 (42.9%)	1 (14.3%)	4 (57.1%)
	[3]p	**0.035***	0.057	0.201	0.369
Breastfeeding history	Yes	101 (27.6%)	250 (68.3%)	93 (25.4%)	232 (63.4%)
	No	4 (30.8%)	8 (61.5%)	3 (23.1%)	9 (69.2%)
	[3]p	0.760	0.563	1.000	0.776
Antibiotic use during the first year of life	Yes	61 (34.1%)	131 (73.2%)	54 (30.2%)	128 (71.5%)
	No	44 (22.0%)	127 (63.5%)	42 (21.0%)	113 (56.5%)
	[1]p	**0.009***	**0.043***	**0.040***	**0.002***
Respiratory illness before the age of two	Yes	35 (50%)	61 (87.1%)	31 (44.3%)	58 (82.9%)
	No	70 (22.7%)	197 (63.8%)	65 (21%)	183 (59.2%)
	[1]p	**<0.001***	**<0.001***	**<0.001***	**< 0.001***
History of hospitalization due to pneumonia	Yes	14 (48.3%)	20 (69%)	10 (34.5%)	20 (69%)
	No	91 (26%)	238 (68%)	86 (24.6%)	221 (63.1%)
	[2]p	**0.018***	1.000	0.338	0.671
Packaged/processed food consumption	Never/almost never	7 (22.6%)	13 (41.9%)	5 (16.1%)	17 (54.8%)
	Rarely	64 (24.9%)	176 (68.5%)	64 (24.9%)	155 (60.3%)
	Often	34 (37.4%)	69 (75.8%)	27 (29.7%)	69 (75.8%)
	[1]p	0.059	**0.002***	0.314	**0.017***
Household smoking exposure	Yes	50 (27.5%)	127 (69.8%)	47 (25.8%)	122 (67.0%)
	No	55 (27.9%)	131 (66.5%)	49 (24.9%)	119 (60.4%)
	[1]p	0.923	0.493	0.832	0.180

[1]Chi-square test, [2]Yates' continuity correction, [3]Fisher's exact test, *p<0.05

Data presented as number (%) of participants. C/S: Cesarean section, PQ: Parent/caregiver questionnaire, SQ: Student questionnaire

Table 5. Distribution of screening-positive results for asthma- and allergy-related symptoms according to parental sociodemographic and clinical characteristics

		Asthma-related symptoms (PQ)	Allergy-related symptoms (PQ)	Asthma-related symptoms (SQ)	Allergy-related symptoms (SQ)
		n (%)	n (%)	n (%)	n (%)
Maternal smoking status	Current smoker	25 (26.9%)	62 (66.7%)	19 (20.4%)	57 (61.3%)
	Former smoker	5 (22.7%)	15 (68.2%)	7 (31.8%)	18 (81.8%)
	Never smoker	75 (28.4%)	181 (68.6%)	70 (26.5%)	166 (62.9%)
	[1]p	0.832	0.945	0.393	0.180
Paternal smoking status	Current smoker	62 (29.5%)	146 (69.5%)	57 (27.1%)	137 (65.2%)
	Former smoker	18 (31.6%)	42 (73.7%)	19 (33.3%)	37 (64.9%)
	Never smoker	25 (22.3%)	70 (62.5%)	20 (17.9%)	67 (59.8%)
	[1]p	0.302	0.269	0.061	0.614
Maternal asthma/allergy history	No	85 (25.9%)	215 (65.5%)	77 (23.5%)	201 (61.3%)
	Yes	20 (39.2%)	43 (84.3%)	19 (37.3%)	40 (78.4%)
	[2]p	0.071	**0.012***	0.053	**0.027***
Paternal asthma/allergy history	No	94 (26.4%)	238 (66.9%)	85 (23.9%)	221 (62.1%)
	Yes	11 (47.8%)	20 (87%)	11 (47.8%)	20 (87%)
	[2]p	**0.047***	0.076	**0.021***	**0.029***
Household income level	Low	41 (33.3%)	82 (66.7%)	39 (31.7%)	78 (63.4%)
	Middle	57 (25.3%)	156 (69.3%)	48 (21.3%)	140 (62.2%)
	High	7 (22.6%)	20 (64.5%)	9 (29%)	23 (74.2%)
	[1]p	0.225	0.796	0.092	0.430

[1]Chi-square test, [2]Fisher's exact test, *p<0.05, screening-positive results were defined according to SBASQ cut-off scores

PQ: Parent/caregiver questionnaire, SQ: Student questionnaire, SBASQ: School-Based Asthma and Allergy Screening Questionnaire

respiratory and allergic outcomes through mechanisms involving immune system maturation and lung development[22-25]. Parental asthma or allergy further amplifies this risk via both genetic susceptibility and shared environmental influences[26]. In line with this evidence, our findings showed that early-life exposures—particularly respiratory illness in early childhood and antibiotic use during the first year of life—are associated with higher screening-positive rates for asthma- and allergy-related symptoms, together with established risk factors such as low birth weight and parental atopy. Collectively, these findings support the notion of a cumulative risk profile shaped by interacting biological and familial factors, which can be effectively captured through school-based symptom screening approaches.

Environmental and behavioral influences appear to further modulate these underlying vulnerabilities. Although passive smoke exposure has been widely associated with increased asthma risk, its effects vary across settings, and no significant associations were detected in this study[27,28]. Conversely, dietary patterns—particularly frequent consumption of packaged/processed foods—were associated with allergy-related screening positivity, underscoring the interplay between lifestyle-related exposures and inherent susceptibility[29]. Together, these findings illustrate a multifactorial risk landscape in which biological, familial, and environmental factors converge to shape symptom burden in school-age children.

At a system level, school-based screening can address a critical gap by identifying children who experience symptoms yet remain outside routine clinical detection pathways. Integrating such screening outputs into family medicine follow-up could support earlier evaluation and more timely preventive interventions without replacing clinical diagnosis.

This study has notable strengths, including use of a validated screening instrument incorporating both parent- and student-reported components and a school-based design capturing community-level symptom burden. Inclusion of both child- and parent-level variables enabled multidimensional evaluation of screening-positive profiles.

Study Limitations

Several limitations should be acknowledged. First, the cross-sectional design precludes causal inference. Second, screening-positive results were based on questionnaire responses without clinical confirmation and should therefore be interpreted as reflecting symptom burden rather than diagnosed disease. Third, the study was conducted in a single school representing a middle socioeconomic level, which may limit the generalisability

of the findings to populations with different socioeconomic, environmental, and healthcare-access characteristics, as socioeconomic status is a known determinant of asthma and allergic disease prevalence. In additon, the self-reported nature of early-life and household exposures may introduce under- or misreporting, particularly for socially sensitive variables such as smoking. Finally, as analyses were primarily unadjusted, residual confounding cannot be excluded; multivariate analyses are warranted in future studies.

CONCLUSION

In this school-based cross-sectional screening study, a substantial proportion of school-age children screened positive for asthma- and allergy-related symptoms, with rates appearing higher than those typically reported for physician-diagnosed disease. Positive screening results were associated with several child- and parent-level characteristics, including early-life exposures and family history. Although screening positivity does not constitute a clinical diagnosis, these findings highlight the potential value of school-based screening approaches in identifying children who may benefit from further clinical evaluation. Integration of such strategies with primary care and family medicine practices may enhance early recognition of symptom burden and support timely referral and preventive interventions.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the University of Health Sciences Türkiye, Gaziosmanpaşa Training and Research Hospital Ethics Committee (approval no: 398, date: 22.12.2021) and the İstanbul Governorship Provincial Directorate of National Education (24.02.2022, no: E-59090411).

Informed Consent: Parents were informed about the study objectives and procedures through written information sheets provided together with the questionnaires, and written informed consent was obtained prior to participation.

Footnotes

Authorship Contributions

Concept: Z.Y.E., S.T.K., O.B., Design: Z.Y.E., S.T.K., O.B., Data Collection or Processing: Z.Y.E., S.T.K., Analysis or Interpretation: Z.Y.E., S.T.K., Literature Search: Z.Y.E., S.T.K., Writing: Z.Y.E., S.T.K., O.B.

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Effects of Multiple Sclerosis on the Medial Olivocholear System

Multipl Sklerozun Medial Olivokolear Sistem Üzerine Etkileri

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ABSTRACT

Aim: Multiple sclerosis (MS) is a chronic inflammatory disease characterized by demyelination within the central nervous system. This study aimed to investigate the effects of MS on the medial olivocochlear (MOC) efferent system using transient evoked otoacoustic emissions (TEOAE) and contralateral suppression testing.

Materials and Methods: Peripheral hearing was evaluated using pure-tone audiometry. The function of the MOC system was assessed using TEOAE recordings obtained with and without contralateral broadband noise stimulation. The study included 30 patients with MS and 32 healthy controls. TEOAE measurements were performed bilaterally at 1000, 1500, 2000, 3000, and 4000 Hz. Contralateral suppression was calculated to evaluate MOC reflex activity.

Results: TEOAE amplitudes were significantly reduced in patients with MS compared to controls across all tested frequencies (1000-4000 Hz). In addition, contralateral suppression values at 4000 Hz were significantly lower in the MS group bilaterally ($p<0.05$). Overall, MOC suppression responses were markedly diminished in patients with MS, indicating impaired efferent auditory function.

Conclusion: Given that otoacoustic emissions reflect cochlear Outer hair cell (OHC) function, reduced TEOAE amplitudes in MS patients may indicate early subclinical involvement of OHCs. The observed reduction in contralateral suppression, particularly at 4000 Hz, suggests dysfunction of the MOC efferent system. These findings demonstrate that MS affects the auditory efferent pathways and highlight the importance of evaluating subclinical auditory involvement in this population.

Keywords: Medial olivocochlear reflex, multiple sclerosis, otoacoustic emissions, contralateral suppression, auditory efferent system

ÖZ

Amaç: Multipl skleroz (MS), merkezi sinir sistemi ve omurilikte miyelin hasarı ile karakterize, kronik enflamatuvar bir hastalıktır. Bu çalışmanın amacı, MSin işitsel efferent sistemlerden medioolivokoklear (MOK) sistem üzerindeki etkilerini değerlendirmektir.

Gereç ve Yöntem: Bu çalışmada periferik işitme, saf ses odyometrisi ile değerlendirilmiştir. MOK sistemi ise transient otoakustik emisyon (TEOAE) testi ve kontralateral geniş bant gürültü eşliğinde yapılan supresyon testi ile incelenmiştir. Çalışmaya 30 MS hastası ve 32 sağlıklı kontrol dahil edilmiştir. Tüm katılımcılara sağ ve sol kulakta 1000, 1500, 2000, 3000 ve 4000 Hz frekanslarında TEOAE ölçümleri yapılmış ve MOK refleksini değerlendirmek amacıyla kontralateral supresyon testi uygulanmıştır.

Bulgular: MS hastalarında TEOAE amplitüdlerinin, kontrol grubuna kıyasla tüm frekanslarda (1000-4000 Hz) anlamlı derecede azaldığı saptanmıştır. Ayrıca, bilateral 4000 Hz frekansında kontralateral supresyon değerleri açısından MS ve kontrol grupları arasında anlamlı fark bulunmuştur ($p<0.05$). MS grubunda MOK supresyon yanıtlarının belirgin olarak azaldığı gözlenmiştir.

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Sonuç: Elde edilen bulgular, otoakustik emisyonların koklear fonksiyonları yansıttığı göz önüne alındığında, MS hastalarında düşük emisyon yanıtlarının dış tüylü hücrelerin erken subklinik etkilenmesine bağlı olabileceğini düşündürmektedir. Özellikle 4000 Hz'de supresyon değerlerindeki azalma, MOK sistemin etkilendiğini ve MS'in işitsel efferent yollar üzerinde etkisi olduğunu göstermektedir.

Anahtar Kelimeler: Medioolivokoklear refleks, multipl skleroz, otoakustik emisyon, kontralateral supresyon, işitsel efferent sistem

INTRODUCTION

Multiple sclerosis (MS) is a chronic immune-mediated disorder of the central nervous system, characterized by inflammatory demyelination and axonal damage affecting the brain and spinal cord[1,2]. Demyelinating lesions are primarily located in the cerebral white matter but may also involve cortical regions, particularly subpial areas, as well as the spinal cord and optic nerve[2,3]. Clinically, MS presents with a wide spectrum of neurological symptoms, including optic neuritis, diplopia, ataxia, tremor, muscle weakness, and sensory deficits[1].

In addition to these manifestations, demyelinating processes may affect central auditory and vestibular pathways, leading to auditory dysfunction and balance disturbances[4]. Lesions involving the brainstem are of particular importance, as both afferent and efferent components of the auditory system are localized in this region. Previous studies have demonstrated abnormalities in auditory brainstem responses (ABR) in patients with MS, suggesting impaired neural conduction within auditory pathways[5].

Outer hair cells (OHCs), although primarily involved in afferent auditory processing, also play a crucial role in efferent auditory mechanisms. These functions are mediated by the medial olivocochlear (MOC) system, which originates in the medial superior olivary complex and projects predominantly to the contralateral cochlea[6]. A schematic representation of the MOC system is shown in Figure 1. Activation of this pathway modulates cochlear amplification through hyperpolarization of OHCs, thereby improving signal detection in noise and protecting the auditory system from acoustic trauma[7,8].

The functional integrity of the MOC system can be assessed non-invasively using otoacoustic emissions (OAEs) in conjunction with contralateral acoustic stimulation. Specifically, suppression of transient evoked OAEs (TEOAEs) by contralateral noise is considered an indirect indicator of efferent auditory pathway activity[9]. Stronger suppression responses have been associated with improved speech perception in noisy environments, highlighting the clinical relevance of this measure[10].

Despite increasing evidence regarding auditory involvement in MS, the effects of the disease on efferent auditory mechanisms, particularly the MOC system, remain insufficiently understood. Most previous studies have focused on afferent pathways, while limited data are available on MOC reflex function and its potential role in early or subclinical auditory dysfunction in MS.

Therefore, the present study aimed to investigate the integrity of the MOC system in patients with MS using TEOAE-based contralateral suppression measurements. Additionally, TEOAE

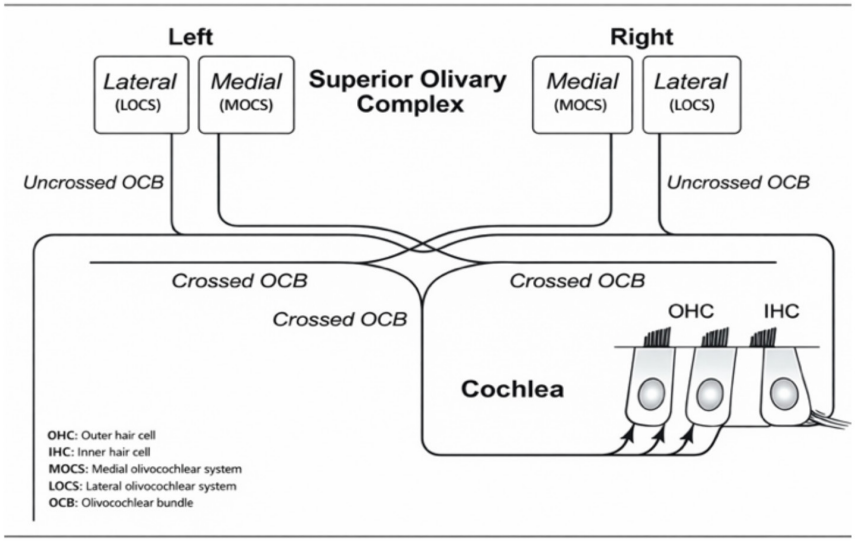

Figure 1. Schematic representation of the medial and lateral olivocochlear pathways and their projections to the cochlea

amplitudes and suppression values across multiple frequency bands were compared between MS patients and healthy controls to evaluate potential alterations in efferent auditory function.

MATERIALS AND METHODS

A total of 30 MS patients, between the ages of 26-63, diagnosed by the Department of Neurology at the at a tertiary care university hospital were included as the study group, and 32 healthy individuals from the same age group who presented to the Department of Otorhinolaryngology at the same hospital were included in the study, which was conducted in the same hospital Department of Audiology. Ethical approval for this study was obtained from the İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee (approval no: 2017/0332, date: 07.11.2017). Since participation in the study was voluntary, an informed consent form was signed by all volunteers in the study after being informed by the evaluator. Otoscopic examination, hearing test to evaluate peripheral hearing, and TEOAE test was performed, and the MOC reflex was evaluated by applying the contralateral suppression test. First of all, an otoscopic examination was performed by an otorhinolaryngologist and the plug in the outer ear canal was cleaned when necessary. After this examination, individuals with a scar on the tympanic membrane, acute or chronic otitis, any pathology in the external ear canal and hearing loss were excluded from the study. The following audiological evaluations were performed on the participants who were examined.

Audiometric Tests

Audiological examinations were performed using the Interacoustics AC40 (Denmark) device.

Measurements were made at 250, 500, 1000, 2000, 4000, 6000, 8000 Hz in a sound-treated room meeting industrial acoustics company standards.

Transient Evoked Otoacoustic Emission: TEOAE tests were performed with Otometrics Madsen Capella (Denmark) in a quiet room. Non-linear click stimuli were used at an intensity of 80±3 dB sound pressure level (SPL). Recordings were obtained across frequency bands of 1, 1.5, 2, 3, and 4 kHz. Only responses with reproducibility exceeding 65% and stimulus stability above 70% were accepted. A total of 260 transient averages were collected within a 20 ms analysis window. A signal-to-noise ratio (SNR) of ≥3 dB SPL was considered indicative of a valid response.

Contralateral Suppression Test with TEOAE: TEOAE measurements were performed in a quiet room. For suppression evaluation, white noise at 70 dB SPL was presented to the contralateral ear. Recordings were obtained in two stages: without noise and with contralateral noise. Suppression was calculated as the difference between baseline OAE amplitudes and those measured during noise stimulation across all frequency bands. A decrease in emission amplitude in the noise condition was interpreted as the presence of the suppression reflex. If there was no reduction in emission values of more than 3dB between the thresholds with and without a mask, the reflex was considered absent

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences) for Windows version 21.0. Data distribution was assessed for normality, and for normally distributed variables, the independent samples t-test was applied, while non-normally distributed variables were analyzed using the Mann-Whitney U test. The chi-square test was used for categorical variables, and Pearson correlation analysis was performed to assess relationships between quantitative variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Thirty MS patients constituted the study group, while 32 healthy individuals served as the control group. The mean age of the MS patients is 40.8±7.4, and the mean age of the control group is 37.4±7.6 (Table 1).

As a result of the audiometric examination, hearing was obtained within normal limits in both MS patients and the control group. The average hearing values of the MS patient group and the control group for right and left ears are shown in Table 2, and no statistically significant difference was found between the two groups ($p>0.05$).

In this study, OAEs values in the right and left ears showed a significant difference between MS patients and the control group ($p<0.05$). OAE values in both ears were lower in the MS group than in the control group. These results show that the functions of OHCs in both ears are affected in MS patients (Figure 2).

Table 1. Age and sex distribution of the study and control group

	MS group (n=30)	Control group (n=32)
Age (years)		
Mean ± SD	40.8±7.4	39.4±7.6
Min-max	26-63	24-61
Sex, n (%)		
Male	26 (86.6%)	13 (40.6%)
Female	4 (13.4%)	19 (59.4%)

SD: Standard deviation, MS: Multiple sclerosis

Table 2. Right and left ear multiple sclerosis and control group hearing thresholds and statistical comparison						
Frequency (Hz)	Left ear MS (dB)	Left ear control (dB)	p-value	Right ear MS (dB)	Right ear control (dB)	p-value
500	11.6	9.6	>0.05	11.3	10.3	>0.05
1000	9.5	8.3	>0.05	10.3	9.5	>0.05
2000	9.8	8.8	>0.05	10.6	9.6	>0.05
4000	9.8	12.5	>0.05	10.6	12.0	>0.05
8000	11.5	13.0	>0.05	12.1	13.6	>0.05
MS: Multiple sclerosis. No statistically significant differences were observed (p>0.05)						

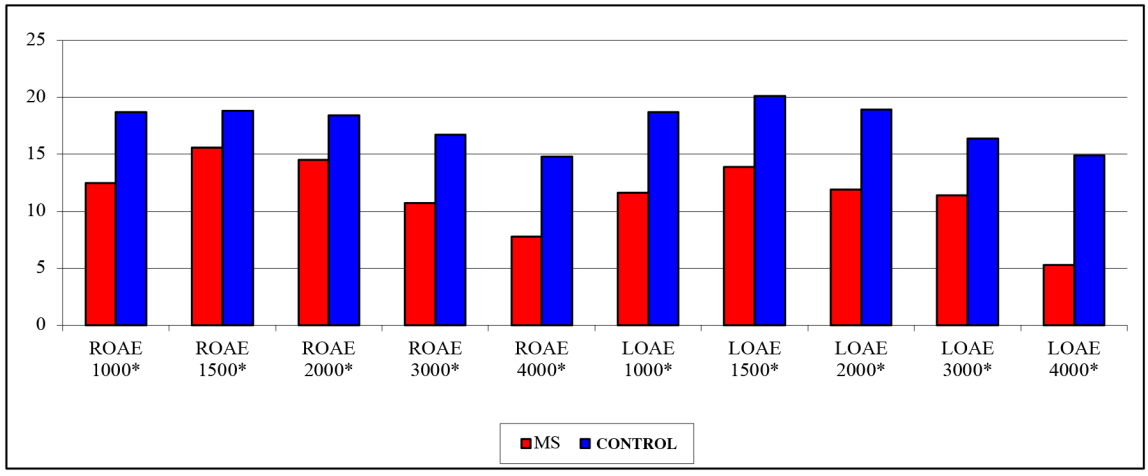

Figure 2. Comparison of TEOAE measurement differences between MS and control

*MS: Multiple sclerosis, TEOAE: Transient evoked otoacoustic emissions, ROAE: Right otoacoustic emission, LOAE: Left otoacoustic emission, MS: Multiple sclerosis, *p<0.05 was considered statistically significant*

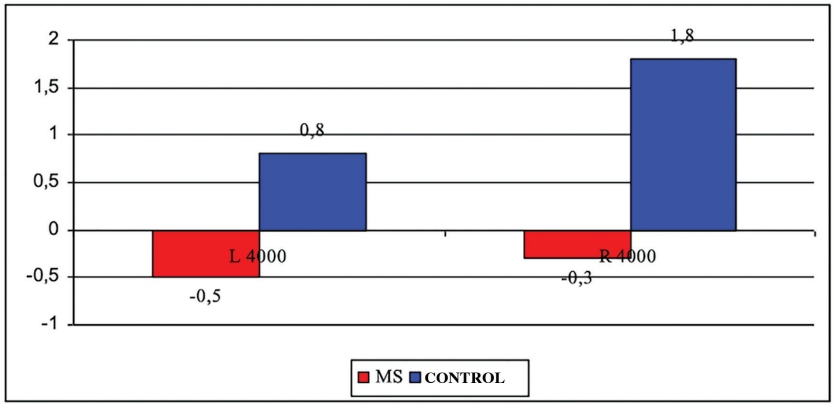

Figure 3. Comparison of differences in measurement results of TEOAE and TEOAE with contralateral noise between MS and control group in right and left ear

*R: Right, L: Left, MS: Multiple sclerosis, TEOAE: Transient evoked otoacoustic emissions, *p<0.05 was considered statistically significant*

Evaluation of the MOC reflex using the contralateral suppression test demonstrated a significant difference at 4000 Hz in both ears when comparing the MS group with the control group ($p<0.05$) (Figure 3).

A significant inverse correlation was found between the Expanded Disability Status scale (EDSS) values indicating the severity of MS disease and the MOC reflex being affected at 4000 Hz in the left ear. Accordingly, as the EDSS value increased, the difference between TEOAE and contralateral suppression measurements at a frequency of 4000 in the left ear decreased (no suppression was observed) ($p=0.033$) (Table 3). According to these results, it was found that the MOC reflex decreased as the severity of the disease increased. In addition, a significant inverse correlation was found between the duration of the disease in the right ear and the involvement of the MOC reflex in the right ear at 1000 Hz and 4000 Hz. These results showed that as the duration of the disease increases, the MOC reflex is negatively affected at 1000 Hz and 4000 Hz in the right ear ($p=0.038$, $p=0.010$) (Table 3).

DISCUSSION

In the present study, we observed that patients with MS showed reduced TEOAE amplitudes together with weaker contralateral suppression responses, particularly at 4000 Hz. These findings point to a possible involvement of both cochlear and efferent auditory pathways, even in patients with clinically normal hearing thresholds.

Previous research has suggested that auditory dysfunction in MS may remain subclinical for a long period. For instance, Di Mauro et al.[12] reported reduced OAEs amplitudes in newly diagnosed patients without detectable brainstem involvement, indicating that cochlear changes may occur early in the disease process. In line with these findings, the decreased TEOAE amplitudes in our study may reflect early OHC dysfunction.

Beyond cochlear involvement, our results also suggest an alteration in efferent auditory function. We found that suppression responses, especially at higher frequencies, were reduced in MS patients. Since the MOC system originates from the superior olivary complex in the brainstem, this finding may indicate that demyelinating processes affect efferent pathways at the brainstem level. This is not unexpected, as the brainstem is known to be particularly vulnerable in MS[4]

Another important observation in our study was the relationship between disease severity and MOC function. As EDSS scores increased, suppression responses tended to decrease. A similar pattern was also seen with longer disease duration. Taken together, these findings suggest that efferent auditory dysfunction may progress over time and may be related to the overall disease burden. This highlights the potential of efferent auditory measures as early biomarkers of neural involvement in MS.

From a functional perspective, impairment of the MOC system may have consequences beyond cochlear mechanics. The efferent auditory system plays a role in improving speech perception in noisy environments by enhancing the SNR[10,11]. Therefore, even in the absence of measurable hearing loss, patients with MS may experience difficulties in speech understanding in daily listening situations.

Di Mauro et al.[12] evaluated newly diagnosed relapsing MS patients in remission with clinically normal hearing using a comprehensive audiological battery. Although pure tone audiometry and ABR findings were within normal limits, both transient-evoked and distortion product OAE amplitudes were significantly reduced at mid frequencies (1000-3000 Hz) compared to controls. These findings suggest subclinical cochlear involvement in early-stage MS, even in the absence of detectable brainstem pathology. In line with these results, the reduced OAE amplitudes observed in our study further support the presence of early peripheral auditory dysfunction and may reflect early dysfunction of OHC electromotility and impaired MOC efferent regulation. Accordingly, OAE measurements appear to be a sensitive tool for detecting early auditory involvement in MS patients[12].

In addition, previous studies have emphasized that sudden sensorineural hearing loss (SNHL) can occasionally be an early manifestation of MS. Di Stadio et al.[13] conducted a systematic review evaluating hearing loss characteristics in MS patients using studies that included both audiological assessments and magnetic resonance imaging findings. Their results demonstrated that SNHL is more frequently observed

Table 3. Correlation of MOC reflex with disease duration and EDSS values

Parameter	p-value	Correlation coefficient (r)
EDSS-left ear (4000 Hz)	**0.033***	−0.455
Disease duration-right ear (1000 Hz)	**0.010***	0.447
Disease duration-right ear (4000 Hz)	**0.038***	−0.394

r: Correlation coefficient, EDSS: Expanded Disability Status scale, MOC: Medial olivocochlear, *p<0.05 was considered statistically significant

in the early stages of MS, whereas progressive SNHL tends to occur in later stages. Lesions were often identified in the brain or internal auditory canal in patients presenting with sudden hearing loss, suggesting early involvement of auditory pathways[13]. These findings support the notion that auditory dysfunction may emerge before overt neurological progression. In line with this, the reduced TEOAE amplitudes and altered suppression responses observed in our study further indicate that both cochlear and efferent auditory mechanisms may be affected at early stages of the disease, even in the absence of clinically evident hearing loss.

The reduced OAE amplitudes and the absence of contralateral suppression at 4000 Hz observed in our study suggest impairment of the MOC reflex pathways in MS. Demyelination, a key pathological feature of MS, is known to disrupt neural conduction and synaptic transmission, particularly within central auditory structures such as the thalamocortical network. This disruption may affect neuronal firing patterns and auditory signal processing, contributing to subclinical auditory dysfunction[14]. In our study, the association between reduced suppression responses and higher EDSS scores further supports the notion that efferent auditory pathway involvement increases with disease severity. Moreover, previous studies have shown that focal brainstem lesions, particularly those involving the superior olivary complex, can impair binaural auditory processing and sound localization abilities[15]. Taken together, these findings indicate that both cochlear and central auditory pathways, including efferent mechanisms, may be progressively affected in MS, even in the absence of overt hearing loss.

Overall, our results suggest that MS is not limited to afferent auditory dysfunction but also involves efferent regulatory mechanisms, particularly the MOC system. Evaluating both TEOAE amplitudes and contralateral suppression responses may therefore provide useful information for detecting subtle auditory changes in MS patients.

Study Limitations

This study has some limitations. The relatively small sample size and the cross-sectional design restrict the generalizability of the findings. In addition, longitudinal data were not available, making it difficult to assess the progression of auditory dysfunction over time. Future studies including larger cohorts and follow-up assessments would help to clarify these issues.

CONCLUSION

In conclusion, our findings indicate that MS may affect both cochlear function and efferent auditory pathways. Reduced TEOAE amplitudes together with decreased suppression responses suggest early involvement of the MOC system. These changes may occur even in patients with normal hearing thresholds and may be associated with disease severity and duration. These findings highlight the importance of incorporating efferent auditory system assessment into the clinical evaluation of MS patients, even in the absence of overt hearing loss.

From a clinical perspective, the combined use of OAEs and contralateral suppression testing may provide a practical and non-invasive approach for identifying early auditory involvement in MS. Further studies are needed to confirm these findings and to better understand their potential role in clinical follow-up.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the İstanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee (approval no: 2017/0332, date: 07.11.2017).

Presentation: This study was presented as an oral presentation at the 4th International Congress of the Mirko Tos Hearing Research Center, "Preclinic, Clinic and Innovative Approaches in Inner Ear Diseases: A Multidisciplinary Symposium," held on October 23–25, 2025, in Ankara, Türkiye.

Informed Consent: Since participation in the study was voluntary, an informed consent form was signed by all volunteers in the study after being informed by the evaluator.

Footnotes

Authorship Contributions

Concept: Ö.E., G.Ö.A., Design: Ö.E., O.T., Data Collection or Processing: Ö.E., A.O.V., Analysis or Interpretation: G.Ö.A., O.T., A.O., A.O.V., Literature Search: Ö.E., G.Ö.A., O.T., A.O., A.O.V., Writing: Ö.E., O.T.

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The Relationship between Toilet Training Experiences and Nocturnal Enuresis in Children Aged 6-15 Years

6-15 Yaş Arası Çocuklarda Tuvalet Eğitimi Deneyimleri ile Nokturnal Enürezis Arasındaki İlişki

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ABSTRACT

Aim: This study aimed to determine the relationship between toilet training experiences and the development of primary monosymptomatic nocturnal enuresis (PMNE) in children aged 6-15 years, and to evaluate the potential protective effect of child-oriented approaches.

