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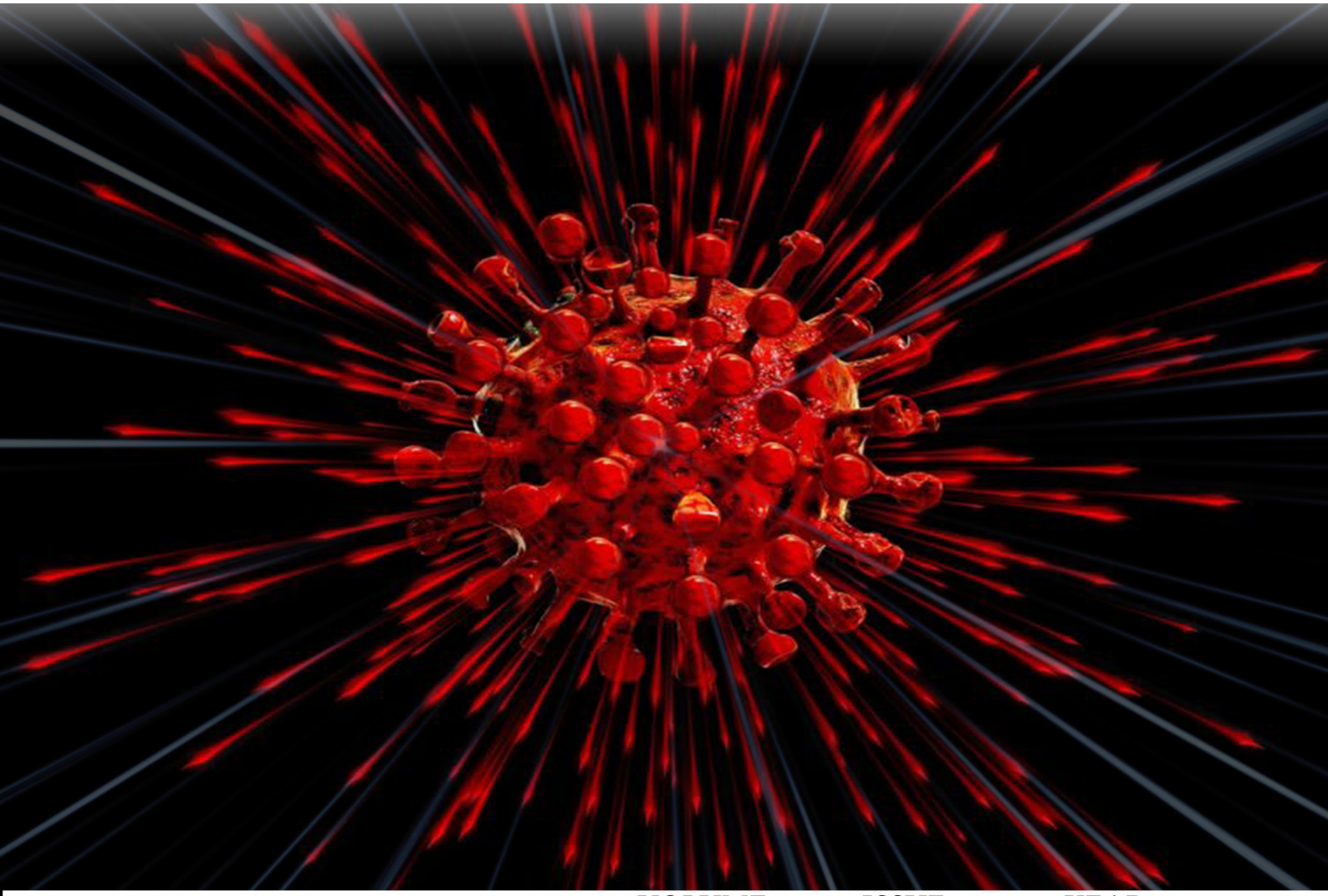

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CONTENTS

Original Articles

HALP score can predict the no-reflow phenomenon and in-hospital mortality after saphenous vein graft intervention 1-7
Demir ÖF, Şensoy B.

The effects of patient triage management strategies on clinical outcomes and risk management in emergency departments: a prospective comparative study 8-14
Boğa E.

Evaluation of critical factors predicting the development of hepatorenal syndrome in hospitalized cirrhotic patients 15-21
Erdoğan Ç, Karpuzcu HC.

The effect of different polishing systems on the discoloration of composite resins: examples of commonly consumed beverages 22-26
Gümüş Ayaz S, Bakır EP, Bakır Ş.

Elevated expression of let-7b-3p enhances aggressiveness of larynx squamous cell carcinoma cells 27-32
Kaya M, Güzel Tanoğlu E, Suer İ et al.

Prevalence of neoplasms in acromegaly: a Turkish single-center retrospective study 33-36
Yüzbaşıoğlu Mirza G, Takır M, Torun C, Bahadır Ö.

Assessment of the ROX index as a predictor of invasive ventilation in patients with community-acquired pneumonia 37-42
Aydın ÖF, Tatlıparmak AC.

Influence of *Enterococcus faecium*, a probiotic component, on ion channels in colon cancer 43-47
Seçer Çelik F, Altveş S.

Assessment of the relationship between vascular diseases and exposure to toxic metals vascular diseases and toxic metals 48-53
Şahin S, Zekey FS, Er ZC, Türksoy VA.

Odontogenic and non-odontogenic cysts in the jaws: a retrospective analysis 54-59
Çoban E, Altay B, Chodarov A.

Does greater richness of experience lead to greater happiness in older adults? 60-66
Gümüş Demir Z.

The effect of inflammatory scores on the prognosis of malignant mesothelioma 67-71
Akkurt ES, Düvenci Birben Ö, Yenibertiz D, Dağlı D.

Evaluation of the long-term autonomic dysfunction after the recovery of COVID-19 disease 72-76
Koçak A, Bağlan Uzunget S, Şahin KE.

The impact of health workforce and health expenditures on life expectancy and infant mortality rates in Turkiye 77-83

Sarıyıldız AY.

Evaluation of prenatal-postnatal outcomes and risk factors in fetal jejunoileal atresia 84-88

Taşdemir Ü, Eyisoy ÖG, Gezer M, Celayir A, Eriç Özdemir M, Demirci O.

Review

Current approaches in the diagnosis and treatment of organizing pneumonia 89-93

Arı M.

Letter to the Editor

Insights on the relationship between essential tremor and carpal tunnel syndrome: a letter to the editor 94-96

Çelik G.

Original Article

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HALP score can predict the no-reflow phenomenon and in-hospital mortality after saphenous vein graft intervention

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ABSTRACT

Aims: The no-reflow phenomenon (NRP) is one of the most frequently observed complications in saphenous vein graft (SVG) interventions. The aim of this study was to investigate the effect of the hemoglobin, albumin, lymphocyte, and platelet (HALP) score on the development of NRP in patients with acute coronary syndrome (ACS) undergoing percutaneous SVG intervention.

Methods: This retrospective study included 263 patients who applied to our center with the diagnosis of ACS and underwent saphenous vein grafting procedure. The patients were divided into two groups according to whether no-reflow developed or not, and the HALP scores of the groups were compared. In addition, in-hospital mortality was compared between the study groups according to their HALP score values. The predictive ability of the HALP score for no-reflow was evaluated using a receiver operating characteristic curve.

Results: NRP developed in 103 (39.2%) of the patients included in the study patients. HALP score value was found to be significantly lower in the no-reflow group (45.3±20 vs 53.8±18, p:0.001). In the receiver operating characteristic (ROC) analysis, the cutoff value for the HALP score was calculated as 46.5. After multivariable adjustment, the HALP score <46.5 was an independent predictor of no-reflow (OR=4.95, 95% CI:2.48-9.89; p<0.001). Additionally, HALP score was found to be an indicator for in-hospital mortality (0.036).

Conclusion: The HALP score proves to be a valuable predictive tool for NRP and in-hospital mortality in patients with presenting to the emergency department with ACS and undergoing SVG intervention.

Keywords: HALP score, no-reflow phenomenon, saphenous vein graft, percutaneous coronary intervention, acute coronary syndrome

INTRODUCTION

In recent years, significant progress has been made in treating coronary artery disease (CAD) with respect to percutaneous coronary intervention (PCI) and the timing of coronary surgeries.[1] Coronary artery bypass graft (CABG) surgery is often considered the main treatment option for individuals diagnosed with disease in all three major coronary arteries and/or the left main coronary artery. In addition to improving ischaemia, angina, and living conditions, coronary surgery also improves the prognosis in some patients.[2] Despite the worse patency rates of saphenous vein grafts (SVGs) compared to arterial grafts, their easy accessibility plays a role in their more frequent preference in surgeries.[2] During the initial year following CABG surgery, 10-15% of saphenous vein grafts become occluded,[3] and over the first decade, their patency rates decline by 50% as a result of degenerative or obstructive conditions.[4] In procedures involving saphenous vein grafts, various challenges arise, chiefly including flow quantities and distal embolization.[5] The no-reflow phenomenon (NRP) is an adverse event occurring with a frequency of up to 15 percent during SVG interventions.[6,7] NRP deteriotes reverse remodelling of the left ventricle leading to congestive heart failure related topoor prognosis.[8] Although the exact mechanisms behind the development of NRP are not fully understood, capillary bed embolism, endothelial dysfunction, ischemic damage, inflammatory reaction, and stress response are suggested elements in the NRP mechanism.[9] Various comorbid conditions, delayed intervention and excess thrombogenic burden of the vessel are the main factors suggested for the development of NRP.[10] By identifying independent predictors of NRP would be advantageous for managing to limit NRP related clinical adverse events associated with SVG procedures.

Hemoglobin, albumin, lymphocyte and platelet (HALP) score is obtained from four variables that can be easily calculated from blood samples and has been suggested as a biomarker that can express the health prognosis and inflammatory status of some patient groups.[11] Each of these parameters provides important insights into the patient's overall health, and numerous clinical studies have demonstrated their close

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association with the occurrence of no-reflow.[12,13] Because the HALP score indicates conditions like anemia, malnutrition, and proinflammatory states, studies have demonstrated an inverse relationship between cardiovascular mortality risk in the general population and negative clinical outcomes, such as in-hospital death and acute heart failure, within patients experiencing coronary syndrome.[11,14]

The purpose of this research was to explore how the HALP score influences the occurrence of NRP and in-hospital mortality in patients with acute coronary syndrome (ACS) who received SVG intervention. Additionally, the study aimed to assess the independent predictors of NRP occurrence.

METHODS

Ethics

All procedures involving human participants in this study adhered to the ethical standards set by the institutional research committee, as well as the 1964 Declaration of Helsinki and its later amendments or equivalent ethical guidelines. The study did not involve any animal subjects. Approval was obtained from the Clinical Researches Ethics Committee of University of Health Sciences Bursa Higher Specialization Training and Research Hospital (Date: 11.09.2024, Decision No: 2024-TBEK 2024/09-02).

Data Collection and Laboratory Analysis

The study included individuals with previous coronary operation who presented at our hospital with ACS needing SVG intervention. All eligible patients presenting from January 2017 to January 2024 were consecutively enrolled. The study included only those with unstable angina or NSTEMI, while STEMI patients were excluded. The reason for excluding STEMI patients is that in this patient group, optimal conditions cannot be provided in the procedure due to the possibility of hemodynamic deterioration and the possibility of NRP development is higher due to intense thrombus burden. The mentioned situations will reduce the reliability of the HALP score.

The criteria for inclusion were: (1) ages ranging from 20 to 80 years, (2) having undergone CABG more than 6 months prior, and (3) identification of a saphenous vein lesion with a subsequent decision for intervention. Exclusion criteria were: (1) having a prior diagnosis of hemoglobinopathy, (2) existence of mechanical complications, (3) indications of active infection, (4) undergoing active cancer treatment, and (5) having inadequate or missing data. A total of 263 patients meeting these criteria were included. All participants received in-patient care following currrent ACS management guidelines. Demographic information and clinical details, including comorbid status, as well as laboratory and angiographic results, were collected from the hospital's electronic records. Further additional data, such as ritm and vital sign records and previous medications, were gathered through an archive review.

Routine blood tests were conducted at admission. Blood samples taken after an 8-12 hour overnight fast were used for studies on lipid parameters.

Coronary Angiography and Percutaneous Coronary Intervention

All patients underwent evaluation with standard coronary angiography, and a stent with suitable diameter and length was placed in the artery associated with the infarct. An experienced cardiologist, who was not privy to patient details, examined the digital angiographic images and assessed the results before and after the angioplasty. In this study, angiographic NRP was characterized by a thrombolysis in myocardial infarction (TIMI) flow grade below 3, with no signs of coronary spasm or dissection.[15] Thrombus burden was assessed on a scale from 1 to 5, where 1 indicated no thrombus and 5 signified a large thrombus fully obstructing the vessel.[16] After recanalization with a guidewire or small balloon, a grade 5 thrombus was reclassified to between grades 1 and 4. No embolic protection devices were used for any patient, regardless of the thrombus burden in the SVG, because such devices were unavailable at our center.

Definitions

ACS was defined according to the latest universal guidelines for the definition of myocardial infarction.[17] Based on the American diabetes association criteria, patients were defined as diabetic by their first blood sugar measurement at the time of admission and monitoring of fasting blood sugar or use of antidiabetic treatment.[18] Weight (kg)/ height (m^2) was the formula used to determine body-mass index (BMI). The modified Simpson method was preferred to calculate ventricular ejection fraction (LVEF), which was evaluated hours after the procedure. MDRD formula used to calculate eGFR.[19] The HALP score is calculated as follows: HALP score=hemoglobin (g/L)×albumin (g/L)×lymphocyte count (10^9/L)/platelet count (10^9/L).[11]

Statistical Analysis

The statistical software SPSS 26.0 (SPSS Inc., Chicago, IL, U.S.A.) and MedCalc statistical software (trial version 12.7.8, Mariakerke, Belgium) was used to run the analyses. The Kolmogorov–Smirnov or Shapiro–Wilk tests were used to test the normality of quantitative data. Variables were reported as mean±standard deviation (SD) or median and interquartile range values. To analyze categorical data, a $\chi 2$ test was used or Fisher's Exact test if any expected cell count was <5, and descriptive statistics were presented as number (n) and percentage (%). Student's t-test was used to compare normally distributed continuous variables, and the Mann-Whitney U test was used for variables without normal distribution. The Mann-Whitney U test was utilized to analyze two groups, and the subgroup comparisons were described using medians and interquartile ranges. Pairwise comparisons of receiver operating characteristic (ROC) curves were conducted to assess the risk of the NRP and to evaluate the predictive capability by comparing optimal cutoff points of the HALP score along with its components. The optimal cutoff value derived from the ROC analysis for the HALP score was 46.5 and was utilized to categorize groups into low and high HALP score categories. The sensitivity and specificity of these points were identified and the area under the curve (AUC) between the HALP score and its individual components were

compared. When indicated, analyses performed using HALP score as a continuous variable were also reported.

Logistic regression analyses, including both univariate and multivariate approaches, were performed to identify the independent risk factors associated with the NRP. To prevent multicollinearity, the individual components constituting the HALP score were excluded from the regression analysis. Variables found to be significant in the univariate analysis, such as a HALP score below 46.5, age, smoking, stent placement, predilatation, and thrombus grade, were included in a multivariate logistic regression analysis. The impact of each predictor on the NRP was quantified using odds ratios (OR) and 95% confidence intervals (CI). A p-value of less than 0.05 was deemed statistically significant, and all statistical tests were conducted as two-tailed.

RESULTS

An overall number of 263 patients with ACS and a history of CABG surgery were assessed. Among these patients, 211 (80.2%) were male and 52 (19.8%) were female, with an average age of 70±9 years. NRP was observed in 103 (39.2%) of the patients. The number of in-hospital mortality was found to be 13 (4.9%). The average HALP score of the patients included in the study was calculated as 50.5±19.6.

Table 1 presents the comparisons of demographic characteristics, as well as clinical and laboratory findings, between patients who developed NRP and those who did not. The analysis revealed that the average age of patients who did not develop NRP was significantly older than that of those who did (p=0.001). Moreover, there was a significantly higher number of smokers in the group that developed NRP

Table 1. The baseline characteristics and laboratory investigations of all patients

		All patients (n=263)	No-reflow (+) (n=103)	No-reflow (-) (n=160)	p-value
Demographic characteristics					
Age, years		70±9	68±9	72±9	0.001
Male gender, n (%)		211 (80.2)	83 (80.6)	128 (80)	0.908
Body-mass index, kg/m^2		27.6±3.3	27.6±3.5	27.6±3.2	0.916
Comorbidites					
Hypertension, n (%)		224 (85.2)	89 (86.4)	135 (84.4)	0.724
Diabetes mellitus, n (%)		119 (45.2)	40 (38.8)	79 (49.4)	0.126
Hyperlipidemia, n (%)		135 (51.3)	49 (47.6)	86 (53.8)	0.377
Smoking, n (%)		110 (41.8)	53 (51.5)	57 (35.6)	0.015
Chronic kidney disease, n (%)		84 (31.9)	32 (31.1)	52 (32.5)	0.892
On admission					
Systolic blood pressure, mmHg		132±22	131±22	133±22	0.429
Heart rate, beats/min		77±14	77±16	76±13	0.530
Killip class, %	1	201 (76.2)	80 (77.5)	121 (75.4)	0.437
	2	49 (18.8)	16 (15.7)	33 (20.9)	
	3	12 (4.5)	6 (5.6)	6 (3.7)	
	4	1 (0.4)	1 (1.1)	0	
ACE inh use, n (%)		180 (68.4)	69 (67)	111 (69.4)	0.686
Statin use, n (%)		144 (54.8)	54 (52.4)	90 (56.3)	0.612
OAD use, n (%)		78 (29.7)	27 (26.2)	51 (31.9)	0.337
Insulin use, n (%)		20 (7.6)	5 (4.9)	15 (9.4)	0.235
Laboratory assessment					
HbA1c, %		7.16±2.1	7.21±2.5	7.13±1.8	0.790
ABG, mg/dl		175±84	172±72	161±59	0.118
Hemoglobin, g/dl		12.6±1	12.5±0.7	12.7±1.1	0.018
Platelet count, x10^9/L		233.4±43.4	244.3±43.8	226.3±41.8	0.001
Lymphocyte, x10^9/L		2.22±0.8	2.12±0.8	2.29±0.7	0.097
Albumin, g/L		40.8±3.4	40.3±3.8	41.1±3	0.079
Peak troponin I, ng/L		1532 (281-5956)	2322 (437-8700)	945 (220-4523)	0.266
Total cholesterol, mg/dl		183.8±50.7	186.7±50.6	182±50,9	0.463
LDL cholesterol, mg/dl		110.3±43.9	111.3±42.5	109.7±44.9	0.766
eGFR, ml/min/1.73 m^2		70.5±25	72±25.9	69.6±24.4	0.451
HALP score		50.5±19.6	45.3±20.8	53.8±18	0.001
HALP score <46.5		124 (47.1)	62 (60.2)	62 (38.8)	0.001
In-hospital mortality, n (%)		16 (6.1)	12 (11.7)	4 (2.5)	0.003

The data are presented as the median (interquartile range), the mean±SDs or numbers (percentage) of patients. Abbreviations: ABG: Admission blood glucose, ACE: Angiotensin converting enzyme, eGFR: Estimated glomerular filtration rate, HALP: The hemoglobin, albumin, lymphocyte and platelet, IQR: Interquartile range, LDL: Low-density lipoprotein, LVEF: Left ventricular ejection fraction, OAD: Oral antidiabetic

(p=0.015). No notable differences were found regarding other demographic information and comorbid conditions. Both groups had similar mean values for blood pressure, heart rate, killip class and left ventricular ejection fraction at admission. Upon examining laboratory values, it was found that hemoglobin levels (12.5±0.7 vs. 12.7±1.1 mg/dl, p<0.018) and the HALP scores (45.3±20.8 vs. 53.8±18, p=0.001) were significantly lower in patients who developed NRP. Conversely, platelet count values (244.3±43.8 vs. 226.3±41.8, p=0.001) were significantly higher in the same group. There were no statistically significant differences observed in the other laboratory parameters. In the group of patients who developed NRP, the in-hospital mortality rate was found to be significantly higher (p:0.003).

Table 2 illustrates the angiographic parameters based on the presence of NRP. The thrombus burden was found to be significantly greater in patients who developed NRP (p<0.001). The occurrence of NRP was notably lower in patients who received a stent (p=0.002). Conversely, NRP was significantly more common in those who underwent predilatation (p<0.001). There was no significant difference between the groups concerning the length of the stent placed and the occurrence of post-dilatation.

The results of the ROC analysis performed according to the NRP development of the patients are shown in **Figure**. In order to predict the development of NRP in the ROC curve, HALP and its components were compared on the same curve. In this comparison, the ability of the HALP score to predict the development of NRP was found to be superior to its components. As a result of ROC analysis, the optimal cutoff value of the HALP score in predicting the development of NRP was determined to be 46.5 (AUC: 0.645, 95% CI: 0.57-0.71; p<0.001).

According to the results obtained in the ROC analysis, the patient population was divided into 2 groups: those with a HALP score <46.5 and those with a HALP score ≥46.5

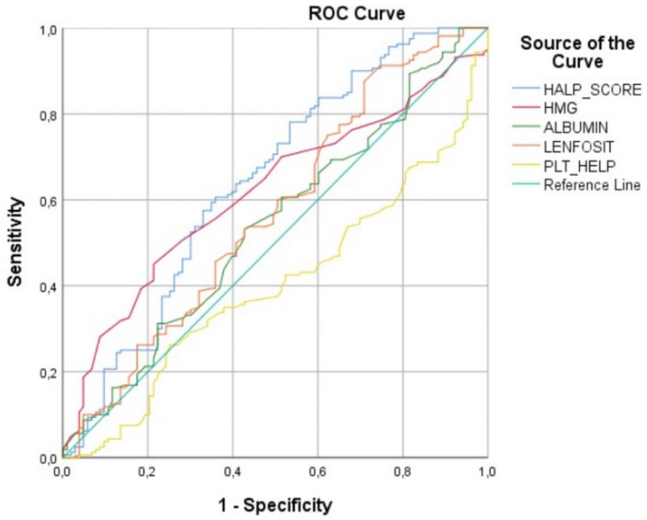

Figure. ROC analysis of the HALP score and the parameters included in this score

(**Table 3**). The prevalence of chronic kidney disease was significantly greater among patients exhibiting a low HALP score (p<0.001). In contrast, no noteworthy disparities were observed in the demographic characteristics of those with low versus high HALP scores. Upon examining laboratory parameters, it was revealed that patients with a HALP score below 46.5 had considerably lower values for hemoglobin (p<0.001), lymphocytes (p<0.001), albumin (p=0.003), and estimated glomerular filtration rate (eGFR) (p=0.001). In the cohort of patients with a HALP score below 46.5, a significantly higher platelet count was observed (p<0.001). However, no statistically significant differences were found in other laboratory parameters. When assessing in-hospital mortality rates, it became evident that patients with a HALP score under 46.5 experienced higher rates of in-hospital mortality (p=0.036). Additionally, the incidence of NRP was notably elevated in this same patient group (p=0.001).

Table 2. Angiographic and procedural status of patients according to NRP

Angiographic parameters		All patients (n=263)	No-reflow (+) (n=103)	No-reflow (-) (n=160)	p-value
Location of the saphenous graft					
LAD, n (%)		16 (6.1)	3 (2.9)	13 (8.1)	0.152
RCA, n (%)		89 (33.8)	32 (31.1)	57 (35.6)	
Cx, n (%)		112 (42.6)	46 (44.7)	66 (41.3)	
Diagonal, n (%)		38 (14.4)	19 (18.4)	19 (11.9)	
OM, n (%)		3 (1.1)	0	3 (1.9)	
IM, n (%)		5 (1.9)	3 (2.9)	2 (1.3)	
Procedural data					
Pre-PCI antiplatelet treatment, n (%)	Clopidogrel	226 (85.9)	83 (80.6)	143 (89.4)	0.068
	Ticagrelor	37 (14.1)	20 (19.4)	17 (10.6)	
Stent implantation, n (%)		251 (95.4)	93 (90.3)	158 (98.8)	0.002
Stent length, (mm)		24 (18-38)	24 (18-42)	24 (20-38)	0.532
Predilatation, n (%)		181 (68.8)	87 (84.3)	94 (58.8)	<0.001
Postdilatation, n (%)		58 (22.1)	22 (21.4)	36 (22.5)	0.880
Thrombus grade, n (%)	1	4 (1.8)	0	4 (1.5)	<0.001
	2	41 (15.6)	0	41 (25,6)	
	3	81 (30.8)	23 (22.3)	58 (36.3)	
	4	88 (33.5)	48 (46.6)	40 (25)	
	5	49 (18.6)	32 (31.1)	17 (10.6)	
Total ischemia time, h		15.6±6.7	14.± 6.9	16.3±6.5	0.051

The data are presented as the median (interquartile range), the mean±SDs or numbers (percentage) of patients. Abbreviations: Cx: Circumflex artery, LAD: Left anterior descending artery, PCI: Percutaneous coronary intervention, RCA: Right coronary artery, TIMI: Thrombolysis in myocardial infarction, NRP: No-reflow phenomenon

Table 3. Basic characteristics and laboratory examinations of all patients according to HALP score

		All patients (n=263)	HALP <46.5 (n=124)	HALP ≥46.5 (n=139)	p-value
Age, years		70± 9	71±10	69±9	0.058
Male gender, n (%)		211 (80.2)	94 (75.8)	117 (84.2)	0.120
Hypertension, n (%)		224 (85.2)	111 (89.5)	113 (81.3)	0.081
Hyperlipidemia, n (%)		135 (51.3)	57 (46)	78 (56.1)	0.109
DM, n (%)		119 (45.2)	58 (46.8)	61 (43.9)	0.586
Chronic kidney disease, n (%)		84 (31.9)	53 (42.7)	31 (22.3)	<0.001
Hemoglobin, g/dl		12.6±1	12.4±0.9	12.9±0.9	<0.001
Lymphocyte, x10^9/L		2.2±0.8	1.71±0.45	2,68±0.74	<0.001
Platelet count, x10^9/L		223±43	248±41	220±41	<0.001
eGFR, ml/min/1.73 m^2		70.5±25	65.2±27	75.3±21.7	0.001
Total cholesterol, mg/dl		183.8±50.7	181.7±56	185.7±45.7	0.518
Albumin, g/L		40.8±3.4	40.1±3.7	41.3±2.9	0.003
LDL cholesterol, mg/dl		110.3±44	110.7±48.8	110±39.3	0.893
LVEF, (%)		41±11	41±12	42±11	0.252
In-hospital mortality, n (%)		16 (6.1)	12 (9.7)	4 (2.9)	0.036
No-reflow, n(%)	(+)	103 (39.2)	62 (50)	41 (29.5)	0,001
	(-)	160 (60.8)	62 (50)	98 (70.5)	

The data are presented as the mean±SDs or numbers (percentage) of patients. Abbreviations: DM: Diabetes mellitus, eGFR: Estimated glomerular filtration rate, HALP: The hemoglobin, albumin, lymphocyte and platelet, LDL: Low-density lipoprotein, LVEF: Left ventricular ejection fraction

The findings from the adjustment analysis are detailed in **Table 4**. In the univariate analysis, several factors, including age, smoking status, hemoglobin levels, platelet counts, stent insertion, predilatation, thrombus grading, and a HALP score of less than 46.5, were identified as significant contributors to the occurrence of NRP in patients undergoing SVG PCI. When these factors were further analyzed through multivariate logistic regression, the HALP score of less than 46.5 was identified as an independent predictor for the development of NRP, regardless of other variables (OR=4.95, 95% CI: 2.48-9.89; p<0.001). Furthermore, a high thrombus burden, the process of predilatation, and stent placement were identified as additional predictors for the development of NRP, independently of other factors (OR=6.77, 95% CI:3.41-13.42; p<0.001, OR=2.43, 95% CI: 1.16-5.10; p:0.019 and OR=0.09, 95% CI: 0.02-0.49; p:0.005). Due to the multicollinearity between the HALP score and the parameters it includes, hemoglobin and platelet counts, hemoglobin and platelet counts were not included in the multivariate analysis.

DISCUSSION

The key finding of this study indicates that the HALP score serves as an important indicator of NRP risk in patients with ACS who receive saphenous graft procedures. Presenting with a low HALP score is independently associated with a heightened risk of NRP, even after accounting for other common factors. Additionally, low HALP score was found to be significantly associated with in-hospital mortality. As far as we are aware, this study is the first to demonstrate a significant link between the HALP score and both the risk of developing NRP and in-hospital mortality in these patients.

The HALP score, primarily evaluated for its efficacy in forecasting the risk of negative clinical outcomes in cancer patients, is a scoring system derived from standard blood parameters, serving as an uncomplicated and readily available biomarker for the overall inflammatory condition.[20,21] Based on these studies, decreased levels of hemoglobin and albumin suggest anemia and malnutrition, whereas a lower lymphocyte count and higher platelet count are linked to inflammation and an impaired immune system. Drawing from this information, the HALP score, which integrates hemoglobin, albumin, lymphocytes, and platelets into one ratio, has been regarded as a novel metric that effectively captures systemic inflammation and nutritional status with a synergistic impact.[22] In STEMI patients, a similar relationship between survival before discharge and the value of the HALP score has been reported in the literature.[14] It has also been demonstrated that the HALP score can forecast the occurrence of NRP and short-term mortality in patients with STEMI who undergo invasive coronary intervention.[23]

Table 4. Analysis of independent predictors of NRP by logistic regression analyses

	Univariate odds ratio (95% CI)	P value	Multivariate odds ratio (95% CI)	p value
Age	1.04 (1.02-1.08)	0.001	1.03 (0.97-1.08)	0.079
Smoking	1.91 (1.16-3.17)	0.011	1.90 (0.90-3.99)	0.089
Hemoglobin**	1.34 (1.03-1.75)	0.030		
Platelet count**	0.99 (0.98-1.00)	0.001		
HALP score <46.5	2.39 (1.44-3.97)	0.001	4.95 (2.48-9.89)	**<0.001**
Stent implantation	0.12 (0.25-0.55)	0.006	0.09 (0.02-0.49)	**0.005**
Predilatation	3.82 (2.06-7.09)	<0.001	2.43 (1.16-5.10)	**0.019**
Thrombus grade *	6.28 (3.57-11.06)	<0.001	6.77 (3.41-13.42)	<0.001

Abbreviations: CI: Confidence interval, HALP: The hemoglobin, albumin, lymphocyte and platelet, NRP: No-reflow phenomenon, * The thrombus grade parameter consists of 5 degrees. Grade 4 and 5 parameters were analyzed according to grade 1-2-3 parameters by binary logistic regression, ** Due to the multicollinearity between the HALP score and its hemoglobin and platelet parameters, hemoglobin and platelet parameters were not included in the multivariate analysis

In our research, we discovered a strong correlation between the HALP score and the development of NRP in patients with ACS whose saphenous grafts treated with percutane invasive way. A low HALP score, potentially linked to oxidative stress and inflammation, has been shown to adversely affect in-hospital survival, correlated with fluctuations in immune function. This relationship might be partially elucidated by the components of the HALP score. Reduced levels of hemoglobin and albumin suggest anemia and malnutrition, which can impair oxygen supply to the heart muscle.[12,13] The occurrence of no-reflow is strongly linked to heightened systemic inflammation and pro-oxidant conditions, while albumin is known for its antioxidant and anti-inflammatory characteristics.[24,25] Thus, reduced albumin levels may contribute to the development of no-reflow through a potential mechanism.[13] Moreover, variability in lymphocyte and platelet numbers may indicate a proinflammatory state that can negatively affect microvascular functions, exacerbating the NRP.[13] In this framework, given its parameters, the HALP score is poised to offer a thorough risk evaluation as a biomarker for predicting the onset of no-reflow. Hence, it can be proposed that these factors together heighten the risk of NRP in patients with a low HALP score who undergo SVG procedures following an ACS diagnosis.

