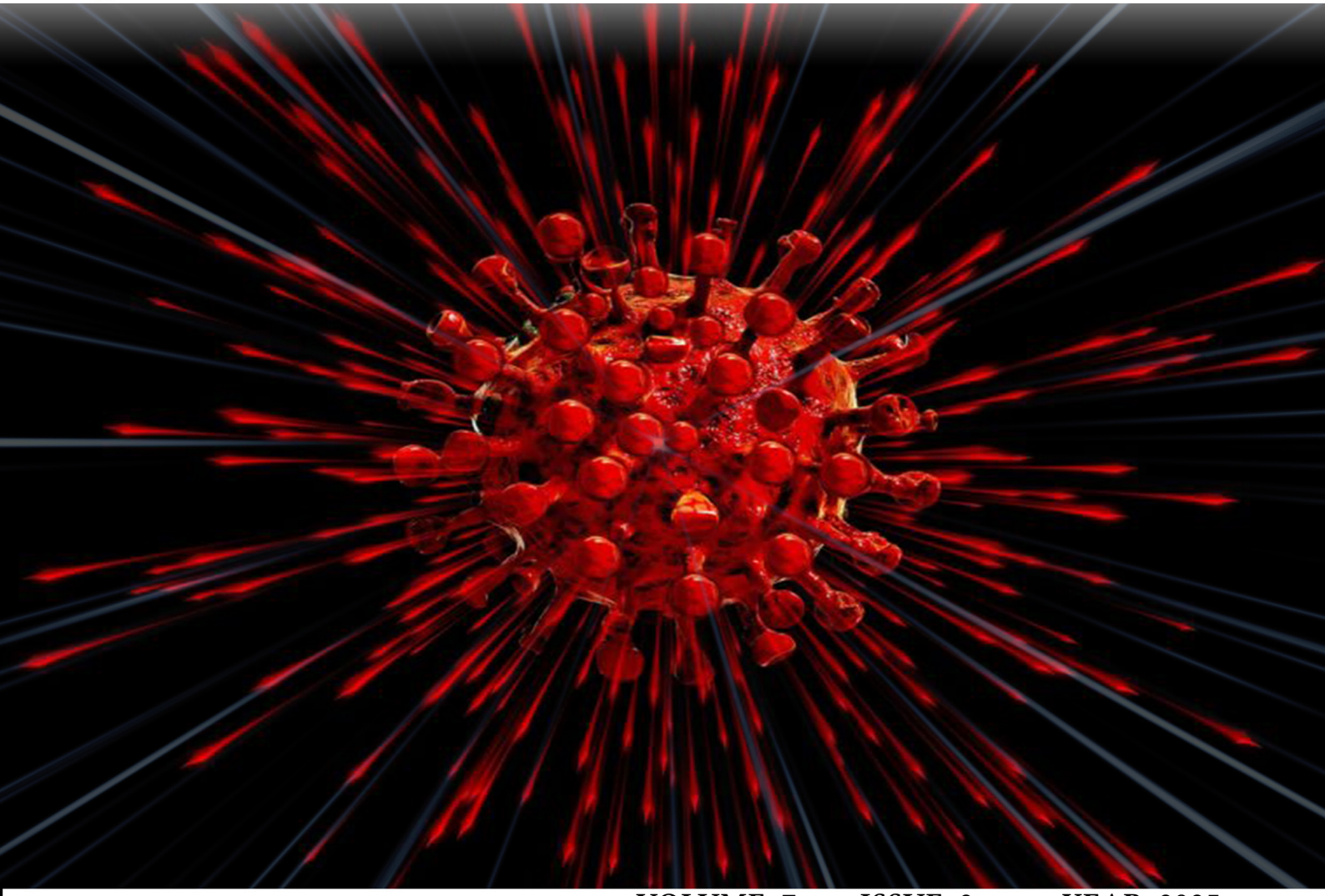
e-ISSN: 2718-0115

ACMJ

Anatolian Current Medical Journal



VOLUME: 7 ISSUE: 3 YEAR: 2025

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ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1614804

Anatolian Curr Med J. 2025;7(3):266-270

Special needs reports for children: diagnosis distribution and age relationship in visual function*

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Cite this article as: Tınkır Kayıtmazbatır E, Bozkurt Oflaz A, Acar Duyan Ş. Special needs reports for children: diagnosis distribution and age relationship in visual function. *Anatolian Curr Med J.* 2025;7(3):266-270.

Received: 07.01.2025 ◆ **Accepted**: 25.03.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: This study aimed to analyze the most common eye disease diagnoses in children with special needs and their distribution by age and special needs levels.

Methods: Records of 1771 patients evaluated by the health board of our hospital between February 2019 and March 2024 were reviewed. Data from 134 children assessed in the visual function domain were categorized based on special needs levels: presence of special needs (PSN), presence of significant special needs (PSSN), and presence of special conditions (PSC). Diagnoses were analyzed by age groups.

Results: The most common diagnoses among children evaluated for special needs reports were refractive errors (20.8%), optic atrophy (18.6%), and strabismus (14.1%). Among children identified with PSSN, optic atrophy (37.5%) was the most frequent diagnosis, followed by nystagmus (16.7%), hereditary retinal dystrophies (16.7%), and retinopathy of prematurity (ROP) (12.5%). In children identified with PSC, the most common diagnosis was also optic atrophy (37.1%), followed by hereditary retinal dystrophies (14.3%) and congenital glaucoma (11.4%). Of the 25 children diagnosed with optic atrophy, 15 had accompanying conditions such as hydrocephalus, cerebral palsy, and intracranial pressure elevation caused by masses.

Conclusion: The diagnoses in special needs reports for children vary according to the visual function category. However, optic atrophy appears as a frequently observed diagnosis across all age groups. Age-specific diagnostic distributions may serve as a guide in planning early intervention and treatment strategies.

Keywords: Assessment of healthcare needs, optic atrophy, vision disorders

*This study was presented as an oral presentation at the 8th Live Surgery Symposium of the Turkish Ophthalmological Association (June 6-9, 2024, Ankara).

INTRODUCTION

Vision loss significantly restricts individuals' cognitive, motor, and social development[1], limiting their ability to perceive the environment, learn, and move independently.[2] Developmental delays in achieving milestones, alongside deficiencies in social relationships, cognitive skills, and motor abilities, are frequently observed in children with vision loss.[3] It is estimated that approximately 40 million children worldwide experience mild vision loss, 22 million suffer from moderate to severe vision loss, and 1.4 million children are blind.[5] Reports indicate that 72% of children with vision loss also have other clinically significant conditions unrelated to the eye. Regular monitoring of at-risk groups, particularly those born prematurely or diagnosed with cerebral palsy or neurodevelopmental disorders such as Down syndrome, is emphasized.[6]

Early-onset vision loss restricts a child's ability to perceive the environment, learn, and move independently[2], resulting in individual and familial challenges that necessitate special needs.

In Turkiye, the "Regulation on Special Needs Assessment for Children" (ÇÖZGER) adopts a comprehensive approach to assessing and reporting special needs, aiming to address these children's needs within a holistic framework. The presence of special needs (PSN) is classified into mild, moderate, advanced, and severe levels of PSN, as well as distinct categories such as presence of significant special needs (PSSN) and presence of special conditions (PSC), with disability rates determined accordingly.[7] In the visual function category, the classification is based on the degree of visual impairment, ranging from mild vision loss to complete blindness, with special attention to functional limitations in daily activities.

This study aims to evaluate the distribution of special needs statuses and diagnoses related to visual function among children who applied to the health board under ÇÖZGER, based on age groups.

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METHODS

The study was initiated with the approval of the Selçuk University Medical Faculty Clinical Researches Ethics Committee (Date: 02.07.2024, Decision No: 326), which was planned and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The medical records of patients who applied for a ÇÖZGER report to our hospital's health board between February 2019 and March 2024 were reviewed. Patients assessed for special needs in the visual function category were included in the study. Data were classified based on the types of special needs into ASN (absence of special needs), mild PSN, moderate PSN, advanced PSN, severe PSN, PSSN, and PSC, and the diagnoses in the visual function category were recorded. The distribution of diagnoses by age groups (<12 months, 1–3 years, 3–6 years, 6–12 years, and 12–18 years) was analyzed.

Statistical Analysis

The data analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive analyses of numerical variables were presented as mean±standard deviation or median (minimum–maximum) values, depending on the distribution. Categorical data were expressed as numbers and percentages. The Chi-square test was used to evaluate the relationship between age groups, gender, special needs status, and diagnoses. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 1771 medical records were reviewed, and 134 cases were evaluated for visual function. Of the evaluated cases, 52.2% were male (n=70), and 47.8% were female (n=64). The mean age was 94.6±52.7 months (minimum 4–maximum 211 months). When distributed by age groups, cases aged 0–1 years accounted for 6.7% (n=9), those aged 1–3 years for 8.9% (n=12), those aged 3–6 years for 23.8% (n=32), those aged 6–12 years for 40.2% (n=54), and those aged 12–18 years for 20.1% (n=27) (**Figure 1**).

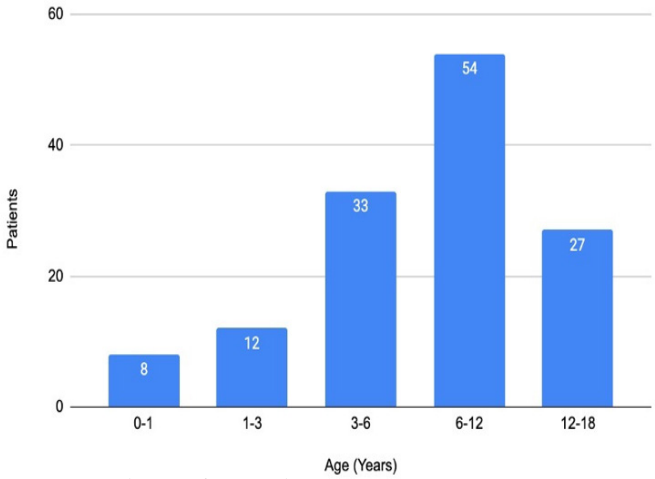

Figure 1. Distribution of patients by age groups

When the distribution of cases by the level of special needs was examined, 55.2% (n=74) of cases had no special condition requirements (ASN). Mild PSN was present in one case, while 35 cases (26.1%) had PSC, and 24 cases (17.9%) had PSSN (**Figure 2**). When diagnoses of all cases were examined, 28 cases (20.8%) had refractive errors, 25 cases (18.6%) had optic atrophy, and 19 cases (14.1%) had strabismus (**Figure 3**).

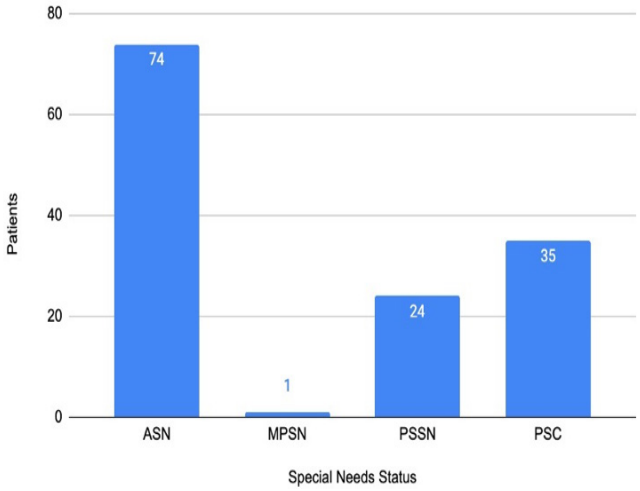

Figure 2. Distribution of patients by special needs status

ASN: Absence of special needs, MPSN: Mild presence of special needs, PSSN: Presence of significant special needs, PSC: Presence of special conditions

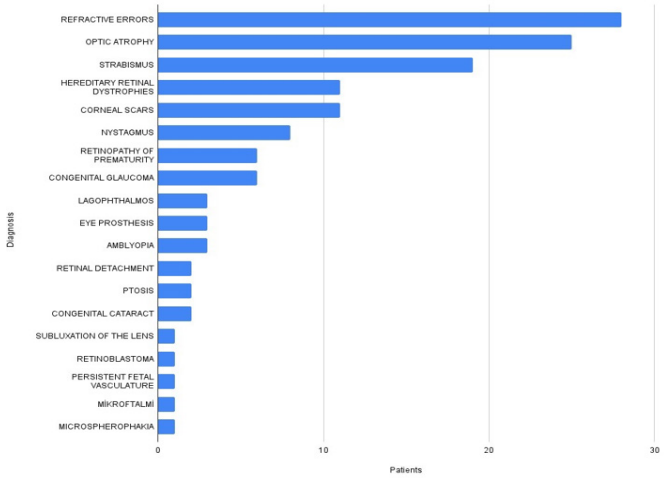

Figure 3. Distribution of patients by diagnoses

In ASN group (n=74), 33.8% (n=25) had refractive errors, 24.3% (n=18) had strabismus, and 10.8% (n=8) had corneal scars and opacities (**Table 1**). The single case with mild PSN had a refractive error accompanied by high astigmatism (-6.50@15/-7.00@160). Among 35 cases with PSC, 13 (37.1%) had optic atrophy, five (14.3%) had hereditary retinal dystrophy, four (11.4%) had vision loss due to congenital glaucoma, and three (8.6%) had retinopathy of prematurity (ROP). Two cases with PSC had refractive errors accompanied by high hyperopia (5.7%) (**Table 2**). Among 24 cases with PSSN, nine (37.5%) had optic atrophy, four (16.7%) had nystagmus, four (16.7%) had hereditary retinal dystrophy, and three (12.5%) had ROP (**Table 3**). One case diagnosed with nystagmus also had accompanying albinism and foveal hypoplasia.

When diagnoses were analyzed by age groups, the most common diagnosis in the 0–1-year age group was optic atrophy (n=2), strabismus (n=5) in the 1–3-year age group, optic atrophy (n=8) and refractive errors (n=8) in the 3–6-

Table 1. Diagnosis distribution of patients in the ASN group

Diagnosis	Patients	
	(n)	%
Refractive errors	25	33.8
Strabismus	18	24.3
Corneal scars	8	10.8
Eye prosthesis	3	4.1
Optic atrophy	3	4.1
Lagophthalmos	3	4.1
Amblyopia	3	4.1
Ptosis	2	2.7
Nystagmus	2	2.7
Hereditary retinal dystrophies	2	2.7
Retinal detachment	1	1.4
Microspherophakia	1	1.4
Subluxation of the lens	1	1.4
Congenital cataract	1	1.4
Congenital glaucoma	1	1.4

ASN: Absence of special needs

Table 2. Diagnosis distribution of patients in the PSC group

Diagnosis	Patients	
	n	%
Optic atrophy	13	37.1%
Hereditary retinal dystrophies	5	14.3%
Congenital glaucoma	4	11.4%
Retinopathy of prematurity	3	8.6%
Nystagmus	2	5.7%
Refractive errors	2	5.7%
Strabismus	1	2.9%
Retinoblastoma	1	2.9%
Retinal detachment	1	2.9%
Persistent fetal vasculature	1	2.9%
Microphtalmia	1	2.9%
Corneal scar	1	2.9%

PSC: Presence of special conditions

Table 3. Diagnosis distribution of patients in the PSSN group

Diagnosis	Patients	
	n	%
Optic atrophy	9	37.5%
Nystagmus	4	16.7%
Hereditary retinal dystrophies	4	16.7%
Retinopathy of prematurity	3	12.5%
Corneal scar	2	8.3%
Congenital cataract	1	4.2%
Congenital glaucoma	1	4.2%

PSSN: Presence of significant special needs

year age group, refractive errors (n=15) and optic atrophy (n=9) in the 6–12-year age group, and refractive errors (n=5) and hereditary retinal dystrophies (n=5) in the 12–18-year age group.

Among 25 cases diagnosed with optic atrophy, 15 had accompanying neurological pathologies such as hydrocephalus (n=6), cerebral palsy (n=8), and medulloblastoma causing increased intracranial pressure (n=1). Bilateral involvement was present in 21 cases (84%).

Statistical analyses were conducted to further examine the relationship between age groups, gender, special needs status, and diagnoses. There was no statistically significant relationship between gender and overall diagnoses (p=0.414). A significant relationship was observed between special needs status and diagnoses ($p<0.05$). Diagnoses such as optic atrophy and hereditary retinal dystrophies were more frequently seen in children classified under PSC, while refractive errors and strabismus were commonly found in children without special condition (ASN). Trend analysis revealed that nystagmus and hereditary retinal dystrophies were more prevalent in early childhood, while refractive errors were significantly more common in school-age children.

DISCUSSION

Studies examining children with special needs have reported that boys are more frequently affected.[8,9] Similarly, in our study, boys were more common; however, the male-to-female ratio (1.09) was lower than in other studies. This discrepancy may be due to the demographic characteristics of families applying for ÇÖZGER reports and the limitation of the sample population to a specific healthcare facility.

There are limited studies on ÇÖZGER reports from different centers and specialties in our country. A study by Temeltürk et al.[10] reported that 18.6% of cases required special needs in multiple areas, while Kaba et al.[11] found this rate to be 34.7% in cases referred for psychiatric evaluation. In a study evaluating physical therapy and rehabilitation patients by Büyükavcı et al.[12], 71.6% of cases had PSN. In our study, 7.5% of all applicants for ÇÖZGER reports were evaluated for visual function, and 44.2% of them were found to have special needs.

In this study, diagnoses in the visual function category were frequently observed not only in children with special needs but also in children without special needs. This finding indicates that visual function problems extend beyond children with special needs, affecting a broader population. A study from Latin America reported a high prevalence (45%) of refractive errors and ophthalmological diseases in children with developmental disorders and behavioral problems.[13]

There are two studies from our country that evaluate the visual function domain in ÇÖZGER reports. In Güner and Bozbıyık's[14] study, involving 1026 cases, 5.6% of children were found to have special needs in ophthalmological terms, with 26 cases categorized as PSN, 21 cases as PSSN, and 10 cases as PSC. Refractive errors and accommodation disorders, strabismus, amblyopia, nystagmus, optic atrophy, and hereditary retinal dystrophy were the most common diagnoses. Similarly, in our study, refractive errors, optic atrophy, and strabismus were the most common diagnoses.

In the study by Sayın et al.[15], optic atrophy was the most common diagnosis among children requiring special needs reports. Similarly, in our study, optic atrophy was the most

frequent diagnosis, among cases requiring special needs reports, followed by hereditary retinal dystrophies, ROP, and nystagmus. Optic atrophy was accompanied by neurological conditions such as hydrocephalus, cerebral palsy, and intracranial mass-related pressure increases in 14 cases. This finding aligns with the literature, supporting the relationship between optic atrophy and neurological conditions.[16] Bilateral involvement was present in 84% of cases, aligning with previous studies showing a higher prevalence of intellectual disabilities and neurodevelopmental disorders, such as autism spectrum disorder, in bilateral optic atrophy cases.[17,18]

The study by İdil[19] evaluating visually impaired children reported that the most common diagnoses among children aged 7–18 were hereditary macular degeneration, albinism, and optic atrophy. In Turkiye, a study by Tunay[20] covering diagnoses of 150 visually impaired children aged 6–18 years identified hereditary macular dystrophies as the leading diagnosis, followed by cortical visual impairment. Albinism, optic atrophy, structural anomalies, retinitis pigmentosa, and ROP were also reported as common diagnoses. The study emphasized the importance of low vision rehabilitation, highlighting significant improvements in both distance and near vision with rehabilitation in school-aged visually impaired children, and the importance of referral to visual rehabilitation services by both pediatricians and ophthalmologists.[20]

A study investigating the eye health needs of individuals with learning difficulties in England found high prevalence rates of eye problems across all age groups. It also revealed challenges in accessing primary eye health services, leading to preventable and/or undiagnosed vision loss among individuals with learning difficulties.[21] International studies emphasize the importance of recognizing special educational needs before the age of four to ensure appropriate support services are in place. Sethi and Trend reported that delayed identification may result in missed opportunities for early intervention, especially in regions with inconsistent child health surveillance programs.[22] This highlights the need for structured and comprehensive screening programs, both at national and regional levels, to prevent delays in diagnosis and improve long-term outcomes for children with visual impairments. In Turkiye, ÇÖZGER reports not only enable individuals and their families to access social rights and support but also facilitate comprehensive evaluation and referral to appropriate educational and rehabilitation services for eye health.

In addition to these findings, a diagnostic algorithm is crucial for early identification and management of visual impairments in children. The algorithm begins with a comprehensive initial eye examination, including age-appropriate visual acuity assessment, light reflex testing, ocular motility evaluation, anterior segment examination, and fundus evaluation. For children diagnosed with optic atrophy, referral to pediatric neurology is essential to investigate associated neurological conditions. Children with a history of ROP should be closely monitored for potential future complications such as refractive errors, strabismus, and retinal disorders. In cases of nystagmus and hereditary retinal dystrophies, electrophysiological tests are recommended, with genetic counseling offered if necessary. Refractive errors should be corrected, amblyopia treatment initiated, and families informed about low-vision rehabilitation services when needed. For serious conditions like retinoblastoma or congenital glaucoma, immediate referral and treatment planning are critical to prevent vision loss and ensure timely intervention.

Limitations

As it is single-centered, the generalizability of the results to different populations and regions is limited. The retrospective design and limited sample size restrict the representation of findings for a broader population. Socioeconomic status, education level, or cultural factors were not evaluated in this study; considering their effects on access to eye health and treatment outcomes could be beneficial. Additionally, the lack of comprehensive data on genetic factors and consanguineous marriages limits the evaluation of the etiology of hereditary retinal dystrophies. Another limitation of our study is the absence of a control group of typically developing children. Including such a control group in future research would allow for a more robust comparison of visual impairment prevalence. Addressing these limitations in future multi-center, prospective studies could provide more comprehensive insights.

CONCLUSION

This study demonstrated that diagnoses related to visual function are not limited to children with special needs but are also prevalent in a broader pediatric population. Ophthalmological issues such as refractive errors, optic atrophy, and strabismus were among the most common diagnoses in children evaluated within the scope of special needs reports. The relationship between optic atrophy, conditions requiring special needs, and neurological pathologies underscores the importance of a multidisciplinary approach. Implementing targeted screening programs focusing on early identification of these conditions is crucial. Collaboration between ophthalmologists, pediatricians, and rehabilitation specialists is essential for comprehensive care. Enhancing access to low-vision rehabilitation services and raising awareness among families about the importance of early intervention may significantly improve long-term visual and developmental outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Selçuk University Medical Faculty Clinical Researches Ethics Committee (Date: 02.07.2024, Decision No: 326).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1629140

Anatolian Curr Med J. 2025;7(3):271-277

Evaluating the predictive performance of nutritional indices in postoperative outcomes following pancreaticoduodenectomy in the elderly

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Cite this article as: Özdemir G, Şeker A, Sözütek A, Coşkun HT, Kahyaoğlu Z. Evaluating the predictive performance of nutritional indices in postoperative outcomes following pancreaticoduodenectomy in the elderly. *Anatolian Curr Med J.* 2025;7(3):271-277.

Received: 29.01.2025 ◆ **Accepted**: 25.03.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: The aim of the study was to evaluate the prognostic significance of nutritional indices including geriatric nutritional risk index (GNRI), prognostic nutritional index (PNI), and total bilirubin-albumin ratio (TBAR) in predicting postoperative outcomes following pancreaticoduodenectomy (PD) among elderly patients.

Methods: This study retrospectively analyzed 192 patients aged 65 and older who underwent PD at a single center. Postoperative complications were graded using the Clavien-Dindo classification. Postoperative survival was defined as survival beyond 90 days. All deaths that occurred during follow-up were included in the assessment of long-term mortality. In addition, the duration of hospital stay was assessed.

Results: The mean age of the participants was 71.6±5.3 (range: 65–87) years. The mean follow-up time was 22.5±20.9 months (median: 15.0 months, IQR: 6.0-36.0). Postoperative complications occurred in 51.0% of patients, with pancreatic fistulae developing in 27.6%. GNRI demonstrated superior predictive accuracy for both 90-day and long-term mortality compared to PNI and TBAR. Lower GNRI scores were significantly associated with worse survival outcomes. Multivariate Analysis revealed that age, GNRI, and the presence of postoperative complications were independent predictors of 90-day mortality. GNRI was the only significant predictor of long-term mortality in the Cox regression model.

Conclusion: Preoperative GNRI demonstrated superior predictive performance compared to PNI and TBAR in predicting postoperative survival following PD in elderly patients. Lower GNRI scores were strongly associated with increased mortality risk. We suggest routine screening for malnutrition using tools like GNRI to identify these vulnerable patients at increased risk of mortality following PD.

Keywords: Elderly, geriatrics, geriatric nutritional risk index, nutrition, pancreaticoduodenectomy, prognostic nutritional index, survival

INTRODUCTION

Pancreaticoduodenectomy (PD) remains a complex gastrointestinal surgery primarily indicated for malignant pancreatic head tumors. Despite advancements in surgical techniques and postoperative care, it is associated with significant morbidity and mortality, with rates as high as 60% and 5%, respectively.[1,2] Patient characteristics, preoperative clinical status, and ability to tolerate the procedure and its complications are key factors influencing outcomes.[3]

Ongoing research aims to reduce these risks by addressing both patient-related and surgical factors.

The pancreas plays a crucial role in both digestion and glycemic control. Unfortunately, up to 80% of pancreatic cancer patients experience nutritional deficiencies due to pancreatic exocrine and endocrine insufficiency.[4] Various scoring systems are employed to assess the nutritional status of these patients. The geriatric nutritional risk index (GNRI) is a widely used index for estimating nutritional status in elderly patients with chronic kidney disease and heart failure.[5] Another common tool is the prognostic nutritional index (PNI), which measures a patient's nutritional and systemic immunological status. PNI is calculated based on serum albumin concentrations and total lymphocyte counts in peripheral blood and is used to assess perioperative immune nutritional status.[6]

Total bilirubin albumin ratio (TBAR) is another important prognostic factor for pancreatic cancer patients. Preoperative total bilirubin, a marker of biliary obstruction, is elevated in most patients with pancreatic tumors at diagnosis. Albumin, reflecting immune and nutritional status, has also been widely used. TBAR, a combination of these two, has been shown to

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predict prognosis in pancreatic cancer.[7] While these indices have been studied for predicting postoperative outcomes in PD patients, their comparative performance in elderly patients remains unexplored. Therefore, the aim of this study was to evaluate the prognostic significance of nutritional indices including GNRI, PNI, and TBAR in predicting postoperative outcomes following PD among elderly patients.

METHODS

Ethics

The study was conducted with the permission of the Clinical Researches Ethics Committee of Adana City Training and Research Hospital (Date: 18.01.2024, Decision No: 3103). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients and Data Collection

Patient data was collected from the hospital information management system. A flowchart of the study population is shown in **Figure 1**. Tumor diameter was defined as the maximum diameter of the lesion in the surgical specimen.

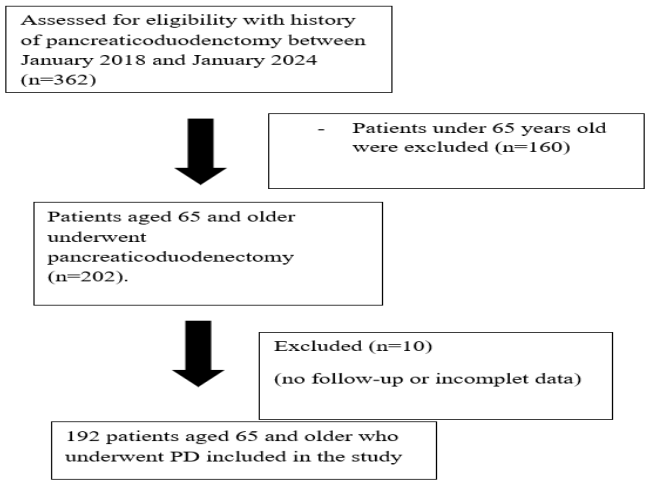

Figure 1. Flowchart of the study population

Postoperative survival was defined as survival beyond 90 days. All deaths that occurred during the follow-up were included in the assessment of long-term mortality.

All surgeries were performed by a specialized surgical team.

Existing diagnoses in hospital medical records were evaluated, and diagnoses were compiled according to the International Classification of Diseases (ICD) system. Postoperative complications were graded using the Clavien-Dindo classification, a widely used system for categorizing complications based on severity.[8]

The Clavien-Dindo classification ranges from grade I (minor complications requiring pharmacological treatment or minor interventions) to grade V (death), with increasing severity. Grade II includes complications requiring invasive intervention (e.g., drainage, endoscopic procedures). Grade IIIa encompasses serious complications requiring non-operative intervention, while Grade IIIb involves serious complications requiring operative, endoscopic, or radiological intervention. Grade IV represents life-threatening complications.

In addition, the duration of hospital stay, and The American Society of Anesthesiologists (ASA) physical status classification system score of the patients were noted.

GNRI and PNI Calculation

The GNRI was calculated based on serum albumin concentration and body weight.[9-11]

The PNI was calculated using the formula:

PNI=Serum albumin level (g/L)+5×total lymphocyte count (10^9/L).[6]

Unit changes were made as required by the formula.

Serum albumin and total lymphocyte counts were obtained within one week before surgery.

Statistical Analysis

Numerical variables were summarized as mean±standard deviation or median with interquartile range (IQR). Categorical variables were summarized as frequencies and percentages. Normality of distribution was assessed using the Kolmogorov-Smirnov test.

The Chi-square test was used to compare categorical variables between groups. In cases where the expected value was lower, cells were merged and Fisher's exact test was used where necessary. An independent sample t-test was used for normally distributed data. The Mann-Whitney U test was used for non-normally distributed data.

The Kaplan-Meier method was used to estimate survival probabilities. The log-rank test was used to compare survival curves between groups. Cox proportional hazards regression analysis was performed to identify predictors of overall survival. A forward stepwise selection procedure was used to build the final model.

Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive ability of GNRI and PNI for 90-days and overall mortality. Optimal cut-off points were determined using the Youden index. Sensitivity and specificity were calculated to evaluate diagnostic accuracy.

Statistical analyzes were conducted using IBM SPSS Statistics 20.0. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The study included 192 participants (52.6% female, 47.4% male) with a mean age of 71.6±5.3 years (range: 65–87 years).

56.3% of participants had at least one systemic comorbidity, such as diabetes mellitus (19.3%), hypertension (28.6%), or coronary artery disease (19.3%).

The mean follow-up time was 22.5±20.9 months (median: 15.0 months, IQR: 6.0-36.0).

Demographic characteristics, clinical findings, and patient scores are summarized in **Table 1**. Continuous variables are presented as mean±standard deviation or median with IQR. Categorical variables are presented as frequencies and percentages.

Table 1. Demographic characteristics and clinical findings of the pancreaticoduodenectomy patients

Age	71.6±5.3
Median follow-up time (month)	15.0 (6.0-36.0)
Lymphocyte (10^3/μL)	1550 (1200-2200)
PNI (mean±SD)	42.5±7.5
GNRI, median (IQR)	92.0 (82.0-100.0)
Total bilirubin-albumin ratio median (IQR)	0.2 (0.1-1.0)
Total bilirubin (μmol/L) median (IQR)	7.2 (3.3-28.8)
Albumin (g/L) (mean±SD)	33.5±5.2
Duration of hospital stay (day) median (IQR)	12.0 (8.0-19.0)
Tumor diameter (cm) median (IQR)	3.0 (2.0-4.0)
Gender (female/male) n (%)	101 (52.6)/ 91 (47.4)
Long term mortality alive/exitus, n (%)	109 (56.8)/ 83 (43.2)
90 day mortality alive/exitus, n (%)	161 (83.9)/31 (16.1)
ASA score n (%)	
1	1 (0.5)
2	41 (21.4)
3	122 (63.5)
4	28 (14.6)
Systemic disease (+/-) n (%)	108 (56.3)/84 (43.8)
Diabetes mellitus (+/-) n (%)	37 (19.3)/155 (80.7)
Hypertension (+/-) n (%)	55 (28.6)/137 (71.4)
Coroner artery disease (+/-) n (%)	37 (19.3)/155 (80.7)
Systemic complication (+/-) n (%)	98 (51.0)/94 (49.0)
Pancreatic fistula (+/-) n (%)	53 (27.6)/139 (72.4)
GNRI category n (%)	
Low risk	70 (36.5)
Moderate risk	29 (15.1)
High risk	93 (48.4)
Malignant etiology/benign etiology	157 (81.8)/35 (18.2)

PNI: Prognostic nutritional index, SD: Standard deviation, GNRI: Geriatric nutritional risk index, IQR: Interquartile range, ASA: The American Society of Anesthesiologists

Comparison of patients who died within 90 days (exitus group) versus those who survived (alive group) revealed that the exitus group had a significantly higher mean age (p=0.012).

The exitus group exhibited significantly lower mean PNI scores (39.4±8.4 vs. 43.1±7.2, p=0.012) and lower median GNRI (80, IQR: 75-86 vs. 85-101, p<0.001). The exitus group experienced a significantly higher rate of postoperative complications (80.6% vs. 45.1%, p<0.001).

Notably, no significant differences were found between the groups with respect to lymphocyte counts, gender distribution, prevalence of systemic diseases (including diabetes, hypertension, and coronary artery disease), malignancy rates, tumor diameter, or total bilirubin levels (Table 2).

A multivariate logistic regression model was constructed using variables that demonstrated statistical significance in the univariate analysis. Age, GNRI, and the presence of postoperative complications were included as independent variables. PNI was excluded from the model due to its high correlation with GNRI. Albumin was also excluded as it is a component of both PNI and GNRI and exhibited strong correlations with these variables. Pancreatic fistulae were observed in only three patients in the mortality group, precluding their inclusion in the multivariate model.

The model revealed the following significant predictors of 90-day mortality:

Increasing age was associated with a 1.08-fold increase in the odds of mortality (OR: 1.08, 95% CI: 1.01-1.17). A decrease in GNRI was associated with a 1.1-fold increase in the odds of mortality (OR: 0.89, 95% CI: 0.86-0.94). The presence of postoperative complications was associated with a 6-fold increase in the odds of mortality (OR: 6.0, 95% CI: 2.1-17.2).

Receiver Operating Characteristic (ROC) Curve Analysis

The AUC for PNI was 0.635 (p=0.017, 95% CI: 0.523-0.747), indicating moderate accuracy in predicting 90-day mortality. The optimal cut-off point for PNI was determined to be <36.65, yielding a sensitivity of 45.2% and a specificity of 80.1%.

The AUC for GNRI was significantly higher at 0.799 (p<0.001, 95% CI: 0.725-0.872), suggesting strong discriminatory ability. The optimal cut-off point for GNRI, determined using the Youden index, was <91.5, achieving a sensitivity of 93.5% and a specificity of 60.2%.

The AUC for TBAR was 0.438 (p=0.272, 95% CI: 0.348-0.527), which was not statistically significant (Figure 2).

Long-Term Mortality Analysis

Table 3 presents the results of the analysis of factors associated with long-term mortality. The exitus group exhibited a significantly higher mean age (p=0.018).

The exitus group had significantly lower lymphocyte levels (p=0.027).

Mean PNI scores were significantly lower in the exitus group (p=0.001).

Median GNRI scores were significantly lower in the exitus group [81 (IQR: 77-88)] compared to the alive group [99 (IQR: 94-103)] (p<0.001).

The exitus group had significantly higher levels of TBAR (p=0.029).

Statistical Analysis

The analysis revealed a significant difference in survival rates across Clavien-Dindo classification grades (χ^2=50.837, p<0.001). The exitus group demonstrated a significantly higher malignancy rate (90.4% vs. 75.2%, p=0.008). 59.6% of the Alive group was classified as low-risk according to GNRI, while 85.5% of the exitus group was classified as high-risk (p<0.001). No significant differences were observed between the groups regarding gender, systemic diseases (including diabetes, hypertension, and coronary artery disease), complications, or pancreatic fistula (Table 3).

Receiver Operating Characteristic (ROC) Curve Analysis

ROC curve analysis demonstrated an AUC of 0.649 (95% CI: 0.570-0.728) for PNI, indicating moderate accuracy in

Table 2. Risk factors affecting 90-day in pancreaticoduodenectomy patients

	Alive	Ex	p value
Age (years)	71.1±5.0	73.7±6.1	0.012
Lymphocyte (10^3/μL)	1600 (1200-2200)	1500 (1000-2300)	0.588
PNI (mean±SD)	43.1±7.2	39.4±8.4	0.012
GNRI (mean±SD)	94 (85-101)	80 (75-86)	<0.001
Total bilirubin-albumin ratio (TBAR)	0.2 (0.1-1)	0.3 (0.2-0.9)	0.272
Total bilirubin (μmol/L)	7.2 (3.3-28.9)	7.2 (5-21.1)	0.512
Albumin (g/L)	34.1±5.0	30.5±5.4	<0.001
Duration of hospital of stay (day)	12 (9-18)	11 (4-23)	0.233
Tumor diameter (cm)	2.8 (2-4)	3.5 (2.5-4)	0.079
Gender (F/M) n (%)	84 (52.2)/77 (47.8)	17 (54.8)/14 (45.2)	0.846
ASA			
1+2	36 (22.4)	6 (19.3)	0.816
3+4	125 (77.3)	25 (80.6)	
Systemic disease (+/-) n (%)	90 (55.9)/71 (44.1)	18 (58.1)/13 (41.9)	0.846
DM (+/-) n (%)	33 (20.5)/128 (79.5)	4 (12.9)/27 (87.1)	0.457
HT (+/-) n (%)	46 (28.6)/115 (71.4)	9 (29)/22 (71)	0.959
CAD (+/-) n (%)	30 (18.6)/131 (81.4)	7 (22.6)/24 (77.4)	0.622
Complication (+/-) n (%)	73 (45.3)/88 (54.7)	25 (80.6)/6 (19.4)	<0.001
Pancreatic fistula (+/-) n (%)	50 (31.1)/111 (68.9)	3 (9.7)/28 (90.3)	0.015
Etiology n (%) Malignant Benign	 130 (80.7) 31 (19.3)	 27 (87.1) 4 (12.9)	0.611

PNI: Prognostic nutritional index, SD: Standard deviation, GNRI: Geriatric nutritional risk index, ASA: The American Society of Anesthesiologists, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease

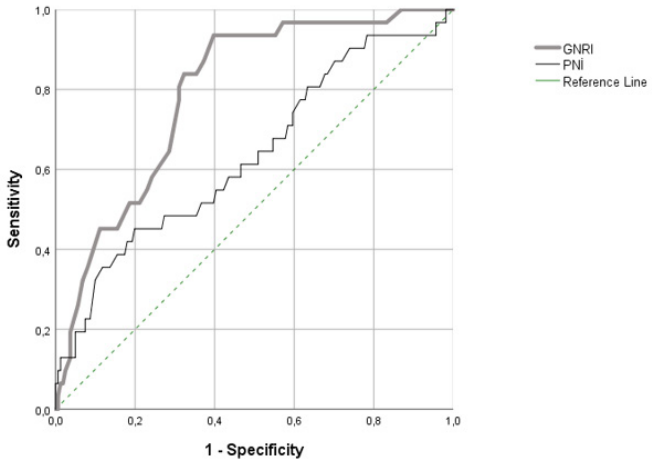

Figure 2. ROC curve of PNI and GNRI for 90-day in PD

ROC: Receiver operating characteristic, PNI: Prognostic nutritional index, GNRI: Geriatric nutritional risk index, PD: Pancreaticoduodenectomy patients

predicting long-term mortality (p<0.001). The optimal cut-off point for PNI, determined using the Youden index, was <42.55, with a sensitivity of 65.1% and a specificity of 62.4%.

In contrast, GNRI exhibited a significantly higher AUC of 0.890 (95% CI: 0.842-0.938), suggesting strong discriminatory ability in predicting long-term mortality (p<0.001). The optimal cut-off point for GNRI was <92.5, with a sensitivity of 91.6% and a specificity of 78.9% (**Figure 3**).

Cox Regression Analysis

Cox regression analysis was performed to assess the impact of prognostic factors on survival. Variables included in the analysis were age, PNI, GNRI-score, tumor diameter, and etiology, all of which demonstrated significance in univariate Cox regression.

The final Cox regression model was constructed using the Forward LR method, incorporating only statistically significant variables.

The results revealed that only the GNRI significantly affected mortality. Decreased GNRI score was found to be a risk factor for mortality (HR:1.09, 95%ci: 1.07-1.12).

DISCUSSION

The world's elderly population is rapidly expanding. While surgical techniques and medical cancer treatments for older adults have advanced significantly, deciding on surgery for this group remains challenging. PD is a potentially curative surgical option widely used in pancreatic cancer treatment. However, its safety in the elderly is debated due to higher observed mortality and morbidity rates in this population. Researchers have highlighted that geriatric assessment can help identify elderly patients at high risk for complications from PD.[12] In our study, preoperative GNRI demonstrated superior predictive performance compared to PNI and TBAR in predicting postoperative survival following PD in elderly patients. Lower GNRI scores were strongly associated with increased mortality risk.

Ito et al.[13] reported that there was no significant difference between the two groups in terms of PD results in their study comparing patients over 75 years of age and younger group.

Table 3. Risk factors affecting long-term mortality mortality in the pancreaticoduodenectomy patients

	Mortality		
	Alive	**Ex**	**p value**
Age (years)	70.7±4.5	72.6±6.1	0.018
Lymphocyte (10^3/μL)	1700 (1300-2300)	1400 (1000-2200)	0.027
PNI (mean±SD)	44.1±7.1	40.4±7.7	0.001
GNRI median (IQR)	99 (94-103)	81 (77-88)	<0.001
Total bilirubin-albumin ratio (TBAR)	0.2 (0.1-0.8)	0.3 (0.1-1)	0.029
Total bilirubin (μmol/L) median (IQR)	5.6 (2.8-26.1)	11.7 (4.4-29.4)	0.057
Albumin (g/L) (mean±SD)	34.7±5.2	31.9±4.8	<0.001
Duration of hospital of stay (day) median (IQR)	12 (9-17)	12 (8-19)	0.892
Tumor diameter (cm) median (IQR)	2.5 (1.7-4)	3 (2.1-4)	0.025
Clavien-Dindo classification n (%)			
0	2 (1.8)	0 (0.0)	<0.001
1	14 (12.8)	1 (1.2)	
2	49 (45.0)	30 (36.1)	
3	34 (31.2)	18 (21.7)	
4	10 (9.2)	5 (6.0)	
5	0 (0.0)	29 (34.9)	
Gender (female/male) n (%)	56 (51.4)/53 (48.6)	45 (54.2)/38 (45.8)	0.696
ASA n (%)			
1+2	28 (25.7)	14 (16.9)	0.161
3+4	81 (74.3)	69 (83.1)	
Systemic disease (+/-)	60 (55.0)/49 (45.0)	48 (57.8)/35 (42.2)	0.700
DM	24 (22.0)/85 (78.0)	13 (15.7)/70 (84.3)	0.269
HT	31 (28.4)/78 (71.6)	24 (28.9)/59 (71.1)	0.942
CAD	20 (18.3)/89 (81.7)	17 (20.5)/66 (79.5)	0.710
Complication (+/-) n (%)	54 (49.5)/55 (50.5)	44 (53)/39 (47)	0.634
Etiology n(%)			
Malignant	82 (75.2)	75 (90.4)	0.008
Benign	27 (24.8)	8 (9.6)	

PNI: Prognostic nutritional index, SD: Standard deviation, GNRI: Geriatric nutritional risk index, IQR: Interquartile range, ASA: The American Society of Anesthesiologists, DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery disease

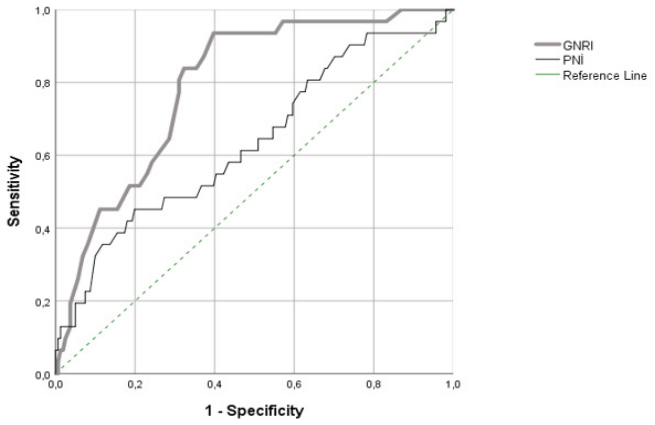

Figure 3. ROC curve of PNI and GNRI for long term mortality

ROC: Receiver operating characteristic, PNI: Prognostic nutritional index, GNRI: Geriatric nutritional risk index

A different study reported that age-related care should be designed to reduce the impact of complications in elderly patients, including geriatric consultation, supplemental enteral nutrition and early rehabilitation placement planning.[14]

Flores et al.[15] observed higher postoperative mortality and nonsurgical complications in elderly patients. While their study did not find a direct correlation between age and survival, it emphasized the importance of considering patient selection to mitigate complication risks.

In contrast, our study focused on comparing patients aged above 65 years based on 90-day survival outcomes. We observed a statistically significant difference in mean age, with the surviving group demonstrating a lower mean age compared to the non-surviving group (73.7 years). Furthermore, the group with a shorter survival time (less than 90 days) exhibited a statistically significant increase in complications, with pancreatic fistula identified as the most prevalent complication.

The elderly are at risk of physical, psychological and/or physiological dysfunctions and associated malnutrition as a result of a cascade of events triggered by cellular aging.[7] In addition, the impact of malnutrition extends beyond its physiological consequences. Contributes to an increased risk of a decline in quality of life, performance status and

resistance to infections due to reduced immune function.[16] However, nutritional disorders due to hormonal and enzymatic effects in pancreatic tumors make elderly patients particularly vulnerable to malnutrition.[4,17,18] Therefore, it is recommended to determine the nutritional status of elderly patients before PD. Kim et al.[19] investigated the effects of preoperative nutritional status on PD outcomes and reported that preoperative malnourished patients suffered from poor clinical outcomes, therefore, necessary intervention should be performed before surgery in patients with malnutrition.

A study conducted in Japan reported that preoperative nutritional status was effective in predicting complications after PD. Therefore, the use of scales indicating nutritional status before PD was recommended.[20] A study by Kanda et al.[21] on pancreatic cancer patients found that a low preoperative PNI score was associated with more postoperative complications, including pancreatic fistula, but was insufficient to predict long-term survival.

In a study on patients undergoing various surgical interventions, Gibbs et al.[22] showed that the 30-day postoperative mortality rate increased from 1% in patients with albumin levels >4.6 mg/dl to 28% in patients with albumin levels <2.1 mg/dl, indicating a positive relationship between preoperative low albumin levels and mortality. Several other studies have also used hypoalbuminemia as a component of perioperative predictive scoring models assessing frailty and fitness to predict pancreatic cancer and pancreatic surgery outcomes.[23,24] While the ASA score is a widely utilized tool for pre-operative risk assessment, our analysis revealed no statistically significant difference in ASA scores between patients who survived and those who died following Whipple surgery. This suggests that the ASA score, which primarily reflects pre-existing comorbidities and is subject to inter-observer variability, it may not be able to accurately show the physiological stress of the surgery itself or the development of post-operative complications, which are major determinants of mortality after a Whipple surgery. Specifically, post-operative complications and pancreatic fistulas emerged as significant predictors of 90-day mortality, indicating that post-operative events likely play a critical role in patient outcomes.

Low albumin values cause low GNRI and PNI results.[10,11] Our study showed that preoperative nutritional status, as assessed by albumin levels, PNI, and GNRI, significantly impacts 90-day survival in geriatric patients undergoing PD. Patients with higher albumin levels and lower PNI/GNRI scores had significantly higher mortality rates.

ROC curve analysis revealed that GNRI exhibited strong predictive ability for 90-day mortality compared to PNI. Multivariate analysis confirmed GNRI as an independent predictor of mortality. Unlike GNRI, the PNI calculation takes into account the number of lymphocytes in addition to albumin, which is also suggestive of immunity.[10,11] Therefore, PNI was preferred more in determining the preoperative nutritional status in our center previously. However, our results have shown that preoperative GNRI values are more successful in predicting postoperative PD survival. Therefore, we think that it is important to consider preoperative GNRI results.

Unlike the GNRI, PNI calculation considers both albumin levels and lymphocyte counts, which reflect immune function.[10,11] This broader assessment makes PNI more commonly used for evaluating preoperative nutritional status at our institution. However, our findings indicate that preoperative GNRI values are more effective in predicting postoperative mortality. Therefore, we believe that preoperative GNRI assessment remains crucial.

Limitations

The most important limitation of this study is that it is retrospective, and the sample size is limited. Excluding patients younger than 65 years was the potential selection bias for this study because it may limit the generalizability of the findings to the broader population of PD patients.

CONCLUSION

Preoperative GNRI demonstrated superior predictive performance compared to PNI and TBAR in predicting postoperative survival following PD in elderly patients.

Lower GNRI scores were strongly associated with increased mortality risk. We suggest routine screening for malnutrition using tools like GNRI to identify these vulnerable patients at increased risk of mortality following PD.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Clinical Researches Ethics Committee of Adana City Training and Research Hospital (Date: 18.01.2024, Decision No: 3103).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

DOI: 10.38053/acmj.1652714

ANATOLIAN CURRENT MEDICAL

Anatolian Curr Med J. 2025;7(3):278-282

Evaluation of mood disorders in healthcare workers working in COVID-19 services/polyclinics and their first-degree relatives

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Cite this article as: Şahin B, Evrin T, Gül A, Jaradat Ö, Katipoğlu B, Dolu Z. Evaluation of mood disorders in healthcare workers working in COVID-19 services/polyclinics and their first-degree relatives. *Anatolian Curr Med J.* 2025;7(3):278-282.

Received: 06.03.2025 • **Accepted**: 26.03.2025 • **Published**: 30.05.2025

ABSTRACT

Aims: The COVID-19 pandemic has impacted the entire world; however, certain individuals and groups have been affected more significantly or are at a higher risk. Among these groups are medical workers, who face unique challenges. In addition to the physical consequences of the pandemic, there have been notable psychological effects. This study aims to examine the prevalence of emotional disorders in healthcare personnel working in COVID-19 services and polyclinics, as well as in their first-degree relatives.

Methods: This study was conducted in 2022 on COVID-19 Service Personnel at Ufuk University Hospital and their first-degree relatives. It included doctors, nurses, and auxiliary medical personnel who worked in either COVID-19 services or polyclinics, along with their non-medical first-degree relatives. In total, 375 participants were surveyed. The survey consisted of three sections: socio-demographic information, the short symptom inventory, and the short form for Burnout scale. The Mann-Whitney U test and the Kruskal-Wallis test were utilized for data analysis, with a p-value of <0.05 considered statistically significant.

Results: The scores for somatization, obsessive-compulsive symptoms (OCS), interpersonal sensitivity (IS), depression, anxiety, hostility, phobic anxiety (PA), paranoid ideation (PI), psychoticism, additional items (AI), sum of symptoms (SS), discomfort severity index (DSI), symptom discomfort index (SDI), and Burnout Scale were significantly higher among doctors compared to other groups. Auxiliary medical workers had the second highest scores, followed by nurses, while the non-medical control group had significantly lower scores than all medical personnel groups. It was observed that psychiatric symptoms and burnout were significantly higher among medical workers at all levels compared to their relatives in other professions.

Conclusion: Our study concludes that the pandemic has psychologically affected medical workers more than individuals in other professions, with doctors being the most affected group.

Keywords: Pandemic, COVID-19, healthcare worker, anxiety, depression

INTRODUCTION

COVID-19, an outbreak of the SARS-CoV-2 virus, first appeared in the city of Wuhan in December 2019. Earlier this virus had not been thought to infect humans before and has since triggered a global pandemic. It has caused serious changes and impacts in health, economic, and social areas all over the world. Moreover, there are psychological effects related to the virus. Information and experiences from the pandemic demonstrate that people worldwide are encountering new psychological and physical manifestations of the disease.[1] The pandemic and quarantine measures profoundly affected mental health through prolonged isolation, fear of infection, and socioeconomic stressors such as unemployment and inadequate social support. Additional contributors included fatigue, stigmatization, and insufficient resources. These factors harmed individuals' psychological well-being.[2] Comprehensive research revealed that the prevalence of anxiety, stress, and depressive symptoms in the general population during the COVID-19 outbreak was 29.6%, 31.9%, and 33.7%, respectfully.[3] Recent research has also identified a connection between COVID-19-related anxiety and the severity of insomnia and suicidal thoughts.[4] Healthcare workers generally work in a very stressful environment, such as saving and sustaining lives. This high-pressure situation places significant psychological, social, and professional demands on them.[5] Although the whole world has been affected by the pandemic, some individuals and groups have been affected more or are at higher risk of being affected. Healthcare workers face significant vulnerability and are one of the most

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at-risk groups. Healthcare workers face numerous challenges, including exposure to SARS-CoV-2, constant vigilance, team cohesion needs, home/work conflicts, long working hours, and psychological burdens. They also experience fatigue, professional exhaustion, discrimination, stigmatization, and harassment.[1] The transition toward normalization during the ongoing pandemic is resulting in increased anxiety, grief, and anger among healthcare workers, along with rising levels of burnout among professionals in hospitals and the field. The fact that healthcare workers in hospitals continue to struggle with the consequences of the pandemic leads to negative emotions such as loneliness and abandonment. It contributes to the deterioration of mental health.[1] A report published by Amnesty International revealed that as of September 3, 2020, a minimum of 7.000 healthcare professionals globally had succumbed to COVID-19 after contracting the virus.[6] With the deaths experienced, the thought that healthcare workers should protect their own health and life concurrently while combating the pandemic may cause stress. Due to this stress, an increase in behaviors such as tension, anxiety, restlessness, sleep disorders, depressive disorders, etc., can be observed.[7,8] Research during the SARS outbreak shows that healthcare workers' mental health declines in epidemic situations. Studies indicate that healthcare professionals felt considerable anxiety about potentially transmitting the virus to their families, friends, and colleagues. This fear contributed to feelings of uncertainty and social stigma associated with their roles. Furthermore, some healthcare workers contemplated resigning from their positions due to the overwhelming stress and fear of infection. The findings underscore the substantial psychological impact that infectious disease outbreaks can have on individuals working within the healthcare sector.[9] The purpose of this study was to investigate the prevalence of mood disorders among healthcare workers in the COVID-19 ward and outpatient clinic of a hospital and their first-degree relatives.

METHODS

Our cross-sectional study was conducted at Ufuk University Hospital after the approval of Ufuk University Non-interventional Clinical Researches Evaluation Ethics Committee (Date: 16.02.2022, Decision No: 22.02.16.02/04). The study's population comprised health personnel of Ufuk University Hospital and their first-degree relatives. Two groups were planned in the study: the first group consisted of healthcare personnel; the second group consisted of a person who was a first-degree relative of this personnel and who was not a healthcare worker. The minimum number of participants was found to be 176 in each group and 352 in total, with a ratio of 1:1, α=0.05, power=80%, and effect size=0.3 for the sample size. The sample size was determined a priori based on α=0.05, power=80%, and effect size=0.3, ensuring statistical adequacy. However, the single-center design may limit generalizability to broader healthcare settings. In the study, the healthcare personnel group (first group) included doctors, nurses, or other healthcare personnel working in the COVID-19 service or polyclinic of Ufuk University; the second group included a first-degree relative of each healthcare personnel who was not healthcare personnel. Those older than 18 years of age, working in the COVID-19 service or outpatient clinic, and voluntarily agreeing to participate in the study were included. Non-healthcare workers, first-degree relatives of healthcare workers, those who had not worked in a COVID-19 service or outpatient clinic, those with a previous diagnosis of psychiatric illness, those taking psychiatric medication and those who declined to be involved in the study were excluded. Informed consent was received from all the volunteers before the questionnaire was administered. The study was designed in accordance with the principles of the Declaration of Helsinki. A total of 375 people were reached: 208 in the first group (healthcare workers) and 167 in the second group (relatives of healthcare workers).

The data collection form utilized in the study is divided into three sections. In the first part, sociodemographic characteristics of the participants, such as gender, age, occupation, and working period, were asked. In the second part, the Brief symptom inventory (BSI) scale was used to assess the general psychopathology of the participants. The BSI consists of 9 subscales, 3 global indices, and additional items. The nine subscales of the scale are somatization, obsessive-compulsive symptoms (OCS), IS, depression, anxiety, hostility, phobic anxiety (PA), paranoid ideation (PI) and psychoticism. The global indices of the scale are discomfort severity index (DSI), sum of symptoms (SS), and symptom discomfort index (SDI). Additional items (AI) are items related to sleep disorders, eating and drinking disorders, considerations and thoughts regarding death and dying, as well as experiences of guilt. The BSI is a 5-point Likert-type scale. Each item is calculated by scoring between 0 and 4.[10] Şahin et al.[11] conducted the validation of the scale in Turkey and found that the Cronbach's alpha coefficient for the entire scale was 0.94. In the third section, the Burnout scale short form was used to assess the burnout status of the participants. The scale contains 10 items that assess an individual's physical, emotional, and mental exhaustion levels. It utilizes a 7-point Likert scale (1=never and 7=always). The scale, created by Pines and Aronson in 1988, originally had 21 items. In 2005, Pines created a shorter 10-item version. The scale score is calculated by summing the scores of the 10 items and dividing by 10. A high score indicates a high level of burnout. Çapri[12] conducted the validation of the scale in Turkiye in 2013.