Materials and Methods: This retrospective and analytical study included 357 children (165 with PMNE and 192 controls) who were admitted to the Child Health Surveillance Outpatient Clinics of Tekirdağ Namık Kemal University between January 2022 and March 2025 and had complete medical records. Data were obtained through a retrospective review of patient files and follow-up records and were transferred into a structured data collection form including demographic characteristics, toilet training history, and factors associated with enuresis. For statistical analysis, Student's t-test was used for continuous variables and the chi-square test for categorical variables. Multivariable logistic regression analysis was performed to identify independent risk factors. Statistical significance was set at $p<0.05$.

Results: Children with enuresis started toilet training earlier (19.5±5.4 months) and were more frequently subjected to parent-directed methods ($p<0.001$). The child-oriented approach showed an independent protective effect against PMNE [odds ratio (OR)=0.42; 95% confidence interval (CI): 0.25-0.70; $p<0.001$], while starting toilet training before 18 months increased the risk (OR=1.89; 95% CI: 1.10-3.27; $p=0.021$). Family history of enuresis, constipation, and difficulty initiating sleep were also significantly associated with PMNE ($p<0.05$).

Conclusion: Supportive, developmentally appropriate, and non-punitive toilet training methods reduce the risk of PMNE, whereas early, coercive, or parent-centered approaches increase it. These findings highlight the importance of addressing toilet training as a biopsychosocial process and underscore the need for parental education in this context.

Keywords: Toilet training, nocturnal enuresis, child-oriented approach, parental attitude, child development

ÖZ

Amaç: Bu çalışmada, 6-15 yaş arası çocuklarda tuvalet eğitimi deneyimleri ile primer monosemptomatik nokturnal enürezis (PMNE) gelişimi arasındaki ilişkinin belirlenmesi ve çocuk odaklı yaklaşımların potansiyel koruyucu etkisinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Bu retrospektif ve analitik çalışmaya, Ocak 2022-Mart 2025 tarihleri arasında Tekirdağ Namık Kemal Üniversitesi Çocuk Sağlığı İzlem Poliklinikleri'ne başvuran ve tıbbi kayıtları eksiksiz olan 357 çocuk (165 PMNE'li ve 192 kontrol) dahil edildi. Veriler, hasta dosyaları ve takip kayıtlarının retrospektif olarak incelenmesiyle elde edildi ve demografik özellikler, tuvalet eğitimi öyküsü ve enürezis ile ilişkili faktörleri içeren yapılandırılmış bir veri toplama formuna aktarıldı. İstatistiksel analizde sürekli değişkenler için Student t-testi, kategorik değişkenler için ki-kare testi kullanıldı. Bağımsız risk faktörlerini belirlemek amacıyla çok değişkenli lojistik regresyon analizi yapıldı. İstatistiksel anlamlılık düzeyi $p<0,05$ olarak kabul edildi.

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Bulgular: Enürezisi olan çocukların tuvalet eğitimine daha erken başladığı (19,5±5,4 ay) ve ebeveyn yönlendirmeli yöntemlere daha sık maruz kaldığı belirlendi (p<0,001). Çocuk odaklı yaklaşımın PMNE'ye karşı bağımsız koruyucu etki gösterdiği [olasılık oranı (OR)=0,42; %95 güven aralığı (GA): 0,25-0,70; p<0,001], tuvalet eğitimine 18 aydan önce başlanmasının ise riski artırdığı saptandı (OR=1,89; %95 GA: 1,10-3,27; p=0,021). Ailede enürezis öyküsü, kabızlık ve uykuya dalmada güçlük de PMNE ile anlamlı düzeyde ilişkili bulundu (p<0,05).

Sonuç: Destekleyici, gelişimsel olarak uygun ve cezalandırıcı olmayan tuvalet eğitimi yöntemleri PMNE riskini azaltırken, erken, zorlayıcı veya ebeveyn merkezli yaklaşımlar riski artırmaktadır. Bu bulgular, tuvalet eğitiminin biyopsikososyal bir süreç olarak ele alınmasının önemini ortaya koymakta ve bu bağlamda ebeveyn eğitiminin gerekliliğini vurgulamaktadır.

Anahtar Kelimeler: Tuvalet eğitimi, nokturnal enürezis, çocuk odaklı yaklaşım, ebeveyn tutumu, çocuk gelişimi

INTRODUCTION

Toilet training represents a complex developmental transition that extends beyond the acquisition of bladder and bowel control. It involves the integration of neurological maturation, cognitive awareness, emotional regulation, and the quality of parent-child interaction. Although often perceived as a routine milestone, the process varies widely depending on cultural expectations, parental attitudes, and individual child readiness. These variations may shape early voiding behaviors and potentially influence later continence outcomes[1].

When toilet training is initiated in alignment with a child's developmental signals and conducted in a supportive, non-coercive manner, it may promote adaptive recognition of bladder and bowel cues and facilitate healthy toileting habits. In contrast, approaches characterized by premature initiation, rigid scheduling, or punitive responses may generate stress and negative toileting experiences. Such experiences have been hypothesized to interfere with the child's ability to develop consistent voluntary control, possibly contributing to subsequent urinary control difficulties[2,3].

Nocturnal enuresis is defined as involuntary urinary incontinence during sleep in children aged five years and older. Primary monosymptomatic nocturnal enuresis (PMNE) refers to bedwetting in the absence of daytime lower urinary tract symptoms, anatomical abnormalities, or underlying neurological conditions[2]. Although the prevalence of PMNE declines with age, it remains a common pediatric concern and is reported more frequently in boys. Beyond its clinical presentation, PMNE may impose a substantial psychosocial burden, affecting children's self-esteem, emotional well-being, and family dynamics[3].

The pathophysiology of PMNE is considered multifaceted, involving the interplay of genetic susceptibility, nocturnal urine production, functional bladder capacity, arousal mechanisms during sleep, and hormonal regulation. In addition to these biological factors, environmental and behavioral influences have gained increasing attention[4-6]. Toilet training characteristics—including the age at initiation, training approach, parental responses, and the emotional context of the training process—have therefore been proposed as modifiable factors that may contribute to continence development. Potential mechanisms include stress-induced alterations in voiding behavior, reduced interoceptive awareness of bladder sensations, and the establishment of maladaptive toileting patterns in response to coercive practices[7].

Contemporary pediatric guidance emphasizes the importance of a child-oriented toilet training approach that respects individual developmental readiness and discourages punitive strategies[8]. However, despite these recommendations, considerable heterogeneity persists in both parental practices and research findings. Existing studies differ in their definitions of toilet training methods, assessment tools, and cultural contexts, limiting the comparability of results and the generalizability of conclusions[9].

In this context, the present study aimed to evaluate the association between toilet training characteristics—specifically the timing of initiation, training approach, parental attitudes, and selected training-related experiences—and PMNE in children aged 6–15 years. This age range allows assessment beyond the expected period of continence acquisition and provides an opportunity to examine long-term associations. In addition, we sought to describe accompanying clinical and familial factors relevant to routine pediatric follow-up and preventive counseling.

MATERIALS AND METHODS

Study Design and Setting

This investigation was conducted using a retrospective analytical cross-sectional design to evaluate the association between toilet training practices and PMNE in school-aged children.

The study was carried out at the Child Health Surveillance Outpatient Clinics Tekirdağ Namık Kemal University between January 2022 and March 2025. Medical records of children aged 6–15 years who attended routine pediatric follow-up visits during the study period were retrospectively reviewed.

Selecting children within this age range allowed evaluation beyond the expected age of physiological continence acquisition.

Study Population and Sample Size

The study population consisted of children aged 6-15 years with complete medical records available in the hospital database during the study period.

Sample size estimation was based on previously reported prevalence rates of nocturnal enuresis, assuming a statistical power of 80% and a two-sided significance level of 0.05.

A total of 357 children who met the eligibility criteria were included in the final analysis.

• Children were excluded if they had:

• Neurodevelopmental delay

• Congenital or acquired urinary tract abnormalities

• Known neurological disorders

• Diabetes mellitus

• Chronic systemic disease

• Regular medication use that could affect bladder function

These criteria were applied to minimize confounding factors influencing bladder control.

Group Classification

Participants were categorized retrospectively into two groups based on documented clinical diagnosis and parental reports recorded in medical files:

Enuresis Group (n=165)

Children fulfilling internationally accepted criteria for PMNE, defined as recurrent involuntary urinary incontinence during sleep in children aged five years or older, without accompanying daytime lower urinary tract symptoms[10].

Control Group (n=192)

Age- and sex-comparable children with no current or previous history of nocturnal enuresis according to medical records and parental reporting.

Data Collection

Data were obtained retrospectively from two sources:

1. Electronic medical records

2. Structured parental information forms recorded during clinic visits.

Where necessary, missing historical information regarding toilet training was confirmed through standardized follow-up phone interviews conducted by trained investigators.

All data were anonymized prior to statistical analysis.

Study Variables

Data collection covered three principal domains.

Sociodemographic characteristics

• Child's age and sex

• Number of siblings

• Parental education level

• Parental occupation

• Household income status

Toilet training characteristics

• Age at initiation of toilet training

• Predominant training approach (child-oriented vs. parent-directed)

• Type of toileting equipment used (potty chair, toilet seat adapter, footrest)

• Parental attitudes during training (supportive, neutral, punitive)

• Duration of toilet training process

Factors potentially associated with PMNE

• Frequency of nocturnal bedwetting episodes

• Family history of enuresis

• Sleep characteristics (deep sleep, difficulty awakening)

• History of constipation

• Habitual fluid intake patterns

Classification of Toilet Training Approach

Toilet training approaches were retrospectively categorized based on recorded parental descriptions regarding timing of initiation, presence of developmental readiness cues (e.g., communication of toileting needs, expressed interest in toilet use), and reported disciplinary strategies.

Training characterized by responsiveness to developmental readiness and non-punitive guidance was classified as child-oriented, whereas training primarily initiated according to parental scheduling or involving coercive strategies was classified as parent-directed.

Validity Procedures

Questionnaire-based variables had previously been developed following literature review and were assessed for content validity by three pediatric specialists. Prior to implementation in clinical practice, pilot testing had been conducted and minor wording adjustments were made to enhance clarity and reliability. Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (approval no: 2026.17.01.17, date: 27.01.2026). Given the retrospective nature of the study, written informed consent had been obtained during routine clinical evaluations, and additional consent was secured when follow-up contact was required. The study adhered to the principles of the Declaration of Helsinki.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 20.0). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), while categorical variables were summarized as frequencies and percentages.

Between-group comparisons were conducted using:

- Student's t-test (normally distributed variables)
- Mann-Whitney U test (non-normal distribution)
- Chi-square or Fisher's exact test (categorical variables)

To determine independent predictors of PMNE, a multivariable logistic regression model was constructed. Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test.

Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. A p-value <0.05 was considered statistically significant.

RESULTS

Participant Characteristics

A total of 357 children were included in the analysis, comprising 165 children in the enuresis group and 192 children in the control group. The mean age of the overall study population was 9.2±2.7 years, with no statistically significant difference in age distribution between the two groups (p>0.05) (Table 1).

Male participants constituted 57% of the total sample. The proportion of boys was significantly higher in the enuresis group compared with the control group (65.5% vs. 49.0%, respectively; p=0.004) (Table 1).

No significant differences were observed between groups with respect to socioeconomic variables, including parental education level, household income status, or number of siblings (all p>0.05). In both groups, the majority of participants were from families with a middle socioeconomic background, and parental education levels were predominantly high school or above (Table 1).

Toilet Training Characteristics

Across the entire cohort, the mean age at initiation of toilet training was 20.8±5.9 months. Children in the enuresis group began toilet training at a younger age than those in

Table 1. Demographic characteristics of the participants by study group

	Enuresis group (n=165)	Control group (n=192)	Total (n=357)	p-value
Age (years, mean ± SD)	9.3±2.8	9.1±2.6	9.2±2.7	>0.05
Sex				
• Male, n (%)	108 (65.5)	94 (49.0)	202 (56.6)	**0.004**
• Female, n (%)	57 (34.5)	98 (51.0)	155 (43.4)	
Socioeconomic status				>0.05
• Low, n (%)	36 (21.8)	38 (19.8)	74 (20.7)	
• Middle, n (%)	104 (63.0)	122 (63.5)	226 (63.3)	
• High, n (%)	25 (15.2)	32 (16.7)	57 (16.0)	
Parental education level				>0.05
• Primary school or below, n (%)	41 (24.8)	47 (24.5)	88 (24.6)	
• High school, n (%)	79 (47.9)	89 (46.4)	168 (47.1)	
• University or above, n (%)	45 (27.3)	56 (29.1)	101 (28.3)	
Number of siblings (mean ± SD)	1.8±0.9	1.7±0.8	1.8±0.8	>0.05

Data are presented as mean ± SD or percentage (%). Statistical significance was defined as p<0.05, SD: Standard deviation

the control group (19.5±5.4 months vs. 21.9±6.2 months; p=0.018) (Table 2).

The age at achievement of daytime urinary continence did not differ significantly between the enuresis and control groups (26.3±8.1 months vs. 24.5±6.9 months; p=0.065). In contrast, nighttime urinary continence was achieved at a later age among children with enuresis compared with controls (35.2±9.8 months vs. 32.4±8.7 months; p=0.041) (Table 2).

Child-oriented toilet training approaches were reported more frequently in the control group than in the enuresis group (76.6% vs. 56.4%; p<0.001). Conversely, parent-directed training methods were more common among children with enuresis (43.6% vs. 23.4%; p<0.001) (Table 2).

With respect to toileting equipment, the use of potty chairs did not differ significantly between groups (61.2% in the enuresis group vs. 68.8% in the control group; p=0.132). However, toilet seat adapters or footrests were used more frequently in the control group than in the enuresis group (35.9% vs. 23.0%; p=0.012) (Table 2).

Association between Toilet Training Characteristics and Nocturnal Enuresis

The prevalence of nocturnal enuresis varied significantly according to toilet training approach. Among children trained using a child-oriented approach, 38.8% had nocturnal enuresis, whereas this proportion increased to 61.2% among those trained using parent-directed methods (p<0.001) (Table 3).

In multivariable logistic regression analysis, child-oriented toilet training was independently associated with a reduced likelihood of nocturnal enuresis (OR=0.42; 95% CI: 0.25-0.70; p<0.001). Initiation of toilet training before 18 months of age was independently associated with an increased likelihood of enuresis (OR=1.89; 95% CI: 1.10-3.27; p=0.021) (Table 3).

Table 2. Distribution of toilet training-related variables according to study group

	Enuresis group (n=165)	Control group (n=192)	p-value
Age at initiation of toilet training (months, mean ± SD)	19.5±5.4	21.9±6.2	**0.018**
Age at attainment of daytime continence (months, mean ± SD)	26.3±8.1	24.5±6.9	0.065
Age at attainment of nighttime continence (months, mean ± SD)	35.2±9.8	32.4±8.7	**0.041**
Child-oriented method, n (%)	93 (56.4)	147 (76.6)	**<0.001**
Parent-directed method, n (%)	72 (43.6)	45 (23.4)	**<0.001**
Use of potty chair, n (%)	101 (61.2)	132 (68.8)	0.132
Use of toilet seat adapter/footrest, n (%)	38 (23.0)	69 (35.9)	**0.012**

Data are presented as mean ± SD or percentage (%). Statistical significance was defined as p<0.05, SD: Standard deviation

Table 3. Multivariate logistic regression analysis of factors associated with nocturnal enuresis

	B (β coefficient)	OR	95% CI	p-value
Toilet training method				
• Child-oriented method	-0.87	0.42	0.25-0.70	**<0.001**
• Parent-directed method*	—	1.00 (reference)	—	**—**
Age at initiation of toilet training				
• <18 months	0.64	1.89	1.10-3.27	**0.021**
• ≥18 months*>*	—	1.00 (reference)	—	**—**
Sex (Male)	0.48	1.61	1.02-2.55	**0.039**
Family history of enuresis (present)	0.53	1.70	1.04-2.78	**0.033**
History of constipation (present)	0.29	1.34	0.79-2.26	**0.028**
Socioeconomic status (middle and above)	-0.22	0.80	0.48-1.33	0.394

*Reference category, OR: Odds ratio, CI: Confidence interval

Table 4. Distribution of additional factors associated with enuresis

	Enuresis group (n=165)	Control group (n=192)	p-value
Family history of enuresis, n (%)	79 (47.9)	47 (24.5)	**<0.001**
History of constipation, n (%)	48 (29.1)	31 (16.1)	**0.012**
Difficulty falling asleep, n (%)	37 (22.4)	24 (12.5)	**0.039**

Data are presented as percentages (%). Statistical significance was defined as p<0.05

Male sex (OR=1.61; 95% CI: 1.02-2.55; p=0.039), a positive family history of enuresis (OR=1.70; 95% CI: 1.04-2.78; p=0.033), and a history of constipation (OR=1.34; 95% CI: 0.79-2.26; p=0.028) were also identified as independent factors associated with nocturnal enuresis. Socioeconomic status was not independently associated with enuresis in the multivariable model (Table 3, Figure 1).

Associated Clinical and Familial Factors

A family history of nocturnal enuresis was reported in nearly half of the children in the enuresis group (47.9%), compared with 24.5% of children in the control group (p<0.001) (Table 4).

Constipation was more frequently reported among children with enuresis than among controls (29.1% vs. 16.1%; p=0.012). In addition, difficulties initiating sleep were reported more commonly in the enuresis group than in the control group (22.4% vs. 12.5%; p=0.039) (Table 4).

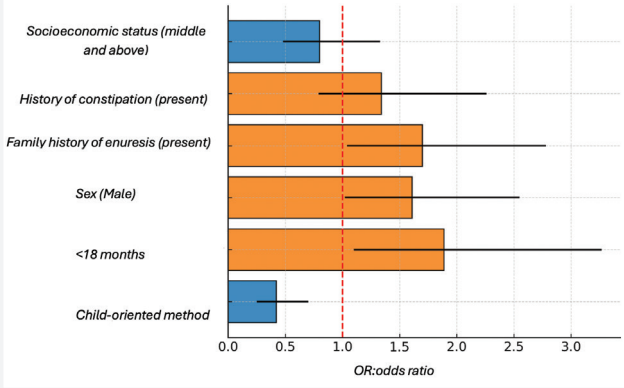

Figure 1. Logistic regression analysis of factors associated with nocturnal enuresis

DISCUSSION

Principal Findings

In this cross-sectional study evaluating children aged 6-15 years, we found that toilet training practices were significantly associated with the presence of PMNE. Specifically, child-oriented toilet training approaches were independently associated with a lower likelihood of PMNE, whereas parent-directed and early-initiated training practices were associated with an increased likelihood[11]. In addition, male sex, positive family history of enuresis, and constipation were more frequently observed among children with PMNE. These findings underscore the multifactorial nature of nocturnal enuresis and highlight the potential relevance of early-life behavioral experiences in continence development[12].

Toilet Training Approach and PMNE

The observed association between child-oriented toilet training and a reduced likelihood of PMNE aligns with previous studies emphasizing the importance of developmental readiness and supportive parental attitudes during the toilet training process[13]. Rather than focusing solely on the timing of training initiation, our findings suggest that how toilet training is conducted may be more influential than when it is initiated. This observation is consistent with reports indicating that coercive or performance-oriented parental approaches may introduce stress and anxiety into toileting experiences, potentially interfering with adaptive voiding behaviors[14,15].

The child-oriented model, originally described by Brazelton, emphasizes responsiveness to the child's physiological and psychological readiness cues. Such an approach may facilitate the development of appropriate bladder awareness and voluntary control by allowing children to internalize bodily signals at their own pace[16,17]. In contrast, parent-directed strategies may prioritize parental expectations over child readiness, which could contribute to maladaptive toileting behaviors or avoidance responses[18]. Although causal inference cannot be established due to the study design, the independent association observed in our multivariable analysis supports the clinical relevance of training quality in relation to continence outcomes.

Timing of Toilet Training and Developmental Readiness

In the present study, initiation of toilet training before 18 months of age was independently associated with an increased likelihood of PMNE. Early initiation may precede sufficient neurological maturation and cognitive readiness, limiting the child's capacity to consistently recognize and respond to bladder fullness. This finding is consistent with studies suggesting that premature training may be associated with later urinary control difficulties[19,20].

However, the literature regarding the optimal timing of toilet training remains inconsistent. Some studies have reported no adverse outcomes associated with early training, while others have suggested potential associations with dysfunctional voiding or delayed continence acquisition[21,22]. These discrepancies likely reflect differences in cultural norms, parental expectations, and training methods across populations[23]. Taken together, our findings support the notion that chronological age alone is an insufficient determinant of successful toilet training and that developmental readiness and training approach should be considered jointly.

Familial and Clinical Factors

A positive family history of nocturnal enuresis was significantly more common among children with PMNE in our cohort, consistent with previous studies demonstrating a strong familial component[24-26]. While genetic susceptibility is likely to play a central role, shared environmental factors and parental responses to toileting behaviors may also contribute to this association. Children raised in households where enuresis is normalized or managed with heightened anxiety may experience different toileting dynamics that influence continence outcomes[27].

Constipation was also more frequently reported among children with PMNE. Although constipation did not emerge as a strong independent predictor in the multivariable model, its higher prevalence suggests a potential interaction within the broader framework of bladder–bowel dysfunction[28,29]. Rectal distension and altered pelvic floor dynamics may adversely affect bladder function, while shared behavioral and sensory factors could further complicate continence regulation[30,31].

Sleep-related difficulties, particularly problems initiating sleep, were more common among children with PMNE[30-32]. Altered sleep patterns and increased arousal thresholds have been proposed as contributing factors in nocturnal enuresis, potentially limiting the child's ability to awaken in response to bladder signals during sleep. While causality cannot be determined, these findings reinforce the importance of considering sleep characteristics in the clinical evaluation of enuretic children.

Toileting Equipment and Environmental Factors

An interesting finding of this study was the higher use of toilet seat adapters and footrests among children without PMNE[33,34]. Ergonomic toileting equipment may enhance postural stability and promote pelvic floor relaxation, facilitating effective bladder emptying[35,36]. Although this association should be interpreted cautiously, as it may reflect broader parental awareness rather than a direct causal effect, it highlights a potentially modifiable environmental factor that has received limited attention in the existing literature. Future studies are warranted to further explore the role of toileting ergonomics in continence development.

Study Limitations

This study has several notable strengths. First, it was conducted in a tertiary university hospital setting with a relatively large sample size, enhancing the statistical power and reliability of the findings. The inclusion of both clinical record review and structured parental data allowed comprehensive assessment of toilet training characteristics and factors associated with PMNE.

Second, strict exclusion criteria were applied to minimize confounding conditions that could independently affect bladder function, thereby increasing internal validity. Additionally, the use of multivariable logistic regression analysis enabled adjustment for potential confounders and identification of variables independently associated with PMNE.

Third, the classification of toilet training approaches was based on predefined developmental and behavioral criteria rather than solely on timing, allowing a more nuanced evaluation of training quality.

However, several limitations should be acknowledged. The retrospective design inherently limits the ability to establish causal relationships between toilet training practices and PMNE. Data regarding toilet training experiences were partly based on parental recall, which may introduce recall bias, particularly given the time interval between training and evaluation.

Furthermore, although efforts were made to verify missing data through follow-up contact, when possible, some variables may have been subject to incomplete documentation in medical records. The study was conducted in a single-center tertiary care institution, which may limit the generalizability of the findings to different sociocultural or primary care settings.

Finally, unmeasured factors such as parental psychological profiles, detailed parenting styles, and environmental stressors were not systematically evaluated and may have influenced continence outcomes.

Despite these limitations, the study provides clinically meaningful insight into the association between toilet training approaches and PMNE, highlighting the potential role of developmental readiness and supportive parental strategies in continence outcomes. Prospective longitudinal studies are warranted to clarify temporal relationships and better establish potential causal pathways between early toilet training experiences and later bladder control outcomes.

Clinical Implications

The findings of this study support a biopsychosocial perspective on PMNE. Pediatric counseling regarding toilet training should emphasize developmental readiness, supportive parental attitudes, and avoidance of punitive practices. Addressing coexisting factors such as constipation and sleep-related difficulties may further improve continence outcomes. Integrating guidance on ergonomic toileting environments into routine pediatric care may represent an additional, low-risk strategy to support healthy voiding habits.

CONCLUSION

The findings of this study indicate that toilet training practices are meaningfully associated with the presence of PMNE in children aged 6-15 years. Child-oriented approaches that respect developmental readiness and emphasize supportive parental attitudes were associated with more favorable continence outcomes, whereas early and parent-directed training practices were linked to an increased likelihood of nocturnal enuresis. These observations reinforce the concept that continence development is shaped not only by biological maturation but also by early behavioral experiences and the emotional context in which toileting skills are acquired.

In addition to toilet training characteristics, familial predisposition and coexisting factors such as constipation and sleep-related difficulties were more frequently observed among children with nocturnal enuresis, underscoring the multifactorial nature of this condition. Taken together, these findings support a holistic, biopsychosocial approach to the evaluation and management of enuretic children.

From a clinical perspective, pediatric guidance on toilet training should prioritize developmental readiness, avoid punitive strategies, and encourage positive parent–child interactions. Addressing accompanying bowel and sleep issues and promoting appropriate toileting environments may further support healthy voiding behaviors. Future longitudinal studies are warranted to clarify causal pathways and to determine whether early modifications in toilet training practices can contribute to the prevention of nocturnal enuresis.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Non-Interventional Clinical Research Ethics Committee of Tekirdağ Namık Kemal University (approval no: 2026.17.01.17, date: 27.01.2026).

Informed Consent: Given the retrospective nature of the study, written informed consent had been obtained during routine clinical evaluations, and additional consent was secured when follow-up contact was required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.N., Concept: A.N., E.T., Design: A.N., C.T., Data Collection or Processing: A.N., E.T., C.T., Analysis or Interpretation: B.N., Literature Search: E.T., C.T., Writing: A.N., B.N.

Conflict of Interest: Two authors of this article, Ayşin NALBANTOĞLU and Burçin NALBANTOĞLU, are members of the Editorial Board of the Namık Kemal Medical Journal. However, they did not involved in any stage of the editorial decision of the manuscript. The editors who evaluated this manuscript are from different institutions. The other authors declared no conflict of interest.

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ORIGINAL ARTICLE

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Combination Medical Treatment for Difficult-to-manage Cushing's Disease: A Single Tertiary Pituitary Center's Experience

Yönetimi Zor Cushing Hastalığında Kombine Medikal Tedavi: Tek Merkez Üçüncü Basamak Hipofiz Merkezi Deneyimi

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ABSTRACT

Aim: The primary treatment for cushing's disease (CD) is transsphenoidal surgery (TSS). However, in refractory cases where medical monotherapy fails, combination therapy may enhance efficacy through synergistic mechanisms and reduce side effects by using lower drug doses. This study aimed to evaluate the efficacy of mono- and combination therapies in difficult-to-manage patients with CD treated at our center.

Materials and Methods: This retrospective, single-center study included 55 patients with persistent CD treated between 2010 and 2025 with monotherapy or combination therapy after TSS. Clinical and biochemical parameters were compared between pretreatment and the last follow-up following mono- or combination therapy, and remission status was also assessed.

Results: Following TSS, all 55 patients received medical management [median duration of therapy: 21.0 (12.0-61.0) months]; therapy was initiated postoperatively in 44 patients (80%), while the remaining 11 (20%) continued their preoperatively initiated treatment. At the last follow-up, 77.5% of patients achieved remission. The most common regimens were pasireotide (30.9%), cabergoline + metyrapone (18.2%), and cabergoline + ketoconazole (14.5%). Overall, cabergoline (67.3%) and pasireotide (58.2%) were the most frequently administered agents across all treatment periods. Twenty-three patients (41.8%) required treatment changes, mostly due to lack of remission (23.6%). Medical therapy decreased baseline cortisol, adrenocorticotropic hormone, urinary free cortisol, late-night salivary cortisol, and adenoma size, with a significant reduction in dexamethasone suppression test (p=0.016). Monotherapy and combination therapy showed no significant differences in hormonal control, metabolic outcomes, remission rates, or adverse events.

Conclusion: Our findings suggest that medical combination therapy is a feasible, safe, and effective treatment option for the long-term treatment of CD in patients who could not achieve remission after TSS or who have persistent disease activity.

Keywords: Cushing's disease, medical therapy, monotherapy, combination therapy, remission, hypercortisolism

ÖZ

Amaç: Cushing hastalığının (CH) primer tedavisi transsfenoidal cerrahidir (TSS). Bununla birlikte, medikal monoterapinin başarısız olduğu dirençli olgularda kombinasyon tedavisi, sinerjistik mekanizmalar yoluyla etkinliği artırabilir ve daha düşük ilaç dozlarının kullanılmasına olanak sağlayarak yan etkileri azaltabilir. Bu çalışmada, merkezimizde tedavi edilen ve yönetimi güç olan CH hastalarında mono- ve kombinasyon tedavilerinin etkinliğinin değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Bu retrospektif, tek merkezli çalışmaya, 2010-2025 yılları arasında TSS sonrasında persistan CH nedeniyle monoterapi veya kombinasyon tedavisi uygulanan 55 hasta dahil edildi. Klinik ve biyokimyasal parametreler, mono- veya kombinasyon tedavisi öncesi ile son takip arasında karşılaştırıldı ve remisyon durumu da değerlendirildi.

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Bulgular: TSS sonrasında 55 hastanın tamamına medikal tedavi uygulandı [medyan tedavi süresi: 21,0 (12,0-61,0) ay]; 44 hastada (%80) tedavi postoperatif dönemde başlanırken, kalan 11 hasta (%20) preoperatif dönemde başlanmış olan tedavilerine devam etti. Son takipte hastaların %77,5'inde remisyon sağlandı. En sık kullanılan tedavi rejimleri pasireotid (%30,9), kabergolin + metirapon (%18,2) ve kabergolin + ketokonazol (%14,5) idi. Tüm tedavi dönemleri değerlendirildiğinde en sık kullanılan ajanlar kabergolin (%67,3) ve pasireotid (%58,2) idi. Yirmi üç hastada (%41,8) tedavi değişikliği gerekti ve bunun en sık nedeni remisyon sağlanamamasıydı (%23,6). Medikal tedavi başlangıca kıyasla kortizol, adrenokortikotropik hormon, idrar serbest kortizolü, gece geç saat tükürük kortizolü ve adenom boyutunda azalma sağlarken, deksametazon supresyon testinde anlamlı bir düşüş saptandı (p=0,016). Monoterapi ve kombinasyon tedavisi arasında hormonal kontrol, metabolik sonuçlar, remisyon oranları veya advers olaylar açısından anlamlı fark saptanmadı.

Sonuç: Bulgularımız, TSS sonrasında remisyon sağlanamayan veya persistan hastalık aktivitesi bulunan CH hastalarının uzun dönem tedavisinde medikal kombinasyon tedavisinin uygulanabilir, güvenli ve etkili bir tedavi seçeneği olduğunu göstermektedir.