Estimates of how often NRP occurs differ based on the evaluation technique, with literature reports indicating a range between 5% and 60%.[26] For STEMI patients undergoing percutaneous coronary stenting, the occurrence of NRP can be as high as 32%, and it may rise even further, particularly following procedures like degenerate vein graft intervention and rotational atherectomy.[27] ACS and procedures involving the saphenous vein are major risk factors for the onset of NRP.[27] When we evaluated our results in our study, there was a similar NRP development rate as the previously mentioned studies (39.2%). In the present study, the occurrence of NRP was inversely related to age. The average age of patients who developed NRP was 68, whereas it was 72 for those who did not. There was no significant variation in LVEF values between those who developed NRP and those who did not, with values standing at 42 and 41, respectively). Similarly, earlier research in this area has also found no difference in LVEF values relative to the presence or absence of NRP development.[28]

In our research, we identified that the initial thrombus grade and predilatation prior to stent placement are independent predictors of NRP. Our analysis revealed a significantly increased incidence of NRP in patients who had a high thrombus load in the saphenous graft at the onset of the procedure. Previous studies have similarly reported higher rates of NRP in patients undergoing saphenous graft interventions with a high thrombus burden.[29] Furthermore, it was discovered that patients who underwent predilatation experienced a significantly higher incidence of NRP. Earlier studies have indicated that predilatation is associated with increased rates of MACE and mortality during saphenous graft interventions.[30]

Based on these findings, the HALP score can be viewed as a noninvasive indicator for assessing NRP and predicting in-hospital mortality in patients presenting to the emergency department with ACS who undergo SVG intervention. Consequently, for patients deemed at high risk for developing NRP and in-hospital mortality, there is an opportunity to arrange early coronary intervention. Future larger-scale studies are necessary to clarify the mechanism linking the HALP score with the likelihood of NRP development.

Limitations

Some limitations of our study should be noted before interpreting the results. Our study is a single-center retrospective study with a limited sample size. Additionally, since our study is a retrospective study, short and long-term follow-up data of the patients after discharge are not available. While collecting patient data, data about saphenous vein grafts other than the operated saphenous graft (number of saphenous vein grafts, patency status) were not collected. This is because even if there were lesions in other saphenous vein grafts, these lesions did not have an impact on the in-hospital mortality of the patients, as they were not culprit lesions or acute lesions.

CONCLUSION

The HALP score serves as an effective predictor for NRP development and short term mortality in patients with ACS undergoing SVG interventions. Additionally, the presence of a high thrombus burden and predilation prior to stenting were identified as factors that elevate the risk of NRP development. Further research is necessary to confirm and enhance the HALP score's usefulness in larger patient groups and to investigate its potential use in clinical settings.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval was obtained from the clinical Researches Ethics Committee of University of Health Sciences Bursa Higher Specialization Training and Research Hospital (Date: 11.09.2024, Decision No: 2024-TBEK 2024/09-02).

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

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ANATOLIAN CURRENT MEDICAL

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The effects of patient triage management strategies on clinical outcomes and risk management in emergency departments: a prospective comparative study

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ABSTRACT

Aims: The aim of this study is to compare the impact of the emergency severity index (ESI) and the Manchester triage system (MTS) on clinical outcomes, patients' satisfaction, and risk management using a prospective approach.

Methods: In this study, which includes 12,000 patients who visited the emergency department of Esenyurt Necmi Kadıoğlu State Hospital between September 1, 2024, 2024, and October 15, 2024, 6,000 patients were triaged using the ESI, and 6,000 patients were triaged using the MTS. The study was conducted by randomly selecting patients between the ages of 18-85 who were visiting the emergency department for the first time. Data were collected using the observations of healthcare personnel, electronic health system data, and patient admission records. The primary variables include treatment times, clinical outcomes, resource utilization in the emergency department, and patient waiting times. Surveys were used to measure patients' satisfaction, and medical inaccuracies were evaluated based on error reports and inconsistencies in medical records. Statistical analyses were performed using SPSS software, applying independent sample t-tests, chi-square tests, and logistic regression analyses.

Results: It was found that patients triaged using the ESI had significantly lower waiting times compared to those triaged using the MTS (OR: 0.65, 95% CI: 0.50-0.85, $p<0.05$). Mortality rates in the ESI group were also significantly lower compared to the MTS group (OR: 0.72, 95% CI: 0.55-0.92, $p<0.05$). In terms of complication rates, patients triaged with ESI also showed a significant reduction compared to those triaged with MTS (OR: 0.60, 95% CI: 0.45-0.80, $p<0.01$). ESI-triaged patients showed a significant improvement in resource utilization compared to patients triaged using MTS (OR: 0.70, 95% CI: 0.55-0.88, $p < 0.05$). Patient satisfaction results also showed a significant difference in favor of ESI (OR: 1.50, 95% CI: 1.25-1.80, $p<0.001$). Medical errors and legal issues were observed to be less frequent among patients triaged with ESI, a finding that was significant in terms of risk management (OR: 0.55, 95% CI: 0.40-0.75, $p<0.05$).

Conclusion: The use of the ESI as a triage method may be an effective approach for reducing medical inaccuracies, mortality, and complication rates, as well as optimizing emergency department management. These findings suggest the need for reviewing triage systems in clinical practice and expanding the use of ESI. I believe that incorporating ESI, a triage method that enhances patients' satisfaction and optimizes resource utilization, into future emergency department management is crucial.

Keywords: Emergency severity index, Manchester triage system, clinical outcomes, risk management, patient satisfaction, medical error

INTRODUCTION

In recent years, the increasing demand for healthcare services, driven by population growth and easier access to healthcare, has also been reflected in emergency departments. This situation has led to significant overcrowding and increasing pressure on healthcare institutions.[1,2] Among healthcare service providers, emergency departments are one of the most dynamic and busiest areas of the healthcare system, requiring the rapid and effective management of patients using limited resources. Timely, swift, and appropriate evaluation of patients in emergency departments is essential for both patient safety and the efficient use of healthcare services. This, in turn, improves the efficiency and quality of healthcare services.

The growing patient volume in emergency departments significantly affects both the quality of care and the workload, along with the use of resources. Triage systems have been developed to manage the impact of overcrowding and ensure the efficient use of resources in emergency departments.[3] These systems contribute significantly to improving the efficiency of limited resources in emergency departments by enabling the rapid assessment of patients and prioritizing

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those who require urgent intervention. The effective use of triage systems not only ensures that patients in need of urgent intervention are treated quickly but also shortens waiting times in the emergency department, thereby contributing to increased patients' satisfaction.[4]

Two widely used triage systems are the emergency severity index (ESI) and the Manchester triage system (MTS). The ESI, which categorizes patients into five levels based on the urgency of their condition, is one of the most commonly used triage systems in the United States.[5] The primary goal of the ESI is to quickly assess patients to ensure timely critical interventions.[6] One of the key advantages of the ESI is that it supports rapid decision-making processes, thereby contributing to the reduction of mortality and morbidity rates.[7] However, the ESI may be insufficient in cases where symptoms are complex.[8]

In the MTS, which is widely used in many European countries and the UK, patients are categorized by color codes based on their symptoms.[9] Waiting and treatment times are determined according to these color codes. Classifying patients based on their clinical symptoms facilitates the decision-making process for healthcare personnel, which gives MTS a significant advantage. However, evaluating patients with complex symptoms may take longer and cause difficulties, especially in busy emergency departments.[10]

When evaluated in terms of patients' satisfaction, medical error rates, patient outcomes, resource utilization, and waiting times, these two triage systems can produce different results. Comparing the impact of these two systems on clinical outcomes and risk management can provide significant contributions to developing more effective triage systems.

This study, conducted with 12,000 patients who visited Esenyurt Necmi Kadıoğlu State Hospital between October 1, 2024, and November 1, 2024, used the ESI and the Manchester MTS as triage systems. The study compares the impact of the triage process on clinical outcomes and risk management using a prospective approach. The ESI was applied to 6.000 patients, while the MTS was applied to the other 6.000 patients. In this analysis, the impact of both triage systems on patient waiting times, clinical outcomes (mortality and complication rates), resource utilization in the healthcare system, patients' satisfaction, and the reduction of medical inaccuracies were examined in detail.

This study, which aims to provide important insights into the development of triage management systems, shows that the data obtained from the comparative analysis of triage methods can improve the quality of healthcare services. The findings of this study may offer valuable insights for enhancing risk management in healthcare institutions and ensuring patient safety.

METHODS

The study was conducted with the permission of the Ethics Committee of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 12.09.2024, Decision No: 898). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This prospective and comparative study was conducted with 12,000 patients who visited the emergency department of Esenyurt Necmi Kadıoğlu State Hospital between September 1, 2024, and October 15, 2024, with random patient inclusion. The ESI was applied to 6,000 patients, while the MTS was applied to the remaining 6.000. Data were collected from patient admission records, healthcare personnel observations, and electronic health system records.

In this comparative study, patients were closely monitored to determine whether they required immediate intervention. During their treatment in the emergency department, the frequency of emergency interventions, patient waiting times, complications, mortality rates, and hospital admission rates were systematically recorded. Resource utilization in the hospital, patients' satisfaction, and medical error rates were used to assess the effectiveness of the triage processes.

Patients were randomly selected from those who visited the emergency department during the study period. The study included first-time emergency department patients aged 18-85. Triage was performed using either the ESI or MTS. Detailed data were collected on the patients' age, gender, vital signs, medical history, clinical and demographic data, current clinical condition, and reason for admission. Patients were classified according to age groups, which were considered in the statistical analyses. Clinical evaluations were performed following the protocols of the respective triage systems.

Patients excluded from the study were those under 18 years of age, patients who made multiple visits during the study period, pregnant patients, those with insufficient clinical data at the time of admission, patients transferred to other facilities after stabilization, and those requiring psychiatric evaluation during their emergency visit.

Patient complaints, vital signs, demographic data, laboratory results, imaging results, and clinical evaluations conducted during triage were recorded in the electronic patient record system. Data collection was based on patient records and healthcare personnel observations. Special attention was given to analyzing age groups to thoroughly examine the impact of each triage system on clinical outcomes.

Throughout the study, patient privacy and data security were maintained, with access to the data restricted to authorized personnel. The data were anonymized to ensure confidentiality, while ensuring compliance with ethical standards in data management.

The primary variables were clinical outcomes (mortality and complications), patient waiting times, resource utilization in the emergency department, and treatment times. These primary variables were thoroughly examined to understand the impact of the two triage systems on emergency department processes and patient outcomes.

Potential legal issues, medical error rates, and patients' satisfaction were secondary variables. Patient satisfaction was assessed through surveys conducted after discharge, rated on a scale from 1 to 10. Medical errors were evaluated based on errors reported during triage and inconsistencies in medical records. Legal issues arising from triage, including medical

lawsuits and legal processes, were analyzed through the related data.

The differences between the ESI and MTS in terms of clinical outcomes and risk management were comprehensively assessed using these measurements.

Efforts were made to minimize subjectivity, in the satisfaction survey data by using questions and anonymous survey collection methods. Furthermore the analysis considered factors like response bias and variations, in expectations that can affect data.

For resource utilization, hospital billing and accounting records were reviewed. Billing data from all procedures, materials used, and treatments administered in the emergency department were collected, and the average cost per procedure was calculated. The costs of medications and equipment used during the triage process were obtained from the electronic health records (EHR). A total cost analysis was performed by combining the costs of procedures, medications, materials, and personnel to calculate the average cost for patients triaged by each method. This comprehensive analysis assessed the financial impact of emergency department triage management strategies on resource utilization.

Statistical Analysis

The data were analyzed using SPSS 28.0 statistical software. The Kolmogorov-Smirnov test was used to check the normal distribution of the data. Continuous variables such as clinical outcomes, patients' satisfaction, resource utilization, and waiting times were examined using independent sample t-tests. The chi-square test was used for categorical variables. Logistic regression analysis was performed to further investigate critical outcomes, including complications, mortality rates, and triage accuracy.

Additionally, medical error rates and legal issues were assessed based on healthcare personnel feedback and analysis of legal records as part of risk management. A p-value of <0.05 was considered statistically significant in all analyses.

RESULTS

This study included 1.189 patients aged 18-25, 1.849 patients aged 26-35, 1.749 patients aged 36-45, 1.736 patients aged 46-55, 1.703 patients aged 56-65, 1.821 patients aged 66-75, and 1.773 patients aged 76-85 (**Figure 1, Table 1**).

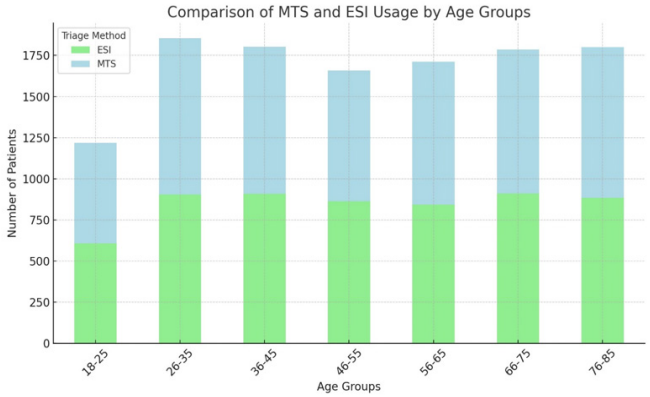

Figure 1. Comparison of Manchester triage system and emergency severity index usage by age groups

Table 1. Patient distribution by age group

Age group	Number of patients
18-25	1189
26-35	1849
36-45	1749
46-55	1736
56-65	1703
66-75	1821
76-85	1773

Of the patients participating in the study, 6,008 were male, and 5.992 were female (**Figure 2, Table 2**).

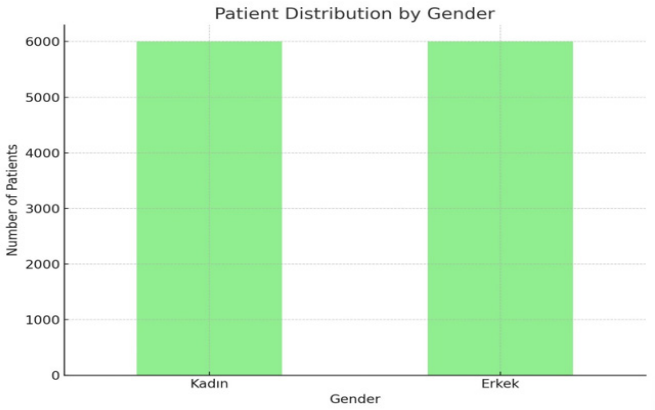

Figure 2. Patient distribution by gender

Table 2. Patient distribution by gender

Gender	Number of patients
Male	6008
Female	5992

When comparing the ESI and the MTS in terms of risk management, the ESI group consisted of 6,000 patients, of whom 4,164 (69.5%) were categorized as having "Good" risk management, 1.210 (20.2%) as having "Moderate" risk management, and 626 (10.4%) as having "Poor" risk management (**Figure 3, Table 3**).

In the MTS group of 6.000 patients, 2.377 (47.5%) were categorized as having "Good" risk management, 2,392 (47.8%) as having "Moderate" risk management, and 1,231 (24.7%) as having "Poor" risk management (**Figure 3, Table 3**).

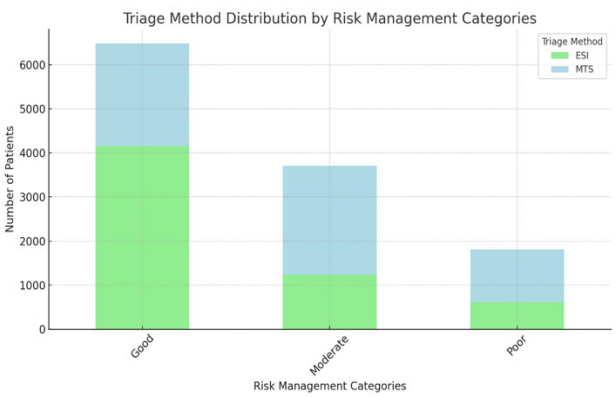

Figure 3. Triage method distribution by risk management categories

The results show that patients triaged using the ESI had a higher rate of "Good" risk management (69.5%), whereas those triaged using the MTS had higher rates of "Moderate" (47.8%) and "Poor" (24.7%) risk management (**Figure 3, Table 3**).

Table 3. Distribution of ESI and MTS triage methods by risk management categories

Triage method	Good	Moderate	Poor
ESI	4164	1210	622
MTS	2377	2392	1237

ESI: Emergency severity index, MTS: Manchester triage system

In the ESI group of 6.000 patients, 59 (0.95%) died, 320 (5.27%) were admitted to the intensive care unit (ICU), and 5.621 (93.78%) recovered. In the MTS group of 6.000 patients, 170 (2.86%) died, 600 (9.99%) were admitted to the ICU, and 5.230 (87.15%) recovered. These results indicate that the ESI provided better clinical outcomes compared to the MTS. The recovery rate was higher, and the rates of death and ICU admission were lower in the ESI group than in the MTS group (**Figure 4, Table 4**).

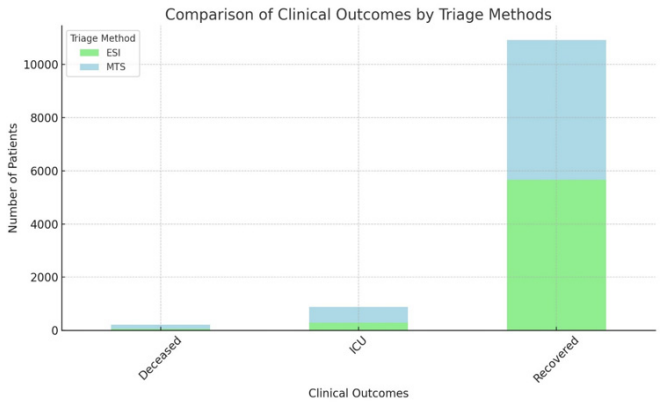

Figure 4. Comparison of clinical outcomes by triage methods

Table 4. Clinical outcomes analysis

Triage method	Deceased patient	ICU	Recovered patient
ESI	59	320	5621
MTS	170	600	5230

ESI: Emergency severity index, MTS: Manchester triage system, ICU: Number of intensive care patients

The average satisfaction score for the 6,000 patients triaged using the ESI was 8.25, meaning that 82.5% of patients were satisfied. Meanwhile, the average satisfaction score for the 6.000 patients triaged using the MTS was 7.15, with 71.5% patients' satisfaction. The difference in average satisfaction scores between the two methods was 1.10 points, showing that the ESI had a more positive impact on patients' satisfaction than the MTS (**Table 5, Figure 5**).

Table 5. Patient satisfaction analysis

Triage method	Number of patients	ASP	SR%
ESI	6000	8.25	82.5
MTS	6000	7.15	71.5

ESI: Emergency severity index, MTS: Manchester triage system, ASP: Average satisfaction score, SR: Satisfaction rate

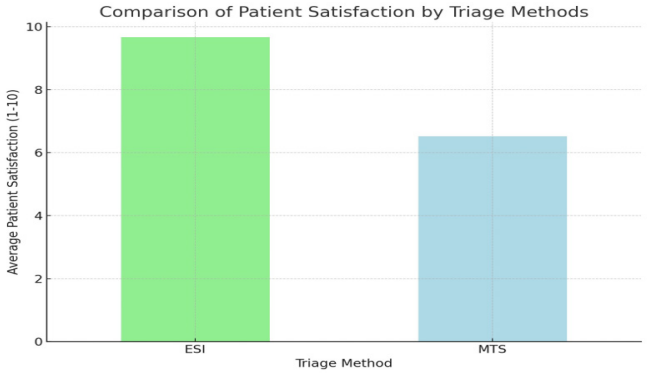

Figure 5. Comparison of patient satisfaction by triage methods

In the ESI group of 6,000 patients, 298 (4.97%) developed complications, while in the MTS group, 715 (11.90%) developed complications. These results show that the ESI posed a lower risk of complications compared to the MTS (**Figure 6, Table 6**).

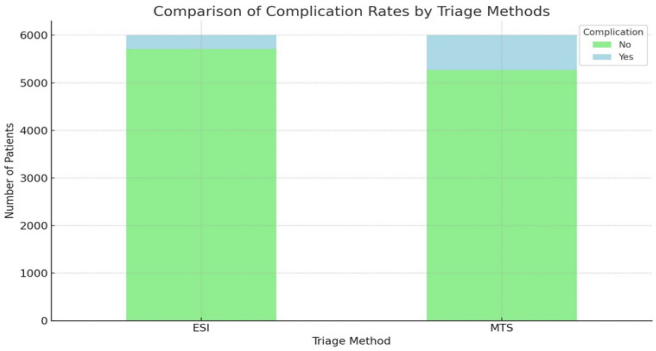

Figure 6. Comparison of complcation rates by triage methods

Table 6 . Complication rate analysis

Triage method	Number of patients	Number of complications	Complication rate %
ASİ	6000	298	4.97
MTS	6000	715	11.9

ESI: Emergency severity index, MTS: Manchester triage system

In the ESI group, 122 out of 6.000 patients (2.04%) experienced mortality, while in the MTS group, 328 out of 6.000 patients (5.46%) experienced mortality. These results indicate that the ESI carries a lower risk of mortality compared to the MTS (**Figure 7, Table 7**).

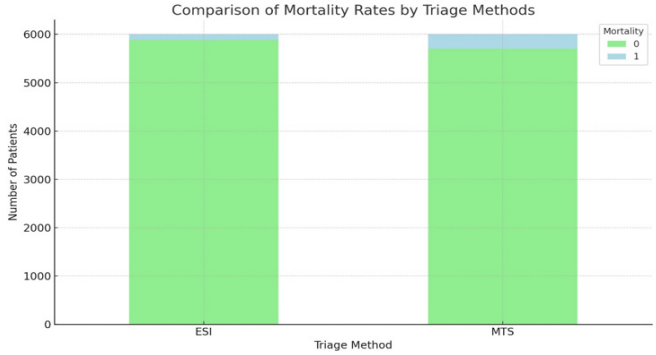

Figure 7. Comparison of mortality rates by triage methods

Table 7. Mortality rate analysis

Triage method	Number of patients	Number of mortalities	Mortality rate %
ASİ	6000	122	2.04
MTS	6000	328	5.46

ESI: Emergency severity index, MTS: Manchester triage system

The waiting time of 6,000 patients triaged using the ESI was analyzed. The average waiting time was found to be 20.05 minutes, with a standard deviation of 4.01 minutes. The shortest waiting time was 4.59 minutes, and the longest was 35.24 minutes. Twenty-five percent of patients waited less than 17.40 minutes, 50% waited less than 19.99 minutes (median), and 75% waited less than 22.72 minutes (**Figure 8, Table 8**).

For the MTS group of 6,000 patients, the average waiting time was 44.87 minutes, with a standard deviation of 10.17 minutes. The shortest waiting time was 8.65 minutes, and the longest was 81.90 minutes. Twenty-five percent of patients waited less than 37.92 minutes, 50% waited less than 44.96 minutes (median), and 75% waited less than 51.50 minutes (**Figure 8, Table 8**).

In conclusion, the ESI group exhibited significantly shorter and less variable waiting times compared to the MTS group.

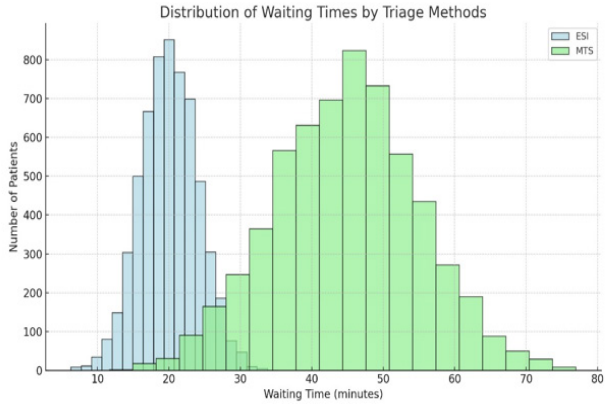

Figure 8. Distribution of waiting times by triage methods

Table 8. Waiting times

Triage method	Number of patients	Average	Standard deviation
ESI	6000	20.04	4.01
MTS	6000	44.8	10.01
Triage method	**Number of patients**	**Shortest waiting time**	**Longest waiting time**
ESI	6000	4.5	35.2
MTS	6000	8.6	81.9

ESI: Emergency severity index, MTS: Manchester triage system

In the ASI triage method, 1.525 patients are in the low resource utilization group, representing 25.42% of the total patients. In the moderate resource utilization group, there are 4.386 patients, accounting for 73.10% of the total. In the high resource utilization group, there are 89 patients, corresponding to a rate of 1.48% (**Figure 9, Table 9**).

In the MTS triage method, 208 patients are in the low resource utilization group, representing 3.47% of the total patients. In the moderate resource utilization group, there are 4.617 patients, accounting for 76.95% of the total. In the high resource utilization group, there are 1.175 patients, corresponding to a rate of 19.58% (**Figure 9, Table 9**).

These results indicate that ASI has higher rates of low and moderate resource utilization compared to MTS, while MTS has a higher rate of high resource utilization than ASI.

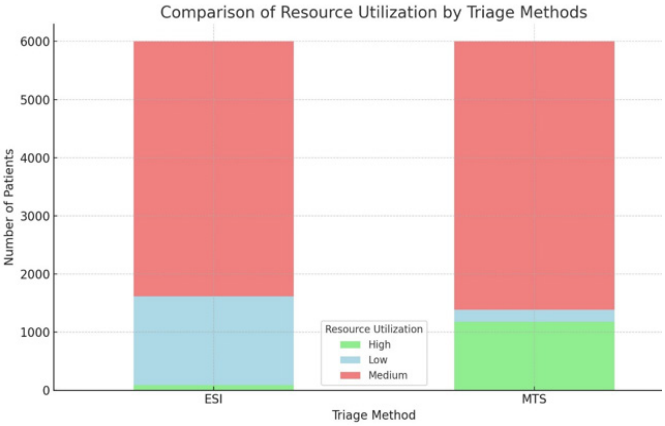

Figure 9. Comparison of resource utilization by triage methods

Table 9. Resource utilization

Triage method	Number of patients	Resource utilization	Resource utilization %
ESI	1525	Low	25.42
MTS	208	Low	3.47
ESI	4386	Medium	73.10
MTS	4617	Medium	76.95
ESI	89	High	1.48
MTS	1175	High	19.58

ESI: Emergency severity index, MTS: Manchester triage system

Among the total of 6.000 patients evaluated using the ASI triage method, medical inaccuracies were identified in 119 patients. This indicates a medical error rate of 1.99% for patients triaged with the ASI method (**Figure 10, Table 10**).

Among the total of 6,000 patients evaluated using the MTS triage method, medical inaccuracies were made in 515 patients. This indicates a medical error rate of 8.57% for patients triaged with the MTS method (**Figure 10, Table 10**).

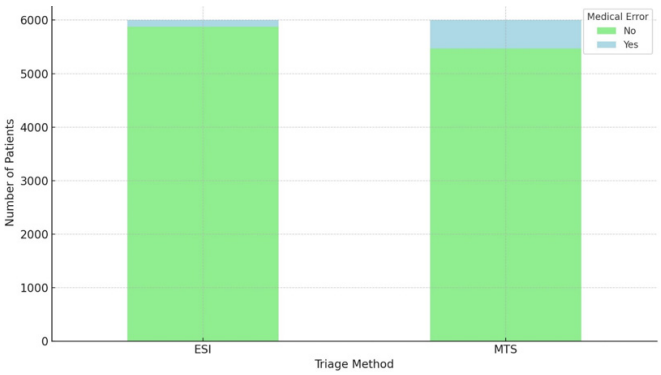

Figure 10. Comparison of medical errors by triage methods

Table 10. Medical error analysis

Triage method	Number of patients	Number of medical errors	Medical error rate %
ESI	6000	119	1.98
MTS	6000	515	8.57

ESI: Emergency severity index, MTS: Manchester triage system

Among the total of 6.000 patients evaluated using the ASI triage method, legal issues were identified in 52 patients. This indicates that 0.87% of patients triaged with the ASI method encountered legal issues (**Figure 11, Table 11**).

Among the total of 6.000 patients triaged using the MTS method, legal issues occurred in 291 patients. This indicates that 4.84% of patients triaged with the MTS method encountered legal issues (**Figure 11, Table 11**).

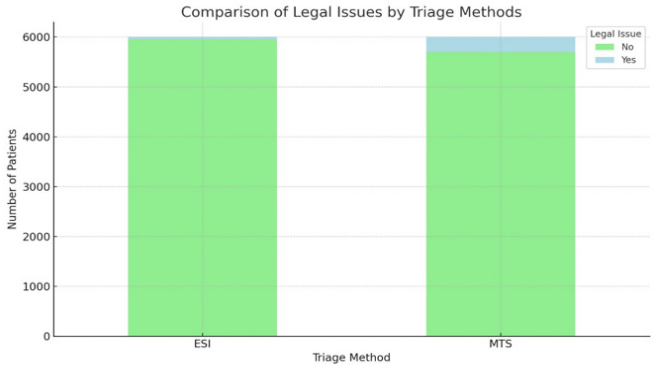

Figure 11. Comparison of legal issues by triage methods

Table 11. Legal issue analysis

Triage method	Number of patients	Number of legal issues	Legal issue rate %
ASİ	6000	52	0.86
MTS	6000	291	4.84

ESI: Emergency severity index, MTS: Manchester triage system

DISCUSSION

This study aimed to compare the impact of two commonly used triage methods in emergency departments -the ESI and the MTS- in terms of risk management, patients' satisfaction, and clinical outcomes. The results showed that the ESI is a superior triage method compared to the MTS. Based on these findings, it is clear that careful consideration should be given when selecting triage methods to manage patient flow in emergency departments, with the ESI emerging as a significant alternative.

This study demonstrated that using the ESI for triage led to shorter waiting times, which in turn reduced mortality and complication rates. This finding highlights the importance of time management in emergency departments and its decisive impact on clinical outcomes. The core of effective patient management in emergency departments is the early and accurate intervention in critical cases. The advantage of the ESI in reducing waiting times makes it a suitable option as an effective triage method in emergency departments.

The ESI, offering a patient-centered and faster evaluation process, proved to be a superior triage method in terms of patients' satisfaction compared to the MTS.[11] It enables patients to be assessed more quickly and accurately. These findings highlight that not only clinical effectiveness but also patients' satisfaction is crucial in the delivery of healthcare services. Given its positive impact on patients' satisfaction,[12] the ESI presents a significant advantage in patient management in emergency departments. This advantage positions the ESI as an important option for triage in emergency departments.

In terms of risk management, the ESI was found to reduce medical error rates and legal issues, as it offers a more systematic and structured approach to triage.[13] Risk management in healthcare is critical for both patient safety and institutional responsibility. By standardizing the decision-making process for healthcare personnel, the ESI reduces the risk of errors.[14] This can be a key factor in choosing the ESI. In reducing medical inaccuracies and complication rates, the ESI also contributes to improved quality of healthcare services.

This study suggests that the ESI is a more effective and efficient triage method in emergency departments. However, similar studies in different populations and healthcare settings are needed to determine the generalizability of these findings. Future research could examine how triage methods perform in various cultural and healthcare systems, contributing to the optimization of triage methods globally.

Limitations

This study has several limitations. First, it was conducted solely at Esenyurt Necmi Kadıoğlu State Hospital, and the findings may not be generalizable to other regions or healthcare institutions. Second, the experience and training level of healthcare personnel could have influenced the results of the triage methods. The success of triage methods depends on how effectively healthcare personnel utilize these systems, and the lack of control over this factor should be considered when interpreting the results.

Additionally, as patients' satisfaction data were collected through surveys, the results may be subject to bias due to the subjective nature of the assessments. Patients' perceptions and expectations regarding the triage process may have influenced the survey results, limiting the accuracy and validity of the patients' satisfaction data.

Future studies should involve larger, multicenter investigations to evaluate the long-term effects of different triage methods on clinical outcomes. Such studies would enable a more comprehensive evaluation of the effectiveness of triage methods across various patient populations and healthcare institutions.

The results of this study indicate that the ESI is an effective tool for managing patient flow in emergency departments, and it is superior to the MTS in terms of clinical outcomes, patients' satisfaction, and risk management. However, to improve the efficiency and effectiveness of triage methods and optimize patient safety, these triage systems should be adapted according to local conditions and the competence levels of healthcare personnel. Additionally, triage methods should be regularly reviewed and updated.

The findings suggest that the ESI could be a more efficient triage method in emergency departments with high patient volumes. However, it is important to note that the MTS may still be a valid and reliable option for certain patient groups. In this context, healthcare institutions should consider factors such as patient population characteristics, emergency department workload, and available resources when selecting a triage system.

While this study sheds light on various aspects of the ESI and MTS, further research involving larger patient populations and diverse emergency department settings is needed. Studies examining the long-term effects of triage methods on patient outcomes could contribute to more effective decision-making processes in emergency departments and provide new insights for optimizing healthcare services.