Statistical Analysis

In this study, Cronbach's alpha coefficient for the overall scale was confidently determined to be 0.91. Statistical Package for Social Sciences (SPSS) version 22.0 (IBM, New York, USA) was used for data analysis. Mean±standard deviation (SD), median-quartiles (Q1-Q3), and number/percentage were used to present descriptive data. Mann-Whitney U and Kruskal-Wallis tests were used in statistical analyses because the dependent variables did not fit the normal distribution in the normality assessment. When a significant difference was detected in variables with more than two groups, the post-hoc Bonferroni test was used to determine the groups with a difference. The limit of statistical significance was accepted as $p<0.05$.

RESULTS

A total of 375 people participated in the study. Of the participants, 217 (57.9%) were female, and 202 (53.9%) were single. Most were between the ages of 25 and 34 and had not yet completed 10 years in the profession. 64 (17.1%) of the healthcare workers said they worked 16 hours or more daily. The sociodemographic information of the participants is given in Table 1.

Table 1. Sociodemographic characteristics of the participants

Feature	n	%
Gender		
Female	217	57.9
Male	158	42.1
Age		
18-24	74	19.7
25-34	185	49.3
35-50	79	21.1
51-64	34	9.1
65 and over	3	0.8
Marital status		
Married	173	46.1
Single	202	53.9
Profession year		
0-9 years	252	67.2
10-19 years	65	17.3
20-29 years	38	10.1
30 and above	20	5.3
Profession		
Doctor	97	25.9
Nurse	63	16.8
Other health personnel	48	12.8
A relative of a health worker	167	44.5
Working unit		
COVID-19 service	72	19.2
COVID-19 polyclinic	94	25.1
COVID-19 intensive care	39	10.9
Daily working hours		
0-8 hours	86	22.9
8-16 hours	93	24.9
16 hours or more	64	17.1
Total	375	100.0

*: Bonferroni test, Mann Whitney-U test was used for pairwise comparisons, and Kruskal-Wallis test was used for three or more comparisons

Demographic characteristics of healthcare workers were used to compare DSI index scores with BSI burnout scale results. The DSI index score was higher in single healthcare workers than in married healthcare workers. COVID-19 service workers scored higher on the burnout scale than COVID-19 intensive care unit workers, and those who had been in the profession for 0-9 years scored higher on the burnout scale than those who had been in the profession for 20-29 years (Table 2).

A statistically significant difference was found when the short symptom inventory sub- dimensions and burnout scale scores were compared according to occupational groups. Physicians exhibited markedly elevated scores across somatization, OCS, interpersonal sensitivity (IS), anxiety, and depression, Hostility, Psychoticism, PA, PI, AI, SS, DSI, SDI, and Burnout scale scores compared to other groups. Other health personnel had the second-highest scores, while nurses ranked third. Post-hoc analyses found that the scores of the control group without healthcare personnel were significantly lower than all healthcare personnel groups (Table 3).

Table 2. Comparison of DSI and burnout scale scores according to some characteristics of healthcare workers

	DSI score	p-value	Burnout	p-value
Gender				
Female	0.51±0.40	0.607	4.18±1.85	0.458
Male	0.54±0.39		3.97±1.93	
Age				
18-24	0.51±0.44	0.556	3.82±2.02	0.186
25-34	0.56±0.40		4.35±1.82	
35-50	0.43±0.31		3.74±1.75	
51-64	0.57±0.39		3.64±2.20	
65 and over	0.18		1.70	
Marital status				
Married	0.44±0.34	0.032	3.89±1.84	0.202
Single	0.58±0.42		4.22±1.91	
Working unit				
COVID-19 service (1)	0.62±0.39	0.037 3<1*	4.47±1.92	0.018 3<1*
COVID-19 polyclinic (2)	0.53±0.40		4.33±1.84	
COVID-19 ICU (3)	0.41±0.37		3.43±1.84	
Daily working hours				
0-8 hours	0.50±0.37	0.298	3.92±1.70	0.154
8-16 hours	0.49±0.41		4.00±1.95	
16 hours or more	0.59±0.40		4.50±1.93	
Profession year				
0-9 years (1)	0.56±0.41	0.058	4.29±1.87	0.033 3<1*
10-19 years (2)	0.47±0.36		3.77±1.85	
20-29 years (3)	0.31±0.28		2.97±1.42	
30 and above (4)	0.71±0.48		4.28±2.92	

DSI: Discomfort severity index, ICU: Intensive care unit, *: Bonferroni test, Mann-Whitney U test was used for pairwise comparisons, and Kruskal-Wallis test was used for three or more comparisons

DISCUSSION

At the center of the COVID-19 crisis, healthcare workers must successfully manage both COVID-19 patients and other patients, while also taking care of their families and maintaining their personal responsibilities. The psychological health and general wellbeing of healthcare workers has garnered attention, with studies indicating high levels of burnout, psychological stress, and suicide rates.[13] In our study, we compared healthcare workers to individuals from other professional groups regarding burnout and psychiatric symptoms. We found that all healthcare workers scored higher on both scales than the scores of the control group of non-healthcare workers. In a study by Mete et al.[14] during the early pandemic, the prevalence of psychiatric disorders in healthcare workers was between 36.7% and 51.6%. Anxiety symptoms were reported in 50% of cases. Among nurses, the prevalence ranged from 50.2% to 70.3%; for physicians, it was 31.4% to 68.3%; and for other healthcare workers, it was 37.5% to 49.7%. The study found that psychiatric symptoms were observed to be 1.50 to 3.46 times more frequent in individuals who experienced COVID-19 symptoms in the past month. Additionally, these symptoms were 1.76 to 2.74 times more prevalent in those diagnosed with COVID-19, and 1.77 to 2.25 times higher in individuals who had a COVID-19 diagnosis within their immediate family, and 1.76 to 3.15 times higher in healthcare workers who had lost someone to COVID-19 in their immediate family.[14] In our study, psychiatric symptom scores were higher in all healthcare workers compared to their relatives. A study conducted in Wuhan during the COVID-19 outbreak revealed that no less than one-third of healthcare professionals reported experiencing mental health symptoms.[15] A separate investigation involving 1.257 healthcare workers in China revealed that 35.6% exhibited depressive symptoms, while 33.2% reported experiencing

Table 3. Comparison of BSI and Burnout Scale scores according to occupational groups

	Profession group *					
	Doctor (1) mean±SD	Nurse (2) mean±SD	Other HP (3) mean±SD	HP's relative (4) mean±SD	p-value	
Somatization	1.69±1.35	0.79±0.77	1.09±1.10	0.54±0.74	<0.001	4<2<3<1
OCS	2.12±1.28	1.19±0.84	1.37±1.11	0.81±0.91	<0.001	4<2<3<1
IS	2.06±1.37	1.16±0.95	1.23±1.17	0.77±0.94	<0.001	4<2<3<1
Depression	2.16±1.29	1.21±0.88	1.36±1.15	0.82±0.93	<0.001	4<2<3<1
Anxiety	2.04±1.31	1.01±0.78	1.10±1.14	0.62±0.82	<0.001	4<2<3<1
Hostility	1.99±1.31	1.03±0.85	1.30±1.13	0.71±0.89	<0.001	4<2<3<1
PA	1.69±1.37	0.84±0.86	1.18±1.18	0.53±0.80	<0.001	4<2<3<1
PI	2.17±1.28	1.42±0.98	1.43±1.12	0.79±0.89	<0.001	4<2<3<1
Psychoticism	1.75±1.39	0.87±0.77	1.07±0.96	0.57±0.79	<0.001	4<2<3<1
Additional items	1.93±1.33	1.03±0.81	1.18±1.10	0.69±0.87	<0.001	4<2<3<1
SS	39.13±16.45	31.95±15.66	32.10±16.86	21.61±16.35	<0.001	4<2<3<1
DSI	0.66±0.44	0.34±0.25	0.47±0.35	0.22±0.27	<0.001	4<2<3<1
SDI	0.80±0.34	0.52±0.23	0.63±0.28	0.46±0.24	<0.001	4<2<3<1
Burnout	4.81±1.31	3.58±1.50	3.36±2.00	2.58±1.65	<0.001	4<2<3<1

HP: Health personnel, OCS: Obsessive-compulsive symptom, IS: Interpersonal sensitivity, PA: Phobic anxiety, PI: Paranoid ideation, SS: Sum of symptoms, DSI: Disturbance severity index, SDI: Symptom discomfort index, *: Kruskal-Wallis test, Bonferroni test was used in post-hoc analyses

symptoms of anxiety.[16] Additional research on the psychological burden of COVID-19 on healthcare workers indicated a significant impact on their mental well-being. Lai et al.[16] documented experiences of anxiety, depression, sleep disturbance, and stress amongst healthcare workers. Moreover, Li et al.[17] identified that these individuals faced symptoms of anxiety and depression, alongside reductions in positive affect and overall life satisfaction scores. Zhang et al.[18] further reported occurrences of insomnia, anxiety, depression, somatization, and OCS within this population. Additionally, Tan et al.[19] underscored that anxiety, depression, and post-traumatic stress disorder were present within this population. A systematic review highlighted anxiety, depression, and insomnia among COVID-19 healthcare workers, underscoring the urgent need for targeted mental health interventions.[20] Given the literature, our study found that healthcare workers scored higher on all subscales and indices of the BSI and the burnout scale compared to the control group. Research into the psychosocial impact of the COVID-19 outbreak on hospital workers has shown that nurses were the most affected occupational group.[21] A study conducted in a Chinese COVID-19 ward clearly demonstrated that nurses experienced higher levels of psychological symptoms than doctors, with women showing a significantly higher incidence than men.[22] In our study, physicians were the group with the highest score, and no gender differences were found. Contrary to studies identifying nurses as the most affected group, our findings highlighted physicians' elevated psychological burden. This discrepancy may stem from physicians' heightened decision-making responsibilities, prolonged exposure to critically ill patients, and administrative pressures during the pandemic. Additionally, physicians often face longer working hours and ethical dilemmas regarding resource allocation, which may exacerbate burnout. The interaction among different occupational groups with patients varies globally due to the diversity of health systems, which may clarify these findings. A study conducted in China examined trauma levels among three groups: healthcare professionals on the front line, those on the back line, and the general population throughout the pandemic. Interestingly, frontline healthcare professionals were found to have lower levels of trauma symptoms than backline workers.[17] This finding is attributed to the public spending more time at home and engaging with media, due to the strict isolation policies implemented in China during the study period. In our study, on the contrary, the scale scores were highest in physicians working in the forefront and lowest in relatives of healthcare workers. Experiencing the effects of the disease more closely, working conditions and the intensity of working hours may have led to this result, as expected. Similar to our study, a meta-analysis of the psychological impact of the pandemic on healthcare professionals found that working conditions would also play an important role. There is a noteworthy prevalence of anxiety and depression among frontline health care professionals in the majority of studies conducted.[23] Based on research, it is inevitable that mental health assessment, support, treatment, and services will be developed and implemented to overcome the pandemic at this time.[24] The accuracy of survey studies is often affected by respondents' ability to recall information, which can lead to incorrect or incomplete answers.

Limitations

Our study has some limitations. First, because we used a cross-sectional design, we cannot determine cause-and-effect relationships. Also, since participation was voluntary, it might have created a selection bias. The research took place at just one healthcare facility, so the results may not apply to other places or healthcare workers. We also had difficulty recruiting enough relatives of healthcare workers for the control group, which could have affected our sample. Future studies that follow participants over time are needed to understand

how work-related stress affects mental health. Despite these limitations, our findings provide important insights into the psychological impact of the pandemic on healthcare workers.

CONCLUSION

Our study concludes that the pandemic has psychologically affected medical workers more than individuals in other professions, with doctors being the most affected group. These findings underscore the urgent need for systemic interventions, such as mental health screenings, accessible counseling services, and workload redistribution policies, to safeguard healthcare workers' wellbeing. Prioritizing physician support programs, given their disproportionate burden, could enhance resilience during future crises. Ensuring the protection of healthcare professionals is essential for the effective implementation of public health initiatives during large-scale health crises.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was with the approval of the Ufuk University Non-interventional Clinical Researches Ethics Committee (Date: 16.02.2022, Decision No: 22.02.16.02/04).

Informed Consent

All patients signed and filled and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1647855

Anatolian Curr Med J. 2025;7(3):283-290

Predictors of left atrial strain recovery in patients hospitalized with acute heart failure with reduced ejection fraction

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Cite this article as: Demirtola Aİ, İnan D, Mammadli A, et al. Predictors of left atrial strain recovery in patients hospitalized with acute heart failure with reduced ejection fraction. *Anatolian Curr Med J.* 2025;7(3):283-290.

Received: 01.03.2025 ◆ **Accepted**: 04.04.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: Left atrial (LA) function is crucial in heart failure (HF) pathophysiology, and its impairment is associated with adverse outcomes. LA reservoir strain (LASr), assessed via speckle-tracking echocardiography, has emerged as a sensitive marker of LA mechanics, yet its recovery during acute HF remains unclear. This study aimed to identify the clinical and echocardiographic predictors of LASr improvement in patients hospitalized with acute decompensated HF with reduced ejection fraction (HFrEF).

Methods: This retrospective study included 63 hospitalized patients with acute decompensated HFrEF (LVEF <40%). Patients were classified into improvers (≥15% increase in LASr) and non-improvers based on LASr recovery during hospitalization. Clinical and echocardiographic parameters were compared between groups, and independent predictors of LASr improvement were identified through logistic regression analysis. Model performance was evaluated using ROC and decision curve analyses.

Results: LASr improved in 38% of patients (improvers: n=24), increasing from 7.8% (IQR: 4.8–11.5) to 10.0% (IQR: 7.0–13.0, p=0.035). Compared to non-improvers, improvers had higher LVEF (p=0.009), smaller LV end-diastolic diameter (p=0.015), and lower prevalence of moderate-to-severe mitral regurgitation (p=0.012). In multivariate analysis, LVEF (OR: 1.204, 95% CI: 1.040–1.395) and LV end-diastolic diameter (OR: 0.879, 95% CI: 0.780–0.990) predicted LASr recovery, while moderate-to-severe MR was associated with lower recovery (OR: 0.170, 95% CI: 0.029–0.988). ROC analysis confirmed model performance (AUC: LVEF 0.852, EDD 0.831, MR 0.779).

Conclusion: LASr improvement during hospitalization is closely linked to baseline LV function, ventricular dimensions, and MR severity, highlighting its dynamic nature in acute HF and potential as a marker of cardiac recovery.

Keywords: Left atrial reservoir strain, heart failure with reduced ejection fraction, acute heart failure, strain recovery, echocardiographic assessment

INTRODUCTION

The left atrium (LA) plays a crucial role in cardiovascular hemodynamics by regulating left ventricular (LV) filling and adapting to changing circulatory demands.[1] However, in heart failure (HF), increased LV filling pressures and structural remodeling impair LA function, contributing to pulmonary congestion and worsening symptoms.[2] Conventional volumetric assessments may not fully capture these functional impairments, highlighting the need for more refined imaging techniques.[3]

Speckle-tracking echocardiography (STE)-derived LA strain (LAS) has emerged as a valuable tool for assessing LA function beyond traditional measurements.[4] Among its components, reservoir strain is particularly relevant, as it reflects LA distensibility and compliance during ventricular systole, integrating both atrial and ventricular interactions for a more comprehensive assessment of LA function.[5] Reduced LAS has been linked to adverse outcomes, including higher rates of hospitalization and mortality, independent of LV function.[3] While LAS changes during hospitalization may provide insights into treatment response, its dynamic trajectory remains incompletely understood.

Although LAS improves in some patients following decongestive therapy, others exhibit persistent dysfunction despite volume optimization.[4] Given its prognostic significance, identifying the clinical and echocardiographic predictors of LAS recovery in acute heart failure (AHF) is

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essential. However, this area remains largely unexplored. In this study, we aimed to investigate the determinants of LAS improvement in patients with AHF and reduced ejection fraction (HFrEF).

METHODS

Ethics

The study was conducted in accordance with the Declaration of Helsinki and this study was initiated with the approval of the Clinical Researches Ethics Committee of Başakşehir Çam and Sakura City Hospital (Date: 27.04.2022, Decision No: 135). Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Study Population

This retrospective study included patients presenting to the emergency department (ED) with AHF and a reduced ejection fraction (EF <40%), who were subsequently hospitalized in the cardiology ward. AHF was defined according to current guidelines as the rapid or progressive onset of symptoms and/or signs of HF, severe enough to necessitate urgent medical evaluation, resulting in unplanned hospital admission or an ED visit.[6]

Patients were excluded if they met any of the following criteria: delayed admission to the cardiology ward (>24 hours from ED presentation to ensure consistency in the timing of echocardiographic evaluation following early diuretic administration and to avoid variability in volume status that could affect strain measurements.), recent acute coronary syndrome (<1 month), requirement for inotropic support during hospitalization, presence of primary valvular heart disease or prior mitral valve interventions, suboptimal imaging quality insufficient for speckle-tracking echocardiographic analysis, or advanced chronic kidney disease (CKD) defined as an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 or dependence on dialysis.

Transthoracic echocardiography was performed 2 to 4 hours after intravenous diuretic administration to ensure that imaging was conducted before significant hemodynamic alterations in LA function occurred, while avoiding delays in patient management. Discharge decisions were made based on clinical stability, resolution of congestion symptoms, and improvement in standard HF parameters, as per institutional HF management protocols. Patients' demographic data, laboratory parameters, and echocardiographic measurements were systematically recorded.

Echocardiographic Examination

Transthoracic echocardiographic (TTE) evaluations were performed using an EPIQ CVx (Philips, Netherlands) ultrasound system equipped with an S5-1 phased-array transducer. Measurements of LV and LA dimensions, LV ejection fraction (LVEF), and diastolic LV filling velocities were obtained in accordance with the recommendations of the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE).[7] Right ventricular (RV) systolic function was assessed using tricuspid annular plane systolic excursion (TAPSE) and RV systolic myocardial velocity (RVSm), while systolic pulmonary arterial pressure (sPAP) was estimated based on the tricuspid regurgitation (TR) velocity. LV and LA volumes were calculated using the biplane Simpson's method and the LA volume index (LAVi) was obtained by indexing LA volume to body surface area (BSA). Mitral and TR severity was assessed according to current echocardiographic guidelines.[8]

Strain Analysis

LA strain (LAS) was assessed using two-dimensional speckle-tracking echocardiography (2D-STE) in accordance with current guidelines.[9] Apical four-chamber (A4C) and two-chamber (A2C) views were acquired, and the average was used to enhance reproducibility. The endocardial border was automatically traced with manual adjustments as needed, ensuring optimal tracking. Frame rates were set between 50–70 frames per second, and offline analyses were performed using QLAB software (Philips, Netherlands).

LAS components included reservoir strain (LASr), reflecting LA expansion during LV systole, conduit strain (LAScd), representing passive emptying in early diastole, and contraction strain (LASct), corresponding to active contraction in late diastole. In atrial fibrillation (AF) patients, only LASr was analyzed due to the absence of atrial contraction. A representative LA strain analysis is shown in **Figure 1**.

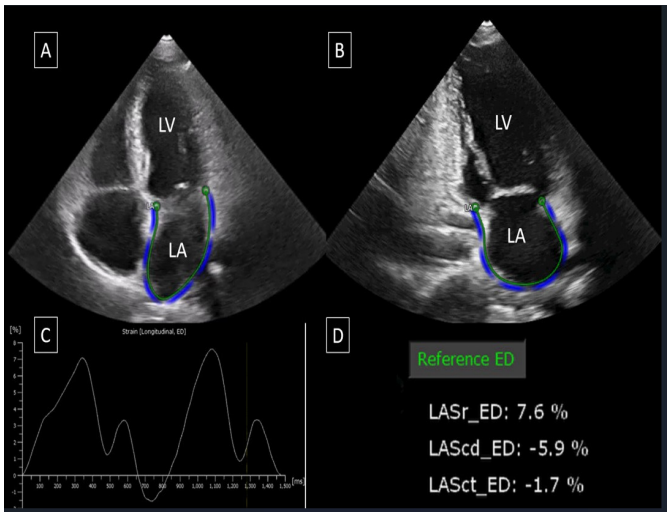

Figure 1. Left atrial strain assessment using speckle-tracking echocardiography (**A**) Apical four-chamber (A4C) and (**B**) apical two-chamber (A2C) views demonstrating left atrial (LA) strain analysis. The endocardial border is manually traced, and strain curves are generated. (**C**) Strain-time curve showing longitudinal strain measurements of the left atrium. (**D**) Strain values at end-diastole (ED), including LA reservoir strain (LASr_ED), conduit strain (LAScd_ED), and contractile strain (LASct_ED), are displayed

For LV global longitudinal strain (LV-GLS), A4C, A2C, and apical long-axis (APLAX) views were analyzed. RV and right atrial (RA) strain were obtained from an RV-focused A4C and optimized A4C view, respectively. As with LA strain, only RASr was analyzed in AF patients.

Statistical Analysis

Patients were classified as improvers (≥15% increase in LASr from admission to discharge) or non-improvers, based on previously established thresholds.[10] Group comparisons for

demographic, laboratory, and echocardiographic parameters were conducted. Continuous variables were assessed for normality using the Shapiro-Wilk test; normally distributed data were reported as mean±standard deviation (SD) and compared using the independent Samples t-test, while non-normally distributed data were presented as median (IQR) and analyzed using the Mann-Whitney U test. Categorical variables were expressed as n (%) and compared using the Chi-square or Fisher's exact test.

Univariate and multivariate logistic regression analyses were performed to identify predictors of LASr recovery. Variables with p<0.25 in univariate analysis and those deemed clinically relevant were included in the multivariate model. Model performance was assessed using the Hosmer-Lemeshow test. Multicollinearity among independent variables was assessed using the variance inflation factor (VIF), and all variables included in the final multivariate model had VIF values <2, indicating no significant collinearity. The association between LASr improvement and continuous variables was evaluated using Spearman or Pearson correlation, as appropriate.

Receiver operating characteristic (ROC) analysis was used to determine cutoff values, area under the curve (AUC), sensitivity, and specificity for significant predictors. Model performance was further assessed with decision curve analysis (DCA) and calibration plots.

To ensure measurement reliability, interobserver and intraobserver variability of strain analyses was evaluated in a randomly selected subset of 15 patients, quantified using intraclass correlation coefficients (ICC).

Statistical analyses were performed using SPSS version 30 (IBM, Armonk, NY, USA) and R version 4.4.2, with p<0.05 considered statistically significant.

RESULTS

A total of 72 patients were initially screened, and after applying the exclusion criteria, 63 patients were included in the final analysis. The median age of the study population was 68 years (IQR: 58–76), and 40 patients (63%) were male. The median LVEF was 33.5% (IQR: 29.8–38.3). Ischemic cardiomyopathy was the predominant etiology, observed in 73% of patients. The prevalence of coronary artery disease (CAD) was 83%, while diabetes mellitus (DM) and hypertension (HT) were present in 49% and 68% of patients, respectively. At admission, 44 patients (70%) were classified as NYHA class IV. Although not statistically significant, hypertension (p=0.054) and CKD (p=0.074) were more prevalent among non-improvers, indicating a possible trend toward association with limited LASr recovery. Baseline demographic, clinical and echocardiographic characteristics of the study population are summarized in **Table 1, 2**.

Decongestive therapy resulted in significant reductions in E/e' ratio, TR velocity, and sPAP. The E/e' ratio decreased from a median of 18.6 (IQR: 13.1–19.8) at admission to 12.2 (IQR: 11.7–12.9) at discharge (p=0.017). TR velocity reduced from 2.4 m/s (IQR: 2.1–3.2) to 2.2 m/s (IQR: 2.0–2.6) (p=0.041). sPAP

Table 1. Baseline and echocardiographic characteristics of non-improvers and improvers

Variable	Non-improver (n=35)	Improver (n=28)	Total (n=63)	p-value*
Baseline demographics				
Age, years	63 (55.5-74)	70.5 (63.75-78)	68 (58-76)	0.231
Male, n(%)	23 (66%)	17 (61%)	40 (63%)	0.682
CAD, n(%)	29 (83%)	23 (82%)	52 (83%)	0.941
DM, n(%)	19 (54%)	12 (43%)	31 (49%)	0.311
HL, n(%)	15 (43%)	8 (29%)	23 (37%)	0.301
HT, n(%)	27 (77%)	16 (57%)	43 (68%)	0.054
CMP type n(%)				0.854
Dilated	8 (23%)	6 (21%)	14 (22%)	
Ischemic	25 (71%)	21 (75%)	46 (73%)	
History of stroke, n(%)	4 (11%)	2 (7%)	6 (10%)	0.545
CKD, n(%)	16 (46%)	7 (25%)	23 (37%)	0.074
AF, n(%)	15 (43%)	8 (29%)	23 (37%)	0.211
COPD, n(%)	5 (14%)	4 (14%)	9 (14%)	0.982
ICD, n(%)	7 (20%)	6 (21%)	13 (21%)	0.864
Systolic BP, mmHg	117.5 (110.2-124.9)	118.9 (111.3-125.7)	118.2 (110.8-125.3)	0.617
HR, bpm	76 (70-88)	85 (74-97)	78 (70-91)	0.139
BMI, kg/m²	26.81 (22.9-32.2)	29.3 (29.3-29.3)	29.3 (23.5-31.3)	1.000
Hospitalization duration, days	7 (5-8)	6 (4.25-8)	7 (5-8)	0.118
NYHA, n(%)				0.789
Class 3	11 (31%)	8 (29%)	19 (30%)	
Class 4	24 (69%)	20 (71%)	44 (70%)	
Heart failure medications				
Loop diuretic, n (%)	34 (97%)	27 (96%)	55 (87%)	0.874
Thiazide, n (%)	9 (26%)	6 (21%)	15 (24%)	0.653
Beta-blocker, n(%)	30 (86%)	21 (75%)	51 (81%)	0.156
ACEi/ARB, n(%)	28 (80%)	23 (82%)	51 (81%)	0.875
MRA, n(%)	12 (34%)	13 (46%)	25 (40%)	0.254
SGLT-2 inhibitor	14 (40%)	11 (39%	25 (40%)	0.812
ARNI	8 (23%)	6 (21%)	14 (22%)	0.729
Laboratory findings				
Creatinine, mg/dl	1.4 (1.0-1.8)	1.4 (1.1-1.6)	1.4 (1.0-1.7)	0.606
eGFR, ml/min/1.73m²	46 (31.7-71.5)	47 (35.5-59.5)	47 (34.5-64)	0.527
HB, g/dl	11.4 (9.9-13.8)	11.7 (10.6-13.5)	11.6 (10.4-13.5)	0.571
Admission BNP, pg/ml	10880.5 (5635.2-21062)	8761 (4042.2-17219.2)	9884 (4285-17376)	0.191
Discharge BNP pg/ml	8065 (3512.5-13294.7)	5715 (3464-10255)	6850 (3820-12792.2)	0.768

* Continuous variables are presented as median (interquartile range), and categorical variables are expressed as n (%). A p-value < 0.05 was considered statistically significant. Abbreviations: AF: Atrial fibrillation, ARNI: Angiotensin receptor-neprilysin inhibitor, BMI: Body-mass index (kg/m²), BNP: B-type natriuretic peptide (pg/ml) CAD: Coronary artery disease, CKD: Chronic kidney disease, CMP type: Cardiomyopathy type, COPD: Chronic obstructive pulmonary disease, Diastolic BP: Diastolic blood pressure (mmHg), DM: Diabetes mellitus, eGFR: Estimated glomerular filtration rate (ml/min/1.73m²), HB: Hemoglobin (g/dl), HL: Hyperlipidemia, HR: Heart rate (bpm), HT: Hypertension, ICD: Implantable cardioverter defibrillator, MRA: Mineralocorticoid receptor antagonist, NYHA: New York Heart Association functional classification, SGLT2: Sodium-glucose cotransporter-2

Table 2. Comparison of echocardiographic parameters between non-improvers and improvers at admission and discharge

Variable	Non-Improver (n=35)	Improver (n=28)	Total (n=63)	p-value*
Admission				
Left ventricle				
EDD, mm	60 (57-63)	56 (53-59)	58 (55-61)	0.014
ESD, mm	50 (47-53)	46 (43-48)	48 (45-51)	0.046
EF, %	32 (26-35)	38 (32-39)	33.5 (29.75-38.25)	0.004
E/e'	12 (11.5-12.8)	12.9 (12.1-13.75)	12.1 (11.6- 12.8)	0.061
TR vel, cm/s	2.38 (2.1-3.2)	2.5 (2.2-3)	2.38 (2.1-3.2)	0.715
SPAP, mmHg	25 (25-27)	25.3 (25-27.1)	25 (25-27)	0.833
TAPSE, mm	17 (12-20)	17 (16-18)	17 (12-19)	0.752
RVSM, mm	9 (7-10)	9.7 (8.5-12.5)	9.1 (7.75-10)	0.906
LA (A-P), mm	43 (40-46)	42 (39-45)	42.5 (39.5-45.5)	0.782
LA Volume, ml	92 (80-129)	84 (72-104)	93.5 (75-127)	0.170
LAVI, mL/m²	51.1 (44.4-71.6)	46.6 (40-57.7)	51.9 (41.6- 70.5)	0.170
Mitral regurgitation, n (%)				0.032
None	2 (6%)	5 (18%)	7 (11%)	
Mild	6 (17%)	12 (43%)	18 (29%)	
Moderate	16 (46%)	7 (25%)	23 (37%)	
Severe	11 (31%)	4 (14%)	15 (24%)	
Tricuspit regurgitation, n (%)				0.512
Mild	8 (23%)	8 (29%)	23 (37%)	
Moderate	19 (54%)	14 (50%)	28 (44%)	
Severe	8 (23%)	6 (21%)	12 (19%)	
Strain parameters				
LASr, %	5.6 (4.2-10.3)	8.2 (6.9-13.0)	7.8 (4.8-11.5)	0.004
LAScd, % **	-6.1 (-9.3--3.9)	-5.7 (-7.3--3.3)	-5.8 (-8--3.3)	0.449
LASct, %	-3.6 (-5.8--1)	-1.1 (-2-0)	-1.7 (-5.15--0.4)	0.023
RASr, %	9.9 (6.2-17)	12.2 (9.6-16)	11.2 (6.3-16)	0.447
RAScd, %	-8.2 (-10.4--4.6)	-7.0 (-10.7--4.15)	-7.9 (-10.4--4.3)	0.643
RASct, %	-3.8 (-9.6--1.7)	-6.15 (-11.4--1.4)	-4.1 (-9.9--1.45)	0.597
RVFW, %	-12.6 (-17--6.9)	-14.1 (-14.2--8.6)	-12.6 (-14.2--8.6)	0.971
RV4C, %	-10.6 (-10.6--7.5)	-9.3 (-10.1--6.6)	-10.1 (-10.6--7.5)	0.409
LV, %	-10.7 (-12.2--8.7)	-12.7 (-15.8--9.2)	-11.2 (-12.5--9)	0.046
Discharge				
Left ventricle				
EDD, mm	58 (55-62)	55 (52-59)	57 (54-61)	0.031
ESD, mm	49 (46-52)	44 (41-47)	46 (42-49)	0.046
EF, %	34 (26-40)	40 (36-44)	36 (33-38)	0.015
LA, mm	42.8 (39.7-45.8)	41 (38.5-44)	42.5 (41-44)	0.083
E/e'	18.5 (13.1-19.8)	18.5 (18.5-18.5)	18.5 (13.1-19.8)	0.900
TR vel, cm/s	2.6 (2.6-2.6)	2.5 (2.3-2.7)	2.6 (2.3-2.7)	1.000
SPAP, mmHg	32 (32-32)	31.5 (30-33)	32 (30-33)	1.000
TAPSE, mm	15 (12-21)	22 (22-22)	15 (12-21)	0.194
RVSM, mm	9.9 (7-9.95)	11.3 (11-11.6)	9.9 (7-11)	0.004
LA volume, ml	94 (81-120)	111 (97.75-120)	106 (87-120)	0.084
LAVI, ml/m²	52.7 (45-66.6)	61.6 (55.2-66.6)	58.8 (48.3-66.6)	0.084
Mitral regurgitation, n (%)				0.044
None	6 (17%)	8 (29%)	14 (22%)	

The table continues

Table 2. Comparison of echocardiographic parameters between non-improvers and improvers at admission and discharge (continues)

Mild	18 (51%)	12 (43%)	30 (48%)	
Moderate	9 (26%)	8 (29%)	17 (27%)	
Severe	2 (6%)	0	2 (3%)	
Tricuspit regurgitation, n (%)				
Mild	19 (54%)	21 (75%)	40 (63%)	0.221
Moderate	10 (29%)	5 (18%)	15 (24%)	
Severe	6 (17%)	2 (7%)	8 (13%)	
Strain parameters				
LASr, %	6.2 (4.5-10.8)	12 (7.5-18.1)	8.3 (5.9-14.4)	0.001
LAScd, %	-5.1 (-9.3--3.6)	-6.7 (-7.8--4.6)	-6.7 (-9.2--4)	0.073
LASct, %	-1.3 (-4.2--0.6)	-3.9 (-9.1--0.9)	-1.8 (-5.6--0.8)	0.009
RASr, %	7.85 (4.9-14.8)	13.8 (7.9-22.8)	11.6 (5.4-20.1)	0.088
RAScd, %	-4.9 (-5.6--2.5)	-5.6 (-8.7--3.7)	-5 (-7.7--3.05)	0.152
RASct, %	-3.4 (-8.05--1.0)	-6.4 (-11.4--4.7)	-5.5 (-9.3--2.4)	0.088
RVFW, %	-9.8 (-11.6--5.6)	-17.1 (-21--13.2)	-11.6 (-13.2--9.8)	0.007
RV4C, %	-7.6 (-9.6--3.8)	-16.3 (-22--10.6)	-9.6 (-10.6--7.6)	0.007
LV, %	-11.5 (-12--8.8)	-13.1 (-17--9)	-11.7% (-13.0-9.5)	0.025

* Continuous variables are presented as median (interquartile range), and categorical variables are expressed as n (%). A p-value < 0.05 was considered statistically significant. **LAScd, LASct, RAScd and RASct values are reported only for patients in sinus rhythm. Abbreviations: EDD: End-diastolic diameter (mm), EF: Ejection fraction (%), ESD: End-systolic diameter (mm), LA (A-P): Left Atrium antero-posterior (mm), LAScd: Left atrial strain (Conduit) (%), LASct: Left atrial strain (contraction) (%), LASr: Left atrial strain (reservoir) (%), LAVI: Left atrial volume index (ml/m^2), LA volume: Left atrial volume (ml), LV: Left ventricle (mm), RAScd: Right atrial strain (conduit) (%), RASct: Right atrial strain (contraction) (%), RASr: Right atrial strain (reservoir) (%), RV4c: Right ventricular 4C strain (%), RVFW: Right ventricular free wall strain (%), RVSM: Right ventricular systolic motion (mm), SPAP: Systolic pulmonary artery pressure (mmHg), Systolic BP: Systolic blood pressure (mmHg), TAPSE: Tricuspid annular plane systolic excursion (mm), TR: Tricuspid regurgitation, TR vel: Tricuspid regurgitation velocity (cm/s)

declined from 25.0 mmHg (IQR: 25.0–27.0) to 22.5 mmHg (IQR: 21.0–24.0) (p=0.037). LASr improved significantly, increasing from 7.8% (IQR: 4.8–11.5) at admission to 10.0% (IQR: 7.0–13.0) at discharge (p=0.035). Mitral regurgitation (MR) severity decreased significantly (p=0.011), with the proportion of patients with no MR increasing from 11% to 22% and those with severe MR decreasing from 24% to 3%. These findings are presented in detail in **Table 3**.

Univariate analysis identified several parameters associated with LASr recovery, which were further assessed in the multivariate logistic regression model. EF was found to be an independent predictor of recovery (OR: 1.204, 95% CI: 1.040–1.395, p=0.013), while left ventricle end-diastolic diameter (EDD) was inversely associated (OR: 0.879, 95% CI: 0.780–0.990, p=0.034). Moderate-to-severe MR also demonstrated a significant negative predictive value (OR: 0.170, 95% CI: 0.029–0.988, p=0.048). The regression results are summarized in **Table 4**. The graphical representation of the model is shown in **Figure 2A**, while the decision curve analysis (**Figure 2B**) demonstrated its clinical utility across a range of risk thresholds. The calibration plot (**Figure 2C**) confirmed good model performance, further supported by the Hosmer-Lemeshow test (Chi-square=12.82, df=8, p=0.118). The model demonstrated a sensitivity of 82% and a specificity of 86% and demonstrated good overall performance, with a Nagelkerke R^2 of 0.698 and a Cox & Snell R^2 of 0.490. Model calibration was acceptable based on the non-significant Hosmer–Lemeshow test (χ^2=11.287, df=8, p=0.186), and the -2 log likelihood value was 44.101.

ROC analysis was conducted to assess the predictive performance of EF, reversed EDD, and none-mild MR for LASr recovery. MR was categorized as none-mild versus moderate-severe to ensure a clinically meaningful distinction between patients with minimal versus significant volume overload. Since larger EDD values were associated with a lower probability of recovery, EDD values were reversed to maintain consistency in AUC interpretation. The analysis yielded an AUC of 0.852 (95% CI: 0.752–0.951) for EF, 0.831 (95% CI: 0.725–0.936) for reversed EDD, and 0.779 (95% CI: 0.659–0.898) for None-Mild MR (**Figure 3A**). Restricted cubic spline plots were used to illustrate the association between EF, EDD, and the probability of LASr recovery (**Figure 3B, 3C**). EF showed a positive association with recovery probability, while EDD demonstrated a non-linear relationship, with lower values being linked to higher recovery probability, followed by a plateau at larger values.

For reliability assessment, interobserver and intraobserver variability of echocardiographic parameters, including strain measurements, were evaluated in a subset of 15 patients. The ICC were 0.89 (95% CI: 0.82–0.94) for interobserver variability and 0.93 (95% CI: 0.88–0.96) for intraobserver variability, demonstrating good overall agreement.

DISCUSSION

The present study demonstrated that in patients hospitalized with AHF and HFrEF, LASr significantly improved following decongestive therapy, highlighting the responsiveness of LA mechanics to volume optimization, and this improvement was independently predicted by higher baseline EF, smaller LV dimensions, and less severe MR assessed at hospital admission. As the first study to specifically investigate LA strain recovery in this population, our findings emphasize that LASr recovery during hospitalization reflects not only acute decongestion but also underlying cardiac structure and valvular function.

Table 3. Changes in echocardiographic and strain parameters from admission to discharge

Parameter	Admission	Discharge	p-value
EDD, mm	58 (55-61)	57 (54-61)	0.679
ESD, mm	48 (45-51)	47 (44-50)	0.138
EF, %	34 (29.7-38.2)	35 (31-39)	0.102
LA, mm	42.5 (39.5-45.5)	42.5 (41-44)	0.159
E/e'	18.5 (13.1-19.8)	12.1 (11.6-12.8)	0.017
TR velosity,	2.38 (2.1-3.2)	2.2 (2-2.6)	0.041
SPAP, mmHg	25 (25-27)	22.5 (21-24)	0.037
TAPSE, mm	17 (12-19)	15 (12-21)	0.208
RVSM	9.1 (7.7-10)	9.9 (7-11)	0.679
LAVI	51.9 (41.6-70.5)	58.8 (48.3-66.6)	0.455
Strain parameters			
LASr, %	7.8 (4.8-11.5)	10 (7-13)	0.035
LAScd, %	-5.85 (-8--3.3)	-6.7 (-9.2--4)	0.935
LASct, %	-1.7 (-5.1--0.4)	-1.8 (-5.6--0.8)	0.058
RASr, %	11.2 (6.3-16)	11.6 (5.4-20.1)	0.970
RAScd, %	-7.9 (-10.4--4.35)	-5 (-7.7--3.05)	0.236
RASct, %	-4.1 (-9.9--1.45)	-5.5 (-9.3--2.4)	0.922
RVFW, %	-12.6 (-14.2--8.6)	-11.6 (-13.2--9.8)	0.172
RV4C, %	-10.1 (-10.6--7.5)	-9.6 (-10.6--7.6)	0.172
LV, %	-11.2 (-12.5--9)	-11.7% (-13.0 -9.5)	0.057
Mitral regurgitation, n (%)			0.011
None	7 (11%)	14 (22%)	
Mild	18 (29%)	30 (48%)	
Moderate	23 (37%)	17 (27%)	
Severe	15 (24%)	2 (3%)	
Tricuspid regurgitation, n (%)			0.221
Mild	23 (37%)	40 (63%)	
Moderate	28 (44%)	15 (24%)	
Severe	12 (19%)	8 (13%)	

Continuous variables are presented as median (interquartile range), and categorical variables are expressed as n (%). A p-value < 0.05 was considered statistically significant. Abbreviations: EDD: End-diastolic diameter (mm), EF: Ejection fraction (%), ESD: End-systolic diameter (mm), LA (A-P): Left Atrium antero-posterior (mm), LAScd: Left atrial strain (Conduit) (%), LASct: Left atrial strain (contraction) (%), LASr: Left atrial strain (reservoir) (%), LAVI: Left atrial volume index (ml/m^2), LA volume: Left atrial volume (ml), LV: Left ventricle (mm), RAScd: Right atrial strain (conduit) (%), RASct: Right atrial strain (contraction) (%), RASr: Right atrial strain (reservoir) (%), RV4c: Right ventricular 4C strain (%), RVFW: Right ventricular free wall strain (%), RVSM: Right ventricular systolic motion (mm), SPAP: Systolic pulmonary artery pressure (mmHg), Systolic BP: Systolic blood pressure (mmHg), TAPSE: Tricuspid annular plane systolic excursion (mm), TR: Tricuspid regurgitation, TR vel: Tricuspid regurgitation velocity (cm/s)

LAS assessed by 2D-STE has emerged as a sensitive marker of atrial structural remodeling and functional impairment, providing insights beyond conventional echocardiographic parameters.[11] LAS is closely coupled with ventricular function throughout the cardiac cycle, reflecting the dynamic interplay between atrial compliance, ventricular filling pressures, and ventricular longitudinal shortening.[1] Although LA mechanics include reservoir, conduit, and contraction strains, we focused on reservoir strain due to its reliability across all patients, including those with AF, where other strain components cannot be accurately assessed.[12]

LAS has increasingly gained attention as a sensitive marker of cardiac hemodynamics and therapeutic response in patients with AHF.[4] Previous studies have evaluated the dynamics of LAS in diverse patient populations and HF phenotypes. Barki et al.[13] demonstrated that improvement in LAS following decongestion was strongly associated with better clinical outcomes, including reduced hospitalization rates, across patients with different EF. Similarly, Park et al.[3] highlighted LAS as a robust predictor of prognosis in AHF. Deferm et al.[4] further demonstrated that LASr improved from 6.4% to 8.8% during hospitalization and continued to rise to 13.4% at 6 weeks ($p<0.001$), emphasizing its role as a marker of treatment response. While their study provided valuable insights into the time course of LAS recovery, our study, which included a larger cohort, demonstrated that significant LASr improvement occurs even within the hospitalization period. Unlike prior studies with mixed HF phenotypes, we focused exclusively on HFrEF patients and assessed LA mechanics solely through reservoir strain, ensuring a consistent and rhythm-independent evaluation despite the relatively high prevalence of AF.

A novel finding of our study was that baseline cardiac structure significantly influenced LAS improvement. Specifically, patients with a higher baseline EF and smaller LV dimensions exhibited a greater magnitude of improvement in LAS after decongestive therapy. This may be explained by the fact that patients with relatively preserved LV function and less adverse cardiac remodeling at baseline have better myocardial reserve, allowing more complete recovery of LA mechanics after alleviating congestion.[14]

Our findings highlight baseline MR severity as an essential determinant of LAS improvement following treatment in AHF. Patients with less severe MR experienced more pronounced recovery in LA mechanics, supporting the notion that ongoing volume overload associated with significant MR imposes sustained mechanical stress on the LA, impairing its capacity for functional restoration despite adequate decongestion.[10] Interestingly, among patients with lower MR severity, those with higher baseline LASr values exhibited greater improvement. This suggests that preserved atrial mechanics may allow for a more dynamic recovery, whereas severely impaired LA function, potentially reflecting advanced structural remodeling, may limit the extent of reversibility. This aligns with prior studies suggesting that chronic MR adversely affects LA remodeling and compliance, ultimately limiting the potential for atrial functional recovery.[15] Additionally, in our cohort, RV strain improvement was more pronounced in patients with significant LA strain recovery. This suggests that enhanced LA function may contribute to better pulmonary venous unloading, reducing RV afterload and facilitating improved RV performance.[16] This compensatory response may reflect a more effective hemodynamic adaptation to decongestive therapy, warranting further investigation.

Given its sensitivity to hemodynamic changes and its association with structural remodeling, LASr recovery may serve as a valuable marker for assessing therapeutic response and identifying patients at risk of persistent atrial dysfunction despite decongestive treatment. Our findings suggest that beyond simply reflecting volume reduction, LASr improvement integrates information on baseline ventricular function and valvular integrity, which could have important

Table 4. Univariate and multivariate logistic regression analysis for predictors of left atrial reservoir strain recovery

	Univariate analysis				Multivariate analysis			
	p-value	OR	95% CI		p-value	OR	95% CI	
			Lower	Upper			Lower	Upper
Age, years	0.061	1.046	0.998	1.097	0.259	1.043	0.970	1.121
Male	0.621	0.754	0.246	2.312				
Diabetes mellitus	0.608	0.736	0.229	2.371				
Hypertension,	0.105	0.350	0.099	1.243	0.351	0.387	0.053	2.844
Atrial fibrillation	0.167	0.426	0.127	1.430	0.266	0.356	0.058	2.196
Systolic BP, mmHg	0.261	0.968	0.916	1.023				
eGFR, ml/min/1.73 m²	0.973	1.000	0.975	1.024				
BNP, pg/ml	0.246	1.000	1.000	1.000	0.980	1.000	1.000	1.000
End-diastolic diameter, mm	0.122	1.080	0.980	1.190	0.034	0.879	0.780	0.990
Ejection fraction, %	0.004	1.158	1.049	1.279	0.013	1.204	1.040	1.395
Left atrial volume index, ml/m²	0.305	0.977	0.933	1.022				
TAPSE, mm	0.991	1.001	0.787	1.274				
Systolic pulmonary artery pressure, mmHg	0.229	1.029	0.982	1.078				
Moderate-severe mitral regurgitation, %	<0.001	0.081	0.024	0.268	0.048	0.170	0.029	0.988

OR: Odds ratio, CI: Confidence interval, Systolic BP: Systolic blood pressure (mmHg), eGFR: Estimated glomerular filtration rate, BNP: Brain natriuretic peptide, TAPSE: Tricuspid annular plane systolic excursion

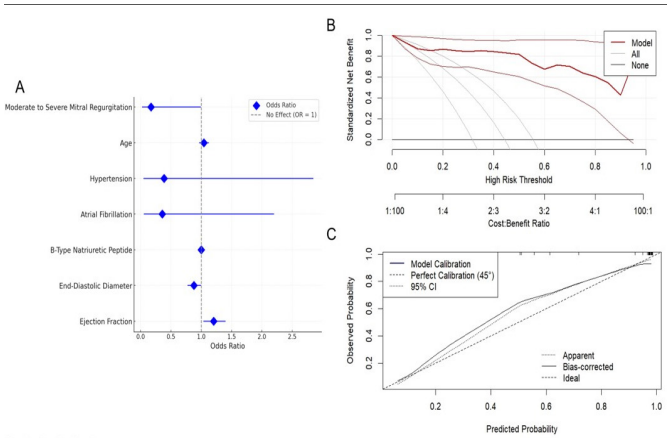

Figure 2. Predictive model for left atrial strain recovery in acute decompensated HFrEF (**A**) Forest plot displaying odds ratios for independent predictors of LASr recovery. (**B**) Decision curve analysis demonstrating the clinical utility of the predictive model across different risk thresholds. (**C**) Calibration plot assessing agreement between predicted and observed probabilities, indicating good model performance

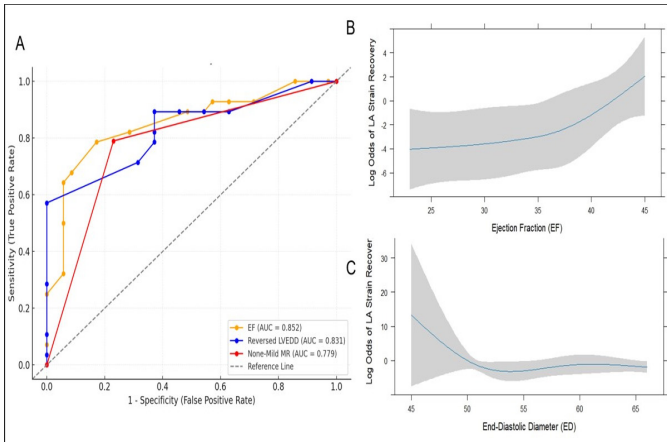

Figure 3. Echocardiographic predictors of LA strain recovery, (**A**) ROC curves for EF, reversed LVEDD, and none-mild MR. (**B**) Spline plot showing a positive association between EF and LA strain recovery. (**C**) Spline plot illustrating a non-linear relationship between EDD and recovery probability.

prognostic implications. Incorporating LASr recovery into routine echocardiographic assessment may aid in refining risk stratification and guiding management strategies in AHF, particularly in patients with significant MR or advanced cardiac remodeling. In addition, it may help support discharge decisions and identify patients who require closer follow-up, especially those with limited improvement despite decongestive therapy.

Limitations

This study has several limitations. First, the relatively small sample size may limit the generalizability of our findings. Second, LAS measurements were obtained using a single vendor's software, which may affect reproducibility across different platforms. Third, hemodynamic parameters, such as pulmonary artery wedge pressure, were not routinely assessed at discharge; instead, decisions were based on clinical stability rather than invasive measurements, potentially introducing variability in defining decongestion status. Moreover, due to the retrospective design, a certain degree of selection bias may exist, particularly related to the availability of adequate imaging and complete strain data, which may have resulted in the inclusion of relatively stable patients and thus could limit the applicability of our findings to the broader HF population. Additionally, factors such as neurohormonal activation and myocardial fibrosis, which could influence atrial function, were not evaluated. Lastly, the lack of long-term follow-up precludes determining whether LASr recovery translates into improved clinical outcomes.

CONCLUSION

As a result, this study is the first to investigate the determinants of LA strain recovery in acute decompensated HFrEF. Our findings highlight that LASr improvement during hospitalization is closely linked to baseline LV function, ventricular dimensions, and MR severity, suggesting that it

reflects not only volume status but also underlying cardiac structure. These results provide new insights into LA mechanics in HF and lay the foundation for future research to determine whether LASr recovery can serve as a prognostic marker or guide therapeutic strategies in this population.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was initiated with the approval of the Clinical Researches Ethics Committee of Başakşehir Çam and Sakura City Hospital (Date: 27.04.2022, Decision No: 135).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1667024

Anatolian Curr Med J. 2025;7(3):291-296

Inflammatory biomarkers in Hashimoto's thyroiditis: a comparative cross-sectional study

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Cite this article as: Deniz MS, Coşkun A. Inflammatory biomarkers in Hashimoto's thyroiditis: a comparative cross-sectional study. *Anatolian Curr Med J.* 2025;7(3):291-296.

Received: 28.03.2025 • **Accepted**: 13.04.2025 • **Published**: 30.05.2025

ABSTRACT

Aims: Hashimoto's thyroiditis (HT) is an autoimmune disorder impacting majorly females. HT is asymptomatic long-term and known to be affected by metabolic factors, genetics, and inflammation. The study aimed to compare inflammatory and metabolic markers in HT and assess their value in the diagnosis.

Methods: An HT group (n=103) and a control group with euthyroidism (n=103) were included in the study. The demographics, anthropometric measurements, and circulation-based inflammatory and metabolic markers, triglyceride-glucose index, FIB-4 score, non-alcoholic fatty liver disease score, APRI, ATH score, systemic immune-inflammation index, systemic inflammation response index, prognostic nutritional index, monocyte-to-HDL cholesterol ratio, atherogenic index of plasma, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, PV, PDW, and RDW were recorded.

Results: Consistent with the literature, we found a 10-fold difference in the HT prevalence in females (90.3%) compared with males (9.7%). Anthropometric measurements revealed that increased hip circumference increases the risk of HT (118.0 cm [107.0–132.0]) compared to control (110.0 cm [103.0–119.0]). We failed to find any difference in metabolic or inflammatory indices in the HT vs. control group.

Conclusion: This study reinforces the well-documented association between HT and female predominance and metabolic factors such as obesity and diabetes. However, inflammatory markers did not show a significant association with HT, urging the need for larger cohorts.

Keywords: Hashimoto thyroiditis, inflammatory markers, hip circumference, metabolic markers

INTRODUCTION

Hashimoto's thyroiditis (HT) is an autoimmune condition that arises when the body's immune system fails to tolerate key thyroid-specific proteins—thyroglobulin (TG) and thyroid peroxidase (TPO). This loss of tolerance leads to chronic inflammation and gradual destruction of the thyroid gland.[1-3] HT is one of the most common endocrine disorders, affecting about 7.5% of the global population, with a notably higher prevalence in women.[4] It also increases the risk of certain thyroid cancers, particularly papillary thyroid carcinoma.[1,5]

Both genetic predisposition and environmental exposures—along with metabolic comorbidities such as obesity and diabetes—are believed to contribute to HT development.[2,3,6] The underlying autoimmune activity is often driven by immune cell infiltration and the formation of structures known as tertiary lymphoid organs within the thyroid tissue.

Recently, there has been growing interest in whether certain blood-based inflammatory markers—including the neutrophil-to-lymphocyte ratio (NLR),[7-9] platelet-to-lymphocyte ratio (PLR),[8,10,11] and systemic immune-inflammation index (SII)[9,11]-might help identify disease severity or progression. However, findings remain inconsistent. This study aimed to explore these markers in patients with HT and compare them with healthy, euthyroid individuals to better understand their potential diagnostic value.

METHODS

Ethics

This cross-sectional comparative study was conducted with patients who were diagnosed with HT previously, and a control group consisted of patients referred to the endocrinology clinic with symptoms related to a possible thyroid pathology between October 2021 and August 2023. Necessary ethical compliance and approvals were granted by the Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 06.01.2025, Decision No: 2025/2055). The study was carried out according to the Declaration of Helsinki, and the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines[12] were implemented.

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Written consent was obtained from the patient participating in this study.

Study Population

The inclusion criteria of the HT group were: (a) being 18 years and older, (b) holding a prior HT diagnosis, (c) having a heterogeneous thyroid pattern in USG, and (d) anti-TG and anti-TPO larger than 4.5 U/ml and 60 U/ml. For the control group, adults who were referred to the department with a possible thyroid disease with a biochemical euthyroid, homogenous thyroid in USG, and have anti-TG lower than 4.5 U/ml and anti-TPO lower than 60 U/ml were included. Within the HT study group patients who (a) do not have heterogenous thyroid in USG, who have (b) anti-TG lower than 4.5 U/ml or anti-TPO U/ml lower than 60 U/ml, (c) hepatic, renal and/or heart failure, (d) diabetes mellitus, (e) any active malignancy, (f) history of organ transplantation, (g) pregnancy, (h) chronic inflammatory disease, (i) anemia or polycythemia, (j) acute or chronic infection, (k) lipid-lowering or hepatotoxic medication use, (l) received medications affecting CBC, (m) alcohol and tobacco use, (n) major surgery within the last six months were excluded. For the control group with a possible thyroid disease the patients who (a) are not biochemically euthyroid, (b) do not have homogenous thyroid in USG, who have (c) anti-TG larger than 4.5 U/ml or anti-TPO larger than 60 U/ml, (d) hepatic, renal and/or heart failure, (e) diabetes mellitus, (f) any active malignancy, (g) history of organ transplantation, (h) pregnancy, (i) chronic inflammatory disease, (j) anemia or polycythemia, (k) acute or chronic infection, (l) lipid-lowering or hepatotoxic medication use, (m) received medications affecting CBC, (n) alcohol and tobacco use, (o) major surgery within the last six months were excluded.

Data and Variables

The HT diagnosis of the patients was confirmed according to previous guidelines (Caturegli 2014). In this study, we examined a range of metabolic and inflammatory markers. These included the triglyceride-glucose (TyG) index, non-alcoholic fatty liver disease (NAFLD) score, and prognostic nutritional index (PNI), along with SII, systemic inflammation response index (SIRI), monocyte-to-HDL cholesterol ratio (MHR), atherogenic index of plasma (AIP), and the NLR and PLR ratios. Each of these markers has been proposed in earlier research as a potential indicator of metabolic or immune activity. The age, gender, body-mass index (BMI), anthropometric, and laboratory measurements were recorded.

Weight was measured using a digital scale (Omron, Japan), and height was recorded with a stadiometer. BMI was then calculated.

$$BMI=\text{weight [kg]}/\text{height [m]}^2$$

Waist circumference (WC) was assessed using a measuring tape while subjects stood in a standard position—with feet together, arms at their sides, and an unflexed abdomen—with the measurement taken between the subcostal plane and the iliac crest. Hip circumference (HC) was measured at the point of maximum hip girth, and the waist-to-hip ratio (WHR) was subsequently calculated by dividing WC (cm) by HC (cm).