Anahtar Kelimeler: Cushing hastalığı, medikal tedavi, monoterapi, kombinasyon tedavisi, remisyon, hiperkortizolizm

INTRODUCTION

Cushing's syndrome is a clinical condition that arises due to prolonged exposure of body tissues to excessive levels of glucocorticoids, regardless of the underlying cause. The most common endogenous etiology is an adrenocorticotropic hormone (ACTH) secreting pituitary adenoma. The disease predominantly affects women, with a female-to-male ratio ranging from 3/1 to 5/1[1]. Although cushing's disease (CD) is statistically classified as a rare disorder, it represents a clinical entity that is not actually uncommon[2]. The clinical manifestations of Cushing's syndrome are diverse and may vary significantly among patients. Traditionally, the disease is recognized by its distinct Cushingoid stigmata, which encompass a wide range of severe metabolic, cardiovascular, and neuropsychiatric comorbidities[3]. However, despite the well-defined nature of these classic signs, the clinical presentation of CD has evolved over the years. Contemporary patient profiles may deviate from the historical descriptions, often displaying a more variable phenotype rather than the classic symptoms.

Cushing syndrome can cause significant morbidity and mortality; however, early diagnosis and effective treatment can significantly improve outcomes. Therefore, comprehensive assessment of the disease's clinical features, diagnostic challenges, and treatment strategies is crucial to optimize patient management.

The primary treatment for CD is transsphenoidal surgery (TSS)[4]. However, surgical intervention alone may not always provide definitive disease control. When performed by an experienced neurosurgeon, remission can be achieved in approximately 80% of patients with microadenomas and 60% of those with macroadenomas[5]. In cases where remission is not achieved or disease recurrence occurs, secondary treatment options include repeat surgery, medical therapy, radiotherapy, and bilateral adrenalectomy (AX)[6]. Medical management plays an important role in controlling hypercortisolism, particularly in patients who are not suitable candidates for surgery or in whom surgical and radiotherapeutic interventions have failed. Available pharmacological options include adrenal steroidogenesis inhibitors (ketoconazole, metyrapone, mitotane, levoketoconazole, osilodrostat), dopamine agonists (cabergoline), somatostatin receptor ligands (pasireotide), and glucocorticoid receptor blocker (mifepristone)[7,8].

In certain patients, despite surgery and subsequent medical monotherapy, remission cannot be achieved. In such cases, combination medical therapy may be necessary to attain adequate disease control. Although specific standardized regimens for combination therapy have not been clearly defined, this approach represents a valuable therapeutic alternative, as no currently available single-agent treatment achieves complete normalization of cortisol levels or full reversal of hypercortisolism-related clinical manifestations and comorbidities[9]. Combination therapy may enhance the overall efficacy of individual drugs through synergistic mechanisms, allowing the use of lower doses for each agent and potentially reducing the risk of adverse effects[7]. In the present study, we aimed to evaluate the effectiveness, remission rates, and adverse effect profiles of medical monotherapy and combination therapy in patients with CD treated at our center.

MATERIALS AND METHODS

This retrospective, single-center study was conducted at the Pituitary Center of İstanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Endocrinology and Metabolic Diseases. Ethical approval was obtained by the İstanbul University-Cerrahpaşa Medical Research Ethics Committee (approval number: E-83045809-604.01-909825, date: 06.02.2024) and written informed consent was obtained from all participants prior to inclusion in the study.

Participants

Patients' data were scanned from the archives of the university and the hospital's electronic medical records between 2010 and 2025. The study included individuals aged 18 years or older with a confirmed diagnosis of CD who had undergone TSS but exhibited persistent disease requiring postoperative medical management (monotherapy or combination therapy). While some of these patients may have also received medical

treatment prior to surgery to control severe hypercortisolism, the primary inclusion criterion was the absolute necessity for post-operative medical therapy due to unremitting disease. Patients were excluded if they were pregnant, diagnosed with non-pituitary (ectopic or adrenal) cushing's syndrome, or if they achieved remission solely with surgical intervention and did not require any form of medical therapy during follow-up (Figure 1). All participants were evaluated from baseline to their last follow-up visit, and comparisons were made between pre-treatment and last follow-up clinical and biochemical parameters following mono or combination medical therapy.

Clinical Evaluation

The diagnosis of CD was made by evaluating clinical findings, biochemical tests, and radiological imaging. Initially, a one mg overnight dexamethasone suppression test (DST) was performed to biochemically confirm hypercortisolism. Patients with DST >1.8 mcg/dL underwent midnight serum cortisol levels x2, 24-hour urinary free cortisol x2 (UFC), and a late-night salivary cortisol (LNSC) test. Abnormal results in at least two of these tests were considered suggestive of hypercortisolism. To determine the cause of the endogenous cortisol excess, morning plasma ACTH levels were measured. Pituitary-mediated CD was suspected when ACTH levels were > 20 pg/mL. A high-dose DST and/or, if possible, a corticotropin-releasing hormone stimulation test were performed to confirm the diagnosis. Depending on availability, 1.5T or 3T contrast-enhanced pituitary magnetic resonance imaging (MRI) was used to determine the location of pituitary adenomas. In cases where adenomas were not detected on MRI or were suspected, bilateral inferior petrosal sinus sampling was performed to assess the central/peripheral ACTH gradient. Patients with pituitary ACTH excess detected through these methods were considered to have CD.

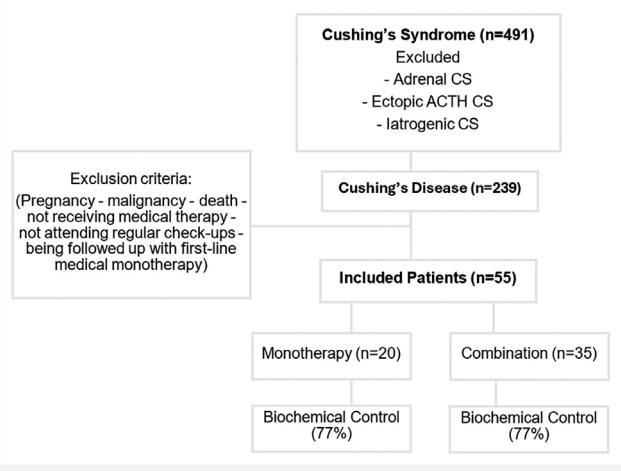

Figure 1. Flowchart of the study

CS: Cushing's syndrome, ACTH: Adrenocorticotropic hormone

Clinical data were retrospectively extracted from medical records at each follow-up visit. The parameters assessed both prior to and following medical therapy included demographic details, clinical characteristics, and history of surgical or radiotherapeutic interventions. Treatment-specific data, such as the regimen type (monotherapy or combination therapy) and treatment duration, were also recorded. Additionally, metabolic indicators comprising glycated Hemoglobin A1c, fasting plasma glucose (FPG), low-density lipoprotein (LDL) cholesterol LDL, triglycerides, systolic and diastolic blood pressure were also analyzed before the medical treatment and at the last follow-up. Biochemical and hormonal assays were performed using fasting blood samples obtained between 08:00 and 08:30 am LNSC samples were collected at 23:00 pm Hormonal parameters were measured via electrochemiluminescence immunoassay using the Cobas e801 platform (Roche Diagnostics GmbH, Mannheim, Germany). The institutional normal reference ranges for the evaluated biochemical parameters were as follows: serum basal morning cortisol, (N: 6.2-19.4 µg/dL); plasma ACTH, (N: 0-46 pg/mL); 24-hour UFC, (N: <140 mcg/day); and LNSC, (N: <0.276 µg/dL). As per standard guidelines, adequate suppression for the 1-mg overnight DST was defined as a serum cortisol level <1.8 µg/dL.

Clinical improvement and biochemical disease control were systematically documented. Systemic arterial hypertension was defined according to current clinical practice guidelines as a systolic blood pressure ≥140 mmHg and/or a diastolic pressure ≥90 mmHg, or the use of antihypertensive medication in patients with a prior diagnosis of hypertension[10]. Hyperlipidemia HL was diagnosed in individuals receiving lipid lowering therapy or exhibiting LDL levels exceeding 130 mg/dL and/or triglyceride levels above 200 mg/dL. The largest tumor size was determined using MRI, and surgical interventions were classified as TSS or TSS combined with AX. Patients who underwent radiotherapy were stratified by technique into Gamma Knife and Cyber-Knife subgroups.

Evaluation of Medical Treatment

Patients were categorized into two groups based on their entire treatment history. The "Monotherapy" group (n=20), comprising patients who received monotherapy throughout the study, and the "Combination Therapy" group (n=35), comprising patients who required more than one agent at any point during their follow-up. The efficacy of medical therapy was assessed by comparing serum cortisol, ACTH, UFC, DST, LNSC, adenoma size, HbA1c, FPG, LDL and triglyceride levels before and after treatment. Patients demonstrating biochemical improvement were classified as achieving adequate biochemical control, while those without improvement were defined as uncontrolled. Adequate biochemical control was determined based on UFC and, when available, LNSC levels. A UFC level

less than 1.5 times the upper limit of normal and an LNSC value within the reference range were considered indicative of adequate biochemical control. All patients were also evaluated for potential adverse effects of the medical therapy and for any new symptoms related to CD.

In our cohort, all included patients were classified as having persistent CD. Persistent CD was defined as the failure to achieve clinical and adequate biochemical control following the initial TSS, in accordance with established clinical practice guidelines[5]. Regarding surgical interventions, all 55 patients underwent TSS as the primary treatment; among them, 6 patients (10.9%) required a repeat TSS due to unremitting disease, and 6 patients (10.9%) eventually underwent bilateral AX. While all 55 patients were included in the overall demographic and safety analyses, 15 patients were excluded from the final adequate biochemical control calculation due to missing biochemical data at the final visit. Consequently, the biochemical control analysis was conducted on the remaining 40 patients.

Medical Treatment Protocol

Due to the retrospective and real-world nature of this study spanning 15 years, medical treatment was highly individualized rather than strictly standardized. However, our institutional approach to combination therapy consistently followed a stepwise, "add-on" strategy. When maximum tolerated doses of first-line monotherapy failed to achieve biochemical remission, or when dose escalation was precluded by adverse effects, a second complementary agent with a different mechanism of action was sequentially added to the regimen. The sequence of drugs was determined primarily by the patient's clinical severity, metabolic comorbidities (e.g., hyperglycemia), and national drug availability at the time.

The general posology for the most frequently used agents in our cohort was as follows: cabergoline was typically initiated at 0.5-1.0 mg/week and titrated up to a maximum of 3.0-4.5 mg/week. Subcutaneous pasireotide was started at 0.6 mg twice daily and increased up to 0.9 mg twice daily if tolerated. Metyrapone was initiated at 500-750 mg/day and titrated up to a maximum of 2000-3000 mg/day based on cortisol levels. Ketoconazole was generally started at 400 mg/day and increased up to 600-800 mg/day, with strict monitoring of liver function tests.

Statistical Analysis

Data analysis was conducted using SPSS 24.0 (SPSS, Inc, USA). Descriptive statistics for categorical variables were presented as frequencies and percentages, while continuous variables were summarized using the mean, standard deviation, median, minimum, and maximum values. To compare categorical variables such as disease control, gender, and disease severity (comparing biochemically controlled and uncontrolled groups), the chi-square (χ^2) test was applied. The normality of the variables was assessed with the Shapiro-Wilk test. For continuous variables with a normal distribution, paired sample t-tests were used to compare values before and after treatment. For non-normally distributed variables, the Wilcoxon signed ranks test was employed. Furthermore, for comparisons between the biochemically controlled and uncontrolled groups, the independent sample t-test was used for normally distributed parameters, while the Mann-Whitney U test was applied for those with non-normal distributions. In the correlation analysis, Pearson's correlation coefficient was used for normally distributed data, while Spearman's correlation coefficient was used for non-normally distributed data. Statistical significance was considered at $p<0.05$ with a 95% confidence level. Given the exploratory nature of this study and the large number of comparisons, we did not adjust for multiple testing; results should be interpreted as hypothesis-generating and p-values are nominal. Confirmation in independent cohorts is required.

RESULTS

The study included a total of 55 patients with difficult-to-manage pituitary CD. Of these, 45 (81.8%) were female and 10 (18.2%) were male, with a mean age of 39.63±13.65 years. The median duration of medical therapy was 21.0 (12.0-61.0) months. The median pretreatment UFC and LNSC levels were 162.45 (96.12-346.50) mcg/day and 0.47 (0.09-5.00) µg/dL, respectively. The median adenoma size on initial MRI was 8.0 (4.50-13.0) mm. General baseline characteristics are summarized in Table 1. All 55 patients underwent TSS and received medical management; therapy was initiated in the postoperative period for 44 patients (80%), while the remaining 11 patients (20%) continued their preoperatively initiated treatment (Table 1).

The most common reason for switching therapy was lack of remission in 13 (23.6%) patients (Figure 2). When the treatments received by the patients in different time periods were evaluated collectively, it was seen that a total of 37 (67.3%) patients were treated with cabergoline, 32 (58.2%) patients were treated with pasireotide and 18 (32.7%) patients received metyrapone (Table 1).

Regarding treatment patterns, 20 patients (36.4%) were treated exclusively with monotherapy, while 35 patients (63.6%) required combination therapy at some point during the study. At the last follow-up visit, although 35 patients had a history of combination therapy, 7 of these patients had been successfully tapered back to a single agent after achieving biochemical control. Consequently, at the final visit, 27 patients were receiving monotherapy and 28 were on combination therapy, as detailed in Table 2. At the last follow-up, among the 40 patients eligible for final efficacy evaluation, 31 (77.5%) achieved adequate biochemical control. Pasireotide emerged as the most frequently used monotherapy agent (n=17; 30.9%).

Table 1. Characteristics of patients

	n (%), mean ± SD or median (IQR)
Sex, female	45 (81.80)
Age (years)	39.63±13.65
Treatment duration (month)	21 (12-61)
Biochemical control (n=40)	31 (77.50)
Diabetes mellitus	11 (20.00)
Hyperlipidemia	17 (30.90)
Hypertension	25 (45.45)
Treatment modalities	
TSS	55 (100)
TSS + radiotherapy Gamma knife Cyber-knife	18 (32.7) 13 (23.6) 5 (9.1)
TSS + AX	6 (10.9)
TSS + multiple medical treatment modifications	23 (41.8)
Initiation of medical treatment Pre-op Post-op	11 (20.0) 44 (80.0)
Total patients' number of drugs use in time of periods Cabergoline Pasireotide Ketoconazole Metyrapone Fluconazole	 37 (67.3) 32 (58.2) 19 (34.5) 18 (32.7) 1 (1.8)

SD: Standard deviation, IQR: Interquartile range, TSS: Transsphenoidal surgery, AX: Adrenalectomy, Pre-op: Pre-operative, post-op: Post-operative

Among combination therapies, the most commonly preferred regimen was cabergoline + metyrapone (n=10; 18.2%) (Table 2).

In the overall cohort, while medical therapy led to observable reductions in basal cortisol, ACTH, UFC, LNSC, and adenoma size, these trends did not achieve statistical significance (p>0.05 for all). Conversely, a marked and statistically significant reduction was observed in DST values from baseline to the last follow-up [5.80 (3.17-13.00) vs. 2.83 (1.80-7.4), p=0.016] (Figure 3, Table 3). In contrast, metabolic parameters (FPG, HbA1c, LDL, triglyceride) showed clinical stability with no significant variations observed.

When stratified by adequate biochemical control status, patients in the biochemically controlled and uncontrolled groups displayed comparable biochemical profiles prior to treatment, with no statistical differences observed at baseline. However, at the last follow-up, a pronounced divergence was evident.

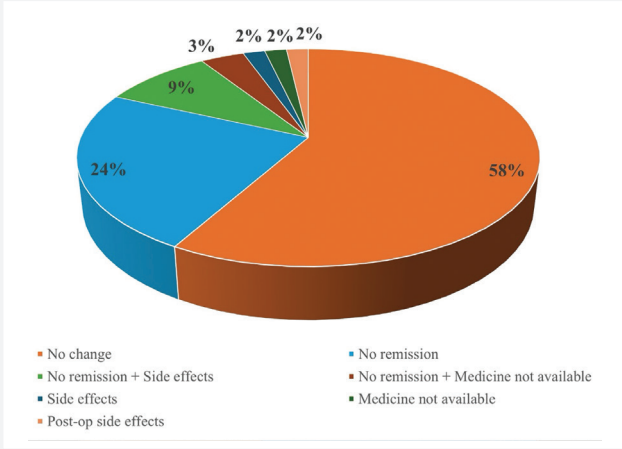

Figure 2. Reasons for changing medical treatment

Table 2. Medical treatments used in the last visit

	n (%)
Monotherapy	
Pasireotide	17 (30.9)
Cabergoline	3 (5.5)
Ketoconazole	3 (5.5)
Metyrapone	3 (5.5)
Fluconazole	1 (1.8)
Combination therapy	
Cabergoline + metyrapone	10 (18.2)
Cabergoline + ketoconazole	8 (14.5)
Cabergoline + pasireotide	4 (7.3)
Pasireotide + ketoconazole	2 (3.6)
Cabergoline + pasireotide + metyrapone	2 (3.6)
Cabergoline + metyrapone + ketoconazole	2 (3.6)

The biochemically controlled group demonstrated significantly lower serum basal cortisol (p=0.02), UFC (p<0.001), and LNSC levels (p=0.002) compared to the uncontrolled group (Table 4).

To evaluate treatment modalities, the cohort was divided into monotherapy and combination therapy subgroups. The groups were found to be comparable in demographic characteristics and treatment duration. The analysis yielded no statistically significant differences between the two therapeutic approaches in terms of hormonal efficacy, metabolic endpoints, biochemical control rates, or safety profiles (Table 5).

DISCUSSION

In this study, we examined the management strategies, medical treatment approaches, treatment combinations, medication related adverse effects and clinical outcomes of patients

diagnosed with pituitary CD which are difficult to manage and followed in our tertiary care center. We observed that combination medical therapies were required in the majority of patients, the rate of adverse effects leading to treatment discontinuation was low and biochemical control could be achieved even in difficult-to-manage cases when individualized combination therapy was implemented.

CD is known to occur predominantly in women[11]. Although the female-to-male ratio is commonly reported around 3:1, some studies have noted ratios as high as 4:1, 5:1, or even 8:1[12-14]. Consistent with the literature, our cohort also demonstrated a female predominance, with a female-to-male ratio of approximately 4:1. Most patients with CD present with microadenomas. Neurosurgical series have reported that microadenomas constitute 75% to 90% of all pituitary tumors in CD[15,16]. Similarly, in our study, 50 patients (90.09%) had microadenomas. The slightly higher percentage in our cohort may be related to earlier referral to specialized centers, improved MRI resolution, or selection bias inherent to tertiary referral centers, as patients with smaller tumors who fail initial management are more likely to be referred for advanced treatment and follow-up.

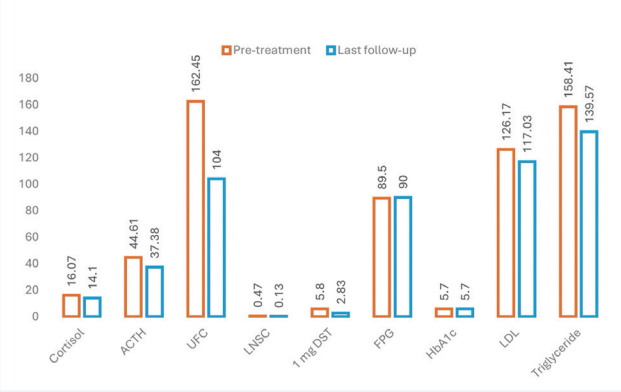

Figure 3. Comparison of patients' pre-treatment and last follow-up laboratory findings

ACTH: Adrenocorticotropic hormone, UFC: Urinary free cortisol, LNSC: Late-night salivary cortisol DST: Dexamethasone suppression test, FPG: Fasting plasma glucose, HbA1c: Hemoglobin LDL: Low-density lipoprotein

CD is associated with various metabolic comorbidities, including diabetes mellitus (DM), hypertension, and hyperlipidemia. In our study, one in five patients had diabetes, nearly half had hypertension, and approximately one in three had hyperlipidemia. Reported prevalence rates in the literature vary depending on diagnostic criteria and disease stage. When only the diagnosis of diabetes is considered, DM is present in approximately 20-45% of patients[17]. Hyperlipidemia has been reported within a broad range, from 12% to 72%, and hypertension in 49-78% of patients; moreover, hypertension may persist in up to 50% of cases even after remission[18,19]. In this context, metabolic comorbidity rates in our cohort were comparable to those reported in the literature. Differences between studies may be explained by variations in disease severity at presentation, duration of hypercortisolism prior to diagnosis, and heterogeneity in comorbidity definitions.

Remission rates in CD are influenced by several factors, including adenoma size and localization, type of intervention, surgical expertise, and management strategies used at high-volume centers. In patients undergoing first-line TSS, remission rates are approximately 80% in microadenomas and 60% in macroadenomas[5]. In cases where remission is not achieved with TSS, remission rates of around 75% may be obtained with postoperative medical therapy, and 64-80% remission

Table 3. Changes in laboratory parameters in patients receiving medical treatment for cushing's disease

	Pretreatment	Last follow-up	Difference*	p value
	Mean ± SD or median (IQR)			
Baseline cortisol (µg/dL)	16.07 (12.39-20.04)	14.10 (10.65-18.25)	-1.97	0.420
ACTH (pg/mL)	44.61 (24.64-67.22)	37.38 (24.22-61.21)	-7.23	0.216
UFC (mcg/day)	162.45 (96.12-346.50)	104.00 (68.85-191.01)	-58.45	0.249
LNSC (µg/dL)	0.47 (0.09-5.00)	0.13 (0.09-0.58)	-0.34	0.272
1 mg DST (µg/dL)	5.80 (3.17-13.00)	2.83 (1.80-7.44)	**-2.97**	**0.016**
The adenoma size in the pituitary MRI (mm)	8.00 (4.50-13.00)	6.00 (5.00-18.25)	-2.00	0.202
FPG (mg/dL)	89.50 (80.25-111.75)	90.00 (82.00-111.00)	+0.50	0.610
HbA1c (%)	5.70 (5.40-6.50)	5.70 (5.20-6.80)	0.00	0.353
LDL (mg/dL)	126.17±38.40	117.03±37.63	-9.14	0.340
Triglyceride (mg/dL)	158.41±70.43	139.57±68.54	-18.84	0.286

*Difference values represent median differences, except for LDL and triglyceride where mean differences are presented

ACTH: Adrenocorticotropic hormone, UFC: Urinary free cortisol, LNSC: Late-night salivary cortisol, DST: Dexamethasone suppression test, MRI: Magnetic resonance imaging. FPG: Fasting plasma glucose, LDL: Low-density lipoprotein, SD: Standard deviation, IQR: Interquartile range, HbA1c: Glycated hemoglobin

may be achieved with radiotherapy in patients who remain uncontrolled or experience recurrence[20,21]. In our study, all patients underwent TSS as the initial intervention, but the cohort consisted entirely of individuals who did not achieve remission after surgery and were therefore more challenging to manage. All received mono- or combination medical therapy, and a subset also underwent radiotherapy (32.7%). Despite the complexity of this population, 77.5% of our patients achieved biochemical control during follow-up, a rate consistent with the literature on multimodal and sequential treatment strategies. The comparable biochemical control rate, despite the inclusion of more refractory patients, may reflect individualized combination therapy, early treatment escalation, and close clinical monitoring in a tertiary referral center.

TSS is the first-line treatment for CD; however, medical therapy with or without radiotherapy is recommended for persistent or recurrent cases. In a real-world study by Broder et al.[22] using large US national datasets, 78.9% of patients underwent initial TSS, while 8.3% received radiotherapy and 7.8% required medical therapy during follow-up. Similarly, Giustina et al.[20] evaluated patients across nine international Pituitary Tumor Centers of Excellence. They reported a median medical therapy utilization rate of 13.3% (4.8-82.9%). In their cohort, the most frequently prescribed agents were ketoconazole (26.5%), metyrapone (17.2%), pasireotide (9.3%), cabergoline (2.8%), and osilodrostat (1.7%). In our study, medication preference patterns differed notably from these international cohorts. Throughout the follow-up period, cabergoline (67.3%) and pasireotide (58.2%) were the most frequently used agents. This variation is likely driven by several local factors, including restricted access to specific medications, variable insurance coverage, and fluctuating drug availability over time. Additionally, our patients received different agents across various treatment phases. This highlights the necessity for individualized therapy and stepwise treatment escalation in difficult-to-manage cases.

Preoperative medical therapy may be used in selected patients before TSS. This approach helps manage severe hypercortisolism and associated comorbidities (e.g., hyperglycemia, hypertension, infection, and thromboembolism risks) prior to surgery. Furthermore, it serves as a "bridge" treatment when surgery is delayed due to required stabilization, preoperative risk reduction, or logistical issues[23,24]. However, routine

Table 4. Clinical and laboratory characteristics of the biochemically controlled versus uncontrolled patients

	Biochemically controlled (n=31)	Uncontrolled (n=9)	p-value
	n (%), mean ± SD or median [IQR]		
Sex, female	23 (74.2)	7 (77.8)	0.601
Age, years	40.87±13.88	31±12.35	0.059
Treatment duration, month	42.29±38.26	32.33±32.30	0.448
Combination therapy	17 (54.8)	5 (55.6)	0.636
Pretreatment baseline cortisol (µg/dL)	15.05 (11.64-19.39)	19.31 (13.06-22.49)	0.215
Pretreatment ACTH (pg/mL)	58.24 (22.73-67.88)	61.30 (23.25-64.70)	0.849
Pretreatment UFC (mcg/day)	168.91 (100-371)	186 (92-340)	0.858
Pretreatment salivary cortisol (µg/dL)	0.35 (0.12-1.01)	3.60 (0.06-7.12)	0.878
Last follow-up baseline cortisol (µg/dL)	13.60 (9-16.60)	18.40 (11.80-31.09)	**0.002**
Last follow-up ACTH (pg/mL)	36.7 (24.16-53)	55.5 (23.9-130.37)	0.249
Last follow-up UFC (mcg/day)	92.75 (55.10-111.25)	381.90 (246.91-778.4)	**<0.001**
Last follow-up salivary cortisol (µg/dL)	0.11 (0.08-0.23)	4.38 (1.24-4.80)	**0.002**
The adenoma size in the initial pituitary MRI (mm)	10 (4.25-14)	6.75 (3.35-7.75)	0.368
Pretreatment FPG (mg/dL)	89.5 (81.75-127.5)	78.5 (67.75-105.5)	0.096
Pretreatment HbA1c (%)	5.8 (5.47-6.57)	5.9 (5.0-6.3)	0.409
Pretreatment LDL (mg/dL)	128.00±37.06	132.57±39.73	0.790
Pretreatment triglyceride (mg/dL)	164.36±76.53	155.14±44.74	0.691
Last follow-up FPG (mg/dL)	86 (82-120)	101 (78-107.5)	1.000
Last follow-up HbA1c (%)	5.8 (5.6-7.3)	5.3 (5.1-6.5)	0.257
Last follow-up LDL (mg/dL)	121.50±37.68	111.56±33.14	0.465
Last triglyceride (mg/dL)	140.56±58.91	148.00±90.59	0.823

SD: Standard deviation, IQR: Interquartile range, MRI: Magnetic resonance imaging, ACTH: Adrenocorticotropic hormone, UFC: Urinary free cortiso, LNSC: Late-night salivary cortisol, DST: Dexamethasone suppression test, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, LDL: Low-density lipoprotein

use of preoperative medical treatment is not supported by strong evidence; therefore, it should be reserved for selected cases. Notably, this preoperative intervention may suppress cortisol levels, thereby complicating the assessment of early postoperative remission. In a study by Valassi et al.[25] utilizing data from the European Register on Cushing's Syndrome (ERCUSYN), preoperative medical treatment was administered to approximately 20% of patients. Among these, ketoconazole was used in 62%, metyrapone in 16%, and their combination in 12%. Consistent with the ERCUSYN cohort, 20% of the patients in our study also required the initiation of preoperative medical treatment for similar clinical reasons.

Although medical therapy is an important option in patients with persistent or recurrent CD, combination regimens, despite being used less frequently, may provide an effective therapeutic alternative. Combination medical treatment can be preferred in patients with persistent hypercortisolism who fail to achieve remission after surgery, as a bridge therapy during the interval before radiotherapy becomes effective, in cases where monotherapy is insufficient, or to reduce adverse effects by using lower doses of each drug while achieving synergistic efficacy through different mechanisms of action[4,5,7,26].

A meta-analysis by Broersen et al.[27], involving 1520 patients from 35 studies, reported a cortisol normalization rate of

Table 5. Clinical and laboratory characteristics of patients received monotherapy and combination therapy

	Monotherapy (n=20)	Combination (n=35)	p-value
	n (%), mean ± SD or median (IQR)		
Sex, female	14 (70.00)	31 (88.60)	0.144
Age	38.15±16.20	40.50±12.08	0.577
Treatment duration	19.50 (11.25-42.75)	23.00 (13.00-71.50)	0.446
Radiothetapy	8 (40.00)	10 (28.57)	0.397
Biochemical control (n=40)	14 (77.77)	17 (77.27)	1.0
Side effects (n=45)	2 (10.52)	7 (26.92)	0.264
Diabetes mellitus	3 (15)	8 (22.9)	0.281
Hyperlipidemia	4 (20)	13 (37.1)	0.148
Hypertension	7 (35)	18 (51.4)	0.224
The adenoma size in the initial pituitary MRI (mm)	6.50±3.10	9.75±5.56	0.303
Pretreatment			
Baseline cortisol (µg/dL)	17.42 (11.50-20.02)	14.04 (12.66-20.08)	0.916
ACTH (pg/mL)	42.78 (31.30-68.99)	47.05 (20.25-67.66)	0.859
UFC (mcg/day)	226.57 (104.24-725.00)	129.30 (70.25-281.00)	0.162
LNSC (µg/dL)	0.47 (0.09-5.00)	0.36 (0.10-5.58)	0.902
1 mg DST (µg/dL)	8.46 (3.20-12.50)	4.97 (3.08-14.80)	0.772
FPG (mg/dL)	84.00 (75.50-97.50)	96.50 (84.00-130.50)	0.084
HbA1c (%)	5.65 (5.37-6.15)	5.90 (5.40-6.50)	0.493
LDL (mg/dL)	124.00±37.43	127.62±39.88	0.789
Triglyceride (mg/dL)	133.71±56.02	175.70±75.52	0.087
Last follow-up			
Baseline cortisol (µg/dL)	15.01 (11.25-18.45)	13.60 (9.00-18.40)	0.520
ACTH (pg/mL)	37.38 (24.55-47.35)	42.15 (20.70-70.96)	0.849
UFC (mcg/day)	109.00 (68.85-205.00)	100.10 (62.80-191.02)	0.892
LNSC (µg/dL)	0.10 (0.09-0.57)	0.14 (0.11-1.88)	0.332
1 mg DST (µg/dL)	4.12 (2.47-7.79)	2.05 (1.39-6.83)	0.164
FPG (mg/dL)	90.00 (82.00-102.00)	91.00 (81.75-141.25)	0.593
HbA1c (%)	5.80 (5.60-6.10)	5.65 (5.10-7.45)	0.681
LDL (mg/dL)	107.36±22.10	123.18±44.22	0.164
Triglyceride (mg/dL)	135.43±74.61	142.33±65.93	0.775

SD: Standard deviation, IQR: Interquartile range, MRI: Magnetic resonance imaging, ACTH: Adrenocorticotropic hormone, UFC: Urinary free cortisol, LNSC: Late-night salivary cortisol, DST: Dexamethasone suppression test, FPG: Fasting plasma glucose, HbA1c: Glycated hemoglobin, LDL: Low-density lipoprotein

49.4% with monotherapy. Notably, this rate increased to 65.7% in patients receiving combination therapy (≥2 agents). Regarding safety, the same study reported mild side effects in 24% of patients using cabergoline, 30.8% with metyrapone, and 58.3% with pasireotide. Interestingly, the incidence of mild side effects decreased to 18% in patients receiving combination therapy. However, serious side effects were observed in 20.9% of patients treated with multiple (≥2 agents) medications[27]. The literature indicates that combining ketoconazole with metyrapone or using a steroidogenesis inhibitor together with a tumor-targeted agent, may be beneficial due to complementary mechanisms that enhance adrenal steroid blockade or allow lower individual drug doses. Triple combinations such as cabergoline–pasireotide–ketoconazole or metyrapone–ketoconazole–mitotane have also been described; however, monitoring is advised due to the potential risk of QTc prolongation and hepatotoxicity[28,29]. Feelders et al.[30] added cabergoline to patients who failed to achieve UFC normalization after starting pasireotide therapy and compared the two groups. At follow-up, the mean UFC normalization was 50% (17 monotherapy, 17 combination), and the remission rate was similar in the two arms (50% each). In a study combining pasireotide, cabergoline, and ketoconazole treatments in 17 CD patients, the combination treatment resulted in UFC normalization in 15 (88.2%) patients, and clinical improvement was observed with reductions in body weight, waist circumference, and blood pressure[9]. Differences in response rates among studies may be related to variations in patient selection (treatment-naive vs. refractory cases), treatment sequencing, disease severity, and drug availability.