It should be noted that secondary variables such as medical error rates and legal issues, which were assessed in this study, were based on hospital records and reports from healthcare personnel. In some cases, incomplete or inaccurate records could have affected the accuracy of the findings. Potential gaps or inconsistencies in such data should be considered in future research.

Level of Expertise, Among Healthcare Staff

The efficiency of triage procedures depends greatly on the expertise and training of healthcare professionals involved in the process. This research did not prioritize examining the level of experience of the personnel. Recognized its influence, on the outcomes. The level of experience plays a role, in determining how quickly and accurately decisions are made during triage and can also affect outcomes. Henceforth it is important for upcoming studies to thoroughly assess the experience levels of staff members and explore how they impact results in detail. In our research project we have acknowledged the existence of this complicating factor. Have analyzed the results considering this aspect.

Generalisability and Multi-Center Study Proposal

Single-center studies have inherent limitations. To test the generalisability of the findings to a broader population, it is recommended that a similar study be conducted as a multi-center investigation. Such studies conducted in different healthcare delivery settings and patient populations would allow for the validation of the current findings and enable a more extensive evaluation of the effectiveness of triage systems. This approach would contribute to a better understanding of how triage systems perform in various cultural and operational contexts.

CONCLUSION

This study prospectively evaluated and compared the impact of two of the most commonly used triage methods in emergency departments- ESI and MTS-on patient management and flow in emergency departments. The findings of the research revealed that the ESI is a more effective triage method than the MTS, especially in emergency departments with high patient volumes, as it reduces waiting times and improves patients' satisfaction. Additionally, the ESI was observed to play a significant role in enabling more efficient use of emergency department resources and reducing medical error rates. Furthermore, in terms of mortality rates and complication management, the ESI showed lower mortality and complication rates compared to the MTS.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Ethics Committee of İstanbul Medipol University Non-interventional Clinical Researches Ethics Committee (Date: 12.09.2024, Decision No: 898).

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

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Evaluation of critical factors predicting the development of hepatorenal syndrome in hospitalized cirrhotic patients

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ABSTRACT

Aims: This study aimed to determine the factors predicting the development of hepatorenal syndrome (HRS) in cirrhotic patients presenting with acute kidney injury (AKI).

Methods: We retrospectively analyzed 263 cirrhotic patients diagnosed with AKI between September 2022 and March 2024. Demographic characteristics, clinical findings, and laboratory results were analyzed. We diagnosed HRS using the 2019 International Club of Ascites criteria. We used bivariate and multivariate logistic regression models in our statistical analysis.

Results: HRS developed in 31 patients (11.8%). MELD-Na scores were significantly higher in the HRS group (28 vs. 18, p<0.05). In multivariate analysis, independent predictors of HRS development were history of ascites (OR 5.8, 95% CI 2.6-13.0), serum creatinine >2.5 mg/dl (OR 2.5, 95% CI 1.2-5.5), albumin <2 g/dl (OR 3.9, 95% CI 1.1-13.5), bilirubin >2 mg/dl (OR 7.9, 95% CI 3.7-17.0), and presence of spontaneous bacterial peritonitis (OR 5.5, 95% CI 1.4-12.2). Hemodialysis requirement (61.3% vs. 8.6%, p<0.05) and mortality rates (45.2% vs. 6.0%, p<0.05) were significantly higher in the HRS group.

Conclusion: This study revealed important factors predicting the development of HRS in cirrhotic patients presenting with AKI. These findings may help clinicians to identify high-risk patients early and develop appropriate treatment strategies.

Keywords: Hepatorenal syndrome, risk factors, acute kidney injury, hospitalization, liver cirrhosis

INTRODUCTION

Hepatorenal syndrome (HRS) is a serious complication of advanced stages of cirrhosis characterized by both hepatic and renal failure and is a potential cause of acute kidney injury (AKI).[1] This syndrome is usually associated with portal hypertension due to causes such as cirrhosis, severe alcoholic hepatitis or, more rarely, metastatic tumors.[2] HRS represents the end-stage of reductions in renal perfusion as a result of progressive exacerbation of liver injury and is considered a diagnosis of exclusion.[3] The syndrome is usually associated with a poor prognosis.[4]

Systemic inflammation, increased splanchnic blood flow, decreased central volume, hypoperfusion, and excessive renal vasoconstriction, which play a role in the pathophysiology of HRS, result in a hyperdynamic state and a decrease in glomerular filtration rate.[1]

The incidence of AKI in cirrhotic patients hospitalized as a result of acute decompensation has been reported to be between 25-50%.[5] In cirrhotic patients with ascites, the 1-year incidence of HRS development ranged between 8% and 18%, while the 5-year incidence of HRS development was reported to be 39%.[6,7] In patients with cirrhosis and renal failure, the prevalence of HRS was reported to be 45.8%.[8] As can be understood, HRS is an important clinical problem seen frequently in patients with cirrhosis.

Well-known risk factors for the development of HRS include the presence of ascites, serum creatinine levels >2.5 mg/dl, low serum sodium concentration, albumin levels <3 g/dl, infections (especially spontaneous bacterial peritonitis, SBP), serum bilirubin level >2 mg/dl, high plasma renin activity, absence of hepatomegaly, fragility, alcoholic hepatitis, and bleeding[7,9-13]

Depending on the rate of decline in renal function, two types of HRS, HRS-AKI ("type 1" in the old classification) and non-AKI-HRS (NAKI, "type 2" in the old classification), have been defined.[14] HRS-AKI is a more severe form, characterized by a rapid increase in serum creatinine values and oliguria, whereas NAKI is characterized by a slower and less severe renal dysfunction. Currently, the criteria described in a revised consensus report published by the International Club of Ascites in 2019 are used in the diagnosis of HRS.[15] Clinically, HRS is characterized by a progressive increase in serum creatinine, usually normal urine sediment, minimal proteinuria, and a very low sodium excretion rate. The majority of patients are nonoliguric, and urine volume may exceed 400 ml per day in the early stages of the disease.

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HRS represents a significant challenge not only for the affected individuals but also for the healthcare system in general. The management of this condition results in a significant increase in healthcare expenditure due to the need for frequent hospitalization, the use of intensive care services, and the application of advanced treatment modalities. Furthermore, the development of HRS severely reduces the quality of life of patients and places a huge emotional and economic burden on their families. This can lead to psychological and financial distress for family members caring for the patient.

In this study, we aimed to determine the factors that predict the development of HRS, which is an important problem in the management of cirrhotic patients, and thus shed light on the development of strategies to be used in the management of high-risk patients.

METHODS

Study Design and Patient Population

The study was designed as a retrospective study. The study included cirrhotic patients aged 18 years or older who were admitted to the gastroenterology clinic of Ankara Etlik City Hospital between September 2022 and March 2024 with AKI or who developed AKI during their hospitalization. After excluding patients with missing data, the remaining patient files were included in the study. Data were collected from the hospital information management system and patient files, and the demographic characteristics, clinical findings, and laboratory results of the patients were analyzed in detail.

The inclusion criteria were as follows: a diagnosis of cirrhosis, The kidney disease: improving global outcomes (KDIGO) guidelines and being older than 18 years of age. Exclusion criteria were patients with a history of chronic kidney disease not related to cirrhosis, patients receiving renal replacement therapy before the diagnosis of AKI, and patients with incomplete medical records.

This study was approved by the Ethics Committee of Ankara Etlik City Hospital (Date: 24.04.2024, Decision No: AEŞH-BADEK-2024-320). The informed consent form prepared in accordance with the principles of the Declaration of Helsinki was signed by all participants. This process ensured that the study was conducted in accordance with ethical and legal requirements.

Data Collection and Evaluation

Since our study was retrospective in nature, patient data were collected retrospectively from hospital records. Using patient files and data obtained from the electronic medical record system, patients' demographic information, clinical findings, laboratory results and all medical data available from the time of admission were analyzed in detail. The records of 371 patients were analysed in total and 263 patients whose complete data were available were included in the study. Data collected included age, gender, body-mass index (BMI), blood pressure measurements, etiology of liver disease (hepatitis B, hepatitis C, alcoholic liver disease, non-alcoholic steatohepatitis, autoimmune hepatitis and cryptogenic cirrhosis/other), MELD-Na score, presence of ascites, presence of SBP, presence of other infections and other clinical information.

Laboratory data include serum creatinine, albumin, bilirubin, sodium, hemoglobin, platelet and INR values. AKI was diagnosed according to KDIGO criteria. The diagnosis of HRS was made according to the criteria described in a revised consensus report published by the International Club of Ascites in 2019.

In this study, the diagnosis of portal hypertension was based on non-invasive methods and clinical features. The diagnostic criteria were the presence of splenomegaly on ultrasonography, gastroesophageal varices on endoscopic evaluation, visualisation of spontaneous portosystemic shunts and thrombocytopenia (<100 x $10^3/\mu L$) on laboratory tests. Abdominal ultrasonography findings were used in the study, especially to evaluate the presence of ascites, to detect splenomegaly and to support other findings of portal hypertension.

The clinical course and treatment responses of the patients were also obtained from the files and evaluated. These evaluations included important clinical outcomes such as hemodialysis requirement, HRS development and mortality rates.

Statistical Analysis

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as means with standard deviations (SD), and categorical variables were expressed as frequencies and percentages. Comparisons between patients with HRS and those with other causes of AKI were conducted using independent sample t-tests for continuous variables and chi-square tests for categorical variables. Bivariate analysis was initially performed to identify potential predictors of HRS. Odds ratios (OR) and 95% confidence intervals (CI) were calculated for each variable. Variables found to be significant ($p<0.05$) in the bivariate analysis were subsequently included in a multivariate logistic regression model to determine independent predictors of HRS. The multivariate logistic regression analysis included variables such as history of ascites, serum creatinine >2.5 mg/dl, albumin <2 g/dl, bilirubin >2 mg/dl, and spontaneous bacterial peritonitis. Adjusted odds ratios (AOR) and 95% confidence intervals were reported for each predictor. Additionally, logistic regression analysis was used to further evaluate the OR and confidence intervals for various clinical and laboratory parameters associated with the risk of developing HRS. This analysis allowed us to assess the relative impact of these factors while controlling for potential confounders. Statistical significance was defined as a p-value less than 0.05. The results of the statistical analyses were used to identify and confirm the key factors predicting the development of HRS in cirrhosis patients with acute renal failure.

RESULTS

In this study, we analyzed data from 263 cirrhosis patients admitted with acute renal failure to identify factors predicting the development of HRS. Bivariate and multivariate analyses

were conducted to determine significant predictors. HRS was identified in 31 (11.8%) of the patients. According to the KDIGO criteria, AKI staging in this study was based on both serum creatinine levels and urine output measurements. For stage 1 AKI, which accounted for 55% of patients, urine output was maintained at an average of 0.4–0.5 ml/kg/h over a period of 6-12 hours, resulting in a total output of approximately 189-378 ml. For stage 2 AKI, comprising 23% of patients, the average urine output was around 0.3-0.4 ml/kg/h, sustained for more than 12 hours, yielding an estimated total of 294 ml. In stage 3 AKI, which included 17% of patients, urine output was reduced to approximately 0.1-0.2 ml/kg/h over 24 hours (or anuria for at least 12 hours), with a total urine output around 252 ml. Significant predictors of HRS included a history of ascites, elevated creatinine, low albumin, high bilirubin, and the presence of spontaneous bacterial peritonitis. The cohort had a mean age of 63.2 years (SD 13.1), with 64.3% being male. The primary etiologies of cirrhosis included Hepatitis B (33.6%), Hepatitis C (20.9%), and alcoholic liver disease (16.3%) (**Table 1**).

Table 1. Patient demographics and clinical characteristics

	Patients n=263
Age (years), (SD)	63.2 (±13.1)
Gender, male, n (%)	169 (±64.3)
BMI (kg/m²) (SD)	24.95 (±4.1)
Systolic blood pressure (SD)	119 (±24)
Diastolic blood pressure (SD)	63 (±13)
Etiology	
Hepatitis B, n (%)	88 (33.6)
Hepatitis C, n (%)	55 (20.9)
Alcoholic, n (%)	43 (16.3)
Non-alcoholic steatohepatitis, n (%)	36 (13.7)
Autoimmune hepatitis, n (%)	21 (7.9)
Cryptogenic/other, n (%)	20 (7.6)
KDIGO AKI stage	
Stage 1, n (%)	145 (55)
Stage 2, n (%)	61 (23)
Stage 3, n (%)	45 (17)
Unclassified, other, n (%)	12 (5)
MELD-Na score (SD)	20 (±8)
Ascites	
History of ascites, n (%)	118 (44.9)
Ascites on current admission, n (%)	126 (47.9)
Spontaneous bacterial peritonitis, n (%)	21 (7.9)
Other infection, n (%)	69 (26.2)
Portal hypertension, n (%)	164 (62.4)
Esophageal varices, n (%)	111 (42.2)
Hepatic encephalopathy, n (%)	105 (39.9)
Acute kidney injury etiology	
Pre-renal, n (%)	92 (34.9)
Hepato-renal syndrome, n (%)	31 (11.8)
Cardiac, n (%)	16 (6.1)
Other renal, n (%)	26 (9.9)
Hemoglobin (g/dl)	10.6 (±2.3)
Platelet (x1000)	128 (±94)
Na (meq/L)	132 (±11)
Creatinine (mg/dl)	2.3 (±1.7)
Albumin (g/dl)	3.0 (±0.7)
Bilirubin (mg/dl)	2.1 (±3.8)
INR	1.7 (±0.9)
Hemodialysis	39 (±14.9)
Hospital stays, days (SD)	16 (±9)
Mortality, n (%)	28 (10.6)

SD: Standard deviation, BMI: Body-mass index, MELD-Na: Model for end-stage liver disease-sodium, INR: International normalized ratio

Patients with HRS constituted 11.8% of the study population. These patients exhibited significantly higher MELD-Na scores (28 vs. 18, p<0.05) compared to those with other causes of AKI. HRS patients were more likely to have a history of ascites (74.2% vs. 40.9%, p<0.05) and to present with ascites on current admission (83.9% vs. 43.1%, p<0.05) (**Table 2**).

Key laboratory differences were noted between the HRS group and non-HRS group. HRS patients had lower hemoglobin levels (9.7 g/dl vs. 11.0 g/dl, p<0.05), lower platelet counts (109 x10^3 vs. 161 x10^3, p<0.05), and lower sodium levels (129 meq/L vs. 137 meq/L, p<0.05). Additionally, they exhibited higher serum creatinine (2.9 mg/dl vs. 2.0 mg/dl, p<0.05), higher bilirubin levels (3.8 mg/dl vs. 1.8 mg/dl, p<0.05), and higher INR (2.1 vs. 1.5, p<0.05). The presence of spontaneous bacterial peritonitis was significantly more common in the HRS group (38.7% vs. 3.9%, p<0.05). Hemodialysis was required in 61.3% of HRS patients compared to 8.6% of patients with other AKI causes (p<0.05). Mortality was notably higher in the HRS group (45.2% vs. 6.0%, p<0.05) (**Table 2**).

Bivariate analysis identified several factors associated with HRS, including alcoholic cirrhosis (OR 2.0, 95% CI 1.1–3.6, p<0.05), history of ascites (OR 5.7, 95% CI 2.9-10.9, p<0.05), and spontaneous bacterial peritonitis (OR 4.9, 95% CI 1.9-12.7, p<0.05). Other significant predictors included hemoglobin <11 g/dl (OR 2.6, 95% CI 1.4–5.0, p<0.05), platelets <150 x10^3 (OR 2.4, 95% CI 1.3–4.4, p<0.05), sodium <135 meq/L (OR 3.1, 95% CI 1.7-5.8, p<0.05), creatinine >2.5 mg/dL (OR 3.0, 95% CI 1.7–5.6, p<0.05), albumin <2 g/dL (OR 3.8, 95% CI 1.5–9.5, p<0.05), bilirubin >2 mg/dL (OR 9.5, 95% CI 5.1-17.7, p<0.05), and INR >1.5 (OR 5.6, 95% CI 2.9-11.1, p<0.05) (**Table 3**).

In multivariate analysis, independent predictors of HRS were identified. A history of ascites was a strong predictor (OR 5.8, 95% CI 2.6-13.0, p<0.05), as were serum creatinine >2.5 mg/dl (OR 2.5, 95% CI 1.2-5.5, p<0.05), albumin <2 g/dl (OR 3.9, 95% CI 1.1–13.5, p<0.05), bilirubin >2 mg/dl (OR 7.9, 95% CI 3.7-17.0, p<0.05), and spontaneous bacterial peritonitis (OR 5.5, 95% CI 1.4-12.2, p<0.05) (**Table 3**).

The logistic regression analysis further emphasized the significance of these predictors. Alcoholic liver disease (OR 4.62, 95% CI 2.0-10.68, p<0.05), ascites on current admission (OR 5.0, 95% CI 3.4-8.0, p<0.05), portal hypertension (OR 3.76, 95% CI 2.23-6.33, p<0.05), esophageal varices (OR 3.16, 95% CI 1.71–5.83, p<0.05), and spontaneous bacterial peritonitis (OR 14.77, 95% CI 5.89-37.06, p<0.05) were all strongly associated with an increased risk of developing HRS. The need for hemodialysis (OR 17.72, 95% CI 6.88-45.72, p<0.05) was also significantly higher among HRS patients, highlighting the severity of this condition (**Table 4**).

DISCUSSION

HRS is a common and serious complication in cirrhotic patients. The objective of this study was to identify the critical factors that predict the development of HRS in cirrhotic patients presenting with AKI. The results of our study

Table 2. Comparison of hepatorenal syndrome and other causes of acute kidney injury

	Hepatorenal syndrome n=31	Other causes of AKI n=232	p
Age (years), (SD)	61.7 (±9.7)	64.6 (±12.2)	0.191
Gender (male), n (%)	20 (64.5)	149 (64.2)	0.784
Etiology			
Hepatitis B, n (%)	9 (29.1)	79 (34.0)	0.145
Hepatitis C, n (%)	5 (16.1)	50 (21.5)	0.108
Alcoholic, n (%)	13 (41.9)	30 (11.4)	**<0.05**
Non-alcoholic steatohepatitis, n (%)	3 (9.7)	33 (14.2)	**0.02**
Autoimmune hepatitis, n (%)	1 (3.2)	20 (8.6)	**0.03**
Cryptogenic/other, n (%)	0	20 (8.6)	**<0.05**
MELD-Na score (SD)	28 (±7)	18 (±8)	<0.05
Ascites			
History of ascites, n (%)	23 (74.2)	95 (40.9)	**<0.05**
Ascites on current admission, n (%)	26 (83.9)	100 (43.1)	**<0.05**
Portal hypertension, n (%)	26 (83.9)	138 (59.5)	<0.05
Esophageal varices, n (%)	21 (67.7)	90 (38.8)	<0.05
Hepatic encephalopathy, n (%)	19 (61.3)	86 (37.1)	<0.05
Hemoglobin (g/dl)	9.7 (±1.9)	11.0 (±2.4)	<0.05
Platelet (x1000)	109 (±98)	161 (±101)	<0.05
Na (meq/L)	129 (±7)	137 (±8)	<0.05
Creatinine (mg/dl)	2.9 (±1.0)	2.0 (±0.8)	<0.05
Albumin (g/dl)	2.6 (±0.7)	3.4 (±0.8)	<0.05
Bilirubin (mg/dl)	3.8 (±2.2)	1.8 (±1.6)	<0.05
INR	2.1 (±0.9)	1.5 (±0.7)	<0.05
Spontaneous bacterial peritonitis, n (%)	12 (38.7)	9 (3.9)	<0.05
Other infection, n (%)	8 (25.8)	61 (26.2)	0.742
Hemodialysis	19 (61.3)	20 (8.6)	**<0.05**
Mortality, n (%)	14 (45.2)	14 (6.0)	<0.05

AKI: Acute kidney injury, SD: Standard deviation, MELD-Na: Model for end-stage liver disease-sodium, INR: International normalized ratio

Table 3. Bivariate and multivariate analysis of predictors for hepatorenal syndrome

Variable	Bivariate OR (95% CI)	Bivariate p-value	Multivariate OR (95% CI)	Multivariate p-value
Alcoholic cirrhosis	2.0 (1.1–3.6)	<0.05	1.2 (0.5–2.4)	0.678
History of ascites	5.7 (2.9–10.9)	<0.05	5.8 (2.6–13.0)	<0.05
History of hepatic encephalopathy	3.3 (1.8–6.0)	<0.05	1.5 (0.7–3.1)	0.256
Hb<11 g/dl	2.6 (1.4–5.0)	<0.05	1.7 (0.8–3.7)	0.160
Platelets<150 (x10^3)	2.4 (1.3–4.4)	<0.05	1.5 (0.7–3.2)	0.308
Sodium<135 meq/L	3.1 (1.7–5.8)	<0.05	2.2 (0.9–4.7)	0.053
Cr>2.5 mg/dl	3.0 (1.7–5.6)	<0.05	2.5 (1.2–5.5)	**<0.05**
Albumin<2 g/dl	3.8 (1.5–9.5–8.0)	<0.05	3.9 (1.1–13.5)	**<0.05**
Bilirubin>2 mg/dl	9.5 (5.1–17.7)	<0.05	7.9 (3.7–17.0)	**<0.05**
INR>1.5	5.6 (2.9–11.1)	<0.05	1.4 (0.3–5.8)	0.630
Spontaneous bacterial peritonitis	4.9 (1.9–12.7)	<0.05	5.5 (1.4–12.2)	<0.05

INR: International normalized ratio, OR: Odds ratio

indicate that a history of ascites, elevated creatinine levels, low albumin, elevated bilirubin values, and the presence of SBP are significant predictors of HRS. Furthermore, the MELD-Na scores of patients with HRS were significantly higher than those of patients with other causes of AKI. These findings are of critical importance in determining key clinical and laboratory parameters for the diagnosis and management of HRS.

Our secondary findings revealed notable differences in laboratory parameters between HRS patients and the control group. These included lower hemoglobin levels, lower platelet counts, and lower sodium levels. Moreover, the incidence of hemodialysis and mortality rates were markedly elevated in patients with HRS in comparison to those with other causes of AKI. In the bivariate analysis, several factors were identified as being associated with HRS, including alcoholic cirrhosis, a history of ascites, and SBP. The multivariate analysis confirmed the presence of ascites history, high serum creatinine, low albumin, high bilirubin, and SBP as independent predictors. These findings are critical for the identification and management of patients at risk for the development of HRS.

In the initial comprehensive observational study in the literature to investigate the risk factors associated with HRS, Gines et al.[7] examined 234 non-azotemic cirrhosis patients with ascites. Their findings indicated that a history of ascites and serum sodium concentration ≤133mEq/L were among the factors that increased the risk of developing HRS. The results

Table 4. Odds ratios and confidence intervals for predictors of hepatorenal syndrome

Variable	Odds ratio (OR)	95% CI (lower)	95% CI (upper)	p-value
Age (years)	0.97	0.94	1.01	0.191
Gender (male)	0.99	0.63	1.53	0.784
Alcoholic liver disease	4.62	2.0	10.68	0.0
Non-alcoholic steatohepatitis	0.43	0.12	1.51	0.02
Autoimmune hepatitis	0.35	0.04	2.99	0.03
MELD-Na score	1.17	1.08	1.33	0.0
History of ascites	4.0	2.5	6.5	0.0
Ascites on current admission	5.0	3.4	8.0	0.0
Portal hypertension	3.76	2.23	6.33	0.0
Esophageal varices	3.16	1.71	5.83	0.0
Hepatic encephalopathy	2.74	1.54	4.89	0.0
Hemoglobin (g/dl)	0.78	0.66	0.92	0.005
Platelet count (x1000)	0.67	0.56	0.79	0.0
Sodium (meq/L)	0.59	0.48	0.71	0.0
Creatinine (mg/dl)	2.45	1.22	4.91	0.0
Albumin (g/dl)	0.39	0.3	0.51	0.0
Bilirubin (mg/dl)	2.72	1.41	5.23	0.0
INR	1.67	1.12	2.48	0.005
Spontaneous bacterial peritonitis	14.77	5.89	37.06	0.0
Other infection	0.98	0.58	1.67	0.742
Hemodialysis	17.72	6.88	45.72	0.0

INR: İnternational normalized ratio

of our study yielded comparable findings. In the bivariate analysis, a serum sodium level of less than 135 mEq/L was identified as a significant predictor for the development of HRS, with an odds ratio of 3.1 (95% confidence interval 1.7-5.8, p<0.05). However, this association was found to be borderline significant in multivariate analysis (OR 2.2, 95% CI 0.9-4.7, p=0.053). This discrepancy indicates that serum sodium level ceased to be an independent predictor when we controlled for the effect of other variables. Gines et al.[7] reported that serum sodium level played an important role in the development of HRS. However, our multivariate analysis results demonstrate that serum sodium level alone is not a sufficient predictor of HRS risk and should be evaluated together with other factors.

In a retrospective study conducted by Sasso and colleagues,[9] 529 cirrhotic patients presenting with ascites were examined. The researchers identified that 9.8% of patients had HRS, and that a history of ascites, serum creatinine >2.5 mg/dl, albumin <3 g/dl, bilirubin >2 mg/dl, and SBP were independent factors predicting the development of HRS. Similarly, in our study, significant predictors for the development of HRS included a history of ascites (OR 5.8, 95% CI 2.6-13.0, p<0.05), elevated serum creatinine (OR 2.5, 95% CI 1.2–5.5, p<0.05), low albumin (OR 3.9, 95% CI 1.1-13.5, p<0.05), elevated bilirubin (OR 7.9, 95% CI 3.7-17.0, p<0.05), and the presence of SBP (OR 5.5, 95% CI 1.4-12.2, p<0.05). In both studies, history of ascites and SBP were found to be important predictors for the development of HRS. However, the fact that serum albumin level was found to be <3 g/dl in the study by Sasso et al.[9] and <2 g/dl in our study suggests that different thresholds for determining albumin level should be considered in clinical practice.

Alcoholic cirrhosis was defined as the most common etiology in the study by Sasso et al.[9] In our study, alcoholic cirrhosis was found to be an important factor for the development of HRS in bivariate analysis (OR 2.0, 95% CI 1.1-3.6, p<0.05), but it was not significant in multivariate analysis (OR 1.2, 95% CI 0.5-2.4, p=0.678). Alcohol is the most common cause of cirrhosis in Western societies and it may be misleading to consider it as a risk factor for HRS in a cirrhosis population with a high prevalence of alcoholic cirrhosis in general. In our study, we found that the development of HRS was observed at a significantly higher rate in patients with alcoholic cirrhosis etiology. The lack of a significant association between alcoholic liver disease and the development of HRS in multivariate analysis may be explained by the low rate of alcoholic cirrhosis in our study. In future studies, cohorts with a higher rate of alcoholic cirrhosis should be evaluated. This finding suggests that HRS is more common among patients with alcoholic cirrhosis in our study. Our multivariate analysis results show that the etiology of alcoholic cirrhosis alone is not sufficient to predict the risk of HRS and should be evaluated together with other factors. This finding suggests that further studies in different populations are necessary to further clarify the independent effect of alcoholic cirrhosis on HRS.

Active alcohol consumption can lead to hypovolemia, a major risk factor for AKI in cirrhosis. This is due to the diuretic effect of alcohol, which exacerbates fluid loss and reduces effective intravascular volume, leading to decreased renal perfusion.[16] Alcohol-induced liver injury may accelerate HRS and further compromise renal perfusion by worsening portal hypertension and systemic vasodilation.[17,18] Alcohol increases the production of reactive oxygen species and the systemic inflammatory response resulting from oxidative stress can lead to renal endothelial dysfunction and tubular damage.[19] In conclusion, active alcohol consumption is thought to be both a pathophysiologic and clinical risk factor for HRS in alcohol abusers. However, considering that the alcoholic cirrhosis patients in our study were mostly alcohol abstinent and waiting on the liver transplantation list, we may not have been able to show an independent association between alcohol

etiology and HRS in the multivariate analysis in our study. Therefore, further research by separating alcoholic cirrhosis patients with and without alcohol dependence will provide a better understanding of the effect of alcohol on the risk of HRS.

In an observational study conducted by Montoliu et al.[20] 263 cirrhotic patients were followed for approximately 41 (±3) months after the initial detection of ascites. During the follow-up period, 27.4% of patients developed pre-renal AKI, 14.1% developed infection-related AKI, and approximately 7.6% developed HRS; in total, nearly half of the patients (49%) experienced some form of functional renal failure. While the study by Montoliu et al.[20] focused on general risk factors for AKI, our study specifically examined risk factors for HRS. In both studies, serum creatinine level was identified as a significant predictor. In Montoliu et al.'s study, serum creatinine was found to be an independent predictor of functional renal failure. Similarly, in our study, elevated creatinine levels were found to be a significant predictor of HRS in both bivariate (OR 3.0, 95% CI 1.7-5.6, $p<0.05$) and multivariate analyses (OR 2.5, 95% CI 1.2-5.5, $p<0.05$). This finding indicates that creatinine level is a critical risk factor for the development of both overall AKI and HRS in cirrhotic patients.

In a phase-3 clinical study conducted by Curry et al.[21] it was observed that patients diagnosed with HRS type 1 who were undergoing terlipressin treatment exhibited a diminished response to the medication and experienced more unfavorable outcomes when their serum creatinine levels were elevated. The results of this study demonstrate that patients who receive treatment during the early stages of the disease tend to have more favorable outcomes. Our findings also highlight the role of serum creatinine levels as a key predictor in the development of HRS. These observations underscore the necessity of promptly identifying the risk of HRS and developing effective treatment strategies in clinical practice.

In a retrospective observational cohort study conducted by Janíčko et al. in decompensated cirrhotic patients (n=202), it was reported that serum sodium levels were significantly lower in patients who developed HRS. Additionally, bilirubin and MELD scores were identified as important predictors of HRS.[22] The findings of the Janíčko et al.[22] study bear notable resemblance to those of our own investigation. The results of both studies indicate that serum sodium and creatinine levels, as well as bilirubin and MELD scores, are significant predictors of the development of HRS. Given the sub-parameters included in the MELD-Na score (creatinine, bilirubin, INR, and sodium), it is unsurprising that a high MELD-Na score is associated with an increased risk of HRS. This risk factor has been demonstrated in our study. In our analysis, serum sodium level was a significant risk factor for HRS in the bivariate analysis (OR 3.1, $p<0.05$); however, in the multivariate analysis, it yielded a p-value of 0.053, suggesting it is not an independent predictor when adjusted for other variables. Nonetheless, the lower sodium levels observed in the HRS group may still be clinically relevant and warrant attention in patient management. The use of patient data from disparate populations indicates that caution should be exercised when generalizing the findings.

In a multicenter retrospective cohort study by Oliveira et al.[23] 139 patients with SBP were examined, and it was reported that type 1 HRS developed in 30% of the patients. Furthermore, multivariate analyses demonstrated that the development of HRS increased 30-day mortality in patients with SBP. In a prospective study by El Sharawy et al.[24] that included 121 cirrhosis patients with SBP, HRS was reported to develop in 24.8% of patients. In this study, high MELD-Na scores and high serum bilirubin values were identified as risk factors for the development of HRS in patients with SBP. The observation that HRS was identified with greater frequency in these studies conducted in a specific patient population with SBP in comparison to the general cirrhotic patient population lends support to the conclusion that SBP is an independent risk factor for HRS, as was determined in our study. These findings collectively indicate a robust correlation between SBP and the onset of severe renal dysfunction in patients with cirrhosis and portal hypertension.

A meta-analysis by Salerno et al.[25] encompassing four distinct controlled studies, demonstrated that albumin infusion therapy was associated with a reduced incidence of renal dysfunction in patients with SBP. These observations, derived from treatment approaches, provide indirect support for the identification of SBP and hypoalbuminemia as risk factors for HRS in our study.

In our study, patients with HRS exhibited significantly lower hemoglobin and platelet levels and higher INR levels compared to patients with other causes of AKI. However, bivariate and multivariate analyses demonstrated that these variables were not independent risk factors. Given that the presence of these parameters collectively reflects the findings of advanced portal hypertension, it can be concluded that they are not independent risk factors in and of themselves.

Limitations

The retrospective nature of the study and its single-center design represent the primary limitations of this investigation. In retrospective studies, there may be concerns about the complete collection of patient data. However, the advent of electronic patient files recorded through hospital information management systems has largely mitigated this issue, minimizing the potential for data loss due to human error. Additionally, the reliance on historical data limits our ability to control for certain confounding variables that may influence outcomes, such as treatment responses or socio-economic factors. Furthermore, the single-center design may restrict the generalizability of our findings to cirrhosis patients in other centers. Nevertheless, the inclusion of a substantial number of cirrhosis patients (263 patients) enhances the statistical power and reliability of our findings, providing a solid foundation for identifying predictors of HRS.