Laboratory evaluations including triglycerides, free T3 and T4, TSH, TG, anti-TG, anti-TPO, calcitonin, liver enzymes, full hemogram panel, and serum albumin were measured from blood samples. Blood draws were generally performed in the morning, ensuring an 8-hour fasting period. The TyG was calculated using the formula:

$$TyG=Ln(\text{(fasting triglycerides [mg/dl]}\times\text{fasting blood glucose [mg/dl])}/2)$$

The FIB-4 score is calculated to assess liver fibrosis according to

$$\text{FIB-4 score}=(\text{age (years)}\times\text{AST (U/L)})/(\text{Platelet }(10^9/L)\times\sqrt{}\text{ALT (U/L)})$$

NAFLD score assists the severity of liver fibrosis; mild (F1-F2) vs. advanced (F3-F4) and calculated as follows:

$$\text{NAFLD score}=-1.675+0.037\times\text{age (years)}+0.094\times\text{BMI (kg/m}^2)+1.13\times(\text{IFG/DM [yes=1, no=0]})+0.99\times(\text{AST/ALT})-0.013\times\text{platelets }(10^9/L)-0.66\times\text{albumin (g/dl)}$$

The aspartate-to-platelet ratio (ASPI) score measures the likelihood of hepatic fibrosis and cirrhosis according to the formulae below:

$$\text{APRI score}=[(\text{AST/ULN})\times100]/\text{platelet }(10^9/L)$$

The PNI determines the balance between albumin and immunological cell accumulation,

$$PNI=10\times\text{serum albumin (g/dl)}+0.005\times\text{total lymphocyte count (/mm}^3)$$

The inflammatory markers, SII, SIRI, MHR, AIP, PLR and NLR were calculated accordingly:

$$SIRI=(\text{neutrophil}\times\text{monocyte})/\text{lymphocyte}$$

$$MHR=\text{monocyte/HDL}$$

$$AIP=Ln\ [TG/HDL]$$

$$NLR=\text{neutrophil/lymphocyte}$$

$$PLR=\text{platelet/lymphocyte}$$

Statistical Analysis

No prior sample size was calculated because we intended to include all eligible patients in the study. Statistical analyses were performed using SPSS version 23 (IBM Corp. in Armonk, NY). The distributions of numerical variables were evaluated using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Descriptive statistics were presented as frequency (n) and percentage (%) for categorical variables, and median with an interquartile range (IQR) for non-normally distributed numerical variables. Numerical data were analyzed using the Mann-Whitney U test to compare differences between the HT group and the control group. Categorical data were analyzed using the Pearson Chi-square test or Fisher's exact test. $p<0.05$ was accepted as the statistical significance level.

RESULTS

A total of 823 patients were assessed for eligibility, including 249 patients with a prior diagnosis of HT and 574 individuals presenting symptoms of a possible thyroid disease. HT patient; without a heterogenous thyroid in USG (n=8), have

an anti-TG or anti-TGO levels lower than 4.5 U/ml and 60 U/ml (n=14), and have hepatic (n=2), renal (n=5), heart (n=3) failure, diabetes (n=28), any other active malignancy (n=4), history of solid organ transplantation (n=3), are pregnant (n=2), have chronic inflammatory diseases (n=7), have any anemia or polycythemia (n=23), acute or chronic infection (n=6), who are taking lipid-lowering (n=14) or hepatotoxic (n=5) medication or taking any medication affecting their CBC (n=2), using alcohol and tobacco (n=19) and who had major surgery within the past six months (n=1) were excluded from the study (n=146). Within the control group, patients who are not biochemically euthyroid (n=43), do not have homogenous thyroid in USG (n=26), have an anti-TG level larger than 4.5 U/ml or anti-TGO levels larger than 60 U/ml (n=39), who have hepatic (n=3), renal (n=11), heart (n=4) failure, diabetes (n=77), any other active malignancy (n=6), history of solid organ transplantation (n=3), are pregnant (n=7), have chronic inflammatory diseases (n=12), have any anemia or polycythemia (n=32), acute or chronic infection (n=15), who are taking lipid-lowering (n=31) or hepatotoxic (n=11) medication or taking any medication affecting their CBC (n=9), using alcohol and tobacco (n=33) and who had major surgery within the past six months (n=7) were excluded from the study (n=369). Of the eligible patients for the control group (n=205), 103 were randomly selected and allocated to the control group. All eligible patients for the HT group (n=103) were included in the HT group. Totally, the data of 206 patients were analyzed (**Figure**).

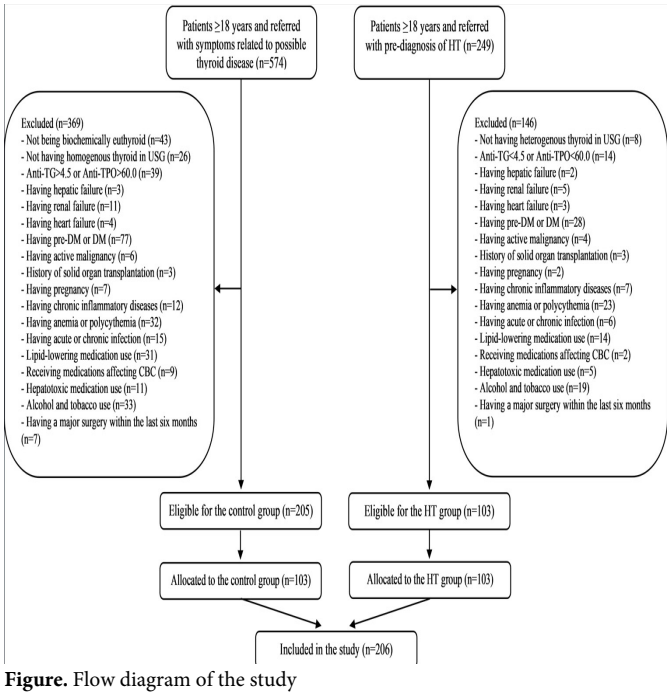

Figure. Flow diagram of the study

Demographic and clinical findings are presented in **Table 1**. Although the groups were comparable in terms of age, BMI, and WC, the HT group had a significantly increased proportion of females (90.3% vs. 76.7%, p=0.009) and a larger HC (median 118.0 cm vs. 110.0 cm, p<0.001). The thyroid function was uniformly distributed within the control group, all presented with euthyroid (n=103, 100%), whereas in the study group, only 57.3% of the HT group were euthyroid, 34% were hypothyroidism, and the rest 8.7% presented with subclinical hypothyroidism (p<0.001). Free T3 and T4 levels were comparable between groups; however, the HT group had significantly higher TSH levels (median 3.45 vs. 1.70 μIU/ml, p<0.001), elevated anti-TG (7.00 vs. 0.10 IU/ml, p<0.001) and anti-TPO levels (782.0 vs. 35.8 IU/ml, p<0.001), along with a significantly lower TG concentration (11.4 vs. 24.3 ng/ml, p<0.001). We also found a moderate positive correlation between anti-TG antibody levels and TG concentration (r=0.548, p<0.001), indicating that patients with measurable TG levels often had correspondingly elevated anti-TG antibodies. No significant differences were observed in terms of family history of thyroid cancer, history of neck radiotherapy, or calcitonin levels (**Table 1**).

Table 2 compares various inflammatory markers between the HT and control groups. No statistically significant differences were observed in any of the parameters, including the TyG index, FIB-4 score, NAFLD score, APRI, ATH score, SII, SIRI, PNI, MHR, AIP, NLR, PLR, MPV, PDW, and RDW (all p>0.05), indicating that the inflammatory profiles are similar between the two groups (**Table 2**).

DISCUSSION

This cross-sectional study compares the inflammatory biomarkers between patients with HT and a non-HT euthyroid control group. We found that despite the differences in thyroid function and autoantibody levels, the two groups did not significantly differ in various inflammatory indices, including hepatic and cardiometabolic markers. The gender difference in HT is well documented.[2,13] Studies have shown that females are more commonly impacted, and the female-to-male ratio is 7-10:1.[2,14] Similar to the literature, our findings show a 10-fold gender difference, with a pronounced female predominance. The disparity is mainly attributed to hormonal differences, specifically the imbalance between estradiol and progesterone in patients with polycystic ovary syndrome,[15] increased concentrations of estradiol, and reduced levels of testosterone in female HT patients.[16] However, studies also show that sex hormones are not the only culprit.[17] Increased BMI, signs of metabolic obesity, and WC correlated with the risk of HT.[18] Another study found that gender introduces differential fat distribution; within the same BMI range, females possess more adiposity, indirectly indicating a more insulin-sensitive environment, predisposing female diabetics to HT.[19] Our findings presented that increased HC (median in men 107.0 cm [IQR:101.2-110.0], and median HC in women 115.0 cm [IQR:106.0-125.0]) was associated with HT risk. Recent studies also have shown that changing diet to a gluten-free, Mediterranean diet[20,21] supplemented with vitamin D[22] improves anthropometric measures and regulates TSH levels. This link between TSH levels and anthropometric measurements is evident in our cohort, where the median HC was 110.5 cm (IQR:104.0-122.3) in euthyroid, 124.0 cm (IQR:116.5-140.0) in subclinical hypothyroid, and 120.0 cm (IQR:107.0-133.0) in hypothyroid HT patients (data not shown).

Our results emphasize the heterogeneous nature of thyroid function among patients with HT. While a substantial proportion of HT patients (57.3%) remained euthyroid,

Table 1. Demographics and laboratory findings of Hashimoto's thyroiditis and the control groups

Variables	Control group (n=103)	HT group (n=103)	p
Age (year), median (IQR)	50.0 (47.0-57.0)	51.0 (43.0-59.0)	0.810[a]
Gender, n (%)			0.009[b]
Male	24 (23.3)	10 (9.7)	
Female	79 (76.7)	93 (90.3)	
Family history of thyroid cancer, n (%)	5 (4.9)	3 (2.9)	0.721[c]
History of neck radiotherapy, n (%)	3 (2.9)	2 (1.9)	0.999[c]
BMI (kg/m²), median (IQR)	29.5 (26.7-33.0)	28.5 (24.5-33.5)	0.304[a]
WC (cm), median IQR)	100.0 (94.0-109.0)	102.0 (90.0-115.0)	0.729[a]
HC (cm), median (IQR)	110.0 (103.0-119.0)	118.0 (107.0-132.0)	<0.001[a]
Thyroid function status, n (%)			<0.001[c]
Hypothyroidism	0 (0.0)	35 (34.0)	
Subclinical hypothyroidism	0 (0.0)	9 (8.7)	
Euthyroidism	103 (100.0)	59 (57.3)	
Free T_3 (pg/ml), median (IQR)	3.33 (3.09-3.58)	3.29 (2.97-3.47)	0.139[a]
Free T_4 (pg/ml), median (IQR)	1.24 (1.10-1.38)	1.21 (1.06-1.34)	0.116[a]
TSH (µIU/ml), median (IQR)	1.70 (0.96-2.65)	3.45 (1.50-4.62)	<0.001[a]
Thyroglobulin (ng/ml), median (IQR)	24.3 (11.6-62.8)	11.4 (1.47-40.2)	<0.001[a]
Anti-TG (IU/ml), median (IQR)	0.10 (0.00-0.50)	7.00 (1.10-73.00)	<0.001[a]
Anti-TPO (IU/ml), median (IQR)	35.8 (28.0-46.2)	782.0 (131.0-1300.0)	<0.001[a]
Calcitonin, n (%)			0.999[c]
Normal	101 (98.1)	102 (99.0)	
High	2 (1.9)	1 (1.0)	

[a]Mann-Whitney U Test was used. [b]Pearson Chi-square Test was used. [c]Fisher's Exact Test was used. HT: Hashimoto's thyroiditis, IQR: Inter-quartile range, BMI: Body-mass index, WC: Waist circumference, HC: Hip circumference, T_3: Triiodothyronine, T_4: Thyroxine, TSH: Thyroid-stimulating hormone, Anti-TG: Anti-thyroglobulin antibody, Anti-TPO: Anti-thyroid peroxidase antibody

Table 2. Comparison of inflammation markers between Hashimoto's thyroiditis and control groups

Parameters	Control group (n=103)	HT group (n=103)	p
TyG index, median (IQR)	4.66 (4.44-4.85)	4.70 (4.47-4.86)	0.526[a]
FIB-4 score, median (IQR)	0.86 (0.65-1.12)	0.85 (0.55-1.13)	0.682[a]
NAFLD score, median (IQR)	-2.27 (-2.91--1.57)	-2.41 (-3.27--1.62)	0.395[a]
APRI, median (IQR)	0.20 (0.15-0.27)	0.21 (0.15-0.26)	0.918[a]
ATH score, median (IQR)	0.39 (0.15-0.57)	0.37 (0.21-0.56)	0.916[a]
SII, median (IQR)	488.7 (358.3-717.5)	581.0 (396.0-822.9)	0.121[a]
SIRI, median (IQR)	0.72 (0.53-1.01)	0.82 (0.57-1.25)	0.116[a]
PNI, median (IQR)	54.5 (52.0-57.0)	55.0 (52.5-58.0)	0.492[a]
MHR, median (IQR)	7.35 (5.75-10.25)	8.37 (5.85-10.73)	0.411[a]
AIP, median (IQR)	0.39 (0.15-0.57)	0.37 (0.21-0.56)	0.916[a]
NLR, median (IQR)	1.89 (1.42-2.47)	1.94 (1.56-2.65)	0.280[a]
PLR, median (IQR)	130.8 (103.5-170.0)	136.0 (108.7-169.3)	0.462[a]
MPV, median (IQR)	10.2 (9.5-10.9)	10.2 (9.7-11.0)	0.350[a]
PDW, median (IQR)	16.1 (15.9-16.3)	16.1 (15.9-16.3)	0.770[a]
RDW, median (IQR)	42.7 (41.0-44.8)	42.9 (40.9-45.2)	0.872[a]

[a]Mann-Whitney U Test was used. TyG: Triglyceride-glucose index, FIB-4 score: Fibrosis-4 score, SIRI: Systemic inflammation response index, PNI: Prognostic nutritional index, MHR: Monocyte-to-high-density lipoprotein cholesterol ratio, AIP: Atherogenic index of plasma, PLR: Platelet-to-lymphocyte ratio, PDW: Platelet distribution width, SII: Systemic immune-inflammation index

over 42% exhibited thyroid dysfunction; 34% had overt hypothyroidism, and 8.7% subclinical hypothyroidism, which reflects the dynamic spectrum of thyroid damage. Euthyroidism in HT may indicate an early or compensatory phase[2] of the disease where the gland is still able to meet hormonal demands despite underlying autoimmunity, whereas progression to overt hypothyroidism suggests a more advanced stage of glandular destruction with potential implications for metabolic and cardiovascular risk.[2,19,23] Euthyroid status was better maintained following surgical interventions such as thyroidectomy, while hormonal treatments were ineffective against the progression of the disease.[24]

The marked elevation of anti-thyroid antibodies, both anti-TG and anti-TPO in the HT group, is consistent with the autoimmune nature of the disease.[25,26] These antibodies not only confirm the diagnosis of HT but may also serve as predictors for the progression of hypothyroidism.[23,27] Although the detection of TPO antibodies in the sera has a predictive value, only 75% of the patients diagnosed with HT suggest circulating autoantibodies are the outcome but not the initiator of the disease.[3,28] The significantly lower TG levels observed in HT patients further support the notion of a destructive process in the thyroid gland, where the loss of functional thyroid tissue corresponds with diminished hormone synthesis.[3,26]

The comparison of inflammatory markers in the circulation, such as the SIRI, SII, NLR, PLR, and others, revealed no significant differences between the HT and control groups. Similarly, Bozdag et al.[9] found that NLR and PLR failed to differentiate neither HT vs control groups nor between euthyroid, hypothyroid, and subclinical hypothyroid patients, whereas hematologic markers like NLR, PLR, and SII were deemed impractical in pediatric HT patients.[11] In contrast, two of the studies provide evidence that NLR[8] and PLR[8,10] were significantly elevated in HT patients, and PLR was able to differentiate euthyroid and hypothyroid patients.[10]

Limitations

The cross-sectional design prevents us from establishing causal relationships between metabolic factors and HT. While we analyzed various inflammatory markers, other potential contributors to immune activation, such as cytokine profiles, were not included. Also, the study did not assess dietary habits, which have been shown to influence thyroid function and inflammation.

CONCLUSION

In conclusion, our study found no significant differences in inflammatory indices between HT patients and euthyroid controls, despite the clear thyroid dysfunction and elevated thyroid autoantibodies, anti-TG, and anti-TPO in the HT group. The gender differences and correlation with anthropometric measures emphasize the complex interplay between metabolic factors and thyroid autoimmunity. Further longitudinal studies incorporating dietary, genetic, and cytokine analyses are needed to elucidate the underlying mechanisms of HT progression and inflammation.

ETHICAL DECLARATIONS

Ethics Committee Approval

Necessary ethical compliance and approvals were granted by the Karabük University Non-interventional Clinical Researches Ethics Committee (Date: 06.01.2025, Decision No: 2025/2055).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1634095

Anatolian Curr Med J. 2025;7(3):297-303

Evaluation of socioeconomic status, nutritional habits and periodontal disease status of patients applying to the department of periodontology

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Cite this article as: Özcan Bulut S, Özel Erçel N. Evaluation of socioeconomic status, nutritional habits and periodontal disease status of patients applying to the department of periodontology. *Anatolian Curr Med J.* 2025;7(3):297-303.

Received: 05.02.2025 ◆ **Accepted**: 18.04.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: To analyze the socioeconomic status, nutritional habits and periodontal disease status of patients who applied to the periodontology clinic for treatment.

Methods: 191 patients (149 female, 42 male) participated in the study. The diagnosis of periodontal disease was made according to the 2017 Periodontal Disease Classification. Using a survey, data on eating habits (using the Wilhom Index (WI) survey), Body-mass index (BMI), socioeconomic levels and education level were obtained. All data were analyzed.

Results: It was observed that 61.3% of the patients were not university graduates, 27.7% had low income, 53% had unhealthy BMI, nutritional habits were at a moderate level. The prevalence of periodontal disease was 42.4% for gingivitis and 48.7% for periodontitis. According to periodontal disease diagnoses, a significant difference was observed in socioeconomic status, education level, WI score and BMI.

Conclusion: In order to reduce the prevalence of periodontal disease and improve public health, comprehensive health policies and educational programs should be developed regarding socioeconomic status, education level, awareness of healthy nutrition and oral health.

Keywords: Education, nutrition surveys, nutritional status, periodontal diseases, socioeconomic factors

INTRODUCTION

Periodontal diseases are among the most important public health problems in many countries around the world.[1] The most significant of these diseases are gingivitis and periodontitis. Gingivitis occurs when microbial dental plaque accumulates at the gingival margin and is known to be reversible.[2,3] Periodontitis is an inflammatory disease of periodontal tissues characterized by periodontal pocket formation and gingival recession caused by specific microorganisms and loss of periodontal ligament and alveolar bone.[2,3] If oral hygiene is maintained during the gingivitis phase and/or with appropriate periodontal treatment by a dentist, it is possible to achieve periodontal health.[2-6]

Although microbial dental plaque is accepted as the primary factor in the etiology of periodontal disease, it has been observed that oral health status can vary depending on individuals' habits, systemic diseases, and socioeconomic and demographic factors, particularly in epidemiological studies conducted on this subject.[2,5-7]

In developed Western countries such as Finland, Norway, and Germany, it has been shown that the prevalence of caries in children and young individuals decreased rapidly in the 1970s and 1980s.[1] This decrease has been attributed to various factors, including fluoride-containing toothpastes, reduced sugar consumption, higher socioeconomic status, widespread use of dental services, and increased awareness of personal hygiene practices.[1] However, in developing countries such as Turkiye, where preventive dentistry practices have not yet become widespread, oral and dental health problems present serious economic and social challenges.[1] For this reason, in dentistry, the perspective that protective and preventive measures should be implemented before oral and dental health deteriorates, and that treatment services should focus on conservative methods aimed at preserving teeth, has gained importance.[1,6] Nutritional problems can lead to deficiencies in vitamins, minerals, and proteins, glucose resistance, diabetes, obesity, growth and development issues, mental retardation, dental and periodontal diseases, and even cancer.[8-10] Proteins, glucose, and fats must be consumed in a balanced manner. In addition to serving as an energy source, they are essential for the formation of tissues as building blocks of cells, as well as for growth and development.[1,8,10] When consumed in excess,

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they can lead to obesity, diabetes, cardiovascular problems, inflammatory diseases (such as periodontal disease), and more.[1,8,10] When deficient, growth and development can be impaired. Nutritional deficiencies have been shown to increase a risk for periodontal diseases.[7,8,11]

There are studies showing that socioeconomic status and nutritional habits are associated with periodontal disease, as well as epidemiological studies conducted in this context in developed countries. However, these studies have been conducted in only a few provinces in Turkiye.[1,12,13] Furthermore, epidemiological studies need to be updated at regular intervals; unfortunately, these limited studies have not been updated. There are no epidemiological studies in the literature evaluating the nutritional habits, periodontal status, and socioeconomic status of the Niğde population. In order to fill this gap in the literature, the socioeconomic status, nutritional habits and periodontal disease status of patients who applied to Niğde Ömer Halisdemir University, Faculty of Dentistry, Periodontology Clinic for treatment were analyzed in our study.

METHODS

Ethics

The study was conducted in the Department of Periodontics, Faculty of Dentistry, Niğde Ömer Halisdemir University, in 2024, in accordance with the Helsinki Declaration of 1975, as revised in 2000. Ethical approval for the study protocol was obtained from the Non-interventional Researches Ethics Committee of Niğde Ömer Halisdemir University (Date: 25.07.2024, Decision No: 2024/78).

Study Design and Patient Selection

In our prospectively planned study, patients who applied to the Niğde Ömer Halisdemir University, Faculty of Dentistry Departments of Periodontology for treatment and were examined by a single physician (SOB) between 5 August 2024 and 5 November 2024 were included.

The patients were diagnosed with periodontal disease according to the 2017 Periodontal Disease Classification. In addition, the patients were asked to complete a questionnaire regarding their nutritional habits and socioeconomic status. Written consent was obtained from the patients who volunteered to participate in the study.

The periodontal disease diagnosis, nutritional habits, body-mass index (BMI), education levels and socioeconomic status of the patients were analyzed.

Inclusion criteria

-Patients who volunteered to participate in the study between the ages of 18 and 65 were included in the study.

Exclusion criteria

-Patients under 18 years old or over 65 years old

-Patients with a systemic disease (diabetes, hypertension, etc.),

-Pregnant and breastfeeding patients,

-Patients who have received periodontal treatment in the last 6 months

-Patients with incomplete data and/or who did not want to volunteer for the study were not included in the study.

Data Collection

Demographic data including age, gender, socioeconomic status, and nutritional habits, were obtained from the questionnaire administered to the patients who volunteered for the study. The questionnaire included the following information:

a.Demographic data

This section includes questions about age, gender, weight, height, sociocultural (the education level of the individual and their family) and socioeconomic status (total family income).

a.1. Socioeconomic status

Family income was grouped as follows:

1- Less than the minimum wage (17.000TL for 2024)

2- Between 17.000TL and 34.000TL

3- More than 34.000 TL

a.2. Education level of the individual and their family

Education level was scored as follows;

1-Primary school

2-Middle school

3-High school

4-University

b. Eating habits data

The Wilhom Index (WI) survey was used. It includes questions about which foods they consume and how often. The answers given to the questions in the WI survey are scored and the total score is evaluated. Those with a WI score between 65-75 are classified as (category 1) "aware of what they eat and how to eat" (category 2), 40-64 points as "careful in this regard" and less than 40 points as "poor nutrition"(category 3).[14]

c. Body-mass index

BMI is calculated by dividing body weight by the square of height (BMI = kg/m^2). The value obtained as a result of the calculation can give a clue as to whether you are at a healthy weight. Below 18.5 is classified as underweight, between 18.5-24.9 is normal, between 25-29.9 is overweight, 30-34.9 is 1st degree obese, 35-39.9 is 2nd degree obese, and 40 and above is 3rd degree obese.[15]

d. Clinical-radiology examination and periodontal disease diagnosis data

All 191 patients received a detailed periodontal evaluation, and the following parameters were recorded: Gingival index, plaque index, periodontal pocket depths (PD), the level of interdental clinical attachment loss (CAL), and bleeding on probing (BOP). Clinical evaluations were performed using the Williams periodontal probe, and the reference values of Silness and Löe[16] were used for the plaque index and gingival index.

Periodontitis stages were determined based on the percentage of interdental bone loss on panoramic radiographs, clinical periodontal parameters, and the number of tooth losses.[2,4,16,18] Periodontal disease diagnosis was made according to the 2017 classification of periodontal and peri-implant diseases.[2,4] The diagnoses were scored as follows:

Score 0: BOP <10% and PD <4 mm (periodontally healthy)

Score 1: BOP >10% and PD <4 mm (gingivitis)

Score 2: 0-15% interdental bone loss and CAL=1-2 mm (stage 1 periodontitis)

Score 3: 15-33% interdental bone loss and CAL=3-4 mm (stage 2 periodontitis)

Score 4: More than 33% interdental bone loss, tooth loss (<5) and CAL >5 mm (stage 3 periodontitis)

Score 5: More than 33% interdental bone loss, dentition loss (more than 5 teeth lost) and CAL >5 mm (stage 4 periodontitis)

Statistical Analysis

According to the power analysis conducted prior to the study, the required sample size was at least 53 individuals per group, totaling 159 individuals. This was calculated with 80% power, a 5% type I error rate, and a small effect size (d=0.25) among socioeconomic status groups using G*power 3.1.9.7.

Data analysis was performed with IBM SPSS Statistics Version 26 package program. The conformity of the data to normal distribution was tested with the Kolmogorov-Smirnov normality test. Descriptive statistics are given in terms of frequency, percentage, median, mean and standard deviation. Chi-square test was used to examine the distribution of socio-demographic characteristics according to the WI and periodontal diagnosis classification. Mann-Whitney U and Kruskal-Wallis tests were used to compare the WI score medians according to socio-demographic and periodontal diagnosis. Spearman correlation test was used to determine the relationship between age, BMI and WI score. All results obtained were considered statistically significant at p<0.05.

RESULTS

A total of 191 patients, including 42 males (mean age 35.6) and 149 females (mean age 30.43), were included in the study. Males had higher WI scores than females, but there was no statistically significant difference in WI score averages according to gender (p=0.852). Those with a family income in category 3 had higher WI scores, but there was no statistically significant difference in WI score averages based on income (p=0.202). Patients with an education level of 4 had higher WI scores, but there was no statistically significant difference in WI score averages according to education level (p=0.479). Patients with a father's education level of 3 had higher WI scores, but there was no statistically significant difference in WI score averages according to father's education level (p=0.890). Patients with a mother's education level of 3 had higher WI scores, but there was no statistically significant difference in WI score averages according to mother's education level (p=0.562) (**Table 1**).

Table 1. Comparison of Wilhom index scores according to demographic and socioeconomic characteristics

	n (%)	*Median* (Q_1-Q_3)	$\bar{X}$±SD	p
Gender				
Female	149 (78)	53 (47-58)	51.97±8.44	0.852
Male	42 (22)	53 (46-58)	52.21±8.37	
Family income status				
1- Low	53 (27.7)	51 (46-56)	51.06±7.47	
2- Medium	74 (38.7)	53 (47-58)	51.50±9.05	0.202
3- High	64 (33.5)	53 (49-59)	53.42±8.30	
Education level				
1- Primary school	12 (6.3)	53 (48-61)	52.58±10.86	
2- Middle school	16 (8.4)	54 (46-57)	52.44±7.74	0.479
3- High school	89 (46.6)	52 (46-58)	50.93±8.65	
4- University	74 (38.7)	53 (50-58)	53.15±7.79	
Father's education level				
1-Primary school	90 (47.1)	53 (45-58)	51.66±8.75	
2-Middle school	46 (24.1)	53 (47-58)	51.85±7.70	0.890
3-High school	33 (17.3)	52 (50-57)	53±8.16	
4-University	22 (11.5)	54 (50-58)	52.41±9.14	
Mother's education level				
1-Primary school	87 (45.5)	53 (46-58)	52.39±8.57	
2-Middle school	43 (22.5)	52 (46-59)	51.79±7.50	0.562
3-High school	37 (19.4)	53 (50-58)	53.05±8.04	
4-University	24 (12.6)	52 (47-56)	49.50±9.78	

Mann Whitney U, Kruskal Wallis test, SD: Standard deviation

The WI score of patients with a periodontal diagnosis classification score of 0 was higher, and a statistically significant difference was found in WI scores according to periodontal diagnosis (p<0.001). This difference was due to the significantly higher nutritional scores of patients with a diagnosis of score 0 and score 3 (p<0.05) (**Table 2**).

Table 2. Comparison of Wilhom index scores according to periodontal diagnosis

Periodontal diagnosis	n (%)	Median (Q_1-Q_3)	$\bar{X}$±SD	p
Score 0 (healthy)	17 (8.9)	59 (54-62)	58.47±4.61[1,2,4,5]	<0.001
Score 1(gingivitis)	81 (42.4)	52 (47-57)	51.81±7.85	
Score 2 (stage 1 periodontitis)	52 (27.2)	50 (44-55)	49.10±8.91	
Score 3 (stage 2 periodontitis)	23 (12)	57 (53-63)	56.96±7.03[1,2,4,5]	
Score 4 (stage 3 periodontitis)	11 (5.8)	53 (46-56)	50.09±6.80	
Score 5 (stage 4 periodontitis)	7 (3.7)	52 (41-55)	47.29±10.26	

Kruskal Wallis test, SD: Standard deviation

While there was no statistically significant correlation between the WI score and BMI, a positive and significant correlation was found between the WI score and age (r=0.218, p=0.002) (**Table 3**).

Table 3. Correlation between age, BMI and Wilhom index score

	Age		BMI	
	r	p	r	p
Wilhom index score	0.218	0.002	0.104	0.154

BMI: Body-mass index, r: Spearman correlation coefficient

There was a statistically significant relationship between periodontal diagnosis and gender (p<0.001). The proportion of women with a periodontal diagnosis of 0 was significantly higher than women with a periodontal diagnosis of 2, 3 and 4+, and women with a periodontal diagnosis of 1, 2, 3 were significantly higher than women with a diagnosis of 4 (p<0.05). The proportion of men with a periodontal diagnosis of 0 was significantly lower than men with a periodontal diagnosis of 2, 3 and 4+, and men with a periodontal diagnosis of 1, 2, 3 were significantly lower than men with a diagnosis of 4 (p<0.05). There was a statistically significant relationship between periodontal diagnosis and BMI (p<0.001). BMI 2 rates were significantly higher in patient with a periodontal diagnosis of 0 and 1, while BMI 4 rates were significantly lower in those with a periodontal diagnosis of 0, 1 and 2 (p<0.05) (**Table 4**).

There was a statistically significant relationship in terms of family average income distribution according to periodontal diagnosis (p=0.026). It was observed that the proportion of patients with income level 2 was significantly higher in patients with periodontal diagnosis 0, while the distribution of patients with income level 3 was significantly lower in patients with periodontal diagnosis 0 and 1 (p<0.05) (**Table 4**).

There was a statistically significant relationship in terms of education levels according to periodontal diagnosis (p<0.001). The distribution of patients with education level 1 was significantly lower in patient with periodontal diagnoses 0, 1 and 2, and the distribution of patient with education level 3 was significantly higher in those with periodontal diagnoses 0 and 1 (p<0.05) (**Table 4**).

According to periodontal diagnosis, there was no statistically significant difference in terms of distribution of mother education, father education and WI category (p>0.05) (**Table 4**).

There was no statistically significant relationship in terms of gender, BMI, income level, education level, mother education distribution according to WI category (p>0.05). According to WI category, there was a significant difference in terms of father education level (p=0.036). It was observed that the rate of those with father education level 2 was significantly lower in patient with WI category 1, and the rate of patient with father education level 3 was significantly higher in patient with WI category 1 (p<0.05) (**Table 5**).

DISCUSSION

Although dental plaque is the main factor in the etiology of periodontal disease, epidemiological studies on the subject show that oral health levels can vary according to individuals' habits, systemic diseases, and socioeconomic and demographic factors.[1,3,5,7,8,17]Many factors influence the development of periodontal disease.[1-5,7,8,17] Socioeconomic status, education level, nutritional habits and general health awareness are among these factors.[6,8,11,17,18] Studies on socioeconomics and oral health in Turkiye have been limited to only a few provinces and, unfortunately, have not been updated.[1,13,18] In our study, in addition to socioeconomic data, the current 2017 periodontal disease classification was used in the Niğde population, which has not had a study sample on this subject in Turkiye before, and the nutritional status of the patients was investigated using the WI survey. It was observed that 61.3% of the study population was not university graduates, 27.7% earned less than the minimum wage, 53% had an unhealthy BMI, nutritional habits were at a moderate level, and 42.4% had gingivitis while 48.7% had periodontitis in terms of periodontal status. Our study yielded results that support the literature, and while no difference was found in the WI category in periodontal disease cases, it was observed that the WI score was higher in periodontally healthy individuals. A statistically significant difference was found in education level, socioeconomic status, and BMI in periodontal disease cases. In a study conducted in Konya in 2021, it was reported that 87.84% of the study population had a low income level, 80.49% were not university graduates, and 50.40% had periodontitis.[18] Küçükeşmen et al.[13], in their 2014 study conducted on children and adolescents, observed that the number of individuals with periodontal disease was higher than the number of healthy individuals at all socioeconomic levels, and they suggested that this could be explained by their consumption of carbohydrate-rich foods and poor oral hygiene habits.

Studies have found that socioeconomic factors, as well as low education levels and low social class, are significantly associated with a higher prevalence of periodontal disease in the adult population. Socioeconomic status is an important determinant that directly affects individuals' access to health services and health-related behaviors, and low-income individuals may have limited access to health services, which can lead to the progression of periodontal diseases without treatment.[17,19-21] In addition, individuals with low socioeconomic status generally have less health knowledge and may have incomplete information about dental health. Low education levels lead to a lack of awareness about oral hygiene and the treatment of periodontal diseases.[20,21] Additionally, individuals with higher income and education are generally more conscious about protecting their dental health and visit the dentist more regularly.[20-22] These individuals are able to adopt healthier eating habits, whereas low-income individuals tend to consume more processed foods and foods high in sugar, which leads to an increase in periodontal diseases.[23-25] Because sugary foods and processed foods encourage the proliferation of bacteria in the mouth, which can lead to plaque formation, and pathogenic plaque is the primary etiological factor of periodontal diseases.[26,27] Nutrition is a factor that directly affects the development of periodontal diseases.[8,11,25] Inadequate nutrition and unbalanced diets can lead to weakening of gingival defenses, increased inflammation and more serious periodontal problems.[8,11,25] For example, vitamin C is an antioxidant that protects periodontal health and reduces inflammation. Vitamin C deficiency can cause inflammation, bleeding and swelling of the gingiva.[28,29] In our study, no significant relationship was found between family

Table 4. Distribution of demographic. socioeconomic characteristics, BMI and Wilhom index category according to periodontal diagnosis

	Periodontal diagnoses						
Gender, n (%)	**Score 0 (periodontal health)**	**Score 1 (gingivitis)**	**Score 2 (stage 1 periodontitis**	**Score 3 (stage 2 periodontitis)**	**Score 4-5 (stage 3-4 periodontitis)**	**Total**	**p**
Female	17 (100)[2.3.4]	69 (85.2)	40 (76.9)	16 (69.6)	7 (38.9)[1.2.3]	149 (78)	<0.001
Male	0 (0)[2.3.4]	12 (14.8)	12 (23.1)	7 (30.4)	11 (61.1)[1.2.3]	42 (22)	
BMI category, n (%)							
1-Underweight	5 (29.4)	12 (14.8)	8 (15.4)	0 (0)	0 (0)	25 (13.1)	<0.001
2-Normal	10 (58.8)[4]	49 (60.5)[3.4]	24 (46.2)	6 (26.1)	2 (11.1)	91 (47.6)	
3-Overweight	2 (11.8)	18 (22.2)	19 (36.5)	12 (52.2)	8 (44.4)	59 (30.9)	
4-Obese	0 (0)[4]	2 (2.5)[3.4]	1 (1.9)[3.4]	5 (21.7)	8 (44.4)	16 (8.4)	
Family income status, n (%)							
1-Low	5 (29.4)	28 (34.6)	11 (21.2)	6 (26.1)	3 (16.7)	53 (27.7)	0.026
2-Medium	10 (58.8)[3]	34 (42)	19 (36.5)	5 (21.7)	6 (33.3)	74 (38.7)	
3-High	2 (11.8)[2.3.4]	19 (23.5)[2.3.4]	22 (42.3)	12 (52.2)	9 (50)	64 (33.5)	
Education level, n (%)							
1- Primary school	0 (0)[3.4]	0 (0)[3.4]	0 (0)[3.4]	5 (21.7)	7 (38.9)	12 (6.3)	<0.001
2- Middle school	0 (0)	4 (4.9)[3]	5 (9.6)	4 (17.4)	3 (16.7)	16 (8.4)	
3- High school	10 (58.8)[3.4]	45 (55.6)[3.4]	24 (46.2)	6 (26.1)	4 (22.2)	89 (46.6)	
4- University	7 (41.2)	32 (39.5)	23 (44.2)	8 (34.8)	4 (22.2)	74 (38.7)	
Father's education level, n (%)							
1-Primary school	6 (35.3)	32 (39.5)	26 (50)	13 (56.5)	13 (72.2)	90 (47.1)	0.061
2-Middle school	4 (23.5)	24 (29.6)	11 (21.2)	4 (17.4)	3 (16.7)	46 (24.1)	
3-High school	3 (17.6)	20 (24.7)	8 (15.4)	1 (4.3)	1 (5.6)	33 (17.3)	
4-University	4 (23.5)	5 (6.2)	7 (13.5)	5 (21.7)	1 (5.6)	22 (11.5)	
Mother's education level, n (%)							
1-Primary school	6 (35.3)	29 (35.8)	23 (44.2)	15 (65.2)	14 (77.8)	87 (45.5)	0.124
2-Middle school	4 (23.5)	21 (25.9)	14 (26.9)	3 (13)	1 (5.6)	43 (22.5)	
3-High school	3 (17.6)	19 (23.5)	10 (19.2)	3 (13)	2 (11.1)	37 (19.4)	
4-University	4 (23.5)	12 (14.8)	5 (9.6)	2 (8.7)	1 (5.6)	24 (12.6)	
Wilhom index category, n (%)							
1	1 (5.9)	3 (3.7)	3 (5.8)	5 (21.7)	1 (5.6)	13 (6.8)	0.124
2	16 (94.1)	72 (88.9)	42 (80.8)	16 (69.6)	14 (77.8)	160 (83.8)	
3	0 (0)	6 (7.4)	7 (13.5)	2 (8.7)	3 (16.7)	18 (9.4)	

Ki kare test, BMI: Body-mass index

income status and WI score and category, but supporting the literature, it was observed that WI survey score was higher in healthy periodontal status. Although this result can be considered as an increase in the accessibility of healthy food and increased awareness of nutrition regardless of the education level and socioeconomic level of individuals today, it should be kept in mind that WI survey has limitations in measuring nutrition and its objectivity and use alone. Another measure of healthy nutrition is BMI.[15] In the study conducted by Başçıl et al.[12] with the participation of 357 patients, nutrition, BMI, and periodontal status were evaluated, and the rate of periodontitis cases in obese patients was reported as 71.4%. Similarly, in our current study, it was determined that periodontal disease increased (increased in the stage of periodontitis) as the BMI category shifted from health to obesity. In our study, it was observed that there was no correlation between WI and BMI.

It has been seen in the literature that the level of education has a great effect on the health knowledge and health-related behaviors of individuals. In our study, patients who applied to the department of periodontology and who had not had any periodontal procedures in the last 6 months were included. This population generally had low to medium education levels and socioeconomic status. In our study, a significant difference in family income and education level was observed between the periodontal disease groups. As income and education levels decreased, the prevalence of periodontal disease increased. A strong relationship was determined between periodontal disease, socioeconomic status, education level, and nutritional habits. Low income and low education levels can lead to unhealthy eating habits. An unhealthy diet and high BMI can contribute to the development of periodontal diseases. Additionally, when the literature is examined, parents' education level, socioeconomic status, and their own

Table 5. Distribution of socioeconomic and demographic characteristics according to Wihom index category

	Wilhom index category				
Gender, n (%)	**1**	**2**	**3**	**Total**	**p**
Female	8 (61.5)	127 (79.4)	14 (77.8)	149 (78)	0.373
Male	5 (38.5)	33 (20.6)	4 (22.2)	42 (22)	
BMI category, n (%)					
1-Underweight	2 (15.4)	20 (12.5)	3 (16.7)	25 (13.1)	0.191
2-Normal	3 (23.1)	78 (48.8)	10 (55.6)	91 (47.6)	
3-Overweight	6 (46.2)	51 (31.9)	2 (11.1)	59 (30.9)	
4-Obese 1-3	2 (15.4)	11 (6.9)	3 (16.7)	16 (8.4)	
Family income status, n (%)					
1-Low	3 (23.1)	48 (30)	2 (11.1)	53 (27.7)	0.213
2-Medium	4 (30.8)	59 (36.9)	11 (61.1)	74 (38.7)	
3-High	6 (46.2)	53 (33.1)	5 (27.8)	64 (33.5)	
Education level, n (%)					
1- Primary school	3 (23.1)	7 (4.4)	2 (11.1)	12 (6.3)	0.067
2- Middle school	0 (0)	14 (8.8)	2 (11.1)	16 (8.4)	
3- High school	3 (23.1)	76 (47.5)	10 (55.6)	89 (46.6)	
4- University	7 (53.8)	63 (39.4)	4 (22.2)	74 (38.7)	
Father's education level, n (%)					
1-Primary school	7 (53.8)	71 (44.4)	12 (66.7)	90 (47.1)	0.036
2-Middle school	0 (0)[2]	44 (27.5)	2 (11.1)	46 (24.1)	
3-High school	5 (38.5)[2]	26 (16.3)	2 (11.1)	33 (17.3)	
4-University	1 (7.7)	19 (11.9)	2 (11.1)	22 (11.5)	
Mother's education level, n (%)					
1-Primary school	9 (69.2)	68 (42.5)	10 (55.6)	87 (45.5)	0.123
2-Middle school	0 (0)	40 (25)	3 (16.7)	43 (22.5)	
3-High school	3 (23.1)	32 (20)	2 (11.1)	37 (19.4)	
4-University	1 (7.7)	20 (12.5)	3 (16.7)	24 (12.6)	

Ki kare test, BMI: Body-mass index

nutritional habits influence their children's nutritional and oral health habits.[30] By raising awareness about healthy eating habits and improving both the education and income levels of individuals, the prevalence of periodontal diseases can be reduced.

Limitations

Our study has some limitations. The patients' socioeconomic data, education level, systemic disease status, and WI questionnaire are based on patient statements. In our study, the number of male and female participants is unequal, and the total family income was used as the basis for evaluating socioeconomic status. The number of individuals in a family can affect per capita income and outcomes. In future studies, other indices can be used in addition to the WI questionnaire to assess patients' nutrition. Blood parameters could provide more objective data.

CONCLUSION

Sociodemographic factors, such as socioeconomic status, education level, and eating habits, have an important effect on the development of periodontal diseases. Low socioeconomic status and education levels generally pave the way for unhealthy eating habits, inadequate oral hygiene, and periodontal disease. As a result, it is clear that comprehensive health policies and educational programs should be developed regarding these factors to improve public health.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for the study protocol was obtained from the Non-interventional Researches Ethics Committee of Niğde Ömer Halisdemir University (Date: 25.07.2024, Decision No: 2024/78).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

DOI: 10.38053/acmj.1649819

ANATOLIAN CURRENT MEDICAL

Anatolian Curr Med J. 2025;7(3):304-310

The relationship between advanced maternal age and adverse pregnancy outcomes

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Cite this article as: Temur İ. The relationship between advanced maternal age and adverse pregnancy outcomes. *Anatolian Curr Med J.* 2025;7(3):304-310.

Received: 02.03.2025 ◆ **Accepted**: 22.04.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: This study aimed to evaluate the impact of advanced maternal age on pregnancy and neonatal outcomes.

Methods: In this retrospective study, singleton pregnancies delivered at a tertiary care center between January 2021 and December 2023 were assessed. Participants were divided into two groups based on maternal age at delivery: 18–35 years and >35 years. Maternal and perinatal outcomes were compared between the groups using Chi-square tests.

Results: The mean maternal age was 32.12±5.37 years (range: 19–45 years). For women aged ≥35 years, the mean age was 38.27±2.66 years, while for those under 35 years, it was 25.98±4.28 years. No statistically significant differences were observed between the groups in terms of gestational diabetes mellitus, placental abruption, placenta previa, macrosomia, 5th-minute Apgar score, stillbirth, or the need for neonatal intensive care (p>0.05). However, pregnancy-induced hypertensive disorders, preterm birth, and postpartum hemorrhage (PPH) were significantly more common in women over 35 years (p=0.033, p=0.039, and p=0.043, respectively). Maternal age was identified as a significant positive predictor for preterm birth, PPH, and hypertensive disorders of pregnancy, with preterm birth being the most strongly associated. Receiver operating characteristic (ROC) analysis revealed optimal maternal age cutoff values for predicting adverse outcomes as follows: >37 years for preterm birth (AUC=0.687; p<0.001) and >33 years for pregnancy-induced hypertensive disorders (AUC=0.633; p=0.006).

Conclusion: The risk of pregnancy-induced hypertensive disorders, preterm birth, and PPH increases with maternal age. These findings underscore the need for enhanced antenatal monitoring in women of advanced maternal age.

Keywords: Advanced maternal age, preterm birth, postpartum hemorrhage, pregnancy-induced hypertensive disorders

INTRODUCTION

Advanced maternal age (AMA) is commonly defined as childbirth in women over the age of 35.[1] The global prevalence of AMA has been steadily increasing.[2] Several factors contribute to this trend, including shifts in social and economic conditions, higher levels of educational attainment, and advancements in reproductive healthcare that have improved access to fertility services.[3,4] Moreover, the widespread use of assisted reproductive technologies has enabled women to conceive well into their forties.[5]

Numerous studies have examined the association between maternal age and pregnancy outcomes, although findings remain inconsistent.[6] Some research has identified AMA as a significant risk factor for adverse perinatal outcomes such as gestational diabetes, preeclampsia, placenta previa, cesarean delivery, preterm birth, low birth weight, maternal mortality, and perinatal death.[3,7] Conversely, other studies have failed to demonstrate a strong association between AMA and these complications.[2,4,8]

The potential impact of maternal age on pregnancy outcomes remains a subject of ongoing debate. This study aims to clarify the hypothesis that AMA is associated with an increased risk of obstetric and neonatal complications.[9] Specifically, we sought to evaluate the influence of AMA on various pregnancy outcomes, including mode of delivery, preterm birth, pregnancy-induced hypertensive disorders, gestational diabetes mellitus (GDM), placenta previa, placental abruption, postpartum hemorrhage (PPH), macrosomia, 5th-minute Apgar score, stillbirth, and the need for neonatal intensive care.

METHODS

Ethics

This study was approved by the Non-interventional Ethics Committee of Niğde Ömer Halisdemir University Faculty of Medicine (Date: 19.09.2024, Decision No: 2024/83). The study was conducted in accordance with the principles of the latest version of the Declaration of Helsinki.

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Study Design and Participants
This retrospective study included women who delivered at the Obstetrics and Gynecology Clinic of Niğde Ömer Halisdemir University Hospital between January 2021 and December 2023. During the study period, approximately 9.000 deliveries were recorded. Based on maternal age at delivery, 200 women were categorized into two groups: those aged 18–35 years and those aged 35–45 years (100 participants per group).

Sample Size Determination
The effect size in this study was calculated as 0.477, which is considered a medium effect according to Cohen's classification (small=0.2, medium=0.5, large=0.8). Based on this effect size, a power analysis assuming 100 participants per group yielded a statistical power of 95%, indicating strong reliability. A power of 95% reflects a high probability of detecting a true effect, minimizing the risk of a type II error (β=0.05). This high power is a major strength in terms of the study's validity, as it reduces the likelihood of failing to detect real associations due to insufficient sample size.[10,11]

Study Variables
Perinatal outcomes were evaluated in relation to the following parameters: mode of delivery, preterm birth, pregnancy-induced hypertensive disorders, GDM, placenta previa, placental abruption, PPH, macrosomia, 5th-minute Apgar score, stillbirth, and the need for neonatal intensive care unit (NICU) admission.

Stillbirth was defined as fetal death at ≥22 weeks of gestation or with a birth weight of ≥500 grams in cases where gestational age was unknown. This definition also included intrapartum deaths. Preterm birth was defined as delivery occurring before 37 completed weeks of gestation, whether spontaneous or medically indicated. Hypertensive disorders were clinically diagnosed by gynecologists based on standard guidelines. This group included patients with chronic hypertension, gestational hypertension, preeclampsia, HELLP syndrome, or combinations thereof. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg.

- Preeclampsia was defined as new-onset hypertension after 20 weeks of gestation accompanied by proteinuria (≥0.3 g protein in a 24-hour urine sample or ≥30 mg/dl on a random urine test).
- Gestational hypertension was defined similarly but without proteinuria.
- Eclampsia was defined as preeclampsia accompanied by seizures.
- Chronic hypertension was diagnosed when hypertension was present before 20 weeks of gestation.[12]

GDM was diagnosed based on results from a 75-g oral glucose tolerance test (OGTT) performed during pregnancy. Diagnostic thresholds included fasting glucose >90 mg/dl, ≥180 mg/dl at 1 hour, and ≥155 mg/dl at 2 hours.[13] Both insulin-dependent and non-insulin-dependent patients were included in the GDM group. The diagnosis of placenta previa (complete or marginal) was confirmed via ultrasound between 32 and 35 weeks of gestation. Both vaginal and cesarean deliveries (elective and emergency) were analyzed.

Exclusion Criteria
Multiple pregnancies and pregnancies with fetal anomalies were excluded from the study.

Data Collection
Data including demographic characteristics, medical and obstetric history, pregnancy progression, and perinatal outcomes were obtained from the hospital's electronic obstetric database.

Statistical Analysis
The data obtained from the study were evaluated with SPSS 22.0 package program. The compatibility of the variables with normal distribution was analyzed by Kolmogorov-Smirnov/Shapiro-Wilk tests and homogeneity of variances was analyzed by Levene's test. Descriptive statistical methods (number, percentage, mean and SD) were used for the individual characteristics of the participants. Receiver operating characteristic (ROC) curve analysis and hierarchical binomial logistic regression analysis were used. Pearson Chi-square test and regression analysis were used in the analyses and $p<0.05$ was considered significant.

RESULTS
The mean age of the pregnant women was 32.12±5.37 years (range: 19–45). For women aged 35 years and older, the mean age was 38.27±2.66 years (range: 35–45), while for women aged 35 years and younger, it was 25.98±4.28 years (range: 19–34). It was found that 36.5% of the pregnant women had a gravidity of four or more, and 28.5% had a parity of one. Additionally, 71% of the pregnant women gave birth between 38 and 42 weeks, including 65% of those aged 35 years and older and 77% of those younger than 35 years.

Among pregnant women under 35 years of age, 12% had GDM, 10% had pregnancy-induced hypertensive disorders, 8% had placental abruption and placenta previa, and 13% had macrosomia. In contrast, among pregnant women aged 35 years and older, 18% had GDM, 16% had pregnancy-induced hypertensive disorders, 11% had placental abruption, 9% had macrosomia, and 5% had placenta previa. When the occurrence of pregnancy-related risky conditions was evaluated according to age, it was found that only pregnancy-induced hypertensive disorders increased with age, and this difference was statistically significant (p=0.033) (**Table 1**).

While 57% of pregnant women under 35 years of age delivered vaginally, 23% experienced preterm birth, and 8% had PPH, 46% of pregnant women aged 35 years and older delivered vaginally, 35% experienced preterm delivery, and 17% had PPH. In the analysis of neonatal outcomes, the 5th minute APGAR score was 14%, stillbirth rate was 2%, and the need for neonatal intensive care was 15% among women under 35 years of age, compared to a 5th minute APGAR score of 19%, stillbirth rate of 2%, and neonatal intensive care need of 21% among women aged 35 years and older. When the postpartum period was evaluated according to the age variable, preterm

Table 1. Pregnancy outcomes of pregnant women according to age

Features	Pregnant women under 35 years of age, n (%)	Pregnant women aged 35 years and older, n (%)	Total, n (%)	p-value
Gestational diabetes mellitus	12 (12.0%)	18 (18.0%)	30 (15.5%)	p=0.322
Pregnancy-induced hypertensive disorders	10 (10.0%)	22 (22.0%)	32 (16.0%)	p=0.033
Abruption of placenta	8 (8.0%)	11 (11.0%)	19 (9.5%)	p=0.631
Macrosomia	13 (13.0%)	9 (9.0%)	22 (11.0%)	p=0.499
Placenta previa	8 (8.0%)	5 (5.0%)	13 (6.5%)	p=0.631
Preterm birth (<37 weeks)	23 (23.0%)	35 (35.0%)	58 (29.0%)	p=0.065

X^2=Pearson Chi-square test

birth and PPH were found to increase with age, and the differences were statistically significant (p=0.039, p=0.043) (**Table 2**).

Table 3 presents the results of the linear regression analysis conducted to evaluate the predictive effect of maternal age on specific obstetric complications. The findings indicate that AMA is a significant and positive predictor of preterm birth, PPH, and pregnancy-induced hypertensive disorders. Examination of the standardized beta (β) coefficients reveals that the relative impact of maternal age on these risk factors is ranked as follows: preterm birth, PPH, and pregnancy-induced hypertensive disorders. Moreover, the unstandardized regression coefficients (B) and their corresponding 95% confidence intervals support the statistical robustness of these associations (**Table 3**).

In **Table 4**, the ROC analysis identified maternal age >37 as the optimal cutoff value for predicting adverse pregnancy outcomes, specifically preterm birth. The area under the ROC curve (AUC) for this threshold was 0.687 (p<0.001) (**Figure 1**), indicating a higher likelihood of preterm birth in individuals older than 37 years. Similarly, for predicting pregnancy-induced hypertensive disorders, the optimal maternal age cutoff was >33 years, with an AUC of 0.633 (p=0.006) (**Figure 2**), suggesting an increased risk of hypertensive disorders in women older than 33 years.

Table 5 shows that there was no significant difference between preterm delivery and pregnancy-induced hypertension when comparing the frequency of composite adverse outcomes in women under and over 35 years of age (p=0.421).

DISCUSSION

The number of pregnancies among women of AMA has increased significantly worldwide, and this trend is expected to continue in the coming years. This demographic shift is associated with an elevated risk of complications affecting both maternal and neonatal health.

In our study, regression analysis revealed that AMA was significantly associated with an increased risk of pregnancy-related hypertensive disorders, preterm delivery, and PPH. AMA was identified as a positive and statistically significant predictor for each of these adverse outcomes. To quantify these risks, ROC analysis was performed to determine optimal

Table 2. Birth outcomes of pregnant women according to age

Features	Pregnant women under 35 years of age, n (%)	Pregnant women aged 35 years and older, n (%)	Total, n (%)	p-value
Type of birth-vaginal delivery Type of birth-caesarean section	57 (57.0%) 43 (43.0%)	46 (46.0%) 54 (54.0%)	103 (51.5%) 97 (48.5%)	X^2=2.422 p=0.078
Preterm birth	16 (16.0%)	29 (29.0%)	45 (22.5%)	X^2=3.676 **p=0.039**
5th-minute Apgar ≤ 7	14 (14.0%)	19 (19.0%)	33 (16.5%)	X^2=0.907 p=0.223
Stillbirth	2 (2.0%)	2 (2.0%)	4 (2.0%)	X^2=0.000 p=0.689
Neonatal intensive care need	15 (15.0%)	21 (21.0%)	36 (18.0%)	X^2=1.220 p=0.179
Postpartum hemorrhage	8 (8.0%)	17 (17.0%)	25 (12.5%)	X^2=3.703 **p=0.043**

X^2=Pearson Chi-square test

Table 3. Results of the linear regression analysis predicting obstetric characteristics by age variable

	Scales	B (95% CI)	t	β	R^2	F	p
Age variables	Preterm birth	7.914(2.21-13.62)	2.573	.180	.032	6.620	0.000
	Postpartum hemorrhage	8.274(0.60-15.94)	2.119	.149	.022	4.492	0.035
	Pregnancy-induced hypertensive disorders	8.296(1.35-15.25)	5.351	.166	.027	5.579	0.019

B: Unstandardized coefficient of regression, β: Standardized coefficient of regression, R^2: Coefficient of determination

Table 4. ROC analyses to determine maternal age cut-off point for predicting adverse pregnancy outcomes

Scales	AUC	p value	Cut-off point	Sensitivity	Descriptiveness	PLR	NLR
Preterm birth	0.687	<0.001	>37	53.33	78.06	2.43	0.60
Postpartum hemorrhage	0.623	0.069	>35	64.00	65.71	1.87	0.55
Pregnancy-induced hypertensive disorders	0.633	0.006	>33	78.12	52.98	1.66	0.41

ROC: Receiver operating characteristic, AUC: Area under the ROC curve, PLR: Positive likelihood ratio, NLR: Negative likelihood ratio

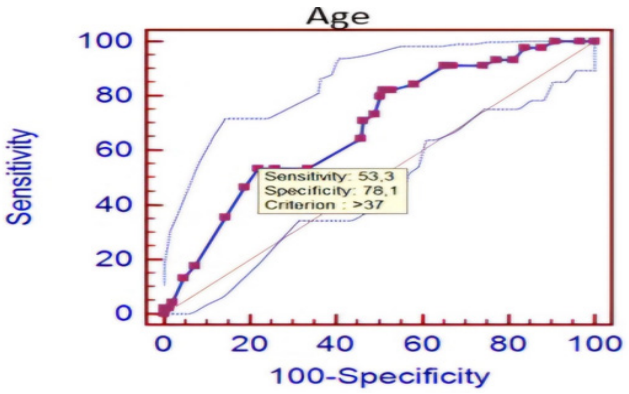

Figure 1. Cut-off point value for maternal age predicting preterm birth >37 (AUC= 0.687, p<0.001)

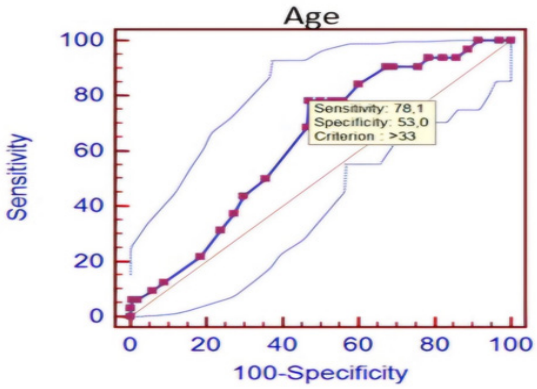

Figure 2. Cut-off point value of and pregnancy-induced hypertensive disorders predicting maternal age >33 (AUC= 0.633, p=0.006)

maternal age cut-off values. The analysis identified >33 years as the optimal threshold for predicting pregnancy-induced hypertensive disorders (AUC=0.633, p=0.006), and >37 years for predicting preterm birth (AUC=0.687, p<0.001).