In our study, six different combination regimens were used at the last follow-up visit. The most commonly used combination was cabergoline + metyrapone, whereas pasireotide was the most frequently used monotherapy. At the last follow-up, adequate biochemical control was observed in approximately 77% of patients in both monotherapy and combination therapy groups, with no significant difference between them. However, basal cortisol, UFC, and one mg overnight DST levels were lower in the combination therapy group, suggesting that individualized combination therapy may provide better biochemical control than dose escalation of a single agent, particularly in more severe or refractory disease. Although treatment combinations changed during follow-up, major adverse effects were not observed. The most frequently reported side effects were nausea, diarrhea, and mild fasting blood glucose elevations, none of which required treatment discontinuation or regimen modification. The low side-effect rate in our cohort may be attributed to the stepwise escalation of therapy, use of lower doses in combination regimens, and close monitoring during follow-up.

Study Limitations

There are several limitations to our study. First, the sample size was relatively small, which limited the ability to compare the superiority of specific combination treatment regimens. Second, the retrospective nature of the study may have introduced selection and information bias. Third, difficulties in accessing certain medications during the study period sometimes prevented continuation of treatment according to the planned protocol or maintaining follow-up for the desired duration. Fourth, the retrospective chart-review design over a 15-year period resulted in missing granular data regarding the exact grading and precise quantitative severity of some drug-related adverse events. Finally, the inclusion of a heterogeneous patient profile, with a subset of individuals undergoing concurrent adjuvant treatments such as radiotherapy or subsequent bilateral AX, introduces potential confounding factors that may complicate the isolated assessment of medical treatment efficacy. For these reasons, prospective studies with larger patient populations and standardized treatment protocols are required to better evaluate combination treatment strategies.

CONCLUSION

Our findings indicate that while combination medical therapy does not demonstrate statistical superiority over monotherapy in our cohort, it represents a viable, comparable, and safe therapeutic alternative for patients with CD who do not achieve remission after TSS. Rather than a first-line medical approach, combination therapy provides a crucial step-up strategy when monotherapy fails or is limited by dose-dependent side effects, offering meaningful biochemical control without significantly increasing the rate of adverse events. This individualized approach facilitates effective disease management and may help reduce medication-related side effects. The success of combination therapy is further supported by close follow-up and multidisciplinary decision-making, which play a critical role in optimizing treatment outcomes and preventing complications.

Ethics

Ethics Committee Approval: Ethical approval was obtained the Pituitary Center of İstanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Endocrinology and Metabolic Diseases (approval number: E-83045809-604.01-909825, date: 06.02.2024). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: All participants provided written informed consent prior to enrollment.

Footnotes

Authorship Contributions

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

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

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Relationships between Balance, Gait, and Falls in Dementia Subtypes: A Comprehensive Geriatric Assessment Study

Demans Alt Tiplerinde Denge, Yürüyüş ve Düşmeler Arasındaki İlişkiler: Bir Ayrıntılı Geriatrik Değerlendirme Çalışması

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ABSTRACT

Aim: We aimed to examine the relationship between balance, gait, and falls across the most common dementia subtypes.

Materials and Methods: A total of 260 older adults diagnosed with Alzheimer's disease (AD), dementia with lewy bodies (DLB), behavioral variant frontotemporal dementia, and normal pressure hydrocephalus (NPH), along with 338 cognitively healthy controls, were included in this retrospective, cross-sectional study. Comprehensive geriatric assessment results, including comorbidities, medications, balance-gait analysis, and neurocognitive testing, were compared.

Results: Statistical differences were observed between controls and dementia subtypes in sex, comorbidity burden, obesity, nutritional status, frailty, sarcopenia, slow walking speed, balance, postural instability (PI), falls, and use of walking assistive devices. DLB diagnosis was associated with falls, PI, and slow walking speed [odds ratio (OR): 4.67, 95% confidence interval (CI): 1.37-15.92; p=0.014; OR: 7.38, 95% CI: 1.67-32.50; p=0.008; and OR: 5.99, 95% CI: 1.66-21.53; p=0.006, respectively]. NPH diagnosis was associated with falls, performance-oriented mobility assessment, PI, slow walking speed, and use of walking assistive devices (OR: 5.70, CI: 95% 1.83-17.70; p=0.003; OR: 0.82, CI: 95% 0.73-0.93; p<0.003; OR: 14.87, CI: 95% 3.64-60.68; p<0.001; OR: 13.37, CI: 95% 3.65-49.02; p<0.001; and OR: 4.92, CI: 95% 1.15-21.07; p<0.031, respectively).

Conclusion: A comprehensive assessment of balance, gait, and falls, along with understanding their links to various etiological subtypes of dementia, can be useful in many clinical settings, such as monitoring disease progression and identifying at-risk individuals.

Keywords: Dementia, balance; gait, falls, comprehensive geriatric assessment

ÖZ

Amaç: En sık görülen demans alt tiplerinde denge, yürüme ve düşmeler arasındaki ilişkinin incelenmesi amaçlandı.

Gereç ve Yöntem: Bu retrospektif, kesitsel çalışmaya Alzheimer hastalığı (AH), Lewy cisimcikli demans (LCD), davranışsal varyant frontotemporal demans ve normal basınçlı hidrosefali (NBH) tanısı almış toplam 260 yaşlı birey ile bilişsel olarak sağlıklı 338 kontrol dahil edildi. Komorbiditeler, ilaçlar, denge-yürüme analizi ve nörokognitif testleri içeren kapsamlı geriatrik değerlendirme sonuçları karşılaştırıldı.

Bulgular: Kontroller ile demans alt tipleri arasında cinsiyet, komorbidite yükü, obezite, beslenme durumu, kırılganlık, sarkopeni, yavaş yürüme hızı, denge, postüral instabilite (Pİ), düşmeler ve yürümeye yardımcı cihaz kullanımı açısından istatistiksel olarak anlamlı farklılıklar saptandı. LCD tanısı düşmeler, Pİ ve yavaş yürüme hızı ile ilişkiliydi [olasılık oranı (OR): 4,67, %95 güven aralığı (GA): 1,37-15,92; p=0,014; OR: 7,38, %95 GA: 1,67-32,50; p=0,008 ve OR: 5,99, %95 GA: 1,66-21,53; p=0,006, sırasıyla]. NBH tanısı; düşmeler, performansa dayalı mobilite değerlendirmesi, Pİ, yavaş yürüme hızı ve yürümeye yardımcı cihaz kullanımı ile ilişkiliydi (OR: 5,70, %95 GA: 1,83-17,70; p=0,003; OR: 0,82, %95 GA: 0,73-0,93; p<0,003; OR: 14,87, %95 GA: 3,64-60,68; p<0,001; OR: 13,37, %95 GA: 3,65-49,02; p<0,001 ve OR: 4,92, %95 GA: 1,15-21,07; p<0,031, sırasıyla).

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Sonuç: Denge, yürüme ve düşmelerin kapsamlı biçimde değerlendirilmesi ve bunların farklı etiyolojik demans alt tipleriyle ilişkilerinin anlaşılması; hastalık progresyonunun izlenmesi ve risk altındaki bireylerin belirlenmesi gibi birçok klinik alanda yararlı olabilir.

Anahtar Kelimeler: Demans, denge, yürüme, düşme, ayrıntılı geriatrik değerlendirme

INTRODUCTION

Balance is the postural adjustment needed to keep the center of gravity over the support surface, both at rest and during activity. Both static and dynamic balance are impaired in older adults due to issues with postural control impairments[1]. Balance problems occur in 13% of patients aged 65, 35% of patients aged 75, and 46% of patients aged 85[2]. In a study conducted with older individuals, the frequency of falls was 33.6%[3]. The fall rate among older adults with dementia is twice that of a cognitively healthy population, and nearly two-thirds of individuals with dementia fall each year[4].

Postural balance problems are common in neurodegenerative disorders. Balance relies on the integration of somatosensory, vestibular, and visual inputs. A disorder in any of these systems negatively affects postural control[5]. In neurodegenerative diseases, postural abnormalities arise through numerous mechanisms, including damage to motor and sensory pathways, loss of proprioception, impaired vestibular and visual integration, changes in muscle tone, and delayed reflexes[6-8]. Postural instability (PI), often identified through physical examination, is commonly observed in Parkinson's disease and Parkinson's-plus syndromes [dementia with lewy bodies (DLB), multiple system atrophy, corticobasal degeneration, and progressive supranuclear palsy][9]. Additionally, PI aids in the diagnosis, monitoring, and therapeutic evaluation of normal-pressure hydrocephalus (NPH)[10].

The ability to walk is essential for many basic social functions needed for independence. Gait control is a complex process that involves the integration of motor, perceptual, and cognitive systems[11]. A gait disorder is defined as when the patient walks slower than expected for their age or when abnormalities in movement, such as balance issues, are observed[12]. The normal walking speed ranges from 1.2 to 1.4 m/s, although it can vary with age, sex, and body size. Speeds below 0.8 m/s are linked to limited mobility and higher mortality risk[13,14]. Walking assistive devices improve gait by alleviating pain or compensating for balance deficits. Additionally, studies have shown that using walking aids can provide benefits by reducing cognitive load[15]. However, no studies in the current literature compare the use of walking assistive devices among Alzheimer's disease (AD), DLB, frontotemporal dementia (FTD), and NPH.

Older adults with mobility limitations, such as slower walking speeds, face a higher risk of falls. Research has identified both intrinsic (individual) and extrinsic (environmental) factors that contribute to falls. However, the complexity of these factors makes it difficult to manage at-risk older adults effectively[16]. The physical consequences of falls include fractures, dislocations, sprains, bruises, open wounds, and head injuries. Indirect consequences include pressure sores, pneumonia, and other infections that may result from hospitalization. Fear of falling—defined as persistent anxiety about falls that prevents individuals from performing activities, they are capable of—relates to loss of independence, depression, low self-esteem, and diminished self-confidence. This fear is part of the long-term complications that can result from falls in older adults. An injurious fall can lead to increased caregiving needs, loss of independence, and reduced social participation. These issues impose a significant burden on older adults, their families, caregivers, and society as a whole[17].

Despite growing awareness that dementia is a global public health issue, there is currently no cure. As a result, early detection of potentially modifiable factors, such as physical performance deficits and falls, is increasingly important[18]. Although the link between dementia and balance issues in older adults is well-established, few studies have shown how different dementia subtypes impact balance, gait, and falls. Our study aimed to evaluate balance and gait in older adults with different types of dementia, identify those at high fall risk, and explore related factors.

MATERIALS AND METHODS

Participants

Data from 598 patients who visited our geriatric clinic for any reason and underwent a comprehensive geriatric assessment (CGA) were retrospectively and cross-sectionally analyzed from July 2018 to June 2021. This number represents the final cohort after applying all inclusion and exclusion criteria. The control group included individuals without a diagnosed dementia subtype; some participants had mild cognitive impairment clinical dementia rating scale (CDR 0.5) or very mild dementia (CDR 1.0). Patient demographics, comorbidities, medications, laboratory data, and CGA parameters were obtained from medical records. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its later amendments. The University This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its later amendments. Dokuz Eylül University Ethics Committee granted permission to carry out the study (decision no: 2021/18-14, date: 09.06.2021).. As this was a

retrospective study of patients included in our CGA database, a formal a priori power or sample-size calculation was not performed; however, all eligible patients during the study period were included to maximize statistical power. Written informed consent was obtained from all patients, and all data were anonymized before analysis.

Exclusion Criteria

Patients under 65 years of age, those with sequelae of cerebrovascular disease, those with severe musculoskeletal, orthopedic, or peripheral neuromuscular disorders that impair walking and balance (major lower extremity amputation, recent hip fracture/surgery, severe osteoarthritic pain, spinal stenosis with neurogenic claudication), those with uncorrected severe visual impairment or active vestibular disorder, those with an acute, clinically unstable illness at the time of evaluation (e.g., decompensated heart failure, recent stroke or transient ischemic attack, subdural hematoma, delirium, gastrointestinal bleeding, sepsis, acute renal failure, acute coronary syndrome, respiratory failure, liver failure), those under the influence of significant sedative medication during the assessment, patients who are non-ambulatory or unable to stand or walk safely even with standard assistive devices, and patients who are unable to understand and follow the simple instructions required for the standard walking assessment were excluded from the study. Additionally, patients with mixed dementia and those with non-AD, non-DLB, non-basicFTD (bvFTD), non-NPH dementia, and patients with missing data in medical records were also excluded.

Diagnosis of Dementia Subtypes

Clinical, laboratory, radiographic (cranial computed tomography, magnetic resonance imaging, or positron emission tomography), and neurocognitive tests were performed for all cases. For neurocognitive evaluation, the Montreal Cognitive Assessment (MoCA)[19], CDR[20] and the clock drawing test[21] were used.

Dementia (major neurocognitive disorder) was diagnosed based on the diagnostic criteria of Diagnostic and Statistical Manual of Mental Disorders[22]. Then, probable AD[23,24], probable DLB[25,26], bvFTD[27], and NPH[28,29] were diagnosed according to current diagnostic criteria. A geriatrician evaluated all patients, and CGA was performed. Dementia was diagnosed by a geriatrician trained in neurodegenerative diseases.

Comprehensive Geriatric Assessment

Age, sex, education level, medications, comorbidities, Charlson Comorbidity index (CCI)[30], and falls were recorded. Polypharmacy was defined as the regular use of five or more medications, in line with common geriatric literature. Obesity was defined as body mass index (BMI) ≥30 kg/m^2. Mahoney and Barthel[31] and Lawton and Brody[32] scales were used to assess basic and instrumental activities of daily living. Data were recorded for measurements of Romberg, PI, balance and gait analysis performance-oriented mobility assessment (POMA)[33], and orthostatic hypotension[34,35], a routine component of physical assessment in CGA. PI was evaluated using the retropulsion test[36]. The use of a cane, crutches, a walker, and a wheelchair as assistive devices for walking was reviewed in the file. Recurrent falls were defined as two or more falls in the past year (≥2), in line with the majority of the literature[37]. Walking speed below 0.8 m/sec on the 4-meter walking test was recorded as slow walking speed[16]. Participants' nutritional status was assessed using the Mini Nutritional Assessment-Short Form (MNA-sf). Patients with an MNA-sf score of 11 or below were regarded as malnutrition or malnutrition risk. Sarcopenia was diagnosed according to the European Working Group on Sarcopenia in Older People-2[38] criteria. For muscle strength and skeletal muscle index cut-off values, the values established for the Turkish population were used[39]. A FRIED[40] score of three or higher was considered frailty. Hospital biochemistry laboratory records for all participants were also obtained. All biochemical tests were performed on a Diagnostic Modular Systems autoanalyzer (Roche E170 and P-800). 25(OH) vitamin D was measured using radioimmunoassay.

Statistical Analysis

Statistical analyses were conducted using SPSS v 29.0 for Windows (SPSS Inc., Chicago, IL). Patients were divided into five groups: control (cognitively healthy), AD, bvFTD, DLB, and NPH. Descriptive statistics for these groups were reported as mean ± standard deviation for continuous variables and as percentages (%). Continuous variables were compared using ANOVA. Categorical variables were evaluated using Pearson's χ^2 or Fisher's exact test. Logistic regression was performed to examine whether measures, including falls, POMA score, slow walking speed, PI, and use of walking assistive devices, were independently associated with each dementia subtype (compared with controls). Regression models were built using backward stepwise logistic regression. Age and sex were forced into the model; other covariates were entered using backward stepwise selection with entry $p<0.05$ and removal $p>0.10$. For each dementia subtype, the risk relative to the control group was expressed as the odds ratio (OR). Results with $p<0.05$ were considered statistically significant.

RESULTS

After selecting participants based on the inclusion and exclusion criteria, a total of 598 older adults were included in the study: 260 with dementia (136 AD, 31 bvFTD, 51 DLB, 42 NPH) and 338 cognitively healthy individuals serving as the control group. There were statistically significant differences between the control group and the dementia subtype groups in sex, BMI,

Table 1. Characteristics of participants among groups

		Control group (n=338)	AD (n=136)	bvFTD (n=31)	DLB (n=51)	NPH (n=42)	p
Demographics							
Age* (years)		76.36 (5.77)	75.85 (7.89)	76.74 (8.53)	78.11 (6.02)	77.04 (6.53)	0.316
Sex, % male		35.80	50.70	61.30	43.10	45.20	**0.006**
Education* (years)		7.80 (4.78)	7.88 (4.65)	6.74 (4.44)	6.22 (4.23)	7.02 (5.11)	0.137
Polypharmacy (%)		55.30	61.00	64.50	70.60	73.80	0.059
CCI*		1.45 (1.37)	1.97 (1.52)	2.41 (1.62)	2.33 (1.62)	2.95 (1.69)	**<0.001**
Obesity %		31.60	13.50	29.20	32.40	50.00	**0.001**
Comorbidities							
Osteoarthritis %		36.50	15.10	9.70	17.40	28.90	**<0.001**
Cerebrovascular disease %		7.10	4.40	12.90	3.90	11.90	0.245
Diabetes mellitus %		34.60	28.70	29.00	27.50	50.00	0.097
Hypertension %		76.00	58.80	48.40	58.80	69.00	**<0.001**
Peripheral artery disease %		5.30	4.40	6.50	3.9	9.5	0.743
Congestive heart failure %		8.00	5.10	6.50	5.90	9.50	0.796
Coronary artery disease %		21.60	16.20	12.90	21.60	19.00	0.581
Depression %		30.00	25.70	35.50	43.10	31.00	0.222
Drugs							
Antipsychotic %		2.30	19.90	12.90	29.40	14.30	**<0.001**
Antidepressant %		10.70	58.20	64.50	66.70	45.20	**<0.001**
Antihypertensive drugs %		63.90	64.70	58.10	64.70	81.00	0.236
Comprehensive geriatric assessment							
OH %		32.20	28.60	23.30	38.30	20.00	0.308
Malnutrition and malnutrition risk %		23.20	45.90	38.70	60.80	39.00	**<0.001**
Frailty %		25.90	38.50	45.50	56.30	48.60	**<0.001**
Sarcopenia confirmed %		4.20	26.00	10.00	12.90	17.90	**<0.001**
CDR %	0.0	55.30	5.30	0	0	17.10	**<0.001**
	0.5	34.30	25.00	16.70	16.30	34.10	
	1.0	10.40	34.10	60.00	34.70	36.60	
	2.0	0	25.80	20.00	36.70	7.30	
	3.0	0	9.80	3.30	12.20	4.90	
Clock drawing test*		4.43 (0.90)	2.80 (1.71)	2.81 (1.46)	1.85 (1.45)	3.15 (1.79)	**<0.001**
MoCA*		24.26 (3.34)	15.82 (6.79)	19.87 (5.19)	13.66 (4.45)	20.81 (4.04)	**<0.001**
BADL*		94.06 (7.55)	89.08 (14.94)	91.12 (9.37)	79.11 (21.41)	82.26 (20.66)	**<0.001**
IADL*		19.26 (4.37)	12.41 (6.33)	12.35 (6.37)	9.66 (6.24)	14.35 (6.64)	**<0.001**
Laboratory							
Hemoglobin*		12.84 (1.26)	12.97 (1.32)	13.29 (1.27)	12.73 (1.16)	12.59 (1.61)	0.146
25 (OH) vit D*		21.89 (11.58)	19.28 (10.46)	21.94 (11.72)	20.40 (12.08)	20.24 (9.28)	0.217
Vitamin B12*		398.97 (225.80)	378.16 (230.25)	339.06 (178.16)	327.69 (164.50)	416.00 (268.28)	0.152
TSH*		1.96 (3.91)	4.74 (35.93)	1.32 (1.45)	1.44 (0.79)	1.45 (1.35)	0.557
eGFR*		70.79 (16.70)	71.93 (18.25)	77.66 (23.01)	72.06 (18.19)	70.96 (22.47)	0.384
Gait and balance							
Slow gait speed %		29.70	41.80	32.30	62.50	81.00	**<0.001**
POMA*		25.11 (4.11)	23.77 (5.29)	24.61 (3.90)	21.64 (7.15)	20.78 (6.64)	**<0.001**

Table 1. Continued

	Control group (n=338)	AD (n=136)	bvFTD (n=31)	DLB (n=51)	NPH (n=42)	p
Postural instability %	4.70	20.60	22.60	39.20	45.20	**<0.001**
Falls %	31.40	29.40	41.90	68.60	66.70	**<0.001**
Walking assistive devices %	14.10	11.50	7.70	22.50	30.80	0.023

*Mean (SD); AD: Alzheimer's disease, BADL: Basic activities of daily living, bvFTD: Behavioral variant frontotemporal dementia, CCI: Charlson Comorbidity index, CDR: Clinical dementia rating, DLB: Dementia with lewy bodies, eGFR: Estimated glomerular filtration rate, IADL: Instrumental activities of daily living, MoCA: Montreal cognitive assessment, NPH: Normal pressure hydrocephalus, OH: Orthostatic hypotension, POMA: Performance-oriented mobility assessment, SD: Standard deviation, TSH: Thyroid-stimulating hormone

obesity, malnutrition, malnutrition risk, frailty, sarcopenia, slow walking speed, POMA, PI, falls, and use of walking assistive devices (Table 1).

Additionally, the use of antidepressant and antipsychotic medications was significantly lower in the control group compared to the dementia groups (p<0.001; p<0.001, respectively). Laboratory data (hemoglobin, 25(OH) vitamin D, vitamin B12, thyroid-stimulating hormone, and estimated glomerular filtration rate showed no significant differences between the control and dementia subgroups. The results of activities of daily living, MoCA, CDR, and clock drawing tests, which are part of the neurocognitive assessment, showed significant differences between the control and dementia subgroups (p<0.001 for each).

According to the regression analysis, no significant relationship was found between falls, POMA, PI, slow walking speed, use of a walking assistive device, and the AD and bvFTD groups, separately.

DLB was significantly associated with falls, PI, and slow walking speed (OR: 4.67, CI: 95%: 1.37-15.92; p=0.014; OR: 7.38, CI: 95%: 1.67-32.50; p=0.008; and OR: 5.99, CI: 95%: 1.66-21.53; p=0.006, respectively) (Table 2).

NPH was significantly associated with falls, POMA, PI, slow walking speed, and the use of a walking assistive device (OR: 5.70 CI: 95% 1.83-17.70; p=0.003; OR: 0.82 CI: 95% 0.73-0.93; p<0.003; OR: 14.87 CI: 95% 3.64-60.68; p<0.001, OR: 13.37 CI: 95% 3.65-49.02; p<0.001; and OR: 4.92 CI: 95% 1.15-21.07; p<0.031, respectively) (Table 2). In the fully adjusted analyses, AS and FTD were not significantly associated with the outcomes. Full model results, including ORs and 95% CIs for all dementia subtypes, are provided in Supplementary Table S1.

DISCUSSION

In this cross-sectional and retrospective study, we observed that older adults with AD, bvFTD, DLB, and NPH had a higher prevalence of malnutrition and malnutrition risk, frailty, sarcopenia, slow walking speed, PI, falls, use of walking aids, and use of antidepressants and antipsychotics, along with lower POMA scores compared to cognitively healthy older adults. We also demonstrated that DLB was associated with falls, PI, and slow walking speed. In contrast, NPH was associated with falls, PI, lower POMA scores, slow walking speed, and use of walking assistive devices.

Current evidence highlights the significant role of multiple cognitive domains, especially attention and executive functions, in explaining the high variability in mobility performance among cognitively healthy and dementia-diagnosed older adults[41]. The relationship between motor and cognitive impairments has garnered significant interest from researchers and healthcare providers because it could facilitate early detection of those at highest risk for dementia and enable personalized interventions to best preserve cognitive function best[42]. Falls are a significant public health issue worldwide due

Table 2. Comparison of falls, POMA scores, postural instability, slow gait speed, and use of walking assistive devices across DLB and NPH patients

	Control	DLB			NPH		
	OR (95% CI)	OR	95% CI	p	OR	95% CI	p
Falls	Reference (control)	**4.671**	1.371-15.920	**0.014**	**5.706**	1.838-17.709	**0.003**
POMA		1.039	0.905-1.194	0.588	**0.827**	0.731-0.937	**0.003**
Postural instability		**7.385**	1.678-32.502	**0.008**	**14.870**	3.644-60.684	**<0.001**
Slow gait speed		**5.994**	1.668-21.533	**0.006**	13.375	3.650-49.020	**<0.001**
Walking assistive device		0.895	0.171-4.698	0.896	**4.928**	1.152-21.072	**0.031**

CI: Confidence interval, DLB: Dementia with lewy bodies, NPH: Normal pressure hydrocephalus, OR: Odds ratio, POMA: Performance-oriented mobility assessment

Regression model: Age, sex, obesity, sarcopenia, malnutrition, hypertension, osteoarthritis, antidepressant, and antipsychotic use for POMA (continuous), OR represents change in odds of being in the dementia group per 1-point higher POMA score. OR <1 indicates lower POMA scores (worse mobility) are associated with higher odds of dementia

to their high prevalence, morbidity, mortality, healthcare costs, and clinical complications. Many subtypes of dementia exhibit motor impairment as the disease progresses[43]. The occurrence of falls and fall injuries increases with age and is higher in individuals with dementia. All types of dementia are associated with varying degrees of reduced physical and cognitive abilities. In a study by Farup et al.[44] the prevalence of falls across dementia subtypes was 22.4% in early-onset AD, 33.6% in late-onset AD, 50.6% in mixed [AD and vascular dementia (VAD)], 55.3% in VAD, 28.6% in FTD, and 55% in DLB. They suggested that age, comorbidities, and dementia features help explain the differences in fall rates among dementia groups.

In our study, we observed that DLB was associated with falls, PI, and slow walking speed. This finding is consistent with previous studies demonstrating greater gait impairment in DLB than in ADClick or tap here to enter text. DLB patients have extrapyramidal symptoms and signs (akinesia, rigidity) that slow walking and significantly alter spatial and temporal parameters, such as step length[45].

Our results indicate that NPH is associated with falls, PI, slow walking speed, and use of walking aids. It is well known that urinary incontinence and cognitive impairment in NPH patients are accompanied by gait apraxia and falls[46]. Therefore, this is a predictable outcome. Gait disturbance in NPH typically represents a hypokinetic gait with slow walking speed, reduced step length, and increased step width[47]. Our research revealed a link between NPH and low POMA scores. The stronger association of NPH with slow gait and PI, compared with DLB, likely reflects differences in their pathophysiology. In NPH, frontal-subcortical disconnection causes a hypokinetic, short-stepped, and wide-based gait with impaired postural reflexes, whereas DLB gait impairment is mainly due to extrapyramidal motor dysfunction[25,28]. Although our study did not categorize patients by disease stage, gait and balance disturbances generally worsen as the disease progresses in both conditions. Several studies support the finding that POMA (gait, balance, and total) scores are lower in patients diagnosed with idiopathic NPH and may improve with therapeutic cerebrospinal fluid drainage[48]. Although previous studies have suggested that POMA performance is linked to falls in patients with dementia, our cross-sectional design does not allow direct conclusions about the test's predictive (prognostic) value. Nevertheless, our findings emphasize the association between lower POMA scores and a history of falls, underscoring its usefulness as a practical tool for evaluating balance and gait in older adults with dementia. It is important to note that performance on this test depends heavily on participants' understanding and adherence to instructions[49].

Our regression results did not show a significant association between AD diagnosis and factors such as falls, gait issues, or balance problems. In a cohort study of 11,466 people, Sverdrup et al.[50] found that older adults with AD exhibited better physical performance than those with other forms of dementia subtypes. This is consistent with our results. Furthermore, studies highlight the relationship between AD and physical performance decline, showing that among patients with mild cognitive impairment, those with gait, balance, and motor issues are at greater risk of developing AD[51]. Another study supports the notion that gait disturbance in AD is associated with disease stage. Ala and Frey investigated documented gait disturbance in patients with autopsy-proven AD. They found that 16% and 32% of patients with moderate and severe disease, respectively, experienced gait disturbances, while none of the patients with mild AD reported them[52]. Verghese et al.[53] showed in their research that walking speed was slower in patients with AD who had the Apolipoprotein E4 genotype and declined more rapidly than in those without this allele. The lack of significant differences in fall and gait parameters between the control group and the AD or bvFTD groups may be affected by patient selection. Our cohort included patients with mild-to-moderate disease severity, and those with severe functional impairments were less common. Additionally, bvFTD patients mainly exhibit behavioral and executive symptoms rather than motor deficits, which might explain the lack of significant associations. Selection criteria and the exclusion of patients with vascular or mixed dementias may also have contributed to these results.

Our findings show no association between bvFTD diagnosis and falls, gait, or balance problems. Patients with bvFTD, a subtype of frontotemporal lobar degeneration, typically present with a neurobehavioral syndrome. Clinical diagnostic criteria for bvFTD include early declines in social and interpersonal behavior, early impairments in personal behavior regulation, emotional blunting, and loss of insight. Although motor and gait abnormalities have been reported, they usually do not involve a frontal gait pattern. On the other hand, Samra et al.[54] reported that bvFTD patients experienced stepping difficulties more frequently than those with ADClick or tap here to enter text. Some patients diagnosed with DLB or bvFTD had a CDR stage of 0. This likely reflects CDR's limitations in detecting early-stage or non-amnestic presentations and underscores the importance of interpreting CDR stage alongside other cognitive and functional assessments in these groups.