In terms of strengths, the study utilized the International Club of Ascites 2019 criteria for diagnosing HRS, ensuring consistency with current global standards. The large sample size and the comprehensive analysis of a wide range of clinical and laboratory parameters also enhance the validity of our

findings. Moreover, both bivariate and multivariate analyses were conducted, allowing for a robust identification of independent predictors. These factors collectively contribute to the scientific rigor and potential applicability of the results, offering valuable insights for the management of cirrhotic patients with AKI.

CONCLUSION

In conclusion, this study revealed important factors predicting the development of HRS in cirrhotic patients presenting with AKI. A history of ascites, high serum creatinine and bilirubin levels, low albumin levels and the presence of spontaneous bacterial peritonitis were found to be independent risk factors for the development of HRS. These findings may help clinicians to identify high-risk patients early and develop appropriate treatment strategies.

The results of this study emphasize the importance of early diagnosis and treatment of HRS. Further research should focus on the development of prognostic models that take these risk factors into account and the creation of new strategies for the prevention and management of HRS. This approach may contribute to reducing the morbidity and mortality associated with HRS in cirrhotic patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Ethics Committee of Ankara Etlik City Hospital (Date: 24.04.2024, Decision No: AEŞH-BADEK-2024-320).

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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The effect of different polishing systems on the discoloration of composite resins: examples of commonly consumed beverages

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ABSTRACT

Aims: The aim of this study is to evaluate the color stability of composite resin materials subjected to different polishing systems when exposed to commonly consumed beverages.

Methods: In this study, four different composite polishing systems (Zenit, 3M Sof-Lex, Sofu, Kerr) and three types of beverages (Nescafé 3-in-1, Lipton tea bags, and distilled water) were used. A micro-hybrid resin composite (Tokuyama) was selected for the study. A total of 84 disk-shaped composite resin samples (8 mm in diameter and 2 mm thick) were prepared. The samples were divided into four main groups according to the polishing systems used, and further divided into three subgroups based on the beverage types, with seven samples in each subgroup, resulting in a total of 12 study groups. Initial color measurements, as well as measurements taken on days 1, 7, and 28, were recorded using a vita easyshade spectrophotometer. The data were tabulated and statistically analyzed using SPSS 25.0 software, employing one-way ANOVA and Tukey HSD post-hoc tests ($p=0.05$).

Results: Examination of the 28-day staining results revealed a statistically significant difference between the results for distilled water and coffee, depending on the brand ($p<0.05$). Specifically, it was observed that the distilled water results for the Shofu and Zenit brands were higher compared to those of the Kerr brand, while the coffee results for the Kerr brand were higher than those of the Zenit brand. Additionally, there was a statistically significant difference among the 28-day staining results for the 3M, Kerr, Shofu, and Zenit brands ($p<0.05$). The results for tea from the 3M, Kerr, Shofu, and Zenit brands were observed to be higher compared to their results for distilled water and coffee.

Conclusion: Within the limits of this study, the color stability of composite resin materials varied depending on the type of composite resin and polishing system used. It was determined that the Kerr Opti-Disc polishing system had the highest success rate among all systems. Additionally, it was found that frequently consumed tea caused a higher degree of color change compared to coffee. Further supportive studies should be conducted with different composite materials and polishing systems.

Keywords: Composite resin, color stability, finishing and polishing, discoloration

*Our research's data was presented in FDI World Dental Congress as 'Oral Presentation' on September 2024.

INTRODUCTION

Recent increases in aesthetic demands and rising societal awareness, which have also been felt in the field of dentistry, have led patients to request long-lasting aesthetic restorations.[1] Composite resins, frequently chosen by clinicians for their superior aesthetic properties, have enhanced their ability to natural tooth structures due to their color match and stability.[2]

By examining the reasons for the failure of commonly used composite resins, it is believed that their properties can be better understood, thereby improving treatment success and material performance. In addition to the application technique, long-term clinical success of aesthetic restorations depends on factors such as particle size, resin matrix structure, color match, and polishability. The color stability of the chosen composite resin is crucial for successful restorations that can be used over the long term. Color changes due to inadequate color stability of composites are among the primary reasons for the replacement of aesthetic restorations, particularly in the anterior region.[3]

One of the most common issues with composite resins is color change, which can result from various factors.[4] Changes in color due to the physicochemical properties of the resin are termed internal staining, while color changes due to application issues are referred to as external staining. While the composition of the composite resin and the percentage of inorganic fillers affect internal staining, external staining is influenced by factors such as contamination with saliva

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or blood during application, inadequate polymerization and polishing procedures, improper finishing techniques, smoking habits, poor oral hygiene, and dietary habits.[4,5]

External colorations resulting from factors such as smoking, dietary habits, and inadequate oral hygiene can be easily removed from the surface of restorations. However, internal colorations, caused by intrinsic factors, necessitate the complete removal and replacement of the restoration.[3]

Although the human eye has the sensitivity to distinguish even minimal color differences, color discrimination is a complex process involving various factors. Light reflected from an object is focused on the retina of the eye, where it stimulates cone cells, and this stimulation is then transmitted to the brain through a neural reaction chain. Consequently, an individual perceives the color of the object through this mechanism.[5,6] In clinical dentistry, color matching can be performed using a color scale or current digital measurement devices. Measurements taken using a color scale can be influenced by numerous factors such as the clinician's experience, light intensity, source, the color of the working environment's floor and walls, the patient's clothing, and any makeup present.[5,7] Modern digital measurement devices, such as colorimeters, spectroradiometers, and spectrophotometers, are advantageous due to their ability to provide more reliable and repeatable results.[8,9]

Increasingly digital clinical applications are also influencing color measurement systems. Current color measurement devices include colorimeters, spectroradiometers, spectrophotometers, and digital cameras.[10] These devices are based on various digital color analysis systems, which can be categorized as Munsell, CIE Lab (Commission Internationale de l'Eclairage), and RGB (red, green, blue).[9] The most commonly used system is CIE, a three-dimensional color model developed to define color. In this model, the L* value (Lightness) represents the lightness/darkness of the color and ranges from 0 to 100. A value of 100 indicates pure white, where light is fully dispersed, while a value of 0 represents ideal black. Positive a* values denote shades of red or purple, while negative a* values indicate green. Positive b* values represent yellowness, whereas negative b* values signify blueness. In this analysis system, the color difference between objects is calculated using the ΔEab* formula.[11]

The aim of this study is to compare the color stability of composite resins polished with four different composite polishing systems when exposed to three commonly consumed beverages. The null hypothesis of this study is that there will be no difference in color stability among composite resins polished with different polishing systems.

METHODS

Since the research did not involve any biological tissue, fluid or waste and was based solely on the use of manufactured artificial materials, ethics committee approval was not required.

In this study, G*Power (G*Power Ver. 3.1.9.2, Kiel, Germany) package program was used to determine the number of samples. The effect size was found to be 3.608 by taking a study with similar characteristics as a reference. For this effect size of 95% and 0.05 significance level, the minimum number of samples for each group was determined as 4. 7 samples were used in each group in the study. In this study, the supra-nano hybrid composite resin Tokuyama Estelite Sigma Quick (Tokuyama Dental Corporation, Tokyo, Japan) was used. The composite resin was polished with four different polishing systems to examine color changes in various beverages.

The color shade A2 composite resin was placed into cylindrical Teflon molds, measuring 6 mm in diameter and 2 mm in thickness, using an oral spatula. To prevent air bubbles within the sample, achieve a smooth surface, and remove excess material, light pressure was applied using glass ionomer cement and transparent tape. The polymerization of the composite samples was achieved using an LED light source (Hilux LEDMAX, Benlioğlu Dental AŞ, Ankara, Turkey) placed at the center of the samples for 20 seconds, as specified in the manufacturer's instructions. During the process, the light intensity of the device (approximately 1000 mW/cm^2) was also monitored with a radiometer (Hilux UltraPlus Curing Units, Benlioğlu Dental, İstanbul, Turkey). The samples were grouped according to the polishing systems used as follows:

1.Sof-Lex; 3M ESPE, St. Paul, MN, USA.

2.OptiDisc; Kerr, Bioggio, Switzerland.

3.SUPER Snap; Shofu, Japan.

4.Zenit Flex; President Dental, München, Germany.

A total of 84 samples were prepared, with 21 samples from each polishing system. After being removed from the molds, the samples were polished using four different polishing systems and then divided into subgroups for immersion in three different solutions:

1.Distilled water,

2.Tea (Lipton),

3.Coffee (Nescafe 3 in 1)

After the groups were randomly created, the polishing systems were applied for 60 seconds each, dry and at medium speed, using a clinical handpiece and micromotor to ensure standardization. Following the polishing procedures, all samples were stored in an incubator at 37°C in distilled water for 24 hours. The samples were then washed, dried, and prepared for initial measurements. Initial measurements were recorded using a spectrophotometer (Vita Easyshade Advance 4.0, VITA Zahnfabrik, Bad Säckingen, Germany).

The measurements of samples immersed in the three different solutions were repeated on days 1, 7, and 28, following each immersion period. For samples immersed in coffee and tea solutions, prior to measurement, they were washed with distilled water for 5 minutes and dried before recording the values.

Measurements were performed in a white room, on a white surface, and under D65 standard lighting conditions. Calibration of the device was conducted before each measurement. Each sample was measured three times to obtain an average value. The changes in the recorded values

were calculated using the formula $\Delta E^*=[(L1^*-L0^*)^2+(a1^*-a0^*)^2+(b1^*-b0^*)^2]^{1}/^{2}$.[11]

Statistical Analysis

The data obtained from the study were analyzed using the SPSS (Statistical Package for Social Sciences) for Windows 25.0 program. Descriptive statistical methods (mean, standard deviation) were employed for data evaluation. Normality was assessed using normal distribution tests and skewness-kurtosis values. For data showing normal distribution, one-way analysis of variance (ANOVA) was used to compare variables with more than two categories, and the Tukey test was applied to determine which groups exhibited significant differences. The significance level was set at 95%.

RESULTS

Upon examining the 24-hour discoloration results, no statistically significant differences were observed among the results for distilled water, coffee, and tea based on brand (p>0.05) (**Table 1**).

Regarding the solutions, no statistically significant differences were found in the 24-hour discoloration results among the 3M, Shofu, and Zenit brands (p>0.05). However, significant differences were noted for the Kerr brand (p<0.05), with tea discoloration results being higher than those for distilled water.

Table 1. 24-hours discoloration

	24-hours-discoloration			p
	Distilled water	Coffee	Tea	
3M	2.14±0.68	2.61±1.20	3.64±1.98	0.151
Kerr	2.36±0.73	2.78±1.17	4.19±1.35	0.017*
Shofu	2.51±0.75	3.46±1.55	3.06±0.70	0.276
Zenit	2.40±1.31	3.06±1.16	3.39±1.28	0.344
p	0.895	0.628	0.505	

The analysis of the 7-day discoloration results revealed that there were no statistically significant differences among the coffee results for different brands (p>0.05). However, significant differences were observed between the distilled water and tea results among the brands (p<0.05). Specifically, the Zenit brand showed higher discoloration results for distilled water compared to the Kerr brand, and the Zenit brand also had higher discoloration results for tea compared to the Shofu brand (**Table 2**).

Table 2. 7-days discoloration

	7-days discoloration			p
	Distilled water	Coffee	Tea	
3M	3.16±0.74	3.99±1.17	6.93±2.77	0.002*
Kerr	3.01±0.48	4.59±0.96	5.87±1.73	0.001*
Shofu	4.17±1.19	4.69±1.97	5.53±2.46	0.439
Zenit	4.44±1.10	4.15±1.63	9.35±2.18	0.000*
p	0.016*	0.776	0.021*	

Regarding solutions, no statistically significant differences were found in the 7-day discoloration results for the Shofu brand (p>0.05). In contrast, significant differences were noted among the 3M, Kerr, and Zenit brands (p<0.05). The 3M and Zenit brands exhibited higher discoloration results for tea compared to distilled water and coffee, while the Kerr brand showed higher discoloration results for tea compared to distilled water.

The analysis of the 28-day discoloration results revealed that there were no statistically significant differences among the tea results for different brands (p>0.05). However, significant differences were observed between the distilled water and coffee results among the brands (p<0.05). Specifically, the Shofu and Zenit brands showed higher discoloration results for distilled water compared to the Kerr brand, while the Kerr brand exhibited higher discoloration results for coffee compared to the Zenit brand (**Tablo 3**).

Regarding solutions, statistically significant differences were found among the 3M, Kerr, Shofu, and Zenit brands (p<0.05). The discoloration results for tea were higher for all brands (3M, Kerr, Shofu, and Zenit) compared to distilled water and coffee.

Table 3. 28-days discoloration

	28-days discoloration			p
	Distelled water	Coffee	Tea	
3M	5.30±1.08	7.86±3.17	15.79±7.88	0.002*
Kerr	3.62±0.78	11.05±4.8	22.02±7.36	0.000*
Shofu	5.75±1.06	6.87±1.99	15.58±8.30	0.003*
Zenit	5.82±1.99	6.25±2.02	15.99±2.63	0.000*
p	0.014*	0.046*	0.261	

DISCUSSION

In this study, the discoloration of composites polished with four commonly used polishing systems was evaluated against coffee, tea, and distilled water. After application of different polishing systems, composites immersed in coffee, tea, and distilled water exhibited clinically acceptable levels of discoloration without significant differences among them. Therefore, the null hypothesis of the study was rejected, as differences in color stability were observed among composites polished with different systems.

Recent advancements in adhesive technologies and the successes achieved in enamel and dentin adhesion have contributed to the widespread use of composite resins.[1] While the primary expectation from restorations made with composite resins is to provide long-lasting aesthetic appearance, color changes remain one of the significant disadvantages of these restorations. Studies have shown that dissatisfaction with dental treatments is attributed to color mismatch in 38% of cases.[12] Various factors such as inadequate polymerization, insufficient polishing, water absorption, oral hygiene, and dietary habits have been reported to affect the color stability of composite resin restorations.[13] Literature reviews reveal an increasing trend in coffee consumption

due to the growing number of coffee shops and the extended duration of tea consumption, influenced by cultural habits in our country. This study focuses on the relationship between the color changes of supra-nano hybrid resin composites against frequently consumed tea and coffee and different polishing systems.[14,15]

The color detection phase is a multifactorial and highly complex process, influenced by factors such as ambient light source, material opacity, light transmission, light reflection, and varying subjective assessments.[11] To minimize potential visual discrepancies during this phase, digital color measurement devices have been developed. In this study, we utilized one such device, the spectrophotometer (Vita Easyshade Advance 4.0). The success and reliability of the Vita Easyshade device have been supported by various recent studies.[16-18]

The data obtained from the measurements using the spectrophotometer were analyzed using the L* a* b* color system to calculate ΔE values. Differences were interpreted using the ranges specified in the literature. In a recent study by Drubi-Filho et al.[19] ΔE values of 3.3 and above were reported as the clinically unacceptable threshold for color differences. Additionally, the literature indicates that a clinically acceptable ΔE value is 2.7 within a 50:50 confidence interval.[20] Therefore, in our study, values of ΔE 2.7 or lower were considered acceptable. The findings of our study indicated that, due to ΔE values exceeding 2.7 in all groups, the color changes were not clinically acceptable.

Studies have indicated that composite resins with a higher inorganic filler content exhibit less color change.[21] Contrary to these findings, Bagheri et al.[22] reported that composites with a high filler content experienced the greatest color change, suggesting that color change is not always directly related to the amount of filler. Another recent study on discoloration from 2022 also did not observe a direct relationship between filler content and color change.[23] Therefore, in our study, we aimed to evaluate the effects of polishing systems by using a single type of composite to isolate the impact of the polishing methods.

To ensure that composite restorations are long-lasting, successful, and aesthetic, a smooth composite surface must be achieved regardless of the carious lesion's location or classification.[24] Inadequate polishing results in a rough composite surface, leading to adverse clinical outcomes such as increased plaque accumulation, secondary caries risk, gingival inflammation, and discoloration.[25] Moreover, numerous studies have reported that the most successful smoothness in composites is achieved using transparent strips.[24] However, the outermost surface of the composite under the strip remains in contact with oxygen, resulting in an unstable condition and incomplete polymerization. This surface, exhibiting low microhardness, must be eliminated to prevent discoloration and wear in the restoration. Therefore, thorough finishing and polishing procedures are essential for composite resin restorations.[26] In this study, transparent strips were used prior to finishing and polishing procedures to obtain standardized surfaces. Although there is extensive research on finishing and polishing systems for composite resins, a universally accepted standard procedure for ideal finishing and polishing does not yet exist.[27]

Previous studies have indicated that the surface roughness obtained from polishing processes depends on the material's properties and type.[28] For an effective polishing procedure, the abrasive particles in the polishing system should be harder than the filler particles of the polished composite resin.[29] Consequently, polishing materials often use abrasives such as aluminum oxide or diamond particles, which are harder than the filler particles. In this study, all polishing materials used contained Al_2O_3 as the abrasive agent. According to our results, the highest color change was observed in the Zenit group, which may be explained by the softer abrasive particle composition used in this brand compared to the particles used in other polishing sets. The Optidisc Kerr and 3M Sof-Lex sets demonstrated better performance. This finding aligns with recent studies by Yılmaz et al.[30] which reported successful outcomes with aluminum oxide-impregnated rubber polishing systems (Sof-Lex, One-Gloss, Enhance). Additionally, Korkut et al.[31] in their 2021 study, noted that composite discoloration varied according to the polishing material rather than the composite resin type and that multi-step polishing systems have advantages.

Limitations

The findings of this research should be considered within certain limitations. First, it is important to note that this is an in-vitro study and that there are inherent limitations in simulating a natural in-vivo environment. In such studies, the evaluation of color changes is based solely on objective assessment without considering visual perception limitations and clinical impacts.

CONCLUSION

Within the limitations of this study, the color stability of composite resin materials varied depending on the type of composite resin and polishing system used. The findings indicate that the Opti-Disc from Kerr polishing system demonstrated the highest success rate among all systems evaluated. Additionally, it was determined that tea, which is frequently consumed, caused a higher degree of color change compared to coffee. Further research with different composite materials and polishing systems should be conducted to support these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since the research did not involve any biological tissue, fluid or waste and was based solely on the use of manufactured artificial materials, ethics committee approval was not required.

Informed Consent

Written informed consent was not required as the research was based on the use of manufactured artificial materials.

Referee Evaluation Process
Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
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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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Elevated expression of let-7b-3p enhances aggressiveness of larynx squamous cell carcinoma cells

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ABSTRACT

Aims: Larynx squamous cell carcinoma (LSCC) is the second most common head and neck malignancy. While let-7b-3p has been shown to have a role in cancer progression in malignancies, there is no research examining the association between LSCC and let-7b-3p. This study aimed to investigate the expression status of let-7b-3p and the potential roles of this microRNA (miRNA) in LSCC.

Methods: Using quantitative real-time polymerase chain reaction (qRT-PCR), we examined the expression status of let-7b-3p in 36 LSCC samples and the neighboring normal tissues. Then, the let-7b-3p miRNA mimic was transfected into Hep-2 cells via lipofectamine 2000 reagents. Cell viability was determined using the cell viability detection (CVDK-8) kit, and cell migration was evaluated with the scratch assay. To identify differentially expressed genes (DEGs) in larynx cancer GSE137308 and GSE130605 datasets were downloaded and reanalyzed using Gene Expression Omnibus (GEO2R) tool. Potential target genes of let-7b-3p were investigated in the miRNA target prediction and functional annotation database (miRDB). Shared genes between geo datasets and miRDB results were identified and the relationship between these genes and LSCC was investigated in the literature.

Results: We demonstrated that the expression levels of let-7b-3p was significantly upregulated in LSCC tumor tissues in comparison to the corresponding normal tissues. Mimic let-7b-3p transfection enhanced Hep-2 cell proliferation and migration. In vitro and bioinformatics analysis showed that overexpression of let-7b-3p can enhance the larynx cancer cell proliferation and migration through MYBPC1.

Conclusion: It was evaluated that let-7b-3p/MYBPC1 axis could potentially affect the LSCC process. Let-7b-3p has the potential to be a biomarker for LSCC, therefore, the let-7b-3p/ MYBPC1/LSCC relationship should be elucidated with new studies.

Keywords: Let-7b-3p, larynx squamous cell carcinoma, MYBPC1, bioinformatics

INTRODUCTION

Larynx squamous cell carcinoma (LSCC) is the second most prevalent malignant tumor in the upper aerodigestive tract, behind lung cancer. The majority of laryngeal cancers, precisely more than 90%, arise from the mucosal lining. Among these tumors, the most prevalent cytotype is distinguished squamous cell carcinoma.[1]

MicroRNAs (miRNAs) are short regulatory RNAs that consist of 18-22 nucleotides.[2,3] MiRNAs, which may exhibit either tumor suppressor or oncogenic functions, have been shown to be capable of differentiating various stages of many cancer types.[4-6] Genetic changes, such as deletion, translocation, or amplification, as well as epigenetic modifications, such as Deoxyribonucleic acid (DNA) methylation and histone modification, may either boost or reduce the levels of miRNA expression in the cell.[4,7]

For a considerable amount of time, it has been known that miRNAs consist of -5p and -3p strands, and dysregulation of these arms may be linked to a wide range of disorders.[8] The -5p strand is initially situated in the forward (5'-3') position of the precursor miRNA stem-loop structure, whereas the -3p

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strand, which will nearly complement the -5p strand, has been placed in the reverse location.[9] -5p and -3p strands may bind to distinct mRNAs and have diverse effects in the cell.[9,10] Several investigations have shown that let-7b-5p is a tumor suppressor in many cancer types.[11-13] However, the relationship between let-7b-3p and cancer has been investigated in limited studies. Therefore, the present study aimed to reveal the role of the let-7b-3p in LSCC.

METHODS

Clinical Samples

The study was conducted with the permission of the Institutional Review Ethics Committee of İstanbul University Cerrahpaşa Faculty of Medicine (Date: 23.10.2014, Decision No: 83045809/604.01/02-4221477). This study was conducted using the doctoral thesis data of the corresponding author. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed written consents were acquired from all patients prior to their inclusion in the research. The Department of Otorhinolaryngology at Cerrahpaşa Faculty of Medicine Hospital, İstanbul University-Cerrahpaşa, collected tumor tissue and corresponding adjacent normal tissue samples from 36 individuals who underwent surgical treatment for LSCC. Following the surgery, the freshly resected normal and tumor samples were rapidly snap frozen in liquid nitrogen and stored at −80˚C until they were required. Chemotherapy, radiotherapy, or immunotherapy was administered to any of the patients who participated in the study prior to the surgical operation. The following information about the patients was presented in **Table 1**: age, gender, histological grade, and T classification. The obtained data were not subjected to clinical analysis due to the limited number of LSCC patient samples included in the study. Rather, molecular analysis data and bioinformatics analysis results were assessed concurrently.

Table 1. The patients' clinicopathological information

	LSCC Subjects	Percentage
Age		
≤60	15	41.6%
>60	21	58.3%
Gender		
Male	32	88.8%
Female	4	11.1%
T Classification		
T1 and T2	6	16.6%
T3 and T4	30	83.3%
Histological grade		
II	14	38.8%
III	22	61.1%

T: Size and extend of the tumor, LSCC: Larynx squamous cell carcinoma

Hep-2 Cell Culture

The Hep-2 cell line was obtained from the SAP Institute in Turkey, which is affiliated with the Ministry of Food, Agriculture, and Livestock. Hep-2 cells were cultured with RPMI1640 medium supplemented with 10% fetal bovine serum, 100 µg/ml streptomycin and 100 U/ml penicillin in a 5% CO2, 37°C incubator.

Let-7b-3p Mimic Transfection

Hep2 cells were seeded at 60% confluence into 96-well plates or 6-well culture plates. After 24 hours, according to the supplier's method for transient 30 nM let-7b-3p mimic or miR-NC (Thermo Fisher Scientific), were transfected via lipofectamine 2000 (Invitrogen, Carlsbad, CA, USA).

Cell Viability Assay

The CVDK-8 method, that colorimetrically reveals knowledge of viability, was employed to investigate the potential influence of the let-7b-3p on cell proliferation. In order to accomplish the goal, 5x103 cells were seeded in three wells of a 96-well culture plate for let-7b-3p mimic and non targeting (nt) control mimic. At 48 and 72 hours, cell proliferation was assessed by measuring absorbance at 450 nm using the CVDK-8 reagent (EcoTech Biotechnology) protocol and the MultiScan FC microplate reader (Thermo).

Scratch Assay

In order to assess the migration capabilities of Hep-2 cells transfected with let-7b-3p mimics, a scratch wound-healing method was conducted. Following the cells reached a confluency level of 95-100%, sterile 200 µl pipette tips were used to create wounds of comparable size. An inverted microscope was used to capture images of the wounds at 0 and 48 hours. The varying migration of cells was evaluated by analyzing wound closure by the measurement of gap sizes in 10 randomly chosen locations of the wound. The mean gap size was accepted as 100% at 0 hours.

RNA Isolation, Complementary DNA Synthesis and Quantitative Real Time PCR

Total RNA from tissues and Hep-2 cells were extracted using TRIzol (Invitrogen, San Diego, CA) according to the manufacturer's instructions. Spectrophotometric measurement and gel electrophoresis were used to evaluate the quantity and quality of RNA samples. Complementary DNA (cDNA) was synthesized using TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems, Foster City, CA) and miRNA specific primers. MiRNA expression analysis was carried out using TaqMan Universal Master Mix (Applied Biosystems) and miRNA specific probes (Applied Biosystems) were used. Quantitative real-time PCR (qRT-PCR) tests were conducted using a Roche LightCycler 480-II real-time thermal cycler (Roche, Switzerland) in accordance with established protocols. RNU43 was used for the internal control. Each experiment was conducted in duplicate. Relative expression levels were determined using the delta-delta-Ct method.

Identification of Potential Targets of Let-7b-3p

To determine Differently Expressed Genes (DEGs) associated with larynx cancer GSE130605 and GSE137308 geo datasets were used. GEO2R was utilized to analyze geo datasets. The parameters logFC>2 and p<0.01 were considered in the DEGs analysis. Since let-7b-3p expression was found to be increased in LSCC tissues potential target gene expression was expected to be decreased. Therefore, downregulated genes were considered in DEGs analysis of the geo datasets. In

silico potential target genes of let-7b-3p were investigated in the miRDB tool. Shared genes in GSE130605 and GSE137308 geo datasets and miRDB were identified.

Statistical Analysis

The data were represented as mean±standard deviation of the mean. The differences were assessed for statistical significance using Student's t-test. P values equal to or less than 0.05 were considered statistically significant. Statistical analyses were performed with GraphPad Prism 10.0 (GraphPad Software, Inc., San Diego, CA).

RESULTS

Let-7b-3p is Overexpressed in LSCC Tumor Tissue Samples

The clinicopathological characteristics of the patients are demonstrated in **Table 1**. Measurement of the expression level of let-7b-3p in LSCC samples and the corresponding adjacent normal tissue sapmles obtained from the same patients were performed using qRT-PCR. Our findings revealed that in 32 of all 36 normal-tumor tissue pairs, let-7b-3p expression was significantly upregulated in tumor samples compared to the adjacent normal tissue specimens. When all samples are considered together, let-7b-3p expression was found to be upregulated almost 1.5-fold in tumor samples compared to normal tissue specimens (**Figure 1**; p=0.004).

Let-7b-3p Enhances Hep-2 Cell Proliferation and Cancer Aggressiveness

The mimic let-7b-3p was effectively transfected into Hep-2 cells (**Figure 2A**). Ectopic expression of let-7b-3p was seen to enhance Hep-2 cell proliferation relative to the control group (**Figure 2B**). Cellular migration is a crucial determinant in the development of cancer metastases. An examination of wound healing investigated the impact of let-7b-3p overexpression on the migration of Hep-2 cells. The findings demonstrated that the wound closure rate had been significantly increased in let-7b-3p transfected cells relative to the control group (**Figure 3**).

Let-7b-3p May Influence the LSCC Cancer Process by Altering MYBPC1 Expression

The analysis of the geo datasets revealed that 549 genes were downregulated in the GSE130605 dataset and 944 genes were downregulated in the GSE137308 dataset, both of which fulfilled the criteria of logFC>, p<0.01. In the miRDB in silico tool, let-7b-3p was found to target 1770 genes. It was defined that 14 genes were shared in GSE130605, GSE137308 geo datasets and miRDB (**Figure 4** and **Table 2**).