In clinical research, a composite outcome refers to the combination of multiple clinically relevant endpoints into a single metric, allowing for a more holistic assessment of overall health status or treatment efficacy. In our study, no statistically significant difference was observed in the frequency of composite adverse outcomes—specifically preterm birth and pregnancy-induced hypertension—between women under and over 35 years of age. This non-significant result may be attributed to the limited number of participants experiencing these complications, thereby reducing the statistical power to detect group differences.

An increased incidence of gestational hypertensive disorders among women of AMA has been frequently reported in the literature.[7,28,33] In particular, the heightened risk of early-onset preeclampsia is often attributed to age-related vascular endothelial damage and dysfunction, which can compromise the maternal cardiovascular system's ability to adapt adequately to pregnancy.[14] Similarly, Timofeev et al.[15] reported that the risk of pregnancy-induced hypertension increases with advancing age in women over 35 years. In contrast, Cleary-Goldman et al.[16] found that women aged 35–39 had a lower risk of pregnancy-induced hypertension compared to those under 35. Likewise, a study conducted in Turkiye by Çakmak Çelik et al.[17] reported no significant difference in the incidence of preeclampsia among women in the AMA group.

These contradictory findings suggest that although advancing maternal age may contribute to vascular pathologies that predispose women to preeclampsia, other individual and environmental factors likely play a decisive role in this association. Our study's findings underscore the importance of regular blood pressure monitoring in women over the age of 35. These results can inform both preconception and antenatal counseling strategies. Moreover, encouraging home-based blood pressure monitoring during the third trimester may offer an effective approach for early detection and intervention in this high-risk population.

The literature presents conflicting findings regarding the risk of PPH. While earlier studies have linked advanced AMA to an increased risk of PPH, a definitive consensus has yet to be reached.[18,19] For example, Kramer et al.[19] reported that maternal age of 35 years is associated with a heightened risk of postpartum bleeding. Similarly, Sheen et al.[18] suggested that women over the age of 45 face the highest risk of PPH during delivery-related hospitalizations. In contrast, a meta-analysis found no significant association between maternal age of 35 and the risk of PPH.[20] Furthermore, Lao et al.[21] reported that advancing maternal age may actually be associated with a reduced risk of PPH, with incidence rates declining progressively from the 25–29 age group to those aged ≥40.

Table 5. Comparison of the frequency of composite adverse outcomes in women under and over 35 years of age

Features	Pregnant women under 35 years of age (n=100)		Pregnant women aged 35 years and older (n=100)		Total (n=200)		Test
	n%		n%		n%		
Preterm birth+pregnancy-induced hypertensive disordes							
Yes	6	6.0	9	9.0	15	7.5	X^2=0.649
No	94	94.0	91	91.0	185	92.5	p=0.421

X^2=Pearson Chi-square test

In our study, we observed an increased risk of PPH among women of AMA. Several physiological mechanisms may contribute to this finding. One possible explanation is the age-related decline in oxytocin receptor density and desensitization due to prolonged oxytocin exposure, both of which may impair uterine contractility.[22] This condition can result in uterine atony and subsequently elevate the risk of PPH. Additional contributing factors may include uterine muscle fatigue following prolonged labor and impaired contractility associated with cesarean delivery. Collectively, these mechanisms render older mothers more susceptible to PPH. Therefore, in cases where additional risk factors for PPH are present, healthcare providers should consider early preparation of blood products as part of the delivery plan to ensure timely intervention and improve maternal outcomes.

Although the precise etiology of preterm birth remains unclear, one of the most widely accepted underlying mechanisms involves placental vascular pathology. Spontaneous preterm birth has been associated with placental hemorrhage, compromised vascular integrity, and inadequate remodeling of the maternal spiral arteries.[23] Additionally, preeclampsia and other hypertensive disorders may contribute to preterm birth through uteroplacental ischemia.

In the context of AMA, declining progesterone levels may represent an additional contributing factor. Low progesterone concentrations have been linked to an increased risk of preterm birth, whereas progesterone supplementation has demonstrated preventive efficacy.[24] Numerous studies have reported that women of AMA are at greater risk of preterm delivery and giving birth to low birth weight infants compared to younger counterparts.[25,26] Similarly, other research has also identified elevated rates of preterm birth among older mothers.[7] Our findings are consistent with these studies. However, a study conducted by Schimmel et al.[5] found no statistically significant association between AMA and preterm birth. Such conflicting results may be attributable to variations in sociodemographic profiles and clinical risk factors across different populations. Nevertheless, the most plausible explanation for the increased incidence of preterm birth in AMA is the higher prevalence of pregnancy-related complications in this group.

In our study, AMA was not significantly associated with differences in mode of delivery, the incidence of gestational diabetes, placental abruption, placenta previa, macrosomia, 5-minute Apgar scores, stillbirth, or the need for neonatal intensive care.

AMA has been associated with adverse lipid profiles, including decreased insulin sensitivity and elevated levels of triglycerides and cholesterol, all of which may contribute to impaired glucose tolerance and an increased risk of gestational GDM.[7,26] Clinical studies have shown that insulin resistance tends to increase with age, often resulting in mild hyperglycemia. In a study conducted by Yogev et al.[7] in Israel, the prevalence of GDM rose markedly with advancing age: 1.4% among women aged 20–29, 4.2% in those aged 30–39, 10.2% in the 40–44 age group, and 17% in women aged 45 and older. Furthermore, Cleary-Goldman et al.[16] identified maternal age ≥40 as an independent risk factor for the development of GDM.

In our study, a rising trend in the prevalence of GDM was observed with increasing maternal age; however, this difference did not reach statistical significance. This outcome contrasts with a recent study by Iman et al.[27], who divided maternal age into three categories and reported a significantly higher risk of GDM among women aged 31–40 years. In our study, maternal age was classified into only two groups, and the relatively small sample size in the AMA group may have limited the statistical power to detect significant differences. Future research employing more refined age stratifications and ensuring adequate representation within each subgroup may yield a more accurate evaluation of the relationship between maternal age and GDM risk. Nevertheless, considering the well-documented physiological effects of aging on glucose metabolism, this observation may still hold clinical relevance. GDM has been linked to various adverse outcomes, including increased rates of cesarean delivery, macrosomia, low Apgar scores, preterm birth, and admissions to the NICU.[7] Therefore, our findings may serve as a useful clinical indicator of the potential risks associated with GDM in women of AMA.

In our study, analysis of delivery mode data revealed that 54% of pregnant women aged over 35 years underwent cesarean section (CS), compared to 43% of women under 35 years of age. Karlström et al.[28] reported that CS rates were two to four times higher among older pregnant women compared to younger reference groups. Similarly, Pawde et al.[29] observed elevated CS rates in women over 35, although the difference was not statistically significant. Ritzinger[32] and Usta et al.[30] attributed the rising CS rates not only to medical indications but also to heightened physician and maternal anxiety related to AMA, previous obstetric complications, and negative birth experiences among multiparous women. In addition, clinical indications play a major role in the increased CS rates. Goldmann et al.[16] emphasized that preterm labor and obstetric complications were more prevalent among older women, leading to a greater reliance on cesarean deliveries. In line with these findings, our study also demonstrated that maternal complications associated with advanced age likely contributed to the higher CS rates observed in this group.

In our study, no significant association was found between AMA and either placental abruption or placenta previa, likely due to the low incidence of these conditions. However, existing literature suggests that AMA may increase the risk of both conditions, particularly in the presence of additional risk factors such as multiparity and hypertension.[7,18] Population-based studies have demonstrated a significant association between AMA and a higher likelihood of placenta previa. For example, Biro et al.[31] identified AMA as an independent risk factor for placenta previa. Similarly, Cleary-Goldman et al.[16] attributed this increased risk to progressive vascular damage associated with aging. Conversely, some researchers argue that when varying risk profiles are taken into consideration, maternal age alone may not be a decisive factor in the development of placenta previa.[32]

Nevertheless, the elevated risk of placenta previa in older women has important implications not only for individual

clinical outcomes but also from a broader public health perspective. The growing number of pregnancies among women of advanced age may lead to increased rates of hospitalizations, cesarean deliveries, and blood transfusion needs associated with placenta previa. Therefore, meticulous monitoring and strategic clinical planning are essential in the management of this high-risk population.[7]

In this study, the impact of AMA on neonatal outcomes was also assessed. Our analysis revealed no statistically significant differences between the age groups in terms of stillbirth, NICU admission, 5-minute Apgar scores, or macrosomia. However, the literature presents mixed findings on this topic. Some studies have reported no differences in Apgar scores among infants born to older mothers,[6,30] while others have found lower Apgar scores and higher NICU admission rates in this population.[7,33] Conversely, several studies have reported no significant differences in either Apgar scores or NICU length of stay.[25] These inconsistencies may be explained by variations in sociodemographic characteristics and clinical risk profiles among study populations.

Despite a higher frequency of antenatal complications among women aged 35 and above in our study, neonatal outcomes were comparable to those observed in younger mothers. This finding suggests that early diagnosis, appropriate follow-up, and timely interventions can effectively improve neonatal outcomes in high-risk pregnancies. Moreover, protective strategies—such as the administration of antenatal corticosteroids, a conservative approach to cesarean delivery, and childbirth occurring in perinatal care centers—may have contributed to these favorable outcomes. Collectively, these results imply that older mothers can potentially mitigate the risks associated with pregnancy complications by engaging more consistently in prenatal care.

Limitations

One of the strengths of our study is the high quality of the registry and its consistency with birth records. We conducted a comprehensive analysis of pregnancy, delivery, and neonatal outcomes associated with AMA. The sample size was sufficient to capture the obstetric challenges linked to AMA pregnancies during the study period. However, the retrospective design represents a limitation, and the study did not include data from a national cohort. Furthermore, some important sociodemographic variables—such as body-mass index (BMI) and socioeconomic status—were not available. As a result, we were unable to assess the impact of prenatal screening tests or fetal chromosomal abnormalities. Since the study population included only women aged 35 years and older, the statistical power to detect rare outcomes was limited. Subgroup analyses evaluating the effects of very AMA could not be performed. In AMA pregnancies, it is essential to inform patients about potential maternal and neonatal complications and to establish follow-up protocols tailored to this group. Given the inconsistencies in the literature, further studies are needed to address these gaps.

CONCLUSION

Our results emphasize the importance of informing women over 35 years of age about PPH, preterm delivery risks, and the need for blood pressure control.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the University Medical Faculty Clinical Researches Ethics Committee (Date:19.09.2024, Decision No: 2024/83).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1675007

Anatolian Curr Med J. 2025;7(3):311-319

Morphometric analysis of the spine in patients with single-level lumbar disc herniations: clinical study

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Cite this article as: Bakar B, Özdemir A, Erdoğan AM, et al. Morphometric analysis of the spine in patients with single-level lumbar disc herniations: clinical study. *Anatolian Curr Med J.* 2025;7(3):311-319.

Received: 12.04.2025 ◆ **Accepted**: 23.04.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: It was reported in the literature that sagittal balance may be impaired in patients with spinal deformities and lumbar degenerative diseases. In this study, we analyzed the relationship between disc herniation and the results of spinal column morphological measurements related to sagittal balance on lumbar direct radiographs and preoperative blood biochemistry results in patients with single-level lumbar disc herniation and healthy subjects.

Methods: Patients who underwent surgery for L4-L5 or L5-S1 intervertebral disc herniation and healthy individuals were included in the study. The participants were then grouped into the control group (n=15) and the LDH group (n=30). Patients were also grouped into the L4-5 HNP group (n=15) and the L5-S1 HNP group (n=15). Age, gender, blood count, and serum C-reactive protein values of all individuals and L1-S1 Cobb angles, T12 and S1 slope angles, L4-S1 Cobb angles, each disc height, and L1-L5 vertebral column height were measured on lumbar direct radiographs.

Results: Age (p=0.035), T12 slope angle (p=0.032), L4-S1 Cobb angle (t=3.649, p=0.001), L1-L2 intervertebral disc height (p=0.032), L5-S1 intervertebral disc height (p=0.033), and eosinophil counts (p=0.039) were different between the control group and LDH group. However, there was no statistical difference between patients with L4-L5 disc herniation and patients with L5-S1 disc herniation in terms of study parameters. ROC-curve and regression analysis revealed that if age over 39 years if the T12 slope angle was less than 21.50 degrees if the L4-S1 Cobb angle was less than 32.43 degrees if L1-L2 disc height was above 7.45 mm and if L5-S1 disc height was below 8.15 mm (p=0.041) these parameters could be used predictive markers for the diagnosis of the lumbar disc herniation (p<0.05).

Conclusion: At the end of the study, it was argued that patient age, T12 slope angle, L4-S1 Cobb angle, L1-L2, and L5-S1 intervertebral disc heights measured on lumbar X-ray images could be used as predictive parameters for the diagnosis of lumbar disc herniation in these patients.

Keywords: Lumbar disc herniation, Cobb angle, T12 slope angle, S1 slope angle

INTRODUCTION

The prevalence of symptomatic lumbar disc herniation (LDH) in the general population ranges from 1% to 3%. Intervertebral disc degeneration is a multifactorial condition, with several factors contributing to its development, including spinal biomechanics, injury, inflammation, and nutrition.[1]

It is well established that a person can maintain a stable standing position with minimal muscular effort through sagittal balance while standing. The extant literature defines sagittal balance as the configuration of the bones (particularly the pelvis and the vertebral column), the mechanical behaviour of the discs and ligaments, the strength and resistance of the muscles, and the capacity to engage compensatory mechanisms.[2,3] When one or more of these factors is disrupted, the sagittal balance has deteriorated. This may have a detrimental effect on the spinal column on a global scale, potentially resulting in conditions such as spinal stenosis or intervertebral disc degeneration. Indeed, studies have demonstrated that patients with spinal deformities and lumbar degenerative diseases exhibit alterations in spinal pelvic sagittal force lines. However, the extant literature on the subject is inconclusive, with only a few studies investigating the effects of these force lines on LDH in patients with LDH.[3-7]

The present study evaluated the relationship between spinal column morphometric measurement results on lumbar X-ray, blood count results, and disc herniation in patients with LDH.

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METHODS

Ethics

This study was approved by the Kırıkkale University, Faculty of Medicine, Non-interventional Clinical Trials Ethics Committee (Date: 29.01.2025, Decision No: 2025.01.10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Groups

After retrospective screening from the hospital digital record system, patients who had undergone surgery for L4-5 or L5-S1 intervertebral disc herniation between January 2024 and December 2024 were included in this study. In addition, individuals without any metabolic and rheumatologic disease who presented to the outpatient clinic with low back pain but whose lumbar radiologic images did not reveal pathologic images requiring surgical treatment were also included.

The individuals were then divided into two groups as follows:

- Control group (healthy individuals, n=15)
- LDH group (patients operated for L4-L5 or L5-S1 intervertebral disc herniation, n=30)

After excluding the control group individuals, the patients (LDH group) were then divided into two groups as follows:

- L4-L5 HNP group (n=15)
- L5-S1 HNP group (n=15)

The patients were divided into two groups as follows:

- Male patients (n=13)
- Female patients (n=17)

The patients who had congenital spinal anomalies (such as scoliosis, spondylolisthesis), who had lumbar spinal deformities detected on coronal or sagittal X-ray images, who had a history of previous spine surgery, who had disc herniation at more than one level, who had infection, tumor, or rheumatologic involvement at the spine or intervertebral disc level, who had spine fracture or slippage, and patients at pediatric age group were excluded from the study.

Material

The age, gender, and duration of stay in the hospital were recorded. In addition, preoperative leukocyte (normal range 4400-11300/uL), neutrophil (normal range 1.100-9600/uL), lymphocyte (normal range 500-6000/uL), monocyte (normal range 0.12-1.2 10^3uL), basophil (normal range 0-300 10^3uL), eosinophil (normal range 0.02-0.5 10^3uL) and platelet (normal range 150-500 10^3/uL) counts and serum C-reactive protein (CRP) levels (normal range 0-5 mg/L) were recorded in the venous blood samples.

In addition, the following measurements were made on the standing lateral lumbar X-rays of the control group without disc herniation and on the preoperative standing lateral lumbar X-rays of the patients (**Figure 1**):

- L1-S1 Cobb angle: The angle between the upper end-plate of the L1 vertebra and the upper end-plate of the sacrum.

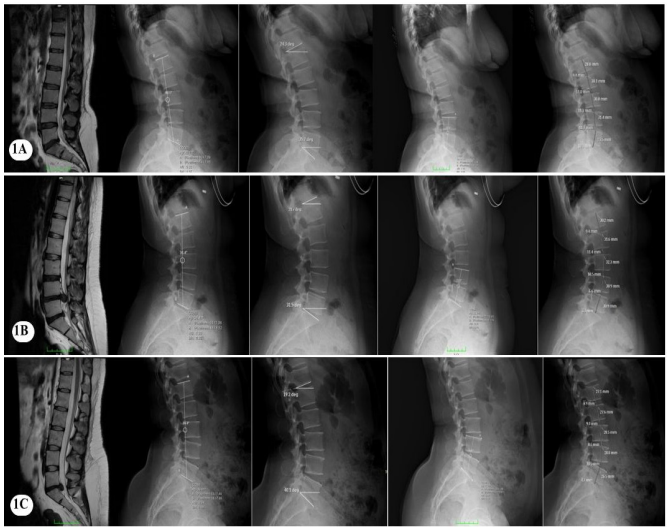

Figure 1. Photographs show sagittal T2-weighted MR images and morphometric measurements on lateral lumbar radiographs of healthy individuals **(1A)**, individuals with L4-5 intervertebral disc herniation **(1B)**, and individuals with L5-S1 intervertebral disc herniation **(1C)**

- T12 slope angle: The angle between the lower end-plate of the T12 vertebra and the line drawn parallel to the ground.
- S1 slope angle: Angle between the upper end-plate of the sacrum and a line drawn parallel to the ground.
- L4-S1 Cobb angle: The angle between the upper end-plate of the L4 vertebra and the upper end-plate of the sacrum.
- Intervertebral disc height: The height of the widest distance between the upper end-plate and the lower end-plate of each vertebra for each disc size.
- L1-L5 vertebral column height: Sum of the sagittal height of each intervertebral disc height and vertebra height.

In addition, the side (right, left), location (central, foraminal, mixed), extension of the herniated disc into the spinal canal (protrusion, extrusion, sequestration), and the orientation of the herniated disc in the sagittal plane (no migration, down migration, up migration) were recorded on the lumbar MR images of each individual included in the study.

Using posterior-anterior X-ray images, postural scoliosis (lateral bending) was assessed and recorded for all participants. In addition, all participants' lumbar spines were classified based on their sagittal X-ray images, according to Roussouly et al.[12]

Statistical Analysis

The data analysis was conducted using SPSS v20.0, a statistical program. The Kolmogorov-Smirnov test was utilized to analyze the normal distribution of data. Categorical data were evaluated using the Pearson Chi-square test ($p<0.05$). The Mann-Whitney U test was employed to compare non-parametric data between groups, and the Independent Samples t-test was used to compare parametric data ($p<0.05$). Spearman's rho correlation test was used to ascertain the correlations among the parameters ($p<0.05$). The ROC-curve test was used to investigate which study parameters could predict the diagnosis of LDH, and the sensitivity

and specificity rates of the parameters were determined by obtaining "cut-off" values. The logistic regression test was also utilized to ascertain the most effective predictive parameters ($p<0.05$). The model validity was tested using Factor analysis, and a reliability test was performed to assess the reliability of the predictive parameters.

RESULTS

Age (t=-2.174, p=0.035), T12 slope angle (t=2.213, p=0.032), L4-S1 Cobb angle (t=3.649, p=0.001), L1-L2 intervertebral disc height (t=-2.401, p=0.021), L5-S1 intervertebral disc height (t=2.201, p=0.033), and eosinophil counts (Z=-2.061, p=0.039) were different between the control and LDH groups (**Table 1**).

Correlation test results revealed a positive correlation between the study group and age (r=0.307, p=0.040), between the study group and herniation type (r=0.367, p=0.046), between age and the direction of herniated disc migration (r=0.413, p=0.023), between the direction of disc migration and L1-S1 Cobb angle (r=0.448, p=0.013), between the direction of disc migration and S1 slope angle (r=0.422, p=0.020), between the direction of disc migration and L4-S1 Cobb angle (r=0.489, p=0.006), between the direction of disc migration and L5-S1 disc height (r=0.429, p=0.018), between L1-S1 Cobb angle and T12 slope angle (r=0.398, p=0.007), between L1-S1 Cobb angle and S1 slope angle (r=0. 605, p<0.001), between L1-S1 Cobb angle and L1-L2 disc height (r=0.348, p=0.019), between T12 slope angle and L4-S1 Cobb angle (r=0.425, p=0.004), between T12 slope angle and L5-S1 disc height (r=0.425, p=0.004), between S1 slope angle and L4-S1 Cobb angle (r=0.442, p=0.002), between S1 slope angle and "Roussouly classification" (r=0.498, p=0.001), between L4-S1 Cobb angle and L4-L5 disc height (r=0.359, p=0.015), between L4-S1 Cobb angle and L5-S1 disc height (r=0.606, p<0.001), between L1-L2 disc height and L2-L3 disc height (r=0.797, p<0.001), between L1-L2 disc height and L3-L4 disc height (r=0.470, p=0.001), between L1-L2 disc height and L1-L5 vertebral column height (r=0.424, p=0.004), between L2-L3 disc height and L3-L4 disc height (r=0.666, p<0.001), between L2-L3 disc height and L1-L5 vertebral column height (r=0.466, p=0.001), between L3-L4 disc height and L4-L5 disc height (r=0.380, p=0.010), between L3-L4 disc height and L1-L5 vertebral column height (r=0.458, p=0.002), between L4-L5 disc height and L5-S1 disc height (r=0.441, p=0.002), between L5-S1 disc height and L1-L5 vertebral column height (r=0.305, p=0.041) (**Table 2**).

On the other hand, there was a negative correlation between the study group and T12 slope angle (r=-0.300, p=0.045), between the study group and L5-S1 disc height (r=-0.330, p=0.027), between gender and L2-L3 disc height (r=-0.326, p=0.029), between gender and L3-L4 disc height (r=-0.370, p=0.012), between gender and L1-L5 vertebral column height (r=-0.651, p<0.001), between L4-S1 Cobb angle and the direction of disc migration (r=0.428, p=0.003), and between disc herniation type and L1-L5 vertebral column height (r=-0.402, p=0.028) (**Table 2**).

ROC-curve analysis applied to all participants' data showed that if the age is >39 years (area=0.688, p=0.042, 73% sensitivity and 60% specificity, 95% CI 0.494-0.881) if the T12 slope angle measured on lumbar X-ray images is <21.50 degrees (area=0.282, p=0.018, 63% sensitivity and 68% specificity, 95% CI 0.136-0.428) if the L4-S1 Cobb angle measured on lumbar X-ray images is <32.43 degrees (area=0.184, p=0.001, 73% sensitivity and 80% specificity, 95% CI 0.055-0.313) if the L1-L2 disc height is >7.45 mm (area=0.732, p=0.012, 70% sensitivity and 60% specificity, 95%CI 0.580-0.885), and if the L5-S1 disc height is <8.15 mm (area=0.311, p=0.041, 60% sensitivity and 60% specificity, 95%CI 0.160-0.463), these parameters could be predictive markers in decision-making for LDH on lumbar X-ray images. In addition, Logistic regression analysis revealed that age (B=0.053, Wald=4.109, p=0.043, OR=1.055, 95% CI 1.002-1.110), T12 slope angle (B=-0.122, Wald=4.022, p=0.045, OR=0.885, 95% CI 0.785-0.997), L4-S1 Cobb angle (B=-0.142, Wald=7.737, p=0.005, OR=0.868, 95% CI 0.785-0.959), L1-L2 disc height (B=0.576, Wald=4.711, p=0.030, OR=1.780, 95% CI 1.058-2.995) and L5-S1 disc height (B=-0.346, Wald=4.162, p=0.041, OR=0.707, 95% CI 0.507-0.986) could be used as predictive markers for diagnosis of the LDH on lumbar X-ray images (**Table 3, Figure 2**).

However, Factor analysis applied to test the validity of these parameters showed that these parameters could not be valid parameters for predicting the diagnosis of LDH on lumbar X-ray images (Kayser-Meyer-Olkin test=0.414, Barlett's test of Sphericity=24.553, p=0.006). A Reliability test was performed to test the reliability of these parameters, and it was concluded that they could not be reliably used for diagnosing the disc herniation on lumbar X-ray images (Cronbach's alpha value=-0.115, interclass correlation=-0.115, 95% CI -0.728-0.328, F=0.897, p=0.656).

On the other hand, after the control group individuals were excluded from the study, no statistical difference was found in terms of study parameters between patients with L4-L5 disc herniation and patients with L5-S1 disc herniation (**Table 4**).

When patients with LDH were divided into two groups male and female gender, L1-L2 disc height (t=2.319, p=0.028), L2-L3 disc height (t=2.246, p=0.033), L3-L4 disc height (t=2.351, p=0.026), L1-5 vertebral column height (t=4.103, p<0.001) and monocyte counts (t=2.287, p=0.030) were different between male and female patients (**Table 5**).

DISCUSSION

Research has indicated that patients diagnosed with disc degeneration exhibit a reduced sacral incidence and a diminished sacral slope angle compared to healthy individuals. Therefore, it was argued that patients with disc degeneration tend to have more vertical sacrum, sacral kyphosis, and severe low back pain, thus developing more disc degeneration.[9] In addition, it has been shown that individuals with reduced lumbar lordosis have more axial loading on the vertebral endplates, which leads to more dehydration and degeneration of the intervertebral disc. It has been posited that the L3-L4, L4-L5, and L5-S1 intervertebral discs were subject to these overloads, which led to the onset of degenerative processes.[5,10-12]

The findings of this study indicated that patients afflicted with LDH were characterized by advanced age, elevated L1-L2 disc height and eosinophil counts, and diminished T12 slope angles, L4-S1 Cobb angles, and L5-S1 disc heights

Table 1. Descriptive table of the study groups

		Control	LDH		
Variable		**Mean±SD/median (min-max)/n (%)**	**Mean±SD/median (min-max)/n (%)**	**t/Z/X²**	**p**
Age		38.67±16.38	48.10±12.23	-2.174*	0.035
Sex	Male	7 (15.6%)	13 (28.9%)	0.045‡	0.832
	Female	8 (17.8%)	17 (37.8%)	-	-
Roussouly's classification	Type 1	4 (8.9%)	12 (26.7%)	4.647‡	0.200
	Type 2	8 (17.8%)	15 (33.3%)		
	Type 3	2 (4.4%)	0 (0.0%)		
	Type 4	1 (2.2%)	3 (6.7%)		
Lateral bending	Neutral	15 (33.3%)	23 (51.1%)	4.145‡	0.126
	Right	0 (0.0%)	2 (4.4%)		
	Left	0 (0.0%)	5 (11.1%)		
Herniation site	Right	-	14 (46.7%)	-	-
	Left	-	16 (53.3%)	-	-
Disk migration	No	-	14 (46.7%)	-	-
	Below	-	15 (50.0%)	-	-
	Above	-	1 (3.3%)	-	-
Disk location	Central	-	12 (40.0%)	-	-
	Foraminal	-	4 (13.3%)	-	-
	Mixt	-	14 (46.7%)	-	-
Herniation type	Protruded	-	15 (50.0%)	-	-
	Extruded	-	13 (43.3%)	-	-
	Sequestrated	-	2 (6.7%)	-	-
L1-L5 Cobb angle		44.27±12.43	48.67±12.45	-1.118*	0.270
T12 slope angle		23.53±3.85	18.83±7.73	2.213*	0.032
S1 slope angle		38.87±10.25	33.87±8.67	1.716*	0.093
L4-S1 slope angle		37.90±8.73	26.41±10.50	3.649*	0.001
Intervertebral disk height	L1-L2	6.95±1.27	8.01±1.45	-2.401*	0.021
	L2-L3	8.41±1.10	9.17±1.78	-1.527*	0.134
	L3-L4	9.13±1.31	9.07±2.06	0.102*	0.919
	L4-L5	9.57±1.30	8.90±2.35	1.035*	0.307
	L5-S1	8.86±1.27	7.33±2.53	2.201*	0.033
L1-L5 vertebral column height		161.07±9.45	165.23±8.43	-1.498*	0.141
Leukocyte		7130 (4690-10450)	8350 (5070-17630)	-1.661†	0.097
Neutrophil		4610 (2210-7170)	5120 (2800-15530)	-1.734†	0.083
Lymphocyte		2472.67±547.82	2428.67±804.31	0.190*	0.850
Monocyte		432±121.67	539±200.54	-1.893*	0.065
Basophil		40 (20-70)	30 (10-80)	-0.467†	0.640
Eosinophile		22 (20-70)	75 (19-370)	-2.061†	0.039
Platelet (10^3)		269.47±58.67	278.10±54.38	-0.489*	0.627
C-reactive protein		1.80 (0.10-3.40)	1.95 (0.40-9.40)	-0.530†	0.596
Hospitalization		-	3 (2-9)	-	-

(*) t value, Independent Samples t-test, (†) Z value, Mann-Whitney U test, (‡) X2 value, Pearson Chi-square test, p<0.05, LDH: Lumbar disc herniation, SD:Standard deviation, min: Minimum, max: Maximum, n: Number of subjects

when compared with the control group. The findings of this study indicated that patients diagnosed with LDH were predominantly of advanced age. Conversely, the T12 slope angle, L4-S1 Cobb angles, and L5-S1 disc heights in these patients were lower than those observed in healthy individuals. It was hypothesized that the thoracic kyphosis angle would be higher in patients with disc herniation, and thus, the load on the vertebral column would be increased, with the L5-S1 disc space being most affected by this excessive load. In addition, although lumbar lordosis (i.e., L4-S1 Cobb angles) at the herniated disc level was decreased in these patients, L1-S1 Cobb angle was not different between the

Table 2. Correlation table showing the relationship between study data

		Age	Disc migration	Herniation type	L1-S1 Cobb angle	T12 slope angle	S1 slope angle	L4-S1 Cobb angle	Roussouly classification	L 1-L2 height	L 2-L3 height	L 3-L4 height	L 4-L5 height	L 5-1 height	L1-L5 vertebral height
Group	r	0.307	-0.092	0.367	0.211	-0.300	-0.204	-0.428	-0.229	0.231	0.058	0.025	-0.056	-0.330	0.132
	p	0.040	0.629	0.046	0.164	0.045	0.180	0.003	0.130	0.127	0.707	0.870	0.717	0.027	0.387
Age	r	1.000	0.413	0.065	0.147	-0.131	0.035	-0.173	0.238	0.189	0.063	-0.145	-0.111	-00.110	-0.127
	p		0.023	0.734	0.337	0.392	0.817	0.255	0.116	0.214	0.679	0.343	0.469	0.473	0.404
Gender	r		0.022	0.240	0.097	0.041	0.002	-0.003	-0.086	-0.226	-0.326	-0.370	-0.271	0.129	-0.651
	p		0.908	0.202	0.528	0.787	0.991	0.982	0.577	0.136	0.029	0.012	0.072	0.398	<0.001
Disc migration	r		1.000	0.141	0.448	0.337	0.422	0.489	-0.090	0.124	0.261	-0.112	-0.022	0.429	-0.147
	p			0.459	0.013	0.069	0.020	0.006	0.637	0.512	0.164	0.554	0.907	0.018	0.439
Herniation type	r			1.000	0.104	0.235	-0.072	-0.041	-0.172	-0.324	-0.339	-0.069	0.029	-0.194	-0.402
	p				0.583	0.212	0.706	0.829	0.363	0.080	0.067	0.716	0.878	0.303	0.028
L1-S1 Cobb angle	r				1.000	0.398	0.605	0.252	0.274	0.348	0.240	-0.014	-0.224	0.061	0.005
	p					0.007	<0.001	0.096	0.069	0.019	0.112	0.928	0.140	0.690	0.976
T12 slope angle	r					1.000	0.240	0.425	-0.009	-0.063	-0.069	-0.102	0.043	0.421	-0.083
	p						0.112	0.004	0.953	0.680	0.651	0.504	0.777	0.004	0.589
S1 slope angle	r						1.000	0.442	0.498	0.103	0.109	-0.133	-0.143	0.152	-0.077
	p							0.002	0.001	0.499	0.474	0.382	0.349	0.318	0.614
L4-S1Cobb angle	r							1.000	0.056	0.155	0.240	0.143	0.359	0.606	-0.062
	p								0.714	0.308	0.112	0.349	0.015	<0.001	0.684
Roussouly classification	r								1.000	0.162	0.132	0.038	-0.200	-0.151	-0.115
	p									0.289	0.386	0.803	0.187	0.323	0.453
L1-L2 disk height	r									1.000	0.797	0.470	0.238	0.248	0.424
	p										<0.001	0.001	0.115	0.101	0.004
L2-L3 disk height	r										1.000	0.666	0.282	00.284	0.466
	p											<0.001	0.060	0.059	0.001
L3-L4 disk height	r											1.000	0.380	0.038	0.458
	p												0.010	0.805	0.002
L4-L5 disk height	r												1.000	0.441	0.305
	p													0.002	0.041

Table 3. Table describing the patients operated on for lumbar disc herniation

ROC-curve test for decision-making of intervertebral disk herniation							
						95% confidence interval	
Variable	**Area**	**Cut-off value**	**p**	**Sensitivity**	**Specificity**	**Lower**	**Upper**
Age	0.688	>39.50	0.042	73%	60%	0.494	0.881
T12 slope angle	0.282	<21.50	0.018	63%	68%	0.136	0.428
L4-S1 Cobb angle	0.184	<32.43	0.001	73%	80%	0.055	0.313
L1-L2 disk height	0.732	>7.45	0.012	70%	60%	0.580	0.885
L5-S1 disk height	0.311	<8.15	0.041	60%	60%	0.160	0.463
Logistic regression test for decision-making of intervertebral disk herniation							
						95% confidence interval	
Variable	**B**	**Wald**	**p**		**Odds ratio**	**Lower**	**Upper**
Age	0.053	4.109	0.043		1.055	1.002	1.110
T12 slope angle	-0.122	4.022	0.045		0.885	0.785	0.997
L4-S1 Cobb angle	-0.142	7.737	0.005		0.868	0.785	0.959
L1-L2 disk height	0.576	4.711	0.030		1.780	1.058	2.995
L5-S1 disk height	-0.346	4.162	0.041		0.707	0.507	0.986

ROC: Receiver operating characteristic

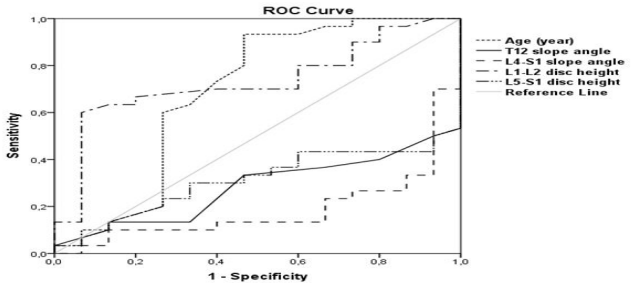

Figure 2. ROC curve plot showing the predictive parameters for the likelihood of lumbar disc herniation
ROC: Receiver operating characteristic

groups. Consequently, it was determined that the lumbar lordosis angle was not associated with an increased risk of disc herniation. However, as the study was retrospective, healthy individuals and patients underwent only routine lumbar X-ray imaging, and measurements were based on these images. As not all individuals included in the study had whole spinal column X-ray images, other parameters that could be used to assess sagittal balance (such as pelvic tilt, pelvic incidence, and thoracic kyphosis angles) could not be measured. Therefore, it was recognized that the risk of bias in the study results could be significant. However, the results

Table 4. Descriptive table of patients operated for lumbar disc herniation

		L4-L5 HNP group	L5-S1 HNP group		
Variable		**Mean±SD/median (min-max)/n (%)**	**Mean±SD/median (min-max)/ n (%)**	**t/Z/X²**	**p**
Age		51.20±14.13	45.00±9.46	1.412*	0.169
Sex	Male	9 (30.0%)	4 (13.3%)	3.394‡	0.065
	Female	6 (20.0%)	11 (36.7%)		
Roussouly's classification	Type 1	5 (16.7%)	7 (23.3%)	3.400‡	0.183
	Type 2	7 (23.3%)	8 (26.7%)		
	Type 3	-	-		
	Type 4	3 (10.0%)	0 (0.0%)		
Lateral bending	Neutral	12 (40.0%)	11 (36.7%)	0.243‡	0.885
	Right	1 (3.3%)	1 (3.3%)		
	Left	2 (6.7%)	3 (10.0%)		
Herniation site	Right	6 (20.0%)	8 (26.7%)	0.536‡	0.464
	Left	9 (30.0%)	7 (23.3%)		
Disk migration	No	6 (20.0%)	8 (26.7%)	1.886‡	0.390
	Below	9 (30.0%)	6 (20.0%)		
	Above	0 (0.0%)	1 (3.3%)		
Disk location	Central	7 (23.3%)	5 (16.7%)	1.333‡	0.513
	Foraminal	1 (3.3%)	3 (10.0%)		
	Mixt	7 (23.3%)	7 (23.3%)		
Herniation type	Protruded	10 (33.3%)	5 (16.7%)	4.359‡	0.113
	Extruded	5 (16.7%)	8 (26.7%)		
	Sequestrated	0 (0.0%)	2 (6.7%)		
L1-L5 Cobb angle		48.73±12.93	48.60±12.41	0.029*	0.977
T12 slope angle		18.53±8.36	19.13±7.33	-0.209*	0.836
S1 slope angle		34.60±9.06	33.13±8.51	0.457*	0.651
L4-S1 slope angle		26.22±9.80	26.60±11.50	-0.099*	0.922
Intervertebral disk height	L1L-2	8.35±1.38	7.67±1.49	1.296*	0.205
	L2-L3	9.65±1.68	8.70±1.80	1.489*	0.148
	L3-L4	8.95±2.58	9.19±1.45	-0.314*	0.756
	L4-L5	8.37±2.47	9.43±2.18	-1.246*	0.223
	L5-S1	7.53±3.04	7.12±1.98	0.441*	0.663
L1-L5 vertebral column height		167.41±6.41	163.05±9.80	1.440*	0.161
Leukocyte		8340 (5070-17630)	8400 (3410-11840)	-0.353†	0.724
Neutrophil		5180 (2800-15530)	4530 (3410-11840)	-0.207†	0.836
Lymphocyte		2348.67±779.06	2508.67±848.16	-0.538*	0.595
Monocyte		510.67±165.77	567.33±232.61	-0.768*	0.449
Basophil		30 (10-50)	30 (10-80)	-0.721†	0.471
Eosinophile		80 (19-260)	70 (20-370)	-0.770†	0.442
Platelet (10^3)		266.87±38.74	289.33±65.99	-1.137*	0.265
C-reactive protein		2.10 (0.40-4.99)	1.80 (0.60-9.40)	-0.581†	0.561
Hospitalization		3 (2-9)	3 (3-4)	-0.089†	0.929

(*) t value, Independent Samples t-test, (†) Z value, Mann-Whitney U test, (‡) X2 value, Pearson Chi-square test, p<0.05, HNP: Herniated nucleus pulposus, SD: Standard deviation, min: Minimum, max: Maximum

Table 5. Descriptive table of male and female patients operated for lumbar disc herniation

		Male group	Female group		
Variable		**Mean±SD/median (min-max)/n (%)**	**Mean±SD/median (min-max)/n (%)**	**t/Z/X²**	**p**
Age		49.92±13.52	46.71±11.37	0.708*	0.485
Roussouly's classification	Type 1	5 (16.7%)	7 (23.3%)	4.548‡	0.103
	Type 2	5 (16.7%)	10 (33.3%)		
	Type 3	-	-		
	Type 4	3 (10.0%)	0 (0.0%)		
Lateral bending	Neutral	9 (30.0%)	14 (46.7%)	0.767‡	0.681
	Right	1 (3.3%)	1 (3.3%)		
	Left	3 (10.0%)	2 (6.7%)		
Herniation site	Right	5 (16.7%)	9 (30.0%)	0.621‡	0.431
	Left	8 (26.7%)	8 (26.7%)		
Disk migration	No	6 (20.0%)	8 (26.7%)	0.834‡	0.659
	Below	7 (23.3%)	8 (26.7%)		
	Above	0 (0.0%)	1 (3.3%)		
Disk location	Central	5 (16.7%)	7 (23.3%)	0.087‡	0.957
	Foraminal	2 (6.7%)	2 (6.7%)		
	Mixt	6 (20.0%)	8 (26.7%)		
Herniation type	Protruded	8 (26.7%)	7 (23.3%)	2.266‡	0.322
	Extruded	5 (16.7%)	8 (26.7%)		
	Sequestrated	0 (0.0%)	2 (6.7%)		
L1-L5 Cobb angle		47.31±13.36	49.71±12.03	-0.516*	0.610
T12 slope angle		17.92±7.84	19.53±7.81	-0.557*	0.582
L4-S1 Cobb angle		26.41±10.62	26.41±10.74	0.001*	0.999
S1 slope angle		33.23±9.07	34.35±8.60	-0.346*	0.732
Intervertebral disk height	L1-L2	8.67±1.25	7.51±1.43	2.319*	0.028
	L2-L3	9.95±1.73	8.5765±1.61	2.246*	0.033
	L3-L4	10.02±1.55	8.35±2.15	2.351*	0.026
	L4-L5	9.78±2.26	8.22±2.26	1.868*	0.072
	L5-S1	6.52±2.76	7.95±2.23	-1.573*	0.127
L1-L5 vertebral column height		171.04±3.72	160.79±8.37	4.103*	<0.001
Leukocyte		8360 (6120-17630)	8340 (5070-14430)	-0.544†	0.586
Neutrophil		5180 (3530-15530)	4530 (2800-11630)	-0.670†	0.503
Lymphocyte		2496.92±799.96	2376.47±828.18	0.401*	0.692
Monocyte		628.46±232.77	470.59±144.16	2.287*	0.030
Basophil		30 (10-80)	30 (10-80)	-1.027†	0.304
Eosinophile		80 (19-280)	70 (20-370)	-0.063†	0.950
Platelet (10^3)		266.23±42.99	287.18±61.42	-1.047*	0.304
C-reactive protein		2.10 (0.45-4.40)	1.60 (0.40-9.40)	-0.398†	0.691
Hospitalization		3 (3-9)	3 (2-4)	-1.769†	0.077

(*) t value, Independent Samples t-test, (†) Z value, Mann-Whitney U test, (‡) X^2 value, Pearson Chi-square test, $p<0.05$, SD: Standard deviation, min: Minimum, max: Maximum

of this study were still convincing, and it was considered that this research could serve as a preliminary step for further investigations.

Conversely, a parallel was observed in the blood count and CRP results between healthy subjects and patients with disc herniation. Consequently, these parameters would not be considered discriminative for disc herniation. Despite the finding of elevated eosinophil count values in patients with disc herniation, these values were found to be within the laboratory's normal range. It was hypothesized that the herniated disc did not induce an inflammatory or immunological response in the patients under consideration.

Following a detailed correlation analysis, it was hypothesized that the probability of disc herniation could be associated with increasing age or decreasing T12 slope angle, L4-S1 Cobb angle, and L5-S1 disc height, as measured on lumbar X-ray images. Conversely, it was observed that disc heights might be higher in males. Furthermore, an observation

was made that as the L1-S1 Cobb angle increased, the T12 slope angle, S1 slope angle, and L1-L2 disc height increased concomitantly. This indicated a potential increase in the migration of the herniated disc. It was hypothesized that an increase in the S1 slope angle and the L5-S1 disc height would result in an elevated probability of migration of the herniated disc. Furthermore, in the event of the L4-S1 Cobb angle being measured low, there is the potential for a decrease in both the T12 and S1 slope angles, as well as a reduction in lumbar lordosis. This may result in an increased probability of disc herniation. Conversely, a decrease in the height of the L1-L5 vertebral column has been hypothesized to increase the risk of protruded, extruded, or sequestered disc herniation.

Furthermore, ROC-curve analysis and logistic regression analysis demonstrated that increased patient age and L1-L2 intervertebral disc heights, as well as decreased T12 slope angle, L4-S1 Cobb angle, and L5-S1 intervertebral disc heights, measured on lumbar X-ray images, could be utilized as predictive markers for the diagnosis of LDH in these patients. Consequently, the hypothesis was proposed that lumbar X-rays of patients with low back pain could serve as a valuable diagnostic tool for identifying LDH. However, following the conclusion of the validity and reliability tests, it was determined that none of these parameters could be considered valid or reliable in predicting the diagnosis of LDH. Nonetheless, it was hypothesized that the implementation of these parameters in clinical practice could prove advantageous in predicting diagnoses and risk factors associated with LDH.

Conversely, following the exclusion of subjects in the control group, the study data exhibited no significant differences between the L4-5 HNP and L5-S1 HNP groups. The results indicated that the spinal column morphometric measurement data showed no significant differences between the two patient groups. Furthermore, no discrepancies were observed in blood counts or CRP levels between the two groups.

Finally, when the patients with intervertebral disc herniation were divided into two groups, male and female, it was observed that the disc heights at L1-L2, L2-L3, and L3-L4, along with L1-L5 vertebral column heights and monocyte counts, were lower in female patients compared to male patients. This difference was thought to be due to the larger body mass of male patients compared to their female counterparts. Monocyte counts were not considered a discriminating factor as they remained within the laboratory's normal range values.

Limitations

It should be noted that the study was not without its limitations. Firstly, given the study's retrospective nature, the number of patients was limited. Secondly, the assessment of morphometric parameters, including the C7 plumb line, thoracic kyphosis angle, pelvic incidence, pelvic tilting angle, sacral inclination, and sacro-femoral distance, was not possible due to the absence of whole-body lateral X-ray radiographs in the patient cohort. Thirdly, the long-term follow-up findings of the study groups were not included in the study, as they were considered to fall outside the study remit. Fourthly, the results of the "body-mass index", "visual analog scale", and "Oswestry disability index" of the patients were not included in the study, as they were deemed to be irrelevant to the purpose of the study. Finally, patients with upper LDH were not included in the study because they are rarely encountered in clinical practice (approximately 5% of all LDH patients).[13]

CONCLUSION

The study demonstrated that, despite their inability to be substantiated as reliable and valid parameters, patient age and T12 slope angle, L4-S1 Cobb angle, L1-L2 and L5-S1 intervertebral disc heights, as measured on lumbar X-ray images, could serve as predictive and helpful parameters for the diagnosis of LDH in patients experiencing low back pain. However, further research is required to ascertain whether these parameters can discriminate between patients with and without the condition. It was posited that the conduct of exhaustive investigations encompassing a more substantial patient cohort would be necessary to substantiate the validity and reliability of these parameters.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Kırıkkale University, Faculty of Medicine, Non-interventional Clinical Trials Ethics Committee (Date: 29.01.2025, Decision No: 2025.01.10).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

DOI: 10.38053/acmj.1659391

ANATOLIAN CURRENT MEDICAL

Anatolian Curr Med J. 2025;7(3):320-325

The relationship between maladaptive daydreaming and academic procrastination, depression, anxiety and stress levels in medical students

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Cite this article as: Karaağaç M, Korkmaz ŞA. The relationship between maladaptive daydreaming and academic procrastination, depression, anxiety and stress levels in medical students. *Anatolian Curr Med J.* 2025;7(3):320-325.

Received: 17.03.2025 ◆ **Accepted**: 25.04.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: Maladaptive daydreaming (MD) is a condition characterized by excessive and immersive daydreaming, often linked to psychological distress and behavioral difficulties. This research examines the correlation between MD, academic procrastination, and psychological distress among medical students.

Methods: A cross-sectional study was conducted with medical students who completed self-report questionnaires, including the MD scale (MDS-16), the Depression, Anxiety, and Stress Scale (DASS-21), and the Tuckman Procrastination Scale (TPS). Pearson correlation and multiple regression analyses were performed to assess associations between MD, academic procrastination, and psychological distress.

Results: The findings revealed a significant positive correlation between MD and academic procrastination ($r=.181$, $p<.05$). Additionally, MD was positively associated with depression ($r=.245$, $p<.001$), anxiety ($r=.222$, $p<.001$), and stress ($r=.216$, $p<.001$). However, MD did not show a significant direct association with academic performance ($\beta=-0.07$, $p=.28$).

Conclusion: While MD is strongly linked to academic procrastination and psychological distress, its direct impact on academic performance remains unclear. Future research should further explore the mechanisms underlying these associations and consider intervention strategies for individuals experiencing MD-related difficulties.

Keywords: Maladaptive daydreaming, academic procrastination, psychological distress, depression, anxiety

INTRODUCTION

Maladaptive daydreaming disorder (MD) is a relatively recently recognized condition in which the individual constructs intense and detailed imaginary situations.[1] These visions can often create a sense of detachment from real life, causing deep sensory and emotional reactions and leading to feelings of shame or embarrassment.[2] MD is generally used as a means of escape from reality and can become compulsive when excessive time is allocated to it, which in turn can negatively affect the daily functioning of the individual. Common symptoms of this disorder include prolonged and detailed daydreaming, inability to resist the urge to daydream, repetitive physical movements while daydreaming, and changes in facial expressions, whispering, or talking. Individuals often listen to music, watch videos, or carry out physical activities while undergoing MD, which may also cause the individual to postpone daily responsibilities.[3] A study of medical students identified that 70% had MD, which had a poor impact on their academic performance.[4]

Academic procrastination is when students delay academic responsibilities such as term papers, weekly assignments, or exam preparations.[5] Research shows that fear of failure, anxiety, low self-esteem, and certain personality traits lead to academic procrastination behavior.[6,7] Academic procrastination rates range from 46% to 95%, according to several studies.[8,9] Research carried out on students at a medical faculty indicated that 28.85% of the participants demonstrated high levels of academic procrastination behavior.[10] Such behaviors are associated with psychological problems such as loss of self-confidence and depression and can negatively affect the quality of life.[11] Individuals with high academic procrastination generally have lower academic achievement.[9,12] Additionally, procrastination behavior was reported to be related to psychological factors such as impulsivity and daydreaming.[13]

In light of these findings, MD can be considered to be widespread among medical students and may lead to various negative consequences. Likewise, academic procrastination can negatively affect the student's psychological state and academic performance. However, the relationship between MD and academic procrastination among medical students

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has not been systematically examined. Our study aimed to investigate the association among depression, anxiety, stress, MD, and academic procrastination, as well as their effects on the academic performance of medical students.

Previous research has suggested that individuals with high levels of MD often experience difficulty in maintaining attention and regulating their cognitive processes. These impairments may contribute to procrastinatory behavior, as daydreaming can serve as a means of cognitive avoidance and emotional escape from academic demands. Moreover, psychological distress such as anxiety, depression, and stress may both result from and contribute to MD, creating a potential bidirectional relationship. Accordingly, this study aims to investigate the interconnectedness of MD, academic procrastination, and emotional distress, and their collective impact on academic functioning. In line with the existing literature, the following hypotheses were put forward:

H1: MD is strongly associated with depression, anxiety, and stress.

H2: MD is strongly related to academic procrastination.

H3: Academic procrastination and grade point average are significantly negatively correlated.

H4: Grade point average and MD are significantly negatively correlated.

METHODS

Ethics

The Faculty of Medicine Ethics Committee approved the study at Karamanoğlu Mehmetbey University (Date:19.12.2023, Decision No: 12-2023/03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Procedure

The current cross-sectional study was conducted on the School of Medicine students at Çanakkale Onsekiz Mart University and Karamanoğlu Mehmetbey University in the 2023-2024 academic term. The data were collected through Google Forms, the link of which was distributed to the students via the WhatsApp application. The initial stage of the form featured an informed consent document. Only those who approved the informed consent form completed the sociodemographic data form, MD scale (MDS-16), TPS, and Depression Anxiety Stress Scale (DASS-21) in the second stage. Participants who did not volunteer to participate in the study, those who had a psychiatric illness and were receiving treatment, and those who left the scales incomplete were excluded. The sample size was determined using a power analysis conducted with G*power software. Previous studies explored the relationship between MD and academic performance; however, findings vary in effect size and methods. Thus, a medium effect size (Cohen's d=0.5) was assumed for power analysis. An independent samples t-test power analysis was conducted using the following parameters: effect size (d)=0.5, alpha=0.05, power=0.80, and a two-tailed test. Based on these criteria, a minimum of 64 participants per group was required. To account for potential data loss and enhance statistical power, the total sample size was set at least 130 participants.

Data Collection Tools

Socio-demographic data form: The researchers prepared a form to obtain information on age, gender, marital status, grade level, average academic score, additional physical illnesses, smoking, alcohol and substance use, current psychiatric illnesses, place of residence, and family structure.

Maladaptive Daydreaming Scale (MDS-16): MDS-16, developed by Somer et al.[14], is the first scale to measure abnormal daydreaming. The MDS-16 is a self-report scale and consists of 16 items. The Cronbach's alpha value of the scale was determined to be 95. The participant completes the scale by marking one of ten possible points (from 0 to 100) under each question on the chart, representing the frequency of the experience (from 0% to 100%). The average of 16 questions is used to determine the scale score. Metin et al.[15] carried out a reliability and validation study for the Turkish version of the scale. Following the analyses, the reliability test of the scale yielded a Cronbach's alpha value of 0.89. The correlations between the items in the MDS scale in the item-total correlation analysis ranged from 0.45 to 0.70. Metin et al.[15] also reported that the convergent validity and content of the scale were both adequate. 'Maladaptive daydreamers' (MDers) were defined as those who scored 50 or higher on the MDS-16 scale, while 'NonMDers' were defined as everybody else.

Tuckman Academic Procrastination Scale (TPS): The TPS was developed by Tuckman[16] to determine the procrastination tendencies of university students and was adapted to the Turkish by Uzun Özer, Saçkes, and Tuckman.[17] An exploratory factor analysis was conducted with 236 students to evaluate the adaptation process to Turkish, followed by a confirmatory factor analysis involving 622 students. The participants rated their feelings on a 5-point Likert scale. Based on this analysis, the adapted scale comprised 14 items grouped under a single factor for college students. The confirmatory factor analysis indicated a good model fit based on the goodness of fit indices.

Furthermore, the scale indicated good reliability, with a Cronbach's alpha value of 0.90 and a test-retest reliability score of 0.80 based on assessments with 22 individuals. Notably, items 6, 10, 12, and 14 are scored reversely. Higher scores are thought to reflect a greater propensity for academic procrastination.

Depression Anxiety Stress Scale-21 (DASS-21): The DASS-21 was created by Lovibond and Lovibond[18] by shortening the DASS-42. The psychometric properties of the Turkish version of the DASS-21 scale were conducted by Sarıçam.[19] A score of 5 or above in depression, 4 or above in anxiety, and 8 or above in stress suggests that the individual is facing significant challenges in these areas. The scores are categorized as "normal," "mild," "moderate," "severe," or "extremely severe,".

Statistical Analysis

The data was analyzed using SPSS v27 software (IBM Corp, Armonk, NY, USA). The Kolmogorov-Smirnov test indicated that the study data was not normally distributed. Based on

the MDS-16 scale score, students scoring 50 or above were classified as MD'ers, while the rest were classified as non-MD'ers. The chi-squared test was employed to compare categorical data, whereas the Mann-Whitney U test was utilized to examine continuous variables. The relationship between academic achievement (GPA) and scores on the DASS-21, MDS-16, and TPS scales was evaluated using the Spearman correlation test. Additionally, the characteristics predicting academic performance (GPA) were examined using linear regression analysis. All analyses were deemed significant at the p<0.05 level.

RESULTS

The demographic attributes and scale scores of 201 participants (42.8% male, 57.2% female) are shown in **Table 1**. The mean age of the participants was 20.63±2.30 years, and the mean scores of the DASS-21 depression, anxiety, and stress subscales were calculated as 8.29±5.19, 7.25±4.29, and 8.66±4.30, respectively. The mean MDS-16 score was 54.11±26.97, and the mean TPS score was 40.83±8.85.