Patients with VAD or mixed dementia were excluded from our study. This is because recent epidemiological and clinicopathological data suggest a significant overlap between cerebrovascular disease and AD, and that both pathologies have additive or synergistic effects[55]. Cases of true VaD without

significant mobility issues are rare, and diagnosing VaD overall remains challenging due to the absence of validated criteria and variability in clinical presentation[56]. We believe this situation could confuse distinguishing between working groups.

Study Limitations

Our current study has several limitations. First, because it is cross-sectional and retrospective, we cannot establish a cause-and-effect relationship. Although we aimed to exclude patients with VaD, we may have overlooked individuals with subclinical cerebrovascular disease. We acknowledge that more comprehensive device-assisted analyses are needed to enable sensitive quantitative gait assessment in clinical practice. This study assessed balance and gait using standard clinical tools such as the POMA, Romberg test, walking speed, and the Retropulsion test. Future research using dual-task or sensor-based gait analysis might provide more sensitive measures of gait issues in dementia.

Beyond its limitations, our study also has notable strengths. It is among the few to assess multiple dementia subtypes within a single geriatric group using CGA measures. Assessing balance, gait, falls, nutritional status, frailty, sarcopenia, and functional abilities provides a comprehensive view of mobility and functional impairment across dementia subtypes. These strengths enhance the clinical relevance of our results and lay a strong foundation for future research.

CONCLUSION

The ability to move independently greatly enhances overall well-being and autonomy in older adults. Enhancing our understanding of gait and balance disorders is crucial for optimizing health and function in seniors. This study contributes to the literature by examining multiple dementia subtypes within a single geriatric cohort using CGA parameters, enabling direct comparison of balance, gait, and fall-related features across subtypes. A detailed assessment of gait and balance, along with an understanding of their associations with various etiological subtypes of dementia, may aid early diagnosis and disease monitoring through cost-effective evaluations. Balance-gait disturbances and falls may serve as early markers to distinguish between dementia subtypes; however, larger future cohort studies with more participants are needed to confirm these findings.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and its later amendments. Dokuz Eylül University Ethics Committee granted permission to carry out the study (decision no: 2021/18-14, date: 09.06.2021).

Informed Consent: Written informed consent was obtained from all patients, and all data were anonymized before analysis.

Footnotes

Authorship Contributions

Concept: F.M., A.T.I., Design: D.K., A.T.I., Data Collection or Processing: F.M., Analysis or Interpretation: F.S.D., A.T.I., Literature Search: F.M., F.S.D., D.K., Writing: F.M., F.S.D., A.T.I.

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ORIGINAL ARTICLE

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The Evolution of *in vivo* Synaptic Plasticity Research in Learning and Memory (1987-2024): A Bibliometric Analysis

Öğrenme ve Bellek Alanındaki *in vivo* Sinaptik Plastisite Araştırmalarının Evrimi (1987-2024): Bibliyometrik Bir Analiz

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ABSTRACT

Aim: Synaptic plasticity forms the neurobiological foundation of learning and memory. Despite the rapid growth of *in vivo* electrophysiological studies, a systematic evaluation of global publication trends remains lacking. This study aimed to map the evolution, research themes, and scientific collaborations related to hippocampal plasticity.

Materials and Methods: A bibliometric analysis evaluated 2,348 English-language articles from the Web of Science Core Collection (1987-2024), extracted on October 2, 2025. To investigate systems-level dynamics, the exact topic (TS) query was TS= ("synaptic plasticity") AND ("hippocampus" OR "learning" OR "memory") AND ["long-term depression (LTD)"] OR "long term potentiation (LTP)" OR "LTP" OR "LTD" AND ("*in vivo*"). VOSviewer and Biblioshiny were utilized to analyze publication trends, thematic maps, co-authorship networks, and institutional distributions.

Results: Publications peaked in 2013 (130 articles) and have gradually declined since. Core keywords included synaptic plasticity, hippocampus, and LTP, while trending topics such as pathology, interleukin-1 beta and gamma oscillations indicated a shift toward clinical neuropathology. The most cited authors were Song S., Miller K.D., Abbott L.F., and Morris R.G.M. The strongest collaboration networks involved Rowan M.J., Bramham C.R., and Korte M. The United States, Germany, and China led the field, with Stanford and Northwestern Universities as top institutions.

Conclusion: Synaptic plasticity and hippocampal mechanisms remain the conceptual core of this research area; however, recent trends highlight a growing emphasis on neuroinflammatory and pathological processes shaping future directions in neuroscience.

Keywords: LTP, synaptic plasticity, hippocampus, learning, memory, bibliometric analysis

ÖZ

Amaç: Sinaptik plastisite, öğrenme ve belleğin nörobiyolojik temelini oluşturur. *İn vivo* elektrofizyolojik çalışmaların hızla artmasına rağmen, küresel yayın eğilimlerinin sistematik olarak değerlendirilmesi hâlen eksiktir. Bu çalışmanın amacı, hipokampal plastisite ile ilişkili gelişimi, araştırma temalarını ve bilimsel iş birliklerini haritalandırmaktır.

Gereç ve Yöntemler: Bu bibliyometrik analizde, Web of Science Core Collection veri tabanından 2 Ekim 2025 tarihinde elde edilen, 1987-2024 yılları arasında yayımlanmış 2.348 İngilizce makale değerlendirilmiştir. Sistem düzeyindeki dinamikleri incelemek amacıyla kullanılan kesin konu araması (TS) sorgusu şu şekildedir: TS= ("sinaptik plastisite") AND ("hipokampus" VEYA "öğrenme" VEYA "bellek") VE ["uzun süreli baskılanma (LTD)" VEYA "uzun süreli güçlenme (LTP)" VEYA "LTP" VEYA "LTD"] VE ("*in vivo*"). Yayın eğilimleri, tematik haritalar, ortak yazarlık ağları ve kurumsal dağılımların analizinde VOSviewer ve Biblioshiny yazılımları kullanılmıştır.

Bulgular: Yayın sayısı 2013 yılında zirveye ulaşmış olup bu yılda 130 makale yayımlanmış, sonrasında ise kademeli olarak azalmıştır. Temel anahtar kelimeler arasında sinaptik plastisite, hipokampus ve uzun süreli güçlenme, LTP yer alırken; patoloji, interlökin-1 beta ve gama osilasyonları gibi öne çıkan güncel konular, klinik nöropatolojiye doğru bir yönelime işaret etmiştir. En çok atıf alan yazarlar Song S., Miller K.D., Abbott L.F. ve Morris

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R.G.M. olmuştur. En güçlü iş birliği ağları Rowan M.J., Bramham C.R. ve Korte M. etrafında şekillenmiştir. Amerika Birleşik Devletleri, Almanya ve Çin bu alanda öne çıkan ülkeler olurken, Stanford ve Northwestern Üniversiteleri başlıca kurumlar arasında yer almıştır.

Sonuç: Sinaptik plastisite ve hipokampal mekanizmalar bu araştırma alanının kavramsal merkezini oluşturmaya devam etmektedir. Bununla birlikte, güncel eğilimler nörobilimde gelecekteki araştırma yönelimlerini şekillendiren nöroenflamatuvar ve patolojik süreçlere yönelik ilginin giderek arttığını göstermektedir.

Anahtar Kelimeler: UDG, sinaptik plastisite, hipokampüs, öğrenme, bellek, bibliyometrik analiz

INTRODUCTION

Electrophysiological methods have played a critical role in understanding neuronal communication and the functional organization of the brain[1]. Following Lord Edgar Adrian's 1920s action potential recordings from single nerve fibers, the field reached a theoretical milestone in 1952 when Hodgkin and Huxley elucidated the ionic mechanisms of the action potential[2-5]. These advancements laid the groundwork for modern electrophysiological analyses. In 1966, Terje Lømo observed that high-frequency stimulation of the hippocampal perforant path led to a sustained enhancement in synaptic transmission[6]. These findings were confirmed in a seminal 1973 publication by Tim Bliss, which established long term potentiation (LTP) and represented a paradigm shift in synaptic plasticity research. Since the 1970s, direct recordings of synaptic transmission, particularly within the hippocampus, has gained substantial empirical attention in the literature[5,7-10].

LTP refers to the long-lasting strengthening of synaptic connections between neurons in an activity-dependent manner and is regarded as the cellular basis of learning and memory[11]. Subsequent studies demonstrated that the sustained enhancement of synaptic transmission observed in LTP was not unidirectional, leading to the introduction of the concept of long-term depression (LTD) into the literature. LTD represents a long-term reduction in synaptic transmission strength following specific stimulation patterns. This process is considered critical for eliminating unnecessary information and maintaining network homeostasis[11]. Currently, *in vivo* electrophysiology remains one of the most robust techniques used to understand how the mechanisms of synaptic plasticity change under both physiological and pathological conditions, such as Alzheimer's disease, epilepsy, and depression[8,12-14]. In this context, the concepts of "synaptic plasticity", "hippocampus", "learning", "memory", and "*in vivo* electrophysiology" are frequently examined together in the literature. The dentate gyrus, CA1, and CA3 regions are the hippocampal structures most sensitive to synaptic plasticity forms such as LTP and LTD[15,16]. Over the past four decades, research has demonstrated that these concepts carry substantial implications not only in basic neuroscience but also in the context of clinical neurobiology[17,18]. In particular, electrophysiological investigations of learning and memory impairments such as those observed in Alzheimer's disease have contributed to the identification of potential therapeutic targets[19]. Currently, electrophysiological recordings related to synaptic plasticity are utilized not only to elucidate the neurobiological foundations of memory but also to reveal the mechanisms disrupted under pathological conditions. Therefore, bibliometric analysis of synaptic plasticity studies using *in vivo* electrophysiological recordings is important for elucidating the historical development, research intensity, prominent themes, and future directions of this field. Despite the large number of publications, comprehensive bibliometric mapping of global trends, leading countries, collaboration networks, and core themes in synaptic plasticity is lacking. Similarly, recent bibliometric reviews widely used in synaptic plasticity and related fields show that this method is one of the most effective ways to systematically map the increase in publication volume and categorize the contributions of countries, regions, and authors, and their relevance to research hotspots[20,21].

Accordingly, the present study aims to construct a systematic map of the research in this field by integrating the themes of synaptic plasticity, *in vivo* electrophysiology, the hippocampus, learning, and memory. The goal is to provide a guiding framework for understanding the developmental dynamics of the research area and to inform new research strategies, thereby offering valuable insights to both basic and clinical neuroscientists.

MATERIALS AND METHODS

Data Sources and Search Strategy

To specifically evaluate the functional dynamics of intact neural networks, the search strategy for this bibliometric analysis was restricted to *in vivo* approaches and foundational electrophysiological paradigms of synaptic plasticity, namely LTP and LTD. While the broader literature on synaptic plasticity includes extensive *in vitro* slice preparations, molecular biological assays, and non-invasive neuroimaging, incorporating these diverse methodologies would have generated a highly heterogeneous dataset. Such heterogeneity may obscure the specific evolutionary trajectory of systems-level electrophysiological research. By focusing strictly on "*in vivo",* "LTP" and "LTD", this study aims to robustly map research that directly links synaptic mechanisms to behavioral outcomes and clinical neuropathologies in living organisms.

Based on this established methodological framework, on October 2, 2025, data were retrieved from the Web of Science (WoS) database using the following topic search query: exact topic (TS) = ("synaptic plasticity") AND ("hippocampus" OR "learning" OR "memory") AND ("LTD" OR "LTP" OR "LTD") AND ("*in vivo*").

The selection criteria were limited to the document type "articles"; only publications indexed in the WoS Core Collection including the Science Citation Index Expanded (SCI-EXPANDED), Emerging Sources Citation index and Social Sciences Citation index were included. The search was further restricted to publications written in English. Most of the identified studies belonged to the field of Neurosciences, followed by multidisciplinary sciences, pharmacology and pharmacy, biochemistry and molecular biology, behavioral sciences, cell biology, clinical neurology, physiology, psychiatry, and psychology, with additional contributions from other related disciplines.

Prior to importing the dataset into VOSviewer and biblioshiny, a rigorous data preprocessing protocol was applied. Initial screening for duplicates yielded no redundant records, as the extraction was limited to a single database, no duplicate records were identified. Finally, the standardization of author names was manually reviewed to prevent the artificial fragmentation or merging of publication records. During this manual inspection, author name consistency was assessed by cross-referencing the authors' institutional affiliations and their historical co-authorship networks to resolve any potential ambiguities. This inspection confirmed a high level of consistency in WoS indexing of the major contributing authors and institutions, therefore, no significant manual unification was required prior to the co-authorship and citation network analyses. As a result, the search yielded 2,348 articles, with publication dates ranging from 1987 to 2024. The complete step-by-step process of literature identification, screening, and inclusion is visually detailed in the flow diagram, provided as Supplementary Figure 1.

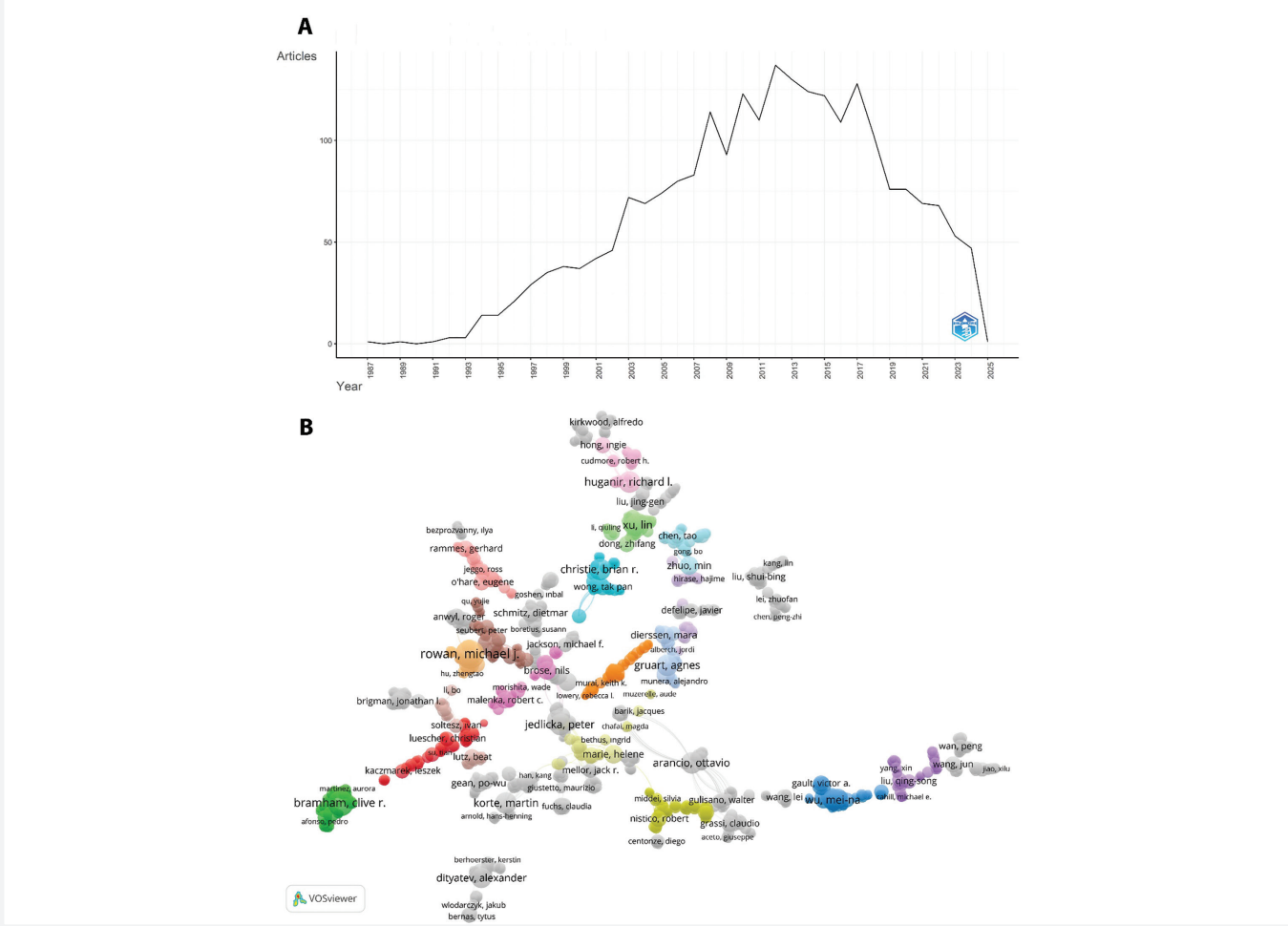

Figure 1. Annual publication counts and co-authorship network. (A) Distribution of annual publication counts from 1987 to 2024, (B) co-authorship network map of prominent researchers

Statistical Analysis

The bibliometric data were exported in plain text format and analyzed using VOSviewer (v.1.6.20; Centre for Science and Technology Studies, Leiden University, Leiden, The Netherlands) and the Biblioshiny interface of the Bibliometrix R package (v.4.1.2)[22]. Descriptive analyses included publication and citation counts, annual publication trends, and productivity distributions by country, institution, author, and journal. To ensure the reproducibility of the results, specific thresholds were applied: for co-authorship analysis, a minimum threshold of one document and one citation per author was set in VOSviewer. To ensure the thematic significance of the results, the "Word Minimum Frequenc" parameter in biblioshiny was set to five, restricting inclusion to terms with at least five occurrences. Additionally, the "Number of Words per Year" metric was limited to three to identify the most prominent and representative keywords for each year. All network visualizations were performed using the "Association Strength" normalization method. Network analyses were conducted to visualize co-authorship, co-citation, and keyword co-occurrence relationships. Additionally, a thematic map was generated to identify major research themes and their interconnections. All bibliometric networks were visualized using VOSviewer's mapping and clustering algorithms. Ethical approval and informed consent were not required, as the study did not involve human or animal subjects.

RESULTS

Annual Publication Count and Co-authorship Analysis

Within the scope of the selected search terms, a total of 2,348 articles were published between 1987 and 2024, with an average of 62 publications per year. In terms of annual output, the fewest publications were recorded between 1987 and 1991 (1 article), whereas the highest number was observed in 2013 (130 articles). As illustrated in Figure 1A, the number of publications shows a declining trend after 2013. Based on the co-authorship analysis using VOSviewer, a network map, shown in Figure 1B, was generated to identify the most interconnected and collaborative authors. To ensure the significance of the collaboration network, the co-authorship analysis was conducted using a minimum threshold of one publication and one citation per author. A total of 2,348 articles were authored by 7,460 unique researchers, corresponding to a mean of 3.18 authors per article. The most highly cited authors were Song S., Miller K. D., and Abbott L. F. with 2,039 citations, followed by Morris R. G. M., with 1,722 citations, and Celnik P., with 1,686 citations. In terms of total link strength (TLS), the top three authors were Rowan M. J. (TLS: 87), Bramham C. R. (TLS: 87), and Korte M. (TLS: 85).

Keyword Co-occurrence Analysis and Trend Topic Terms

From the 2,348 articles analyzed, a total of 2,760 keywords were extracted, comprising both Author Keywords and Keywords Plus terms indexed in the WoS database. The most frequently used keywords (Figure 2A) were synaptic plasticity (257 occurrences), hippocampus (256 occurrences), LTP (102 occurrences), Alzheimer's disease (94 occurrences), and memory (78 occurrences). Trend topic terms (Figure 2B), identified using a minimum word frequency threshold of 5, were primarily pathology, interleukin-1 beta, and gamma oscillations.

Thematic Map of Research Themes

The conceptual structure of research on synaptic plasticity was further explored using the thematic map function in biblioshiny (Figure 3). To ensure a comprehensive yet focused representation, the analysis was conducted with a "number of words" parameter set to 250, allowing for a broad inclusion of terms. Additionally, the "minimum cluster frequency (per thousand docs)" was set at 5, which normalized cluster inclusion by requiring at least five occurrences per thousand documents. According to the map, the cluster consisting of the terms "LTP" synaptic plasticity, and *"in vivo*" is positioned among the basic themes (lower-right quadrant), representing the conceptual core and foundational framework of the field. In contrast, the cluster comprising the terms "dentate gyrus," "LTP," and "rat" falls into the specialized themes category (upper-left quadrant); indicating that while these topics exhibit relatively low centrality, they represent highly developed and well-established specialized sub-domains within the field. Furthermore, the cluster containing the terms "Alzheimer's disease" and "brain" is located among the emerging or declining themes (lower-left quadrant), suggesting that these neurodegenerative disease-related topics, while associated with synaptic plasticity studies, either represent newly emerging research directions or themes experiencing a relative loss of importance. Overall, the thematic map analysis indicates that the concepts of LTP and synaptic plasticity constitute the field's unchanging core research axis, while research associated with Alzheimer's disease forms a subcluster with strong developmental potential, and its integration into the field is ongoing.

Co-citation Analysis of Cited Authors

Co-citation refers to instances where two or more authors or sources are cited together within the same publication. In the present analysis, authors with at least 20 citations were included. Figure 4A illustrates the co-citation network of authors. The most frequently co-cited authors were Bliss (321 citations), Malenka (201 citations), and Abraham W.C. (150 citations). However, as shown in Figure 4B, the annual co-citation rate demonstrated a declining trend after 2019.

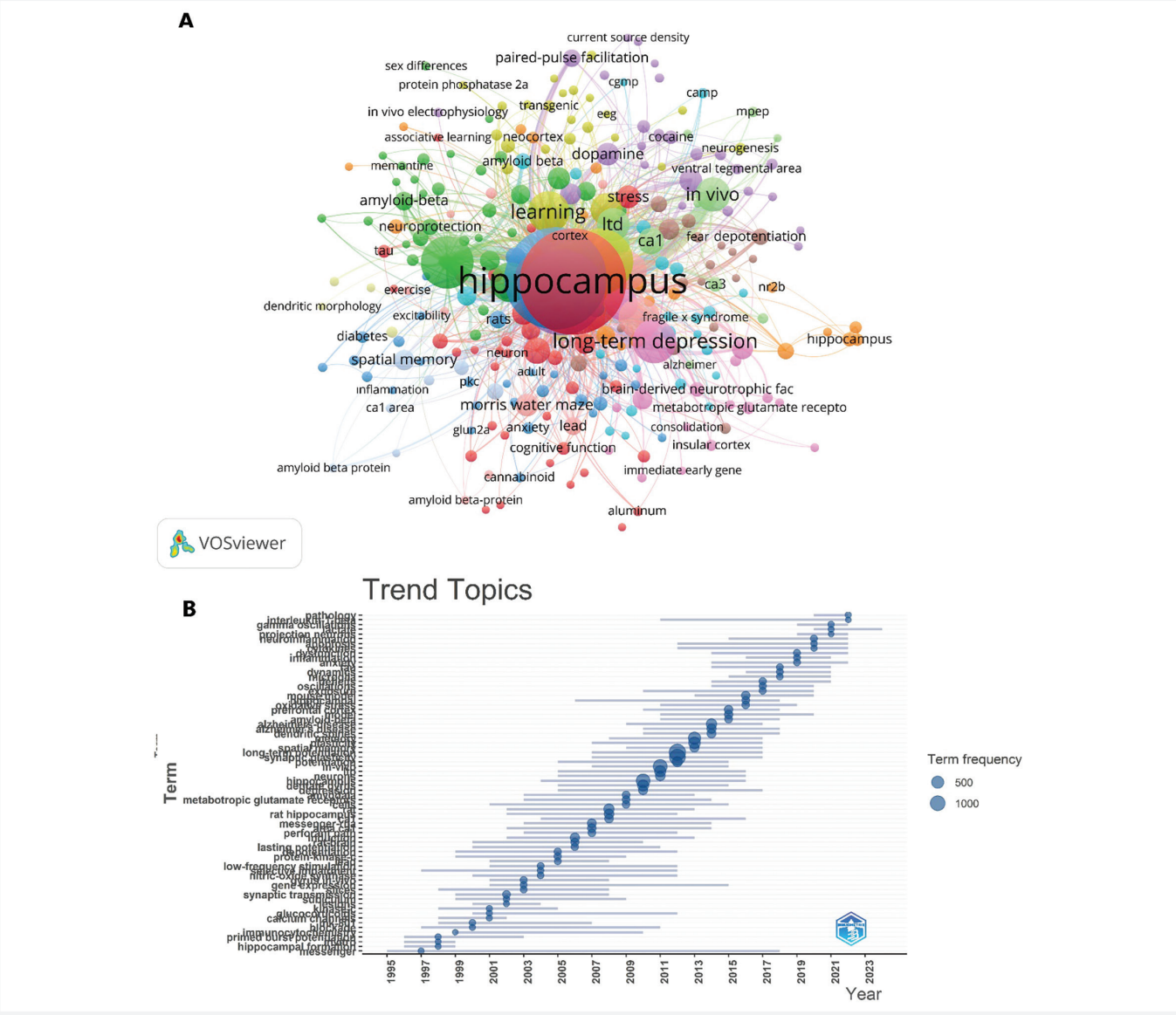

Figure 2. Keyword analysis and emerging trends. (A) Co-occurrence network of keywords showing the most frequent terms, (B) overlay visualization of trend topic terms

Bibliographic Coupling of Organizations

To construct a network map of inter-institutional citation relationships, a bibliographic coupling analysis was performed. To ensure a comprehensive representation of institutional impact, the inclusion criteria were set at a minimum of one published work and one citation per organization.

Figure 5 delineates the citation relationships among institutions. The most represented institutions in terms of publication count were Tokyo University (30 publications), Stanford University (27 publications), and Johns Hopkins University (26 publications). The institutions affiliated with the most highly cited publications were Stanford University (5,159 citations), Northwestern University (3,613 citations), and the University of California, San Francisco (3,071 citations).

Bibliographic Coupling of Countries and Journals

A network map illustrating citation relationships among countries was constructed based on the countries of origin of the publications. To ensure robust analysis of global interactions, the inclusion criteria were set to a minimum of one publication and one citation per country. Analyses of citation relationships were conducted for both countries and journals. Figure 6A shows the publication and citation connections among countries. In this network, the United States of America (USA) dominated both citation counts (51,108 citations) and

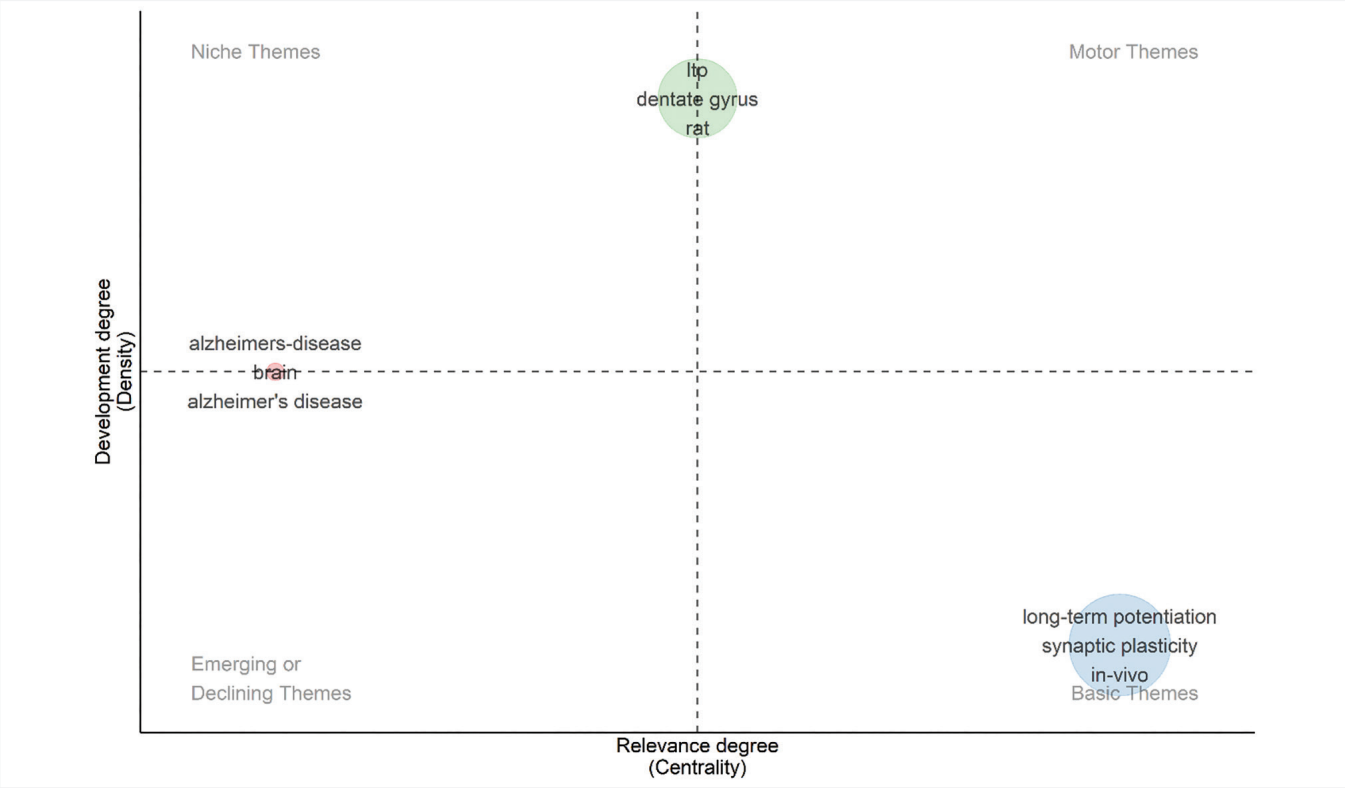

Figure 3. Thematic map of research themes. Visualization of research clusters based on centrality and density, categorized into basic, specialized, and emerging/declining themes

publication output (575 publications); Germany and China ranked second and third in citations, while China and Germany ranked second and third in publications. Figure 6 B shows the citation network of journals. The Journal of Neuroscience led the journal ranking, topping both citation counts (13,818 in the citation network) and publication numbers (132 in the citation network), with Nature Neuroscience (81 in the citation network) and the Proceedings of the National Academy of Sciences of the USA (44 in the citation network) completing the top three in citations and TLS.

DISCUSSION

This bibliometric analysis characterizes research trends from 1987 to 2024 focusing on *in vivo* electrophysiological studies of synaptic plasticity. The scientific framework of the field began to take shape in the 1980s, following the foundational discovery of LTP[6] in the previous decade and the subsequent standardization of electrophysiological techniques. During the first two decades of the analyzed period (the 1990s and 2000s), research was primarily marked by a focus on the hippocampus and its role in learning and memory[15,23]. Our findings confirm that historically, the concept of synaptic plasticity evolved strictly around the core phenomena of LTP and LTD, with the hippocampus receiving particular attention due to its critical role in memory processes. However, bibliometric indicators from 2010 to 2024 reveal a paradigm shift, with a growing emphasis on disease models (e.g., Alzheimer's disease, epilepsy, depression), neuroinflammation, and oxidative stress[19,24]. This thematic evolution provides crucial context for interpreting the observed decline in annual publication counts after 2013 in our dataset. Rather than indicating an actual decrease in scientific interest, this trend likely reflects an evolving terminology in the field. As research shifted toward specialized clinical applications and pathologies, authors may have increasingly utilized highly specific molecular, genetic, or disease-centric keywords rather than the broader, foundational terms ("synaptic plasticity" or "LTP/LTD") required by our search strategy. Furthermore, the diversification of the field toward advanced non-invasive neuroimaging or *in vitro* human-derived cellular models falls outside the scope of our strict *in vivo* electrophysiological criteria and has thereby reduced the retrieval rate of relevant studies in recent years.