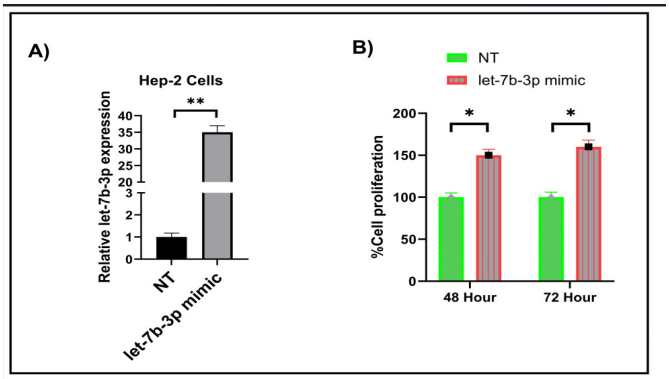

Figure 2. Effect of mimic let-7-3p transfection on Hep-2 cells. **A)** In the expression analysis performed for validation of mimic let-7b-3p transfection, a significant increase was found in mimic let-7b-3p transfected Hep-2 cells compared to the control group. **B)** In the evaluations performed at 48 and 72 hours after mimic let-7b-3p transfection, a significant increase in cell proliferation was found in the let-7b-3p mimic transfection group compared to the control group. (*: p<0,05, ** p<0,01)

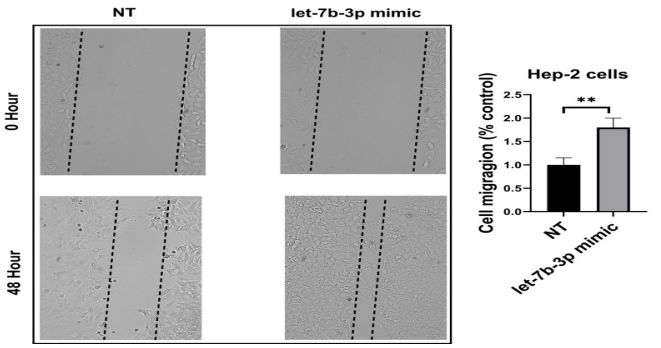

Figure 3. Overexpression of let-7b-3p was found to significantly enhance the migration of Hep-2 cells (p<0.01)

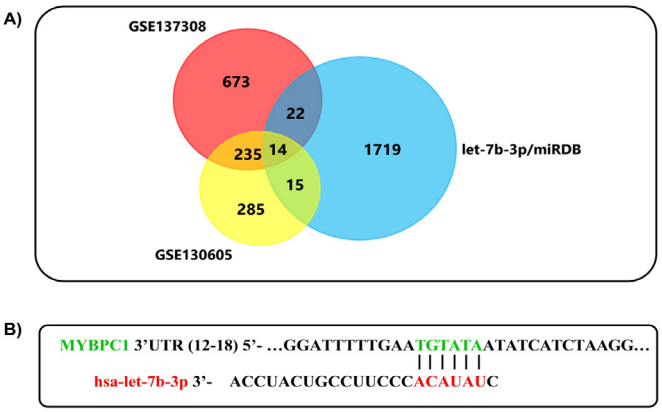

Figure 4. LSCC related genes and let-7b-3p potential target genes. **A)** Venn diagram of DEGs shared in the GSE137308 and GSE130605 geo datasets and included in the miRDB tool. **B)** Base pairing between let-7b-3p and its potential target gene MYBPC1

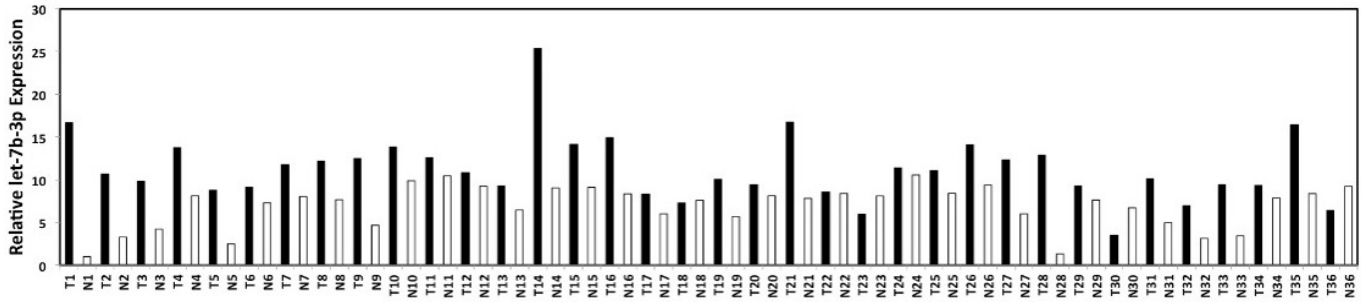

Figure 1. Relative expression of let-7b-3p in each tumor and normal laryngeal tissue specimens (T: Tumor, N: Normal)

Table 2. The expression levels of potential let-7b-3p targets in the GSE130605 and GSE137308 LogFC

	Genes	GSE130605		GSE137308	
Gene symbol	Gene name	p value	logFC	p value	**logFC**
NPY1R	Neuropeptide Y receptor Y1	7.07e-15	-3.53	1.78E-03	-4.59
BMP3	Bone morphogenetic protein 3	4.80e-18	-3.49	7.96E-05	-3.14
MYBPC1	Myosin binding protein C1	1.04e-13	-3.21	1.04E-03	-9.07
NRXN1	Neurexin 1	3.06e-21	-2.98	3.45E-05	-3.95
ESRRG	Estrogen related receptor gamma	1.88e-16	-2.92	9.74E-03	-2.49
NOVA1	NOVA alternative splicing regulator 1	2.81e-27	-2.9	4.04E-02	-2.1
NBEA	Neurobeachin	1.83e-23	-2.83	2.28E-02	-2.03
CA8	Carbonic anhydrase 8	6.40e-14	-2.68	4.26E-02	-2.3
ERBB4	Erb-b2 receptor tyrosine kinase 4	7.40e-09	-2.67	1.04E-03	-3.92
TFAP2B	Transcription factor AP-2 beta	4.09e-12	-2.56	1.67E-02	-2.84
ZMAT1	Zinc finger matrin-type 1	9.71e-39	-2.56	1.09E-01	-2.01
SLC6A4	Solute carrier family 6 member 4	1.04e-19	-2.52	1.35E-04	-4.45
PPP1R9A	Protein phosphatase 1 regulatory subunit 9A	2.47e-08	-2.12	1.33E-02	-2.78
SCN7A	Sodium voltage-gated channel alpha subunit 7	3.74e-61	-4.42	4.44E-04	-4.22

LogFC: Log fold change

DISCUSSION

To date, the dysregulations of many miRNAs have been closely related to the pathogenesis of several human cancers.[3,14-16] MiRNAs released by tumor cells into extracellular fluids, such as blood and saliva, function as signaling compounds to facilitate cell–cell contact and may serve as possible markers for cancer.[17] Thus miRNAs are becoming an increasingly popular topic of study among a variety of molecular components that have the potential to be examined for diagnostic and/or prognostic purposes.[18] A number of researchers have suggested that the let-7 family may serve as creative non-invasive biomarkers, offering promise for cancer detection. In mammals, let-7 is recognized as the regulator of differentiation, and its aberrant regulation and expression are associated with the onset and progression of cancer.[19] There are ten mature let-7 miRNAs in humans, which are generated from thirteen precursor genes. These microRNAs (let-7a, let-7b, let-7c, let-7d, let-7e, let-7f, let-7g, let-7i, miR-98, and miR-202) have critical roles in cellular functions.[20] For example, let-7b-5p has been found to inhibit breast cancer cell growth and metastasis through suppression of hexokinase 2-mediated aerobic glycolysis.[21] Bahojb et al.[22] showed that the overexpression of let-7a-3p enhances chemosensitivity to carmustine and synergistically induces autophagy while inhibiting cell survival in U87MG glioma cells. It was reported that let-7d suppresses the growth of colorectal cancer cells via the CST1/p65 pathway.[23]

In our study, we demonstrated that let-7b-3p is overexpressed in LSCC tumor tissues compared to adjacent normal tissue samples. Furthermore, it was observed that cell proliferation and migration were increased in Hep-2 cells transfected with mimic let-7b-3p in comparison to the control group. These findings suggest that let-7b-3p may function as a possible oncomiR in LSCC.

Dysregulation of let-7b-3p has been linked to several conditions. For instance, Demirel et al.[24] reported that let-7b-3p was dramatically overexpressed in the brain tissue of methamphetamine abusers. In another investigation, the expression of let-7b-3p was shown to be elevated in the patient group with mesangial proliferative glomerulonephritis.[25] Liu et al.[26] showed that the overexpression of let-7b-3p and the deregulation of nine other miRNAs were linked to myocardial ischemic reperfusion injury.

In contrast to other let-7 family members, let-7b-3p has received less attention in cancer research.[27] In one of the few research on this topic, 10 serum miRNAs (including let-7b-3p) were demonstrated as the most abundant miRNAs in the pleuro-pulmonary blastoma cases.[28] Extracellular vesicle miRNAs are critically significant in malignancies, and a recent study has shown that let-7b-3p was increased as an extracellular vesicle miRNA in patients with advanced colorectal cancer.[29] TRIM25, APP, ELAV1, RNF4, and HNRNPL' genes were identified as promising targets for Ewing sarcoma therapy in the bioinformatics analysis conducted by Weaver et al.[30] Let-7b-3p is one of the microRNAs that has the potential to have a function in the regulation of these genes. Li et al.[31] demonstrated that let-7b-3p suppresses tumor proliferation and metastasis by modulating the MAPK/ERK pathway via BRF2 in human lung adenocarcinoma. Li et al.[31] suggested that let-7b-3p might function as a tumor suppressor miRNA in human lung adenocarcinoma. However, our investigation demonstrated that let-7b-3p, which exhibited elevated expression in LSCC cancer tissue samples, enhances cell proliferation. Previous investigations have revealed that miRNAs may have opposing expressions in different malignancies. Therefore, identifying the cancer-specific expression patterns of miRNAs, arising from the intricate nature of cancer is crucial for understanding molecular pathways. To the best of our knowledge, no study has been reported regarding the relationship between LSCC and let-7b-3p.

The bioinformatic analysis of the current investigation identified 14 genes that let-7b-3p could potentially target and play a function in the LSCC process (**Table 2**). It has

been reported that each of these 14 genes are essential for the development of a variety of malignancies including breast cancer, small-cell lung cancer, and gastric cancer.[32-34] For instance, Ma et al.[35] demonstrated that ZMAT1 functions as a tumor suppressor in pancreatic ductal adenocarcinoma by triggering the SIRT3/p53 signaling pathway. Su et al.[36] found that miR-205 enhances tumor proliferation and invasion by targeting ESRRG in endometrial cancer. However, except for Myosin-binding protein C1 (MYBPC1) Pubmed database does not include any research that investigated whether or not there is an association between LSCC and other 13 genes. Thus we suggest MYBPC1 needs to be highlighted as one of the possible target genes of let-7b-3p that may be related to LSCC. MYBPC1 is a protein found in large quantities in skeletal muscle and is mostly secreted by slow-twitch muscle fibers.[37] MYBPC1 has been shown to be dysregulated in many cancers.[38-41] It has been revealed that this gene is downregulated in laryngeal carcinoma, and it has been identified as a crucial regulator of the development of oncogenesis. Furthermore, it was shown that MYBPC1 had a negative association with the stage of individuals who were diagnosed with laryngeal cancer.[38] The function of miRNAs in controlling the expression of MYBPC1 gene remains mostly unknown. The research conducted by Liu et al.[38] proposed that miR-451a may indirectly modulate the function of MYBPC1 via the ATF2-dependent signaling pathway.

The findings of our research provide clues that may be used to guide additional research into the interaction between let-7b-3p and MYBPC1 in LSCC. However, it is recommended that additional studies be conducted using the luciferase reporter assay methods etc. to validate this proposed axis.

CONCLUSION

Let-7b-3p overexpression in LSCC patient tissue samples was shown for the first time by the present study. Additionally, it has been shown that the overexpression of let-7b-3p in Hep-2 cells may lead to an increase in the proliferation and migration of cancer cells. Following that, bioinformatics approaches were used to find the possible target genes of let-7b-3p. The results of this investigation revealed that the link between let-7b-3p and MYBPC1 may be significant in LSCC. Further studies, however, are needed to elucidate the roles of let-7b-3p, in more detail in LSCC pathogenesis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Institutional Review Ethics Committee of İstanbul University Cerrahpaşa Faculty of Medicine (Date: 23.10.2014, Decision No: 83045809/604.01/02-4221477).

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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Prevalence of neoplasms in acromegaly: a Turkish single-center retrospective study

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ABSTRACT

Aims: This study aimed to investigate the prevalence of benign and malignant neoplasms and to assess associated clinical conditions in patients with acromegaly.

Methods: In this single center, retrospective and observational study, data from 71 patients with acromegaly followed at an endocrinology and metabolism diseases outpatient clinic between January 2010 and December 2023 were reviewed through the hospital's electronic database. Patients' medical histories, demographic data, blood examinations, medications, pituitary MRI scans, thyroid ultrasound, mammography, colonoscopy, endoscopy, and pathology reports were evaluated. Acromegaly diagnosis was based on elevated insulin-like growth factor-1 (IGF-1) levels and unsuppressed growth hormone (GH) levels after oral glucose tolerance testing. The chi-square test and Mann-Whitney U test were used to compare patients with malignancy to other patients in terms of demographic and clinical characteristics.

Results: The study included predominantly female patients (60.6%) with an average age of 55.6 years. The mean age at diagnosis was 44.3±11.3 years, and the mean disease duration was 11.3±8.4 years. Malignancies, including breast, thyroid, and colorectal cancers, were detected in 9.9% of patients. Additionally, thyroid nodules were present in 62% of patients, and colon polyps in 14.1%. No significant differences were observed in clinical features including age, gender, disease duration, GH levels, IGF-1 levels, adenoma size, or remission frequency between patients with and without malignancy ($p>0.05$ for all).

Conclusion: This study reveals an increased prevalence of breast, colon, and thyroid cancers in patients with acromegaly. Performing cancer screenings in patients with acromegaly more comprehensively and at an earlier stage compared to the normal population may be beneficial.

Keywords: Acromegaly, neoplasm, cancer screening

INTRODUCTION

Acromegaly is an uncommon disease marked by increased growth hormone (GH) and insulin-like growth factor-1 (IGF-1), typically resulting from the presence of a pituitary adenoma.[1] Its incidence ranges from 3-4 per million per year, with a prevalence of 40 to 70 per million.[2] Acromegaly is typically diagnosed between the ages of 40 and 50. Its insidious onset, slow progression, and variable clinical presentation frequently lead to delayed diagnosis.[3]

Patients with acromegaly face an increased risk of morbidity and mortality due to cardiovascular, respiratory, and metabolic complications.[4] Moreover, the anti-apoptotic and pro-angiogenic effects of IGF-1 are known to contribute to an elevated risk of neoplasms in patients with acromegaly.[5] While conflicting results exist, most studies have shown an increased incidence of malignancies in patients with acromegaly.[6,7] Additionally, an increased frequency of benign tumors in organs such as the thyroid gland, colon, and gallbladder has been reported.[8,9]

With the rise in life expectancy and improved treatment options for acromegaly over the years, malignancies have become one of the leading causes of mortality in these patients.[10] However, there are limited studies investigating the risk of malignancy in Turkish individuals with acromegaly.

This study aims to investigate the prevalence of benign and malignant neoplasms in patients with acromegaly followed at a tertiary care hospital and to elucidate related clinical conditions.

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METHODS

Design and study population

In this single-center retrospective observational study, data from 71 patients with acromegaly followed at our endocrinology and metabolism diseases outpatient clinic between January 2010 and December 2023 were evaluated. The medical histories, demographic data, blood tests, medications, pituitary MRI scans, and pathology results of the patients were reviewed retrospectively. At our center, routine follow-up for acromegaly patients involves colonoscopy and thyroid ultrasound for all patients, and mammography for female patients, as part of standard clinical practice, and the results of these procedures were also reviewed. Because the study was designed retrospectively, no written informed consent form was obtained from patients. The study was conducted following ethical standards outlined in the Helsinki Declaration, with approval from İstanbul Medeniyet University Clinical Researches Ethics Committee (Date: 18.06.2021, Decision No: 2022/0636).

Clinical Assessment

Laboratory examinations were conducted after 8-12 hours overnight fasting. Serum IGF-1 and GH levels measured using chemiluminescence immunoassay. Acromegaly diagnosis was based on elevated IGF-1 levels and unsuppressed GH levels after oral glucose tolerance testing (OGTT).

Patients were classified into remission or active disease groups based on treatment response criteria. Remission was defined as GH suppression to <0.4 µg/L following an OGTT or GH <1 µg/L with normal IGF-1 levels. Active disease was characterized by GH >1 µg/L and elevated IGF-1 levels.

Height (in centimeters) and weight (in kilograms) were measured using a height scale and an automated weight machine, and body-mass index (BMI) was subsequently calculated.

Statistical Analysis

Descriptive statistics for study participant characteristics included mean, standard deviation (SD), and % frequencies. Numerical data were analyzed using the Mann-Whitney U test for independent variables, and categorical data were analyzed using the chi-square test or Fisher's test when chi-square test conditions were not met. SPSS 28.0 software was used for statistical analysis, with a significance level set at $p<0.05$.

RESULTS

The mean age of the patients was 55.6±11.4, with a female predominance (60.6%). The mean age at diagnosis was 44.3±11.3 years, and the mean disease duration was 11.3±8.4 years. At the time of diagnosis, the mean GH and IGF-1 values were 5.3±9.0 µg/L and 410 ± 329 µg/L, respectively. Sixty-two patients (87.3%) underwent transsphenoidal surgery, ten (14.1%) received radiotherapy, and 29 (40.8%) had recurrence or residual adenomas. Medical treatment was administered to 57 patients (80.3%), with 53 (74.6%) achieving remission. Detailed demographic characteristics and clinical features of the patients are presented in Table 1.

Table 1. Demographic and clinical characteristics of patients

Variable (n=71)	Value
Age (year)	55.6±11.4
Female	43 (60.6)
Body-mass index (kg/m^2)	29.1±5.4
Age at diagnosis (year)	44.3±11.3
Disease duration (year)	11.3±8.4
Diabetes mellitus	34 (47.9)
Hypertension	35 (49.3)
Coronary artery disease	11 (15.5)
Chronic obstructive pulmonary disease	7 (9.9)
Size of pituitary adenoma (mm)	16±9.9
GH level at diagnosis (µg/L)	5.3±9
IGF-1 level at diagnosis (µg/L)	410±329
Transsphenoidal surgery	62 (87.3)
Radiotherapy	10 (14.1)
Residue or nux	29 (40.8)
Follow up	14 (19.7)
Dopamine agonist	2 (2.8)
Somatostatin analogue	45 (63.4)
Dopamine agonist+somatostatin analogue	10 (14.1)
Remission	53 (74.6)

Data are presented as mean±standard deviation or as n (%), GH: Growth hormone, IGF-1: Insulin-like growth factor-1

Malignancies were detected in seven patients (9.9%), including two colorectal cancers, two papillary thyroid cancers, and three breast cancers. Additionally, polyps were found in 13 patients (14.1%) in the colon, intestinal metaplasia in one patient (1.4%) in the gastric antrum, and thyroid nodules in 44 patients (62%). The frequencies of benign and malignant tumors detected in patients are shown in Table 2.

Table 2. Prevalence of benign and malignant tumors

Thyroid US±biopsy	Normal	25 (35.2)
	Nodule/MNG	44 (62)
	Papillary carcinoma	2 (2.8)
Colonoscopy±biopsy	Normal	56 (78.9)
	Inflammatory polyp	7 (9.9)
	Hyperplastic polyp	6 (8.4)
	Colorectal cancer	2 (2.8)

US: Ultrasound, MNG: Multinodular goiter, Data were presented as n, (%)

When comparing patients with malignancies (n=7) to the others, no statistically significant differences were observed between the groups in terms of age, gender, comorbid features, disease duration, GH levels, IGF-1 levels, adenoma size, or remission frequency ($p>0.05$ for all) (Table 3).

Table 3. Comparison of demographic and clinical characteristics between patients with malignancy and those without malignancy

Variable	Malignancy (-) n=64	Malignancy (+) n=7	p value
Age (year)	55±11.6	61.1±6.9	0.097
Age at diagnosis (year)	44.1±11.4	46.6±11	0.657
Female	38 (59.4)	5 (71.4)	0.536
Body-mass index (kg/m^2)	29.1±5.5	28.9±4.4	0.309
Disease duration (year)	11±8	14.6±12	0.543
Size of adenoma (mm,)	16.4±9.9	12.4±9.2	0.938
GH level at diagnosis (µg/L)	5.4±9.5	4.2±3.5	0.623
IGF-1 level at diagnosis (µg/L)	422±342	293±133	0.335
Remission (n, %)	49 (76.6)	4 (57.1)	0.359

Data are presented as mean±standard deviation or as n (%), GH: Growth hormone, IGF-1: Insulin-like growth factor-1

DISCUSSION

In this study, we found that one out of every ten patients with acromegaly who were followed at our hospital has malignancy. Additionally, we found that, apart from malignant tumors, thyroid nodules were present in 62% of patients, and colon polyps were found in 14.1% of them.

Untreated acromegaly is associated with a reduction in life expectancy by approximately 10 years and leads to various complications.[11] Among these complications, an increased risk of malignant tumors is of paramount importance. Malignancies are the third leading cause of death in patients with acromegaly, following cardiovascular and respiratory diseases.[12,13]

Numerous studies have investigated the frequency of benign and malignant tumors in acromegaly. Thyroid cancer is believed to be the most prevalent malignant neoplasm in patients with acromegaly.[14] In a study by Woliński et al.[15] involving 205 patients with acromegaly, the frequency of thyroid cancer was reported as 5.4%. The estimated risk of developing thyroid cancer in individuals with acromegaly was found to be 2.5-4.3 times higher than that in the general population.[16] A large cohort study by Baris et al.[7] involving 1634 acromegaly patients reported a statistically significant increase in thyroid cancer incidence compared to the general population. In our study, papillary thyroid cancer was observed in 2.8% of patients, indicating a higher prevalence compared to the general population, although it was not directly compared with a control group.[17]

The association between acromegaly and an increased risk of breast cancer is a subject of debate. Several studies have shown no significant difference in the frequency of breast cancer between patients with acromegaly and control groups.[18,19] However, according to Nabarro, the risk of breast cancer development in acromegaly increases fourfold.[20] Baris et al.[7] observed a slight rise in breast cancer incidence among female patients with acromegaly below the age of 50. In our study, the occurrence of breast cancer in 3 out of the female patients (7%) suggests an increased frequency of breast cancer in patients with acromegaly, emphasizing the need for more vigilant mammography screenings in women with acromegaly.

The prevalence of colorectal cancer in acromegaly has been shown to be elevated in several studies. A British prospective study involving 129 acromegaly patients indicated a significantly higher incidence of colorectal carcinoma.[21] A meta-analysis by Rokkas et al.[9] reported a colorectal cancer incidence ratio of 4.6% in patients with acromegaly, significantly higher than that in control groups. In our study, colorectal cancer was observed in 2.8% of patients, supporting the notion that colorectal cancer incidence is higher in acromegaly, and earlier colonoscopy screening may be beneficial for this patient group.

In addition to malignant tumors, it is well-established that the frequency of benign lesions increases in acromegaly. Our study revealed that 62% of patients had thyroid nodules, 14.1% had colon polyps, and 7% of female patients had breast masses. A study by Can et al.[22] involving 56 patients with acromegaly and an equal number of control subjects, found that 55.4% of patients had thyroid nodules, which was statistically significantly higher compared to the control group. In light of the aforementioned results, it is recommended that patients with acromegaly undergo routine thyroid ultrasound examinations, and biopsies should be considered for thyroid nodules with suspicious features.

Comparative studies on the prevalence of colon polyps in patients with acromegaly and control groups are limited, as performing colonoscopy on asymptomatic individuals in the control group solely for research purposes raises ethical concerns. A meta-analysis conducted by Rokkas et al.[9] which included nine studies and 701 patients, demonstrated a statistically significant higher incidence of both adenomas and hyperplastic polyps in patients with acromegaly. According to both this meta-analysis and other prospective studies, benign colonic neoplasms are estimated to be present in around half of the patients.[9,23,24] In our study, the presence of colon polyps in 14.1% of patients appears to be consistent with the findings of these studies. Based on these findings, colonoscopy at the time of diagnosis is recommended for patients with acromegaly, and our center has data on endoscopy and colonoscopy for all patients with acromegaly. However, some authors argue that, in the absence of evidence supporting an increased risk of developing colorectal cancer, patients with acromegaly should follow guidelines for the general population, which recommend the first colonoscopy after the age of 50.[25]

The most discussed mechanism for the increased malignancy risk in acromegaly is the elevated level of GH, followed by IGF-1. A positive correlation between circulating IGF-1 levels and the risk of colorectal, breast, or thyroid cancer has been established in the general population.[26,27] However, in our study, we did not observe any significant differences in IGF-1 and GH levels between patients with malignancy and those without. We believe that this may be primarily attributed to the retrospective design of our study, which did not account for variables that could affect IGF-1 levels, as well as the relatively small sample size.

Limitations

Our study has certain limitations. Firstly, it was conducted retrospectively at a single center, and its findings cannot be extrapolated to the general population. Secondly, due to the design of our study, there was no control group, and the results could not be compared to those of healthy individuals. Thirdly, there was a lack of detailed evaluation of genetic and environmental factors that may contribute to cancer development in patients. Finally, the endoscopic, colonoscopic, mammographic, and thyroid ultrasound examinations were performed by different physicians over the years, and biopsy results were evaluated by different pathologists, which may have led to variations in the interpretation of the results.

CONCLUSION

In conclusion, our study demonstrated an increased prevalence of breast, colon, and thyroid cancer in acromegaly patients. However, no significant differences in clinical features related to acromegaly were observed between patients with and without malignancy. Considering these results, we believe that cancer screenings in acromegaly patients may be

beneficial if conducted earlier or at more frequent intervals. Nevertheless, these findings need further support from more comprehensive prospective and randomized controlled studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the İstanbul Medeniyet University Clinical Researches Ethics Committee (Date: 18.06.2021, Decision No: 2022/0636).

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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Assessment of the ROX index as a predictor of invasive ventilation in patients with community-acquired pneumonia

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ABSTRACT

Aims: Community-acquired pneumonia (CAP) is a significant cause of morbidity and mortality worldwide, particularly among elderly patients and those with comorbid conditions. CAP can lead to severe respiratory failure, often necessitating invasive mechanical ventilation (IMV). Early identification of patients at high risk for intubation is crucial for optimizing management and improving outcomes. The ROX index, which incorporates respiratory rate, oxygen saturation, and fraction of inspired oxygen, has emerged as a potential tool for predicting the need for IMV in patients with respiratory distress. This study aims to evaluate the effectiveness of the ROX index in predicting IMV in patients hospitalized with CAP.

Methods: This retrospective cohort study included patients diagnosed with CAP who were admitted to a tertiary healthcare institution between January 1, 2019, and January 1, 2024. The ROX index was calculated at hospital admission using respiratory rate, oxygen saturation (SpO_2), and fraction of inspired oxygen (FiO_2). Severe pneumonia was defined as pneumonia severity index (PSI) class IV or V, and subgroup analyses were conducted for these patients to evaluate the diagnostic performance of the ROX index. The primary outcome was the requirement for IMV, and the predictive ability of the ROX index was evaluated.

Results: A total of 416 patients were included, with 30 (7.2%) requiring invasive mechanical ventilation. The mean ROX index was significantly lower in the intubation group (14.4±4.5) compared to the non-intubation group (23.8±5.4) ($p<0.001$). A ROX index ≤18.7 was identified as the optimal cutoff for predicting IMV, with an AUROC of 0.908. Among patients with severe pneumonia, the ROX index demonstrated an AUROC of 0.831, indicating strong predictive performance in this subgroup.

Conclusion: The ROX index is a valuable tool for predicting the need for invasive mechanical ventilation in patients with CAP, particularly in those with severe pneumonia, making it a useful tool for early risk stratification and clinical decision-making.

Keywords: Critical care, mechanical ventilation, pneumonia

INTRODUCTION

Community-acquired pneumonia (CAP) is a significant public health issue worldwide, with high rates of mortality and morbidity.[1-3] As one of the most common and deadly forms of respiratory infections, CAP particularly leads to severe clinical outcomes in elderly individuals and those with underlying chronic conditions. The increasing elderly population and rising burden of comorbidities have made the clinical management of CAP more complex. Common conditions such as hypertension, diabetes, and chronic lung diseases in this patient group negatively affect the course of pneumonia and increase mortality rates. The annual mortality rate due to CAP ranges from 2% to 50% globally, and it is among the infections that frequently require hospitalization and intensive care unit (ICU) admission.[4-6]

One of the most critical aspects of managing CAP is accurate risk assessment at the onset of the disease. This allows for the early identification of high-risk patients and the prompt application of appropriate treatment strategies. Severe CAP cases that are not addressed early often lead to multiple organ failure and respiratory failure, necessitating invasive mechanical ventilation and ICU admission.[7,8] Accurately predicting the need for intubation in this process enables timely interventions that may prevent the worsening of the disease.

The ROX index is a scoring system developed to predict the success of non-invasive ventilation and the need for intubation in patients with respiratory failure. By combining respiratory rate, oxygen saturation, and fraction of inspired oxygen (FiO_2), the ROX index objectively evaluates a patient's respiratory function and clinical course. The ROX index has been shown to be an effective tool for predicting the need for intubation in patients undergoing non-invasive ventilation and is increasingly being used, particularly in cases of acute respiratory distress.[9,10]

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This study hypothesizes that the ROX index can accurately predict the need for invasive mechanical ventilation in patients with CAP. The primary aim of the study is to evaluate the diagnostic performance of the ROX index in predicting intubation across all patients with CAP. Additionally, as a secondary aim, the study evaluates the performance of the ROX index in predicting intubation specifically in patients with severe pneumonia.

METHODS

This study was conducted with the approval of the İstanbul Yeni Yüzyıl University Clinical Researches Ethics Committee (Date: 04.11.2024, Decision No: 2024/11-1356) and was carried out in accordance with the ethical principles of the Declaration of Helsinki.

This retrospective cohort study included patients diagnosed with CAP who were admitted to the emergency department of a tertiary healthcare institution between January 1, 2019, and January 1, 2024. The inclusion criteria were as follows: patients aged 18 and older, a confirmed diagnosis of CAP, and complete clinical and laboratory data available at the time of hospital admission. Exclusion criteria included the presence of a non-pneumonia diagnosis, incomplete data that would hinder the calculation of the ROX index, and patients transferred from other hospitals. Patients diagnosed with COVID-19 pneumonia or admitted during the COVID-19 pandemic period (March 2020 to December 2022) were excluded to prevent confounding effects caused by changes in pneumonia management during this period.

Demographic data (age, gender), clinical characteristics (vital signs at admission, oxygen therapy parameters, comorbidities), laboratory findings, and the need for invasive mechanical ventilation were retrospectively collected from patient medical records. Patient data were retrospectively collected from electronic medical records. Inclusion and exclusion criteria were applied systematically to identify eligible patients. Clinical and laboratory parameters, including the components required to calculate the ROX index, were extracted uniformly for all patients. The ROX index, calculated as the ratio of oxygen saturation as measured by pulse oximetry (SpO_2) to the fraction of inspired oxygen (FiO_2), divided by the respiratory rate, was assessed upon hospital admission.[11] The ROX index was calculated using the formula: (SpO_2/FiO_2)/respiratory rate. SpO_2 was measured via pulse oximetry as a percentage, FiO_2 was documented as the fraction of inspired oxygen delivered to the patient, and respiratory rate was recorded in breaths per minute. These parameters were obtained at hospital admission and documented in the initial patient records to ensure consistency. The PSI was calculated for all patients at the time of hospital admission using the validated scoring system, which incorporates age, comorbidities, vital signs, and laboratory findings to assess pneumonia severity. Severe pneumonia was defined as patients classified into PSI class IV or V based on the PSI scoring system. This classification was used to identify and analyze the subgroup of patients with severe pneumonia. The primary outcome of the study was the requirement for invasive mechanical ventilation. Non-invasive ventilation strategies, including CPAP or BiPAP, and oxygen supplementation (via nasal cannula, face mask, or high-flow nasal cannula), were applied as clinically indicated to stabilize patients prior to assessing the need for invasive ventilation.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 29.0 (IBM Corp., Armonk, NY, USA) and MedCalc version 20.104 (MedCalc Software Ltd., Ostend, Belgium). Descriptive statistics were calculated for each variable, with continuous variables presented as means±standard deviation (SD) for normally distributed data or medians with interquartile ranges (IQR) for non-normally distributed data. Categorical variables were summarized using frequencies and percentages. The normality of continuous data was assessed with histograms and the Shapiro-Wilk test. Comparisons between groups were conducted using the Student's t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Categorical variables were analyzed using the Chi-square test or Fisher's exact test when appropriate.

Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic accuracy of the ROX index for predicting intubation, and the area under the ROC curve (AUROC) was calculated. Sensitivity, specificity, positive likelihood ratio (+LR), and negative likelihood ratio (–LR) were derived at different cutoffs, with the optimal cutoff determined using Youden's Index. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Of the initial 725 patients identified during the study period, 309 were excluded for the following reasons: 198 due to COVID-19 pneumonia, 71 due to incomplete data that hindered the calculation of the ROX index, and 40 due to transfer from other hospitals. A total of 416 patients were included in the study, with 386 (92.8%) in the non-intubation group and 30 (7.2%) in the intubation group. The mean age was statistically significantly higher in the intubation group (72.2±13.4 years) compared to the non-intubation group (54±10.6 years) ($p<0.001$, mean difference 18.3 years, 95% CI 13.2–23.3) (**Table 1**). The proportion of male patients was 70% (n=21) in the intubation group and 63% (n=243) in the non-intubation group, with no statistically significant difference ($p=0.440$).

Hypertension was observed in 50% (n=15) of the intubation group and 33.9% (n=131) of the non-intubation group, with no statistically significant difference ($p=0.076$). Diabetes mellitus was present in 33.3% (n=10) of the intubation group and 21.2% (n=82) of the non-intubation group ($p=0.124$). Coronary artery disease was statistically significantly more frequent in the intubation group, with 33.3% (n=10) compared to 14% (n=54) in the non-intubation group ($p=0.005$). Heart failure was also statistically significantly more common in the intubation group, with 40% (n=12) versus 9.3% (n=36) in the non-intubation group ($p<0.001$). Stroke was found in 20% (n=6) of intubated patients compared to 7.3% (n=28) in non-intubated patients, showing statistical significance ($p=0.014$).

Table 1. Demographics, comorbidities, and symptoms of patients

Variable	Non-intubation (n=386)	Intubation (n=30)	p	Mean difference (95% CI)
Demographics				
Age (years) (mean±SD)	54±10.6	72.2±13.4	<0.001	18.3 (13.2-23.3)
Gender (male) (count [%])	243 (63%)	21 (70%)	0.440	
Comorbidities				
Hypertension (count [%])	131 (33.9%)	15 (50%)	0.076	
Diabetes mellitus (count [%])	82 (21.2%)	10 (33.3%)	0.124	
CAD (count [%])	54 (14%)	10 (33.3%)	0.005	
Heart failure (count [%])	36 (9.3%)	12 (40%)	<0.001	
Stroke (count [%])	28 (7.3%)	6 (20%)	0.014	
Chronic kidney disease (count [%])	23 (6%)	8 (26.7%)	<0.001	
Symptoms and signs				
Cough (count [%])	304 (78.8%)	21 (70%)	0.264	
Shortness of breath (count [%])	248 (64.2%)	28 (93.3%)	0.001	
Fever (count [%])	190 (49.2%)	17 (56.7%)	0.432	
Pleuritic pain (count [%])	90 (23.3%)	12 (40%)	0.041	
Impaired consciousness (count [%])	49 (12.7%)	8 (26.7%)	0.032	

CAD: Coronary artery disease, CI: Confidence interval, SD: Standard deviation

Chronic kidney disease was statistically significantly higher in the intubation group at 26.7% (n=8) compared to 6% (n=23) in the non-intubation group (p<0.001) (**Table 1**).