Table 1. Sociodemographic and descriptive characteristics of the participants

Variable	n (%) or mean±SD
Gender	
Male	86 (42.8%)
Female	115 (57.2%)
Income level	
Low	35 (17.4%)
Medium	151 (75.1%)
High	15 (7.5%)
Living arrangement	
With family	25 (12.4%)
Student housing	47 (23.4%)
Student dormitory	105 (52.2%)
Alone	24 (11.9%)
Parents' marital status	
One parent deceased	5 (2.5%)
Living separately	3 (1.5%)
Living together	187 (93.0%)
Divorced	6 (3.0%)
Current psychiatric disorder	
Yes	17 (8.5%)
No	184 (91.5%)
Age	20.63±2.30
DASS-21 D	8.29±5.19
DASS-21 A	7.25±4.29
DASS-21 S	8.66±4.30
MDS-16	54.11±26.97
TPS	40.83±8.85

DASS-D: Depression subscale of the Depression Anxiety Stress Scale, DASS-A: Anxiety subscale of the Depression Anxiety Stress Scale, DASS-S: Stress subscale of the Depression Anxiety Stress Scale, TPS: Tuckman Procrastination Scale, MDS-16: Maladaptive Daydreaming Scale

Table 2 presents the relationships between the DASS-21, MDS-16, and TPS measures. Scores from the MDS-16 showed a positive relationship with the DASS-21 depression (r=0.245, p<0.01), Anxiety (r=0.222, p<0.01), and stress (r=0.216, p<0.01) subscales. Additionally, TPS showed significant positive correlations with the DASS-21 depression (r=0.486, p<0.01), anxiety (r=0.422, p<0.01), and stress (r=0.353, p<0.01) subscales. In addition, scores from the TPS and the MDS-16 showed a weak but significant correlation (r=0.181, p<0.05), while TPS and GPA had a negative correlation (r=-0.216, p<0.01).

Table 2. Correlations between DASS-21, MDS-16, TPS scales and GPA

Variable	1	2	3	4	5	6
1. DASS-21 D	--					
2. DASS-21 A	.667**	--				
3. DASS-21 S	.672**	.708**	--			
4. MDS-16	.245**	.222**	.216**	--		
5. TPS	.486**	.422**	.353**	.181*	--	
6. GPA	-.103	-.081	-.015	.157	-.216**	--

**: Correlation is significant at the 0.01 level (2-tailed). *: Correlation is significant at the 0.05 level (2-tailed). DASS-D: Depression subscale of the Depression Anxiety Stress Scale, DASS-A: Anxiety subscale of the Depression Anxiety Stress Scale, DASS-S: Stress subscale of the Depression Anxiety Stress Scale, TPS: Tuckman Procrastination Scale, GPA: Grade point average

A comparison of the DASS-21, GPA, and TPS scores between the MD'ers and non-MD'ers is shown in **Table 3**. Participants identified as maladaptive daydreamers had higher DASS-21 scores compared to non-daydreamers. Thus, the depression subscale score was 9.34±5.13 vs 7.19±5.05 (U=3766, p=0.002), anxiety was 8.16±4.39 vs 6.30±3.97 (U=3844, p=0.003) and stress was 9.22±4.32 vs 8.51±4.76 (U=4077, p=0.018) for MD'ers versus non-MD'ers, respectively. No significant difference was found in GPA between maladaptive daydreamers and non-daydreamers (2.93±0.42 vs. 2.84±0.53, U=2685, p=0.319). MD'ers scored significantly higher on the TPS than non-MD'ers (41.93±9.43 vs. 39.66±8.09, U=4176, p=0.034).

Table 3. Comparison of DASS-21, GPA and TPS scores between non-MD'ers and MD'ers

Variable	Non MD'ers (mean±SD)	MD'ers (mean±SD)	U	p
DASS-21 depression	7.19±5.05	9.34±5.13	3766	0.002
DASS-21 anxiety	6.30±3.97	8.16±4.39	3844	0.003
DASS-21 stress	8.51±4.76	9.22±4.32	4077	0.018
GPA	2.84±0.53	2.93±0.42	2685	0.319
TPS	39.66±8.09	41.93±9.43	4176	0.034

MD: Maladaptive daydreaming, SD: Standart deviation, DASS-D: Depression subscale of the Depression Anxiety Stress Scale, DASS-A: Anxiety subscale of the Depression Anxiety Stress Scale, DASS-S: Stress subscale of the Depression Anxiety Stress Scale, TPS: Tuckman Procrastination Scale, GPA: Grade point average

After adjusting for sociodemographic variables, a regression analysis was used to investigate the predictive effects of MD, academic procrastination, and psychological distress (DASS subscales: depression, anxiety, and stress) on the GPA. Academic procrastination was found to be a significant negative predictor of GPA (β=-0.016, p=0.026), suggesting a link between higher levels of procrastination and lower academic achievement. GPA was not significantly predicted by psychological distress characteristics such as stress (β=0.022, p=0.268), anxiety (β=0.009, p=0.673), depression (β=-0.005, p=0.747), or MD (β=0.003, p=0.102) (**Table 4**).

Table 4. Regression analysis for GPA prediction

Predictor	Estimate	SE	t	p
Intercept	2.57	1.02	2.52	0.016
DASS-D	-0.005	0.01	-0.33	0.747
DASS-A	0.009	0.02	0.43	0.673
DASS-S	0.022	0.02	1.12	0.268
MDS-16	0.003	0.002	1.67	0.102
TPS	-0.016	0.007	-2.30	0.026

The model was adjusted for sociodemographic variables, GPA: Grade point average, SE: Standard error, DASS-D: Depression subscale of the Depression Anxiety Stress Scale, DASS-A: Anxiety subscale of the Depression Anxiety Stress Scale, DASS-S: Stress subscale of the Depression Anxiety Stress Scale, MDS-16: Maladaptive Daydreaming Scale, TPS: Tuckman Procrastination Scale

DISCUSSION

This study explored the association between academic procrastination, anxiety, depression, stress, and MD among medical students. The findings showed a positive correlation between academic procrastination and stress, depression, and MD, while academic achievement and procrastination were negatively correlated. Furthermore, a sizable portion of the participants displayed symptoms of MD; moreover, these students also reported higher levels of anxiety, stress, and depression. However, the GPA did not show any difference between the two groups.

Very little research has been reported to date on MD among medical students. The incidence of MD among medical students in Saudi Arabia was reported to be 70%; the exact incidence was 34.3% in Sudan and 18.4% in Basra.[4,20,21] The high variability in the incidence can be attributed to cultural variations, socioeconomic circumstances, and differing cut-off points on the MDS scale used to detect MD.

We observed no direct association between MD and academic performance (represented by the GPA), contradicting our initial hypotheses. The current data in the literature is insufficient to establish any firm conclusion on this relationship. For example, Alenizi et al.[4] reported that students who engaged in MD had worse GPAs. Akhtar et al.[22] demonstrated a link between academic achievement and MD. However, in the study by Akhtar et al.[22], academic performance was measured using a more subjective question, such as "whether they perceived the effects of MD on their exam scores" rather than an objective criterion such as GPA. This difference in methodology may account for the inconsistency in results. We consider the evaluation of academic performance with the GPA to be more objective and, therefore, more representative of the correlation between MD and academic performance. Moreover, cultural context, institutional expectations, and individual coping capacities (i.e. last-minute effort or selective academic focus) likely play a role in shaping both daydreaming behaviors and academic outcomes.

Although the relationship between MD and academic performance is currently unknown, based on the findings mentioned earlier, we propose that a correlation between academic procrastination and MD does exist, i.e., MD increases academic procrastination, which may have a detrimental effect on academic achievement. This finding supports previous research suggesting that procrastination is associated with external distraction and the ability to control one's internal thoughts.[23] Earlier studies also indicate the presence of a link between procrastination and inadequate control over attention.[24] However, our findings suggest that this association may be more closely tied to the individual's ability to govern cognitive processes than environmental cues. The use of MD to avoid stressful situations and responsibilities suggests that scholastic procrastination could be a similar escape mechanism.[25] Excessive daydreaming can lead to poor time management and result in academic procrastination.

Academic procrastination has been linked to a decline in academic performance in prior studies.[26,27] Thus, upon realizing the intensity of the medical school curriculum, medical students may procrastinate more, especially with challenging tasks.[28] Individuals who procrastinate on their tasks have more difficulty sustaining attention, have higher distractibility, and increased reaction time variability.[29] The emergence of time management problems with increased academic procrastination and distraction may lead to worse academic performance. In addition, academic procrastination may lead to examination anxiety, which can negatively affect academic success.[6]

Previous studies have reported that MD often accompanies various psychopathologies, such as depressive disorders, anxiety disorders, and obsessive-compulsive and dissociative disorders.[30,31] Supporting these findings, we observed that the levels of anxiety, stress, and depression were higher in MD'ers. In light of our findings and the existing literature, the presence of a reciprocal relationship between MD and negative emotions can be suggested. For example, MD may be used as an emotional regulation strategy by generating positive emotions and avoiding negative emotions, distressing memories, and feelings of loneliness.[32] In addition, MD'ers tend to be more anxious and sensitive in their interpersonal relationships and tend to direct the focus of their difficulties more on themselves.[32] MD is an escape from the responsibilities and anxieties of the individual's daily life.[33] However, excessive involvement of such daydreams in daily life may lead the individual to ignore their problems, resulting in psychological conditions such as isolation and depression. Excessive use of MD to alleviate depression and anxiety can, therefore, lead to a vicious cycle.

Limitations

Although the current study produced essential data, it is crucial to recognize several limitations when interpreting these findings. Firstly, it's essential to remember that the study's cross-sectional design prevents assessing causal relationships between the variables. Furthermore, using self-report questionnaires for data collection raises the possibility of bias because of participant interpretations. Furthermore, the current study accounted for stress, anxiety, and depression, while additional variables that may be linked to MD, including personality characteristics, attention deficit hyperactivity disorder, and childhood trauma were not considered. Finally, the study's limited sample size restricts the broad applicability of the results.

CONCLUSION

As a result, our findings indicate that MD is linked not only to academic procrastination but also to depression, anxiety, and stress. This highlights the importance of considering internal cognitive processes, such as MD, when addressing procrastination behaviors that can negatively affect the academic functioning of medical students.

By systematically examining MD in a high-stress population like medical students, the present research addresses a largely understudied area. Incorporating both psychological distress and behavioral outcomes such as academic procrastination, it offers a comprehensive perspective that is often lacking in the existing literature. Moreover, the use of objective performance data (GPA) enhances the methodological rigor and fills a critical gap in prior research.

These findings can inform future longitudinal studies with larger samples and provide a valuable foundation for developing targeted intervention strategies aimed at reducing the academic and psychological burden of MD.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval was obtained from the Faculty of Medicine Ethics Committee approved the study at Karamanoğlu Mehmetbey University (Date: 19.12.2023, Decision No: 12-2023/03).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

External peer-reviewed.

Conflict of Interest Statement

The authors claimed no conflict of interest.

Financial Disclosure

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

Author Contributions

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

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Original Article

DOI: 10.38053/acmj.1649283

ANATOLIAN CURRENT MEDICAL

Anatolian Curr Med J. 2025;7(3):326-330

The role of Artificial Intelligence in Celiac disease support: analyzing ChatGPT's effectiveness for healthcare providers and patients

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Cite this article as: Polat YH, Cankurtaran RE. The role of Artificial Intelligence in Celiac disease support: analyzing ChatGPT's effectiveness for healthcare providers and patients. *Anatolian Curr Med J.* 2025;7(3):326-330.

Received: 01.03.2025 ◆ **Accepted**: 28.04.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: Celiac disease is a significant autoimmune disorder that affects a substantial portion of the population, necessitating accurate and reliable information for effective management. Despite its importance, there are currently no studies assessing the performance of Artificial Intelligence (AI) language models, such as ChatGPT, in providing information on this condition. This study aims to evaluates the reliability and usefulness of ChatGPT's responses to frequently asked questions regarding celiac disease, thereby filling a critical gap in understanding the capabilities of AI in this important healthcare context.

Methods: A total of 20 questions (10 for patients/caregivers and 10 for healthcare professionals) were prepared based on the most frequently searched queries about celiac disease using Google Trends. Responses generated by ChatGPT and scored by two independent Likert raters.

Results: The analysis revealed strong inter-rater reliability, with Cronbach's alpha values of α=0.839 for reliability and α=0.753 for usefulness, indicating robust agreement between raters. Notably, the highest reliability and usefulness scores for the patient and caregiver group were associated with questions on symptoms, the celiac disease diet, and gluten-free products. For the healthcare professionals group, key topics included diagnosis, pathological classification, and celiac disease comorbidities. Importantly, no significant differences were found between raters in the evaluation of reliability (p=0.939) and usefulness (p=0.102).

Conclusion: This study demonstrates that AI-based language models like ChatGPT can serve as reliable and useful resources for both patients and healthcare professionals seeking information about celiac disease. While the model excelled in addressing commonly discussed topics, it revealed limitations in handling complex issues, emphasizing the need for ongoing refinement of AI tools. These findings support the integration of AI in healthcare communication, highlighting its potential to enhance access to crucial health information while underscoring the importance of continual improvement to meet diverse user needs.

Keywords: Celiac disease, chatGBT, artificial intelligence

INTRODUCTION

Celiac disease (CD) is a chronic autoimmune disorder triggered by the consumption of gluten-containing foods, leading to damage in the small intestine. There has been a significant increase in the incidence of CD over the last 50 years. This increase is due to the detection of more new cases as a result of improved diagnostic tools and widespread screening of people at high risk. However, the vast majority of patients with CD remain undetected worldwide.[1] In Western countries, the prevalence of CD is approximately 0.6% when confirmed histologically and about 1% based on serological screening of the general population.[2] The primary treatment for this condition is the lifelong adherence to a strict gluten-free diet. Gluten, a protein found in wheat, barley and rye, damages the villi in the small intestine of people with CD, affecting the absorption of nutrients.[3] Strict compliance with a gluten-free diet is essential for alleviating symptoms and preventing long-term complications associated with the disease.[4] However, managing a gluten-free diet can be challenging, particularly in terms of daily food choices. It is crucial that both celiac patients and healthcare professionals have access to accurate and reliable information regarding CD.

In recent years, advancements in artificial intelligence (AI) technologies, such as natural language processing (NLP) and machine learning, have revolutionized access to health information.[5] AI-based tools have the potential to support healthcare by providing rapid and personalized information to both patients and professionals.[6] Various chatbots, such as Woebot, Your.MD, HealthTap, Cancer Chatbot, VitaminBot,

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Babylon Health, Safedrugbot, and Ada Health, are being utilized for a range of functions in the healthcare industry.[7]

Chat Generative Pre-trained Transformer (ChatGPT), developed by OpenAI and released in November 2022, is one of the most advanced examples of large language models (LLMs). As a large language model, ChatGPT can provide human-like responses based on vast amounts of learned data from various sources.[8] However, the effectiveness and reliability of AI-based tools, especially in the context of providing medical information, remain areas of active research.[9]

In the field of gastroenterology, many studies investigating the reliability of ChatGPT for many diseases have been published.[10,11] According to our research, we did not find any study in the literature measuring the reliability and usefulness of ChatGPT in CD disease.

In this study, we aimed to evaluate the reliability and usefulness of ChatGPT in relation to CD, a significant chronic illness expected to gain even more importance. Through this research, we sought to shed light on whether ChatGPT is a reliable resource from the perspectives of both patients and healthcare professionals.

METHODS

The study adhered to the ethical standards outlined in the Helsinki Declaration and complied with national regulations in the respective field. Ethics committee approval was not required as the study did not involve the use of human or animal data.

For this study, we focused on CD and identified specific questions relevant to the condition. A total of 20 questions were selected, with the first 10 based on Google Trends searches to capture the most common questions from patients. The remaining 10 questions were developed according to the latest guidelines[1,12] for healthcare professionals. Separate Google Trends searches were conducted on 26 August 2024 to identify the top search terms related to CD. Search trends for relevant terms were analysed based on global data from 2004 to the present within the Health sub-category. In the results, the "most relevant" option was selected from the "relevant questions" section. This analysis revealed the most frequently searched keywords on Google for CD. Repetitive keywords with similar meanings were filtered out. Based on these keywords, questions were formulated covering various aspects of the disease, including its characteristics, causes, symptoms, treatment options and dietary considerations. The next ten questions were intended for healthcare professionals. These questions were developed by two gastroenterologists.

The questions were entered into the prompt section of the ChatGPT AI chatbot. As the conversation progressed, different users rephrased the next question in separate sessions. This method was employed to ensure that the response to each question was not influenced by previous questions or answers. Each response was recorded in a separate file. The answers provided by ChatGPT-4 were sourced from the premium version available on 14 March 2023.

Each chatbot was rated on a scale of 1-7 (1 being the lowest, 7 being the highest) in two categories for reliability and usefulness.[13] These scales are presented in our study with a slight modification in **Table 1, 2**. All responses were assessed by two independent gastroenterology experts who were blinded to each other's responses to avoid potential bias.

Table 1. Reliability score

1. Completely unsafe: None of the information provided can be verified from medical sources or contains inaccurate and incomplete information.
2. Very unsafe: Most of the information cannot be verified from medical sources or are partially correct but contains important incorrect or incomplete information.
3. Relatively reliable: The majority of the information provided are verified from medical scientific sources, but there are some important incorrect or incomplete information.
4. Reliable: Most of the information provided are verified from medical scientific sources, but there are some minor inaccurate or incomplete information.
5. Relatively very reliable: Most of the information provided are verified from medical scientific sources, and there is very little incorrect or incomplete information.
6. Very reliable: Most of the information provided are verified from medical scientific sources, and there is almost no inaccurate or incomplete information.
7. Absolutely reliable : All of the information provided are verified from medical scientific sources, and there is no inaccurate or incomplete information or missing information.

Table 2. Usefulness score

1. Not useful at all: Unintelligible language, contradictory information, and missing important information. Not useful for users.
2. Very little useful: Partly clear language is used. Some important information are missing or incorrect. For users, limited use is possible.
3. Relatively useful: Clear language is used. Most important information are mentioned, but some important information are incomplete or incorrect. Useful for users.
4. Partly useful: Clear language is used. Some important information are missing or incorrect, but most important information are addressed. Somewhat useful for users.
5. Moderately useful: Clear language is used and most important information are covered, but some important information are still incomplete or incorrect. Useful for users.
6. Very useful: Clear language is used. All important information are mentioned, but some unimportant information or details are also mentioned. Very useful for users.
7. Extremely useful: Clear language is used and all important information are mentioned. Extremely useful to users, and additional information and resources are also provided.

Statistical Analysis

The statistical analyses were performed using Statistical Package for the Social Sciences (SPSS 25.0 for Windows; IBM, Armonk, NY, USA) software package. The inter-rater compliance was assessed with Cronbach α and 95% confidence intervals (CI). According to intraclass correlation coefficient results, positive values ranging from 0 to 0.2 indicate poor agreement; 0.2 to 0.4 indicate fair agreement; 0.4 to 0.6 indicate moderate agreement; 0.6 to 0.8 indicate good agreement; and 0.8 to 1 indicate very good agreement. The variables were evaluated using the Shapiro-Wilk test to determine whether or not they exhibited a normal distribution. In descriptive statistics, the data were expressed as mean±standard

deviation (SD). Independent t test was used to compare two groups difference and statistically significant difference among the groups was performed by analysis of variance test. The significance level for this study was set at p<0.05.

RESULTS

In total, 20 different questions were presented to the OpenAI chatbot. The first ten questions were for CD patients and carers and the next ten questions were highly specific for medical professionals in terms of CD. The supplementary material of the study contains a comprehensive list of all questions and their corresponding answers.

We had two experts evaluate the responses given by ChatGPT on CD. The results of the evaluation for questions related to reliability and usefulness are shown in **Table 3, 4** respectively.

Table 3. Distribution, comparison, and agreement of inter-rater reliability scores

	Rater#1	Rater#2	Cronbach's α (95% CI lower-upper)
1. What's CD?	5	5	0.789 (0.152-0.948)
2. Causes	5	5	
3. Symptoms	6	6	
4. CD diet	6	6	
5. Treatment	5	6	
6. Safe snacks	5	6	
7. Gluten free products	6	6	
8. Exercise and lifestyle	5	5	
9. Vitamin and suplements	6	6	
10. Alcohol consumption	6	6	
11. Diagnose	6	5	
12. Pathological classification	5	5	
13. Association with other diseases	4	4	
14. Pregnancy	5	5	
15. Complications	5	4	0.625 (0.510-0.907)
16. Genetic alleles	5	5	
17. Treatments	5	4	
18. CD and IBS	4	5	
19. CD and drugs	4	4	
20. CD and lactose intolerance	4	4	

CI: Confidence intervals, CD: Celiac disease, IBS: Irritable Bowel syndrome

Inter-rater Cronbach α values for reliability and usefulness total scores between raters showed good and very good agreement (α=0.839 and α=0.753, respectively).

The question topics were rated using Likert scores ranging from 3 to 7.

In terms of topics, the highest reliability score for patient and caregiver group was for both raters: point 6 (rater 1: symptoms, CD diet,gluten free products, vitamin and suplements, alcohol consumption ; rater 2: symptoms, CD diet, treatment, safe snacks, gluten free products, vitamin and suplements, alcohol consumption) and the highest reliability score for proffesionals group was for rater 1: point 6 and was for rater

Table 4. Distribution, comparison, and agreement of inter-rater usefulness scores

	Rater#1	Rater#2	Cronbach's α (95% CI lower-upper)
1. What's CD?	6	6	0.691 (0.243-0.923)
2. Causes	6	5	
3. Symptoms	7	7	
4. CD diet	7	6	
5. Treatment	6	5	
6. Safe snacks	6	6	
7. Gluten free products	7	6	
8. Exercise and lifestyle	6	6	
9. Vitamin and suplements	7	6	
10. Alcohol consumption	6	6	
11. Diagnose	6	6	
12. Pathological classification	6	5	
13. Association with other diseases	5	5	
14. Pregnancy	6	6	0.640 (0.449-0.911)
15. Complications	5	6	
16. Genetic alleles	6	5	
17. Treatments	6	6	
18. CD and IBS	6	6	
19. CD and drugs	5	5	
20. CD and lactose intolerance	5	4	

CI: Confidence intervals, CD: Celiac disease, IBS: Irritable Bowel syndrome

2: point 5 (rater 1: diagnose ; rater: 2: diagnose, pathological classification, pregnancy, genetic alleles, CD and IBS). The highest usefullness score for patient and caregiver group was for both raters: point 7 (rater 1: symptoms, CD diet,gluten free products, vitamin and suplements; rater 2: symptoms) and the highest usefullness score for proffesionals group was for both raters point 6 (rater 1: diagnose, pathological classification, pregnancy, genetic alleles, CD and IBS; rater: 2: diagnose, pregnancy, complications, treatments, CD and IBS).

In terms of topics, the lowest reliability score for patient and caregiver group was for both raters point 5 (rater 1: what's CD?, causes, treatment, safe snacks, exercise and lifestyle ; rater 2: what's CD?, causes, exercise and lifestyle) and the lowest reliability score for proffesionals group was for both raters point 4 (rater 1: association with other diseases, CD and IBS, CD and drugs, CD and lactose intolerance ; rater: 2: association with other diseases, complications, treatments, CD and drugs, CD and lactose intolerance). The lowest usefullness score for patient and caregiver group was for rater 1 point 6 was for rater 2 point 5 (rater 1: what's CD?, causes, treatment, safe snacks, exercise and lifestyle, alcohol consumption ; rater 2: causes, treatment) and the lowest usefullness score for proffesionals group was for rater 1 point 5 was for rater 2 point 4 (rater 1: association with other diseases, complications, CD and drugs, CD and lactose intolerance ; rater: 2: CD and lactose intolerance).

The total scores of the topics and their evaluation by each rater are shown in **Table 5** and **Figure**. There was

no significant difference between the reliability (rater#1 mean:5.10±0.71, rater#2 mean:5.10±0.78) and usefulness (rater#1 mean:6.0±0.64, rater#2 mean:5.65±0.67) total scores of both raters (p=0.939 and p=0.102, respectively).

Table 5. Comparison of the reliability and usefulnes total scores of resources according to patients and professonals

	For patients	For professionals	p
Rater #1			
Reliability	5.50±0.52	4.70±0.67	0.008
Usefulness	6.40±0.51	5.60±0.51	0.003
Rater #2			
Reliability	5.70±0.48	4.50±0.52	0.001
Usefulness	5.90±0.56	5.40±0.69	0.049
Reliability p	0.388	0.470	
Usefulness p	0.054	0.476	

*Mean±standard deviation, independent t test

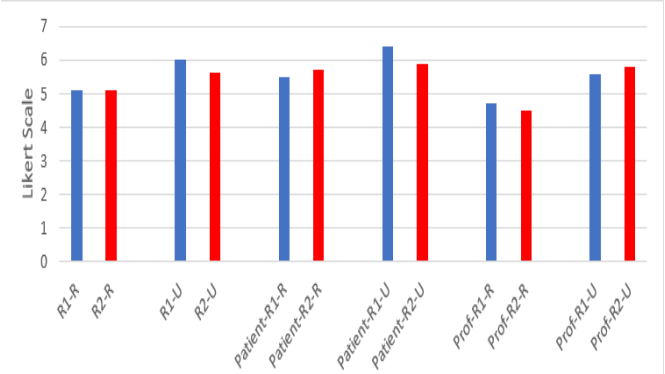

Figure. Total reliability and usefullness scores and scores according to patients, professionals and raters distribution

R: Reliability, U: Usefullness, Prof: Professionals

DISCUSSION

This study evaluated the reliability and usefulness of responses provided by an AI-based language model, ChatGPT, to common questions about CD posed by two distinct groups: patients and caregivers, and healthcare professionals. The results demonstrate that ChatGPT's responses were rated with high inter-rater reliability and usefulness, as evidenced by Cronbach's alpha values of 0.839 for reliability and 0.753 for usefulness. These findings indicate a good to very good level of agreement between raters, confirming that the AI model consistently provided information that was both accurate and relevant.

Reliability and Usefulness of Responses

The analysis showed that the highest reliability and usefulness scores for the patient and caregiver group were consistently awarded for responses addressing common topics such as symptoms, the CD diet, gluten-free products, and the role of vitamins and supplements. This is an indication that ChatGPT was effective in addressing topics that are frequently discussed in public health resources and are central to patient education.[4,14] In contrast, the lowest reliability scores were observed for more general questions, such as "What is CD?" and questions about causes and lifestyle, reflecting potential gaps in how the AI model synthesizes more foundational or lifestyle-related information. This is consistent with previous studies highlighting AI models' variable performance when addressing nuanced or highly specialized information.[15]

For the healthcare professionals group, the highest reliability scores were seen in responses related to diagnostic processes, pathological classification, and the interplay between CD and other gastrointestinal conditions, such as irritable bowel syndrome (IBS). This underscores ChatGPT's strength in addressing medically technical content, likely because such topics are well-documented and discussed in the medical literature.[16] However, reliability and usefulness dropped when the topics involved complex, multi-faceted issues, such as the association between CD and other diseases or lactose intolerance. This trend might reflect the inherent limitations of current AI models in dealing with interdisciplinary or comorbid conditions, which often require a more integrative understanding of disease pathophysiology.[17]

Inter-Rater Consistency

The absence of a significant difference between raters regarding both reliability and usefulness (p=0.939 and p=0.102, respectively) suggests that the AI model's performance was consistent across evaluators with different expertise. This finding is important, as it indicates that the content generated by ChatGPT is perceived similarly by healthcare professionals, regardless of individual biases or interpretative differences. High Cronbach alpha values further reinforce the robustness of these assessments, aligning with previous studies on the reliability of AI-generated content in healthcare settings.[18,19]

Limitations and Future Directions

Despite the promising results, several limitations should be acknowledged. Firstly, while the AI model performed well on well-defined and frequently discussed topics, it showed limitations in providing comprehensive answers to more complex questions, particularly those involving comorbidities or nuanced lifestyle modifications. Future versions of AI tools may benefit from incorporating more diverse training datasets that include interdisciplinary research and guidelines for managing chronic diseases like CD with associated conditions.

Moreover, this study focused on the evaluation of AI responses in the context of CD, a specific and relatively well-documented condition. Generalizability to other chronic diseases remains to be studied. Future research should also examine the impact of AI-generated information on patient outcomes, including how well patients adhere to medical advice received from such tools.

In addition to these limitations, it is important to highlight the ethical considerations associated with the use of AI in healthcare settings. Issues such as accountability for incorrect or harmful advice, the protection of patient privacy, and the necessity for informed consent regarding the use of AI-generated content remain areas of ongoing debate. The absence of clear legal frameworks regulating the medical application of AI systems raises questions about liability, particularly in scenarios where AI-generated suggestions may contribute to adverse patient outcomes. Given these uncertainties,

AI-based tools like ChatGPT should be viewed strictly as supportive educational resources rather than replacements for professional medical judgment.

Furthermore, while AI models can efficiently synthesize well-documented medical knowledge, their use should always be supervised by qualified healthcare professionals, especially when clinical decision-making is involved. Without appropriate oversight, there is a risk that users—whether patients or providers—might misinterpret AI outputs as authoritative medical advice, which could inadvertently affect treatment decisions or health behaviors. These considerations emphasize the need for cautious integration of AI technologies into healthcare, ensuring that their implementation remains ethically sound and clinically responsible.

CONCLUSION

This study provides valuable insights into the potential of AI-based tools, such as ChatGPT, to serve as reliable and useful resources for both patients and healthcare professionals in the context of CD. While AI models are still evolving, they hold significant promise in enhancing access to health information, especially when used to complement traditional healthcare resources. Continued research is necessary to refine these systems and ensure they meet the evolving needs of patients and healthcare providers alike.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since the study did not involve the use of human or animal data, ethics committee approval was not necessary.

Informed Consent

Since the study did not involve the use of human data, informed consent was not necessary.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1684580

Anatolian Curr Med J. 2025;7(3):331-337

The effect of health literacy on spinal surgery decision in neurosurgery patients

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Cite this article as: Saraç ME, Boğa Z. The effect of health literacy on spinal surgery decision in neurosurgery patients. *Anatolian Curr Med J.* 2025;7(3):331-337.

Received: 26.04.2025 ◆ **Accepted**: 05.05.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: The aim of the study was to determine how health literacy affects Turkish neurosurgery patients' spine surgery preferences and to identify barriers to obtaining informed consent and thus create better patient education methods.

Methods: The research included 118 patients who visited the neurosurgery outpatient clinic for spinal complaints. The Turkish Health Literacy Scale (TSOY-32) was used to evaluate patients who received four different health literacy assessments: inadequate (23.7%), problematic (36.4%), sufficient (28.8%), and excellent (11.0%).

Results: Patients who demonstrated better health literacy showed decreased acceptance of surgical procedures (82.1% inadequate vs. 46.2% excellent, p=0.023) and increased second opinion seeking (25.0% vs. 69.2%, p<0.001). The logistic regression analysis demonstrated that patients with sufficient and excellent health literacy showed 72% and 81% decreased odds of accepting surgery when compared to patients with inadequate literacy. The factors that influenced patient choices depended on their literacy level because physician recommendations proved more significant for patients with low literacy (92.9% vs. 53.8%, p=0.008) and personal research became more important for patients with high literacy (25.0% vs. 92.3%, p<0.001). The study found that education level strongly correlated with health literacy (r=0.72, p<0.001) and health literacy strongly correlated with decision satisfaction (r=0.59, p<0.001).

Conclusion: The research demonstrates that health literacy assessment during surgical consultations combined with specific communication approaches helps patients make informed decisions in neurosurgical practice.

Keywords: Health literacy, neurosurgery, patient decision-making, spinal surgery

INTRODUCTION

Spinal disorders create substantial health burdens worldwide because they lead to low back pain and other musculoskeletal disorders which rank as major causes of disability-adjusted life years (DALYs) in 204 countries from 1990 to 2019.[1] The process of choosing spinal surgery requires careful evaluation because excessive surgical procedures in certain areas do not always produce better results thus necessitating thorough evaluation of indications and patient selection to prevent unneeded interventions.[2] Health literacy functions as a vital element which enables people to acquire and process health information and understand and share health knowledge to make knowledgeable healthcare decisions.[3] Health literacy deficits make it harder for patients to grasp anesthesia procedures and their associated dangers because research indicates that better education does not eliminate fears about pain or losing consciousness.[4]

Research has shown growing interest in the connection between health literacy and surgical decision-making during the last few years. Studies demonstrate that surgical patients frequently have poor health literacy which leads to inadequate understanding of perioperative information and non-compliance with preoperative instructions and unequal access to procedures such as kidney transplantation.[5] The understanding of surgical procedures and discharge instructions by patients with limited health literacy becomes difficult in orthopedic surgery which may influence treatment decisions and patient satisfaction with results.[6] The Turkish healthcare system has made progress in patient autonomy and shared decision-making yet research shows that more than half of the population lacks sufficient health literacy which creates obstacles for patient education and participation.[7] The problem of low health literacy affects neurosurgery most severely because it prevents patients from making informed decisions and creates healthcare inequities and worsens surgical results but researchers have not developed sufficient interventions to address this issue.[8]

The research aims to determine how health literacy affects Turkish neurosurgery patients' spine surgery preferences and to identify barriers to obtaining informed consent and thus create better patient education methods. The research results

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will provide essential information for clinical practice and policy development and future healthcare delivery research in this vital field.

METHODS

Ethics

The Scientific Researches Ethics Committee of Adana City Training and Research Hospital approved this study (Date: 10.04.2025, Decision No: 427). The study required all participants to sign written informed consent before joining the research. The analysis of data included anonymization and coding procedures to protect patient privacy. The research team maintained data security through password-protected computers which they accessed exclusively. The research followed both the Declaration of Helsinki principles and Good Clinical Practice guidelines.

Study Population and Sample

The research took place at the Neurosurgery Outpatient Clinic of Adana City Training and Research Hospital. The required sample number was determined by G*power software version 3.1.9.7 which used an effect size of 0.30 and α error probability of 0.05 and power of 0.90 to calculate 112 patients as the minimum sample size. The researchers selected 118 patients to ensure enough participants would complete the survey. A total of 135 patients were initially assessed for eligibility, with 17 patients excluded based on the predefined criteria (**Figure 1**). The study included patients who were at least 18 years old and had spinal complaints while being Turkish speakers and mentally competent to fill out the questionnaire. The study excluded patients with dementia and severe psychiatric conditions as well as those who were under 18 years old and non-Turkish speakers and patients with non-spinal neurosurgical complaints. The most common reasons for exclusion were non-spinal neurosurgical complaints (n=5), severe psychiatric disorders (n=4), dementia (n=3), declined participation (n=3), and non-Turkish speaking status (n=2) (**Figure 1**). The Turkish Health Literacy Scale (TSOY-32) assessed health literacy through its measurement of health information access and understanding and appraisal and application abilities. Following assessment, patients were categorized into four health literacy levels: inadequate (n=28), problematic (n=43), sufficient (n=34), and excellent (n=13) (**Figure 1**). The definition of spinal surgery decision referred to the patient's decision to either accept or decline the proposed surgical treatment.

Study Procedures

The data collection involved two sections of the questionnaire which researchers administered through personal interviews at the outpatient clinic. The first section included sociodemographic details (age, gender, education level, marital status, employment status, income level) together with clinical patient information. The TSOY-32 served as the second part of the assessment which uses 32 validated items from the European Health Literacy Survey Questionnaire (HLS-EU-Q). TSOY-32 evaluates four dimensions of health literacy: accessing information, understanding information, appraisal of information, and application of information. The

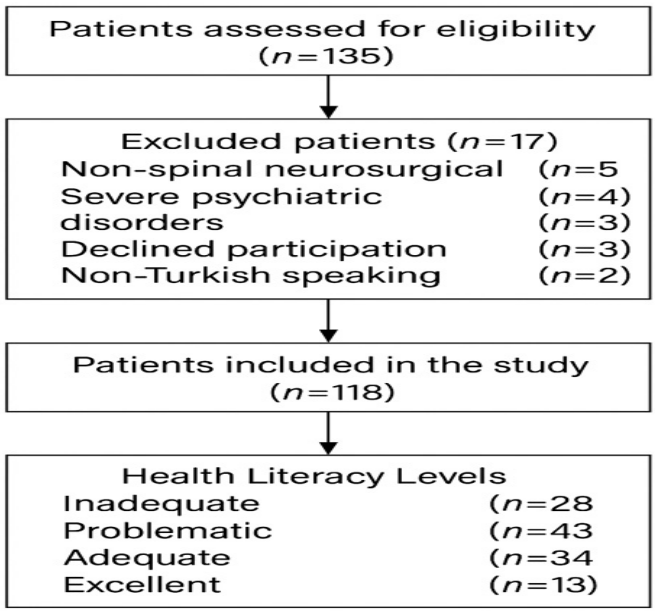

Figure 1. Patient flow diagram: recruitment, exclusion, and classification of study participants

Likert scale used for each item ranges from 1 (very difficult) to 5 (very easy). The scale achieved excellent internal consistency through previous validation studies which reported a Cronbach's alpha coefficient of 0.92 and our study population obtained 0.89. The survey included questions about factors affecting spinal surgery choices as well as surgical concerns and patient satisfaction with their decision-making process. The data collection was performed by two trained research assistants who allowed patients to fill out questionnaires either independently or with help when needed.

Surgical Decision Protocol

The patients received their health literacy scores which placed them into four categories: inadequate (0-25 points), problematic-limited (26-33 points), sufficient (34-42 points) and excellent (43-50 points). All patients had been evaluated by neurosurgeons for spinal complaints and had received a recommendation regarding potential surgical intervention. The surgical decision process was standardized across all participants, consisting of a clinical examination, review of imaging studies (MRI and/or CT scans), and a detailed explanation of the diagnosis, treatment options (conservative management versus surgery), expected outcomes, and potential complications. No randomization was performed as this was an observational study examining the relationship between existing health literacy levels and surgical decision-making. All surgical recommendations were made according to standard clinical practice guidelines by board-certified neurosurgeons with at least five years of experience in spinal procedures.

Statistical Analysis

The data analysis was conducted through SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). The analysis included descriptive statistics for all variables which presented continuous data as mean (SD) and categorical data as frequency and percentage. The Kolmogorov-Smirnov test evaluated the normal distribution of the data. The comparison between

health literacy groups used one-way ANOVA with post-hoc Tukey test for normally distributed continuous variables and Chi-square test for categorical variables. Pearson's correlation coefficient analyzed the relationship between health literacy scores and other continuous variables. The analysis used binary logistic regression to identify independent factors that influenced spinal surgery acceptance after controlling for confounding variables. The analysis of missing data (less than 3% overall) used pairwise deletion. The research performed subgroup analyses to study how education level affects health literacy and surgical decision processes. The statistical significance threshold was set at $p<0.05$ while reporting actual p values to two decimal places for $p\geq0.01$ and to three decimal places for $0.001\leq p<0.01$. The research reported p values below 0.001 as such without showing the actual numerical value.

RESULTS

The research involved 118 participants whose average age was 54.3±15.7 years with female participants outnumbering males by 53.4% to 46.6%. The demographic characteristics differed significantly across health literacy groups, with patients in the inadequate health literacy group being older (58.7±16.2 years) compared to those with excellent health literacy (49.2±13.9 years, p=0.041). The educational attainment of participants showed primary school graduates as the biggest group at 31.4% followed by high school at 26.3% and middle school at 22.0% and university or higher education at 20.3%. A strong association was observed between education level and health literacy, with 64.3% of patients with inadequate literacy having only primary education, while 76.9% of those with excellent literacy had university education (p<0.001). The majority of patients were married (66.1%), and regarding employment status, 43.2% were employed while 35.6% were retired. Employment status also varied significantly across health literacy groups, with higher employment rates observed in patients with sufficient (52.9%) and excellent (61.5%) health literacy compared to those with inadequate literacy (28.6%, p=0.033). The middle income level was reported by 49.2% of participants while 38.1% had low income and 12.7% had high income. Income level was also significantly associated with health literacy, as patients with excellent health literacy were more likely to report high income (30.8%) compared to those with inadequate literacy (3.6%, p=0.027) (**Table 1**).

Analysis of health literacy levels revealed that over half of the participants had limited health literacy, with 23.7% scoring in the inadequate category and 36.4% in the problematic-limited category. Only 28.8% demonstrated sufficient health literacy, while merely 11.0% achieved excellent literacy scores. The mean health literacy score across all participants was 35.8±9.4. Examination of health literacy sub-dimensions showed consistent patterns, with scores progressively increasing from inadequate to excellent literacy groups across all four domains: access to information, understanding information, appraisal, and application (**Table 2**).

The decision-making process of patients regarding spinal surgery depended heavily on their health literacy abilities. The physician recommendations proved to be the most powerful influence in total patient decisions (81.4%) yet their impact diminished when health literacy improved from inadequate to excellent (92.9% vs. 53.8%, p=0.008). The importance of personal research grew more significant as health literacy levels increased (25.0% for inadequate vs. 92.3% for excellent, p<0.001). People with lower health literacy relied more on opinions from family and friends when making decisions (75.0% for inadequate vs. 30.8% for excellent, p=0.004). The ability to access and understand health information demonstrated a strong positive relationship with literacy levels as shown by correlation coefficients of r=0.76 and r=0.72 (p<0.001) (**Table 3**).

Regarding surgery decisions, acceptance rates declined as health literacy increased, from 82.1% among those with inadequate literacy to 46.2% in the excellent category (p=0.023). Correspondingly, patients with higher health literacy were more likely to seek second opinions (25.0% for inadequate vs. 69.2% for excellent, p<0.001). Concerning surgical worries, patients with higher literacy levels were significantly more concerned about complications (57.1% for inadequate vs. 84.6% for excellent, p=0.042) and recovery periods, though less concerned overall as indicated by lower mean concern scores (4.2 for inadequate vs. 3.3 for excellent, p=0.003) (**Table 4**).

The research showed that education level directly correlated with health literacy because scores rose substantially with each level of education (26.4±7.2 for primary school vs. 46.3±4.5 for university graduates, p<0.001, r=0.72). Patient satisfaction with surgical decisions showed a positive relationship with health literacy levels because scores rose from 6.2±2.1 in the inadequate group to 9.2±1.1 in the excellent group (p<0.001, r=0.59) (**Table 5**).

The results of logistic regression analysis showed that better health literacy was linked to decreased odds of accepting spinal surgery after controlling for demographic variables. Patients who had sufficient literacy compared to those in the inadequate literacy reference group showed 72% reduced odds of accepting surgery (OR=0.28, p=0.029) and those with excellent literacy showed 81% reduced odds (OR=0.19, p=0.017). The odds of surgery acceptance increased by 37% with every 10-year age increment (OR=1.37, p=0.015). The associations between education and income levels and lower acceptance rates showed trends but failed to achieve statistical significance (**Figure 2**).

DISCUSSION

The research analyzed the essential connection between health literacy and spinal surgery decision processes among neurosurgery patients. The research showed that patients with better health literacy skills made their surgical decisions independently while those with limited literacy depended more on physician guidance. Patients who had excellent health literacy needed physician recommendations less often and performed their own research better and avoided surgical interventions more frequently than patients with inadequate literacy. The research indicates that better health literacy enables patients to feel more confident about seeking medical information which leads to active participation in their care decisions and reduced total anxiety levels even though they become more aware of surgical risks.

Table 1. Demographic characteristics according to health literacy levels

Characteristic	Total (n=118)	Inadequate (n=28)	Problematic (n=43)	Sufficient (n=34)	Excellent (n=13)	p-value*
Age (years)	54.3±15.7	58.7±16.2	55.4±15.5	52.3±14.8	49.2±13.9	0.041
Gender						0.832
Female	63 (53.4%)	16 (57.1%)	24 (55.8%)	17 (50.0%)	6 (46.2%)	
Male	55 (46.6%)	12 (42.9%)	19 (44.2%)	17 (50.0%)	7 (53.8%)	
Education level						<0.001
Primary school	37 (31.4%)	18 (64.3%)	16 (37.2%)	3 (8.8%)	0 (0.0%)	
Middle school	26 (22.0%)	7 (25.0%)	15 (34.9%)	4 (11.8%)	0 (0.0%)	
High school	31 (26.3%)	3 (10.7%)	10 (23.3%)	15 (44.1%)	3 (23.1%)	
University/higher	24 (20.3%)	0 (0.0%)	2 (4.7%)	12 (35.3%)	10 (76.9%)	
Marital status						0.214
Single	19 (16.1%)	3 (10.7%)	6 (14.0%)	7 (20.6%)	3 (23.1%)	
Married	78 (66.1%)	18 (64.3%)	30 (69.8%)	22 (64.7%)	8 (61.5%)	
Divorced	13 (11.0%)	3 (10.7%)	4 (9.3%)	4 (11.8%)	2 (15.4%)	
Widowed	8 (6.8%)	4 (14.3%)	3 (7.0%)	1 (2.9%)	0 (0.0%)	
Employment status						0.033
Employed	51 (43.2%)	8 (28.6%)	17 (39.5%)	18 (52.9%)	8 (61.5%)	
Retired	42 (35.6%)	14 (50.0%)	16 (37.2%)	9 (26.5%)	3 (23.1%)	
Unemployed	25 (21.2%)	6 (21.4%)	10 (23.3%)	7 (20.6%)	2 (15.4%)	
Income level						0.027
Low	45 (38.1%)	15 (53.6%)	18 (41.9%)	10 (29.4%)	2 (15.4%)	
Middle	58 (49.2%)	12 (42.9%)	21 (48.8%)	18 (52.9%)	7 (53.8%)	
High	15 (12.7%)	1 (3.6%)	4 (9.3%)	6 (17.6%)	4 (30.8%)	

*p-values were calculated using Chi-square test for categorical variables and one-way ANOVA for continuous variables

Table 2. Health literacy levels and sub-dimensions according to TSOY-32 scale

Parameter	Total (n=118)	Inadequate (n=28)	Problematic (n=43)	Sufficient (n=34)	Excellent (n=13)	p-value*
Health literacy level	n (%)	28 (23.7%)	43 (36.4%)	34 (28.8%)	13 (11.0%)	-
Mean score±SD	35.8±9.4	22.4±3.8	31.7±2.6	42.3±3.5	48.9±2.2	<0.001
Sub-dimensions						
Access to information	8.6±2.7	5.2±1.9	7.8±1.5	10.4±1.3	12.7±0.8	<0.001
Understanding information	9.1±2.5	5.7±1.7	8.5±1.3	10.9±1.1	13.1±0.6	<0.001
Appraisal	8.9±2.8	5.4±1.8	7.9±1.6	10.7±1.2	12.9±0.7	<0.001
Application	9.2±2.6	6.1±1.8	8.6±1.4	11.1±1.0	13.2±0.5	<0.001

All values are presented as Mean±SD unless otherwise noted. SD: Standard deviation. p-values were calculated using ANOVA with post-hoc Tukey test. TSOY-32 scale: Turkish Health Literacy Scale

Table 3. Factors influencing spinal surgery decision and information access comfort

Parameter	Total (n=118)	Inadequate HL (n=28)	Problematic HL (n=43)	Sufficient HL (n=34)	Excellent HL (n=13)	p-value*
Decision factors	**n (%)**					
Physician's recommendation	96 (81.4%)	26 (92.9%)	38 (88.4%)	25 (73.5%)	7 (53.8%)	0.008
Personal research	67 (56.8%)	7 (25.0%)	21 (48.8%)	27 (79.4%)	12 (92.3%)	<0.001
Family/friends opinions	72 (61.0%)	21 (75.0%)	31 (72.1%)	16 (47.1%)	4 (30.8%)	0.004
Media information	43 (36.4%)	12 (42.9%)	19 (44.2%)	9 (26.5%)	3 (23.1%)	0.184
Other factors	15 (12.7%)	2 (7.1%)	5 (11.6%)	5 (14.7%)	3 (23.1%)	0.512
Information comfort	**Mean±SD**					
Comfort in accessing information (1-5)	2.9±1.1	1.8±0.7	2.6±0.8	3.5±0.7	4.2±0.6	<0.001
Comfort in understanding information (1-5)	2.7±1.2	1.6±0.6	2.3±0.7	3.4±0.8	4.1±0.7	<0.001

HL: Health literacy, SD: Standard deviation. Multiple responses were allowed for decision factors. p-values were calculated using Chi-square test for frequencies and ANOVA for mean scores. Correlation between HL and comfort in accessing information: r=0.76, p<0.001; correlation between HL and comfort in understanding information: r=0.72, p<0.001.

Table 4. Spinal surgery decisions and concerns according to health literacy levels

Parameter	Total (n=118)	Inadequate HL (n=28)	Problematic HL (n=43)	Sufficient HL (n=34)	Excellent HL (n=13)	p-value*
Surgery decisions, n (%)						
Surgery acceptance	80 (67.8%)	23 (82.1%)	32 (74.4%)	19 (55.9%)	6 (46.2%)	0.023
Surgery rejection	38 (32.2%)	5 (17.9%)	11 (25.6%)	15 (44.1%)	7 (53.8%)	0.023
Seeking second opinion	51 (43.2%)	7 (25.0%)	14 (32.6%)	21 (61.8%)	9 (69.2%)	<0.001
Surgical concerns, n (%)						
Complications	87 (73.7%)	16 (57.1%)	31 (72.1%)	29 (85.3%)	11 (84.6%)	0.042
Pain	92 (78.0%)	22 (78.6%)	36 (83.7%)	25 (73.5%)	9 (69.2%)	0.561
Recovery period	76 (64.4%)	14 (50.0%)	26 (60.5%)	25 (73.5%)	11 (84.6%)	0.077
Cost	64 (54.2%)	17 (60.7%)	25 (58.1%)	16 (47.1%)	6 (46.2%)	0.556
Time off work	59 (50.0%)	9 (32.1%)	21 (48.8%)	20 (58.8%)	9 (69.2%)	0.061
Mean concern level (1-5)	3.8±0.9	4.2±0.8	3.9±0.9	3.6±0.8	3.3±0.7	0.003

HL: Health literacy. p-values were calculated using Chi-square test for frequencies and ANOVA for mean concern level

Table 5. Relationship between education level, health literacy, and patient satisfaction

Parameter	Health literacy score (mean±SD)	Satisfaction score (mean±SD)	p-value*
Education level			
Primary school (n=37)	26.4±7.2	6.7±2.0	<0.001
Middle school (n=26)	32.6±6.8	7.4±1.9	<0.001
High school (n=31)	39.7±5.9	8.1±1.6	<0.001
University/higher (n=24)	46.3±4.5	8.7±1.4	<0.001
Health literacy level			
Inadequate (n=28)	22.4±3.8	6.2±2.1	<0.001
Problematic-limited (n=43)	31.7±2.6	7.3±1.8	<0.001
Sufficient (n=34)	42.3±3.5	8.5±1.5	<0.001
Excellent (n=13)	48.9±2.2	9.2±1.1	<0.001
Total (n=118)	35.8±9.4	7.6±2.0	-

SD: Standard deviation. p-values were calculated using ANOVA with post-hoc Tukey test. All pairwise comparisons between education levels were statistically significant (p<0.05). Correlation between education level and health literacy: r=0.72, p<0.001; correlation between health literacy and satisfaction: r=0.59, p<0.001

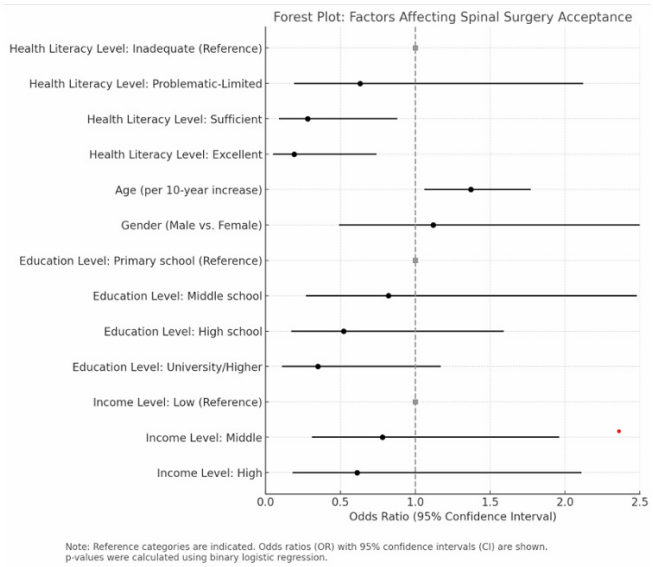

Figure 2. Forest plot of factors affecting spinal surgery acceptance: Odds ratios (OR) with 95% confidence intervals (CI) are displayed for each variable. Reference categories (Health literacy level: Inadequate, Education level: Primary school, Income level: Low) are indicated with grey squares.

CI: Confidence interval; OR: Odds ratio

The research established that health literacy acts as a determining factor for spinal surgery choices made by patients. The study shows that patients who have excellent health literacy tend to reject surgical interventions at a rate of 46.2% compared to 82.1% of those with inadequate health literacy (p=0.023). Research has demonstrated that health literacy functions as a crucial factor for orthopedic surgery patients to comprehend surgical procedures.[6] The results from logistic regression analysis showed that patients with sufficient health literacy had a 72% lower chance of accepting surgery (OR=0.28, p=0.029) and patients with excellent health literacy had an 81% lower chance (OR=0.19, p=0.017) than those with inadequate health literacy. Shahid et al.[9] observed that patients who lack sufficient health literacy experience difficulties when handling surgical or medical treatment procedures and making knowledgeable decisions. The research conducted by Muscat et al.[10] demonstrates that patients who use health literacy-specific decision support tools make better informed treatment choices. The research indicates that patients with high health literacy can evaluate surgical treatment choices more effectively and investigate additional treatment possibilities.

Our research revealed separate elements that affect surgical choices between patients with different health literacy abilities. Patients with low health literacy depended more on physician recommendations (92.9% inadequate vs. 53.8% excellent, p=0.008) and family/friend opinions (75.0% inadequate vs. 30.8% excellent, p=0.004) but personal research (25.0% inadequate vs. 92.3% excellent, p<0.001) was the most important factor for those with high health literacy. The results match those found by Aleid et al.[11] who discovered a positive relationship between health literacy and patient decision-making autonomy (r=0.852, p<0.001). The research showed that patients with higher health literacy levels became more likely to obtain additional medical opinions (25.0% inadequate vs. 69.2% excellent, p<0.001). The study by Gandhi et al.[12] shows that expert opinion stands as a primary consideration for anticoagulation initiation decisions following spinal surgery with a mean importance score of 3.2±1.3. According to Liang et al.[13] doctors believe they should base their decisions on their professional judgment rather

than patient preferences which might explain why low health literacy patients follow physician advice. The results show that better health literacy enables patients to feel more comfortable accessing information and understanding it which leads to increased decision-making autonomy.

Health literacy levels determine the specific concerns patients express about their surgery. Patients who had excellent health literacy showed increased worry about surgical complications and recovery steps but displayed lower anxiety scores (4.2 inadequate vs. 3.3 excellent on a 1-5 scale, p=0.003). The teach-back method described by Seely et al.[14] helps patients understand surgical procedures and risks better which leads to decreased anxiety about the surgical process. Zhu et al.[15] demonstrated that large language model information helps patients feel less anxious about their treatment choices and life expectancy outcomes. Baradaran et al.[16] demonstrated that patient education combined with effective communication serves as a crucial factor to decrease preoperative anxiety in spine surgery patients. The relationship between health literacy and decision satisfaction showed a strong positive correlation in our study (r=0.59, p<0.001) which matched Seely et al.'s[14] results about teach-back method participation leading to better decision satisfaction.

The research reveals that education level shows a powerful connection to health literacy (r=0.72, p<0.001). The research outcome matches Berete et al.'s[17] discovery about the link between low education and insufficient health literacy (OR 1.69, 95% CI: 1.53-1.86, p<0.001). Turhan et al.[18] discovered a weaker relationship between education level and health literacy (r=0.37, p<0.05). Theiss et al.[19] discovered no meaningful relationship between education level and health literacy in colorectal surgery patients (p>0.05). The logistic regression analysis revealed that education level no longer had a statistically significant effect on surgical acceptance rates after controlling for health literacy. Health literacy acts as a partial mediator between education level and health behaviors and health outcomes according to Berete et al.[17] who found that it explains 3.8-16.0% of the total effect. Health literacy emerges as a vital factor for surgical choices and health decision-making because it stands alone from education level and benefits patients with limited education.

Limitations

Our research contains several limitations which need to be acknowledged. The single-center study conducted at a tertiary hospital restricts the ability to generalize findings to different healthcare facilities and socioeconomic settings. The cross-sectional research design makes it impossible to determine whether health literacy causes decision outcomes. Our study benefits from three key strengths which include using validated assessment tools and performing robust statistical methods and including participants from various educational backgrounds and income brackets. Future research needs to study how surgical choices evolve in health literacy subgroups through time and create and evaluate educational programs for neurosurgical patients and analyze how digital health tools can connect with patients who have limited health literacy. Additional research using multiple centers together with qualitative methods would help explain complex decision-making processes and reveal particular educational requirements of patients deciding on spinal surgery.

CONCLUSION

Our research shows that health literacy stands as a key factor which determines how patients approach decisions regarding spinal surgery. Patients who demonstrate higher health literacy skills maintain greater independence in their choices and depend less on doctor advice and seek more information and choose surgery less often yet remain satisfied with their decisions. The strong relationship between patient education level and health literacy demonstrates that healthcare providers need to develop specific communication approaches for various patient groups. Neurosurgeons must evaluate patient health literacy during consultations to deliver communication that enables genuine informed consent. The improvement of health literacy among neurosurgical patients would result in patient-centered care and better decision satisfaction and appropriate surgical intervention use for spinal conditions.