Similarly, the reported decline in co-citation rates after 2019 should be interpreted cautiously. This trend represents a natural bibliometric phenomenon related to the citation time window; recently published articles inherently require a latency

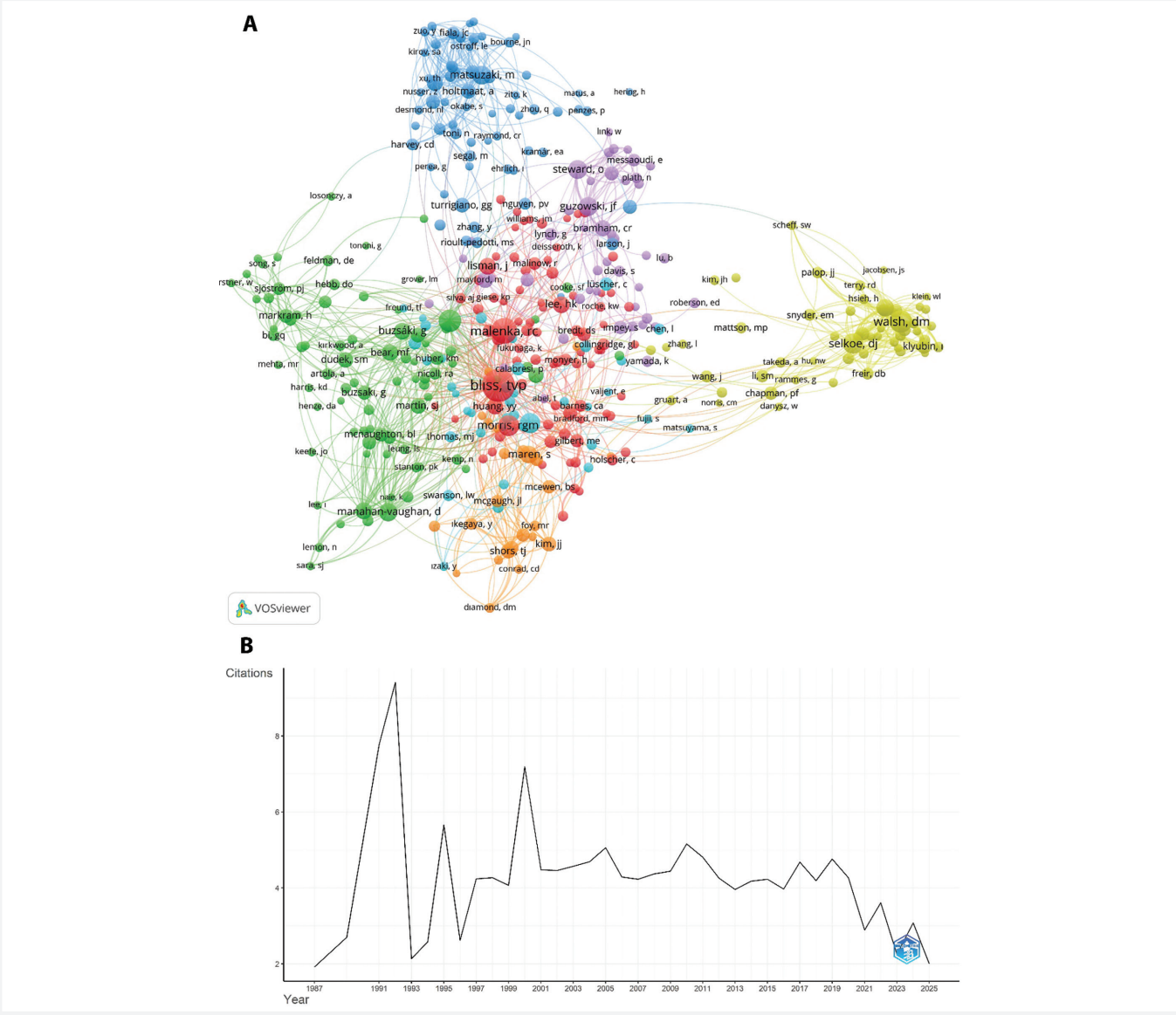

Figure 4. Co-citation analysis. (A) Co-citation network of authors (threshold: minimum 20 citations), (B) annual co-citation rate trends

period of several years to accumulate a substantial number of citations compared to older, foundational papers. Despite these terminological shifts and time-lag limitations, the high citation density of articles published in high-impact journals such as the Journal of Neuroscience, Nature Neuroscience, and Proceedings of the National Academy of Sciences of the United States of America indicates that *in vivo* synaptic plasticity continues to hold a central position in neuroscience research.

Supporting this evolving landscape, our thematic map analysis reveals that while the inclusion of "synaptic plasticity" and "LTP" constitutes a significant research effort, the relatively low centrality of "Alzheimer's disease" data suggests that the full incorporation of neurodegenerative data into the synaptic plasticity paradigm remains a matter of ongoing debate. Furthermore, the most significant thematic shift identified in the trend topic terms analysis is the transition from basic synaptic functions to the specific molecular drivers of these clinical neuropathologies[19,25,26]. In particular, the increasing prominence of emerging keywords highlights a multi-dimensional expansion in the field. This evolution spans from the molecular and neuroinflammatory levels evidenced by terms like interleukin-1 beta and pathology to systems level network dynamics, reflected by the interest in gamma oscillations. This trend confirms that understanding synaptic plasticity impairments now requires integrating immunological mechanisms with large-scale electrophysiological network activities[27-30].

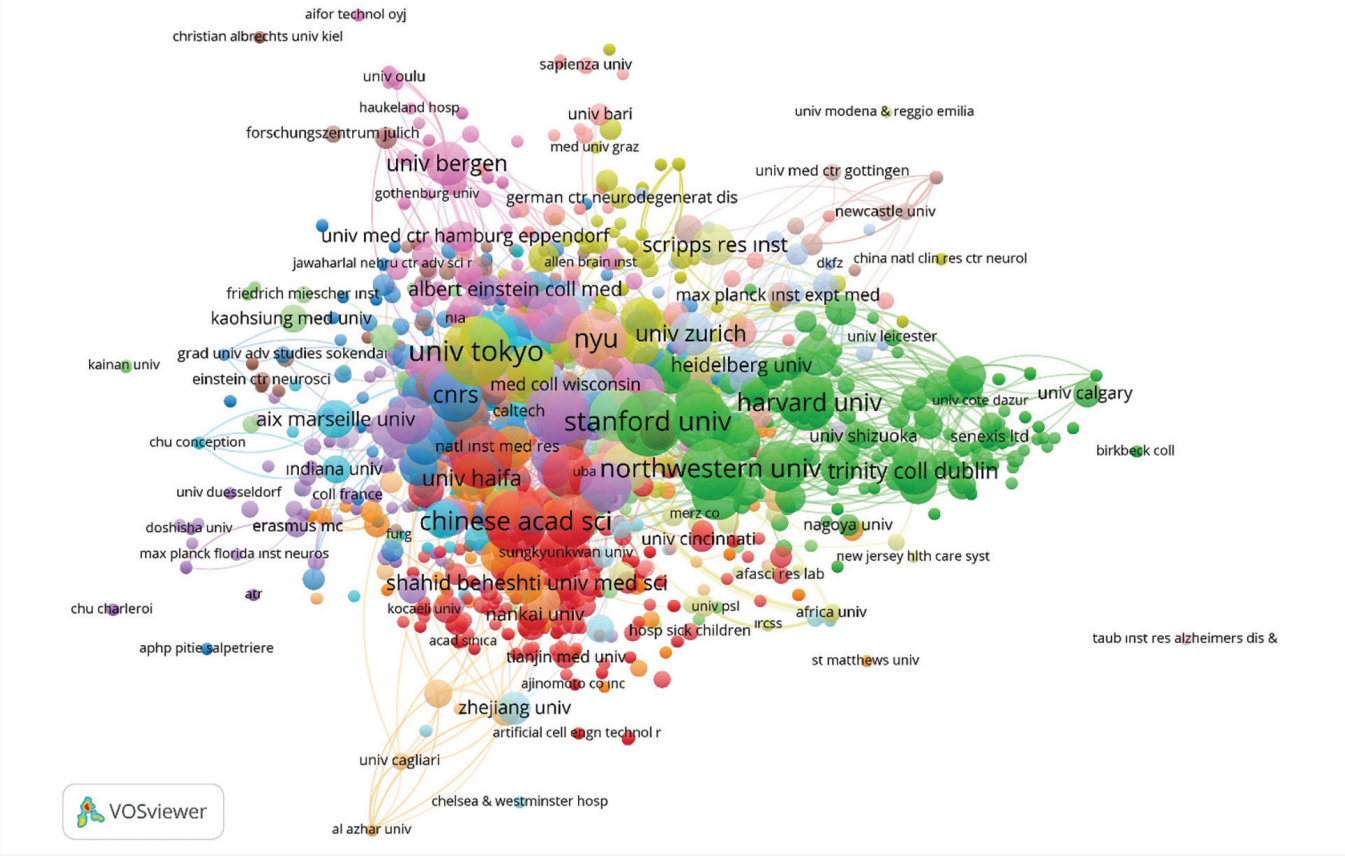

Figure 5. Institutional citation relationships. Network map depicting bibliographic coupling and citation connections among the most productive organizations

Analysis of author and institutional networks revealed that the United States, Germany, and China hold leading positions in research output and collaboration within the field. US-based authors achieved the highest citation rate, with 2,039 citations for the article titled "Competitive Hebbian Learning through Spike-Timing-Dependent Synaptic Plasticity"[31]. The notably high citation counts associated with Stanford University and Northwestern University indicate that these institutions have made influential contributions, shaping the direction of synaptic plasticity research. However, it was observed that most collaboration networks remain confined to regional clusters, with relatively few international partnerships. This pattern suggests benefits of promoting greater interdisciplinary and cross-national collaboration for future studies. In light of these observed trends, advancing the understanding of neural circuits and developing therapeutic targets for neurodegenerative and neuropsychiatric disorders may increasingly rely on multidisciplinary methodological integration.

Study Limitations

Although this study provides a comprehensive bibliometric overview, it is limited to data from the WoS database and to publications written in English. One of its main limitations is the exclusion of research indexed in other databases, such as Scopus and PubMed, which may have led to the omission of relevant studies. Additionally, restricting the analysis to journal articles excluded other forms of scholarly output, such as conference proceedings and book chapters, which potentially limited the early identification of emerging research trends. Future research could broaden the global perspective of the field by incorporating multiple databases and publications in different languages, thereby providing a more comprehensive representation of *in vivo* synaptic plasticity research worldwide.

Furthermore, the restrictive nature of our search strategy specifically the requirement for the terms "*in vivo*" and "LTP/LTD", constitutes a limitation and may introduce selection bias affecting the dataset's representativeness. Consequently, this study does not cover the entirety of research on synaptic plasticity. Substantial bodies of literature employing *in vitro*

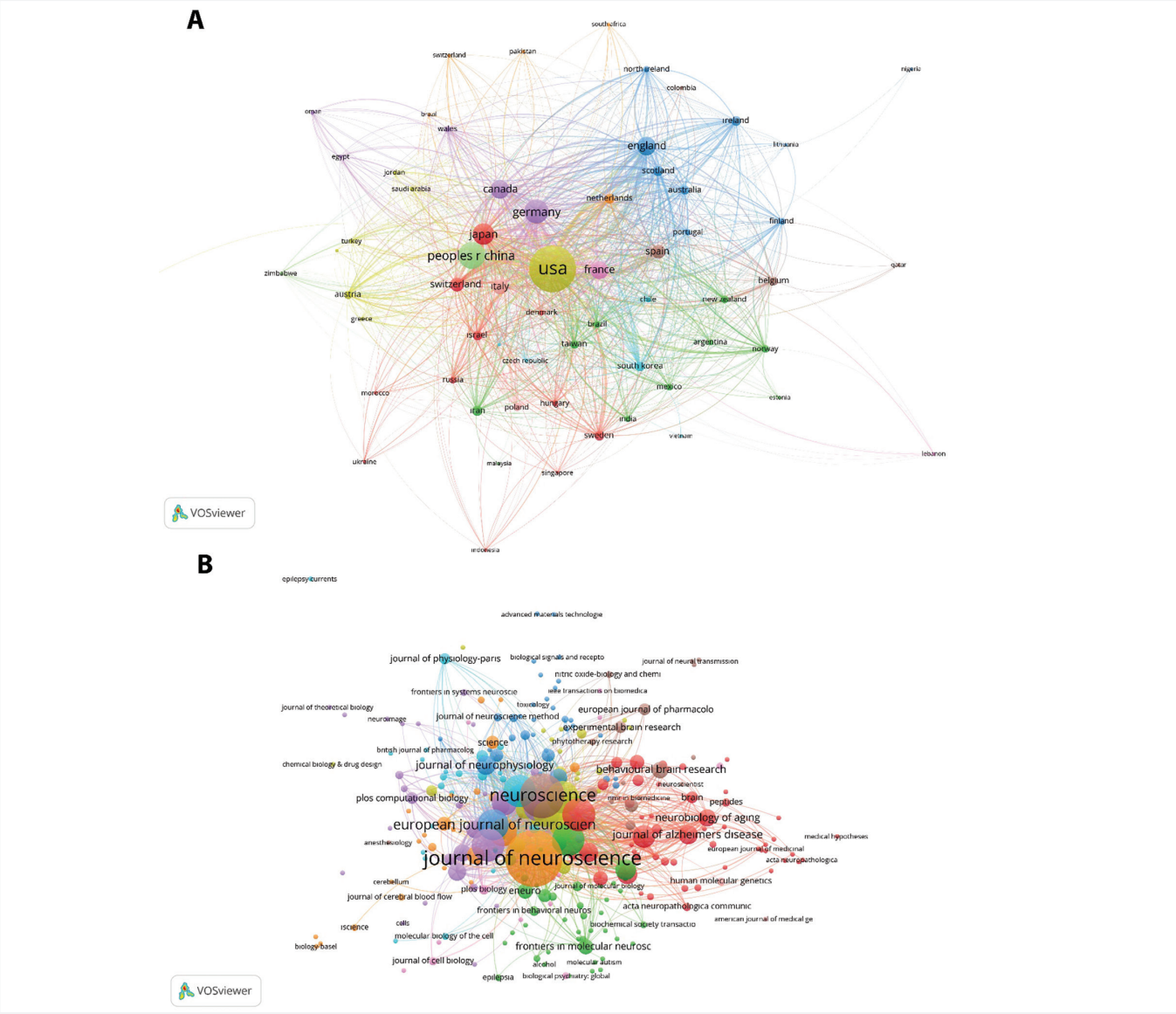

Figure 6. Global and journal-based citation networks. (A) Publication and citation connection maps for the most active countries, (B) citation network of leading journals in the field

slice electrophysiology, advanced cellular imaging, and broader molecular frameworks of plasticity were intentionally excluded. Therefore, our findings should be interpreted not as a universal map of all plasticity research but as a specialized bibliometric representation of systems level *in vivo* functional network dynamics.

CONCLUSION

This study presents a bibliometric mapping of research on synaptic plasticity utilizing *in vivo* electrophysiological methods between 1987 and 2024. The results indicate that the field possesses a well-established core, while appearing to diversify through a growing focus on clinical pathologies and inflammatory mechanisms. Although LTP and LTD remain the central concepts of this research, bibliometric indicators from 2021 to 2024 suggest an increasing interest in specific topics including pathology, interleukin-1 beta, and gamma oscillations. This analysis provides an observational framework for understanding the historical dynamics of the field and highlights potential opportunities for future research and interdisciplinary collaboration.

Ethics

Ethics Committee Approval: Our study did not involve any human or animal research and does not require Ethics Committee Approval.

Informed Consent: Ethical approval and informed consent were not required, as the study did not involve human or animal subjects.

Footnotes

Authorship Contributions

Concept: M.A., Design: M.A., Data Collection or Processing: M.A., N.D., C.S., Analysis or Interpretation: M.A., Literature Search: M.A., Writing: M.A., N.D., C.S.

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

Financial Disclosure: The authors declared that this study received no financial support.

Data availability statement: The raw bibliographic data analyzed during the current study are available in the Web of Science (WoS) Core Collection database. The dataset can be fully replicated using the specific search query and inclusion criteria detailed in the Materials and Methods section.

Supplementary Figure 1 Link: https://d2v96fxpocvxx.cloudfront.net/cf9d60d6-523c-458a-a2e6-78728d3ffbb0/content-images/ffbc68d7-365a-4f8b-bcbb-97489c319f22.pdf

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ORIGINAL ARTICLE

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Immunohistochemical Evaluation of Placental NRG-1 Expression in Pregnant Women with Gestational Diabetes Mellitus

Gestasyonel Diabetes Mellitus Tanısı Alan Gebelerde Plasental NRG-1 Ekspresyonunun İmmünohistokimyasal Olarak İncelenmesi

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ABSTRACT

Aim: Gestational diabetes mellitus (GDM) is a significant pregnancy complication that threatens maternal and fetal health. Understanding the histopathological effects of GDM on the placenta and potential molecular markers is crucial for the diagnosis and treatment of the disease. Neuregulin-1 (NRG-1), which plays a role in cell proliferation, differentiation, and glucose metabolism, is one of the most promising candidate molecules in this context. This study aimed to compare histopathological findings and NRG-1 expression in the placentas of pregnant women diagnosed with GDM and healthy women using immunohistochemical methods and to identify potential micromorphological and molecular changes specific to GDM.

Materials and Methods: Study groups included Group 1 (control, n=22) healthy pregnant women and Group 2 (GDM, n=22) pregnant women diagnosed with GDM. Hematoxylin and eosin (H&E) and NRG-1 immunohistochemical staining were performed on all placental tissues. H&E sections were evaluated for villous edema, fibrinoid accumulation, fetal capillaries, and syncytial knots. Immunohistochemical staining intensity was classified as negative (-), weak (+), moderate (++), and strong (+++). Demographic data and vital signs were analyzed using SPSS.

Results: In the GDM group, compared to the control group, an increase in the number of villi, villous edema, dilatation of fetal capillary structures and an increase in the number of capillaries, an increase in syncytial knot formation, significant fibrinoid accumulation, and an increase in NRG-1 expression in the trophoblast cells around the villi, villous mesenchymal stromal cells, and vascular endothelial cells were detected in the examined placenta sections.

Conclusion: GDM has been shown to cause pathological alterations in the placenta at the light microscopic level while also increasing NRG-1 expression. This study is the first to investigate the role of NRG-1 in placental tissues obtained from GDM cases. NRG-1 appears to be a potential marker in the pathophysiology of GDM, underscoring the need for further studies in this field.

Keywords: Gestational diabetes mellitus, neuregulin-1, placenta, immunohistochemistry

ÖZ

Amaç: Gestasyonel diabetes mellitus (GDM), anne ve fetüs sağlığını tehdit eden önemli bir gebelik komplikasyonudur. GDM'nin plasenta üzerindeki histopatolojik etkilerini ve olası moleküler belirteçleri anlamak, hastalığın tanısı ve tedavisi için çok önemlidir. Hücre proliferasyonu, farklılaşması ve glikoz metabolizmasında rol oynayan nörogulin-1 (NRG-1), bu bağlamda en umut verici aday moleküllerden biridir. Bu çalışmada, GDM tanısı alan ve sağlıklı gebe kadınların plasentalarında histopatolojik bulgular ve NRG-1 ekspresyonunun immünohistokimyasal yöntemlerle karşılaştırılması ve GDM'ye özgü olası mikromorfolojik ve moleküler değişikliklerin belirlenmesi amaçlanmıştır.

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Cite this article as: Günaydın Özcan B, Doğan K, Kasap B, Akın MN, Yücel A, Çetinavcı D, et al. Immunohistochemical evaluation of placental NRG-1 expression in pregnant women with gestational diabetes mellitus. Nam Kem Med J. 2026;14(3):352-360

Gereç ve Yöntem: Çalışma grupları; Grup 1 (kontrol, n=22) sağlıklı gebeler ve Grup 2 (GDM, n=22) GDM tanılı gebelerden oluşmuştur. Tüm plasental dokulara hematoksilen ve eozin (H&E) ve NRG-1 immünohistokimyasal boyama uygulanmıştır. H&E kesitlerinde villöz ödem, fibrinoid birikim, fetal kapiller ve sinsityal düğümler değerlendirilmiştir. İmmünohistokimyasal kesitlerde boyanma yoğunluğu; negatif (-), düşük (+), orta (++), ve yüksek (+++) olarak sınıflandırılmıştır. Demografik veriler ve vital bulgular SPSS programı ile analiz edilmiştir.

Bulgular: GDM grubunda kontrol grubuna göre; incelenen plasenta kesitlerinde villus sayısında artış, villöz ödem, fetal kapiller yapılarında dilatasyon ve kapiller sayısında artış, sinsityal düğüm oluşumunda artış ile belirgin fibrinoid birikimi ve villus çevresindeki trofoblast hücrelerinde, villus mezenkimal bağ doku hücrelerinde ve damar endotel hücrelerinde NRG-1 ekspresyonunda artış tespit edilmiştir.

Sonuç: GDM, plasentada ışık mikroskobik düzeyde patolojik değişikliklere neden olmakla birlikte NRG-1 ekspresyonunu artırmıştır. Bu çalışma, GDM tanılı olgulara ait plasental dokularda NRG-1 rolünü inceleyen literatürdeki ilk çalışmadır. NRG-1, GDM patofizyolojisinde potansiyel bir belirteç görevi görebilmekte ve bu alanda daha fazla araştırma gerekmektedir.

Anahtar Kelimeler: Gestasyonel diabetes mellitus, nörogulin-1, plasenta, immünohistokimya

INTRODUCTION

Gestational diabetes mellitus (GDM) refers to glucose intolerance that begins during pregnancy or is first detected during pregnancy[1]. According to the 2017 guidelines of the International Diabetes Federation, hyperglycemia during pregnancy is estimated to occur in 16.2% of pregnancies, or approximately 21.3 million live births. Of these cases, an estimated 86.4% are due to GDM, 6.2% to pre-gestational diabetes (diagnosed before pregnancy), and 7.4% to other types of diabetes first diagnosed during pregnancy (including type 1 and type 2 diabetes)[2]. Risk factors for GDM include overweight/obesity, advanced maternal age, Western-style diet[3], ethnic background[4], polycystic ovary syndrome, and a family history of insulin resistance and/or diabetes[1,5]. It is noted that each of these risk factors is directly or indirectly associated with impaired pancreatic β-cell function and/or insulin sensitivity[6].

GDM increases the risk of pregnancy complications such as preterm birth and preeclampsia[7]. Exposure to maternal hyperglycemia during pregnancy leads to hyperinsulinemia in the fetus, and it has been shown that this condition increases the risk of macrosomia, neonatal hypoglycemia, hyperbilirubinemia, etc.[8]. Babies born to mothers with GDM are at high risk for obesity, type 2 diabetes mellitus, cardiovascular disease, and related metabolic disorders in the long term[9-11]. It has been reported that women with a history of GDM have an increased risk of developing type 2 diabetes mellitus later in life[12,13], and that their risk of cardiovascular disease also increases due to changes in their vascular structures[14-16].

The placenta functions as a specialized organ that facilitates the exchange of substances between the mother and the fetus during pregnancy. It is responsible for transferring maternal nutrients and oxygen to the fetus and for transporting waste products accumulated in the fetus back into the maternal circulation. Additionally, the placenta produces hormones that regulate maternal physiology during pregnancy and acts as a barrier against the maternal immune system. It separates the maternal and fetal circulations, which are in contact through various surfaces. Because the placenta is situated between the maternal and fetal circulations, it is exposed to both the mother's and the fetus's diabetes-related endocrine and metabolic disorders[17-19]. It has been reported that maternal hyperglycemia can affect fetal development by influencing placental structure and vascularization[20], and may increase the risk of maternal and fetal complications as well as perinatal morbidity and mortality[21].

In the presence of GDM, the placenta is thought to play a triggering role in inflammatory processes. It has been noted that the interaction between adipose tissue and the placenta may contribute to the development of both systemic inflammation and insulin resistance. These two tissue types produce high levels of various pro-inflammatory mediators such as interleukin (IL)-6, IL-8, tumor necrosis factor-alpha, resistin, and leptin[22,23]. In GDM, the balance between pro-inflammatory and anti-inflammatory cytokines in the placenta is disrupted[24]. It has been reported that GDM increases the risk of perinatal mortality and morbidity by causing abnormal development of the placenta and umbilical cord, and is therefore a significant public health issue[25].

Neuregulin-1 (NRG-1) is a member of the neuregulin family. Encoded and produced by the *NRG-1* gene, it undergoes various modifications both within and outside the cell. Different isoforms of the NRG-1 molecule play roles in various signaling pathways. It is noted that NRG-1-related signaling pathways are essential for the proper functioning of many systems in the body. Within the cell, NRG-1 plays a role in numerous mechanisms, including growth, proliferation, differentiation, and cell death. Studies have shown that NRG-1 and its associated signaling pathways play a role in the pathophysiology of neurological, psychiatric, cardiovascular, and many other diseases[26-28]. Glucose metabolism is also among the physiological mechanisms in which NRG-1 is involved. It has been reported that NRG-1 plays a role in the pathophysiology of GDM, a condition characterized by impaired glucose metabolism[29]; however, the exact mechanism by which NRG-1 exerts its effects in GDM remains unclear.

The aim of this study is to evaluate the histopathological effects of GDM on the placenta and changes in NRG-1 expression. Placental samples obtained from healthy and GDM-affected pregnant women were examined histopathologically and for NRG-1 expression using immunohistochemical methods.

MATERIALS AND METHODS

Groups

This study was conducted using placental tissue samples obtained from volunteer pregnant women who presented to the Obstetrics and Gynecology Outpatient Clinic at Muğla Sıtkı Koçman University Faculty of Medicine and who agreed to participate by reading and signing the informed consent form. For this study, approval was obtained from the Muğla Sıtkı Koçman University Clinical Research Ethics Committee on January 16, 2020, under decision no. 01/VI, confirming that the study was ethically appropriate. Human rights were protected in accordance with the principles of the "Declaration of Helsinki as revised in 2013." A total of 44 pregnant women were included in the study. Study groups: The study consisted of two groups: Group 1 (Control group), comprising healthy pregnant women with no underlying conditions (n=22), and Group 2 (GDM group), comprising pregnant women diagnosed with GDM (n=22). The control group consisted of healthy pregnant women who presented to the outpatient clinic and had no history of coronary artery disease, liver disease, kidney disease, or preeclampsia. The pregnant women underwent routine prenatal examinations performed by an obstetrician-gynecologist. The GDM diagnosis was made based on the results of a single-step 75 g oral glucose tolerance test performed between the 24th and 28th weeks of gestation, following at least an 8-hour overnight fast, in women without a known history of diabetes. Fasting, one-hour, and two-hour blood glucose levels were measured; a diagnosis of GDM was made if any of these values were equal to or higher than the threshold values. Threshold values were determined in accordance with the 2010 IADPSG recommendations as fasting ≥92 mg/dL, first hour ≥180 mg/dL, and second hour ≥153 mg/dL[30].

Inclusion Criteria

For the control group, healthy pregnant women aged 18-40 years who were in their 38th-40th week of gestation were included. For the GDM group, pregnant women aged 18-40 years who were in their 38th-40th week of gestation, had been diagnosed with GDM, were managed with diet, and were not receiving insulin therapy were included.

Exclusion Criteria

Participants with severe physical illness, alcohol, tobacco, or illicit drug use; preeclampsia; liver or kidney failure; any endocrine disorder; those with a history of gastric or intestinal surgery, those who had received medical treatment for any reason within the past three months, cases with chronic inflammation or infection, cases with fetal biometry outside the 10th-90th percentile on obstetric ultrasound, and cases diagnosed with GDM who were receiving insulin therapy were excluded from the study.

Histopathological Analysis

Placenta samples obtained from women who had given birth were washed with physiological saline solution. The tissue samples were placed in a 10% formalin solution for fixation and left to stand for 24 hours. Subsequently, the tissues were rinsed under running water for 24 hours to remove the fixative. Following dehydration and clearing using a tissue processor, the tissues were embedded in paraffin. Sections 5 μm thick were cut using a microtome (Thermo Scientific Finesse Me+), stained with hematoxylin and eosin (H&E), and evaluated using a light microscope (Nikon Eclipse 80i).

Immunohistochemical Analysis

Following deparaffinization, the sections were placed in a series of decreasing alcohol concentrations (96%, 96%, 80%, 70%) to initiate the hydration process. Hydration was completed by soaking the sections in distilled water for 5 minutes. For antigen retrieval, the sections were boiled in citrate buffer for 5-10 minutes and then left to cool without removing the citrate buffer. The cooled sections were washed with Phosphate-Buffered Saline (PBS). The borders of the sections were outlined with a hydrophobic pen PAP pen. Endogenous peroxidase was blocked (3% H_2O_2), followed by washing with PBS. Protein blocking solution was applied to the sections and left for 5 minutes, after which the blocking solution was removed without washing. The anti-NRG-1 primary antibody (Santa Cruz Biotechnology, cat: sc-393006) was applied to the sections at the dilution recommended by the manufacturer, and the sections were incubated at 4 °C in a humid environment for 24 hours. Staining procedures were performed in accordance with the manufacturer's protocol. Negative control sections were prepared to assess staining specificity; in the negative control, PBS was used instead of the primary antibody, and no specific staining was observed. The sections were then washed with PBS solution. A biotinylated secondary antibody compatible with the primary antibody was added and incubated at room temperature for 20 minutes. In the next step, horseradish peroxidase was applied and incubated for 10 minutes. After washing with PBS, the chromogenic substrate 3,3′-diaminobenzidine was added and incubated until a color change was observed. After washing with PBS, the nuclei were stained with Mayer's hematoxylin. Following these procedures, the sections were sealed with Entellan.

For immunohistochemistry (IHC) analysis, the sections were evaluated by two independent and blinded histologists using a light microscope (Nikon Eclipse 80i) at 20X magnification. Based on staining intensity, the sections were classified as unstained (–), weakly stained (+), moderately stained (++), and strongly stained (+++). Inter-observer agreement for IHC scoring was assessed using Cohen's kappa test, and the kappa value was found to be 0.82.

Statistical Analysis

The required sample size for the statistical analyses planned in the study was calculated using the G* Power 3.1.9.7 software. For the analysis, the t-test for independent samples was selected to compare the difference between the means of two independent groups. The power analysis was conducted a priori (predefined); the effect size (Cohen's d) was set at 0.78, the α error level at 0.05, and the statistical power (1–β) at 0.80. A one-tailed test was assumed. Based on these parameters, the calculation resulted in a minimum required sample size of 22 for each group (44 in total for both groups).