Regarding symptoms, cough was present in 70% (n=21) of the intubation group and 78.8% (n=304) of the non-intubation group, with no statistically significant difference (p=0.264). Shortness of breath was statistically significantly more common in the intubation group, with 93.3% (n=28) versus 64.2% (n=248) in the non-intubation group (p=0.001). Fever was noted in 56.7% (n=17) of the intubation group and 49.2% (n=190) of the non-intubation group, with no statistically significant difference (p=0.432). Pleuritic pain was observed in 40% (n=12) of the intubation group compared to 23.3% (n=90) of the non-intubation group, reaching statistical significance (p=0.041). Impaired consciousness was statistically significantly more common in the intubation group (26.7%, n=8) compared to the non-intubation group (12.7%, n=49) (p=0.032) (**Table 1**).

In terms of clinical parameters, heart rate was statistically significantly higher in the intubation group, with a mean of 92.9±15.4 beats/min compared to 85.6±10.3 beats/min in the non-intubation group (p<0.001, mean difference 7.3 beats/min, 95% CI 3.3-11.3). Systolic blood pressure (SBP) was statistically significantly lower in the intubation group, with a mean of 101.6±19.7 mmHg compared to 122.3±15.8 mmHg in the non-intubation group (p<0.001, mean difference 20.7 mmHg, 95% CI 14.7-26.6). Diastolic blood pressure (DBP) was also statistically significantly lower in the intubation group, with a mean of 65.9±19.5 mmHg compared to 81.9±12.7 mmHg in the non-intubation group (p<0.001, mean difference 16 mmHg, 95% CI 11-20.9). The respiratory rate was higher in the intubation group, with a median of 19 breaths/min [IQR 15-27] compared to 14 breaths/min [IQR 11-19] in the non-intubation group (p<0.001). Peripheral oxygen saturation (SPO_2) was statistically significantly lower in the intubation group, with a median of 83.5% [IQR 77-88.3] compared to 92% [IQR 90-94] in the non-intubation group (p<0.001). The fraction of inspired oxygen (FiO_2) was higher in the intubation group, with a median of 35% [IQR 30–43.8] compared to 25% [IQR 25–29] in the non-intubation group (p<0.001). The ROX index was statistically significantly lower in the intubation group, with a mean of 14.4±4.5 compared to 23.8±5.4 in the non-intubation group (p<0.001, mean difference 9.4, 95% CI 7.4-11.4). The pneumonia severity index (PSI) was statistically significantly higher in the intubation group (115 [IQR 97-135]) compared to the non-intubation group (67 [IQR 57.8-79]) (p<0.001). Severe pneumonia was significantly more frequent in the intubation group (56.7%, n=17) than in the non-intubation group (10.6%, n=41) (p<0.001) (**Table 2**).

In laboratory parameters, the mean white blood cell count was statistically significantly higher in the intubation group (15105±2014 cells/μL) compared to the non-intubation group (13972±2041 cells/μL) (p=0.004, mean difference 1133 cells/μL, 95% CI 356-1909). Creatinine levels were higher in the intubation group, with a median of 2.35 mg/dl [IQR 1.48-3.83] compared to 0.9 mg/dl [IQR 0.5–1.3] in the non-intubation group (p<0.001). Lactate levels were also statistically significantly higher in the intubation group, with a median of 3.2 mmol/L [IQR 2.38-4.23] compared to 1.9 mmol/L [IQR 1.6-2.3] in the non-intubation group (p<0.001). The partial pressure of oxygen in arterial blood (PaO_2) was statistically significantly lower in the intubation group, with a median of 40 mmHg [IQR 35-50] compared to 55 mmHg [IQR 52-59] in the non-intubation group (p<0.001) (**Table 2**).

The predictive value of the ROX index for intubation was evaluated with an area under the ROC curve (AUROC) of 0.908 (95% CI 0.877–0.934), with a statistically significant p-value of <0.001 (**Figure 1**). The Youden Index J was 0.722, and the optimal criterion for intubation was ≤18.7. Among patients with severe pneumonia, the ROX index demonstrated an AUROC of 0.831 (95% CI 0.709-0.916), with a statistically significant p-value of <0.001, and an optimal criterion of ≤15.1 (Youden Index J=0.756) (**Table 3, Figure 2**).

Table 2. Clinical parameters and laboratory results

Variable	Non-intubation (n=386)	Intubation (n=30)	p	Mean difference (95% CI)
Vital signs				
Heart rate (beats/min) (mean±SD)	85.6±10.3	92.9±15.4	<0.001	7.3 (3.3-11.3)
SBP (mmHg) (mean±SD)	122.3±15.8	101.6±19.7	<0.001	20.7 (14.7-26.6)
DBP (mmHg) (mean±SD)	81.9±12.7	65.9±19.5	<0.001	16 (11-20.9)
Respiratory rate (breaths/min) (median [IQR])	14 [11-19]	19 [15-27]	<0.001	
SPO_2 (%) (median [IQR])	92 [90-94]	83.5 [77-88.3]	<0.001	
FiO_2 (%) (median [IQR])	25 [25-29]	35 [30-43.8]	<0.001	
ROX (mean±SD)	23.8±5.4	14.4±4.5	<0.001	9.4 (7.4-11.4)
Laboratory parameters				
White blood cell (10^3/μL) (mean±SD)	13972±2041	15105±2014	0.004	1133 (356-1909)
Creatinine (mg/dl) (median [IQR])	0.9 [0.5-1.3]	2.35 [1.48-3.83]	<0.001	
Lactate (mmol/L) (median [IQR])	1.9 [1.6-2.3]	3.2 [2.38-4.23]	<0.001	
PaO_2 (mmHg) (median [IQR])	55 [52-59]	40 [35-50]	<0.001	
PSI (median [IQR])	67 [57.8-79]	115 [97-135]	<0.001	
Severe pneumonia (count [%])	41 [10.6%]	17 [56.7%]	<0.001	

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, SPO_2: Peripheral oxygen saturation, FiO_2: Fraction of inspired oxygen, ROX: Respiratory rate-oxygenation index, PaO_2: Partial pressure of oxygen in arterial blood, PSI: Pneumonia severity index, SD: Standard deviation

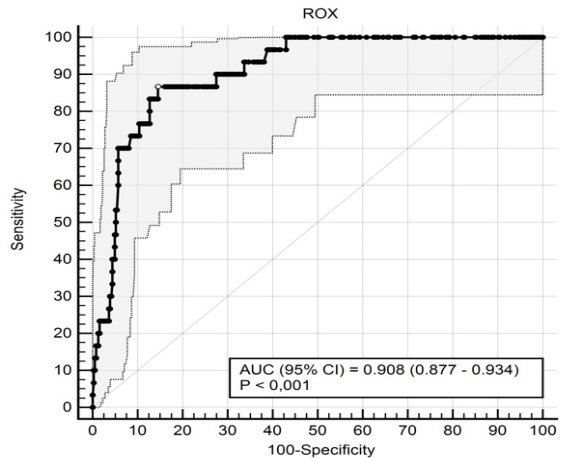

Figure 1. Receiver operating characteristic curve of the respiratory rate-oxygenation index for predicting intubation

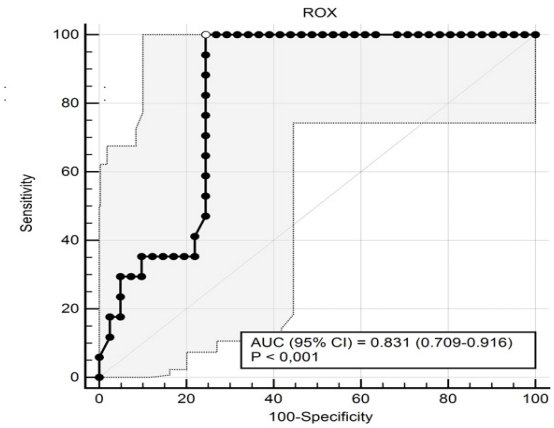

Figure 2. Receiver operating characteristic curve of the respiratory rate-oxygenation index for predicting intubation among severe pneumonia subset

DISCUSSION

The most important finding of our study is that the ROX index can be a useful tool in predicting the need for invasive mechanical ventilation in patients hospitalized with CAP. Our results demonstrate that the ROX index is a reliable tool for identifying patients at high risk for invasive mechanical ventilation, allowing clinicians to prioritize early interventions. Its consistent performance across the entire study population underscores its potential role in routine CAP management. In patients with severe pneumonia, the ROX index proved particularly useful for distinguishing those with significant respiratory effort who may benefit from advanced respiratory support. This finding highlights the practical applicability of the ROX index in guiding clinical decisions, especially in critically ill populations where timely and accurate risk stratification can significantly impact outcomes. Moreover, its simplicity and non-invasive nature make it an ideal tool for resource-limited settings or situations requiring rapid decision-making.

CAP is a serious infectious disease with high morbidity and mortality rates worldwide. This disease, which can progress more severely in elderly patients and those with comorbidities, often requires ICU admission and invasive mechanical ventilation. CAP involves inflammatory processes that severely impair lung function, leading to respiratory failure and increasing the risk of multiple organ failure.[12-14] Patients requiring intensive care are generally in the advanced stages of respiratory failure, making the early identification of these patients and the prediction of intubation needs crucial to reducing mortality. Prognostic tools like the ROX index play a significant role in predicting the clinical course of these

Table 3. Diagnostic performance of respiratory rate-oxygenation index for predicting intubation

Cohort	AUROC (95% CI)	p	Youden index J	Criterion
All patients	0.908 (0.877-0.934)	<0.001	0.722	≤18.7
Severe pneumonia subset	0.831 (0.709-0.916)	<0.001	0.756	≤15.1

AUROC: Receiver operating characteristic curve

patients and help optimize management, especially in settings with limited ICU capacity.[15]

The importance of the ROX index in clinical practice has become even more evident in areas with limited ICU capacity and during large-scale health crises such as pandemics. During the COVID-19 pandemic, when ICU admissions and the need for intubation dramatically increased, the ROX index's ability to predict ventilation needs was utilized as a critical tool for optimizing the use of healthcare resources.[16,17] It has been shown that the ROX index can contribute to clinical decision-making by predicting the need for intubation in situations where ICU beds are limited or when rapid decision-making is required during health crises.[18] In such cases, objective measures like the ROX index can guide healthcare providers to ensure timely and appropriate interventions.

In this study, we found that a lower ROX index was significantly associated with the need for IMV in patients with CAP. This highlights the effectiveness of the ROX index as a predictor for IMV, allowing for early identification of high-risk patients. Similarly, Reyes et al.[19] demonstrated that the ROX index was a reliable tool for predicting IMV in CAP patients. Additionally, Suliman et al.[20] reported that the ROX index successfully predicted the risk of intubation in COVID-19 pneumonia patients, further supporting the utility of the ROX index in respiratory failure scenarios. These studies have demonstrated the utility of the ROX index in various respiratory conditions, our findings provide additional evidence of its specific applicability in CAP and severe pneumonia patients, emphasizing its potential for guiding respiratory support strategies. However, while the ROX index offers considerable utility in predicting the need for invasive mechanical ventilation, its benefits are most pronounced in resource-limited settings or for early risk stratification. In contrast, its use as a routine ICU triage tool for pneumonia requires further validation in diverse clinical contexts.

Limitations

This study has several limitations. First, as a single-center retrospective study, the generalizability of the results may be limited to similar healthcare settings. Additionally, the study relied on medical record data, which could be subject to inaccuracies or missing information. Another limitation is the exclusion of patients who were transferred from other hospitals or those with incomplete data, which may have influenced the study's outcomes. Moreover, the study did not account for other prognostic indices or biomarkers that could potentially improve the prediction of invasive mechanical ventilation in CAP. Additionally the exclusion of patients from the COVID-19 pandemic period limits the generalizability of our findings to this specific context, as pneumonia management strategies during the pandemic differed significantly.

CONCLUSION

This study highlights the potential of the ROX index as a valuable tool for predicting the need for invasive mechanical ventilation in patients with community-acquired pneumonia. By enabling early identification of high-risk patients, the ROX index facilitates timely and targeted interventions, particularly in critically ill populations such as those with severe pneumonia. Its simplicity, non-invasive nature, and applicability in resource-limited settings make it a practical option for clinical use. However, further multicenter studies are warranted to validate its utility across diverse healthcare settings and refine its application in routine practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the İstanbul Yeni Yüzyıl University Clinical Researches Ethics Committee (Date: 04.11.2024, Decision No: 2024/11-1356).

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

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Influence of *Enterococcus faecium*, a probiotic component, on ion channels in colon cancer

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ABSTRACT

Aims: This study aimed to investigate the effect of probiotic bacterium *Enterococcus faecium (E. faecium)* on the gene expression of ion channels in colon cancer cells.

Methods: The cytotoxic effect on SW480 colon cancer cell line was analyzed by MTT cell proliferation test using *E. faecium* bacterial cell culture free supernatants. The effect of *E. faecium* on ion channel genes in SW480 cells was determined by qRT-PCR analysis. STRING analysis was used to reveal protein-protein interactions of ion channel proteins. Bioinformatic analysis of healthy and colon cancer patient data on ion channels was revealed with GEPIA platform.

Results: The SW480 cell line's viability was enhanced by *E. fecieum* bacterial cell culture free supernatants dosages of 0.5 and 1.09 mg/ml, but it dramatically declined between 2.187 and 17.5 mg/ml doses, according the MTT study. Analysis of gene expression revealed that the TRPV2 and TRPM8 genes had significantly increased. The examined ion channel proteins were discovered to be substantially linked to one another based on STRING analysis. The TRPM2 gene we looked at revealed a notable rise in colon cancer patients based on data from both healthy and colon cancer patients on the GEPIA platform.

Conclusion: *E. faecium* has been shown to have many beneficial effects on health. Our study has shown that it also has an effect on ion channels in cancer cells and that ion channels are of great importance for cell survival and death.

Keywords: Colon cancer, ion channels, microbiota, *E. faecium*

INTRODUCTION

Colorectal cancer (CRC) is the second most frequent disease in women after breast cancer and the third most common cancer in males after prostate cancer.[1] The aging of the population and the rise in known risk factors such obesity, sedentary lifestyles, smoking, and chronic inflammatory diseases are contributing to an overall increase in the incidence and prevalence of colorectal cancer.[2,3]

Reactive oxygen species (ROS), reactive nitrogen species (RNS), and other electrophiles are examples of oxidative stress mediators that TRP channels react well to. Hydrogen peroxide (H_2O_2) activates the transient receptor potential melastatin-2 (TRPM2) channel, the first identified ROS-sensitive channel that mediates a variety of cellular responses, such as cell death and chemokine synthesis.[4] TRPM7, also known as transient receptor potential melastatin 7, functions as an ion-channel protein for the transportation of calcium and magnesium.[5] The TRPM7 channel controls cell survival and death physiologically by maintaining calcium and magnesium balance. When cancer cells exhibit malignant characteristics, TRPM7 expression is elevated in many malignancies, and its absence inhibits the proliferation of cancer cells.[6] TRPM8 is often expressed at low levels in epithelial cells, however it is expressed at significantly higher levels in tumor cells.[7] While TRPM8 is significantly downregulated in androgen-independent prostate cancer metastases, it is highly upregulated in a number of malignancies, including those of the prostate, breast, pancreatic, and skin.[8,9]

The genus *Enterococcus*, part of the family Enterococcaceae, comprises gram-positive, facultatively anaerobic bacteria commonly found in the gastrointestinal tracts of humans and animals. These resilient organisms can endure extreme environments, including high salt concentrations, varying pH levels, and temperatures ranging from 10°C to 45°C.[10] This adaptability not only underscores their ecological significance but also their potential applications in various fields, including food microbiology and probiotics. Among the species within this genus, *Enterococcus faecium (E. faecium)* is particularly recognized for its probiotic properties that contribute to gut health. As a member of the lactic acid bacteria (LAB) group, *E. faecium* thrives in the gastrointestinal environment,

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enhancing its effectiveness as a probiotic. It plays essential roles in supporting gut barrier integrity, modulating the immune response, and producing bacteriocins that inhibit pathogenic bacteria. Additionally, certain strains of *E. faecium* have demonstrated cholesterol-lowering properties and antimicrobial activity, further emphasizing its importance in maintaining gut microbiome balance and overall health.[11] These characteristics make *E. faecium* a valuable candidate for probiotic formulations and health intervention.

Our study aimed to investigate the relationship between cancer-related ion channels and *E. faecium*, exploring how this probiotic may influence cancer pathways and potentially contribute to therapeutic strategies. We seek to understand the mechanisms by which *E. faecium* interacts with these ion channels and its implications for cancer treatment outcomes.

METHODS

Ethics

This is cell line culture study. This study was exempt from ethical approval because no direct human or animal samples were used.

Cell Line Culture

The colon cancer cell line SW480 (ATCC® CCL-228TM) was cultured in high glucose Dulbecco's modified eagle medium (DMEM) supplemented with 10% fetal bovine serum, 50 µg/ml L-glutamine, and 1% penicillin-streptomycin. The culture was kept growing until it reached an adequate amount in an incubator with 5% CO_2 and 95% humidity.

Bacterial Cell Culture And Cell-Free Culture Supernatant (CFCS) Preparing

The *E. faecium* strain used in this study was isolated from locally sourced kefir. To confirm its identity, we performed 16S rRNA gene amplification and sequencing (**Supp. Data 1**), which verified that the strain belongs to *E. faecium*. *E. faecium* was inoculated in De Man, Rogosa, and Sharpe (MRS) broth and incubated at 37°C overnight. Following incubation, the culture was centrifuged at 10.000 rpm for 10 minutes to pellet the cells. The supernatant was carefully collected using a sterile syringe with a needle and then filtered through a sterile polyethersulfone (PES) membrane filter with a pore size of 0.45 µm. The freshly prepared cell-free culture supernatant (CFCS) was checked for contamination, while the remaining portions were stored at -20°C for further studies.

Supp. Data 1. The primers used to confirm 16S rRNA gene amplification and sequencing

	Primer sequences	Product lenght
Forward primer (008F)	5' -AGAGTTTGATCMTGGC-3'	1387 bp
Reverse primer (1387r)	5'-GGGCGGWGTGTACAAGRC-3'	

MTT Assay for Cell Viability

The viability of SW480 cells was assessed using the MTT assay. Briefly, SW480 cells were seeded at a density of 5.000 cells per well in a 96-well plate and allowed to adhere overnight. Following treatment with different doses of CFCS, the cells were incubated at 37°C with 5% CO_2 for 24 hours. After the treatment, 10 µL of MTT solution (5 mg/ml in PBS) was added to each well, and the plate was incubated for an additional 4 hours at 37°C. Following the incubation, the medium was carefully removed, and 100 µL of DMSO was added to each well to dissolve the formazan crystals. The absorbance of the solution was measured at 570 nm using a microplate reader. Cell viability was expressed as a percentage relative to untreated control cells. Each experiment was conducted in triplicate, and results were presented as mean±standard deviation (SD).

RNA Isolaton and cDNA Syntesis

Following the manufacturer's directions, RNA was isolated from cancer cells that were suitably removed at the conclusion of the intended times and applications in the indirect culture system (Invitrogen™ TRIzol™ Reagent, USA). Following the manufacturer's instructions, cDNA synthesis was carried out from quality-controlled RNA samples using a kit (Bio-Rad iScript cDNA Synthesis, USA).

Real-Time qPCR Analysis

Target gene primer designs were created with primer quest (http://eu.idtdna.com/home/home.aspx). Using cDNAs containing target gene primers, RT-qPCR analysis was performed using the BioRAD CFX Connect tool to determine variations in gene expression of SW480 (**Table**).

Table. Used primers in this study

Gene	Primers	Amplicon size (bp)
TRPM2	F:5-TCGGACCCAACCACACGCTGTA-3 R:5-CGTCATTCTGGTCCTGGAAGTG-3	339
TRPM7	5-CTTATGAAGAGGCAGGTCATGG-3 5-CATCTTGTCTGAAGGACTG-3	214
TRPM8	F:5-TGAACTCTTCTCCAACCACTTC-3 R:5-CGTGAGGAGGGCATCATTATAG-3	85
TRPV2	F:5-GACCCTTGACATCTCCATCTG-3 R:5-CATCTTCTTGGCCTCCATCTAA-3	127
GAPDH	F:5-TGAACGGGAAGCTCACTGG-3 R:5-TCCACCACCCTGTTGCTGTA-3	307

RT-qPCR was performed with BrightGreen qPCR MasterMixR, using 0.5 pmol of each primer, which was designed with the IDT PrimerQuest™ Tool. The qPCR protocol began with an initial denaturation at 95°C for 10 minutes, followed by 40 cycles of 95°C for 15 seconds and 60°C for 60 seconds. The relative expression levels of the target genes were calculated and GAPDH served as the reference gene for normalization.

Protein-Protein Interaction Network Analysis

To better illustrate the functional link among transient receptor potential cation channel subfamily members, protein-protein interaction network of target genes were constructed using STRING (https://string-db.org/) database. This database utilizes textmining, databases, coexpression, experimentally verified and neigborhood interactions to build an interaction network among multiple proteins. The K means algorithm was used for clustering of the constructed network to identify functional modules. K-means algorithm is a widely-applied clustering approach for anomaly-based

intrusion detection. It attemps to classify a provided set of data into k (a previously defined number) categories.[12,13]

Gene Expression Analysis in Colon Adenocarcinoma and Normal Tissues

The Gene Expression Profiling Interactive Analysis (GEPIA) bioinformatics tool (http://gepia2.cancer-pku.cn/) is utilized to analyze differences between gene expression levels of tumor and normal samples.[14] The transcript levels in tumor tissues are retrieved from The Cancer Genome Atlas (TCGA) dataset while the expression levels in healthy samples are sourced from the Genotype Tissue Expression (GTEx) project. The boxplot diagrams are automatically produced via GEPIA platform. The cut-off values for p-value and log2 fold change are set to 0.05 and 1, respectively.

Statistical Analysis

The Ct values of the genes of investigation in the study were normalized in relation to the reference gene using the $2^{-\Delta\Delta Ct}$ method. The "Multiple t test" was used in GraphPad®Prism version 5 to evaluate the gene expression levels of the groups. If $p<0.05$, the statistics were considered significant.

RESULTS

E. faecium CFCS Reduced the Viability of Colon Cancer Cells

The Figure 1 demonstrates that *E. faecium* CFCS significantly reduces the viability of colon cancer cells across various doses. The control group establishes a baseline viability rate, while the lowest dose (0.5 mg/ml) shows a higher viability rate, indicating a potential proliferative effect at lower concentrations. However, as the lysate dose increases to 2.187, 4.375, 8.75, and 17.5 mg/mL, there is a marked decline in cell viability, with statistical significance represented by asterisks. This trend underscores the effectiveness of higher concentrations of *E. faecium* CFCS in inhibiting the growth of colon cancer cells, suggesting its potential role as a therapeutic agent in cancer management.

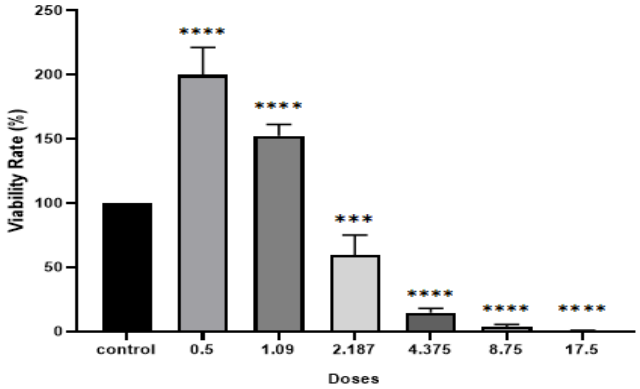

Figure 1. The *E. faecium* cell-free culture supernatant significantly reduces the viability of colon cancer cells

E. faecium Lysates Altered the Expression of Ion Channel-Related Genes in Colon Cancer Cells

The Figure 2 illustrates the expression levels of various TRP channels, highlighting significant differences in fold change between the CFCS-treatment and control groups. Specifically, TRPV2 and TRPM8 exhibited statistically significant increases in expression, while TRPM2 and TRPM7 showed no significant changes (ns). The most notable change was observed in TRPM8, where expression increased over 15-fold, suggesting a potential regulatory role in the response to CFCS-treatment. These findings emphasize the differential modulation of TRP channels by the treatment, pointing to specific targets for further investigation in the context of therapeutic strategies and cellular mechanisms involved in gut health and cancer biology.

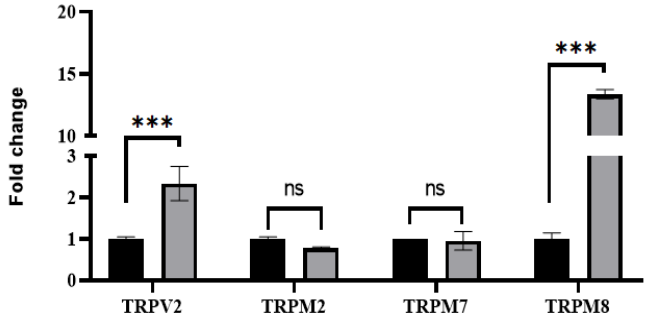

Figure 2. The *E. faecium* cell-free culture supernatant-treatment change the genes expression of transient receptor potential channels

Significant Connections between Ion Channel Proteins were Revealed using STRING Analysis

The functional impacts of target genes were also presented at system levels analysis by constructing protein-protein interaction (PPI) network. The constructed network consisted of 4 nodes (transient receptor potential cation channel subfamily members) and 4 edges, where the strength of interaction score was adjusted to greater than 0.4 (PPI enrichment p-value was 5.49E-09). Performed STRING PPI network analysis revealed significant functional link and close association among investigated genes. The black colored-line between all investigated extrinsic pathway genes confirmed the functional link among them (Figure 3).

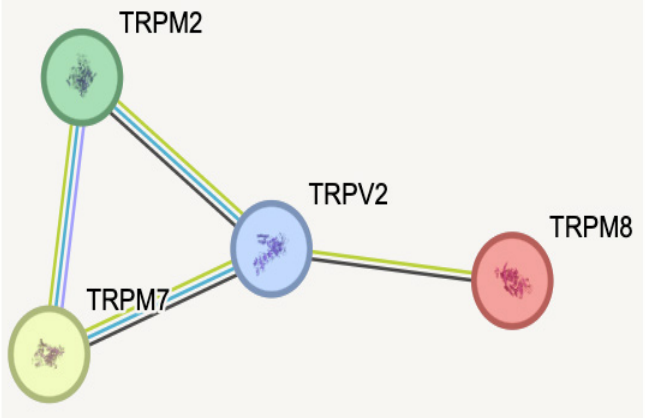

Figure 3. Protein-protein interaction network of TRPM2, TRPM7, TRPM8 and TRPV2 is drawn using STRING v12. The black lines denote confirmed co-expression thereby functional link among proteins while green-colored lines show the interactions based on textmining. Dark-blue lines predict interaction based on gene co-occurance whereas light-blue colored lines indicate protein homology. Moreover, cyan and purple-colored lines show known interactions from curated databases and experimentally-determined results, respectively. The calculated interaction score set on greater than 0.4.

GEPIA Data Showed that Patients with Colon Cancer Had Considerably Higher Levels of TRPM2 Expression

Changes in the transcript levels of genes are highly encountered between normal and tumor tissues. This fact urged us to check the differential expression profiles of target genes between colon adenocarcinoma (COAD) and normal tissues. The transcript levels of transient receptor potential cation channel subfamily members, namely TRPM7, TRPM8 and TRPV2 did not show any significant differences in COAD samples as compared to healthy colon tissues (**Figure 4B-D**, p-values>0.05). We observed a significantly higher expression of TRPM2 (**Figure 4A**, p-value<0.05) in colon cancer tissues than normal samples.

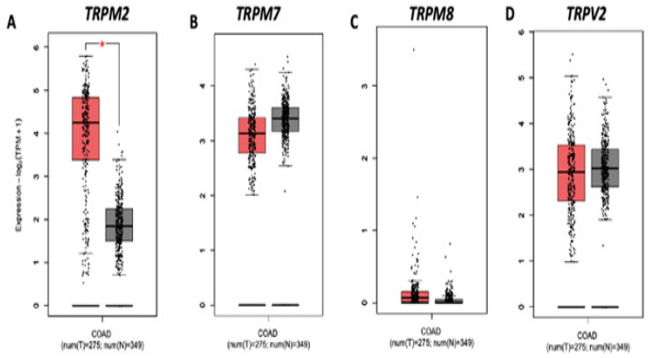

Figure 4. Expression analysis of transient receptor potential cation channel subfamily members performed via GEPIA2 in colon adenocarcinoma (COAD) samples (red, T=275) and normal tissue (grey, n=349) from TCGA and GTEx datasets, respectively. The (log2 (TPM+1)) transformed gene expression data are used in graphical representations for (**A**) TRPM2, (**B**) TRPM7, (**C**) TRPM8, and (**D**) TRPV2. p-values less than 0.05 are considered as statistically significant and represented with asterisk (*).

DISCUSSION

Regulation of ion channels has an effective role in cell survival and death. Numerous recent investigations have demonstrated that different kinds of cancer exhibit aberrant TRP channel expression. The effects of TRP channel subtypes on a wide variety of cancer cells, as well as the connection between TRP channel expression and surveillance in these malignancies, have been eloquently shown in a number of studies.[15] TRP channels have also been shown to play a significant part in the metastatic pathways and to be able to react to the physicochemical signals of metastatic cells in cancer cells.[16] It has been observed that tumor and immune system cells' migration and cell death are significantly impacted by TRPM2 channels.[17] Through bacterial peptide and cytokine activation, cell migration, and oxidative stress, the TRPM2 protein has been demonstrated to directly cause cell death.[18] It has been documented that adenocarcinomas of the head and neck, bladder, liver, and lung, especially breast cancer, exhibit heightened expression of TRPM2 channels.[19] In our study, *E. faecium* decreased the gene expression of TRPM2 ion channel in colon cancer cells, albeit insignificantly. TRPM2, which increased with tumor progression, was decreased when treated with *E. faecium*. As cancer cells exhibit malignant tendencies, TRPM7 expression is elevated in many malignancies, and its absence inhibits the proliferation of cancer cells.[20] In addition to having a detrimental impact on the prognosis of patients and the progressive tumor behavior of gastric cancer, overexpression of TRPM7 has been linked to a lower survival rate in breast cancer.[20,21] According to similar studies, TRPM7 expression was found to decrease in colon cancer cells treated with *E. faecium*, but it was not significant.

TRPM8 is now seen as a prospective target for cancer, especially prostate cancer, because it regulates cell proliferation and apoptosis.[22] Colorectal cancer tissues are among the primary tumors where TRPM8 mRNA has been found.[7] In line with the literature, TRPM8 expression was increased in colon cancer cells in our study, but *E. faecium* application did not change this increase. Therefore, it was determined that TRPM8, which was expected to be suppressed, was not suppressed.

TRPV2 activation causes apoptosis, lowers cell viability, and raises intracellular calcium levels.[23] Mizuno et al.[24] found that the murine MBT2 BC cell line had higher levels of TRPV2 expression than normal mouse urothelial cells; TRPV2 suppression in MBT-2 cells using RNA interference boosted cell proliferation, while TRPV2 activators had the reverse effect. Alptekin et al.[25] showed a strong correlation between TRPV2 overexpression and GBM patient survival, indicating for the first time that TRP channels, particularly TRPV2, play a role in the progression and survival of GBM patients. Studies have shown that overexpression of TRPV2 induces apoptosis. Our study has shown that *E. faecium* application significantly increases TRPV2 expression. Therefore, *E. faecium* has an anticancer effect in colon cancer cells.

CONCLUSION

E. faecium has many beneficial effects in the intestinal system as a probiotic. It plays a major role in regulating the intestinal system and strengthening the immune system. In our study, the cellular effect of *E. faecium* via ion channels was examined. According to the results obtained, results compatible with the literature were obtained in terms of TRPV2, TRPM2 and TRPM7.

However, the effect of TRPM8 observed following *E. faecium* application did not align with the anticipated outcomes. Consequently, further investigations are required to elucidate this relationship. Future studies should focus on exploring the interactions of additional ion channels and their associated cellular pathways to gain deeper insights into the underlying mechanisms.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was exempt from ethical approval because no direct human or animal samples were used.

Informed Consent

Written informed consent is not required in this study as no direct human or animal samples were used.