ETHICAL DECLARATIONS

Ethics Committee Approval

The Scientific Researches Ethics Committee of Adana City Training and Research Hospital approved this study (Date: 10.04.2025, Decision No: 427).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

Acknowledgement

I would like to thank Prof. Dr. Yurdal GEZERCAN for his unique contributions.

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Original Article

DOI: 10.38053/acmj.1659477

ANATOLIAN CURRENT MEDICAL

Anatolian Curr Med J. 2025;7(3):338-342

Clinical and laboratory characteristics of pediatric orthostatic hypertension: a retrospective study

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Cite this article as: Dönmez YN, Celep B, Baltu D, Şener YZ. Clinical and laboratory characteristics of pediatric orthostatic hypertension: a retrospective study. *Anatolian Curr Med J.* 2025;7(3):338-342.

Received: 18.03.2025 ◆ **Accepted**: 12.05.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: Orthostatic hypertension (OHT) is an underrecognized condition in the pediatric population, characterized by an abnormal rise in blood pressure upon standing. Given its potential long-term implications, including cardiovascular remodeling and end-organ damage, early identification and management of OHT are crucial. This study aims to evaluate the clinical and laboratory characteristics of children diagnosed with OHT, providing insights into potential risk factors and associated conditions.

Methods: A retrospective, cross-sectional study was conducted at Ankara Training and Research Hospital between September 2022 and August 2024. A total of 111 pediatric patients diagnosed with OHT based on an active standing test were included. Demographic data, presenting symptoms, laboratory parameters (including vitamin B12, ferritin, and vitamin D levels) were analyzed.

Results: The median age of the cohort was 15.3 years (range: 6.8–17.9), with a female predominance (63%). Nearly half of the patients (46%) were overweight or obese, and 22% had a family history of hypertension. Cardiovascular symptoms were the most common (36%), followed by cerebral hypoperfusion symptoms (35%) and other symptoms, including fatigue and concentration issues (27%). A significant proportion of the patients exhibited vitamin D deficiency (41%), vitamin B12 borderline levels (45%), and iron deficiency anemia (15%). Additionally, postural orthostatic tachycardia syndrome (POTS) was present in 24% of patients, with a notable association between POTS and low body weight (p=0.037).

Conclusion: The descriptive findings of this study illustrate a range of clinical and laboratory characteristics in children with OHT, hinting at potential areas for future investigation. Although associations with pubertal status, obesity, and vitamin deficiencies were observed, the study's design limits causal inference. Future research, including control groups and prospective approaches, is crucial to understand the clinical importance of these observations.

Keywords: Orthostatic hypertension, autonomic dysfunction, pediatric population, active standing test

INTRODUCTION

Orthostatic hypertension (OHT) is characterized by an abnormal increase in blood pressure (BP) upon transitioning from a lying to a standing position, resulting from disrupted autoregulatory mechanism.[1] Identifying OHT in children is essential due to the potential risks of hypertension, such as stroke, end-organ damage, and cardiovascular complications.[2] Given the dangers of target organ damage in adulthood, it is critical to precisely identify patients at heightened risk and establish preventive strategies from an early age to help mitigate endothelial dysfunction and vascular remodeling.[3]

The diagnosis of OHT relies on the activate standing test or tilt testing response of patients exhibiting orthostatic symptoms, following the exclusion of structural cardiac and neurological disorders, and in the absence of pheochromocytoma, central nervous system illness or diabetes mellitus.[3] According to Zhao's[4] study on the response measured at the third minute of the active standing test, OHT can be defined as follows: a) for children aged 6 to 12 years, it is characterized by a systolic pressure increase of 20 mmHg and a diastolic pressure increase of 25 mmHg, or a BP exceeding 130/90 mmHg; b) for those aged 13 to 18 years, it is defined by a systolic and diastolic pressure increase of 20 mmHg, or a BP above 140/90 mmHg.

A limited number of research have been conducted to investigate the clinical characteristics and pathogenesis of OHT, which is an underexplored disorder in the pediatric

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population. To enhance early diagnosis and management strategies, gaining insight into the cardiovascular and autonomic characteristics of OHT in children would be highly beneficial. The aim of the study is to evaluate children with OHT by analyzing their clinical findings and laboratory parameters.

METHODS

The present study was conducted as a retrospective investigation at Ankara Training and Research Hospital from September 2022 to August 2024 to identify the findings of the clinical presentation, physical examination findings, laboratory results and echocardiographic findings in children diagnosed with OHT. The ethical approval of this cross-sectional study was obtained from the Ankara Training and Research Hospital Scientific Researches Ethics Committee (Date: 21.08.2024, Decision No: 217/2024). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Predesignated demographic, clinical characteristics and diagnostic findings pertaining to children were searched through the medical archive of the hospital. The study group comprised children who presented at the outpatient clinic exhibiting symptoms suggestive of orthostatic intolerance, such as dizziness, syncope, headache, or palpitations. The active standing test was performed as a component of their clinical assessment to explore the possibility of autonomic dysfunction within this population. All participants underwent a thorough clinical evaluation. Patients with known endocrinological, cardiovascular, allergic, psychological, or neurological conditions that could potentially confound the interpretation of their symptoms were excluded. In addition to routine laboratory tests (e.g., hemogram, electrolytes, renal and liver function tests), further investigations such as thyroid function test, adrenal hormones or metabolic hormones were performed when atypical findings during clinical evaluation. When necessary, patients were referred to relevant departments (e.g., suspected allergic etiology, neurological concerns) for additional evaluations. Children with a history of chronic illness or follow-up for other medical conditions were not included in the study. For each participant, office BP was measured on the right arm using the auscultatory method by a physician with a correctly sized cuff, following a minimum 20-minute rest period. BP values were interpreted according to the guidelines from the American Academy of Pediatrics.[5]

The evaluation of orthostatic responses in this study relied solely on "the active standing test". The active standing test was conducted after the patients had rested lying down for 10 minutes and then again at 3 and 10 minutes after quickly standing up. The active standing test was performed in a quiet room with a temperature of 22 to 24 °C, and it was ensured that the patients had fasted for 2 h and had not taken any medications. OHT was defined according to BP alterations noted during the standing test. In children aged 6 to 12 years, the condition was characterized by a systolic BP increase of 20 mmHg or greater, accompanied by a diastolic BP increase of 25 mmHg or greater. For children older than 12 years, a systolic BP elevation of 20 mmHg or more was considered sufficient for the diagnosis. Postural orthostatic tachycardia syndrome (POTS) was defined based on cardiovascular responses during orthostatic testing, indicated by either a sustained increase in heart rate of ≥40 bpm from the supine baseline or above 130 bpm in children aged 6 to 12, or above 125 bpm in those older than 13 within 10 minutes of standing.[6]

The initial presenting complaints were categorized into four groups: central nervous system symptoms (dizziness, headache, syncope), cardiovascular system symptoms (chest pain, palpitations), gastrointestinal system symptoms (nausea, abdominal pain) and other (impaired concentration, fatigue). Vitamin B12 deficiency was defined as values below 200 pg/ml, and borderline B12 level ranged from 200 to 300 pmol/L. A vitamin D level below 12 ng/dl was classified as a deficiency, levels between 12 and 20 ng/ml were considered insufficient while levels above 20 ng/ml are regarded as sufficient.[7] Ferritin levels below 12 ng/ml below the age of 5 years and 15 ng/ml above the age of 5 years were considered iron deficiency.[8]

Statistical Analysis

The data analysis was performed using IBM-SPSS Statistics for Windows 22.0 (IBM Corp., Armonk, NY, USA). The distribution properties of the continuous variables were assessed using the Kolmogorov-Smirnov test. The descriptive statistics utilized the mean (SD) for the normally distributed data, and the median and range for the non-normally distributed data. Results for the continuous and categorical variables with normally distributed distributions were assessed using the paired samples t test and chi-squared test. $p<0.05$ was considered statistically significant.

RESULTS

All 111 children participating in the study were diagnosed with OHT, with a median age of 15.3 years (range from 6.8 to 17.9 years). Notably, 27 of these patients also fulfilled the diagnostic criteria for POTS, reflecting a co-occurrence of both conditions. Seven patients (6%) were younger than 11 years and 104 patients (93%) were older than 11 years. A thorough analysis of the demographic and clinical data, as well as the laboratory and diagnostic parameters, was seen in **Table 1**. There was a female gender predominance in the patients 63% of were female, 37% were male. There were 25 (22.5%) patients with a family history of hypertension. In all, 51 patients (46%) were overweight or obese. Besides, 7 patients were underweighted.

A total of 24 (22%) patients displayed high BP or hypertension during the rest. Cardiovascular findings were the most common, observed in 40 (36%) of patients, followed by cerebral hypoperfusion findings in 39 (35%) and gastrointestinal findings in 2 (2%), with 30 (27%) of children presenting with other findings involving fatigue, concentration problems. In response to the active standing test, BP was 123.2/74.0 mmHg (16.7/9.8), and heart rate was 99.2 bpm (15.4) at 3 minutes of standing. At 10 minutes, BP was 122.4±15.3/75.6±9.1 mmHg, and heart rate was 101.2±16.4 bpm.

Ten patients exhibited vitamin B12 deficiency. Fifty patients revealed borderline vitamin B12 levels. Twenty-seven patients (24%) were accompanied by POTS. Seventeen patients were

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Table 1. Baseline demographic, clinical, and laboratory characteristics of the children with orthostatic hypertension

Patients number	111
Age* (year)	15.3 (6.8-17.9)
Gender (F/M)	70 (63%)/41 (37%)
Antropometric measurements	
Weight (kg)*	65.0 (35.6-118.0)
Weight sds *	1.5 (-3-+5.1)
Height (cm) *	162.0 (135.0-190.0)
Height sds+	0.33±1.3
Body-mass index (kg/m^2) *	25.7 (14.6-41.0)
Body-mass index percentile*	87.3 (0.01-99.9)
Blood pressure	
Systolic blood pressure (mmHg)+	115.9±16.3
Diastolic blood pressure (mmHg)+	58.7±8.7
Heart rate+	81.1±14.1
SBP percentile*	71.0 (1.0-99.9)
DBP percentile*	25.0 (1.0-99.9)
Systolic orthostatic hypertension	20 (18%)
Diastolic orthostatic hypertension	64 (57%)
Both systolic and diastolic hypertension	27 (24%)
Laboratory	
Hemoglobin (g/dl) +	13.7±1.4
Creatinine +	0.65±0.13
Albumin*	48.0 (40-55)
Vitamin B12*	289 (116-759)
Ferritin*	31.5 (5.7-160)
Vitamin D*	14.4 (5.3-60)

* Indicates median (minimum to maximum), + Indicates mean (SD), F: Famale, M: Male, SD: Standard deviation

Table 2. Comparative results of children with and without postural orthostatic tachycardia syndrome

	Orthostatic hypertension without POTS (n:84)	Orthostatic hypertension with POTS (n:27)	p value
Age*	14.9±2.1	14.5±1.9	0.584
BMI*	25.7±5.9	24.8±7.2	0.500
Family history	19 (22.6%)	6 (22.2%)	0.966
Obesity	41 (48.8%)	10 (37.0%)	0.286
Low weight	3 (3.6%)	4 (14.8%)	0.037
Hypertension	16 (19%)	8 (29.6%)	0.245
Baseline (mmHg)			
SBP*	114.6±15.2	119.0±19.0	0.185
DBP*	57.4±7.7	63.3±10.4	0.002
Standing after 3 min (mmHg)			
SBP*	121.1±13.7	128±23.4	0.141
DBP*	74.6±8.9	78.7±11.2	0.005
Standing after 10 min (mmHg)			
SBP*	121.4±14.3	124.9±18.2	0.310
DBP*	74.8±9.5	78.4±7.1	0.074

* Indicates median mean±SD, POTS: Postural orthostatic tachycardia syndrome, BMI: Body-mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

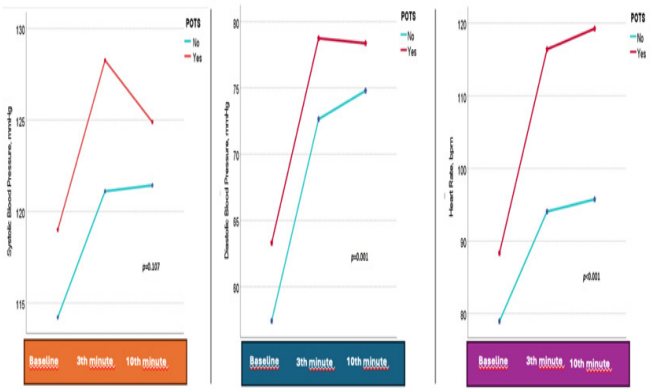

Figure. Changes in systolic blood pressure (ΔSBP) (left), diastolic blood pressure (ΔDBP) (middle), and heart rate (ΔHR) (right) during the active standing test in children with and without postural orthostatic tachycardia syndrome. Measurements were recorded at baseline, 3rd minute, and 10th minute of standing. Repeated measures ANOVA was applied to examine differences in hemodynamic parameters
POTS: Postural orthostatic tachycardia syndrome

diagnosed with iron deficiency anemia. Forty-six patients (41%) exhibited vitamin D deficiency, and another forty-six (41%) presented with vitamin D insufficiency.

POTS has been detected in 27 (24%) patients together with OHT (**Table 2**). The mean age of patients with POTS was 14.5±1.9 years, with the mean of BMI was 24.8±7.2. Among the patients, 8 (30%) were male and 19 (70%) were female. POTS patients predominantly had central nervous system manifestations (40%). Subsequently, the cardiovascular system symptoms accounted for 30%, other symptoms constituted 26%, and gastrointestinal symptoms represented 4%. No significant difference in clinical presentation was observed between patients with OHT with and without POTS (p value 0.692). Furthermore, there was no significant difference between the two groups for the presence of obesity and hypertension (p value 0.286 and 0.245 respectively). Nonetheless, an important statistical difference was noted for low weight. Fifteen percent of the POTS cohort exhibited low body weight, whereas this prevalence was 4% in the cohort without POTS (p value 0.037). Despite a trend towards a larger systolic BP increase in the POTS+OHT group (p=0.107), this difference was not statistically significant. However, the POTS+OHT group demonstrated significantly higher heart rate and diastolic BP values compared to the non-POTS group (p<0.001 and p=0.001, respectively) (**Figure**).

DISCUSSION

According to the findings of this study, approximately half of the children were overweight or obese, suggesting a potential link between altered cardiovascular regulation and orthostatic BP dysregulation in this population. The majority of patients were female, demonstrating a notable gender predominance among the cohort. Furthermore, a significant proportion of the study population was in the pubertal period. One-fourth of the children had a history of hypertension in their family. Taking these findings into consideration, the development of OHT may be attributed to a multifactorial interplay, including genetics, sex-specific characteristics, obesity, and genetic predisposition.

The existing literature does not provide evidence of a clear gender dominance.[9] In contrast, our study revealed a significant predominance of female patients. Research suggests the incidence rises during the pubertal period.[3] Consistent with this in our study, the mean age of the patients showed dominantly pubertal period. In their study, Zhao et al.[4] reported a 67% prevalence of pubertal patients, whereas our research found a significantly higher rate of 93%. This may pertain to neurohormonal dysregulation due to accelerated somatic growth together with relatively slower neurological maturation.[3] Approximately 50% of our patient population fell within the overweight or obese categories. Evidence indicates that these conditions are linked to a heightened risk of OHT.[10]

Moreover, those who have a family history of hypertension may face a greater likelihood of experiencing OHT. A quarter of our patients reported a family history of hypertension. This finding suggests that OHT may be linked to the possibility of genetic inheritance.

Vitamin D influences the arterial wall by reducing its compliance and contributing to vascular stiffness. Furthermore, it may influence the baroreflex and the renin-angiotensin-aldosterone system, potentially disrupting autonomic regulation and contributing to the development of hypertension.[11] Kovalchuk et al.[12] reported reduced levels of 25(OH) in children experiencing vasovagal syncope and orthostatic hypotension. Xiao et al.[13] also detected reduced vitamin D levels in children with orthostatic intolerance. Zhang et al.[14] reported that autonomic dysfunction may occur in children with vasovagal syncope because of vitamin D deficiency. Our investigation also revealed significant amounts of vitamin D deficiency and insufficiency. Given the well-documented high prevalence of vitamin D deficiency and insufficiency in the general pediatric population of our country, shaped by factors such as limited sun exposure, dietary habits, and lifestyle, the similarly high prevalence observed in our OHT cohort warrants cautious interpretation.[15] In the absence of a matched control group, it remains unclear whether this finding reflects a direct etiological role in the pathophysiology of OHT or represents a coincidental association. Therefore, further controlled studies are needed to clarify the potential contribution of vitamin D deficiency to autonomic dysregulation and increased vascular tone in pediatric OHT.

Autonomic dysfunction has been occasionally associated with cobalamin deficiency.[16] Vitamin B12 assumes a pivotal role in the process of myelinogenesis and the maintenance of sympathetic postganglionic fiber functionality.[16-18] Consequently, its deficiency has been correlated with a decrement in both sympathetic and parasympathetic nervous system activity. A study conducted with Öner and her colleagues[19] reported that 62.8% of POTS cases were associated with B12 deficiency. In their findings, Pektaş et al.[20] indicated that vitamin B12 deficiency was observed more often in patients diagnosed with POTS than in those exhibiting a vasodepressor response. The relationship between vitamin B12 deficiency and autonomic dysfunction has been noted in various orthostatic syndromes; however, the specific role of B12 deficiency in the pathophysiological processes of OHT is an area requiring further investigation. For a more comprehensive understanding of the nutritional and metabolic effects, it is essential to conduct long-term studies that not only compare patients with OHT to a control group but also include comparisons with other orthostatic pathologies. These investigations would clarify potential variations in metabolic profiles, nutritional status, and related risk factors, so offering profound insights into the underlying mechanisms and informing more effective approaches to management.

In accordance with the other studies, POTS was linked to approximately one-fourth of patients exhibiting OHT in this study.[2,21] In Zhang's[2] study, no significant statistical difference in gender was observed regarding the connection of OHT and POTS, but our study exhibited a female predominance. The Zhang study identified headache as the prevalent symptom. In support of this, central nervous system symptoms were the main clinical presentation symptom in our investigation. The pathophysiology of POTS is recognized to involve increased sympathetic activity, dysfunctional sympathetic-related vasoconstriction or altered renin angiotension aldosterone regulation.[22,23] Notably, neurovascular and neurohormonal responses can present with overlap in both OHT and POTS. Aligning with the established hyperadrenergic state in POTS, our findings also revealed significantly elevated heart rate and diastolic BP in the POTS+OHT group, further substantiating the role of sympathetic overactivity in shaping their hemodynamic profile. Of interest, a greater proportion of POTS patients exhibited low body weight, a finding that could be associated with dysregulation of fluid volume and ineffective autonomic compensation, both acknowledged as contributing factors to the pathogenesis of POTS.

Limitations

These findings, however, need to be interpreted with the greatest caution, and there are a few limitations that need to be taken into consideration. The inherent limitations of a single-center study design, further compounded by the exclusion of a healthy control group, impede the generalizability of the reported outcomes and complicate the attribution of specificity to the observed clinical characteristics. The prevalence of nutritional inadequacies, the apparent predominance of pubertal development, and the identified patterns of autonomic response within the OHT cohort may not be distinct from those observed in the general pediatric population, thus precluding the definitive establishment of causal associations. However, given the limited research on pediatric OHT, the results provide valuable insights that enhance clinical awareness and guide future research. The assessment of the patients' self-reported symptoms suggests that recall bias, exaggeration, and selective remembering may have an impact on the patients. Employing autonomic symptom assessments scales in future study may produce more accurate and reliable results. Moreover, the study did not evaluate the children's eating habits, physical activity levels, or emotional health. Further research is required to design metrics that can precisely evaluate both physical activity levels and mental well-being. The limitations of this study will provide valuable insights for designing similar studies in the future. The interpretation of our findings is also potentially limited by the adoption of the active standing test as the sole diagnostic modality for orthostatic responses. Despite its simplicity and feasibility in outpatient settings, the absence of established, large-scale normative data and standardized protocols for the pediatric age group necessitates a cautious approach to the interpretation of the observed orthostatic changes. Therefore, while valuable for detecting responses within our study population, the broad applicability and clinical relevance of these results require corroboration through future research employing validated pediatric orthostatic testing paradigms.

CONCLUSION

The clinical, demographic and laboratory features of pediatric population with OHT have been identified in this study. According to results, a family history of hypertension, obesity, pubertal age, and female predominance might all be contributing to OHT in children. Remarkably, a significant percentage of children had iron, vitamin B12, and vitamin D deficiencies, suggesting that these conditions may be metabolic and nutritional factors contributing to autonomic dysfunction. While the pathophysiological mechanisms underlying these associations require further investigation, our study underscores the need for early identification and comprehensive management of pediatric OHT to mitigate potential long-term cardiovascular risks Future research with larger sample sizes and longitudinal follow-ups is warranted to explore the causal relationships and potential therapeutic interventions for this condition.

ETHICAL DECLARATIONS

Ethics Committee Approval

The ethical approval of this cross-sectional study was obtained from the Ankara Training and Research Hospital Scientific Researches Ethics Committee (Date: 21.08.2024, Decision No: 217/2024).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1679398

Anatolian Curr Med J. 2025;7(3):343-352

Determination of knowledge level and vaccination status of nursing students regarding hepatitis B infection and hepatitis B vaccine

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Cite this article as: Bayram R. Determination of knowledge level and vaccination status of nursing students regarding hepatitis B infection and hepatitis B vaccine. *Anatolian Curr Med J.* 2025;7(3):343-352.

Received: 18.04.2025 ◆ **Accepted**: 14.05.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: The study was conducted to determine the knowledge level and vaccination status of nursing students regarding hepatitis B infection and hepatitis B vaccine.

Methods: The universe of this descriptive and cross-sectional study consisted of 747 students studying at the department of nursing. In the study, a 43-item questionnaire form and the vaccine hesitancy scale were used.

Results: Of the students, 77.7% were female. The mean age was 20.68±1.68. Eight percent of the students had a chronic disease and 2.1% were diagnosed with hepatitis (71.4% hepatitis B). Of the students, 77.3% had hepatitis B vaccine. Students stated that those who were injected with the same injector (77.8%), who received blood transfusions (72.2%), and who had heterosexual intercourse ranked in the top three in the hepatitis risk group (63.9%). Students stated that the primary modes of hepatitis transmission were: 93.6% through blood, 78.8% through needlestick injuries with infected injectors, and 72.7% through sexual intercourse. The most accurate information that the students had about hepatitis was the existence of hepatitis B vaccine (96.9%) and hepatitis B carriers (77%). The mean knowledge level of the students about hepatitis was 5.22±1.92. The mean score that the students obtained from the vaccine hesitancy scale was 31.25±6.18. It was found that there was a significant relationship between knowledge level and vaccine hesitancy ($p<0.005$).

Conclusion: Levels of hepatitis B knowledge and vaccine hesitancy are moderate in nursing students. It is recommended to provide training and awareness activities for nursing students in this regard.

Keywords: Hepatitis, health knowledge, vaccine hesitancy, nursing, students

INTRODUCTION

Hepatitis B virus (HBV) is a non-cytopathic and hepatotropic virus with the potential to cause chronic infection, which can lead to cirrhosis and hepatocellular carcinoma.[1] HBV can be transmitted through the use of blood and blood products, sharing living spaces, transfusion, transplantation of infected organs, shared use of contaminated needles, sexual contact, sharp/piercing instruments such as manicure-pedicure sets, razors, and scissors as well as during cosmetic procedures like acupuncture, tattooing and piercing.[2] In a systematic review evaluating the studies conducted in our country in terms of age and region, HBsAg positivity was found as 4.6%, and it was reported that approximately three million people had chronic hepatitis B.[3]

Physicians, dentists, nurses and laboratory personnel are at risk of hepatitis B infection since they come into contact with blood and other body fluids during their daily lives. In the study conducted by Apaydın et al.[2] it was reported that 14.4% of healthcare professionals were infected with HBV. In a study involving 2945 healthcare professionals working in an hospital, 3.2% of the participants were found to have a diagnosis of hepatitis B, and 88.4% of the individuals diagnosed with hepatitis B had chronic HBV in their families.[4]

Transmission to healthcare personnel occurs primarily through percutaneous injuries with contaminated needles and injectors, or by percutaneous or mucosal exposure to small quantities of blood during surgical and dental procedures.[2] HBV transmission among healthcare personnel can be prevented by strict adherence to the standard microbiological practices and techniques and by the routine use of appropriate barrier precautions when handling patients' blood and other body fluids.[2]

In the study of Kader et al.[5] the higher anti-HBs positivity compared to the studies conducted in the last 10 years and where 26-50% anti-HBs positivity was detected was attributed to the increase in awareness and vaccination programs with trainings. In the study conducted by Apaydın et al.[2] HBV immunity was determined to be 85% in physicians and nurses and 70% in other healthcare professionals. Studies reveal that the vaccination rate in healthcare professionals is still not at the desired level. Therefore, it is necessary to increase

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the knowledge levels and vaccination rates of healthcare professionals on hepatitis B.

It is thought that determining the knowledge level and vaccination rates of healthcare professionals about hepatitis B while they are still students, as well as eliminating the lack of knowledge on this subject, will contribute to reducing the risk of hepatitis B transmission, taking protection measures and increasing vaccination rates when transitioning to professional life.

Vaccine hesitancy, defined as the delay in acceptance or refusal of vaccination despite the availability of vaccination services, has become a growing concern in global public health. It is a complex and context-specific phenomenon influenced by various factors. The World Health Organization conceptualizes vaccine hesitancy through the "3C model," which includes confidence (trust in vaccines and health authorities), complacency (low perceived risk of vaccine-preventable diseases), and convenience (accessibility and availability of vaccines).[6]

Recent global trends such as misinformation on social media, distrust in pharmaceutical industries, and low risk perception due to successful immunization programs have contributed to the rise in vaccine hesitancy.[6] Among healthcare professionals and students, this issue is particularly critical, as they are expected to not only protect themselves through vaccination but also guide the public as role models. Nursing students, in particular, play an important role in patient education and public health promotion. Therefore, their attitudes and hesitations toward vaccines, especially those targeting high-risk infections like hepatitis B, warrant careful evaluation.

In this context, the present study was conducted to determine the knowledge level, vaccination status, and vaccine hesitancy of nursing students regarding hepatitis B infection and the hepatitis B vaccine.

METHODS

Ethics
The study was conducted with the permission of Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Date: 30.05.2023, Decision No: 2023-12/8). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Type of the Study
It is a cross-sectional and descriptive study.

Place of the Study
The study was conducted between 30/06/2023 and 31/12/2023 on the students of the nursing department of the faculty of health sciences of a university.

Universe and Sample of the Study
The universe of the study consisted of 747 students enrolled at Bursa Uludağ University, Faculty of Health Sciences, Department of Nursing. Inclusion criteria were being an undergraduate nursing student enrolled at the faculty during the data collection period, having no communication difficulties, and voluntarily agreeing to participate in the study. The required sample size for this known population was calculated as approximately 254 using the standard sample size formula with a 95% confidence level and a 5% margin of error. However, a total of 326 students who met the inclusion criteria and voluntarily agreed to participate were included in the study. This number exceeds the minimum requirement and enhances the statistical power and representativeness of the findings. Students who declined to participate, had communication difficulties, or were of foreign nationality were excluded. A convenience sampling method was used in this study.

Data Collection Tools of the Study
The data were collected with the questionnaire form developed by the researcher in line with the examined literature, and the "vaccine hesitancy scale" whose Turkish validity and reliability process was conducted by Yılmaz et al.[7] In this study, the internal consistency coefficient (Cronbach's alpha) of the vaccine hesitancy scale was calculated as 0.84. The data collection process was carried out between 30 June and 31 December 2023. I administered the questionnaire and the vaccine hesitancy scale face-to-face in a classroom setting. Prior to data collection, i informed the students about the aim of the study and obtained their verbal and written informed consent. The implementation was conducted in a quiet and appropriate environment where the students could complete the questionnaires independently. I was present during the application to provide clarification when needed, without influencing their responses. Each participant completed the questionnaire anonymously, and the entire process took approximately 15–20 minutes. This approach ensured voluntary participation, accuracy, and consistency in data collection.

Questionnaire Form
The questionnaire form consisted of 43 items. The first 35 items of the form included sociodemographic characteristics (age, gender, etc.) while the other 8 items included information questions about hepatitis B infection and hepatitis B vaccine. Knowledge-related items were scored as "correct (1)" and "incorrect/don't know (0)". It was accepted that as the number of correct answers increased, the knowledge level also increased.

Vaccine Hesitancy Scale
The Turkish validity and reliability study of the scale, who was developed by Luyten et al.[8] in 2019, was conducted by Yılmaz et al.[7] The five-point Likert-type (1=strongly disagree, 5=strongly agree) scale consists of 9 items in total with two sub-dimensions, lack of trust (7 items) and risks (2 items). The total score of the scale varies between 9-45. As the score obtained from the scale increases, vaccine hesitancy decreases.

Statistical Analysis
The data were evaluated in the SPSS 22 program by using means, percentages, One-way ANOVA test, t test and Pearson correlation test.

RESULTS

The mean age of the students was 20.68±1.68, and 77.7% of them were female. Of the students, 67.5% graduated from Anatolian high schools and 46% were living in the dormitories. Of the students, 77.3% had a nuclear family type, and the economic status of 76.4% was moderate. The education level of the mothers of 37.1% of the students was primary education, and the education level of the fathers of 28.5% was high school. Of the students, 10.4% were smokers, and 8.6% were drinking alcohol (**Table 1**).

Eight percent of the students had a chronic disease, 2.1% had a diagnosis of hepatitis (71.4% hepatitis B). Thirty-four percent of the students had an individual with chronic disease in their families, and 5.2% had a diagnosis of hepatitis (94.1% hepatitis B). Of the students, 83.1% stated that they obtained information about hepatitis from various sources, and 39.9% of them stated that they obtained this information from the internet. Of the students, 49.4% stated that they received training on hepatitis B infection and hepatitis B vaccine (**Table 1**).

Of the students, 77.3% were vaccinated against hepatitis B, and 67.9% of them were vaccinated after starting their education in the nursing department. Vaccine dose was only completed in only 29% of them. Among the students who were not vaccinated, 56.8% stated that they were not vaccinated because they had sufficient antibody levels. Among the vaccinated students, 77.8% stated that they had sufficient antibody levels. A total of 83.7% of the students had their hepatitis antibody/antigen levels tested after starting their educations in the nursing department. Among the students who were not vaccinated, 44.6% stated that they were considering getting vaccinated. Of the students, 19.9% stated that they had previously cared for a patient diagnosed with hepatitis B, and 62.6% reported being concerned about being infected with hepatitis B while providing care (**Table 2**).

The top three hepatitis risk group was stated by the students as follows; those who injected drugs with the same injector by 77.8%, those who had blood transfusion by 72.2%, and those who were in heterosexual relationships by 63.9%. The students stated that the primary modes of hepatitis transmission were:

Table 1. Distribution of students' sociodemographic and health-related characteristics (n=326)

Variables	Categories	n	%	Variables	Categories	n	%
Class	1 2 3 4	146 54 65 61	44.8 16.6 19.9 18.7	Family type	Nuclear Extended Broken	252 56 18	77.3 17.2 5.5
Age	(Mean±SD)	20.68±1.68	R=17-30	Gender	Male Female	76 250	23.3 76.7
High school graduated from	Anatolian high school Science high school Health vocational high school General high school Other	220 28 21 15 42	67.5 8.6 6.4 4.6 12.9	Economic status	Income is less than expenses Income equals expenses Income exceeds expenses	41 249 36	12.6 76.4 11.0
Mother's educational level	Literate/illiterate Primary school Middle school High school University and higher	37 121 66 69 33	11.3 37.1 20.2 21.2 10.1	Father's educational level	Literate/illiterate Primary school Middle school High school University and higher	16 79 65 93 73	4.9 24.2 19.9 28.5 22.4
Smoking status	I do not use I use I quit	283 34 9	86.8 10.4 2.8	Alcohol consumption status	I do not use I use I quit	296 28 2	90.8 8.6 0.6
Current residence	Living with relatives Living with family Living with friends Living alone Dormitory	20 135 13 8 150	6.1 41.4 4.0 2.5 46.0	Presence of an individual with a chronic disease in the family	Yes No	111 215	34.0 66.0
Presence of an individual with a hepatitis diagnosis in the family	Yes No	17 309	5.2 94.8	Type of hepatitis in an individual diagnosed with hepatitis in the family (n=17)	Hepatitis B Hepatitis C	16 1	94.1 5.9
Presence of chronic disease	Yes No	26 300	8.0 92.0	Presence of hepatitis	Yes No	7 319	2.1 97.9
Type of hepatitis (n=7)	Hepatitis A Hepatitis B Hepatitis B+hepatitis E	1 5 1	14.3 71.4 14.3	Status of receiving education about hepatitis B infection and hepatitis B vaccination	Yes No	161 165	49.4 50.6
Status of obtaining information from various sources about hepatitis acquisition status	Yes No	271 55	83.1 16.9	Sources of information about hepatitis (n=271)	School Internet Social media Healthcare personnel A family member TV Newspaper	52 108 10 93 3 2 3	19.2 39.9 3.7 34.3 1.1 0.7 1.1

SD: Standart deviation, R: Range

Table 2. Students' thoughts and attitudes regarding hepatitis B (n = 326)

Variables	Categories	n	%
Status of receiving the hepatitis B vaccine	Yes No	252 74	77.3 22.7
Time of receiving the hepatitis B vaccination (n=252)	Before starting nursing school After starting nursing school	81 171	32.1 67.9
Number of doses of hepatitis B vaccine received (n=252)	1 2 3	63 116 73	25.0 46.0 29.0
Reason for not receiving the hepatitis B vaccine (n=74)	Natural immunity Sufficient antibody level Physician's recommendation Disregard/lack of concern	5 42 21 6	6.8 56.8 28.4 8.1
Knowledge of having sufficient immunity levels (n=252)	Yes No	196 56	77.8 22.2
Time of testing hepatitis antigens and antibodies	Before starting nursing school After starting nursing school I did not have it tested	24 273 29	7.4 83.7 8.9
Consideration of receiving the hepatitis B vaccine (n=74)	Yes No	33 41	44.6 55.4
Providing care to patients diagnosed with hepatitis B	Yes No	65 261	19.9 80.1
Concerns about hepatitis B transmission while providing care	Yes No	204 122	62.6 37.4

93.6% through blood, 78.8% through needlestick injuries with infected injectors, and 72.7% through sexual intercourse. Of the students, 59.2% stated that HIV, 47.2% stated that chronic liver diseases, and 41.7% stated that being over 40 years old posed a risk for non-response to the hepatitis B vaccine (**Table 3**).

The most accurate information that the students had about hepatitis was the existence of hepatitis B vaccine (96.9%) and hepatitis B carriers (77%). The mean knowledge level of the students about hepatitis was 5.22±1.92. The mean score that the students obtained from the vaccine hesitancy scale was 31.25±6.18 (lack of confidence 25.46±6.21; risks 5.79±1.22) (**Table 4**).

Among the sociodemographic characteristics of the students, grade, father's educational status and smoking status were found to affect the knowledge level about hepatitis B ($p<0.05$) (**Table 5**).

It was found that the students' health-related characteristics and factors related to their thoughts/attitudes towards hepatitis, such as the presence of chronic illness in the family, knowledge about hepatitis, receiving education on hepatitis B infection and hepatitis B vaccine, caring for a patient diagnosed with hepatitis B, and concerns about getting infected with hepatitis B while providing care, influenced their knowledge level about hepatitis B ($p<0.05$) (**Table 6**).

A statistically significant relationship was found between the knowledge level of the students about hepatitis B and vaccine hesitancy ($p<0.005$) (**Table 7**).

DISCUSSION

Among the students, 2.1% were diagnosed with hepatitis (71.4% hepatitis B), and 5.2% reported having a family member diagnosed with hepatitis (94.1% hepatitis B). In a study conducted on nursing students, it was stated that 3.7% of the students had a family member diagnosed with hepatitis B.[9] In a study conducted by Sönmez and Akben[9] on nursing students, 3.7% reported that they had a family member diagnosed with hepatitis B. In the study conducted by Salduz and Özder[10], 0.8% of the students were found to be HBsAg positive, and 5.2% reported having a family member who was a hepatitis B carrier. The minor differences observed among studies may be attributed to factors such as variations in the geographical regions where the research was conducted, the participants' level of knowledge about hepatitis B, and the extent to which family members disclosed the diagnosis to the participants. Additionally, some individuals may be unaware of the diagnosis within their family or may choose not to disclose it, which could also contribute to discrepancies in reported rates. Considering these factors, the findings of the present study appear to be generally consistent with those in the literature, suggesting that the rates of reported hepatitis diagnoses among student populations with similar sociodemographic characteristics remain relatively comparable.

While 83.1% of the students stated that they had knowledge about hepatitis, 39.9% reported that they obtained this information from the internet. In a study conducted on the students of a faculty of medicine, it was found that 77.7% of the students obtained information about HBV from school and 35% from the media.[11] In a study conducted on nursing students in Ghana, it was reported that the sources of information about hepatitis B were school (60.6%), healthcare professionals (21.8%), and media (5%).[12] Our study results differ from the results of certain studies. This difference is thought to result from variations in the geographical locations where the studies were conducted, as well as differences in educational opportunities and access to the internet.

Of the students, 49.4% stated that they had received education about hepatitis B infection and hepatitis B vaccine. In a study conducted by Alkan et al.[11] it was found that 83.2% of medical faculty students eceived education about hepatitis B infection and hepatitis B vaccine. In contrast, a study conducted on university students reported that only 45.2% of them had

Table 3. Students' knowledge about hepatitis B risk groups, modes of transmission, and vaccine unresponsiveness (n=326)

Variables			n	%	Modes of transmission of hepatitis B		n	%
Hepatitis B risk groups	Heterosexual relationships	True False	207 117	63.9 36.1	Bloodborne	Yes No	305 21	93.6 6.4
	Sharing a syringe for drug injection	True False	252 72	77.8 22.2	Sexual contact	Yes No	237 89	72.7 27.3
	Living in the same household as a person with hepatitis B	True False	118 206	36.4 63.6	Sweat and tears	Yes No	69 257	21.2 78.8
	Receiving a blood transfusion	True False	234 90	72.2 27.8	Needle stick injury with an infected syringe	Yes No	257 69	78.8 21.2
	Receiving an organ transplant	True False	193 131	59.6 40.4	Breast milk	Yes No	62 264	19.0 81.0
	Using the same toilet	True False	74 250	22.8 77.2	Birth from an infected mother	Yes No	179 147	54.9 45.1
	Drug use	True False	122 202	37.7 62.3	Hemodialysis	Yes No	107 219	32.8 67.2
	Healthcare workers	True False	190 134	58.6 41.4	Kissing (lip-to-lip)	Yes No	73 253	22.4 77.6
	Born to mothers who are HBV carriers	True False	198 126	61.1 38.9	Shared use of cups, spoons, and forks	Yes No	56 270	17.2 82.8
	Patients with immune deficiencies	True False	115 209	35.5 64.5	Chronic skin wounds	Yes No	87 239	26.7 73.3
	Living in nursing homes and communal living settings	True False	100 224	30.9 69.1	Bed bug or mosquito bites	Yes No	40 286	12.3 87.7
Creating risk of non-response to hepatitis B vaccination	Being over 40 years old	Yes No	136 190	41.7 58.3	Shared use of toothbrushes and razors	Yes No	132 194	40.5 59.5
	Obesity	Yes No	114 212	35.0 65.0	From mother to baby during pregnancy	Yes No	144 182	44.2 55.8
	Gender	Yes No	62 264	19.0 81.0	Tattooing equipment	Yes No	137 189	42.0 58.0
	Chronic liver diseases	Yes No	154 172	47.2 52.8	Ear piercing	Yes No	116 210	35.6 64.4
	HIV	Yes No	193 133	59.2 40.8	Blood transfusion	Yes No	209 117	64.1 35.9
	Diabetes mellitus	Yes No	94 232	28.8 71.2	Dental treatment	Yes No	97 229	29.8 70.2
	Celiac disease	Yes No	59 267	18.1 81.9	Procedures like manicure and pedicure	Yes No	84 242	25.8 74.2
	Smoking	Yes No	110 216	33.7 66.3				

HIV: Human immunodeficiency virus

received education about hepatitis B.[13] The findings of our study fall between these two studies, suggesting that the level of education received about hepatitis B may vary depending on the university, faculty, curriculum, academic year, and particularly the high proportion of first-year students in the sample of the present study.

It was determined that 77.3% of the students received hepatitis B vaccine, and 67.9% of them received the vaccine after starting their education in the nursing department. However, only 29% of them had completed the vaccine dose. It was found that 56.8% of the students did not receive the vaccine since they already had sufficient antibody levels. 77.8% of the students, who received the vaccine, stated that they had sufficient antibody levels. In the studies conducted, it was found that the vaccination rates among students varied between 39.5% and 93%.[9,10,13-15] The 77.3% vaccination rate identified in our study falls within the reported range and represents a relatively high level. Differences in vaccination rates across studies may be attributed to factors such as sample characteristics, institutional vaccination policies, the geographic region where the research was conducted, and whether hepatitis B vaccination is mandatory prior to clinical placements. In the study by Şahin[13], the vaccination rate was reported as 39.5%, which may reflect lower awareness or limited accessibility to vaccines at that time. In contrast, the 93% rate reported by Saç et al.[14] may be associated with mandatory screening protocols implemented before clinical practice or institutional vaccination requirements. These variations indicate that the level of hepatitis B vaccination among healthcare students is shaped not only by individual decisions but also by institutional health policies, the timing of educational interventions, and recommendations based on antibody screening.

While 19.9% of the students stated that they had previously cared for a patient diagnosed with hepatitis B, 62.6% expressed concerns about being infected with hepatitis B while providing care. In a study conducted by Koç et al.[16] it was found that 88.9% of the students were afraid of being

Table 4. Distribution of students' knowledge levels on hepatitis and vaccine hesitancy scores (n=326)

Variables		n	%
There is carrier status in hepatitis B.	True False I don't know	251 24 51	77.0 7.4 15.6
There is a hepatitis B vaccine.	True False I don't know	316 6 4	96.9 1.8 1.2
Among viral hepatitis, hepatitis B has the highest transmission level.	True False I don't know	194 30 102	59.5 9.2 31.3
Hepatitis B virus can survive in inanimate environments.	True False I don't know	117 68 141	35.9 20.9 43.3
When hepatitis B becomes chronic, it can progress to cirrhosis and hepatocellular carcinoma.	True False I don't know	193 17 116	59.2 5.2 35.6
Hepatitis B immunoglobulin should be given to newborns from mothers infected with hepatitis B virus.	True False I don't know	244 15 67	74.8 4.6 20.6
Hepatitis B vaccines prevent the development of hepatocellular carcinoma and cirrhosis.	True False I don't know	149 40 137	45.7 12.3 42.0
Hepatitis B is included in the routine vaccination schedule.	True False I don't know	235 42 49	72.1 12.9 15.0
Number of correct answers/knowledge level	Mean±SD	5.22±1.92	R=0.00-8.00
Lack of trust	Mean±SD	25.46±6.21	R=9.00-35.00
Risks	Mean±SD	5.79±1.22	R=2.00-10.00
Total VHS score	Mean±SD	31.25±6.18	R=15.00-41.00

R: Range, VHS: Vaccine hesitancy scale, SD: Standard deviation

Table 5. The effect of students' sociodemographic characteristics on their knowledge level regarding hepatitis B (n=326)

Variables		Mean±SD	Significance
Class	1 2 3 4	4.81±1.85 5.40±2.17 5.58±1.65 5.63±1.98	F=4.172 p=0.006
Age		20.68±1.68	r=0.082 p=0.142
Gender	Male Female	5.31±1.89 4.92±2.02	t=1.551 p=0.122
Current residence	Living with relatives Living with family Living with friends Living alone Dormitory	5.31±1.74 5.69±1.93 5.00±1.77 5.10±2.00 5.05±1.80	F=0.634 p=0.594
High school graduated from	Anatolian high school Science high school Health vocational high school General high school Other	5.29±1.85 4.96±2.11 5.38±1.49 5.46±2.09 4.83±2.31	F=0.725 p=0.575
Family type	Nuclear Extended Broken	5.25±1.86 5.23±1.83 4.66±2.93	F=0.790 p=0.455
Economic status	Income is less than expenses Income equals expenses Income exceeds expenses	5.36±2.09 5.18±1.85 5.33±2.24	F=0.230 p=0.795
Mother's educational level	Literate/illiterate Primary school Middle school High school University and higher	4.91±1.81 5.27±1.88 5.65±1.84 4.85±2.03 5.27±2.05	F=1.714 p=0.147
Father's educational level	Literate/illiterate Primary school Middle school High school University and higher	4.31±1.85 5.40±1.75 5.50±1.68 5.41±2.03 4.71±2.06	F=3.017 **p=0.018**
Smoking status	I do not use I use I quit	5.29±1.93 5.00±1.70 3.66±1.93	F=3.417 **p=0.034**
Alcohol consumption status	I do not use I use I quit	5.22±1.95 5.21±1.70 5.00±0.00	F=0.013 p=0.987

F: One-way ANOVA test, SD: Standard Deviation

Table 6. The effect of students' health-related characteristics and hepatitis-related thoughts/attitudes on their knowledge level regarding hepatitis B (n=326)

Variables		Mean±SD	Significance
Presence of chronic disease	Yes	4.96±1.90	t-0.714
	No	5.24±1.93	p=0.476
Presence of hepatitis	Yes	4.60±1.64	t=-1.034
	No	5.24±1.93	p=0.302
Presence of an individual with a chronic disease in the family	Yes	5.51±1.73	t=1.978
	No	5.06±2.00	**p=0.049**
Presence of an individual diagnosed with hepatitis in the family	Yes	5.00±1.96	t=-0.485
	No	5.23±1.92	p=0.628
Knowledge of hepatitis	Yes	5.44±1.75	t=3.924
	No	4.12±2.35	**p=0.000**
Receiving education about hepatitis B infection and hepatitis B vaccination	Yes	5.47±1.70	t=2.405
	No	4.96±2.09	**p=0.017**
Receiving hepatitis B vaccination	Yes	5.30±1.80	t=1.292
	No	4.93±2.28	p=0.199
Providing care to patients diagnosed with hepatitis B	Yes	5.76±1.55	t=2.988
	No	5.08±1.98	**p=0.003**
Concerns about hepatitis B transmission while providing care	Yes	5.38±1.88	t=2.025
	No	4.94±1.97	**p=0.044**

t: t test, SD: Standard deviation

Table 7. The relationship between students' knowledge level regarding hepatitis B and vaccine hesitancy (n=326)

Variable		Lack of trust	Risks	VHS total
Knowledge level regarding hepatitis B	r	0.150	-0.061	0.138
	p	**0.007**	0.271	**0.012**

r: Pearson correlation test, VHS: Vaccine hesitancy scale

infected with hepatitis B, and 69.9% experienced stress while caring for a patient with hepatitis B. Similarly, in the study conducted by Abdela et al.[17] 77.2% of medical and health sciences students reported being concerned about the risk of HBV infection. The findings of our study are consistent with the literature, indicating that students tend to experience anxiety in situations involving contact with patients infected with HBV.

The top three hepatitis risk group was stated by the students as follows; those who injected drugs with the same injector by 77.8%, those who had blood transfusion by 72.2%, and those who were in heterosexual relationships by 63.9%. In a study conducted on nursing students, the risk of hepatitis B transmission through contaminated blood and blood products was found to be 77.6%, the risk of transmission through unsterilized injectors and surgical instruments was 88.7%, and the risk of transmission through unprotected sexual intercourse was 81.8%.[18] In a study conducted on nursing students in India, the students ranked the modes of hepatitis B transmission in the following order of risk: multiple sexual partners, blood transfusion, and the use of non-sterile injectors.[19] While the ranking and proportions in our study are generally consistent with trends reported in the literature, the differences observed regarding sexual transmission are particularly noteworthy. These discrepancies may be attributed to cultural factors, the scope of sexual health education and whether such topics are openly discussed within the participants' communities. Additionally, in some studies, participants were asked to rank the risk factors, whereas in our study, they were asked to directly identify high-risk groups, which may have influenced the distribution of responses. Considering all these factors, it can be concluded that students' awareness of the transmission routes of hepatitis B is largely consistent with the existing literature.

The students stated that the primary modes of hepatitis transmission were: 93.6% through blood, 78.8% through needlestick injuries with infected injectors, and 72.7% through sexual intercourse. In a study conducted by Balegha et al.[20] 90.8% of nursing students stated that hepatitis B was transmitted through blood, 81.8% through unprotected sexual intercourse, and 79.8% through mother-to-child transmission. In a study conducted by Barçın and Taşova[21], 84.7% of university students stated that hepatitis B was transmitted through blood, 66.3% through sexual intercourse, and 63.4% through the shared use of needles or sharp objects. In the study of Salduz and Özder[10], 94.7% of the students stated that the hepatitis virus can be transmitted through blood, 64.5% mother-to-child transmission, 72.9% sexual contact, 53.8% body fluids, and 9.2% respiratory transmission. In the study conducted by Ünsar et el.[22] it was found that 94% of nursing students and 71.8% of physiotherapy and rehabilitation students were aware of the transmission modes of HIV/AIDS, hepatitis C, and hepatitis B. Minor differences in the reported rates may be attributed to variables such as the educational level of the sample group, type of faculty, average age of participants, and even the timing of the study in relation to public health awareness events. In addition, variations in the structure of the questions, such as whether they were multiple-choice, ranking, or open-ended, and the data collection environment, whether online or face-to-face, may also contribute to discrepancies in the findings. In our study, parenteral routes such as blood transmission and the use of contaminated needles were the most frequently reported modes of transmission, which may indicate a heightened awareness among nursing students regarding occupational exposure. Overall, it can be concluded that students' level of awareness regarding the primary transmission routes of hepatitis B is consistent with the literature and can be considered satisfactory.

The information that students most accurately knew about hepatitis was the existence of a hepatitis B vaccine (96.9%) and carriers (77%). In a study conducted in Bangladesh, 82.6% of nursing students stated that HBV can be prevented through vaccination, and 75.6% stated that hepatitis B carriers (those who are not ill) can transmit infection to others.[18] In a study conducted on nursing students in India, 76.61% of the students stated that there was a vaccine for hepatitis B.[19] When our findings are compared with the literature, it is observed that there are certain differences in the levels of awareness about the hepatitis B vaccine among students from different regions. This situation is thought to result from the differences in the content of health education programs and awareness campaigns conducted in different regions.

The students' level of knowledge about hepatitis was at the moderate level (5.22±1.92). In studies conducted among healthcare students in Ghana (59.5%) and Egypt (57.85%), the students' level of knowledge was reported to be moderate and

sufficient.[12,23] In another study conducted in Ethiopia among students studying in the healthcare field (86.2%), the students' level of knowledge was determined to be high.[17] Our study results reveal that the level of knowledge about hepatitis B is still not at the desired level. The difference in study results is believed to result from variations in the inclusion criteria, education systems, and sample size.

The total score that students obtained from the vaccine hesitancy scale (31.25±6.18) and the subscale scores were at the moderate level (lack of trust 25.46±6.21; risks 5.79±1.22). In the study conducted by Saç et al.[14] it was stated that nursing students identified vaccination as the best way to protect against hepatitis B. In a study conducted by Shrestha et al.[24] it was found that 86.7% of the students believed that the hepatitis B vaccine is safe and effective. In the study conducted by Açıkgöz et al.[15] on students in health departments, 19% of the students expressed that they did not trust the protective effect of the hepatitis B vaccine, and 48% stated that they were not afraid of hepatitis B infection. Studies report that students studying in the healthcare field have varying levels of hesitancy regarding the vaccine. This situation is believed to result from differences in inclusion criteria, such as whether students have received education on hepatitis B infection and the hepatitis B vaccine, or whether there are individuals diagnosed with hepatitis in their family.

In this study, nursing students were found to have a moderate level of vaccine hesitancy based on the mean scores obtained from the vaccine hesitancy scale. This finding indicates that even individuals who are expected to take an active role in future healthcare services may experience uncertainty in their attitudes toward vaccination. In a systematic review conducted by Pavlovic et al.[25] on healthcare professionals across Europe, it was reported that healthcare workers may experience vaccine hesitancy, and in some studies, students in health-related fields were also included in the study samples. The same review provided specific findings regarding Turkiye, highlighting that healthcare professionals in the country expressed doubts about the necessity of certain vaccines, demonstrated hesitancy regarding the reliability of vaccination information sources, and that negative media coverage contributed to a decline in vaccine confidence. These findings are consistent with the moderate level of hesitancy observed in our study and emphasize the ongoing need for awareness and education on vaccination, particularly within the Turkish context. Moreover, Paterson et al.[26] emphasized that healthcare professionals' attitudes toward vaccines can directly influence public confidence in immunization programs. In this context, the presence of vaccine hesitancy among nursing students should be considered not only an individual-level issue but also a potential risk to public health. Based on these findings, it is important that structured vaccine literacy programs be integrated into nursing curricula. Similarly, national immunization strategies should be designed to target not only the general public but also healthcare students, in order to build long-term vaccine confidence and strengthen public health efforts.

It was found that the students' sociodemographic characteristics, particularly their class level, affected their knowledge level about hepatitis B ($p<0.05$). This situation is believed to result from the fact that the majority of the group included in the study were first-year students. In institutions that provide education and training in the healthcare field, basic information is included in the first-year curriculum, while courses covering diseases, risk factors, prevention methods, treatment and care are thought in later years. A study conducted in Bangladesh also mentioned that students' knowledge level increased since they progressed through their classes, with third-year students, in particular, having more knowledge about hepatitis B. It was stated that this situation indicated the need for basic information provided at the beginning of the educational process to be reinforced with more specific and clinical knowledge in subsequent years.[18,27] In addition, in a study conducted by Çetin et al.[28] to evaluate vaccine hesitancy among health students, it was found that trust in vaccines increased as the year of study progressed.

It was found that father's educational level affected the students' knowledge level about hepatitis B ($p<0.05$). In studies conducted in Ethiopia and Ghana, it was observed that sociodemographic characteristics, particularly the educational level of the mother and father, affected the students' knowledge level about hepatitis B.[12,17] When parents have a higher level of education, their awareness of the importance of having knowledge about health increases, and they motivate their children to learn as well.[29,30] Furthermore, it is believed that the profession of parents, along with the fact that men generally occupy positions in the workforce in a large part of society, and the associated increase in social interaction among men, also affects awareness on this subject.

It was found that the students' smoking status affected their knowledge level about hepatitis B ($p<0.05$). A study conducted among dentists in Monte Carlo reported that lifestyle factors such as alcohol consumption and tobacco use were negatively associated with hepatitis B vaccine uptake.[31] The study estimated that non-smokers and individuals who did not consume alcohol were 2.5 and 3 times more likely, respectively, to receive the hepatitis B vaccine compared to their counterparts. Smoking is one of harmful habits to health. Smoking is an indication of individuals level of care and concern for their own healths. Individuals who care about their health are actively in an effort to maintain and improve their well-being. This effort increases the tendency to seek knowledge on health-related subjects.[32]

It was found that having a family member with a chronic disease affects the students' level of knowledge about hepatitis B ($p<0.05$). The presence of a chronic disease in the family leads to other family members experiencing the entire disease process, from start to finish, and closely observing the symptoms, complications, and limitations associated with the disease. This situation reflects on individuals' attitude towards protecting and improving their own health.[33]

It was found that obtaining information from various sources and receiving education about hepatitis B infection and hepatitis B vaccine affect the level of knowledge about hepatitis B ($p<0.05$). As individuals continuously research and learn about any health-related topic and receive education, their knowledge and awareness levels increase.[20] Education is

the most important and effective tool that contributes to the increase in knowledge level. In a study conducted in India, it was observed that the students' knowledge levels about hepatitis B and C significantly increased after educational intervention.[34]

It was determined that providing care to patients diagnosed with hepatitis B and the concern about being infected with hepatitis B while providing care affected the students' level of knowledge about hepatitis B ($p<0.05$). In the study conducted by Açıkgöz et al.[15], it was detected that as the level of knowledge about HBV infection increased, protective behaviors also increased. As an individual's level of knowledge about infectious diseases, risk factors, modes of transmission, and prevention methods increases, the attitude towards providing care improves positively, and the concern about being infected decreases.[35] Considering that the majority of the sample group consisted of first-year students who had not yet received formal education on hepatitis B infection, and that the number of individuals in this group who obtained information about hepatitis B infection from various sources might be low, this is considered an expected result.

A significant relationship was determined between the students' level of knowledge about hepatitis B and their vaccine hesitancy ($p<0.005$) In the study conducted by Türkoğlu et al.[36] it was determined that the most important reason for vaccine hesitancy/refusal was identified as lack of knowledge (41.6%). In another study conducted in Europe on vaccine hesitancy, lack of knowledge was also determined as one of the most influential factors (50%) affecting vaccine hesitancy.[32] These studies reveal that, even in different geographical regions, lack of knowledge is a significant factor influencing vaccine hesitancy. This situation indicates that increasing students' level of knowledge is an important step in terms of reducing vaccine hesitancy.