Statistical analysis of the data was performed using the SPSS 14 statistical software (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation or median and 25th to 75th percentiles. The normality of the data was assessed using the Kolmogorov-Smirnov or Shapiro-Wilk test. Mean differences between the control and study groups were compared using the Student's t-test. Continuous variables that did not follow a normal distribution were evaluated using the Mann-Whitney U or Kruskal-Wallis tests, depending on the number of independent groups. Variables that followed a normal distribution (gravidity, number of living children, number of miscarriages, gestational age at delivery, birth weight, systolic blood pressure, diastolic blood pressure, and hemoglobin level) were compared between groups using Student's t-test, whereas variables that did not follow a normal distribution (fasting glucose level) were analyzed using the Mann-Whitney U test. NRG-1 expression was assessed semi-quantitatively (– / + / ++ / +++), and differences in distribution between groups were evaluated using the chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

The clinical and demographic characteristics of a total of 44 pregnant women are presented in Table 1. No statistically significant differences were observed between the control and GDM groups in terms of gravidity, number of living children, number of miscarriages, gestational age at delivery, birth weight, systolic blood pressure, diastolic blood pressure, and hemoglobin levels. Blood glucose levels were significantly higher in the GDM group compared to the control group ($p<0.05$).

Histopathological Findings

Placentas from the control and GDM groups were examined in H&E-stained sections. Sections from the control group demonstrated normal histological architecture of stem villi, terminal villi, fetal capillaries within the villous stroma, and the syncytiotrophoblast layer. In the control group, syncytial knots were observed, and fetal capillaries were identified within the villous stroma. The intervillous spaces showed normal histological architecture, with no evidence of pathological dilatation or narrowing. Minimal fibrinoid deposition was observed in the intervillous and perivillous areas (Figure 1). Sections from the GDM group showed an increased number of villi and villous edema. Dilatation and increased number of fetal capillaries within the villous stroma were observed. An increased number of syncytial knots was noted. The intervillous spaces were generally narrowed; however, dilatation was observed in areas with fibrinoid deposition. Prominent fibrinoid deposition was identified in the intervillous, perivillous, and intravillous areas (Figures 1-3).

Immunohistochemical Findings

Placental NRG-1 expression, as previously described in the literature, was observed in both the nucleus and cytoplasm of the cells[31]. In the control group, placental NRG-1 expression showed weak staining (+) in trophoblast cells surrounding the villi, whereas no staining (–) was detected in villous mesenchymal stromal cells and vascular endothelial cells (Table 2, Figure 4). In the GDM group, placental NRG-1 expression showed strong staining (+++) in trophoblast cells surrounding the villi, while

Table 1. Demographic and clinical characteristics and laboratory data of the groups

Groups	Gravidity*	Parity*	Number of miscarriages**	Gestational week**	Infant weight**	Systolic blood pressure*	Diastolic blood pressure**	Blood glucose level**	Blood hemoglobin level**	Maternal age**
Control (n=22)	2 (1-2)	2 (1-2)	0.40±1.14	38 (34-41)	3229.09±623.63	113.13±16.65	72.40±10.41	90.86±12.61	11.82±0.95	27.13±4.38
GDM (n=22)	2 (1-3)	1 (1-2)	0.45±0.73	38 (35-41)	3300.90±386.52	116.36±16.19	71.50±10.04	104.31±17.37[a]	11.78±1.10	28.22±4.38
p-values	0.682	0.399	0.252	0.666	0.622	0.300	0.852	0.015	0.906	0.778

*Expressed as median and 25th-75th percentiles, **Data are presented as frequency (percentages in parentheses) or mean ± standard deviation, except for descriptive statistics. [a]Control vs. gestational diabetes mellitus p=0.015. GDM: Gestational diabetes mellitus

weak staining (+) was detected in villous mesenchymal stromal cells and vascular endothelial cells (Table 2, Figure 4).

DISCUSSION

GDM is defined as glucose intolerance with onset or first recognition during pregnancy[1]. Histopathological changes in placental tissue associated with GDM have been demonstrated in numerous studies, with largely consistent findings reported in the literature. In particular, an increase in syncytial knots, villous stromal edema, and fibrinoid deposition have been

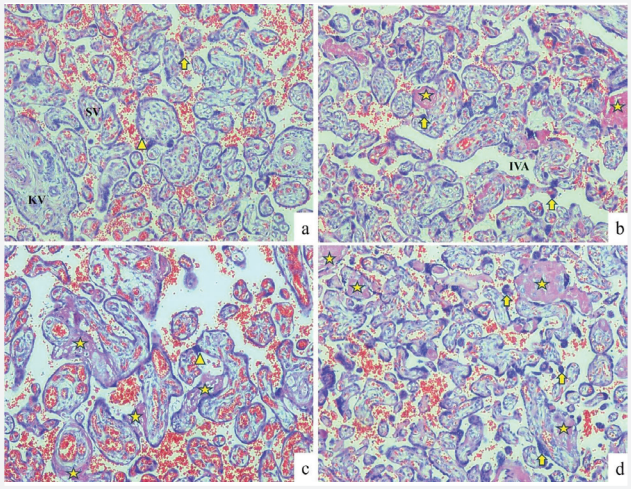

Figure 1. Placental sections from all groups

(a) In the placental section of the control group, stem villus, free villus, syncytial knot (arrow), and syncytial bridge (arrowhead) were observed (H&E; X100). (b) In the placental section of the control group, chorionic villi, syncytial knot (arrow), intervillous space, and fibrinoid material deposits (asterisk) were observed (H&E; X100). (c) In the placental section of the GDM group, chorionic villi, increased fibrinoid material deposition (asterisk), and syncytial bridge (arrowhead) were observed (H&E; X100). (d) In the placental section of the GDM group, chorionic villi, increased fibrinoid material deposition (asterisk), and an increased number of syncytial knots (arrow) were observed (H&E; X100).

GDM: Gestational diabetes mellitus, H&E: Hematoxylin and eosin". No other changes are required

Table 2. Anti-NRG-1 immunoreactivity

Groups	Trophoblast cells around the villi	Villus mesenchymal connective tissue cells	Endothelial cells in the villus mesenchymal connective tissue
Group 1 (Control group)	+	-	-
Group 2 (GDM group)	+++	+	+

GDM: Gestational diabetes mellitus, NRG-1: Neuregulin-1

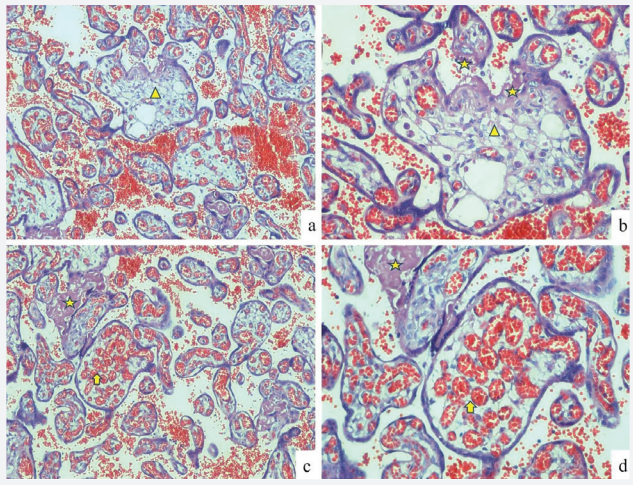

Figure 2. Placental sections from the GDM group

(a) Villous edema (arrowhead) was observed (H&E; X100). (b) Villous edema (arrowhead) and fibrinoid material deposits (asterisk) were observed (H&E; X200). (c) Fetal capillary structures in the villous stroma (arrow) and fibrinoid material deposits (asterisk) were observed (H&E; X100). (d) Fetal capillary structures (arrow) and fibrinoid material deposits (asterisk) were observed (H&E; X200)

GDM: Gestational diabetes mellitus, H&E: Hematoxylin and eosin

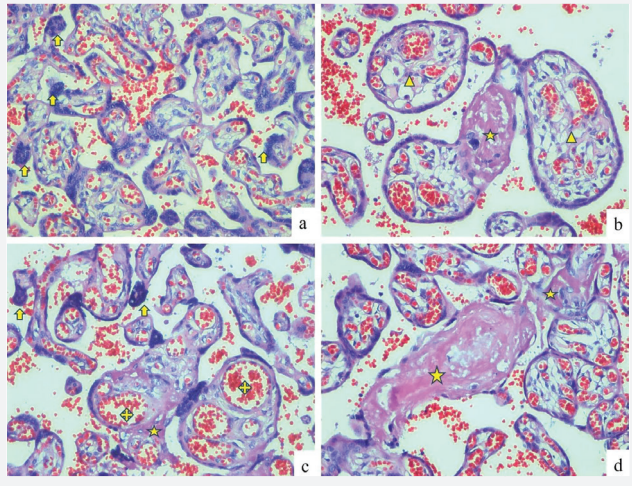

Figure 3. Placental sections from the GDM group (a) Syncytial knot structures (arrow) were observed (H&E; X200). (b) Villous edema (arrowhead) and fibrinoid material deposition (asterisk) were observed (H&E; X200). (c) Syncytial knot structures (arrow), fibrinoid material deposition (asterisk), and dilatation of fetal capillaries within the villous stroma (plus sign) were observed (H&E; X200). (d) Fibrinoid material deposits (asterisk) were observed (H&E; X200)

GDM: Gestational diabetes mellitus, H&E: Hematoxylin and eosin

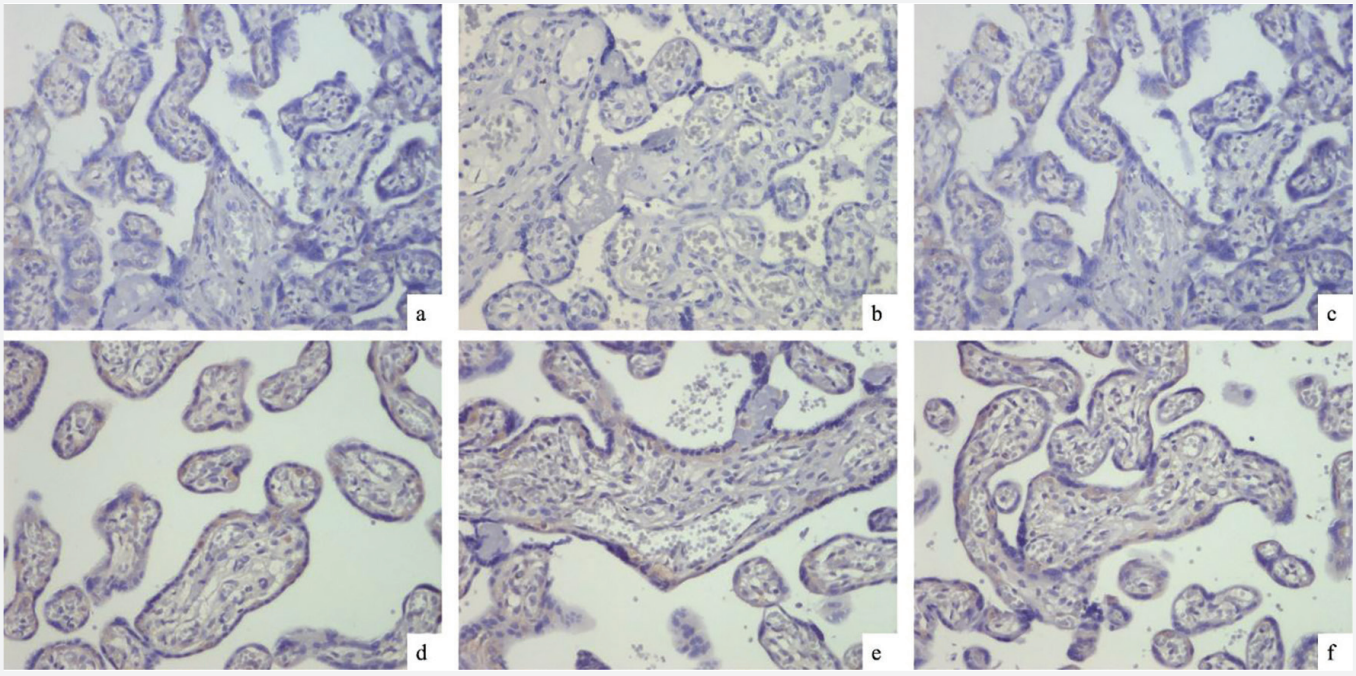

Figure 4. NRG-1 immunoreactivity (a-c) anti-NRG-1 immunoreactivity in placental sections from the control group (X200). (d-f) anti-NRG-1 immunoreactivity in placental sections from the GDM group (X200)

GDM: Gestational diabetes mellitus, NRG-1: Neuregulin-1

consistently reported in multiple studies[32-37]. In addition to these common findings, several specific histopathological alterations have also been reported: villous agglutination and chorangiosis by Aldahmash et al.[32]; increased villous number and villous vascularity by ElSawy et al.[33]; chronic inflammation and villous infarction by Lai et al.[34]; proliferation of fetal capillaries by Verma et al.[35]; fibrinoid deposition in perivillous areas by Meng et al.[36]; and villous immaturity by Gheorman et al.[37]. These differences suggest that GDM exerts complex effects on placental micromorphology not only at the structural level but also at the immunological and vascular levels.

In our study, placental samples obtained from cases diagnosed with GDM were histopathologically evaluated using H&E staining and compared with those of the control group. An increased number of villi, villous edema, dilatation and increased number of fetal capillaries, a marked increase in syncytial knots, and widespread fibrinoid deposition in the intervillous, perivillous, and intravillous areas were identified. A substantial proportion of these findings is consistent with previous studies investigating placental changes associated with GDM. In particular, increased syncytial knots, villous stromal edema, and fibrinoid deposition have been frequently reported in earlier studies[32-37], and these changes are among the characteristic features of placental remodeling associated with GDM. However, some findings observed in our study, particularly prominent dilatation of stromal capillaries and increased capillary density, have been reported to a limited extent in the literature[33,35]; in our study, these vascular changes were more widespread and pronounced. In addition, the accumulation of fibrinoid material not only in the perivillous area but also in the intervillous and intravillous areas represents a noteworthy finding that has been rarely emphasized in the existing literature[36,37]. In this respect, our study may provide novel contributions to the understanding of placental micromorphology in GDM.

NRG-1, a member of the neuregulin family, is thought to play an important role in pathological conditions characterized by impaired glucose metabolism, such as diabetes, obesity, and metabolic syndrome; however, the mechanisms by which NRG-1 contributes to dysregulated glucose metabolism remain unclear. *In vitro* studies have demonstrated that NRG-1 treatment increases the expression of the GLUT4 transporter in muscle cells and activates glucose uptake. These effects have been reported to be mediated through signaling pathways such as PI3K–PDK1–PKCζ and ERK1/2–Akt[29]. These molecular mechanisms suggest that NRG-1 may contribute to glucose homeostasis through insulin-like pathways. Further studies are needed to clarify the mechanisms by which NRG-1 is involved in the pathophysiology of diabetes and to determine whether NRG-1 has potential therapeutic effects.

In a study by Zhang et al.[29], serum NRG-1 levels were evaluated in 36 pregnant women with GDM at 24-28 weeks of gestation; serum NRG-1 levels were found to be higher in the GDM group compared to the control group. In a study by Lee et al.[38] investigating the genetic relationship between pre-pregnancy obesity and GDM, no statistically significant difference in *NRG-1* gene expression was reported between GDM patients with and without pre-pregnancy obesity. In another study by Lee et al.[39], psychiatric conditions such as anxiety, depression, and stress were found to be more prevalent in patients with GDM compared to healthy pregnant women, and one of the genes associated with these conditions was reported to encode the NRG-1 protein.

As previously discussed in the literature, several studies have examined the association between GDM and NRG-1; however, to the best of our knowledge, no study to date has assessed NRG-1 expression in placental samples from patients with GDM.

In our study, NRG-1 expression was evaluated in placental tissue samples from patients with GDM using the IHC method. NRG-1 expression was found to be higher in placental samples obtained from patients with GDM compared to the control group. This finding is consistent with a clinical study reporting elevated serum NRG-1 levels in patients with GDM[29], as well as with findings from diabetic animal models[40]. The observed endogenous increase suggests a compensatory response to oxidative stress, inflammation, and cellular damage associated with hyperglycemia. However, increased NRG-1 expression does not necessarily indicate an improvement in the underlying pathophysiology. Despite this increase, the biological activity of endogenous NRG-1 may remain limited due to impaired receptor sensitivity, dysregulation of intracellular signaling pathways, and insufficient levels of active NRG-1 reaching target tissues. In contrast, recombinant NRG-1 administration provides a pharmacologically potent signal that exceeds physiological levels, thereby enhancing glucose uptake, more robustly activating PI3K/Akt and ERK pathways, and alleviating vascular and mitochondrial damage[40-42]. Therefore, the coexistence of increased endogenous NRG-1 levels and the need for recombinant NRG-1 therapy does not represent a contradiction; rather, it reflects the insufficiency of the endogenous compensatory response and the superior therapeutic potential of exogenous treatment.

In addition to GDM, NRG-1 has also been reported to play a role in other pregnancy-related disorders. In a study by Kilis et al.[31], in which placental NRG-1 expression was evaluated by IHC in pregnancies complicated by preeclampsia, the intensity of anti–NRG-1 staining around the villi was reported to be lower in the preeclampsia group compared with controls. In an experimental study by Arutjunyan et al.[43], decreased placental NRG-1 levels were observed in pregnant rats with prenatal hyperhomocysteinemia. These differences suggest that NRG-1 expression may be subject to distinct regulatory mechanisms depending on the pathophysiological processes occurring during gestation. While the increase observed in GDM may reflect a compensatory response to hyperglycemia, the decrease observed in conditions such as preeclampsia or hyperhomocysteinemia may be related to endothelial dysfunction and placental oxidative stress suppressing NRG-1 expression. Therefore, alterations in NRG-1 levels may be associated with distinct pathways specific to the etiopathogenesis of each condition. In this context, the changes in placental NRG-1 expression observed in GDM may be linked to disease-specific compensatory and pathophysiological mechanisms; however, the clinical significance of this association requires further elucidation through advanced molecular and functional studies.

Study Limitations

Although this study achieved its intended objectives, it has certain limitations. The most notable limitation is the absence of biochemical analyses, given that GDM is a multisystem disorder. In addition, patients receiving insulin therapy were excluded from the GDM group to ensure a homogeneous study population. Future studies are planned to compare patients with and without insulin requirements. Another significant limitation is the absence of body mass index (BMI) data. Given the potential effects of obesity on both the development of GDM and NRG-1 expression, the inability to include BMI in the analyses may limit the interpretation of the findings. Finally, the absence of advanced imaging techniques, such as electron microscopy and fluorescence microscopy, which could enhance the accuracy and interpretability of the data, constitutes another limitation of this study.

CONCLUSION

In conclusion, it appears that diabetes occurring during pregnancy may lead to abnormalities in NRG-1 expression as well as placental defects. It is thought that this condition may stem from the effects of NRG-1 on embryogenesis and angiogenesis. This study is the first to demonstrate histopathological changes in the placenta in cases of GDM and to address the role of NRG-1. In this regard, it will make a significant contribution to the literature at a foundational level.

Ethics

Ethics Committee Approval: Approval for this study was obtained from the Muğla Sıtkı Koçman University Clinical Research Ethics Committee via decision no. 01/VI dated January 16, 2020, confirming that the study is ethically acceptable.

Human rights were protected in accordance with the principles of the "Declaration of Helsinki as revised in 2013."

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

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., M.N.A. Concept: H.E., B.G.Ö., Design: H.E., B.G.Ö., F.Ö. Data Collection or Processing: B.G.Ö., A.Y., K.D. Analysis or Interpretation: H.E., D.Ç., K.D., A.Y. Literature Search: B.G.Ö., H.E., A.Y., K.D. Writing: B.G.Ö., A.Y., K.D., D.Ç.

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

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CASE REPORT

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A Young Woman Diagnosed with Takayasu Arteritis: A Comprehensive Case Report

Takayasu Arteriti Tanısı Almış Genç Bir Kadın: Kapsamlı Bir Olgu Sunumu

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ABSTRACT

Takayasu arteritis (TAK) is a rare, chronic large-vessel vasculitis that primarily affects the aorta and its major branches. It is more prevalent in Asian populations, with significant geographical variations. The disease predominantly affects women, typically in their second or third decade of life. Diagnosis is challenging due to its non-specific symptoms and lack of definitive laboratory tests, relying mainly on clinical suspicion and imaging. The 2022 American College of Rheumatology/European League Against Rheumatism criteria for TAK diagnosis require patients to be under 60 and have imaging findings consistent with large-vessel vasculitis. Additional clinical and imaging features contribute to a scoring system, with a total of 5 or more confirming the diagnosis. This case report describes a 26-year-old woman with no previous medical conditions, presenting with recurrent fever and weight loss. Clinical examination revealed a difference in pulse and blood pressure between the arms, suggestive of vascular involvement. Laboratory findings included elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, with no other abnormalities. Computed tomography (CT) angiography did not reveal vascular changes, but positron emission tomography (PET)/CT demonstrated mild increased fluorodeoxyglucose uptake in the right subclavian artery, consistent with vasculitis. The patient was diagnosed with TAK and treated with methotrexate and corticosteroids, resulting in significant improvement in inflammatory markers and clinical symptoms. By the sixth month, both ESR and CRP had normalized. This case highlights the importance of evaluating acute phase reactants, comparing pulses and blood pressure in both arms, and considering TAK in young female patients with recurrent systemic symptoms. Imaging plays a central role, with PET/CT offering superior sensitivity in detecting early inflammatory changes compared to CT angiography. The patient's classification as type I TAK, with isolated subclavian artery involvement, aligns with common angiographic patterns seen in Türkiye. Overall, this case underlines the diagnostic value of PET/CT and reinforces awareness of TAK's variable presentation.

Keywords: Takayasu arteritis, vasculitis, subclavian artery, PET/CT

ÖZ

Takayasu arteriti (TAK), başlıca aorta ve aortanın ana dallarını tutan nadir, kronik bir büyük damar vaskülitidir. Asya toplumlarında daha sık görülmekte olup belirgin coğrafi farklılıklar göstermektedir. Hastalık çoğunlukla kadınları etkiler ve genellikle yaşamın ikinci veya üçüncü dekadında ortaya çıkar. Tanı, özgül olmayan semptomlar ve kesin tanı koydurucu laboratuvar testlerinin bulunmaması nedeniyle güçtür; bu nedenle temel olarak klinik şüphe ve görüntüleme bulgularına dayanır. Takayasu arteriti tanısı için 2022 American College of Rheumatology/European League Against Rheumatism kriterlerine göre hastaların 60 yaşın altında olması ve büyük damar vasküliti ile uyumlu görüntüleme bulgularının bulunması gerekmektedir. Ek klinik ve görüntüleme özellikleri puanlama sistemine katkı sağlar ve toplam puanın 5 veya üzerinde olması tanıyı destekler. Bu olgu sunumunda, daha önce bilinen herhangi bir hastalığı olmayan, tekrarlayan ateş ve kilo kaybı ile başvuran 26 yaşında bir kadın hasta sunulmaktadır. Klinik muayenede kollar arasında nabız ve kan basıncı farkı saptanmış olup bu bulgu vasküler tutulumu düşündürmüştür. Laboratuvar bulgularında eritrosit sedimantasyon hızı (ESR) ve C-reaktif protein (CRP) düzeylerinde yükseklik izlenmiş, bunun dışında ek bir anormallik saptanmamıştır. Bilgisayarlı tomografi (BT) anjiyografide vasküler değişiklik izlenmezken, pozitron emisyon tomografisi (PET)/BT'de sağ subklavian arterde vaskülit ile uyumlu hafif artmış florodeoksiglukoz tutulumu gösterilmiştir.

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Hastaya TAK tanısı konulmuş ve metotreksat ile kortikosteroid tedavisi başlanmıştır. Tedavi sonucunda enflamatuvar belirteçlerde ve klinik semptomlarda belirgin iyileşme sağlanmıştır. Altıncı ayda hem ESR hem de CRP düzeyleri normale dönmüştür.

Bu olgu, tekrarlayan sistemik semptomları olan genç kadın hastalarda akut faz reaktanlarının değerlendirilmesinin, her iki kolda nabız ve kan basıncının karşılaştırılmasının ve TAK tanısının akılda tutulmasının önemini vurgulamaktadır. Görüntüleme tanıda merkezi bir role sahiptir; PET/BT, erken enflamatuvar değişikliklerin saptanmasında BT anjiyografiye kıyasla daha yüksek duyarlılık sağlayabilir. Hastanın izole subklavian arter tutulumu ile tip I TAK olarak sınıflandırılması, Türkiye'de görülen yaygın anjiyografik paternlerle uyumludur. Genel olarak bu olgu, PET/BT'nin tanısal değerini ortaya koymakta ve TAK'ın değişken klinik sunumu konusunda farkındalığın önemini desteklemektedir.

Anahtar Kelimeler: Takayasu arteriti, vaskülit, subklavyen arter, PET/BT

INTRODUCTION

Takayasu arteritis (TAK) is an uncommon, persistent inflammatory disease targeting large blood vessels, primarily the aorta and its main branches[1]. Although TAK occurs globally, it is believed to affect the Asian population disproportionately more. In Japan, the highest recorded prevalence has been estimated at 40 cases per million people, whereas in the United States, the lowest documented rate is approximately 0.9 cases per million[2]. In a study conducted in the United Kingdom, the average prevalence of TAK was determined to be 4.7 cases per million population[3]. In a retrospective cohort study comprising 1,011 patients diagnosed with TAK, the mean age at disease onset was 32.5±15.1 years. Of the total study cohort, 763 participants were female, comprising 75.5% of the population and yielding a female-to-male ratio of 3.1:1[4]. In another cohort study involving 852 patients diagnosed with TAK, the median age at disease onset was reported to be 25 years[5]. The female-to-male ratio demonstrates regional variability. In a study conducted in Southern Norway, the female-to-male ratio was reported as 6.8:1, whereas in the United States, this ratio was identified as 4.2:1[6,7]. This condition is broadly recognized as panarteritis, with the earliest signs of inflammation commonly appearing near the vasa vasorum and at the interface between the media and adventitia layers[8].

Vascular remodeling characterized by segmental stenosis and/or aneurysm formation is a hallmark of TAK. Gaining insight into the underlying mechanisms of TAK is essential for advancing accurate diagnostic approaches and effective treatment methods. The disease is believed to have an autoimmune basis, in which dysregulated immune responses lead to chronic vascular inflammation. Because clinical symptoms are often vague and there are no conclusive diagnostic tools available, making an accurate diagnosis is especially difficult[9].

Invasive modalities such as angiography have largely been replaced by non-invasive options like fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning, computed tomography angiography (CTA), magnetic resonance imaging/angiography (MRI/MRA), and ultrasound (US). An optimal imaging modality should facilitate early identification of vascular wall inflammation, offer precise delineation of vascular morphology, correlate reliably with clinical disease activity, exhibit sensitivity to therapeutic interventions and possess prognostic value in anticipating future vascular complications[10]. PET/CT has been recognized for its significant diagnostic value in the early identification of vasculitis and is therefore strongly recommended as an imaging modality by both the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR)[11,12].

According to the TAK classification criteria updated by ACR/EULAR in 2022, being under 60 years of age at the time of diagnosis and having imaging findings consistent with large-vessel vasculitis are mandatory requirements for diagnosis. In patients who meet the initial criteria, additional clinical and imaging features are evaluated and scored. A total score of 5 or more confirms the classification of TAK[13].

CASE REPORT

A 26-year-old woman with no prior medical conditions, no regular medications, and no family history of rheumatic diseases presented to the internal medicine outpatient clinic complaining of fever and weight loss. The patient reported that her fever had been recurring every two-three days for the past four years. She reported an unintentional weight loss over the past six months, decreasing from 55 kg to 50 kg. There was no morning stiffness or Raynaud's phenomenon. The pulse rate was recorded as 62 beats per minute in the right upper extremity and 84 beats per minute in the left. Additionally, the pulse amplitude in the right arm was notably diminished compared to the left. Apart from the observed discrepancy in blood pressure between the arms (116/72 mmHg in the right and 133/84 mmHg in the left), physical examination revealed no other abnormalities. Cardiac auscultation demonstrated normal, rhythmic first (S1) and second (S2) heart sounds, without any audible additional heart sounds, gallops, or murmurs. In laboratory tests, no pathology was detected except for an elevated erythrocyte sedimentation rate (ESR) of 63 mm/h and a C-reactive protein (CRP) level of 151 mg/L. The patient's DNA was analyzed for 18 mutations in the *MEFV* gene, with results reported as negative.

Radiological examinations, including neck ultrasonography, revealed significant intima-media thickening measuring up to 2.8 mm in the bilateral common carotid arteries and the right subclavian artery. Considering TAK, CT angiography of the aorta, its branches, and the upper extremity vessels, as well as a FDG-PET scan, were requested. CT angiography of the neck, thoracic aorta, upper extremities, and abdomen showed no stenosis or vascular wall pathology. However, the PET/CT scan demonstrated diffuse mild increased FDG uptake consistent with vasculitis in an approximately 2.5 cm segment of the right subclavian artery extending from the thyroid to the thoracic inlet (see Figures 1, 2). The patient was diagnosed with TAK. A patient experiencing recurrent febrile episodes every two to three days over the past four years, accompanied by a 5 kg unintentional weight loss within the last six months, was diagnosed with TAK one month following her initial presentation to the rheumatology outpatient clinic. Treatment was initiated with methotrexate 15 mg/week, folic acid 5 mg/week, and oral methylprednisolone 40 mg/day. The patient's inflammatory indicators decreased, and both clinical condition and laboratory results demonstrated signs of recovery. Following the initiation of treatment, a reduction of over 50% in ESR and approximately 80% in CRP levels was achieved within 3 months. By the 6th month, ESR had decreased to 5 mm/h and CRP to 0 mg/L (see Table 1). The patient is currently being followed in a stable clinical condition.