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 study and that they have approved the final version.

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Assessment of the relationship between vascular diseases and exposure to toxic metals

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ABSTRACT

Aims: Understanding the factors in the etiology of vascular diseases is crucial for prevention. This study assesses the relationship between toxic metal exposure and vascular disease development.

Methods: Blood samples from 41 healthy volunteers and 48 cardiovascular disease patients were analyzed using inductively coupled plasma mass spectrometry (ICP-MS). The participants' health data were obtained from hospital records.

Results: ICP-MS results showed higher levels of As (5.97 µg/L), Cd (0.44 µg/L), Hg (0.48 µg/L), Pb (37.10 µg/L), Se (75.76 µg/L), Cu (1611.99 µg/L), Mn (14.55 µg/L), Co (0.14 µg/L), Mo (1.93 µg/L), and Ni (0.25 µg/L) in the experimental group. Conversely, Zn (557.0 µg/L), Cr (4.12 µg/L), and Sb (2.35 µg/L) levels were lower. Triglyceride (135.99 mg/dl), folate (8.77 ng/dl), and T3 (1.30 ng/dl) were higher, while HDL (44.13 mg/dl) was lower in the experimental group.

Conclusion: These findings suggest a potential relationship between higher exposure to certain toxic metals and the development of vascular diseases. The higher concentrations of toxic metals in the blood of patients with vascular diseases underline the need for further research to confirm these associations and explore potential mechanisms.

Keywords: Toxic metals, vascular diseases, ICP-MS, cardiovascular health, environmental exposure

INTRODUCTION

Vascular system pathologies, besides affecting their own tissue, also impact the organs it supplies blood to and overall health. Cardiovascular disease is a leading cause of death worldwide.[1,2]

Deaths due to non-communicable diseases were 38 million in 2012, and this number is estimated to rise to 52 million by 2030. Among these, cardiovascular diseases rank first, accounting for 37%.[3] The Lancet Commission on Investing in Health states that every country could reduce premature deaths from major health issues, including cardiovascular diseases, by approximately 50% by 2050 through strategic investments in prevention and treatment.[4] According to the 2019 data from the Turkish Statistical Institute, cardiovascular diseases rank first among causes of death, accounting for 36.8%. They are followed by tumors at 18.4% and respiratory system diseases at 12.9%. Of the deaths caused by cardiovascular diseases, 39.1% are due to ischemic heart disease, 22.2% are due to cerebrovascular diseases, and 25.7% are due to other heart diseases.[3] In the United States, between 8 and 12 million people are affected by peripheral arterial disease (PAD), with an overall prevalence ranging from 3% to 10%. This prevalence rises to nearly 50% in individuals over the age of 85. In Europe, some studies, particularly from the northern regions, have reported a prevalence of up to 17.8%.[5] The presence of PAD is itself an indicator of a poor prognosis, and the survival rates of these patients are worse than many cancer types. In men with advanced PAD, the five-year mortality rate is worse than prostate cancer and similar to colon cancer. Therefore, patients diagnosed with PAD should be effectively treated to address risk factors.[6] Even more importantly, primary prevention by identifying risk factors and preventing the development of the disease is crucial. Risk factors include unhealthy diet, environmental factors, tobacco use, inadequate physical activity, hypertension, obesity, diabetes mellitus, dyslipidemia, as well as gender, age, and family history, among others. The connection between nutrition and lifestyle as preventable risk factors has been established through studies conducted to date.[7]

In recent times, soil pollution, which has increased due to industrialization and urbanization, has reached levels that can pose a threat to living organisms. With the rising environmental and soil pollution, people's exposure to toxic

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metals through air, water, and food has increased. In addition to these factors, the likelihood of exposure to toxic metals is also increasing for individuals working in various industrial sectors. Among these toxic metals, lead (Pb), cadmium (Cd), and arsenic (As) exposure play a significant role. Following exposure to these toxic metals, cell damage and various health problems can occur due to oxidative stress-induced inflammation.[8]

Increasing studies suggest that the harmful effects of metals may largely arise from their specific effects on the vascular system. The functioning of the vascular system involves complex interactions between vascular endothelium, vascular smooth muscle, the immune system, the nervous system, and even the local chemical/metabolic environment of individual organs. Toxic metals contribute to the development of various pathological diseases such as edema, atherosclerosis, and hypertension by targeting the vascular system. Additionally, the vascular effects of toxic metals also contribute to the formation of specific organ damages.[9,10]

Exposure to many metals can lead to bleeding and edema in tissues such as the lungs, and the reason for this is the disruption of endothelial barrier integrity due to exposure to toxic metals. Furthermore, studies have demonstrated that exposure to high concentrations of cadmium and arsenic inhibits angiogenesis.[10-13] Epidemiological studies have shown that lead and cadmium may play a role in the development of hypertension.[14]

This study aimed to determine the relationship between toxic metals, whose adverse effects on the cardiovascular system have been demonstrated in various studies, and vascular diseases.[8-12,15]

METHODS

Research Population

The study population was comprised of individuals attending the Cardiovascular Surgery Clinic (for the patient group) and Family Medicine Clinic (for the control group) at the Yozgat Bozok University Research Hospital. Permission for the study was obtained from the Clinical Researches Ethics Committee of Bozok University (Date: 25.08.2021, Decision No: 2017-KAEK-189-2021.08.25_01). All procedures were carried out in accordance with the ethical rules and the principles.

Research Methodology

The study was completed with the participation of 89 individuals aged 18 and over who applied to the cardiovascular surgery (for the patient group) and family medicine (for the control group) clinics, met the acceptance criteria for the study and agreed to participate in the research. Individuals who refused to fill out the consent form, those who were not in the specified age group, and those in the control group who had chronic and vascular diseases were not included in the study. In addition, hospital records were utilized to obtain information about the health data of the individuals included in the study. The collected blood samples were stored at -20°C until the planned sample size was reached.

Preliminary Preparation of Samples

The pre-preparation process of the samples was conducted with the optimization of the method developed by Türksoy et al.[16] for blood. All pre-preparation processes of the study were carried out in the Bozok University Faculty of Medicine Research Laboratory. One milliliter of blood samples was taken, and then, 5 ml of suprapure nitric acid (HNO_3), 2 ml of hydrogen peroxide (H_2O_2), and 3 ml of distilled water were added for the dissolution process. The dissolved samples were filtered and transferred in 15 ml polypropylene tubes for analysis by inductively coupled plasma mass spectrometry (ICP-MS). The samples were stored at 4°C in 15 ml polypropylene tubes until they were delivered to the device.[16]

Determination of Toxic Metal Levels by ICP-MS

The ICP-MS system was utilized to determine the levels of arsenic (As), copper (Cu), zinc (Zn), manganese (Mn), selenium (Se), chromium (Cr), mercury (Hg), lead (Pb), cadmium (Cd), tin (Sn), cobalt (Co), aluminum (Al), molybdenum (Mo), antimony (Sb), and nickel (Ni) in dissolved blood samples. The method developed by Türksoy et al.[16] was employed for this purpose. Calibration curves with a total of 11 points were constructed for each heavy metal, and the results were evaluated based on these calibration curves.

Statistical Analysis

The statistical analysis of the study was conducted using the SPSS 25.0 (Statistical Package for the Social Sciences) software package. Descriptive statistics, including mean, standard deviation, and minimum-maximum values, were employed to present an overview of the data. The Kolmogorov-Smirnov test was utilized to assess the normal distribution of the data. The Mann-Whitney U test was employed to evaluate data that did not follow a normal distribution.

RESULTS

Our study included the participation of 41 individuals in the control group and 48 individuals in the experimental group. In the control group, 15 participants were male, and 26 were female. In the experimental group, there were 25 male participants and 23 female participants. The potential toxic metal levels in the participants' blood were determined through ICP-MS analysis, and the results revealed statistically significant differences in the levels of most of these metals between the control and experimental groups. The average levels of As (3.86 µg/L), Cu (932.4 µg/L), Mn (5.98 µg/L), Se (60.07 µg/L), Hg (0.04 µg/L), Pb (16 µg/L), Cd (0.20 µg/L), Co (0.05 µg/L), Mo (0.36 µg/L), and Ni (0.02 µg/L) in the blood of the control group were significantly lower than those in the experimental group ($p<0.05$). Additionally, the levels of Zn (1589.1 µg/L), Cr (15.42 µg/L), and Sb (2.45 µg/L) in the control group were significantly higher than those in the experimental group ($p<0.05$). There was no significant difference between the control and experimental groups in terms of Sn (1.68 µg/L) and Al (3.06 µg/L) levels ($p>0.05$). **Table 1** presents the toxic metal levels detected in the control and experimental groups.

In our study, the blood biochemical data of the control and experimental groups were also evaluated. The experimental

Table 1. Toxic metal levels

	Control group				Experimental group				† Normal limits in blood (µg/L)	p
	Mean	Std. deviation	Min.	Max.	Mean	Std. deviation	Min.	Max.		
As (µg/L)	3.86	1.39	1.30	9.71	5.97	1.36	2.90	9.84	<12	**0.001***
Cu (µg/L)	932.40	263.39	600.99	1611.99	1485.44	466.53	924.25	3120.77	850-1900	**0.001***
Zn (µg/L)	1589.10	456.07	1070.32	2802.13	557.00	317.21	218.87	1880.19	660-1100	**0.001***
Mn (µg/L)	5.98	2.94	2.18	14.55	17.77	4.02	11.10	35.35	4.7-18.3	**0.001***
Se (µg/L)	60.07	12.46	34.16	85.67	75.76	16.90	51.19	128.98	70-150	**0.001***
Cr (µg/L)	15.42	3.37	5.25	19.00	4.12	1.53	2.89	10.00	0.7-28	**0.001***
Hg (µg/L)	0.04	0.06	0.01	0.30	0.48	0.32	0.19	1.76	<10	**0.001***
Pb (µg/L)	16.00	6.25	2.15	28.07	37.10	27.63	8.03	92.20	<100	**0.001***
Cd (µg/L)	0.20	0.06	0.10	0.42	0.44	0.27	0.29	1.59	<5	**0.001***
Sn (µg/L)	1.68	0.79	0.65	3.83	1.86	0.78	0.58	3.38	<5	0.228
Co (µg/L)	0.05	0.50	0.01	0.26	0.14	0.06	0.08	0.42	<1	**0.001***
Al (µg/L)	3.06	1.86	0.12	13.33	3.75	4.84	0.10	25.09	<6	0.38
Mo (µg/L)	0.36	0.33	0.02	1.53	1.93	3.43	0.02	24.00	0.3-2	0.001*
Sb (µg/L)	2.45	1.54	0.67	9.32	2.35	0.23	1.72	2.71	<10	**0.001***
Ni (µg/L)	0.02	0.01	0.01	0.08	0.25	0.12	0.02	0.71	<10	0.001*

* p<0,05, † The American Conference of Governmental Industrial Hygienists (ACGIH)
Note: The table displays the mean, standard deviation, minimum, and maximum values for each toxic metal in the control and experimental groups. The p-values indicate the statistical significance of the differences between the groups.
Abbreviations: As: Arsenic, Cu: Copper, Zn: Zinc, Mn: Manganese, Se: Selenium, Cr: Chromium, Hg: Mercury, Pb: Lead, Cd: Cadmium, SN: Tin, Co: Cobalt, Al: Aluminum, Mo: Molybdenum, Sb: Antimony, Ni: Nickel

group showed higher mean values for triglyceride (135.99 mg/dl), folic acid (8.77 ng/dl), BUN (13.32 mg/dl), serum creatinine (0.87 mg/dl), and T3 (1.30 ng/dl) compared to the control group (p<0.05). The mean value of HDL (44.13 mg/dl) in the experimental group was lower than in the control group (p<0.05). There was no significant difference between the groups in LDL, Vit B12, AST, ALT, TSH, albumin, and ferritin values (p>0.05). The blood biochemical values are provided in **Table 2**.

DISCUSSION

Metals, in addition to being present in various environmental settings, are also found in trace amounts in living organisms, playing significant roles in various biological processes. Today, due to industrialization and the impact of environmental pollution, toxic metals have become widespread in ecosystems, posing a threat to human health. It is known that these toxic metals interact with numerous identified and unidentified cellular components and processes in the biological system and cardiovascular system, leading to toxicity.[17] Toxic metal exposure prominently involves the impairment of antioxidant protective mechanisms, leading to oxidative stress. Additionally, toxic metals can induce cardiovascular toxicity through various mechanisms such as DNA damage and lipid peroxidation.[18] Non-communicable diseases, including cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes, account for a significant portion of global disease and mortality rates.[19] Studies have provided evidence that exposure to certain toxic metals is associated with an increased risk of not only strokes but also cardiovascular risks.[10,15] Toxic metals exert negative effects on vascular health by increasing oxidative stress and inflammation, causing endothelial dysfunction, and disrupting calcium balance. Individuals exposed to heavy metals such as As, Pb, Cd, and Hg have been shown to have a higher risk of atherosclerosis, heart disease, and stroke.[20] Determining the etiology of vascular diseases will facilitate the implementation of preventive measures. In this context, our study aims to determine the potential levels of toxic metals in individuals with vascular diseases and

Table 2. Biochemical values

	Control group				Experimental group				p
	Mean	SD	Min.	Max.	Mean	SD	Min.	Max.	
Triglycerides (mg/dl)	107.80	56.69	35.60	254.10	135.99	77.64	52.40	448.00	**0.037***
HDL (mg/dl)	55.59	13.55	30.40	85.60	44.13	9.16	29.40	67.30	**0.001***
LDL (mg/dl)	91.06	30.38	45.52	180.60	95.25	26.39	57.18	149.00	0.403
Vitamin B12 (pg/dl)	372.12	230.33	162.60	1629.00	366.63	142.45	191.60	799.10	0.693
Folic acid (ng/dl)	5.87	2.74	1.63	12.99	8.77	7.79	3.26	44.94	**0.018***
AST (U/L)	17.31	6.02	10.40	40.20	17.34	6.13	9.60	40.10	0.985
ALT (U/L)	18.29	0.21	7.20	65.40	19.67	11.32	9.10	65.40	0.233
BUN (mg/dl)	10.44	3.50	5.30	24.60	13.32	3.86	7.40	22.30	**0.001***
Serum creatinine (mg/dl)	0.78	0.21	0.48	1.48	0.87	0.26	0.49	1.80	**0.047***
TSH (µIU/ml)	2.08	1.11	0.27	5.19	2.49	2.55	0.33	13.00	0.797
T3 (ng/dl)	0.34	0.49	0.23	0.47	1.30	0.11	1.08	1.68	**0.001***
Albumin (g/L)	47.50	3.53	37.50	54.00	45.50	4.08	35.70	52.00	0.052
Ferritin (ng/ml)	52.61	49.55	4.67	239.80	74.18	68.48	4.67	202.80	0.397

* p<0,05
Note: The table displays the mean, standard deviation, minimum, and maximum values for each toxic metal in the control and experimental groups. The p-values indicate the statistical significance of the differences between the groups. SD: Standard deviation, Min: Minimum, Max: Maximum, HDL: High density lipoprotein, LDL: Low density lipoprotein, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, BUN: Blood urea nitrogen, TSH: Thyroid stimulating hormone, T3: Triiodothyronine

compare them with the levels of potential toxic metals in a control group consisting of healthy individuals.

Actually, excessive intake of trace elements essential for the human body, such as Se, Zn, and Mn, can also lead to the development of poisoning symptoms. The high-dose toxicity of Zn can lead to ulcers, pulmonary edema, irritation in mucous membranes, and respiratory tract irritation.[21] Mn can cause Parkinson's disease.[22] The long-term high intake of selenium is associated with hair loss, changes in nail morphology, skin lesions (redness and swelling), and central nervous system disorders (paralysis, paresthesia, and hemiplegia).[23] In our study, the level of Zn identified in the experimental group was found to be lower compared to the control group, while Se and Mn levels were higher. The lower level of Zn in the experimental group consisting of individuals with vascular disease compared to the control group is in line with the literature. This finding is supportive of previous studies conducted on the subject. Zn is crucial for the functioning of over 3000 proteins in the body, involved in various physiological processes, including growth, immune function, tissue maintenance, wound healing, lipid and glucose metabolism, and the synthesis of testicular hormones. It has been suggested that Zn deficiency contributes to the increased vascular calcification.[24] Shin et al.[25] demonstrated that Zn increased smooth muscle viability in rat aortic cell lines. Voelkl et al.[26] found that high phosphate conditions increased the level of NF-KB, a key regulator of vascular calcification, in aortic smooth muscle cells. They also observed that this increase was prevented by supplementation with zinc sulfate ($ZnSO_4$). Chen et al.[27] identified a relationship between a high dietary intake of Zn and a lower likelihood of severe abdominal aortic calcification in adults in the United States during the years 2013-2014.

Although the exact role of Hg in the development of cardiovascular diseases is not fully understood, it is known to play a role in the development of oxidative stress and inflammation, which contribute to endothelial and renal dysfunction.[28] Hu et al.[29] identified an association between chronic exposure to Hg and an increased risk of all-cause mortality, as well as fatal/non-fatal ischemic heart diseases in a study examining the relationship between exposure to mercury and the incidence of cardiovascular disease and death. Lin et al.[30] conducted a study to assess the relationship between heavy metal levels and acute ischemic stroke. They found that individuals who experienced acute ischemic stroke had lower Hg levels according to their research. The results we obtained in our study are supportive of the findings in Hu et al.[29] regarding Hg.

In a study conducted by Ikediobi et al.[31] they investigated the response of antioxidant enzymes and redox metabolites to Cd-induced oxidative stress in rat liver cells. According to the findings, after the application of Cd to the rats, there was a decrease in the levels of superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR), and glutathione peroxidase (GPx), while there was an increase in malondialdehyde (MDA) levels. The study suggested that this oxidative stress may play a role in the harmful effects induced by Cd, such as the development of lung, prostate, and testicular cancers.[31] In Prozialeck et al.[32] review study titled "vascular endothelium as a target of Cd toxicity," it is suggested that vascular endothelium may be one of the primary targets of in-vivo Cd toxicity. The study indicates that non-lethal concentrations of Cd exposure can target vascular endothelial cells at various molecular levels, including cell adhesion molecules, metal ion carriers, and protein kinase signaling pathways.[32] In the studies conducted by Kishimoto et al.[33] to evaluate the effects of Cd on human vascular endothelial cells, they reported that Cd inhibited tube formation in human umbilical vein endothelial cells (HUVEC) in a dose-dependent manner. They suggested that this inhibition could negatively impact capillary network formation.[33] Our study's findings, indicating elevated levels of Cd in the experimental group, are consistent with the views of Kishimoto et al.[33] This alignment supports the idea that high Cd levels may contribute to an increased risk of cardiovascular disease.

Harlan's[34] study, conducted on the U.S. population to assess the relationship between blood Pb levels and blood pressure, indicated that, in line with numerous previous studies, there was a demonstrated association between Pb exposure and hypertension. In his study, Harlan analyzed data obtained from the national health and nutrition examination survey II for individuals aged 12-74, highlighting a significant correlation between hypertension and Pb exposure.[34] The high detection of Pb in the experimental group in our study is in line with Harlan's[34] findings. Although the blood levels of As, Cd, Hg, Pb, Co, Ni, and Mo in our findings were below the accepted toxic values, they were significantly higher compared to the population in the control group without vascular diseases. This result suggests that there may be an association between cardiovascular disease and elevated blood levels of toxic metals, even at low levels. Indeed, previous studies have demonstrated that the mentioned toxic metals can accelerate atherosclerosis and have serious toxic effects on the cardiovascular system.[39-43] In the majority of conducted studies, toxic effect doses of toxic metals have been individually investigated for each substance. In a multifactorial pathology such as atherosclerosis, we consider it possible that heavy metals may play an accelerating role in the process through the cumulative effect of low doses.

Toxic metals can induce oxidative stress by generating reactive oxygen species (ROS), including superoxide radicals, hydrogen peroxide, and nitric oxide. This process triggers lipid peroxidation, leading to impaired immune function and the accumulation of immune complexes. Consequently, it may cause changes in weight, hyperglycemia, an increase in triglycerides, low-density lipoprotein cholesterol (LDL-c), and elevated blood pressure levels.[35] There is a strong relationship between high triglyceride levels and low HDL levels with cardiovascular diseases.[36] In our study, the high triglyceride levels and low HDL levels identified in the experimental group are supportive of the literature. In a study by Liu et al.[37] where they evaluated the relationship between serum folate and vitamin B12 levels in patients with type 2 diabetes and cardiovascular disease mortality, both low and high serum B12 levels, as well as low serum folate levels, were found to be significantly associated with the risk of cardiovascular

disease mortality. In a study conducted by Li et al.[38] to assess the relationship between folic acid supplementation and cardiovascular diseases, they demonstrated that folic acid supplementation was associated with a 4% reduction in the risk of cardiovascular disease. Our study's finding of high levels of folic acid in the experimental group is not in line with the literature. The discrepancy between our study and the literature regarding folic acid suggests that volunteers in the experimental group with cardiovascular disease may have been taking folic acid supplements.

CONCLUSION

We believe that the study contributes to understanding the effects of toxic metal exposure and biochemical changes on human health. However, investigating the effects of exposure with a larger number of participants and through prospective studies that consider multiple factors will provide more enlightening information to better understand these impacts. The findings from this study, demonstrating the association between toxic metal exposure and cardiovascular diseases, will serve as a crucial data source for epidemiological and clinical studies exploring this relationship.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study received ethical approval from Bozok University Clinical Researches Ethics Committee (Date: 25.08.2021, Decision No: 2017-KAEK-189-2021.08.25_01).

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

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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

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Odontogenic and non-odontogenic cysts in the jaws: a retrospective analysis

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ABSTRACT

Aims: This study aims to retrospectively analyze the demographic, clinical, and radiological characteristics of jaw cysts and evaluate the implications of these findings for accurate diagnosis, effective treatment planning, and the prevention of potential complications.

Methods: This retrospective cross-sectional study was conducted at the Kırıkkale University Oral and Maxillofacial Surgery Clinic between April 2023 and May 2024. A total of 178 patients, histopathologically diagnosed with jaw cysts, were included. Data on demographic factors such as age and gender, as well as clinical and radiological features of the cysts, were collected and analyzed.

Results: The mean age of the patients was 48.52±16.56 years, with 56.74% of the cohort being male and 43.25% female. The distribution of lesions was as follows: 53.93% in the mandible, 43.82% in the maxilla, and 2.25% in both jaws. Radiologically, 79.77% of the lesions were radiolucent, while 20.22% exhibited a mixed radiological pattern. Clinically, 86.52% of the lesions were asymptomatic, while 13.48% were symptomatic. The most prevalent cyst types identified were radicular cysts (35.4%), dentigerous cysts (19.1%), and keratocysts (19.1%).

Conclusion: A comprehensive analysis of the demographic and radiological characteristics of jaw cysts plays a pivotal role in achieving precise diagnoses and devising effective treatment strategies. The present study shows that radicular cysts are the most common type, which is consistent with previous studies. However, the findings indicate a lower prevalence of radicular cysts compared to other studies focusing on cystic lesions. Moreover, this study reports higher prevalence rates for dentigerous cysts and keratocysts compared to certain other studies. These findings emphasize the importance of accounting for individual and population-based variability when diagnosing and managing jaw cysts.

Keywords: Jaw cysts, odontogenic cysts, non-odontogenic cysts, retrospective analysis

INTRODUCTION

Odontogenic and non-odontogenic cysts constitute a diverse category of pathological conditions that impact the oral and maxillofacial region. These lesions generally emerge from a range of developmental and inflammatory mechanisms, closely tied to the distinct anatomical and biological features of the jaws. While odontogenic cysts stem from epithelial remnants related to tooth development, non-odontogenic cysts originate from ectodermal tissues involved in craniofacial formation.[1] The most prevalent types of odontogenic cysts include periapical (radicular) cysts, dentigerous cysts, and odontogenic keratocysts.[2] Extensive epidemiological research has highlighted the distribution and clinical behavior of odontogenic cysts, with a particular focus on the more aggressive and destructive variants.[2]

The 2017 classification by the World Health Organization (WHO) serves as a detailed framework for distinguishing between odontogenic and non-odontogenic cysts. Odontogenic cysts are classified into two main types: inflammatory and developmental.[3] Inflammatory cysts encompass radicular cysts, which develop as a consequence of pulp inflammation, and residual cysts, which remain following tooth extraction. Developmental cysts, including dentigerous cysts, odontogenic keratocysts, and lateral periodontal cysts, were also classified under this system and result from interruptions in the normal processes of tooth development.[1,3] Non-odontogenic cysts, including nasopalatine duct cysts and nasolabial cysts, are less frequently encountered and arise from epithelial remnants of embryological structures.[3] Notably, the revised classification redefined keratocystic odontogenic tumors and calcifying epithelial odontogenic tumors as cysts. However, some odontogenic and non-odontogenic cysts were excluded from the classification, potentially leading to diagnostic ambiguities. For example, gingival cysts were incorporated

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into the classification, while others, such as nasolabial cysts, were omitted.[4]

The etiology of jaw cysts is multifactorial, encompassing genetic predisposition, environmental influences, and local inflammatory processes.[5,6] Odontogenic cysts commonly arise due to chronic inflammatory stimuli, such as untreated dental caries or trauma, which lead to epithelial proliferation.[1,7] Conversely, non-odontogenic cysts are often associated with developmental abnormalities.[2,3] The pathogenesis of these lesions reflects their origin, with odontogenic cysts linked to the remnants of the tooth-forming apparatus and non-odontogenic cysts stemming from embryonic epithelial residues. The pathogenesis of these lesions mirrors their origin: odontogenic cysts are linked to remnants of the tooth-forming apparatus, while non-odontogenic cysts originate from epithelial residues of embryonic structures.[3,7]

Jaw cysts are reported to be more common in males than females, with a male-to-female ratio of 1.6:1. They predominantly occur in individuals aged between the fourth and sixth decades of life. Odontogenic cysts are frequently located in the anterior maxilla, followed by the posterior mandible.[8] Due to the overlapping clinical and radiological features of these cysts, misdiagnoses are common. Consequently, precise evaluation of clinical and radiological findings is critical for accurate diagnosis.[1] Definitive diagnosis often requires histopathological examination, as clinical and radiological findings alone may not suffice. Certain cysts, particularly those with aggressive behavior and high recurrence potential, demand careful identification and management.[7]

In most cases, cysts are asymptomatic unless secondary infection occurs. When symptomatic, clinical presentations may include dental and gingival issues, intraoral discharge, bad taste, and painless swelling. In severe cases, complications such as trismus, sensory deficits, and pathological fractures may develop.[9] Surgical interventions, including enucleation, curettage, and marsupialization, are commonly employed in the treatment of jaw cysts. The choice of treatment should be tailored based on the type and aggressiveness of the cyst.[1,9] These interventions not only help control the lesion but also reduce the risk of recurrence. Thus, the accurate identification and effective management of jaw cysts require meticulous clinical and histopathological evaluation.[1,9]

The aim of this study is to retrospectively analyze the distribution of demographic data, such as age and gender, as well as the radiological and clinical characteristics of jaw cysts in a total of 178 patients who were histologically diagnosed with jaw cysts. The information obtained regarding the diagnosis and distribution of jaw cysts may contribute to the literature by facilitating accurate treatment planning and preventing potential complications.

METHODS

This research was designed as a retrospective cross-sectional study, encompassing patients who were histopathologically diagnosed with odontogenic and non-odontogenic jaw cysts. The study was conducted at the Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Kırıkkale University. Ethical approval was granted by the Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 26.06.2024, Decision Number: 2024/06-19). The study adhered strictly to the principles outlined in the Helsinki Declaration of Human Rights. Patients who presented to the Oral and Maxillofacial Surgery Clinic between April 2023 and May 2024 were retrospectively reviewed. Demographic data, including age and gender, along with the radiological and clinical characteristics of the jaw cysts, were systematically collected and analyzed. The inclusion criteria focused on cases with complete clinical, radiological, and histopathological records, ensuring comprehensive data integrity.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 29 software. Descriptive statistics, such as mean and standard deviation, were employed to summarize numerical variables. For categorical variables, chi-square tests were utilized to assess variations across groups. The Mann-Whitney U test was conducted for non-parametric within-group comparisons. Additionally, relationship coefficients, including Phi, Cramer's V, Contingency Coefficient, Eta, and Gamma, were calculated to evaluate the strength and direction of associations between variables. A significance level of $p<0.05$ was set for all statistical tests.

RESULTS

The study included a total of 178 patients, with ages ranging from 18 to 75 years and a mean age of 48.52±16.56 years. Of these, 56.74% (n=101) were male, and 43.25% (n=77) were female. The anatomical distribution of lesions revealed that 53.93% (n=96) were in the mandible, 43.82% (n=78) in the maxilla, and 2.25% (n=4) in both jaws. Radiological analysis indicated that 79.77% (n=142) of the lesions exhibited a radiolucent appearance, while 20.22% (n=36) demonstrated a mixed radiological pattern. Clinically, most lesions (86.52%, n=154) were asymptomatic, whereas 13.48% (n=24) presented with symptoms. Regarding lesion size, 39.33% (n=70) were less than or equal to 1 cm in diameter, and 60.67% (n=108) measured larger than 1 cm. Lesion margins were classified as regular in 85.19% (n=154) of cases and irregular in 14.81% (n=24) (**Table 1**).

Statistical analyses showed no significant association between gender and lesion location ($p=0.83$), radiological appearance ($p=0.71$), size ($p=0.31$), or margin characteristics ($p=0.3$). However, asymptomatic lesions were significantly more common in males than females ($p=0.0004$, $p<0.05$). Similarly, no statistically significant correlation was observed between age and lesion location ($p=0.49$), radiological appearance ($p=0.63$), symptomatology ($p=0.91$), size ($p=0.63$), or margin characteristics ($p=0.42$).

The pathological analysis identified 178 lesions, distributed as follows: radicular cysts (35.4%, n=63), dentigerous cysts (19.1%, n=34), odontogenic keratocysts (19.1%, n=34), lateral periodontal cysts (12.4%, n=22), nasopalatine duct cysts (4.49%, n=8), buccal bifurcation cysts (1.1%, n=2), glandular odontogenic cysts (1.1%, n=2), nasolabial cysts (2.8%, n=5), orthokeratinized odontogenic cysts (2.2%, n=4), and calcifying odontogenic cysts (2.2%, n=4) (**Figure**).

Table 1. Demographic and clinical characteristics of the patients included in the study

Characteristic	Value	Patients (%)	Patients (n)
Mean age	48.52±16.56	-	-
Gender	Male	56.74	101
	Female	43.25	77
Location of lesions	Maxilla	43.82	78
	Mandible	53.93	96
	Both jaws	2.25	4
Radiological appearance of lesions	Radiolucent	79.77	142
	Mixed	20.22	36
Clinical status of lesions	Asymptomatic	86.52	154
	Symptomatic	13.48	24
Size of lesions	≤1 cm	39.33	70
	>1 cm	60.67	108
Borders of lesions	Regular	85.19	154
	Irregular	14.81	24

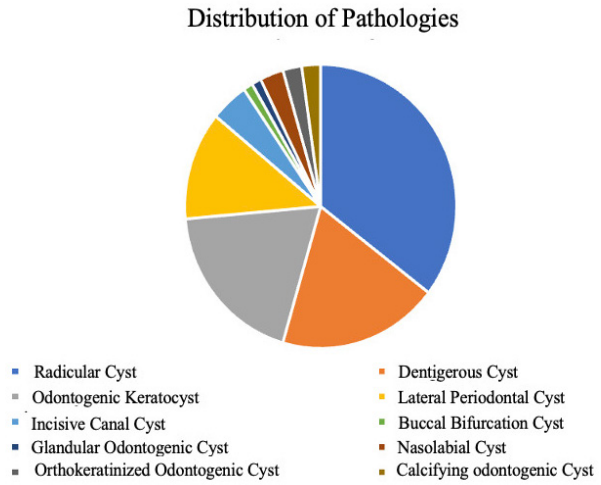

Figure 1. Distribution of pathologies

The mean age of patients with radicular cysts was 42.17±18.04 years. Among them, 64.49% (n=40) were male, and 36.5% (n=23) were female. The mean age of patients with dentigerous cysts was 45.84±17.10 years, with 52.9% (n=18) being male and 47.1% (n=16) female. For odontogenic keratocysts, the mean age was 47.76±15.4 years, with 52.9% (n=18) male and 47.1% (n=16) female. Patients with lateral periodontal cysts had a mean age of 38.36±13.13 years, with 40.9% (n=9) being male and 59.09% (n=13) female. The mean age of patients with nasopalatine duct cysts was 62.5±17.3 years, with 75% (n=6) being male and 25% (n=2) female. For nasolabial cysts, the mean age was 55.3±2.8 years, with 60% (n=3) being male and 40% (n=2) female. Patients with orthokeratinized odontogenic cysts had a mean age of 38.5±15.58 years, with 75% (n=3) being male and 25% (n=1) female. The mean age of patients with calcifying odontogenic cysts was 43.5±21.36 years, with 25% (n=1) male and 75% (n=3) female. For glandular odontogenic cysts, the mean age was 52.5±13.43 years, with 50% (n=1) male and 50% (n=1) female. Patients with buccal bifurcation cysts had a mean age of 42.5±12.72 years, and all cases (100%, n=2) were male (**Table 2**).