Limitations

Due to the use of convenience sampling and the fact that the study was conducted in a single institution, the generalizability of the findings to all nursing students may be limited. Future studies with randomized sampling and multi-center designs are recommended to enhance generalizability. In addition, the lack of questioning the parents' professions and the disregard for the class distribution balance made it difficult to interpret certain results.

CONCLUSION

The knowledge level about hepatitis B and the level of vaccine hesitancy among nursing students are at the moderate level. The level of knowledge is a factor affecting vaccine hesitancy. It is recommended to provide education and awareness programs for nursing students to increase their knowledge level and reduce vaccine hesitancy.

Although the study found that father's educational level affected the level of knowledge about hepatitis B, it could not be determined whether this was due to the level of education or father's profession. In future studies, professions of both the mother and father should be considered for evaluation.

Moreover, since the study was conducted with a small sample group and the class distribution was not balanced, the results of the study cannot be generalized. It is suggested to repeat the study with a larger sample group, ensuring balance between the classes.

In light of the findings, it is recommended to implement structured in-service training programs that emphasize the importance of hepatitis B infection and vaccination, particularly prior to the commencement of clinical practice. Increasing awareness through such initiatives may contribute to improved vaccination uptake and better preventive behaviors among healthcare students.

It is believed that the study, which evaluates the knowledge level and vaccine hesitancy of all healthcare science students, especially nursing students, in the hepatitis B risk group, will lead to new studies by increasing awareness about filling the knowledge gap and reducing vaccine hesitancy. It is predicted that this situation will contribute to a decrease in healthcare expenditures and workforce losses, along with an increase in vaccination rates.

The findings of this study indicate that vaccine hesitancy persists even among nursing students, who are expected to be knowledgeable and proactive regarding preventive health measures.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Uludağ University Faculty of Medicine Clinical Researches Ethics Committee (Date: 30.05.2023, Decision No: 2023-12/8).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author declares no conflicts of interest.

Financial Disclosure

The author declares that this study received no financial support.

Author Contributions

The author declares that they participated in the design, execution, and analysis of the paper, and that they approved the final version.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1671815

Anatolian Curr Med J. 2025;7(3):353-357

Assessment of salt knowledge and habits in patients with high low-density lipoprotein cholesterol

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Cite this article as: Akın B, Dilek M. Assessment of salt knowledge and habits in patients with high low-density lipoprotein cholesterol. *Anatolian Curr Med J.* 2025;7(3):353-357.

Received: 08.04.2025 ◆ **Accepted**: 14.05.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: Excessive dietary salt intake is a major contributor to cardiovascular morbidity and mortality. Patients with elevated low-density lipoprotein cholesterol (LDL-C) are at increased risk, but there is limited data on their salt knowledge and habits. This study aimed to assess salt-related knowledge and dietary behaviour in patients with hyperlipidaemia.

Methods: A prospective cross-sectional study was conducted among 100 patients with LDL-C ≥160 mg/dl attending the Internal Medicine Outpatient Clinic of Ondokuz Mayıs University. Participants completed three face-to-face questionnaires assessing demographic and clinical characteristics, salt knowledge (20-item test), and frequency of consumption of salty foods. Data were analysed using descriptive statistics and comparison tests (t-test, Mann-Whitney U, Chi-square), with $p<0.05$ considered statistically significant.

Results: Salt knowledge scores ranged from 5 to 19 correct answers. Patients with higher education had significantly better salt knowledge ($p<0.0001$), whereas older adults and married individuals had lower scores. There were no significant differences according to sex, BMI or self-reported low-salt diet. Only 10% of participants reported receiving education about salt intake. Feta cheese was the most commonly consumed salty food, while unsalted bread was rarely preferred. Despite high LDL-C levels, many patients lacked an adequate understanding of the health risks associated with salt.

Conclusion: There is a substantial gap in salt-related knowledge in patients with high LDL-C, particularly in older and less educated individuals. Targeted educational interventions addressing salt consumption may improve dietary practices and support cardiovascular risk reduction in this vulnerable group.

Keywords: LDL cholesterol, salt intake, dietary behavior, hyperlipidemia

INTRODUCTION

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality worldwide, accounting for approximately 17.9 million deaths annually, with elevated low-density lipoprotein cholesterol (LDL-C) identified as a major modifiable risk factor.[1] Elevated LDL-C promotes atherosclerosis by facilitating lipid accumulation within arterial walls, contributing to plaque formation and vascular inflammation. Pharmacological interventions, such as statins, have been shown to be effective in lowering LDL-C levels. However, lifestyle modifications, particularly dietary interventions, are also essential for comprehensive cardiovascular risk reduction.[2]

Excessive dietary salt intake has been associated with the development and progression of hypertension, endothelial dysfunction and left ventricular hypertrophy, all of which increase the risk of CVD events.[3] In addition, several studies suggest that high sodium intake may adversely affect lipid metabolism, potentially exacerbating dyslipidaemia by increasing serum total cholesterol and LDL-C levels.[4] Despite global recommendations for a daily salt intake of less than 5 g, actual consumption remains significantly higher in most populations.[5] The interplay between salt intake and lipid parameters, including LDL-C, highlights the importance of public awareness and individualised dietary counselling in patients with dyslipidaemia.[2,3]

In this context, patients knowledge and behaviours regarding salt consumption play a critical role in disease prevention and management. Previous research has highlighted significant gaps in the publics understanding of hidden dietary sources of sodium, recommended intake levels and the health effects of excessive salt consumption.[6] This study aims to assess the level of salt-related knowledge, attitudes and consumption habits in patients with high LDL-C. By identifying behavioural patterns and potential knowledge deficits, this research aims to inform targeted dietary education strategies that may contribute to improved lipid control and overall cardiovascular health.

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METHODS

Ethics

The study was carried out as a thesis at Samsun Ondokuz Mayıs University in 2013 (Thesis No: 340568). Prior the study, institutional approval was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Setting

This study was designed as a prospective cross-sectional analysis and was conducted between 2012 and 2013 at the Internal Medicine Outpatient Clinic of Ondokuz Mayıs University Faculty of Medicine.

Study Population

A total of 100 adult patients (aged ≥18 years) with hyperlipidemia and serum LDL-C levels ≥160 mg/dl were included. Exclusion criteria included the presence of chronic renal insufficiency, diabetes mellitus, high salt intake due to hypotension, and moderate to poor general health that might affect participation or data reliability.

Data Collection Tools

A structured 14-item questionnaire was developed to assess the personal and clinical characteristics of the participants. Seven items focused on demographic variables, while the remaining questions covered duration of hypercholesterolaemia, presence of comorbidities, use of cholesterol-lowering medication, most recent LDL-C level, most recent blood pressure measurement and, for hypertensive patients, seven additional questions related to blood pressure management.

Salt knowledge was assessed using a 20-item multiple-choice questionnaire. This instrument included seven questions to assess general knowledge about salt and its health effects and 13 questions to assess awareness of the salt content of various commonly consumed foods. The questionnaire was developed using a combination of evidence-based sources, including dietary guidelines related to hyperlipidaemia, scientific publications on food content and salt intake, and national data from the Turkish Ministry of Health on the salt content of various foods. In addition, general information on dietary salt and its health effects, as well as food-specific sodium content, was included based on relevant educational materials and previous literature.[7-9]

Dietary habits were assessed with a questionnaire focusing on the frequency of consumption of high-sodium foods traditionally consumed in Turkiye, such as pickles, feta cheese, bagels/pastries and salted nuts. Participants were also asked about the frequency of eating out, daily bread consumption and the use of unsalted bread.

All questionnaires were administered in face-to-face interviews by trained researchers to ensure data consistency, accuracy and completeness.

Statistical Analysis

The data analyses were performed using appropriate parametric or non-parametric tests based on the distribution of the data. Student's t-test or Mann-Whitney U test was used to compare continuous variables between two independent groups. Categorical variables were analysed using the Chi-square test or Fisher's exact test, where appropriate. A two-tailed p-value<0.05 was considered statistically significant.

RESULTS

A total of 100 patients with elevated LDL-C levels (≥160 mg/dl) were included in the study. The majority were male and under 60 years of age. Most participants had a low level of education and a large proportion were illiterate or had only completed primary school. The most common occupational groups were civil servants and homemakers. Nearly two-thirds of participants reported comorbid conditions, with hypertension being the most common, followed by coronary heart disease and other chronic conditions such as hypothyroidism and hepatic steatosis. Detailed demographic and clinical characteristics of the study population are shown in Table 1.

Table 1. Demographic and clinical characteristics of patients and their salt knowledge test scores

Variable	n (%)	Salt knowledge score (mean±SD)	p-value
Age			
<60 years	62 (62)	13.3±2.58	<0.0001
≥60 years	38 (38)	10.8±3.03	
Sex			
Female	56 (56)	12.0±3.06	<0.124
Male	44 (44)	12.6±2.93	
Education level			
Primary school or below	68 (68)	11.6±2.70	<0.0001
Secondary school and above	32 (32)	15.0±2.18	
Marital status			
Married	86 (86)	12.1±2.97	<0.0001
Single/divorced/widowed	14 (14)	13.9±2.65	
Comorbid conditions			
Hypertension (+)	41 (41)	12.8±3.29	0.038
Hypertension (-)	59 (59)	12.4±2.81	
CAD (+)	24 (24)	12.4±3.62	0.007
CAD (-)	76 (76)	12.7±2.96	
BMI			
≥30	30 (30)	13.0±3.10	>0.05
<30	70 (70)	12.0±3.03	

CAD: Coronary artery disease, BMI: Body-mass index

The 20-question salt knowledge test yielded scores ranging from 5 to 19 correct answers. When test scores were analysed by demographic and clinical characteristics (Table 1), patients under 60 years of age scored significantly higher than those aged 60 years and older (p<0.0001). Similarly, patients with a higher level of education had significantly better salt knowledge than those with only primary education or no formal education (p<0.0001). Married individuals and women had lower mean scores than their counterparts (p<0.0001 for both comparisons) (Table 1).

Patients with hypertension and those with CVD had slightly higher scores, with statistically significant differences observed (p=0.038 and p=0.007, respectively). However, there was no statistically significant difference in salt knowledge scores between obese (BMI ≥30) and non-obese patients (p>0.05). In addition, no correlation was found between salt knowledge scores and measured blood pressure or LDL-C levels (**Table 1**).

Of the participants, 58% considered their meals to be low in salt, 39% described them as normally salted and 3% reported higher than normal salt levels. When asked if they followed a low-salt diet, 45% said they did and 55% said they did not. There was no statistically significant difference in salt knowledge scores between those who reported following a salt restricted diet and those who did not (p>0.05). Similarly, no significant difference was found between patients who reported adhering to a salt restricted diet (42%) and those who did not (58%) (p>0.05).

Only 33% of patients were aware that they needed to reduce their salt intake and only 10% had received formal education about salt and its health effects. Sources of information included doctors (30%), nurses (20%), dietitians (10%), peers (10%) and other sources (30%).

The dietary habits of the participants with regard to high-salt foods are summarised in **Table 2**. The most commonly consumed salty food was feta cheese, consumed daily by 68% of patients. Pastries such as bagels, simit and börek were consumed weekly by 29% of the patients. Only 9% of participants reported daily consumption of unsalted bread.

Table 2. Frequency of consumption of selected salty foods

Food item	Daily n (%)	1–3 times/week n (%)	Less than once/week n (%)
Pickles	3 (3.0)	14 (14.0)	83 (83.0)
Feta cheese	68 (68.0)	20 (20.0)	12 (12.0)
Pastry (simit/börek)	9 (9.0)	29 (29.0)	62 (62.0)
Salted nuts	1 (1.0)	17 (17.0)	82 (82.0)
Eating out	11 (11.0)	5 (5.0)	84 (84.0)
Unsalted bread	9 (9.0)	20 (20.0)	71 (71.0)

In terms of bread consumption, 51% of patients ate less than half a loaf a day, 38% ate between half a loaf and a loaf, and 11% ate more than a loaf a day. While 44% of patients reported that meals were cooked without salt at home, only 16% reported that special meals were prepared for them, of which 2% were low-salt, 6% low-fat and 8% both low-fat and low-salt. In addition, 6% of patients used artificial salt and 7% reported adding salt to food before tasting it.

DISCUSSION

Salt, which plays a fundamental role in maintaining intravascular and extravascular volume is essential for human life. However, several studies have shown that excessive salt consumption is associated with many health problems, including hypertension, CVD, metabolic syndrome, cancer, osteoporosis and autoimmune diseases.[10-16]

The health problems caused by a high-salt diet are increasingly recognised, and the World Health Organisation (WHO) recommends that daily salt intake should not exceed 5 g.[17] However, due to cultural differences, the average in many countries exceeds 8 g.[18] The SALTURK study conducted in Turkiye reported an average daily salt intake of 18 g.[19]

Hyperlipidaemia is one of the most important independent risk factors for coronary heart disease. Many studies have shown that endothelium exposed to oxidised forms of LDL-C leads to impairment of endothelium-dependent vasodilation with increasing exposure time.[20]

This study assessed salt knowledge and dietary habits in people with high LDL-C, a group at high risk of cardiovascular disease. The results showed that salt knowledge scores were lower in older age groups, those with a low level of education and married people. Although the general level of awareness is moderate, lack of knowledge about salt intake and its effects on health is still widespread, even in high-risk groups.

Previous studies have shown that excessive salt intake has adverse effects not only on hypertension, but also on lipid metabolism and vascular function, and thus may accelerate the progression of atherosclerosis in hyperlipidaemic individuals.[3,21-23]

It has been reported that 86% of hypertensive individuals in the USA exceed the recommended daily sodium intake of 2.3 g.[24] In our study, no significant difference was observed between hypertensive and normotensive individuals in the preferred salt content of meals. Forty-two per cent of the participants reported that they ate their meals with normal or more than normal salt.

Although 58% of respondents reported having a low/normal salt diet, this behaviour was not associated with higher knowledge scores. This suggests that salt restriction is mostly based on medical advice or routine habits, rather than on a conscious knowledge base.

Education level emerged as a strong determinant of salt knowledge, in line with previous studies.[25] Individuals with at least secondary education had significantly higher knowledge scores than those with only primary education or no education. These results highlight the importance of tailoring dietary recommendations and educational interventions to individuals' health literacy.

The relationship between hypertension and dietary sodium intake has been confirmed in many studies, and obesity is known to be an independent risk factor for hypertension.[26,27] A study conducted in China showed that blood pressure in patients with metabolic syndrome was associated with increased salt sensitivity.[28] In addition, some studies have reported that high salt intake also promotes the development of obesity.[29,30] However, this study did not find a significant difference in salt knowledge scores between obese and non-obese individuals. This suggests that salt knowledge may be independent of body composition and that messages for at-risk groups should be disseminated throughout society.

Another striking finding was that the proportion of people who had received formal education about salt was only 10%. The majority of participants said they received their information from doctors. This finding suggests that health professionals should play a more active role in educating patients. Structured counselling practices during clinical visits can help to fill knowledge gaps.

Processed foods contain high levels of salt for reasons such as enhancing flavour, prolonging shelf life and preventing microbial growth.[31] According to the WHO, the main sources of salt are processed products, ready-to-eat meals and salt added during food preparation or at the table.[32] In a global meta-analysis of dietary salt sources, bread, cereal products, meat and dairy products were shown to be the main sources.[33] It is estimated that 25-40% of the daily salt intake in the USA and other western countries comes from bakery products.[34]

This study provides important insights by showing that individuals with high LDL-C levels have increased salt intake depending on their dietary habits. Our results showed that this group often consumed high-salt foods such as cheese and pastries, which is consistent with trends reported in the literature. It is known that 100 g of bread in Turkiye contains approximately 1.5-2 g of salt and according to the SALTURK 2 study, 34% of the total salt in Turkiye comes from bread.[35,36] In our study, approximately half of the patients consumed more than half a loaf of bread per day, which is not only a carbohydrate but also a significant source of salt. Unfortunately, the consumption of unsalted bread was quite low.

On the other hand, the habit of preparing food at home was more common than eating out, and 44% of patients reported cooking their meals without salt. This suggests that food preparation and consumption habits are culturally based and that these cultural factors should be taken into account in salt reduction strategies.

Although this study did not find a significant association between salt knowledge and LDL-C levels or blood pressure, it is important to remember that knowledge alone is not always effective in changing behaviour or clinical outcomes. Behaviour change is a complex process and requires ongoing interventions, environmental support and repeated incentives.

Important strengths of the study are that it was conducted using a structured face-to-face questionnaire and with a well-defined patient population. However, the cross-sectional design limits the ability to establish causal relationships, and self-report of dietary behaviour may be subject to recall or social desirability bias. In addition, the study was conducted in a single centre, which limits the generalisability of the findings.

Limitations

This study has several limitations that should be considered when interpreting the results. First, the cross-sectional design of the study precludes the establishment of causal relationships between salt knowledge and dietary behaviour or clinical parameters such as LDL cholesterol and blood pressure. In addition, the study was conducted in a single centre with a relatively small sample size, which limits the generalisability of the results to larger populations. Furthermore, although efforts were made to validate the salt knowledge questionnaire through expert review and pilot testing, the instrument was not formally validated on a larger scale, which may affect the robustness of the results. Future multicentre studies with longitudinal designs and larger, more diverse samples are needed to confirm and extend these findings.

CONCLUSION

As a result, this study demonstrates a critical need to improve salt knowledge and dietary behaviour in people with high LDL-C. Culturally appropriate and health literacy sensitive educational interventions should be integrated into routine health care for people with hyperlipidaemia. Increased knowledge of the health effects of salt may support more effective dietary changes and strengthen cardiovascular risk management.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out as a thesis at Samsun Ondokuz Mayıs University in 2013 (Thesis No: 340568).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

DOI: 10.38053/acmj.1618793

ANATOLIAN CURRENT MEDICAL

Anatolian Curr Med J. 2025;7(3):358-362

Association of serum pentraxin 3 levels with co-morbidities in acute ischemic stroke patients

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Cite this article as: Demirdöğen F. Association of serum pentraxin 3 levels with co-morbidities in acute ischemic stroke patients. *Anatolian Curr Med J.* 2025;7(3):358-362.

Received: 13.01.2025 ◆ **Accepted**: 17.05.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: Pentraxin 3 (PTX3), an indicator of the inflammatory process, is an acute-phase protein (AP) with biphasic effect. In the present study, the relationship between PTX3 levels and stroke risk factors in stroke patients were analyzed.

Methods: Acute stroke patients (n=56) were diagnosed using imaging techniques and clinical examination along with and their laboratory results. The control group consisted of thirty healthy individuals. Blood samples of the patient group were obtained within the first 24 hours of stroke onset. Serum pentraxin levels of both groups were analyzed and their relationship with stroke risk factors evaluated.

Results: A total of 86 people, 56 stroke patients and 30 healthy controls were included in the present study. Out of the participants, in both groups, 50% were female (p=1.000). No significant difference was determined between the groups in terms of age (p=0.226). The pentraxin value in the patient group was significantly lower than that in the control group (p=0.003). No significant difference between gender and presence of comorbidities in terms of PTX3 value (p>0.05) were present. Likewise, no significant correlation could be established between PTX3 value and National Institutes of Health Stroke Scale (NIHSS) and age in the patient group.

Conclusion: Serum PTX3 can be used as a biomarker in acute stroke patients. However, it cannot be used as a predicator in determining prognosis during the acute period.

Keywords: Stroke, pentraxin 3, NIHSS, comorbidity

INTRODUCTION

Stroke, either hemorrhagic or ischemic, is associated with high mortality and morbidity rates and is the second top cause of morbidity.[1] The Cui[2] study reported 7.3 million ischemic strokes in 2019. Associated financial burden spike up according to emerging motor deficits, re-hospitalization times, neurotic disorders such as anxiety and depression, loss of workforce, and stroke relevant psychocological, intellectual, functional and socio-professional problems.[3] Therefore, early diagnosis and treatment along a cost-effective disease management are of critical importance.

Various biomarker studies have been conducted for early stroke diagnosis and treatment. Soluble TNF-α receptor concentration was found to be high in recurrent vascular incidents and subsequent seizures.[4] IL-1β was found to have high plasma concentrations in stroke patients with clinical deterioration.[5] There are meta-analyses showing that Leptin with an anti-apoptotic activity, is detected at high levels as a risk biomarker in stroke patients.[6] An experimental study determined a significant association between low adiponectin levels and increased ischemic stroke mortality[7] mediated by NADPH oxidase inhibition and endothelial nitric oxide (NO) synthase phosphorylation.[8] A further study has established it as a potential biomarker for ischemic stroke along with other risk factors.[9] Interleukin-6 (IL-6)[10]and IL-10[11] plasma levels have been found to be significantly correlated with stroke size.

In the pathophysiology of stroke, inflammation increases ischemic injury and plays a role in recovery. Ischemia driven oxygen and glucose deficiency leads to disruption of the ionic gradient. The amount of intracellular calcium increases due to glutamate released from these depolarized neurons and apoptosis, activating necrotic and auto phagocytosis pathways. Intracellular calcium increase leads to mitochondrial dysfunction and activation of proteases, free radicals, and phospholipases. Calcium accumulated in the mitochondria causes the opening of the mitochondrial permeability transition pore (mtPTP) and the release of cytochrome c. As a result, cellular apoptosis occurs due to mitochondrial collapse. The intracellular entry of calcium, nitric oxide synthase (NOS) activation, NO production and free radical formation and inflammation caused by ischemia lead to the release of inducible NOS (iNOS) from neutrophils. Free radicals regulate the PI3-kinase/act pathway

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and r NF-kB transcription factor up. The triggering of P2X7 receptors in oligodendrocytes results with calcium increase and mitochondrial depolarization. There is also an increase in C-reactive protein level due to inflammation in stroke. Pentraxin 3 (PTX3) from the pentraxin family is also an acute-phase protein (APP).[12] Pentraxin 3, consisting of 381 amino acids, is secreted rapidly depending on the soluble receptor recognition pattern. PTX3 is considered to have a protective effect in inflammation.[13] Hemce, there are studies proposing it as a biomarker in cerebral and cardiovascular diseases.[14] In the present study, the relationship of PTX3 blood levels of acute stroke patients with chronic diseases and its potential as a biomarker is investigated.

METHODS

This study was approved by Erzincan Binali Yıldırım University Clinical Researches Ethics Committee (Date: 02.03.2023, Decision No: 2023-05/2). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Neurological examinations were performed and magnetic resonance images were obtained from all patients admitted to the stroke clinic of our hospital. Ischemic stroke was diagnosed using National Institute of Health Stroke Scale (NIHSS) and potential risk factors (diabetes, chronic renal failure, carotid stenosis, atrial fibrillation, congestive heart failure) were recorded. Routine blood samples were collected from patients within the first 24 hours of stroke onset. In the control group participants, blood samples were obtained according to convenience sampling method. Exclusion criteria were less than 18 years of age, presence of a systemic or chronic inflammatory disease history, antibiotype and non-steroidal anti-inflammatory therapy enrollment for the last 2 weeks, and recurrent stroke presence. In the age and gender matched control group, exclusion criteria were presence of lung, neurodegenerative, coronary artery disease history, and atrial fibrillation presence. Blood samples obtained from all participants of the present study were centrifuged at 3000 rpm for 10 minutes. The plasma portion was placed in Eppendorf tubes and stored at -80°C. After the samples were obtained, the blood samples were kept at 20°C overnight to ensure slow thawing. The next day, it was kept at +4°C and then brought to room temperature to enable complete thawing. PTX3 levels were measured using the commercially available enzyme-linked immunosorbent assay, QuantiGlo (R&D System Inc., Minneapolis, Minnesota, USA). MRI studies were performed with Siemens® Magnetom area 1.5-T and GE-HD 3-T MR devices with echo planar imaging system. Imaging protocol was defined with DWI weighted images. The parameters used for imaging were: TR/TE=9000/84 ms for 1.5 T MR examination; field of view (FOV)=230 mm; section thickness=4.0 mm; cross-sectional gap=1.5 mm. 3 for MRI MR/TE=6000/80 ms; field of view (FOV)=240 mm; section thickness=4.0 mm. In order to calculate infarct volume, Cavalieri method based on the diffusion weighted compared magnetic resonance images. In order to perform calculations with this method, special Stereo Investigator software and an image analysis system equipped with a point grid area measurement scale were employed.

Statistical Analysis

SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) 22 software was employed to analyze the data obtained in the present study. Descriptive data were presented as n, percentage values for categorical data, and median interquartile range (25-75 percentile values) for continuous data. Chi-square analysis (Pearson Chi-square) was used to compare categorical variables between groups. Compliance of continuous variables with normal distribution was evaluated using Kolmogorov-Smirnov test. Mann-Whitney U test was used for the comparison of paired groups. Spearman correlation test was used to analyze the relationship between continuous variables. Receiver operating characteristic (ROC) curves were drawn to measure the diagnostic value of venous PTX3 values. $p<0.05$ is the threshold level for statistical significance level is in the present study.

RESULTS

A total of 86 participants, 56 (65.1%) stroke patients and 30 (34.9%) controls, have participated in the study. 28 (50%) of those were male and 28 (50%) were female in the patient group and 15 (50%) of those were male and 15 (50%) were female in the control group. There was no significant difference between the groups in terms of age (p=0.226). The pentraxin value in the patient group is significantly lower compared to the control group (p=0.003) (**Table 1**).

Table 1. Comparison of group characteristics

	Patient (n=56)	Control (n=30)	p*
	n (%)	n (%)	
Gender (male, female)	28 (50.0)/28 (50.0)	15 (50.0)/15 (50.0)	1.000
	Median (IQR)	Median (IQR)	p**
Age	72.0 (61.0-79.0)	68.0 (65.0-76.0)	0.226
PTX3 (ng/ml)	2.8 (2.2-5.1)	5.0 (3.2-9.7)	0.003

*Square analysis, **Mann-Whitney U test, IQR: Interquartile range, PTX3: Pentraxin 3

The ability of venous PTX3 to predict acute ischemic stroke was investigated using ROC analysis and thus the cut-off value was determined. When 3.32 is taken as cut-off value for venous PTX3, a sensitivity of 69.6% and a specificity of 73.3% was determined indicating as PTX3 as a potential predictor (**Figure 1**).

Out of the stroke patients included in the study, 67.9% had hypertension (HT), 30.4% had atrial fibrilation (AF), 30.4% had coronary artery disease (CAD), 25% had hyperlipidemia (HL), and 21.4% had congestive heart failure (CHF), 19.6% had diabetes mellitus (DM), 19.6% had chronic renal failure (CRF) and 10.7% had a history of ischemic cerebrovascular disease (ICD) (**Figure 2**).

No significant difference was observed between gender (p=0.781), presence of DM (p=0.773), HT (p=0.261), CRF (p=0.257), AF (p=0.624), CAD (p=0.527), previous stroke

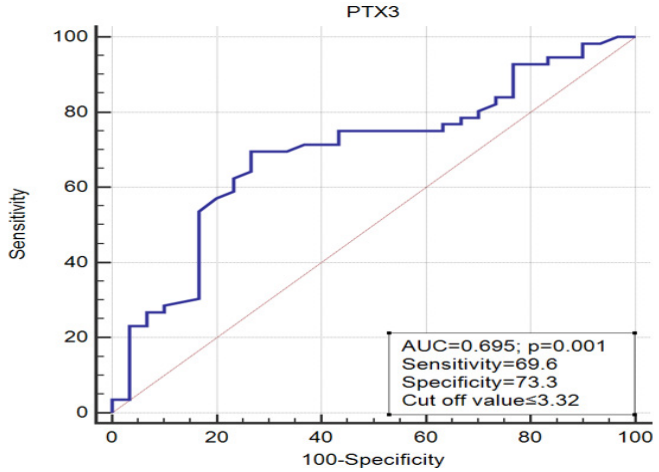

Figure 1. ROC curve of venous PTX3 value for acute ischemic stroke
ROC: Receiver operating characteristic PTX3: Pentraxin 3

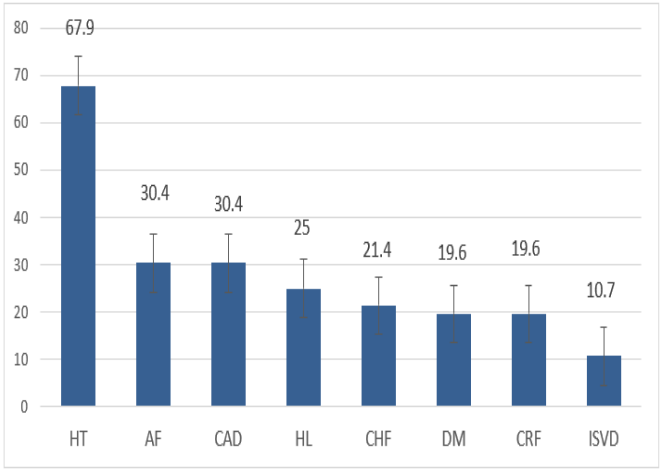

Figure 2. Stroke patients' co-morbidities
HT: Hypertension, AF: Atrial fibrilation, CAD: Coronary artery disease, HL: Hyperlipidemia, CHF: Congestive heart failure, DM: Diabetes mellitus, CRF: Chronic renal failure

(p=0.093), HL (p=0.820), and presence of CHF (p=0.448) in terms of PTX3 value (**Table 2**).

No significant correlation was observed in the patient group in terms of PTX3 value, NIHSS, and age(p= 0.478; p=0.704) respectively). There was no significant correlation between NIHSS value and age (r=0.027; p=0.843).

DISCUSSION

Stroke is a disease with a complex pathophysiology. Whereas activated pathways increase brain injury in the acute period, they also play a role in neurogenesis and angiogenesis in the chronic period. Several studies have shown that some plasma soluble factors have not only positive impacts, but also negative ones on the neurovascular unit (NVU).[15,16] VEGF, for instance, acts by disrupting the blood brain barrier (BBB) in acute ischemia. It also has a significant role in the recovery of brain tissue because it provides angiogenesis in the chronic period.[17] Similarly, MMP-9 damages NVU dysfunction in the acute period[18] and plays a role in neurogenesis and angiogenesis in the chronic period.[19] PTX3 also has a biphasic effect. Akihiro Shindo et al.[20] showed that GFAP-positive astrocytes are the major source of PTX3 in white matter strokes. Another study by Shindo et al.[21], in a rat model of focal

Table 2. Comparison of stroke patients' PTX3 values between gender and comorbidity variables

		PTX3 (ng/ml) Median (IQR)	p*
Gender	Male	2.7 (2.3-3.8)	0.781
	Female	2.9 (1.8-6.1)	
DM	+	2.7 (1.7-4.4)	0.773
	-	2.8 (2.4-5.7)	
HT	+	2.8 (2.0-3.8)	0.261
	-	2.9 (2.6-8.8)	
CRF	+	2.6 (1.9-3.2)	0.257
	-	2.9 (2.3-7.6)	
AF	+	2.9 (2.6-5.7)	0.624
	-	2.8 (2.0-4.4)	
CAD	+	2.9 (2.5-5.7)	0.527
	-	2.8 (2.0-4.4)	
ISVD	+	7.4 (3.2-26.5)	0.093
	-	2.8 (2.2-4.3)	
HL	+	2.8 (2.0-3.2)	0.820
	-	2.8 (2.3-5.7)	
CHF	+	2.7 (1.5-8.3)	0.448
	-	2.9 (2.3-5.1)	

*Mann Whitney U test was applied. PTX3: Pentraxin 3, IQR: Interquartile range, DM: Diabetes mellitus, HT: Hypertension, CRF: Chronic renal failure, AF: Atrial fibrilation, CAD: Coronary artery disease, HL: Hyperlipidemia, CHF: Congestive heart failure

grey matter ischemic stroke, reported that the major source of PTX3 was GFAP-positive astrocytes. PTX3 binds and inhibits VEGF which damages the BBB. Thus, it diminishes the impact of the potential injury. However, studies on the effect of PTX3 on tight junction proteins (such as ZO-1, claudins and occludins) are needed to determine the effectiveness of PTX3 on the BBB. Brain recovery requires coordination in neurogenesis and angiogenesis processes.[22] One study showed that downregulation of PTX3 promotes compensatory angiogenesis, while another study[20] reported that PTX3 in mice exhibited less angiogenesis after stroke.[23] Since cerebral white matter is mainly composed of axonal bundles surrounded by a myelin sheath, the process of differentiation-proliferation of oligodendrocyte precursor cells is very important in the development of effective treatments for white matter stroke.

In a study, it was found that PTX3 plasma levels were higher in acute cerebral ischemia patients compared to the control group. In the same study, it was found that elevated PTX3 level was correlated with elevated NIHSS and inversely correlated with HDL level.[14]

The present study determined that, PTX3 level, as a potential predictor, was significantly lower in the patient group than in the control group with 69.6% sensitivity and 73.3% specificity (p=0.003). The difference between the studies was thought to be due to genetic polymorphism.[24]

In a study on acute myocardial infarction, PTX3 was found to have a higher prognostic value compared to CRP, troponin T and creatine kinase.[25] Ahrițculesei et al.[26] found that PTX3, CRP, TNF-α, and IL-6 levels were higher in type 2 diabetic

patients compared to prediabetic patients. Soeki et al.[27] found that PTX3 levels were higher in blood from the left atrial appendage compared to blood from the peripheral artery in atrial fibration. In an experimental study, PTX3 was shown to lower blood pressure and improve inflammation and cardiomyocyte apoptosis in rats.[28] In a study conducted in patients with chronic kidney disease (CKD), serum PTX3 levels were found to be high.[29] In a study of patients with heart failure (HF) and normal ejection fraction, elevated basal circulating levels of PTX3 have been shown to be associated with increased cardiovascular mortality or worsening of HF (70).[30] In a study by Yi et al.[31] on the severity of carotid artery stenosis, PTX3 and LDL-C levels were correlated. However, Lee et al.[32] showed that PTX3 and HDL-C levels were positively correlated. In the present study, no significant differences in PTX3 levels across both sexes and the presence of comorbidities (diabetes mellitus, atrial fibrillation, hypertension, chronic renal failure, congestive HF, coronary artery disease, hyperlipidemia) were determined (p>0.05).

PTX3, which promotes long-term recovery of cerebral blood flow, angiogenesis and neuronal viability after cerebral ischemia, is among the therapeutic targets.[33] There are studies showing that PTX3 is an indicator of mortality and poor prognosis after ischemic stroke.[34,35]

There was no significant relationship between neurological recovery and long-term prognosis in ischemic stroke patients treated with thrombolytic therapy.[36] Zhang et al.[37] found that serum PTX3 level was elevated in patients with acute minor stroke due to large arterial atherosclerosis and was an indicator of unfavorable outcome together with LDL cholesterol. In the present study, there was no significant correlation between PTX3 and NIHSS (p>0.05, p=0.478). A further study determined that PTX3 level did not change according to gender and increased proportionally with age in stroke patients,[34] whereas no significant difference was determined in terms of gender and age in another study.[38] In the present study, no statistically significant difference was found between PTX3 and gender and age (respectively, p=0.781, p=0.704).

Limitations

The limitations of the present study are as follows; Limited number of participants in both patients and control group, disregard of other inflammatory parameters, lack of cell culture studies, lack of genetic polymorphism analyses.

CONCLUSION

As a result, this study on PTX3 level in acute ischemic stroke patients revealed that PTX3 level may be a potential diagnostic biomarker. The present study has shown that pentraxin value in the patient group is significantly lower compared to the control group (p=0.003). The review of the relevant literature presented differing results in many of the studies related with serum PTX3 level. Only few of the studies in the review of the relevant literature, presented PTX3 level in acute ischemic stroke patients whose blood samples were collected at differing times (in the present study blood samples were taken within the first 24 hours after stroke onset unlike other studies in which the samples were taken within the first 48 hours). Other studies on PTX3 were experimental studies. Unlike these studies in which PTX3 levels were found to be elevated, in the present study serum PTX3 levels were low. The underlying reasons for the different results obtained could be due to differences in methodology and polymorphism. In addition, unlike other studies, this study suggests that PTX3 level is a potential diagnostic marker, not a prognostic one. However, studies with larger patient groups accompanied by pathophysiological investigations are required to verify the findings of the present study.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by Erzincan Binali Yıldırım University Clinical Researches Ethics Committee (Date: 02.03.2023, Decision No: 2023-05/2).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

Acknowledgment

We would like to express our thanks to ELT Dr. Harun Şimşek for proofreading the present manuscript for English Language related aspects.

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1680425

Anatolian Curr Med J. 2025;7(3):363-368

Modified single-patch persus double-patch repair in complete atrioventricular septaldefect: a comparative study of surgical and long-term outcomes

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Cite this article as: Arslan AH, Karahan A, Aksoy T, Üstünsoy H. Modified single-patch persus double-patch repair in complete atrioventricular septaldefect: a comparative study of surgical and long-term outcomes. *Anatolian Curr Med J.* 2025;7(3):363-368.

Received: 22.04.2025 ◆ **Accepted**: 27.05.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: Complete atrioventricular septal defect (CAVSD) is a complex congenital cardiac anomaly, accounting for 3–4% of all congenital heart diseases and frequently associated with Trisomy 21. It involves a common atrioventricular valve (AVV) and large septal defects, often necessitating early surgical intervention to prevent irreversible pulmonary vascular disease. While the double-patch technique (DPT) has been widely used for decades, the modified single-patch technique (MSPT) has recently gained popularity due to its technical simplicity and reduced manipulation of the AVV. However, comparative data on the short- and long-term outcomes of these two approaches remain limited. This study aimed to compare the early and long-term clinical results of the MSPT and DPT, focusing on postoperative mortality and AVV regurgitation.

Methods: We conducted a retrospective review of 56 patients who underwent complete CAVSD repair between 2009 and 2023 at a single center. Thirty-seven patients (66%) were treated with MSPT, and 19 patients (34%) with DPT. Patient demographics, perioperative data, postoperative complications, mortality, and long-term outcomes were evaluated. The mean follow-up duration among 45 patients was 73.2±4.1 months.

Results: The MSPT group had a significantly younger median age (7.5 vs. 14 months; p=0.003) and smaller ventricular septal defect (VSD) diameters (8.2 mm vs. 13.8 mm; p<0.001) than the DPT group. Cardiopulmonary bypass (CPB) and aortic cross-clamp (ACC) times were significantly shorter in the MSPT group (p<0.001). Moderate-to-severe early postoperative left AVV (LAVV) regurgitation was more frequent in the DPT group (p=0.016), while postoperative drainage volume was significantly higher in the DPT group as well (p=0.019). Early postoperative mortality occurred in 2 patients (3.5%) overall, and the total mortality for the entire cohort was 11.1%, with no statistically significant difference observed between the MSPT and DPT Reoperation due to progressive LAVV regurgitation occurred in 3 patients (6.6%)—1 in the MSPT and 2 in the DPT group—again without statistical significance. No cases of left ventricular outflow tract obstruction were observed in either group.

Conclusion: Our findings suggest that MSPT, with its simplicity and favorable outcomes, may be an effective surgical technique for selected CAVSD patients, particularly those with smaller VSDs. Compared to DPT, it is associated with shorter operative times and a significantly lower rate of early moderate-to-severe LAVV regurgitation, while offering comparable long-term mortality and reoperation rates.

Keywords: Complete atrioventricular septal defect, congenital heart disease, modified single-patch technique, Trisomy 21

INTRODUCTION

Complete atrioventricular septal defect (CAVSD), first defined by Lillehei et al. in 1955[1-3], accounts for approximately 3-4% of all congenital heart defects, with an estimated incidence of 2-3 per 1000 live births.[3] CAVSD is most commonly associated with Trisomy 21, observed in 25–71% of cases, and exhibits a higher prevalence in females (female-to-male ratio: 1.3:1).[3-5]

Advancements in the understanding of congenital cardiac anatomy, refinement of surgical techniques, improved management of pulmonary hypertension, and technological progress have significantly reduced the historically high morbidity and mortality rates associated with CAVSD repair.[6-8] Today, with early diagnosis and intervention, the majority of patients can undergo surgical correction with favorable outcomes.[9]

Following the initial surgical repair by Lillehei, the evolution of CAVSD correction techniques began with the introduction of the double-patch technique (DPT) by Trusler in 1975.[3,10-11] More recently, the modified single-patch technique (MSPT),

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as described by Ben Wilcox from North Carolina in 1997 and Graham Nunn in from Sydney, Australia in 1999, has gained popularity due to its simplified approach often avoiding the need for a separate patch to close the ventricular septal defect (VSD) and reduced manipulation of the atrioventricular valve (AVV) apparatus.[8]

Despite these advances, comparative data on perioperative and long-term outcomes between these two approaches remain limited, particularly in diverse clinical settings. Additionally, several aspects of surgical management remain topics of ongoing debate, including the optimal timing of repair, whether to pursue a primary or staged surgical approach.

The present study aims to evaluate and compare the early and mid-term clinical outcomes of MSPT and DPT in patients undergoing CAVSD repair at our center. By examining parameters such as AVV function, morbidity, mortality, and reoperation rates, this study seeks to contribute to the evidence base guiding optimal surgical strategy selection in CAVSD repair.

METHODS

Ethics

This retrospective, single-center study included 56 patients who underwent complete surgical repair for CAVSD between 2009 and 2023. Of these, 37 patients (66%) were operated on using MSPT, while 19 patients (34%) underwent repair with traditional DPT. The surgical technique was primarily selected based on the diameter of VSD, reflecting the surgeon's decision-making. The study protocol was approved by the Ethics Committee of Private Anadolu Medical Centre (Date: 19.03.2025, Decision No: ASM-EK-25/292); and the study was conducted in accordance with the Declaration of Helsinki. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Preoperative Evaluation

All patients were evaluated with transthoracic echocardiography to determine Rastelli classification type, the degree of left and right AVV regurgitation (LAVVR, RAVVR), and VSD diameter. Additional cardiac anomalies, including patent ductus arteriosus (PDA), atrial septal defect (ASD), pulmonary stenosis, and others, were also documented.

Surgical Technique

All procedures were performed via standard median sternotomy under moderate hypothermia with ascending aortic and bicaval venous cannulation. Myocardial protection was achieved with antegrade blood cardioplegia. Mitral cleft closure was routinely performed in all patients. Additional LAVV or RAVV repair were performed as indicated based on intraoperative findings. No patient underwent correction using the conventional single-patch technique.

Data Collection and Outcomes

Patient demographics, perioperative variables (age, sex, weight, VSD diameter, cardiopulmonary bypass (CPB) and aortic cross-clamp (ACC) times, intubation duration, intensive care unit (ICU)/hospital length of stay, drainage volume, and blood product use were collected. Postoperative complications (including mortality, LAVVR/RAVVR, heart failure, infections, cerebrovascular events, and chylothorax) were analyzed.

Follow-Up

Long-term outcomes were assessed in 45 patients with available follow-up data, with a mean follow-up duration of 73.2±4.06 months (range: 22–128 months).

Statistical Analysis

The data analyses were performed using SPSS for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean±standard deviation (SD) or median with range (minimum–maximum), depending on the normality of distribution. Categorical variables were expressed as frequencies and percentages. For comparison between two groups, the independent samples t-test was used for normally distributed continuous variables, while the Mann–Whitney U test was applied for non-normally distributed data. The Chi-square test was employed to analyze categorical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Patient Characteristic among MSPT and DPT Groups

The cohort consisted of 33 females (60%) and 23 males (40%), with a median age at the time of surgery of 9 months (range: 2–180 months). The mean body weight was 9.87±7.96 kg (range: 3.3–41 kg). A total of 56 patients underwent CAVSD repair, with 37 receiving the MSPT and 19 undergoing the DPT. The median age at the time of surgery was 7.5 months in the MSPT group and 14 months in the DPT group. Trisomy 21 was present in 70% of the MSPT group and 64% of the DPT group. Preoperative functional status, based on the New York Heart Association (NYHA) classification, showed that the majority of patients were in class I (28 in MSP, 17 in TPT).

Rastelli type A anatomy was the most common (81% in MSPT, 84% in DPT). The mean diameter of the VSD was 8.2 mm in the MSPT group and 13.78 mm in the DPT group. Moderate to severe LAVVR was observed in 20 MSPT and 17 DPT patients, while RAVVR was present in 18 and 15 patients, respectively. Demographic and baseline clinical and anatomic data of the patients among two groups are summarized in **Table 1**.

Additional cardiac anomalies were observed in both groups, with ASD combined with PDA being the most frequent in the MSPT group (n=15) and tetralogy of Fallot (TOF) in the DPT group (n=4). Other associated defects included pulmonary stenosis, double outlet right ventricle, partial anomalous pulmonary venous connection , and previously palliated cases with pulmonary banding or Blalock-Taussig shunt, as detailed in **Table 2**.

Perioperative and Postoperative Outcomes

The mean CPB time was 98±31 minutes (range: 34–175 minutes), while the ACC time was 70.1±25 minutes (range: 89–140 minutes). The mean postoperative drainage volume was 427±409 ml (range: 10–2200 ml), and the average volume of blood product transfused was 597.4±444.3 ml (range: 0–2750 ml). Postoperative moderate and severe LAVVR was

Table 1. Baseline demographic, clinical and anatomical characteristics of the subjects

Demographic data	MSPT	DPT
Median age (months)	7.5	14
Sex	19 M, 18 F	14 M, 5 F
Weight (kg)	9.26±8.74	11.2±6.59
Trisomy 21	26 (70%)	11 (64%)
NYHA Class I Class II Class III	 8 7 2	 17 2 -
Rastelli		
Type A	30	16
Type B	5	2
Type C	2	1
Mean VSD diameter (mm)	8.2	13.78
Moderate to severe LAVVR	20	17
Moderate to severe RAVVR	18	15

MSPT: Modified single-patch technique, DPT: Double-patch technique, NYHA: New York Heart Association, VSD: Ventricular septal defect, LAVVR: Left atrioventricular valve regurgitation, RAVVR: Right atrioventricular valve regurgitation

Table 2. Additional congenital anomalies of the subjects

Additional anomalies	MSPT	DPT
ASD+PDA	15	3
PDA	8	2
Pulmonary stenosis	4	3
Operation pulmonary banding	2	4
TOF	1	4
DORV+PS	-	3
ASD	1	1
Operated BT shunt	-	2
RV hypoplasia	1	1
PAPVC+mesocardia+LPSVC	-	1
Mesocardia	1	-
Multiple VSD	-	1
LPSVC+PDA	1	-

MSPT: Modified single-patch technique, DPT: Double-patch technique, ASD: Atrial septal defect, TOF: Tetralogy of Fallot, DORV: Double outlet right ventricle, PS: Pulmonary stenosis, BT: Blalock taussig, RV: Right ventricle, PAPVC: Partial abnormal pulmonary venous connection, LPSVC: Left persistent superior vena cava, PDA: Patent ductus arteriosus

observed in 15 and 1 patients, respectively. Moderate RAVVR was seen in 10 patients, with no cases of severe regurgitation. A small residual VSD causing minimal shunt was detected in one patient.

The mean intubation time was 75.1±108.5 hours (range: 4–456 hours), with an average ICU stay of 7.8±7.5 days and hospital stay of 17.1±15.6 days (range: 4–90 days) (**Table 3**).

Among rhythm-related complications, 7 patients developed arrhythmias: 4 (7.1%) experienced complete AV block requiring permanent pacemaker implantation, two developed junctional ectopic tachycardia, and one had right bundle branch block.

Additional postoperative complications included pericardial tamponade (n=2), chylothorax (n=4), Dressler's syndrome

Table 3. Surgical data

	MSPT	TPT
CPB time (min)	93.97±23.65	125.31±27.29
ACC (min)	60.62±22.17	88.63±23.53
Intubation time (h)	78.02±117.76	69.36±93.88
Length of ICU stay (day)	7.59±7.64	8.26±7.47
Length of hospital stay (day)	15.91±2.71	19.52±3.27
Drainage amount (ml)	334.16±320.31	603.15±511.72
Blood product (ml)	505.54±286	776.31±631.43
AV block	2	2
JET	2	-
RBBB	1	-
Pacemaker implantation	2	2

MSPT: Modified single-patch technique, CPB: Cardio-pulmonary bypass, ACC: Aortic cross-clamp, ICU; Intensive care unit, AV: Atrioventricular, JET: Junction ectopic tachycardia, RBBB: Right bundle branch block

requiring pericardial drainage (n=1), and renal failure necessitating peritoneal dialysis (n=8). Infectious complications were also noted, including pneumonia requiring prolonged antibiotic therapy (n=12), urinary tract infection (n=2), and one case each of sepsis and seizure. Inhaled nitric oxide therapy was administered in four patients due to elevated pulmonary pressures.

Comparative Outcomes Between Surgical Techniques

Patients undergoing DPT were significantly older than those undergoing MSPT (median: 14 vs. 7.5 months; p=0.003). The female-to-male ratio was significantly higher in the MSPT group (p=0.023). VSD diameter was also significantly larger in the DPT group compared to the MSPT group (13.8 mm vs. 8.2 mm; Mann-Whitney U test, p<0.001) (**Figure 1**).

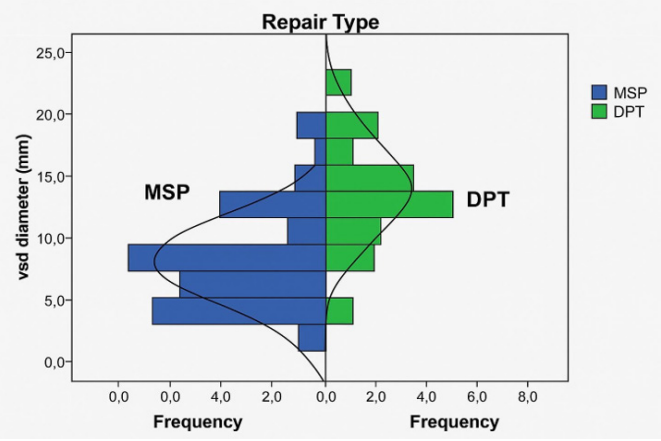

Figure 1. Comparison of VSD diameter between MSPT and DPT
VSD: Ventricular septal defect, MSPT: Modified single-patch technique, DPT: Double-patch technique

While the need for LAVV repair did not differ significantly between groups, RAVV repair was more frequently performed in the MSPT group (p=0.043). CPB and ACC times were significantly longer in the DPT group (CPB: 125.3±27.3 min vs. 83.4±23.8 min; ACC: 88.6±23.5 min vs. 60.1±22.3 min; t-test, both p<0.001) (**Figure 2, 3**). Postoperative moderate-to-severe LAVVR was significantly more common in the DPT group (Chi-square test, p=0.016), and postoperative

drainage volume was also higher (603 ml vs. 334 ml; p=0.019). No statistically significant differences were found in other parameters. Early comparative postoperative outcomes were summarized in **Table 4**.

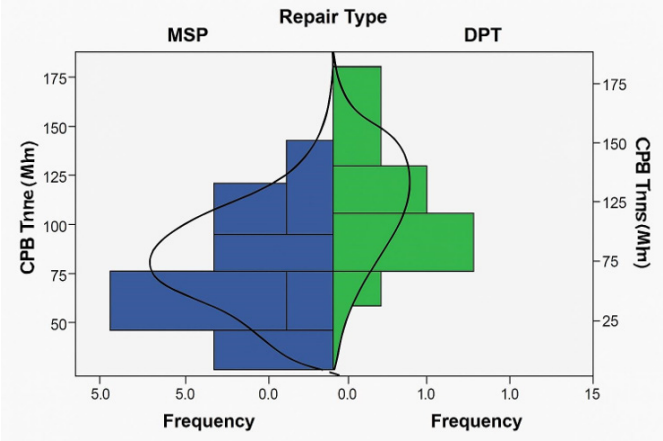

Figure 2. Comparison of CPB time between MSPT and DPT groups
CPB: Cardiopulmonary bypass, MSPT: Modified single-patch technique, DPT: Double-patch technique

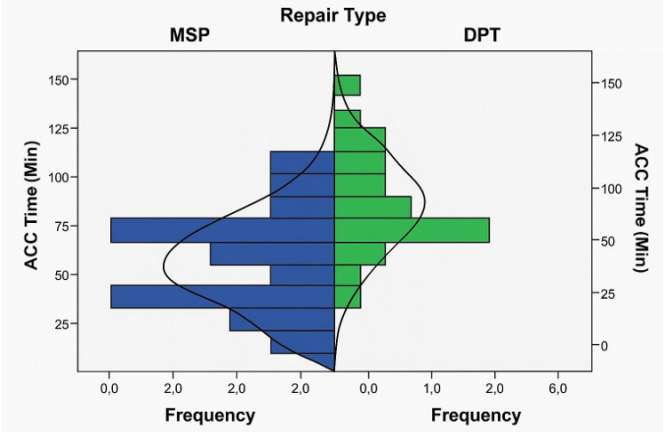

Figure 3. Comparison of aortic cross-clamp time between MSPT and DPT groups
MSPT: Modified single-patch technique, DPT: Double-patch technique, ACC: Aortic cross-clamp

Table 4. Early postoperative morbidity following CAVSD repair in MSPT and DPT groups

	MSPT	DPT
Pneumonia	7	5
UTI	2	-
Sepsis	-	1
Epileptic attack	-	1
Tamponade	1	1
Chylothorax	1	3
Advanced left AV valve regurgitation	1	-
Reintubation	5	3
Peritoneal dialysis catheter	2	6
Pericardial tube	1	-
NO inhalation	2	2

CAVSD: Complete atrioventricular septal defect, MSPT: Modified single-patch technique, DPT: Double-patch technique, UTI: Urinary tract infection, AV: Atrioventricular

Mortality and Long-Term Outcomes

Early hospital mortality occurred in 2 patients (3.5%). One patient with Trisomy 21 and both LAVV and RAVV repair (MSPT) died from aspiration pneumonia shortly after discharge. The second, with multiple muscular VSDs and prior pulmonary banding, underwent DPT repair and required pacemaker implantation; the patient died of respiratory failure in the ICU.

Of the total 5 patients who died during the study period, 2 deaths occurred in the early postoperative phase, while 3 deaths were recorded during long-term follow-up (mean: 73.2±4.06 months), resulting in an overall mortality rate of 11.1%. Among the late deaths, three patients had undergone DPT and two had undergone MSPT. Two deaths were from non-cardiac causes, and the remaining three were cardiac-related—including one sudden death in a pacemaker-dependent patient and one due to LAVV insufficiency following reoperation.

Freedom from reoperation was 95.6% at 5 years and 93.4% at 10 years. Three patients (6.6%) underwent reoperation for LAVV insufficiency—one in the MSPT group and two in the DPT group. There was no statistically significant difference in long-term outcomes between the surgical techniques.

DISCUSSION

In this retrospective cohort study, our findings demonstrated that both approaches were safe, with low early mortality and good long-term survival. However, MSPT was associated with shorter CPB and ACC times, less postoperative drainage, and lower rates of moderate-to-severe LAVVR, suggesting procedural advantages in selected patients, especially with regard to VSD sizes. VSD diameter was significantly smaller in the MSPT group, reflecting its suitability for simpler anatomies. Despite these differences, long-term outcomes were comparable.

Since the Rastelli classification, CAVSD has been recognized as a congenital anomaly with a well-characterized anatomy that can be surgically corrected with high success rates, owing to advancements in technology and surgical techniques. The presence of associated cardiac anomalies does not appear to significantly affect outcomes, which are generally marked by low morbidity and mortality. Atz et al.[12] reported no significant difference in residual lesions or valve regurgitation between the MSPT and DPTs in patients with trisomy 21. In a separate study, Xie et al.[13] recommended performing surgical correction between 3 and 6 months of age, based on a cohort in which 92% of patients were treated with the DPT and only 2.2% with MSPT. Importantly, they found that the presence of Trisomy 21 was not associated with an increased risk of reoperation. In contrast, Tumanyan et al.[14] compared outcomes between 214 patients with isolated CAVSD and 163 patients with concomitant Trisomy 21, using the DPT in 75.4% and MSPT in 24.6% of cases. While they found no significant difference in outcomes based on surgical technique, they noted that the additional morbidity associated with Trisomy 21 affected both recovery time and life expectancy. In our cohort, additional cardiac anomalies

and Trisomy 21 were frequently observed, with the latter present in approximately 65% of patients. However, neither Trisomy 21 nor other associated anomalies were associated with increased morbidity or mortality, and no statistically significant differences were observed in clinical outcomes.

Timely surgical intervention is critical to prevent irreversible pulmonary vascular disease, as the left-to-right shunt in CAVSD can rapidly elevate pulmonary pressures. While the optimal surgical window is generally between 3–6 months of age[15], our series had a slightly delayed median operative age (7.5 months in MSPT vs. 14 months in DPT), largely due to late referrals from abroad or underserved regions. Nonetheless, pulmonary hypertension was not a major concern in our cohort, and only a small number of patients required postoperative inhaled NO therapy.

In recent years, the MSP technique has gained widespread acceptance as an alternative to the conventional DPT. In our study, 66% of cases were repaired with MSP, consistent with contemporary trends. Compared to DPT, MSPT was associated with significantly shorter CPB ACC times and a smaller VSD diameter—findings consistent with other reports.[16-18] Although shorter CPB/ACC times did not translate into shorter ICU or hospital stays, the MSPT group experienced significantly less postoperative drainage, with no difference in transfusion requirements, supporting a more conservative transfusion protocol.