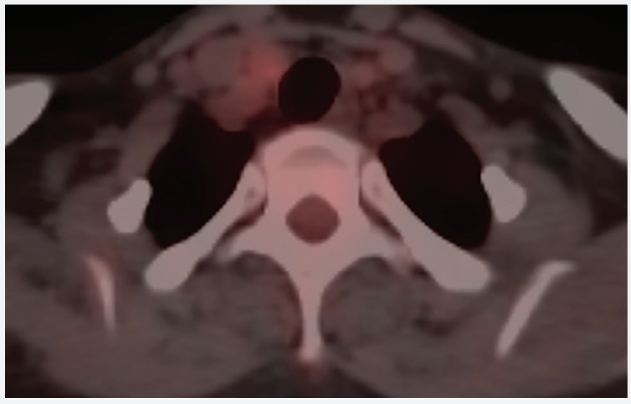

Figure 1. Diffuse, mild increased FDG uptake in the right subclavian artery, axial plane, PET/CT

FDG: Fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography

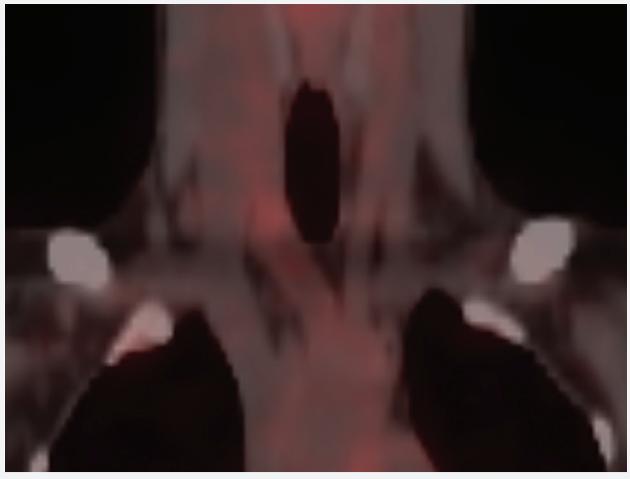

Figure 2. Diffuse, mild increased FDG uptake in the right subclavian artery, coronal plane, PE/CT

FDG: Fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography

DISCUSSION

This case is presented to emphasize the importance of evaluating acute phase reactants in the laboratory, measuring blood pressure and pulses in both arms during physical examination, and considering TAK in the differential diagnosis, especially in young female patients with recurrent fever attacks and weight loss. In cases with strong suspicion of TAK, angiographic imaging should be performed, and PET/CT evaluation considered when clinically indicated.

TAK was initially documented in 1908 by Mikito Takayasu, an ophthalmology professor at Kanazawa University in Japan[14]. The disease is seen predominantly in women (84.6%) with a mean age of onset of 32.3 (±10.4) years[13]. TAK is significantly more common in women than men in Türkiye as well (F/M ratio: 8.2/1), and the average age of onset is 40.1 (±14) years[15]. This case is consistent with the literature in terms of age and gender.

TAK shows geographical variations in distribution. In Asian countries, both the incidence and prevalence are relatively higher. The condition affects between 3.3 and 40 individuals per million, with yearly new cases estimated to fall between 0.34 and 2.4 per million people[16]. It predominantly occurs in regions such as Japan, Southeast Asia, India, and Mexico[17]. A study carried out in Türkiye determined the yearly occurrence rate of TAK to be 1.11 per million individuals, with a 95% confidence interval ranging from 0.54 to 1.67[18].

Table 1. The patient's laboratory values at the initial presentation, 3-month, and 6-month follow-up examinations

Presentation	ESR (mm/h)	CRP (mg/L)	WBC (x10^3/µL)	HGB (g/dL)
Initial presentation	63	151	8.9	10.3
3-month	26	28	5.06	11.1
6-month	5	0	9.23	13.1

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: White blood cell, HGB: Hemoglobin

In published studies on TAK, systemic manifestations like fever (34.7%) and fatigue (12.1%) are the most frequently reported early symptoms, with neck pain (9.7%) following as a less common initial sign[19]. This case also presented to the hospital with fever, which is the most common and non-specific symptom of TAK. Weight loss (9.3%) is an relatively uncommon finding in TAK[20]. In this case, however, weight loss was present. Other complaints observed in patients include syncope (6.98%) and night sweats (4.65%), which were not observed in this case[20]. In a study conducted on patients with TAK, the frequency of having a blood pressure difference between the two arms was found to be 53.8%[21]. In this particular instance, a discrepancy in blood pressure readings between the two arms was also observed.

Imaging plays an important role in the diagnosis and follow-up of TAK. CT angiography is the preferred initial imaging modality due to its availability, better image resolution compared to MR angiography, and lower cost. It serves an important function in pinpointing the regions involved and evaluating the intensity of TAK. CT angiography can reveal changes such as luminal narrowing, dilatation, vessel wall thickening, calcification, and contrast enhancement[22]. PET/CT represents an alternative imaging modality for the evaluation of TAK. As a non-invasive method, PET/CT is becoming an increasingly valuable tool in the diagnostic evaluation of TAK. PET/CT can detect increased metabolic activity in the arterial wall and provide information about vascular inflammation[11]. The capacity of FDG-PET imaging to identify inflammatory activity during the early, pre-edematous phase—prior to the onset of overt vascular structural alterations—represents a clinically valuable advantage. Nonetheless, its broader implementation is constrained by limited accessibility and substantial financial burden[23]. In the assessment of TAK activity, PET/CT parameters including maximum standardized uptake value (SUV_{max}), vascular SUV_{max}-to-liver mean SUV ratio (SUV_{ratio}), and PET vascular activity score (PETVAS) are utilized. As reported in a study, the sensitivity and specificity of SUV_{max}, SUV_{ratio}, and PETVAS for evaluating TAK activity using PET/CT were reported as 100% and 100%, 100% and 90.9%, and 88.9% and 90.9%, respectively[24]. In the case which presented here, although no findings suggestive of TAK were detected on CT angiography, arterial involvement was identified on PET/CT. In the comparative study conducted by Quinn et al.[25] evaluating MRA and FDG-PET in patients with TAK, FDG-PET–derived assessments of disease activity demonstrated a correlation with clinical status. When benchmarked against MRA findings, FDG-PET exhibited a sensitivity of 71% and a specificity of 52% in detecting active disease. Therefore, MRA was not performed in this patient. Digital subtraction angiography (DSA) remains the definitive diagnostic technique for TAK, as it enables detailed imaging of the coronary vessels and facilitates evaluation of pressure within the aorta[26]. Given the vascular involvement identified on PET/CT in this case, it was deemed that a DSA examination might not be required.

The Numano classification, introduced in 1996, remains the most widely utilized angiographic system for categorizing TAK. Based on this classification system, TAK is categorized angiographically according to the specific vessels involved. Type 1 includes the aortic arch branches, such as the brachiocephalic trunk, carotid arteries, and subclavian arteries. Type 2a encompasses the ascending aorta, the aortic arch, and its branches. Type 2b includes all the features of Type 2a with additional involvement of the thoracic descending aorta. Type 3 refers to disease affecting the thoracic descending aorta, abdominal aorta, and/or renal arteries. Type 4 is limited to the abdominal aorta and/or renal arteries. Type 5 presents a combination of vascular involvement seen in both Type 2b and Type 4[27]. In a study evaluating patients with TAK in Türkiye angiographically, the most common types were found to be Type V (51%) and Type I (32%). In the same study, the most frequently involved arteries were observed to be the subclavian (76%), carotid (52%), and renal (28%) arteries, respectively[15]. Current case's PET/CT examination revealed involvement of the right subclavian artery and the patient was classified as Type 1 TAK.

CONCLUSION

In this study, a rare case of TAK was presented. This case is consistent with the literature due to being young and female, presenting to the hospital with fever, having elevated inflammatory markers in laboratory tests, exhibiting a blood pressure difference between the two arms and involvement of the subclavian artery. The detection of vascular involvement on PET/CT rather than on CT angiography supports the increasing importance of PET/CT in the diagnosis of TAK.

Ethics

Informed Consent: The patient provided written informed consent for the publication of this case report, including all associated clinical details and images.

Footnotes

Authorship Contributions

Concept: Ö.A.S., D.B.G., B.S.S., R.M., Design: Ö.A.S., D.B.G., B.S.S., R.M., Data Collection or Processing: Ö.A.S., D.B.G., R.M., Analysis or Interpretation: Ö.A.S., D.B.G., B.S.S., R.M., Literature Search: Ö.A.S., D.B.G., B.S.S., R.M., Writing: Ö.A.S.

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

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CASE REPORT

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Pulmonary Alveolar Microlithiasis: Bedside Lung and Diaphragmatic Ultrasound Findings in Stage III Disease

Pulmoner Alveoler Mikrolitiyazis: Evre III Hastalıkta Yatak Başı Akciğer ve Diyafragma Ultrasonografi Bulguları

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ABSTRACT

Pulmonary alveolar microlithiasis (PAM) is an extremely rare autosomal recessive disorder caused by *SLC34A2* mutations, leading to intra-alveolar calcium-phosphate microlith accumulation. To date, lung ultrasound (LUS) findings in PAM have been reported in only a single case report. We present a 35-year-old male with genetically confirmed stage III PAM who presented with acute hypoxemic respiratory failure. Bedside LUS revealed marked pleural irregularity and thickening (total 5.6 mm; parietal 4.4 mm, visceral 1.2 mm) and complete absence of B-lines despite extensive ground-glass opacities on computed tomography. Diaphragmatic ultrasound showed a thickening fraction of 31.5%, indicating preserved contractile reserve. Arterial blood gas on room air (PaO_2 48 mmHg), normal infection markers, negative D-dimer (0.3 µg/mL), and echocardiography showing no acute right heart strain effectively excluded alternative causes of acute hypoxemia. The absence of B-lines may be attributed to an acoustic barrier created by subpleural microliths and microcysts. Preserved diaphragmatic function suggests that hypoxemia arose from gas-exchange impairment rather than ventilatory pump failure. Given its extreme rarity, this second ever description of LUS in PAM confirms that bedside ultrasound may serve as a radiation-free monitoring tool in this orphan disease.

Keywords: Pulmonary alveolar microlithiasis, lung ultrasound, diaphragm, B-lines, pleural thickening, respiratory failure, *SLC34A2* gene

ÖZ

Pulmoner alveoler mikrolitiyazis (PAM), *SLC34A2* gen mutasyonlarına bağlı son derece nadir görülen otozomal resesif bir hastalık olup alveol boşluklarında kalsiyum-fosfat mikrolitlerinin birikimi ile karakterizedir. Bugüne kadar PAM'da akciğer ultrasonografisi (USG) bulguları literatürde yalnızca tek bir olguda bildirilmiştir. Bu yazıda, genetik olarak doğrulanmış evre III PAM tanılı, akut hipoksemik solunum yetmezliği ile başvuran 35 yaşında bir erkek hasta sunulmaktadır. Yatak başı akciğer USG'de belirgin plevral düzensizlik ve kalınlaşma (toplam 5,6 mm; paryetal 4,4 mm, viseral 1,2 mm) ve bilgisayarlı tomografi'de yaygın buzlu cam dansitelerine rağmen B-çizgileri saptanmadı. Diyafragma USG'de kalınlaşma fraksiyonu %31,5 olarak ölçüldü; bu değer korunmuş kontraktil rezervi göstermektedir. Oda havasında arter kan gazı (PaO_2 48 mmHg), normal enfeksiyon belirteçleri, negatif D-dimer (0,3 µg/mL) ve ekokardiyografide akut sağ kalp yüklenme bulgusu olmaması enfeksiyon, pulmoner emboli ve kardiyak disfonksiyon gibi akut hipoksemi nedenlerini dışlamıştır. B-çizgilerinin olmaması, subplevral mikrolitlerin ve mikrokistlerin oluşturduğu akustik bariyerden kaynaklandığı düşünülmektedir. Korunmuş diyafragma fonksiyonu, hipokseminin gaz değişim bozukluğundan kaynaklandığını düşündürmektedir. Yatak başı USG nadir görülen bu hastalıkta radyasyon içermeyen bir izlem aracı olarak kullanılabilir.

Anahtar Kelimeler: Pulmoner alveoler mikrolitiyazis, akciğer ultrasonografisi, diyafragma, B-çizgileri, plevral kalınlaşma, solunum yetmezliği, *SLC34A2* geni

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INTRODUCTION

Pulmonary alveolar microlithiasis (PAM) is an exceedingly rare, autosomal recessive genetic lung disease characterized by the diffuse accumulation of calcium-phosphate microliths within the alveolar spaces[1]. This condition is primarily caused by inactivating mutations in the *SLC34A2* gene, which encodes the type IIb sodium-phosphate cotransporter in alveolar type II cells[2]. The resulting defect in phosphate clearance leads to intra-alveolar stone formation, progressively impairing gas exchange and leading to pulmonary fibrosis, respiratory failure, and cor pulmonale[1,2].

A hallmark of PAM is the clinico-radiological dissociation, where extensive "sandstorm-like" micronodular patterns on imaging are found in patients with relatively mild or no symptoms for decades[1]. While computed tomography (CT) remains the most useful test for diagnosis and staging, the role of lung ultrasound (LUS) in PAM is documented by only a single case report, which described the sonographic pleural abnormalities in PAM[3,4]. This report aims to expand the sonographic literature by presenting LUS and diaphragmatic ultrasound (DUS) findings in a patient with stage III PAM.

CASE REPORT

A 35-year-old male with a 16-year history of PAM presented to the emergency department with a two-day history of progressively worsening dyspnea and acute-onset hypoxemia. The diagnosis of PAM had been established 16 years earlier based on typical symptoms and high-resolution CT findings. Genetic testing performed at that time confirmed a homozygous inactivating mutation in the *SLC34A2* gene. Over the preceding decade, he had gradual exertional breathlessness, but his dyspnea acutely worsened in the last 48 hours. There was no associated fever, productive cough, chest pain, or hemoptysis. He reported compliance with domiciliary oxygen therapy only intermittently and had never smoked. His family history was unremarkable for pulmonary disease.

On arrival, the patient was tachypneic. Vital signs were as follows: blood pressure 118/76 mmHg, heart rate 102 bpm, temperature 36.7 °C, respiratory rate 26 breaths/min, and peripheral oxygen saturation (SpO_2) 79% on room air. Chest auscultation revealed diffusely audible rhonchi without crackles or wheezing. There was no peripheral edema, jugular venous distension, or clinical evidence of right-sided heart failure.

Arterial blood gas (ABG) analysis on room air revealed: pH 7.38, $PaCO_2$ 42 mmHg, PaO_2 48 mmHg, and HCO_3^- 24 mEq/L. Complete blood count showed leukocytosis (12.4×10^9/L); C-reactive protein was 8 mg/L, and procalcitonin was 0.1 ng/mL, making infection unlikely. Cardiac evaluation included high-sensitivity troponin T (<3 ng/L) and a 12-lead electrocardiography showing sinus tachycardia without ischemic changes or right heart strain. A D-dimer level was 0.3 μg/mL, effectively excluding pulmonary embolism as a cause of acute hypoxemia. A Wells score for pulmonary embolism was 1.5 (low probability).

Immediately after the initiation of supplemental oxygen, a bedside 12-point LUS was performed by an emergency medicine specialist with 7 years of experience in LUS. All ultrasound examinations were performed using SonoHealth® D2CP with high-frequency linear (5-12 MHz) and phased-array probes (SonoHealth Medical Technologies, Guangzhou, China). The 12-point LUS protocol involved systematic scanning of the anterior, lateral, and posterior chest walls, dividing each hemithorax into six zones: anterior-superior, anterior-inferior, lateral-superior, lateral-inferior, posterior-superior, and posterior-inferior. Each zone was scanned in both longitudinal and transverse planes using a standardized approach, with the transducer placed perpendicular to the ribs to avoid acoustic shadowing. Three consecutive respiratory cycles were recorded for each measurement, and the average value was reported. Bilateral anterior-superior, posterior-superior, and posterior-inferior zones were systematically examined with the patient in a semi-recumbent position. The pleural line was markedly thickened and irregular in all evaluated regions. Using the linear probe, total pleural thickness measured 5.6 mm (average of three measurements: 5.5, 5.7, 5.6 mm), comprising a parietal layer of 4.4 mm (4.3, 4.5, 4.4 mm) (Figure 1a) and a visceral layer of 1.2 mm (1.1, 1.3, 1.2 mm) (Figure 1b). The visceral pleura appeared hyperechoic, fragmented, and irregular (Figure 1b and c). No vertical B-lines or comet-tail reverberation artifacts were observed.

DUS was performed using the phased-array probe positioned in the right mid-axillary line, between the 8th and 10th intercostal spaces. The diaphragm was visualized in the zone of apposition, and M-mode was used to capture respiratory-phase thicknesses. End-expiratory thickness was 1.9 mm, and end-inspiratory thickness increased to 2.5 mm. The diaphragmatic thickening fraction was calculated as $[(2.5\text{-}1.9)/1.9] \times 100 = 31.5\%$. Diaphragmatic excursion was visually preserved.

A postero-anterior chest radiograph demonstrated the classic "sandstorm" appearance: diffuse, bilateral, fine micronodular opacities with a ground-glass density, more pronounced in the lower zones (Figure 2a).

As the bedside LUS and portable chest radiograph revealed no evidence of consolidation, cardiogenic pulmonary edema, pleural effusion, or pneumothorax that could otherwise account for the acute deterioration, a thoracic CT scan was obtained to exclude occult parenchymal complications and better delineate the underlying disease status. The scan confirmed symmetrical, dense alveolar microliths distributed predominantly in the posterior and inferior lung segments,

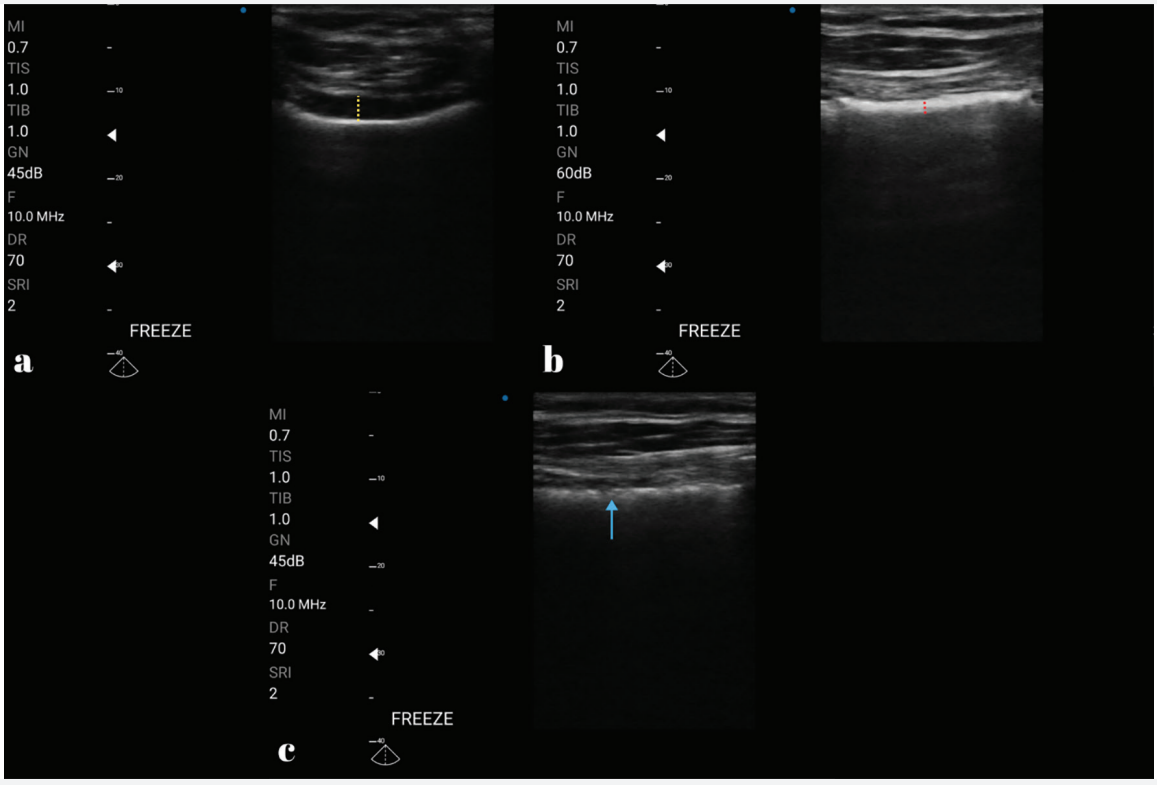

Figure 1. High frequency linear probe LUS of the right anterior superior zone (mid clavicular line, second intercostal space, longitudinal orientation). (a) Markedly thickened parietal pleura (4.4 mm, dashed yellow line). (b) Hyperechoic, thickened visceral visceral pleura (1.2 mm, dashed red line). (c) Hyperechoic fragmented visceral pleural layer

LUS: Lung ultrasound

accompanied by interlobular septal thickening, consistent with a "crazy-paving" pattern, and multiple subpleural traction cysts (Figure 2b). Per established staging criteria[2], the radiographic "sandstorm" appearance with partial obliteration of the lower mediastinal and diaphragmatic borders, alongside these High-resolution CT findings of progressive interstitial fibrosis, are consistent with advanced stage III PAM.

The patient was treated with oxygen 4-6 L/min via mask, inhaled salbutamol and ipratropium, and intravenous hydration. His dyspnea improved, and SpO_2 stabilized at 91-93% on 3 L/min of oxygen. Repeat ABG after 6 hours showed pH 7.41, $PaCO_2$ 40 mmHg, PaO_2 68 mmHg, HCO_3^- 25 mEq/L. He was admitted to the pulmonology ward for further observation and multidisciplinary evaluation, including lung-transplant candidacy assessment, and was discharged home on domiciliary oxygen after five days of follow-up.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. The study was conducted in accordance with the Declaration of Helsinki.

DISCUSSION

This case details the bedside LUS and DUS findings in a patient with stage III PAM. The sonographic appearance of PAM has rarely been reported, with only one prior description[4]. Our observations corroborate their findings of a thickened, irregular hyperechoic pleural line, while offering assessment of diaphragmatic function in PAM.

Rea et al.[4] reported pleural line thicknesses between 1.7 mm and 2.9 mm depending on the transducer used. In our patient, total pleural thickness measured 5.6 mm, comprising 4.4 mm of parietal and 1.2 mm of visceral pleura, both well above the 3 mm threshold considered pathological[5]. This degree of thickening supports the concept that the calcific and inflammatory process of PAM can involve pleura at stage III, paralleling the subpleural interstitial changes and microcysts frequently seen on CT[3,4].

An important observation in both cases is the absence of B-lines despite extensive parenchymal calcifications and ground-glass opacities on CT. In most interstitial lung diseases, such opacities generate vertical comet-tail artifacts due to acoustic

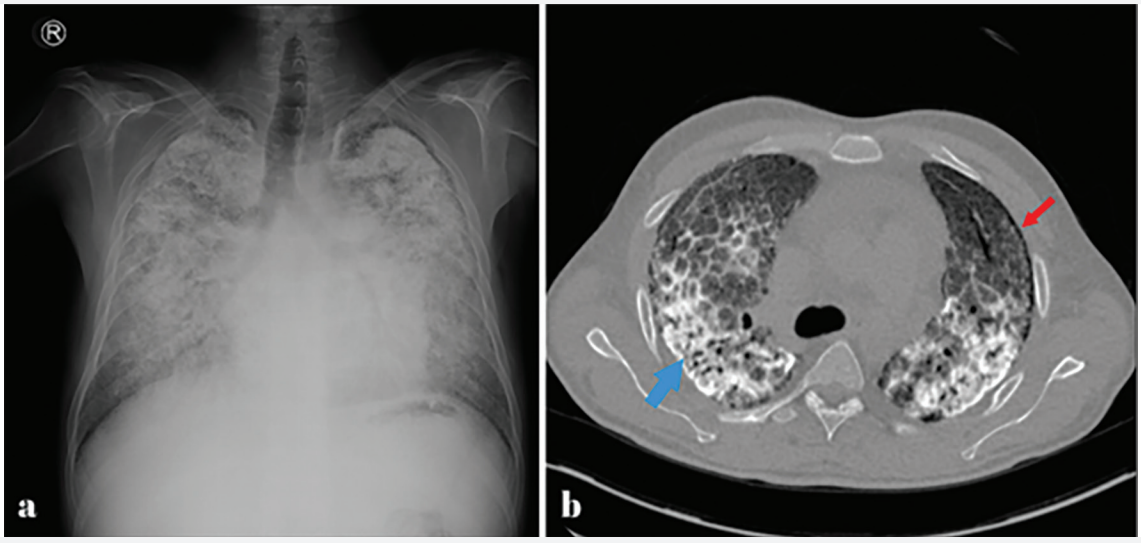

Figure 2. Radiological findings in pulmonary alveolar microlithiasis. (a) Posteroanterior chest radiograph showing diffuse sand like micronodular calcifications. (b) Axial thoracic CT image revealing dense alveolar microliths (blue arrow), air space obliteration, and subpleural cystic changes (red arrow), predominantly in the inferoposterior regions

CT: Computed tomography

impedance mismatches at the air–tissue interface[6]. Rea et al.[4] proposed that subpleural microliths and microcystic changes create a dense acoustic barrier that reflects ultrasound waves, preventing deeper penetration and artifact formation. Our case supports this finding.

In PAM, chronic hypoxia and restrictive physiology increase the work of breathing and may eventually lead to cor pulmonale[1]. Rea et al.[4] observed reduced pleural line motion during respiration, attributing it to parenchymal stiffness and obesity, but did not quantify diaphragmatic function. We measured the TFdi at approximately 31.5%. Although this value lies slightly below the >36% threshold proposed for healthy individuals and the mean of 36.8±6.5% reported in successfully weaned patients, it remains above the cut-offs associated with diaphragmatic dysfunction: <30% for weaning failure and <20% for severe weakness[7-10]. Values in the 15-30% range are considered indicative of adequate activation, placing our patient's measurement within the preserved contractile reserve spectrum[9]. The measurement was obtained during spontaneous breathing without positive pressure ventilation, conditions that yield the most reliable indices[7]. Our patient presented with a room-air SpO_2 of 79%, may suggest that the respiratory distress originated primarily from gas-exchange impairment due to alveolar filling rather than from ventilatory pump failure. The novelty of combining LUS and DUS in PAM lies in its potential to simultaneously assess disease severity at the pleural level and respiratory muscle function, without the need for ionizing radiation. This dual approach may be particularly valuable for monitoring disease progression and assessing functional reserve in PAM patients being evaluated for lung transplantation.

Currently, no proven disease-modifying therapy exists for PAM. Supportive measures include long-term oxygen therapy to maintain SpO_2 ≥88% (or >90% if cor pulmonale develops), and improved gas exchange with nasal continuous positive airway pressure has been described in a single case[1,3]. Disodium etidronate has been used to inhibit hydroxyapatite crystal formation; although radiological and symptomatic improvements have been reported, efficacy in adults remains uncertain[1,2]. Dietary phosphate restriction lacks robust human data, though often advised[3]. Vaccination against influenza, pneumococcus, and coronavirus disease 2019, along with smoking cessation, is recommended[3]. Lung transplantation remains the only definitive treatment, and disease recurrence in the graft has not yet been reported[2,3]. Transplant timing is guided by right-heart failure or severe respiratory failure[2].

Several limitations must be acknowledged. This is a single case report, requiring validation in larger cohorts. The influence of body habitus and inter-operator variability on measurements could not be systematically assessed as all measurements were performed by a single operator. Additionally, the TFdi cut-offs cited derive mainly from critical care populations; disease-specific reference ranges for chronic restrictive disorders are not established.

CONCLUSION

In conclusion, this case suggests that stage III PAM may present with pleural thickening and the absence of B-lines. In this patient, preserved diaphragmatic function suggests that hypoxemia may be due to gas exchange failure, without evidence of respiratory muscle insufficiency. Bedside ultrasound may be useful as a radiation-free tool for monitoring disease progression in PAM.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report and accompanying images. The study was conducted in accordance with the Declaration of Helsinki.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.Y., A.S.G., Concept: K.Y., M.K.A., Ö.J., A.S.G., Design: K.Y., M.K.A., Ö.J., A.S.G., Data Collection or Processing: K.Y., M.K.A., Ö.J., A.S.G., Analysis or Interpretation: K.Y., M.K.A., Ö.J., A.S.G., Literature Search: Ö.J., A.S.G., Writing: K.Y., M.K.A.

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

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LETTER TO THE EDITOR

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The Imperative for Geriatric Emergency Departments in Thrace: Addressing the Regional Aging Crisis

Trakya Bölgesinde Geriatrik Acil Servislerin Gerekliliği: Bölgesel Yaşlanma Krizine Bir Çağrı

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Keywords: Geriatric emergency medicine, delirium, frailty, emergency department boarding, Thrace
Anahtar Kelimeler: Geriatrik acil tıp, deliryum, frajilite, acil serviste yatak bekleme, Trakya

To the Editor,

The Thrace region (TR21 statistical region) is undergoing a demographic shift that warrants targeted, system-level redesign of emergency care. According to Turkish Statistical Institute Elderly Statistics 2024, while Türkiye elderly population is 10.6%, Edirne (17.2%) and Kırklareli (16.3%) are among the fastest-aging provinces nationally[1]. In parallel, Tekirdağ—despite a relatively lower elderly proportion (10.2%)—recorded the country's highest net internal migration in 2023 (+22,674)[2]. This creates a distinct service-delivery paradox: aging rural populations and high-volume, migrant-receiving industrial centers converge within the same regional emergency care ecosystem. As an emergency physician practicing in the Thrace region, I observe daily how this dual pressure increases admission demand, prolongs emergency department (ED) stays, and amplifies risk in frail older adults.

The Clinical Reality

Geriatric emergency medicine extends well beyond atypical presentations. Regional data underscore a predictable yet high-stakes clinical profile. In a regional cohort, falls accounted for 10.9% of geriatric ED presentations and may conceal clinically significant injuries, particularly when initial findings are subtle[3]. Delirium—reported in 10.6% of older ED patients—was an independent predictor of mortality at both 6 months [hazard ratio (HR) 4.5] and 5 years (HR 3.4)[3]. The so-called "3D" syndromes (delirium, dementia, depression) further complicate assessment; depression and dementia were reported in 35.1% and 45.6% of presentations, respectively[3].

The Boarding Crisis

Boarding—prolonged ED stays after an admission decision—is a major threat for older adults. A multicenter French prospective cohort study demonstrated that older patients who spent overnight in the ED had increased in-hospital mortality (adjusted risk ratio 1.39 overall), rising to 1.81 among patients requiring assistance with activities of daily living[4]. A systematic review likewise reported that prolonged boarding of frail individuals in the ED is associated with adverse outcomes and increased mortality risk[5]. Prolonged ED stretcher stays also contribute to hospital-acquired infections, pressure injuries, sleep disruption, delirium amplification, and accelerated functional decline.

Evidence-based Solutions

Structured geriatric ED models aligned with the American College of Emergency Physicians' Geriatric Emergency Department Accreditation framework have been associated

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with reduced ED length of stay without increasing short-term return visits[6]. In Türkiye, a patient- and caregiver-perspective survey also supports the need for dedicated geriatric emergency services[7]. In addition, a geriatric ED innovation program has been associated with lower Medicare expenditures, supporting the health-economic rationale for such models[8]. However, a nationwide survey from Türkiye suggests that adherence to geriatric ED guideline recommendations remains very low, underscoring the implementation gap[9]. For Thrace, a regional geriatric emergency network could be implemented with three measurable objectives: (1) Clinical Frailty scale screening at triage; (2) confusion assessment method-based delirium pathways; (3) boarding escalation thresholds triggering expedited admission or transfer.

CONCLUSION

Thrace's demographic transition is already reshaping emergency care delivery. Boarding of older adults should be regarded as a patient safety risk rather than a system delay. Designating Thrace as a pilot region for geriatric ED implementation may reduce preventable harm and improve outcomes in this rapidly aging population.

Footnote

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