Importantly, early postoperative moderate-to-severe LAVVR was significantly less frequent in the MSPT group compared to the DPT group. This difference may be attributed to several technical advantages inherent to the MSPT. First, MSPT avoids the use of a separate patch for VSD closure, thereby reducing potential distortion or traction on the atrioventricular (AV) valve tissue. Second, by not dividing the common AV valve, the risk of leaflet tethering or malalignment is minimized, preserving the native valve architecture and function. These benefits have been consistently emphasized in prior reports, most notably by Graham Nunn, who reported no significant postoperative LAVVR in his MSPT cohort.[8] In our study, although moderate LAVVR was observed in 15 patients and severe in one patient overall, the incidence was significantly lower in the MSPT group. Furthermore, no cases of left ventricular outflow tract obstruction (LVOTO) were identified in either group during the early or late follow-up, further suggesting that neither technique adversely impacted ventricular outflow dynamics when carefully executed.

Although overall long-term mortality and reoperation rates did not differ significantly between the two techniques in our cohort, LAVVR remained the most common indication for reintervention, aligning with findings from multiple previous studies.[19-21] The pathophysiology of LAVVR progression over time is multifactorial and may be influenced by factors such as annular dilatation, suboptimal initial repair, leaflet prolapse, and valve tissue dysplasia. Some authors have suggested that delayed surgical timing may exacerbate annular stretching due to prolonged volume overload, thereby increasing the risk of residual or recurrent AV valve regurgitation.[22,23] Interestingly, despite the relatively late median age at operation in our series (7.5 months in MSPT and 14 months in DPT), the MSP group demonstrated a significantly lower incidence of LAVVR, suggesting that this technique may offer a protective effect even when repair is not performed during the ideal window of 3–6 months.

The technical simplicity and tissue-preserving nature of the MSP technique offer notable advantages. By avoiding a separate VSD patch, it reduces the risk of injury to conduction tissue and AV valve structures, contributing to shorter CPB and ACC times. Although long-term reoperation rates did not significantly differ between MSPT and DPT, the overall reoperation rate for AV valve dysfunction was low (6.6%), consistent with literature suggesting improved valve preservation with MSPT.[24,25]

The potential superiority of the MSPT technique over the double-patch (DPT) approach has been the subject of continuous discussion. Although a single meta-analysis and recent propensity score-matched studies found no discernible differences in mortality or reoperation rates between the two methods, these analyses primarily matched cohorts based on the size of VSD without taking VSD depth into consideration. Notably, new studies indicate that when MSPT is used, VSD depth may be crucial in the development of late LAVVR.[26,27] VSD diameter and surgical technique selection were closely correlated in our study, indicating the importance of this anatomical factor in procedural decision-making. Notably, however, in a recent review by Backer et al.[26], it is recommended to apply DPT for VSDs deeper than 15mm, a threshold later refined to 11 mm based on longer-term follow-up and larger patient cohorts. This supports the rationale for selecting MSPT in patients with shallower VSDs, aligning with our findings of favorable outcomes in those with smaller defects. Importantly, no cases of LVOTO were observed in either group, further underscoring the hemodynamic safety of both techniques when appropriately selected.

Limitations

This study has several limitations. First, its retrospective and single-center design may limit the generalizability of the findings. Surgical technique selection was based on individual surgeon preference, based on the diameter of VSD rather than randomization, potentially introducing selection bias. Second, the relatively small sample size, particularly in the DPT group, may reduce the statistical power to detect differences in less common outcomes such as late mortality or need for reoperation. Additionally, echocardiographic assessments of AV valve function were not standardized across all time points or operators, which may have introduced variability in grading regurgitation severity. Finally, although follow-up was sufficient to evaluate mid-term outcomes, longer-term surveillance is needed to assess durability of valve function and late reinterventions.

CONCLUSION

MSPT was associated with significantly shorter CPB and ACC times and lower rates of early moderate-to-severe LAVV regurgitation. Although long-term mortality and reoperation rates were comparable between the two groups, the reduced

incidence of AV valve dysfunction and the simplicity of the MSPT suggest it may offer surgical and clinical advantages in appropriately selected patients with small VDSs.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the Ethics Committee of Private Anadolu Medical Centre (Date: 19.03.2025, Decision No: ASM-EK-25/292).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1676243

Anatolian Curr Med J. 2025;7(3):369-374

Investigation of salivary miRNA-199a-5p levels in plaque-induced gingivitis

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Cite this article as: Akdeniz FT, Nalbantoğlu AM, Barut Z, et al. Investigation of salivary miRNA-199a-5p levels in plaque-induced gingivitis. *Anatolian Curr Med J.* 2025;7(3):369-374.

Received: 15.04.2025 • **Accepted**: 29.05.2025 • **Published**: 30.05.2025

ABSTRACT

Aims: Epigenetic mechanisms play a crucial role in regulating the response to chronic inflammation in periodontal diseases and serve as reliable biomarkers. While these biomarkers are traditionally assessed through invasive techniques, analyzing miRNA expression in saliva offers a non-invasive and convenient alternative. Our study aims to investigate salivary miRNA-199a-5p levels in both healthy and diseased conditions and to evaluate its potential role as an early diagnostic indicator of periodontal diseases such as gingivitis.

Methods: Saliva samples from 50 individuals, either diagnosed with gingivitis or exhibiting a healthy periodontal condition, were analyzed using miRNeasy serum/plasma kit (Qiagen). SPSS software was used for statistical analysis. MiRNA-199a-5p expression levels were compared using the Mann-Whitney U test.

Results: In saliva samples collected from 50 individuals, the expression levels of miRNA-199a-5p were significantly elevated in the gingivitis group compared to the healthy control group. Aditionally, the bleeding on probing (BOP %) values were significantly higher in group G compared to the healthy group.

Conclusion: miRNA-199a-5p can be considered an important regulator with potential as both an early diagnostic biomarker and a therapeutic target for periodontal diseases. Although its role in autophagy and inflammation shows promise, further studies are needed to clarify its specific functions and clinical relevance.

Keywords: miRNA-199a-5p, gingivitis, periodontal disease

INTRODUCTION

The natural microbiota of the oral cavity tends to form a polymicrobial biofilm on the mineralized surfaces of teeth, particularly in the presence of periodontal disease. This biofilm exerts detrimental effects on periodontal tissue health.[1] As the dental biofilm matures, an inflammatory response is triggered within the gingival tissue, manifesting clinically as an increased flow of gingival crevicular fluid (GCF), gingival bleeding, and edema.[2] In 1965, Löe and colleagues[3] conducted the classic study titled "experimental gingivitis in man," demonstrating that the accumulation of supragingival biofilm leads to gingival inflammation, which resolves upon its removal. Yamamoto and his team elaborated on gingivitis, defining it as a nonspecific and reversible inflammatory condition that arises due to an increase in gram-negative or gram-positive bacterial populations within or below the gingival sulcus.[4]

MicroRNAs (miRNAs) are short, single-stranded RNA sequences that do not encode proteins and typically comprise around 22 nucleotides. More than 1.000 miRNAs have been identified in the human genome, and they regulate gene expression by binding with the 3'-untranslated region (3'-UTR) of designated target genes.[5,6] Following transcription, miRNAs can bind to complementary mRNA sequences, thereby suppressing, activating, or modulating protein translation and synthesis.[7,8] The relationship between miRNAs and different pathologies has been reported in detail. A single miRNA has the ability to regulate the expression of hundreds of target genes at the same time.[9] Their presence in various

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tissues and bodily fluids, along with their high stability in biological fluids, has led to the recognition of miRNAs as potential biomarkers in different clinical settings.[7]

miRNAs play a crucial role in controlling cellular proliferation, development, differentiation, carcinogenesis, and inflammation. Additionally, miRNA profiles have been compared between healthy and periodontally diseased conditions.[10,11] miRNA-199 targets multiple genes, including TNF-alpha, prostaglandins, IL-1β, IL-6, BMP-2, EGF, and TGF-β.[12,13] Notably, miRNA-199a-5p overexpression disrupts autophagy and activates the mTOR/GSK3β pathway.[14]

The mammalian target of rapamycin (mTOR) plays a crucial role in two distinct protein complexes, mTORC1 and mTORC2, which regulate various cellular processes.[15] It promotes anabolic metabolism while inhibiting autophagy, the primary cellular degradation process responsible for eliminating damaged macromolecules and organelles.[16] Upon mTOR inhibition, autophagic degradation and recycling of cellular components contribute to the reactivation of mTORC1. As a result, autophagy plays a regulatory role in both the upstream and downstream pathways of mTOR signaling.[17]

The studies also demonstrated that hsa-miRNA-199a plays a functional role as a direct inhibitor of IKKβ expression, a key upstream activator of NF-κB. Furthermore, MAPK4 has been identified as a direct target of miRNA-199a-5p, and its inhibition was associated with reduced inflammation and decreased production of proinflammatory cytokines.[18,19]

In this context, several studies have proposed the potential use of miRNA-199a-5p as a biomarker due to its presence during early inflammatory changes.[20,21]

Epigenetic mechanisms in periodontal diseases are considered reliable biomarkers that regulate adaptation to chronic inflammatory stimuli. Although the expression levels of these biomarkers are typically analyzed using invasive methods, investigating miRNA expression in saliva provides a non-invasive and more accessible alternative.[22-24]

A better understanding of the expression dynamics of miRNA-199a-5p may contribute to the development of novel, non-invasive diagnostic approaches for periodontal health monitoring. Accordingly, our study aims to investigate miRNA-199a-5p expression levels under both healthy and diseased conditions and to evaluate its potential role as an early diagnostic biomarker for periodontal diseases such as gingivitis.

METHODS

Ethics

This research was carried out in compliance with the principles outlined in the Declaration of Helsinki. Ethical approval for this study was obtained from the Non-interventional Clinical Researches Ethics Committee of Hitit University (Date: 05.12.2024, Decision No: 323/2024-25).

Clinical Samples

To determine the required sample size, a statistical power analysis was conducted using G*power version 3.1. Based on an effect size of 0.25 and a power of 90%, the total required sample size was calculated. The study was conducted with 50 participants, divided equally into two groups (n=25), consisting of patients admitted to the Faculty of Dentistry at Akdeniz University and healthy individuals attending routine dental assessments.

Participants were required to have no systemic diseases, no current medication use, no crowns, veneers, or restorations, and at least 20 teeth retained in the oral cavity, and to be non-smokers. Exclusion criteria included the presence of systemic diseases, pregnancy, menstrual periods, periodontal treatment within the last six months, or the use of anti-inflammatory drugs or antibiotics within the past two weeks.

Subjects were divided into two groups according to their periodontal condition: the gingivitis group (group G) and the healthy periodontium group (group H). The definitions of gingivitis and health were established according to the 2017 revised Classification of Periodontal and Peri-Implant Diseases and Conditions by the World Workshop on Periodontology.[25]

Group H consisted of individuals exhibiting a clinically healthy periodontal status. Group G comprised individuals who did not exhibit radiographic evidence of clinical attachment loss (CAL) or alveolar bone loss but had BOP scores of 10% or higher. Panoramic radiographs were used to assess alveolar bone loss. Both the clinical examination and periodontal measurements were performed by periodontologists. CAL, probing depth (PD), and plaque index (PI) were evaluated using a periodontal probe at six designated locations on each tooth. The PI was determined based on the criteria established by Silness and Löe[26] CAL measurements were conducted to maintain periodontal status consistency among participants, confirm the absence of attachment loss in the periodontally healthy and gingivitis groups, and comprehensively characterize the clinical and demographic profiles of the study population in accordance with established periodontal research protocols. CAL assessments also served to accurately identify pure gingivitis cases and to exclude participants with any suspicion of prior periodontitis.

Laboratory Measurements

Non-stimulated saliva specimens were obtained for research. Participants were advised to abstain from food, beverages, and gum chewing for a minimum of one hour prior to sample collection. Saliva specimens were obtained under controlled environmental conditions between 09:00 and 11:00 AM, transferred into plastic containers, and then transferred into centrifuge tubes using sterile syringes. To enhance the accuracy of the analysis and reduce turbidity, saliva samples were vortexed at room temperature for 10 minutes to remove cellular debris and food particles. The supernatant was carefully collected and stored at –80°C until miRNA analysis. The samples were transported on dry ice to İstanbul Okan University, where the analyses were performed.

miRNA isolation: On the day of the experiment, saliva samples were thawed and centrifuged at 11.000 g at +4°C for 20 minutes. miRNA isolation was then performed from the supernatant using the miRNeasy serum/plasma kit (Cat. No./ID: 217184, Qiagen, Hilden, Germany) according to the

manufacturer's protocol. The purity and concentration of the isolated miRNAs were assessed using a NanoDrop 2000 spectrophotometer (Thermo Scientific, USA).

cDNA synthesis: Complementary DNA (cDNA) synthesis was performed using the miRCURY LNA RT Kit (Cat. No./ID: 339340, Qiagen, Germany). During the cDNA synthesis process, the isolated miRNA samples underwent reverse transcription.

Determination of miRNA levels using fluorometry: The concentration of transcribed miRNAs was measured using a Qubit 3.0 Fluorometer (Thermo Scientific) following the standard protocol of the Qubit miRNA Assay Kit. After concentration measurements, appropriate dilutions were made.

miRNA expression analysis: Following the quantification of sample concentrations, miRNA-199a-5p expression levels (miRCURY Lot: 201803080050-4, Qiagen, Germany) were measured using the Rotor-Gene Q Real-Time PCR System (Rotor-Gene Q, Qiagen) with the miRCURY LNA SYBR Green PCR Kit (Cat. No./ID: 339346, Qiagen, USA).

The housekeeping gene (RNU6, Lot: 20800469-1, Qiagen) was utilized as an internal reference for normalization of ΔCT values and to calculate the fold change in miRNA expression levels. The Livak formula ($2^{-\Delta\Delta C}{}_T$) was applied to determine miRNA levels. The ΔΔCT value was calculated by subtracting the ΔCT of the target gene from the mean ΔCT of the internal control, and the fold change was subsequently computed as $2^{-\Delta\Delta C}{}_T$.[27]

Statistical Analysis

The data analyses of the study were carried out using SPSS software version 26.0. The Kolmogorov-Smirnov test was employed to evaluate the data's normality, while variance homogeneity was analyzed using Levene's test. Differences in PI, gingival index, and PD among study groups were evaluated using one-way analysis of variance (ANOVA) followed by post-hoc Tukey tests. The miRNA-199a-5p levels between study groups were compared using the Mann-Whitney U test. Statistical significance was set at $p<0.05$ with a 95% confidence interval.

RESULTS

In our investigation, saliva samples from 50 individuals, either diagnosed with gingivitis or exhibiting a healthy periodontal condition, were analyzed. No laboratory losses occurred during the process. The age and gender distribution percentages and mean values of the patient and control groups are presented in **Table 1**.

Periodontal parameters for the study groups are displayed in **Table 2**. While no statistically significant differences were observed in PI, probing depth (PD in mm), or clinical attachment loss (CAL in mm), the bleeding on probing (BOP in %) values were significantly higher in group G compared to the healthy group ($p<0.001$). Additionally, salivary miRNA-199a-5p expression levels in the gingivitis group were significantly higher than those in the healthy group (**Table 3, Figure 1**).

Table 1. Demographic characteristics

	Healthy (n=25)	Gingivitis (n=25)
Age		
Mean (SD)	25.9 (6.03)	27.8 (6.80)
Median (range)	23.0 (19.0, 42.0)	26.0 (18.0, 46.0)
Gender, n (%)		
Male	5 (20.0%)	9 (36.0%)
Female	20 (80.0%)	16 (64.0%)

SD: Standard deviation

Table 2. Periodontal parameters

Periodontal parameters	Healthy	Gingivitis	p value
PI	0.68±0.02	1.19±0.03	<.001
PD (mm)	1.81±0.02	2.14±0.02	<.001
BOP (%)	2.13±0.2	46.93±5.5	<.001
CAL (mm)	0.00±0.002	0.58±0.001	<.001

PI: Plaque index, PD: Probing depth, BOP: Bleeding on probing, CAL: Clinical attachment loss

Table 3. miRNA-199a-5p 2−ΔΔCT values

	Group		
	Gingivitis (n=25)	Healthy (n=25)	p-value
$2^{-\Delta\Delta C}{}_T$			0.0008
Mean (SD)	33.3 (4.01)	29.3 (4.04)	
Median (range)	33.7 (22.3, 37.9)	29.3 (22.3, 36.5)	

SD: Standard deviation

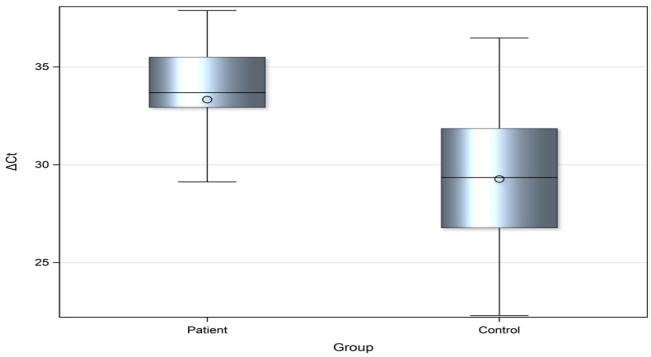

Figure 1. Graphical representation of miRNA199-5p levels in patient and control groups

In our study, sensitivity and specificity calculations were performed for various ΔCT threshold values to predict disease status, and the optimal threshold value for ΔCT was determined along with its corresponding sensitivity and specificity values. An empirical receiver operating characteristic (ROC) curve was generated using a non-parametric method with SAS software. For gingivitis, an area under the curve (AUC) value of 0.77 was obtained, with a 95% confidence interval (CI) of 0.60728–0.93118 and a p-value <0.001 (**Table 4, Figure 2**).

DISCUSSION

Periodontal tissue undergoes continuous remodeling due to tissue regeneration, mechanical stress, and inflammatory components arising from periodontal diseases.

Table 4. ROC analysis of miRNA-199a-5p for gingivitis

	Estimate	95% Confidence limits	
PPV	0.76923	0.60728	0.93118
NPV	0.79167	0.62919	0.95415
Sensitivity	0.80	0.64320	0.95680
Specificity	0.76	0.59258	0.92742
AUC	0.7760	0.60728	0.93118
	Cutoff	**Prob**	**Youden**
$2^{-\Delta\Delta C}{}_{T}$	32.77	0.57903	0.56
	Somers' D	Gamma	Tau-a
	0.5520	0.5538	0.2816
True positive	True negative	False positive	False negative
20	19	6	5

ROC: Receiver operating characteristic, AUC: Area under the curve

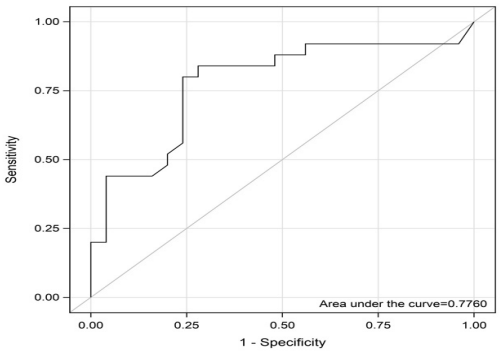

Figure 2. Receiver operating characteristic curve for miRNA199-5p

Biomarkers can be valuable in overcoming challenges encountered in preventive, predictive, and personalized healthcare applications across various medical fields. Therefore, miRNAs may serve as a key factor in the early diagnosis and prognosis prediction of various periodontal diseases.[7] Biological fluids are proposed as a significant research source for miRNA biomarkers. This is attributed to the efficient isolation and detection of miRNAs through quantitative polymerase chain reaction (qPCR), the minimally invasive nature of GCF and saliva sampling, and the high stability of miRNAs across various biological fluids.[28,29]

miRNAs regulate periodontal remodeling and inflammation by modulating key factors involved in osteogenesis (e.g., Bone Morphogenetic Protei-7, Runt-related transcription factor 2, osterix, osteocalcin), osteoclastogenesis (e.g.,Nuclear Factor of Activated T-cells, cytoplasmic 1, NF-κB, Receptor Activator of Nuclear Factor κB Ligand), and inflammatory mediators (e.g., IL-1β, IL-6, IL-8, TNF-α).[30]

The signaling pathways influenced by miRNA-199a-5p can modulate the progression from gingivitis to periodontitis through distinct mechanisms. Among these, the NF-κB pathway plays a pivotal role in orchestrating inflammatory processes by regulating proinflammatory cytokine production, leukocyte recruitment, and cell survival. Intriguingly, the functional outcome of NF-κB activation appears to be highly context-dependent, with its signaling axis capable of either sustaining the inflammatory milieu or promoting the resolution of inflammation through the induction of leukocyte apoptosis.[31] Considering the complexity of the pathways regulated by miRNA-199-5p, it is critical that future studies aim to elucidate their specific roles in the initiation, perpetuation, and resolution of inflammatory diseases.

Given their central role in regulating osteogenesis, osteoclastogenesis, and inflammatory pathways, miRNA-199-5p, could be considered potential biomarkers for the diagnosis and prognosis of periodontal disease. Moreover, the ability to detect these miRNAs in saliva further supports their applicability as non-invasive diagnostic tools.

Previous studies have demonstrated that miRNA-199a-5p is associated with a range of inflammatory disorders, cardiovascular diseases, and stork.[32,33] A review of the existing literature indicates that this study is the first to analyze the expression of miRNA-199a-5p in plaque-induced gingivitis. In this study, salivary miRNA-199a-5p levels in plaque-associated gingivitis were compared with those in individuals with clinically healthy periodontium. The results demonstrated a statistically significant increase in miRNA-199a-5p expression levels in the gingivitis group.

A previous study found that individuals with severe periodontitis exhibited an increased release of miRNA-199a-3p in GCF, which was positively correlated with the amount of GCF compared to individuals with a healthy periodontium.[34] In another study on salivary gland tumors, miRNA-199a was significantly upregulated in serum samples from the malignant group compared to the benign group.[35]

Yuan et al.[36] reported that miRNA-199-5p overexpression significantly suppresses oral fibroblasts proliferation, whereas the inhibition of miRNA-199-5p may lead to increased cell proliferation. Moreover, studies have shown that smokeless tobacco (SLT) users have a higher likelihood of developing periodontitis.[37] Analysis of saliva samples from SLT users revealed a significant increase in miRNA-199a-3p expression compared to non-tobacco users.[38]

Li et al.[39] suggested that increased miRNA-199-5p expression in patients with oral lichen planus (OLP) may contribute to OLP development by modulating mTOR and AKT1 secretion, proposing miRNA-199-5p as a potential therapeutic target. Similarly, Wang et al.[40] reported that miRNA-199 levels were lower in OLP patients compared to the control group. Luminescence assays confirmed that miRNA-199 directly suppressed mTOR secretion. Furthermore, the AKT/mTOR pathway was shown to regulate the autophagy mechanism, contributing to OLP pathogenesis.[40] These findings emphasize the need for more comprehensive studies to better understand the relationship between miRNA-199, OLP, and autophagy.

Increased mTORC1 activity can directly stimulate the maturation of pro-inflammatory T cells in periodontal diseases by enhancing glycolytic flux. Since autophagy is inhibited by mTORC1, these findings suggest that the detrimental effects of mTOR signaling on periodontal diseases may occur through autophagy regulation.[15]

Beyond the autophagy-related mechanisms involving mTORC1, recent evidence highlights the critical role of

miRNA-199a-5p in modulating inflammatory responses and structural alterations in periodontal tissues. miRNA-199a-5p, identified as a key regulator of intercellular junctions, functions as a proinflammatory miRNA, and its elevated expression in gingival tissues, GCF, saliva, and plasma has been associated with the presence and/or severity of periodontal disease.[19,41] These alterations represent crucial stages in the progression from gingivitis to periodontitis.

Gingivitis is a multifactorial, preventable, and treatable disease that develops in response to plaque biofilm. However, if inflammation persists, gingivitis can progress into periodontitis, a chronic inflammatory disease characterized by bone loss, affecting 45–50% of adults worldwide and expected to increase in prevalence.[42]

Given its detectable expression levels in saliva and its association with early inflammatory changes, miRNA-199-5p could serve as a non-invasive biomarker for the early diagnosis of periodontal disease and for monitoring treatment responses. Incorporating miRNA-based diagnostics into routine periodontal assessments may facilitate earlier intervention and improve clinical outcomes.

Limitations

Although the a priori power analysis conducted in this study demonstrated that the number of participants was statistically sufficient, the absence of previous studies specifically investigating miRNA-199-5p in gingivitis patients limits the generalizability of the findings. Therefore, while the current statistical design provides a robust foundation, larger-scale studies are needed to validate and expand these preliminary results across broader populations.

CONCLUSION

miRNA-199-5p emerges as a key regulatory molecule, both as a predictive biomarker for the early recognition of periodontal diseases and as a potential therapeutic target. While studies investigating its effects on autophagy and inflammation are encouraging, further research is required to elucidate its precise functions and clinical significance.

As one of the first studies focusing on the relationship between miRNA-199-5p, autophagy, and periodontal disease, this research aims to contribute to future scientific investigations. We believe that the findings will support the development of new diagnostic and therapeutic approaches through studies conducted on larger patient cohorts.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for this study was obtained from the Non-interventional ClinicalResearches Ethics Committee of Hitit University (Date: 05.12.2024, Decision No: 323/2024-25).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

ANATOLIAN CURRENT MEDICAL

DOI: 10.38053/acmj.1670333

Anatolian Curr Med J. 2025;7(3):375-383

Predictive value of progesterone receptor in advanced-stage breast cancer patients treated with CDK 4/6 inhibitors

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Cite this article as: Öner İ, Kurt İnci B, Kubilay Tolunay P, et al. Predictive value of progesterone receptor in advanced-stage breast cancer patients treated with CDK 4/6 inhibitors. *Anatolian Curr Med J.* 2025;7(3):375-383.

Received: 05.04.2025 ◆ **Accepted**: 29.05.2025 ◆ **Published**: 30.05.2025

ABSTRACT

Aims: Phase III studies investigating CDK 4/6 inhibitors have failed to identify significant predictive or prognostic markers that aid clinicians in therapeutic decision-making. Given the complex treatment landscape in breast cancer, identifying patient and tumor characteristics that optimize the utilization of CDK 4/6 inhibitors across diverse therapeutic approaches is crucial. In our study, we aimed to evaluate the predictive role of progesterone receptor (PR) expression levels in patients with estrogen receptor (ER)-positive and human epidermal growth factor receptor 2 (HER2)-negative advanced-stage breast cancer treated with CDK 4/6 inhibitors.

Methods: This study retrospectively evaluated 244 patients who received a combination of CDK 4/6 inhibitors and endocrine therapy as their first-line treatment. Those with PR levels below 20% were designated as low PR expression patients, and those with levels of 20% or above were classified as high PR expression patients. These two groups were compared in terms of demographic characteristics and progression-free survival (PFS).

Results: Progression events occurred in 37 of 83 patients in the low PR expression group and 55 of 161 patients in the high PR expression group. Patients with low PR expression demonstrated a significantly shorter median PFS of 23.13 months (95% CI, 15.67-30.59) compared to those with high PR expression, who exhibited a median PFS of 34.66 months (95% CI, 24.27-45.05) (p=0.002). This significant difference in mPFS was observed consistently across both ribociclib (p=0.034) and palbociclib (p=0.024) treatment groups.

Conclusion: This study suggests that PR expression may also predict disease progression in patients initiating CDK 4/6 inhibitors and endocrine therapy in addition to ER levels. While these findings are promising, further research is warranted to validate them in more extensive, prospective studies.

Keywords: Advanced stage breast cancer, biomarker, CDK 4/6 inhibitors, endocrine therapy, progesterone receptor

INTRODUCTION

Breast cancer is a heterogeneous disease with various molecular subtypes and biological characteristics. The main subtypes of breast cancer can be identified by immunohistochemical (IHC) markers such as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). These subtypes of breast cancer have different treatment strategies and clinical implications.

The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) recommend routine assessment of both ER and PR status in all invasive breast cancer.[1] This information should be used to guide patient selection for endocrine therapy (ET), as clinical trials have demonstrated that PR positivity, independent of ER status, is predictive of ET response.[1]

A tumor's likelihood of responding to ET is a critical factor in breast cancer management. However, not all patients with breast cancer benefit from ET. Expression of ER or PR is considered the most reliable predictor of which patients are most likely to benefit from ET.

ER expression predicts which patients will benefit from ET. While patients with PR-positive tumors also experience improved outcomes with ET, PR is considered a functional indicator of the ER pathway.[2] It is established that PR status can divide ER-positive tumors into different prognostic categories. Evidence suggests that PR positivity, independent of ER status, predicts ET response, and it is recommended that PR be considered when making ET decisions for patients.[3]

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In first-line treatment of advanced-stage breast cancer (ABC) in women with hormone receptor (HR)-positive HER2-negative status, pivotal trials with cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors (ribociclib, palbociclib, and abemaciclib) have shown significant improvements in progression-free survival (PFS).[4-6] Based on these results, current guidelines recommend the combination of CDK 4/6 inhibitors with ET as first-line treatment in this patient population.

The subgroup analyses of phase III studies on CDK 4/6 inhibitors have not identified any robust predictive or prognostic markers that could assist clinicians in determining therapeutic selection.[7] Considering the complexity of these treatments, it is essential to identify patient and tumor characteristics that could help determine when and in which treatment paradigms CDK 4/6 inhibitors should be used.[8]

Studies examining the predictive significance of PR for CDK 4/6 inhibitors are rare and controversial. Additionally, threshold values for PR to predict prognosis or treatment have yet to be thoroughly investigated. Real-world data can help clarify ongoing debates and guide optimal management in routine clinical practice.

Our study aimed to evaluate the predictive role of PR expression levels in patients with ABC ER-positive/HER2-negative receiving CDK 4/6 inhibitors.

METHODS

This retrospective study included all eligible patients who presented to our center between June 2017 and July 2023. As this was a retrospective study, and the sample size was determined by the number of eligible patients identified during the study period, a formal power analysis was not performed. This retrospective study was conducted in accordance with recognized ethical standards, including the principles of the Declaration of Helsinki, and received approval from the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 08.02.2024, Decision No: 2024-02/04). The Ethics Committee waived the requirement for informed consent, as the study was retrospective and non-interventional, and deemed that obtaining consent was unnecessary in accordance with national regulations.

Based on the number of eligible patients treated at our center in recent years, we initially estimated that we could include approximately 300 patients. However, after applying the exclusion criteria, the final sample size comprised 244 patients with ABC ER-positive/HER2-negative who received first-line treatment with ribociclib or palbociclib in combination with ET, including letrozole or fulvestrant. Amebaciclib, not covered under reimbursement in our country, was not a preferred treatment option. The pathological evaluation was performed according to the ASCO/CAP guidelines. ER, PR and HER2 were evaluated using IHC. The PR IHC evaluation was performed by a single experienced pathologist, and no second observer review was conducted. Inclusion criteria were as follows: being female over 18 years of age, having de novo or recurrent metastatic breast cancer, having an ER level of 10% or higher, having a PR level assessed in the pathology report, having a HER2 score of 0 and 1+ or 2+ by IHC method and negative by in situ hybridization (ISH) method, receiving CDK 4/6 inhibitor plus ET treatment in the first-line setting, having adequate organ functions, and having an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2. Exclusion criteria included being pregnant, breastfeeding, or having male breast cancer, having early-stage breast cancer, having unknown PR levels in pathology reports, having ER levels below 10%, having HER2 IHC scores of 3+ or 2+ with ISH positivity, receiving CDK 4/6 inhibitor plus ET treatment in the second-line or later settings, and having an ECOG PS of 3-4.

For patients with recurrent disease, pathological information, including the percentage of PR expression, was obtained from the relapse biopsy, if available. For patients with de novo disease or without an available relapse biopsy, pathological information, including PR expression, was retrieved from the initial diagnostic biopsy.

According to the St. Gallen guidelines, PR expression and Ki-67 levels were categorized into two groups: less than 20% and 20% or greater.[9] Patients with PR levels below 20% were classified as having low PR expression, while those with 20% and above were classified as having high PR expression. These two groups were compared in terms of PFS. Patients with a HER2 IHC score of 0 were classified into the HER2 negative group, while those with a HER2 IHC score of 1 and those with a score of 2 but negative ISH were included in the HER2 low group. Patient files were retrospectively screened using the hospital archive system and the automation recording system for median age, menopausal status, presence of any comorbid diseases, tumor grade, Ki-67 levels, administration of ribociclib or palbociclib, concurrent use of letrozole or fulvestrant, presence of visceral or non-visceral metastases, and whether the disease was de novo or recurrent.

Endocrine resistance was defined according to the fourth ESO-ESMO International Consensus guidelines. Primary endocrine resistance was defined as disease progression within the first six months of first-line ET for metastatic breast cancer or recurrence within the first two years of adjuvant ET. Secondary endocrine resistance was defined as recurrence during adjuvant ET but after the first two years, recurrence within 12 months of completing adjuvant ET, or disease progression after six months of initiating ET for metastatic breast cancer.[10]

Patients with de novo metastatic disease or without acquired resistance received a CDK 4/6 inhibitor combined with letrozole. Patients who developed primary or secondary resistance while on adjuvant therapy were treated with a CDK 4/6 inhibitor and fulvestrant.

Ribociclib at a dose of 600 mg or palbociclib at 125 mg was initiated in cycles of 28 days, with 21 days of treatment followed by a 7-day break. Concomitant ET consisted of 2.5 mg of letrozole daily or 500 mg of fulvestrant administered intramuscularly every 28 days. Additionally, luteinizing hormone-releasing hormone analog was added to the treatment regimen of pre/perimenopausal patients. Patients

with bone metastases were treated with zoledronic acid or denosumab if there were no contraindications.

PFS is the time from initiating CDK 4/6 inhibitors plus ET treatment to disease progression, death, or the last medical record. Overall survival (OS) is defined as the time from the start of treatment to death or the date of the last follow-up. During the descriptive statistics, non-parametric variables were presented as median (range), while categorical data were presented as frequency (percentage). The Chi-square test was used to compare categorical data between independent groups. PFS and OS durations were calculated using the Kaplan-Meier method. The median values for PFS were calculated. It was not specified since the median value could not be reached for OS. Independent prognostic factors were determined by creating a Cox Regression model with factors found to be statistically significant ($p<0.05$) using Kaplan Meier. IBM Corp. for statistical analysis. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: The IBM Corp program was used.

RESULTS

Of the 244 patients included in the study, 83 (34.0%) had low PR expression, and 161 (66.0%) had high PR expression. The median age of the patients was 55 (range 25-87 years). Among patients aged ≤55 years (n=116), 36 (43.4%) had low PR expression and 80 (49.7%) had high PR expression, while among patients older than 55 years (n=128), 47 (56.6%) had low PR expression and 81 (50.3%) had high PR expression.

Low PR expression was detected in 39 (47.0%) of the patients with visceral metastasis (n=92), and high PR expression in 53 (32.9%). In comparison, low PR expression was detected in 44 (53.0%) of the patients with non-visceral metastasis (n=152) and high PR expression in 108 (67.1%) (p=0.032). Low PR expression was detected in 51 (61.4%) patients who received adjuvant ET before CDK 4/6 inhibitor treatment, and high PR expression in 69 (42.9%). In comparison, low PR expression was detected in 32 (38.6%) of the patients who did not receive adjuvant ET, and high PR expression in 92 (57.1%) (p=0.006).

PR percentages were assessed from primary tumor biopsies in 134 patients (54.9%) and recurrence biopsies in 110 patients (45.1%). Low PR expression was detected in 38 (45.8%) of the primary lesion biopsy samples, and high PR expression was observed in 96 (59.6%). In comparison, low PR expression was detected in 45 (54.2%) of the recurrent lesion biopsy samples and high PR expression in 65 (40.4%) (p=0.039). All patients with de novo disease had PR percentages assessed from their primary tumor biopsies. Among patients with recurrent disease, PR percentages were obtained from the primary tumor biopsy in 24 cases (17.9%) and the recurrence biopsy in 110 cases (82.1%).

Additionally, there was no statistically significant difference between patients with low PR expression and those with high PR expression regarding the presence of median age, menopausal status, tumor grade, Ki-67 proliferation index, Her2 status, CDK 4/6 inhibitors agents, adjuvant endocrine agent, and endocrine resistance (**Table 1**).

The median follow-up duration was 20.8 months (95% CI; 20.35-23.89). Median PFS (mPFS) for patients with low PR expression was 23.13 months (95% CI; 15.67-30.59), whereas it was 34.66 months (95% CI; 24.27-45.05) for patients with high PR expression (p=0.002) (**Figure**).

In those with Ki-67 levels ≤ 20%, the median progression-free survival (mPFS) was not estimated (NE), whereas for those with >20% Ki-67 levels, the mPFS was 24.08 months (95% CI, 18.96-29.21; p=0.004). For grade one tumors, mPFS was not estimable (NE), while for grade two tumors, mPFS was 35.61 months (95% CI, NE), and for grade three tumors, mPFS was 24.08 months (95% CI, 19.94-28.23; p=0.030). Patients with visceral metastases had a mPFS of 21.45 months (95% CI, 10.62-32.29), while those with non-visceral disease had an mPFS of 33.05 months (95% CI, 22.69-43.41) (p=0.049). mPFS was NE in patients with pathological assessment from primary lesion biopsies, whereas those with pathological assessment from recurrent lesion biopsies had an mPFS of 23.85 months (95% CI; 19.29-28.41) (p=0.010). Patients who received adjuvant ET before CDK 4/6 inhibitor treatment had an mPFS of 25.66 months (95% CI; 20.48-30.84), while those who did not receive adjuvant ET had an mPFS of 35.61 months (95% CI; 25.52-45.71) (p=0.044).

Additionally, there was no difference in mPFS based on median age, menopausal status, HER2 status, CDK 4/6 inhibitors, endocrine agent combined with CDK 4/6 inhibitors, adjuvant endocrine agent, and endocrine resistance (**Table 2**).

The mOS was not reached. Five-year OS rates based on PR expression were 34.0% in patients with low PR expression and 72.6% in those with high PR expression (p=0.144). Although this difference did not reach statistical significance, it suggests a potential positive impact of high PR expression on OS. The five-year OS rate was 81.5% in patients with a Ki-67 index below 20%, compared to 40.1% in those with a Ki-67 index above 20% (p=0.005). Regarding HER2 status, the five-year OS rate was 57.9% in HER2-low patients and 67.7% in HER2-negative patients (p=0.034; **Table 3**). These findings suggest that both variables may influence long-term survival outcomes.

In patients receiving ribociclib therapy, the mPFS was 35.61 months (95% CI; 25.55-45.68) in those with high PR expression and 23.85 months (95% CI; 12.84-34.86) in those with low PR expression (p:0.034). In patients receiving palbociclib therapy, the mPFS was NE in those with high PR expression and 16.99 months (95% CI; 5.09-28.89) in those with low PR expression (p:0.024).

Significant factors identified in the univariate analysis, including grade, PR status, Ki-67 levels, and new or recurrent disease status, were evaluated by Cox regression analysis.

The grade, PR status, Ki-67 index, and de novo or recurrent disease status were evaluated using Cox regression analysis after being found significant in univariate analysis. It was demonstrated that both low or high expression of PR (HR: 0.60, 95% CI; 0.36-0.98) (p:0.040) are independent predictive factors (**Table 4**).

Table 1. Baseline characteristics of patients with HR-positive/HER2-negative ABC treated with CDK 4/6 inhibitors plus ET

	Total (n=244)	Low PR expression n=83 (34.0%)	High PR expression n=161 (66.0%)	p-value
Median age (years)				0.349
≤55 y	116 (47.5%)	36 (43.4%)	80 (49.7%)	
>55 y	128 (52.5%)	47 (56.6%)	81 (50.3%)	
Menopausal status (%)				0.730
Pre/perimenopause	74 (30.3%)	24 (28.9%)	50 (31.1%)	
Postmenopause	170 (69.7%)	59 (71.1%)	111 (68.9%)	
Grade				0.211
Grade 1	16 (7.5%)	4 (5.6%)	12 (8.4%)	
Grade 2	116 (54.2%)	34 (47.9%)	82 (57.3%)	
Grade 3	82 (38.3%)	33 (46.5%)	49 (34.3%)	
Ki 67 index-%				0.359
≤20%	91 (39.7%)	27 (35.5%)	64 (41.8%)	
>20%	138 (60.3%)	49 (64.5%)	89 (58.2%)	
HER2 status				0.872
HER 2 low	92 (37.9%)	32 (38.6%)	60 (37.5%)	
HER negative	151 (62.1%)	51 (61.4%)	100 (62.5%)	
CDK 4/6 inhibitors				0.358
Ribociclib	168 (68.9%)	54 (65.1%)	114 (70.8%)	
Palbociclib	79 (32.4%)	28 (33.7%)	51 (31.7%)	
Endocrine agent combined with CDK 4/6 inhibitors				0.181
Letrozole	194 (79.5%)	62 (74.7%)	132 (82.0%)	
Fulvestrant	50 (20.5%)	21 (25.3%)	29 (18.0%)	
Metastatic sites				0.032*
Non-visceral	152 (62.3%)	44 (53.0%)	108 (67.1%)	
Visceral	92 (37.7%)	39 (47.0%)	53 (32.9%)	
Biopsy to evaluate PR percentage				0.039*
Primary lesion biopsy	134 (54.9%)	38 (45.8%)	96 (59.6%)	
Recurrent lesion biopsy	110 (45.1%)	45 (54.2%)	65 (40.4%)	
Adjuvant ET				0.006*
Yes	120 (49.2%)	51 (61.4%)	69 (42.9%)	
No	124 (50.8%)	32 (38.6%)	92 (57.1%)	
Adjuvant endocrine agent				0.880
AI	72 (60.0%)	31 (60.8%)	41 (59.4%)	
Tamoxifen	48 (40.0%)	20 (39.2%)	28 (40.6%)	
Endocrine resistance				0.159
Yes	91 (37.3%)	36 (43.4%)	55 (34.2%)	
No	153 (62.7%)	47 (56.6%)	106 (65.8%)	
Type of endocrine resistance				0.134
Primary	17 (18.7%)	4 (11.1%)	13 (23.6%)	
Secondary	74 (81.3%)	32 (88.9%)	42 (76.4%)	

HR: Hormone receptor, HER2: Human epidermal growth factor receptor 2, ABC: Advanced-stage breast cancer, ET: Endocrine therapy, PR: Progesterone receptor, AI: Aromatase inhibitor, *Significant

DISCUSSION

Following the demonstration of improvement in PFS with CDK 4/6 inhibitors and ET combination in ABC[7], the United States Food and Drug Administration (FDA) has approved all three CDK 4/6 inhibitors.

It is essential to identify patients who will benefit clinically from CDK 4/6 inhibitor treatments, evaluate their tolerability, and assess their impact on quality of life. Sensitivity and resistance mechanisms to CDK 4/6 inhibitors and ET combinations are highly complex. It is known that PR-negative tumors in patients with ER-positive breast cancer

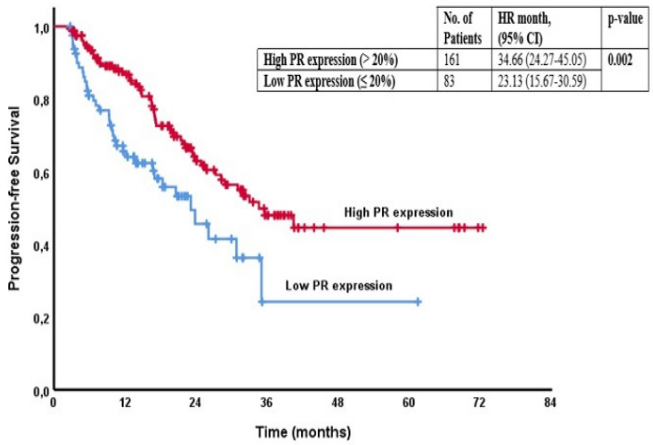

Figure. mPFS curve of low PR expression and high PR expression patients
mPFS: Median progression-free survival, PR: Progesterone receptor, HR: Hormone receptor

are more resistant to ET compared to PR-positive tumors.[11] In recent years, very much evidence has shown that ER-positive/PR-negative tumors exhibit more invasive clinical and pathological characteristics and have a worse prognosis compared to ER-positive/PR-positive tumors.[12] In the 2013 St. Gallen Conference, emphasis was placed on the significant impact of PR loss or low expression (≤20%) on the survival of breast cancer patients.[13]

A study evaluating the impact of PR on metastasis and prognosis in HER2-negative breast cancer patients showed that ER-positive/PR-positive patients had a high incidence of bone metastasis. In contrast, ER-positive/PR-negative patients had a higher incidence of visceral metastasis.[14]

Previous research has identified PR negativity as an independent risk factor for visceral metastasis.[15] Consistent with these findings, our study also revealed that patients with high PR expression exhibited visceral metastasis rates of 32.9%, while the rate of non-visceral disease was 67.1% (p:0.032). A prospective study investigating the predictive role of PR in tamoxifen response in ABC showed that high PR levels are associated with better treatment response, prolonged time to treatment failure, and improvement in OS.[16] Similarly, in another study, PR negativity was shown to be an independent predictive marker for tamoxifen resistance and breast cancer recurrence.[17] Rocca et al.[18] evaluated the impact of PR and Ki-67 levels on the clinical benefit of first-line ET in ABC. In this study, the cut-off value for PR and Ki-67 was determined to be 20%. Patients with PR >20% demonstrated a longer median time to progression (TTP) than those with PR ≤20% (24 months vs. 12 months, p=0.012). In the multivariate analysis, PR was identified as a significant independent determinant of TTP (HR 2.45).

On the contrary, a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showed that tamoxifen improved survival independently of PR status in ER-positive tumors.[2]

Table 2. Progression-free survival rates in patients treated with CDK 4/6 inhibitors plus ET

	PFS median (95% CI)	p-value
Median age (years)		0.566
≤55 y	26.12 (19.08-33.16)	
>55 y	34.66 (24.71-44.61)	
Menopausal status (%)		0.429
Pre/perimenopause	26.12 (18.88-33.36)	
Postmenopause	33.05 (22.02-44.09)	
Grade		0.030*
Grade 1	NE	
Grade 2	35.61 (NE)	
Grade 3	24.08 (19.94-28.23)	
PR status		0.002*
Low PR expression	23.13 (15.67-30.59)	
High PR expression	34.66 (24.27-45.05)	
Ki 67 index-%		0.004*
≤20%	NE	
>20%	24.08 (18.96-29.21)	
HER2 status		0.669
HER 2 low	28.85 (18.06-39.64)	
HER negative	31.05 (23.47-38.63)	
CDK 4/6 inhibitors		0.284
Ribociclib	33.05 (26.77-39.33)	
Palbociclib	26.12 (19.12-33.12)	
Endocrine agent combined with CDK 4/6 inhibitors		0.090
Letrozole	33.05 (26.62-39.49)	
Fulvestrant	21.72 (15.62-27.82)	
Metastatic sites		0.049*
Non-visceral	33.05 (22.69-43.41)	
Visceral	21.45 (10.62-32.29)	
Biopsy to evaluate PR percentage		0.010*
Primary lesion biopsy	NE	
Recurrent lesion biopsy	23.85 (19.29-28.41)	
Adjuvan ET		0.044*
No	35.61 (25.52-45.71)	
Yes	25.66 (20.48-30.84)	
Adjuvant endocrine agent		0.525
AI	23.85 (15.27-32.43)	
Tamoxifen	24.08 (19.77-28.39)	
Endocrine resistance		0.123
Yes	26.12 (18.25-33.99)	
No	35.09 (25.33-44.85)	
Type of endocrine resistance		0.950
Primary	20.24 (10.55-29.93)	
Secondary	27.34 (18.24-36.43)	

HER2: Human epidermal growth factor receptor 2, ET: Endocrine therapy, PR: Progesterone receptor, AI: Aromatase inhibitör, NE: Non-estimated,*Significant

Table 3. Overall survival rates in patients treated with CDK 4/6 inhibitors plus ET

	5-year OS	p-value
Median age (years)		0.370
≤55 y	55.9%	
>55 y	74.8%	
Menopausal status (%)		0.908
Pre/perimenopause	34.3%	
Postmenopause	71.7%	
Grade		0.117
Grade 1	NE	
Grade 2	60.4%	
Grade 3	65.7%	
PR status		0.144
Low PR expression	34.0%	
High PR expression	72.6%	
Ki 67 index-%		0.005*
≤20%	81.5%	
>20%	40.1%	
HER2 status		0.034*
HER 2 low	57.9%	
HER negative	67.7%	
CDK 4/6 inhibitors		0.200
Ribociclib	74.4%	
Palbociclib	31.9%	
Endocrine agent combined with CDK 4/6 inhibitors		0.558
Letrozole	64.1%	
Fulvestrant	73.4%	
Metastatic sites		0.280
Non-visceral	72.9%	
Visceral	53.1%	
Biopsy to evaluate PR percentage		0.124
Primary lesion biopsy	78.4%	
Recurrent lesion biopsy	63.7%	
Adjuvan ET		0.697
No	68.4%	
Yes	64.1%	
Adjuvant endocrine agent		0.440
AI	65.3%	
Tamoxifen	63.8%	
Endocrine resistance		0.312
Yes	56.7%	
No	70.9%	
Type of endocrine resistance		0.408
Primary	64.6%	
Secondary	49.2%	

OS: Overall survival, HER2: Human epidermal growth factor receptor 2, ET: Endocrine therapy, PR: Progesterone receptor, AI: Aromatase inhibitör, NE: Non-estimated, *Significant

Table 4. Cox regression model for predicting the independent factors for PFS

	HR (95% CI)	p-value
Grade		
Grade 1	Ref	
Grade 2	2.15 (0.50-9.20)	0.302
Grade 3	2.79 (0.63-12.40)	0.177
PR status		0.040*
Low PR expression	Ref	
High PR expression	0.60 (0.36-0.98)	
Ki 67 index-%		0.140
≤20%	Ref	
>20%	1.50 (0.88-2.58)	
Metastatic sites		0.126
Non-visceral	Ref	
Visceral	1.44 (0.90-2.30)	
Biopsy to evaluate PR percentage		0.096
Primary lesion biopsy	Ref	
Recurrent lesion biopsy	1.93 (0.89-4.17)	
Adjuvant ET		0.725
No	Ref	
Yes	0.87 (0.40-1.89)	

PFS: Progression-free survival, HR: Hormone receptor, ET: Endocrine therapy, PR: Progesterone receptor, *Significant

Prat et al.[9] found that PR expression is prognostic in luminal A disease, with 20% being the most appropriate cut-off value. In a study, the group with PR <20% and Ki-67 ≥20% was associated with a higher malignancy grade, and these patients were shown to benefit more from chemotherapy. Thus, PR and Ki-67 status are believed to be beneficial in predicting prognosis and determining the most effective treatment strategy in ER-positive/HER2-negative breast cancer.[19] In a different study, patients with ER-positive/PR-negative tumors obtained similar poor outcomes as triple-negative tumors, and particularly in tumors with this tumor biology, chemotherapy has been shown to provide better survival benefits, especially in node-positive tumors.[12]

For CDK 4/6 inhibitor-based therapies, ongoing research investigates parameters such as PIK3CA, ESR1, SMARCA4, PDK1, and many others as potential predictive markers. However, as of now, no other biomarker besides ER expression has been identified to predict treatment for CDK 4/6 inhibitors.[20,21] This ongoing research keeps our field dynamic and engaging.

PALOMA-3 is a randomized study comparing the combination of palbociclib and fulvestrant with placebo and fulvestrant combination in patients with HR-positive/HER2-negative ABC who have previously not responded to prior ET.[22] Although the study demonstrated improved PFS and objective response rates with the combination of palbociclib

and fulvestrant, enhanced quality of life, and a favorable toxicity profile, no specific biomarker to predict response or benefit was identified in the final analysis.[23] A study using data from PALOMA-3 to identify biomarkers that could predict the long-term benefit of palbociclib and fulvestrant showed that the ER level had no impact on treatment duration. In patients with high PR levels, it was demonstrated that long-term responses occurred.[24]

In a study evaluating predictive and prognostic factors in patients with HR-positive ABC receiving the combination of palbociclib and letrozole, the mPFS was found to be 12.99 months in PR-negative tumors and 20.05 months in ER and PR-positive tumors (p:0.046).[26] In a pooled analysis by the FDA[7], with CDK 4/6 inhibitors plus ET, mPFS was found to be 27.5 months (95% CI; 18.2–29.5) in PR-negative patients and 29.1 months (95% CI; 26.2 to NE) in PR-positive patients. In this study, positive ER status was considered the best biomarker for predicting the treatment benefit of CDK 4/6 inhibitors, and PR was thought to have no prognostic value. In another study evaluating the clinical impact of CDK 4/6 inhibitors, subgroup analysis showed that in the palbociclib group, the 5-year PFS was 22.66% in PR-positive patients and 21.07% in PR-negative patients, demonstrating that PR status did not affect survival.[26] The PARSIFAL study presented at ASCO 2020 demonstrated that PR and Ki-67 levels significantly influenced the benefit of palbociclib and aromatase inhibitor (AI) therapy. Patients with low PR and high Ki-67 levels were shown to benefit less from the combination of palbociclib and AI. Palleschi et al.[27] found that PFS was inversely related to Ki-67 levels but not PR status in patients receiving palbociclib and ET.In a retrospective analysis performed by Shao et al.,[28] a cohort treated with the combination of palbociclib and AI achieved a longer PFS in patients with PR values ≥20% compared to those with <20% (not reached vs 5.8 months; p=0.012).

In our study, the mPFS was 23.13 months (95% CI; 15.67-30.59) for patients with low PR expression and 34.66 months (95% CI; 24.27-45.05) for patients with high PR expression (p:0.002). In patients with Ki-67 levels ≤20%, mPFS was NE, while for those with Ki-67 levels >20%, the mPFS was 24.08 months (95% CI; 18.96-29.21) (p:0.004). Thus, we obtained results supporting studies suggesting that PR and Ki-67 levels predict response to CDK 4/6 inhibitors**.**

Tang et al.[26] investigated whether PR expression affected survival outcomes in patients receiving CDK 4/6 inhibitors. mPFS was found to be 38 months in ER-positive/PR-positive tumors and 19.2 months in ER-positive/PR-negative tumors (p=0.0038). In the ribociclib group, the mPFS was 44 months in ER-positive/PR-positive tumors and 10.1 months in ER-positive/PR-negative tumors (p:0.0014). In the palbociclib group, the PR status did not affect survival, and the 5-year PFS rates were 22.66% in PR-positive tumors and 21.07% in PR-negative tumors.

Our study revealed a significant difference in mPFS between patients with high PR expression and those with low PR expression in both the ribociclib and palbociclib treatment groups. Specifically, patients with high PR expression treated with ribociclib demonstrated an mPFS of 35.61 months (95% CI; 25.55-45.68) compared to 23.85 months (95% CI; 12.84-34.86) for those with low PR expression (p=0.034). Similarly, in the palbociclib group, a significant difference in mPFS was observed (NE vs 16.99 months (95% CI; 5.09-28.89), p=0.024) between high and low PR expression groups. In their study, Tang et al.[26] found that both palbociclib and ribociclib were associated with lower mPFS in PR-negative tumors. However, in our study, while there was a difference in mPFS with palbociclib in patients with PR low and high expression, no such difference was observed in those treated with ribociclib. Several factors may contribute to these discrepancies, including limitations in sample size, differences in molecular characteristics beyond PR status, pharmacokinetics and pharmacodynamics of the drugs, genetic variations affecting treatment response, duration of post-treatment follow-up, patient adherence to treatment, and whether the disease is de novo or recurrent. Further comprehensive studies are needed to evaluate whether these results are statistically significant or coincidental.

Limitations

This study is subject to several limitations. Firstly, its retrospective design introduces potential biases and a lack of standardization in data collection. The sample size may be insufficient, particularly for subgroup analyses. Missing data, a common issue in retrospective studies, may also impact the findings. Furthermore, as the study was conducted at a single center, the generalizability of the findings is limited and warrants further validation in diverse patient populations. The short follow-up duration poses a limitation, especially for assessing long-term outcomes such as median OS. The evaluation of pathology specimens by a single pathologist represents a potential source of subjectivity. Technical factors related to PR assessment, including tissue irregularities, staining inconsistencies, antibody selection, and microscope settings, may have introduced variability in the results. The lack of biopsy data from recurrent lesions in approximately half of the patients limits our understanding of disease progression and treatment resistance mechanisms. Finally, the absence of newer-generation CDK 4/6 inhibitors, such as amebasiklib, due to limitations in institutional reimbursement policies, the potential deviations from standard treatment protocols in patients' received therapies, and the lack of assessment of treatment adherence represent additional limitations that should be considered.

Approaches are being investigated to identify patients likely to benefit from single-agent ET in the first line for ABC ER-positive/HER2-negative tumors, thereby avoiding exposure to the toxicities of CDK 4/6 inhibitors. However, ER positivity is currently the only established biomarker for identifying breast cancer patients who may be candidates for CDK 4/6 inhibitor therapy. The use of existing biomarkers and the development of new ones are crucial for identifying these patients.

CONCLUSION

In this study, the potential predictive role of PR expression on the response to CDK 4/6 inhibitor therapy was investigated in patients with ER-positive/HER2-negative metastatic breast cancer. A significant association was found between high PR

expression and prolonged PFS. Similarly, in the subgroups treated with ribociclib and palbociclib, patients with high PR levels achieved significantly longer mPFS. Additionally, lower Ki-67 levels were found to be associated with longer PFS. These results suggest that integrating PR and Ki-67 into clinical practice may contribute to the personalization of treatment strategies. However, given the retrospective nature of the study, the limited sample size, and its single-center design, the findings need to be validated in larger, prospective studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

Received approval from the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital Non-interventional Clinical Researches Ethics Committee (Date: 08.02.2024, Decision No: 2024-02/04).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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