DISCUSSION

Jaw cysts are among the most common causes of chronic swelling in the maxillofacial region, owing to the high density of odontogenic epithelial remnants present in oral tissues.[10] These epithelial residues serve as the origin of odontogenic cysts, which constitute the majority of cystic lesions observed in the jaws.[1,8] Jaw cysts often share overlapping clinical, radiological, and histopathological characteristics, making accurate diagnosis critical. This is especially important for odontogenic cysts with a high likelihood of recurrence and aggressive behavior.[1,9] This retrospective study analyzed patients diagnosed with odontogenic and non-odontogenic jaw cysts at the Department of Oral and Maxillofacial Surgery, Kırıkkale University Faculty of Dentistry, over a one-year period. The analysis encompassed key demographic variables such as age and gender, as well as the clinical and radiological profiles of the identified cysts.

Age is a determining factor in the distribution of jaw cysts. The existing literature indicates that jaw cysts are predominantly observed in middle-aged populations; however, variations among studies highlight discrepancies in age-related patterns.[1,7,8,11] For instance, Tamiolakis et al.[8] reported an average patient age of 42.3 years, with radicular cysts most frequently observed in individuals aged between the fourth and sixth decades. Conversely, Öner et al.[11] noted a predominance of young adults, with an average age of 38.34 years. Similarly, Tekkesin et al.[7] identified an average age of 36.33 years, with radicular cysts occurring at a mean

Table 2. Demographic characteristics by pathology type

Pathology type	Patients	Patients	Mean age (years) (±SD)	Male (%)	Female (%)
Radicular cyst	63	35.4%	42.17±18.04	64.49% (n:40)	36.5% (n:23)
Dentigerous cyst	34	19.1%	45.84±17.10	52.9% (n:18)	47.1% (n:16)
Odontogenic keratocyst	34	19.1%	47.76±15.4	52.9% (n:18)	47.1% (n:16)
Lateral periodontal cyst	22	12.4%	38.36±13.13	40.9% (n:9)	59.09% (n:13)
Incisive canal cyst (nasopalatine cyst)	8	4.49%	62.5±17.3	75% (n:6)	25% (n:2)
Nasolabial cyst	5	2.8%	55.3±2.8	60% (n:3)	40% (n:2)
Orthokeratinized odontogenic cyst	4	2.2%	38.5±15.58	75% (n:3)	25% (n:1)
Calcifying odontogenic cyst	4	2.2%	43.5±21.36	25% (n:1)	75% (n:3)
Glandular odontogenic cyst	2	1.1%	52.5±13.43	50% (n:1)	50% (n:1)
Buccal bifurcation cyst	2	1.1%	42.5±12.72	100% (n:2)	0% (n:0)

SD: Standard deviation

age of 33.7 years. In contrast to these studies, the present study found a mean patient age of 48.52 years, with radicular cysts occurring at a mean age of 42.17 years, indicating an older population. This discrepancy may be attributed to the higher prevalence of residual cysts among older individuals, often linked to post-extraction complications. Supporting this notion, Demirkol et al.[5] reported that residual cysts are predominantly observed in elderly populations, likely due to the increased frequency of tooth extractions in these age groups. This situation is supported by the current study data; it is thought that residual cysts may affect the age distribution. In agreement with present study findings, Du et al.[12] observed a higher prevalence of radicular cysts among middle-aged and older populations, emphasizing the role of chronic inflammatory processes and delayed treatment in this age group.

Gender distribution is a significant determinant in the demographics of jaw cysts. The literature consistently reports a higher prevalence of jaw cysts in males compared to females.[5,7,8,13] In a study by Tamiolakis et al.[8] the male-to-female ratio was reported as 1.6:1. Similarly, Tekkesin et al.[7] identified a male-to-female ratio of 1.36:1, emphasizing the higher prevalence of cysts in males. Two independent studies conducted in Turkey yielded comparable results, reporting a male-to-female ratio of 1.4:1.[5,13] In a systematic review by Johnson et al.[2] it was noted that the male predominance was particularly pronounced for radicular cysts, whereas dentigerous cysts exhibited a higher prevalence in females. Lo Muzio et al.[6] attributed the higher prevalence of radicular cysts in males to environmental and genetic factors that influence inflammatory processes, particularly around the apical regions of teeth, where epithelial remnants of Malassez are stimulated.[6,14] In the present study also demonstrated a higher prevalence of jaw cysts in males compared to females, consistent with the literature. Radicular cysts, dentigerous cysts, and odontogenic keratocysts were more frequently observed in males than in females. This trend may be attributed to untreated dental caries and trauma, which are more common in males, potentially reflecting population-specific characteristics.[15] Factors such as oral hygiene habits and susceptibility to trauma within the studied population may contribute to these gender-based differences. This finding is further supported by Mutinda et al.[16] who reported a male predominance in their 20-year analysis of odontogenic cysts, underscoring similar environmental and genetic factors contributing to this trend.

Anatomical location plays a critical role in the diagnosis and differential diagnosis of jaw cysts.[1,2,8] However, the literature presents varying ratios of maxilla-to-mandible involvement.[2,5,7,8] In a study conducted by Tamiolakis et al.[8] an equal distribution of cysts between the maxilla and mandible was reported. Radicular cysts were more frequently observed in the anterior region of the maxilla, whereas dentigerous cysts and keratocysts were predominantly located in the posterior region of the mandible. In contrast, Tekkesin et al.[7] found that the maxilla was more frequently affected (53.09%) compared to the mandible (46.91%). Similarly, Baştoklu et al.[13] reported a higher prevalence of cysts in the mandible (58.1%) compared to the maxilla. Conversely, Demirkol et al.[5] noted that the maxilla was more commonly involved (53.7%) than the mandible. In the present study, the mandible was found to be more frequently affected, with a prevalence of 53.93%. This finding may be associated with the mandible's increased exposure to masticatory forces, leading to a higher susceptibility to trauma.[15] It is important to note, however, that the anatomical distribution may vary depending on the specific type of cyst, which can influence the overall prevalence patterns.[2] Present study findings align with Du et al.[12] who also reported a higher prevalence of odontogenic cysts in the mandibular region, particularly odontogenic keratocysts, due to their association with impacted molars and developmental disturbances.

Radiological features play a critical role in the diagnosis of jaw cysts.[1] For instance, the multilocular appearance and aggressive nature of odontogenic keratocysts are significant criteria for their differentiation from other cysts.[2] Cysts with irregular margins and large radiolucent areas are known to be associated with biological aggressiveness.[1] In the study by Tamiolakis et al.[8] it was reported that most cysts exhibited regular margins and a radiolucent appearance. Similarly, Tekkesin et al.[7] noted that the majority of cysts displayed regular margins and radiolucent characteristics. In the present study, 85.19% of the lesions were found to have regular margins, and 59.55% demonstrated a radiolucent appearance, findings that are consistent with the literature.

Radicular cysts are the most common inflammatory lesions among jaw cysts, typically developing as a result of pulpitis or periapical infections.[17] In a study conducted by Jones and Franklin[18] in the United Kingdom, involving 6,164 cases, the prevalence of radicular cysts was reported as 52.4%. Similarly, Tamiolakis et al.[8] reported the prevalence of radicular cysts as 57.3% in their study. Baştoklu et al.[13] in their research conducted in the Konya region, documented a prevalence of 54.7%, consistent with the literature . Demirkol et al.[5] emphasized that radicular cysts, with a prevalence of 63%, are the most frequently observed cyst type. Globally, radicular cysts are recognized as the predominant odontogenic cysts, with an estimated prevalence of 54.6%.[2] In the present study, radicular cysts accounted for 35.4% of cases, representing a lower prevalence compared to other studies. Nevertheless, they remained the most frequently observed cyst type, aligning with the literature. This discrepancy may be attributed to variations in dental hygiene practices or diagnostic approaches across different populations. Baştoklu et al.[13] reported a wide age range for radicular cysts, spanning 12–76 years, with a mean age of 35, in their study conducted in the Konya region. Similarly, a study from the Gaziantep region noted that radicular cysts were most frequently observed in individuals in their third and fourth decades.[5] In the present study, the mean age for radicular cysts was found to be 42.17 years, which is consistent with the 41.2 years reported by Tamiolakis et al.[8] These variations may be explained by population-specific factors such as differences in oral hygiene habits and susceptibility to trauma, which can influence the age distribution and prevalence of radicular cysts. Similarly, Mutinda et al.[16] highlighted that

regional factors and healthcare accessibility may contribute to variations in cyst prevalence across populations, further explaining discrepancies in global findings.

Dentigerous cysts are developmental in origin and represent the second most common type of odontogenic cysts.[1] They are most frequently associated with impacted teeth, particularly mandibular third molars.[19] Studies in the literature report varying prevalence rates for dentigerous cysts.[2,5,7,13] A study conducted in the Istanbul region reported a prevalence of 10.39%, while the prevalence in the Konya region was reported as 17.8%.[7,13] In contrast, a study from the Gaziantep region reported a higher prevalence of 26.9%, exceeding typical literature values.[5] In a systematic review by Johnson et al.[2] the global prevalence of dentigerous cysts was estimated at 20.6%. In the present study, the prevalence of dentigerous cysts was found to be 19.1%, making them the second most frequently observed cyst type. This finding is consistent with the global prevalence reported in the literature.

Odontogenic keratocysts hold particular significance due to their biologically aggressive nature and high recurrence rates. They are most commonly observed in the posterior region of the mandible.[1] In a study by Tamiolakis et al.[8] the prevalence of keratocysts was reported as 8.2%. Baştoklu et al.[13] in their study conducted in the Konya region, documented a prevalence of 12.4%. On the other hand, Demirkol et al.[5] reported a lower prevalence of 6.1% in the Gaziantep region. In a global systematic review, Johnson et al.[2] estimated the prevalence of odontogenic keratocysts to be 11.7%. In the present study, the prevalence of keratocysts was found to be 19.1%, equal to that of dentigerous cysts, and higher than the rates reported in most previous studies. However, our findings align with the study by Tekkesin et al.[7] conducted in Istanbul, where the prevalence of keratocysts was reported as 20.6%.

Limitations

This study has several limitations that should be considered. First, as a single-center study, the generalizability of the findings is limited. More comprehensive results could be achieved by incorporating data from different geographical regions and institutions. Additionally, the limited number of patients included in the study, the lack of long-term follow-up data, and the inability to evaluate treatment approaches and recurrence rates are notable constraints. Another limitation is that histopathological analyses were not conducted at a centralized facility, which may have introduced variability in the findings. Furthermore, the retrospective study design covering only a one-year period may not provide sufficient time to collect reliable epidemiological data, which further limits the robustness of the findings.

CONCLUSION

The present study shows that radicular cysts are the most common type, which is consistent with previous studies. However, the findings indicate a lower prevalence of radicular cysts compared to other studies focusing on cystic lesions. Moreover, this study reports higher prevalence rates for dentigerous cysts and keratocysts compared to certain other studies. These differences may be attributed to variables such as the demographic characteristics of the population, environmental factors, and dental health practices. In conclusion, early diagnosis and appropriate treatment approaches are crucial for the effective management of radicular cysts and other cystic lesions. The variations in regional prevalence rates underscore the importance of considering local dynamics during clinical evaluation processes. Furthermore, the prevention and management of jaw cysts heavily rely on regular dental check-ups, the improvement of oral hygiene practices, and raising awareness within the community, all of which play a critical role in promoting dental health. Additionally, present study findings revealed that jaw cysts were more prevalent in males compared to females, with a peak incidence in middle-aged individuals. This highlights the influence of age and gender on cyst distribution, emphasizing the need for targeted preventive measures in these populations. In this context, future studies expanding prevalence data across diverse populations could significantly contribute to the development of more effective strategies for the treatment and prevention of jaw cysts.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Kırıkkale University Non-interventional Clinical Researches Ethics Committee (Date: 26.06.2024, Decision No: 2024/06-19).

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

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Does greater richness of experience lead to greater happiness in older adults?

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ABSTRACT

Aims: The happiness during old age years is closely linked to psychosocial factors such as richness of experience. Richness of experience refers to the level of meaning and fulfillment in individuals' lives through various activities and experiences. This research focused on exploring how the richness of experience is related to the happiness in older adults. In addition, the role of various demographic and psychosocial variables in shaping this relationship were examined.

Methods: The study sample consisted of 179 older adults. 64.2% of the participants were female and 35.8% were male. The participants were administered the psychologically rich life questionnaire, and the psychological well-being in the elderly scale as well as a sociodemographic form. Simple Linear Regression was used to analyze the predictive power of richness of experiences, and pearson correlation analysis was conducted to assess the strength of the relationships between richness of experiences and psychological well-being. Independent Groups t-test and ANOVA were applied to explore if there is a difference on the score based on the sociodemographic differences.

Results: The results of this study indicated a significant positive correlation between a psychologically rich life and psychological well-being in older adults. According to regression analysis, psychologically rich life was found to be a strong predictor of psychological well-being and explained 57% of the variance. Education level and income level were found to significantly affect psychologically rich life and psychological well-being levels such that university graduates and high-income group received the highest scores. Participants without a chronic disease were found to have significantly higher scores on psychological well-being and psychological rich life. No significant differences were found in terms of other sociodemographic variables such as gender, marital status and having children.

Conclusion: These findings suggest that richness of experiences can be an important factor that improves the quality of life of older adults and the value of diversity of experiences for psychological well-being.

Keywords: Richness of experience, psychological well-being, older adults, psychology of old age

INTRODUCTION

Old age represents an important stage of individuals' lives and psychological well-being is among the factors that determine the overall quality of life of individuals in this period. Research on happiness during old age period[1-3] emphasizes the role of life experiences, social interactions and psychological wealth in this process. "Psychological well-being", one of the most well-known eudemonic theories of well-being, is generally represented by positive emotions such as happiness as well as high levels of functioning in individual and social life.[4] According to the literature, main factors positively contributing to the psychological well-being during old age period can be listed as social participation[5], psychological resilience[6], positive perceptions of aging[7] and quality of life.[8] In particular, social participation has been found to increase life satisfaction and decrease depression by means of social support.[9] Resilience positively affects psychological well-being by enabling individuals to stay healthy and cope with challenges more effectively.[10] For example, it was emphasized that physical health and social support during the pandemic period was associated with less mental health conditions such as anxiety and depression in old age individuals.[11] In addition, positive perception of aging and eudaimonic well-being are known to provide a more active aging process by improving quality of life.[12,13]

In recent years, richness of experience has become a more popular research field considering its effects on individuals' life satisfaction and psychological well-being. Basically, richness of experience refers to the level of having various life experiences which might include social, emotional and cognitive dimensions.[14] It has been reported that individuals living a psychologically rich life are more open to new experiences independent of the pursuit of happiness.[15] Psychological richness can be defined as the sum of total

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experiences providing individuals with a wide range of positive and negative emotions that are intense, surprising, interesting and capable of changing one's perspective.[16] Therefore, these experiences help them to deal with complex mental processes. In older adults, richness of experience plays an important role in reducing psychological problems such as loneliness[17], depression and social isolation.[18] Lee[19] found that social interaction and rich life experiences had a significant effect on the overall happiness of older adults. These findings suggest that richness of experience strengthens not only individual happiness but also social relationships. In addition, studies reveal that an active social life positively affect psychological health of elderly.[20,21]

Psychological well-being includes elements such as making sense of individuals' lives, emotional intelligence and personal development. In literature, Ryff and Singer[22] emphasized that psychological well-being increases individuals' life satisfaction and is strengthened by factors such as social relationships and psychological flexibility. In this context, it can be argued that there is an interaction between richness of experience and psychological richness and this interaction increases the happiness of older individuals. Delle Fave et al.[23] examined the relationship between richness of experience and happiness in their study and found that rich life experiences have positive effects on the emotional well-being of individuals. Similarly, Yang et al.[24] found that social interaction and life experiences play an important role in increasing psychological well-being in older individuals. Psychologically rich life is defined as a lifestyle that includes elements of diversity, depth and innovation that enable individuals to experience their lives in a meaningful and satisfying way.[25] This concept allows individuals to develop themselves through complex experiences that bring richness and different perspectives to their lives, rather than being limited to the pursuit of happiness and pleasure.[26] Psychological well-being is defined as a more general state of well-being that expresses individuals' satisfaction with their lives and the predominance of positive emotional experiences.[27] Examining the relationship between these two concepts in depth may contribute to the development of strategies to increase individuals' psychological well-being.

Research on psychological richness in different sociodemographic groups can contribute to a more comprehensive understanding of this concept. This study aims to understand the relationship between the richness of life and happiness of older individuals and therefore to improve their psychological well-being in the long run. This research is important in terms of providing a better understanding of the factors affecting the happiness of individuals in old age and drawing attention to the importance of richness of experience in this process. Does richness of experience significantly predict the happiness levels of older adults? What is the effect of demographic factors (age, gender, socioeconomic status) on the relationship between richness of experience and happiness? The results of this study may contribute to individuals to live in a happier old age period by enriching their life experiences. In this context, an in-depth examination of the interactions between richness of life experiences and psychological richness can guide the development of effective strategies to increase the overall happiness level of older adults.

METHODS

Ethics

The study was approved by Üsküdar University Non-interventional Researches Ethics Committee (Date:20.04.2024, Decision No: 61351342/2024-30). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Purpose of the Research

This research focuses on exploring how the richness of experiences influences happiness in older adults. It seeks to understand the connection between these two factors and examines the role of various demographic and psychosocial variables in shaping this relationship.

Model of the Research

Our research examining the predictive role of richness of experience on happiness level in older adults was designed as a cross-sectional correlational study, in which the degree of relationships between variables are explored at a single time point.[28] In the regression analysis, richness of experience was treated as the independent variable and happiness as the dependent variable. The primary aim was to explore the nature of the relationship between these variables and how they are influenced by various demographic factors.

Sample of the Research

A total of 179 older adults aged between 65 and 85 years were included in the study. The mean age of participants was 70.94±4.77. Female participants comprised 64.2% of the sample. The sample size was determined based on Cohen's (1988) statistical power analysis.[29] Simple random sampling was used to collect the data. Any history of a neuropsychiatric disorder was set as exclusion criteria. An informed consent was taken from all participants before data collection.

Data Collection Tools

The data collection process utilized the "sociodemographic information form," the "psychologically rich life questionnaire," and the "psychological well-being scale in the elderly." These tools were designed to assess participants' demographic characteristics, levels of life richness, and psychological well-being. Completing the questions took approximately 30 minutes per participant. The interviews were conducted face-to-face, with necessary explanations provided to ensure the accuracy and reliability of responses. Details of the data collection instruments are summarized below.

Sociodemographic Information Form: This form was prepared by the researcher to collect sociodemographic information about the participants including age, marital status, gender, education level as well as the employment status and chronic disease status.

Psychologically Rich Life Questionnaire: Developed by Oishi et al. (2019) and adapted into Turkish by Avşar (2021), this

scale measures how psychologically rich individuals perceive their lives. It consists of 11 items rated on a 7-point Likert scale ranging from "strongly disagree" to "strongly agree." The scale is unidimensional, with no reverse-coded items, and higher scores indicate greater psychological richness. The Turkish version demonstrates high internal consistency, with a Cronbach's Alpha coefficient of .93.

Psychological Well-Being Scale in the Elderly: Created by Gümüş Demir (2022), this scale assesses psychological well-being in elderly individuals. It consists of 15 items on a single factor, addressing aspects of satisfaction with social relationships, self-worth, meaning in life, and positive emotions. Responses are rated on a 5-point likert scale from "1: strongly disagree" to "5: strongly agree," with higher scores indicating better psychological well-being. The scale has strong reliability, with a Cronbach's Alpha coefficient of .91.

Statistical Analysis

Statistical analyses were performed using IBM SPSS 27 (SPSS Inc., Chicago, IL, USA). Independent Groups t-test and ANOVA were employed to analyze mean differences based on demographic variables. Post hoc tests were performed for pairwise comparisons. Pearson Correlation analysis was used to determine the strength of relationships between variables. Simple Linear Regression analysis was used to assess the predictive power of the independent variable. All tests were conducted with a 95% confidence interval, and the significance level was set at $p<.05$.

RESULTS

The reliability of the scales was assessed using Cronbach's Alpha coefficients, and all coefficients were found to be above 0.70, indicating that the scales are reliable.[33] Additionally, the suitability of the scales for normal distribution was examined, and the kurtosis and skewness coefficients were determined to fall within the range of ±1. This finding confirms that the scales satisfy the assumption of normal distribution (**Table 1**).[34]

Descriptive analyses showed that 64.2% of the participants are female, 35.8% are male, 55.9% are married, 11.2% are single and 33.0% are widowed, 85.5% have children while 14.5% do not have children, 26.8% are primary school graduates, 24.6% are middle school graduates, 31.3% are high school graduates and 17.3% are university graduates. When the participants were analyzed in terms of employment status, it was observed that 19.6% were working and 80.4% were not working. When income levels were analyzed, 46.9% had low income (when income is less than expenses), 36.3% had medium income (when income is equal to expenses), 16.8% had high income (when income is more than expenses), and finally 63.7% had low income. The participants had a mean age of 70.94 years (SD=4.77), with ages ranging from 65 to 85 years (**Table 2**).

Table 2. Distribution of demographic information of participants

		n	%
Gender	Woman	115	64.2
	Male	64	35.8
Marital status	Married	100	55.9
	Single	20	11.2
	His wife is dead	59	33.0
Child status	Yes	153	85.5
	No	26	14.5
Education status	Primary school	48	26.8
	Middle school	44	24.6
	High school	56	31.3
	University	31	17.3
Employment status	Working	35	19.6
	Not working	144	80.4
Income status	Low (Income less than expenditure)	84	46.9
	Medium (income and expenditure equal)	65	36.3
	High (Income more than expenditure)	30	16.8
Chronic disease status	Yes	114	63.7
	No	65	36.3
	Total	179	100.0

The correlation analysis revealed that a significant and strong positive correlation was present between psychologically rich life and psychological well-being in the elderly ($r=.75$, $p<.01$) (**Table 3**). However, no significant relationship between age and psychologically rich life ($r=0.01$, $p>.05$) and between age and psychological well-being was found ($r=-0.13$, $p>.05$).

Table 3. Relationship between age, psychologically rich life, psychological well-being in the elderly variables

	1	2	3
1-Age	1		
2-Psychologically rich life questionnaire	.01	1	
3- Psychological well-being scale in the elderly	-.13	.75**	1

**p<0.01, *p<0.05 Name of the applied test: Pearson correlation test

The regression analysis indicated that a psychologically rich life is a significant predictor of psychological well-being ($B=0.67$, $SE=0.04$, $\beta=0.75$, $t(777)=15.26$, $p<.001$). The variable "psychologically rich life" accounted for 57% of the variance in psychological well-being ($R=.75$, $R^2=.57$), and the regression model was statistically significant ($F(,777)=232.77$, $p<.001$) (**Table 4**).

Table 1. Findings related to the examination of descriptive statistics and kurtosis, skewness, Cronbach alpha coefficients of the psychologically rich life questionnaire, psychological well-being scale in the elderly

	n	Min	Max	$\overline{X}$	SD	Flatte ned.	Distort ed	(α)
Psychologically rich life questionnaire	179	13	69	42.00	14.65	-0.95	-0.18	0.95
Psychological well-being scale in the elderly	179	15	67	41.39	12.94	-0.82	-0.12	0.96

Min: Minimum, Max: Maximum, SD: Standard deviation

Table 4. Findings related to the prediction of psychological rich life on psychological well-being

	B	SH	β	t	p	Lower limit	Upper limit
Psychologically rich life	0.67	0.04	0.75	15.26	<.001***	0.58	0.75
$R=.75\ R^2=.57\ F_{(1.777)}=232.77\ p<.001$***							

***p<.001, **p<.01, *p<.05; Note, CI: Confidence interval

The analysis revealed a significant difference in psychologically rich life questionnaire scores between individuals with chronic diseases ($\overline{X}$=40.04, SD=14.83) and those without chronic diseases ($\overline{X}$=45.45, SD=13.75) (t(177)=-2.41, p=.017). It was found that there was a significant difference between the group with chronic disease ($\overline{X}$=39.74, SD=12.98) and the group without chronic disease ($\overline{X}$=44.28, SD=12.46) in terms of psychological well-being scale scores (t(177)=-2.28, p=.024) (**Table 5**).

The analysis showed a significant difference among income groups in psychologically rich life questionnaire scores (F(2, 176)=10.28, p<.001). According to the Tukey test, it was concluded that the psychologically rich life levels of the low income group ($\overline{X}$=37.21, SD=14.12) were significantly lower than the middle income group ($\overline{X}$=44.89, SD=13.75) and the high income group ($\overline{X}$=49.13, SD=13.82).

A significant difference was found among income status groups regarding psychological well-being scale scores (F(2, 176)=20.49, p<.001). According to the Tukey test, it was concluded that the psychological well-being levels of the low income group ($\overline{X}$=35.43, SD=11.76) were significantly lower than the middle income group ($\overline{X}$=46.37, SD=11.43) and the high income group ($\overline{X}$=47.27, SD=12.24) (**Table 6**).

The results revealed a significant difference among educational status groups on the psychologically rich life questionnaire (F(3, 175)=9.10, p<.001). According to Tukey test, it was concluded that primary school graduates ($\overline{X}$=34.35, SD=14.06) had significantly lower levels of psychologically rich life than secondary school graduates ($\overline{X}$=44.59, SD=13.45), high school graduates ($\overline{X}$=42.02, SD=14.84) and university graduates ($\overline{X}$=50.13, SD=11.35).

A significant difference was observed in the psychological well-being scale scores for the elderly in terms of the educational status (F(3, 175)=6.28, p<.001). According to the Games-Howell test, it was found that primary school graduates ($\overline{X}$=36.35, SD=10.47) had lower levels of psychological well-being than secondary school graduates ($\overline{X}$=43.59, SD=12.64) and university graduates ($\overline{X}$=48.10, SD=10.45). It was also found that high school graduates ($\overline{X}$=34.35, SD=14.06) had significantly lower levels of psychological rich life than university graduates ($\overline{X}$=50.13, SD=11.35) (**Table 7**).

DISCUSSION

The primary aim of the present study was to investigate the relationship between psychologically rich life and psychological well-being of older adults. The results revealed that a psychologically rich life is a significant predictor of psychological well-being. A psychologically rich life is defined as the extent to which individuals experience diverse, meaningful, and profound life events.[35] Our findings are in line with the previous literature suggesting that a psychologically rich life increases happiness and overall life satisfaction.[36-38]

Additional analyses were conducted to understand whether sociodemographic factors (such as education level, income level) modulate this relationship. It was found that the effect of psychological richness was more pronounced especially in high education and high-income groups. Health status was also found to have an impact on psychological well-being; such that individuals with chronic diseases were found to have lower levels of psychological well-being. In general, our

Table 5. Comparison of psychologically rich life questionnaire and psychological well-being scale scale scores in the elderly according to chronic disease status

Group with chronic disease (n=114)			Group without chronic disease (n=65)				
Dependent variables	$\overline{X}$	SS	$\overline{X}$	SS	t	Sd.	p
Psychologically rich life questionnaire	40.04	14.83	45.45	13.75	-2.41	177	0.017*
Psychological well-being scale in the elderly	39.74	12.98	44.28	12.46	-2.28	177	0.024*

***p<.001, **p<.01, *p<.05 Test Used: Independent Samples T-Test, Sd: Standard deviation

Table 6. Comparison of psychologically rich life questionnaire and psychological well-being scale scale scores in the elderly according to income status

	Income Status								
	Low (Income less than expenditure)[1] (n=84)		Medium (income and expenditure equal)[2] (n=65)		High (Income more than expenditure)[3] (n=30)				
Dependent variables	$\overline{X}$	SS	$\overline{X}$	SS	$\overline{X}$	SS	F(2.176)	p	Post-Hoc
Psychologically rich life questionnaire	37.21	14.12	44.89	13.75	49.13	13.82	10.28	<.001***	3.2>1
Psychological well-being	35.4	11.76	46.37	11.4	47.27	12.24	20.49	<.001**	3.2>1
Scale in the elderly	3			3				*	

***p<.001, **p<.01, *p<.05 Test Used: One-way analysis of variance (ANOVA)

Table 7. Comparison of psychologically rich life questionnaire and psychological well-being scale scale scores in the elderly according to educational status

	Education status										
	Primary school[1] (n=48)		Secondary school[2] (n=44)		High school[3] (n=56)		University[4] (n=31)				
Dependent variables	$\overline{X}$	SS	$\overline{X}$	SS	$\overline{X}$	SS	$\overline{X}$	SS	F(3.175)	p	Post- Hoc
Psychologically rich life questionnaire	34.3	14.0	44.5	13.4	42.0	14.8	50.1	11.3	9.10	<.001**	4,3,2>1
	5	6	9	5	2	4	3	5		*	4>3
Psychological well-being	36.3	10.4	43.5	12.6	40.2	14.5	48.1	10.4	6.28	<.001**	4,2>1
Scale in the elderly	5	7	9	4	5	4	0	5		*	4>3

***p<.001, **p<.01, *p<.05 Test Used: One-way analysis of variance (ANOVA)

findings support the existing literature where plenty of studies indicate psychological well-being is associated to various biopsychosocial factors. Diener and Ryan[27] for instance, emphasized that socially rich experiences positively influence individuals' happiness levels. Similarly, the findings of Manav and colleagues[28] demonstrated that a psychologically rich life significantly enhances the psychological well-being of older adults.

It was found that the relationship between psychological rich life and psychological well-being was more pronounced especially in university graduates and higher income groups. This finding is consistent with previous studies suggesting that economic and educational advantages may support individuals' psychological well-being.[39,40] The significantly higher psychological well-being in individuals with higher income indicate that economic security supports the general happiness and well-being. In the study, while no significant differences were observed regarding factors such as having children or employment status, individuals with chronic diseases showed significantly lower levels of psychological well-being and psychologically rich life compared to those without chronic diseases. This finding shows that health status is a determinant factor of psychological well-being in older adults. There are many studies supporting the findings[41-43], which points to the importance of a holistic health approach in old age.

This study reveals that psychologically rich life is an important factor supporting psychological well- being in elderly individuals and emphasizes the importance of practices that encourage such experiences. In literature, positive psychology interaction group program positively impacted the levels of hope and anger among the older adults.[44] Similarly, art therapy program resulted in increased positive emotions and self-compassion levels in older adults.[45] Therefore, in order to support the psychological well-being levels of older adults, it is important to develop programs that promote a psychologically rich life. Encouraging social activities and group programs for elderly individuals may help to enrich their social connections and life experiences.

Limitations

First of all, the cross-sectional design of the study restricts the ability to establish cause-and-effect relationships. Therefore, longitudinal studies are recommended for future research, which could provide deeper insights into the long-term effects of living a psychologically rich life. The lack of demographic diversity of participants might be listed as another limitation. Most of the participants of this study were university graduates and had moderate economic income that may limit the generalizability of the findings.

CONCLUSION

This study highlights the role of living a psychologically rich life on psychological well-being in older adults. Our findings suggest that being rich in psychological experiences has a positive impact on happiness and overall life satisfaction. Higher education and higher income levels were found to strengthen this relationship and enhance psychological well-being. Additionally, participants without chronic illnesses exhibited higher levels of psychological well-being. Overall, these findings suggest that encouraging social activities and expanding group programs can be beneficial for old age individuals. Developing tailored programs to increase psychologically rich experiences, particularly for individuals with lower education and lower income, may be helpful to increase the overall happiness level of soceity. Adopting a holistic health approach could help mitigate the adverse effects of chronic illnesses on well-being. Future research could include longitudinal studies to explore the long-term benefits of a psychologically rich life. Policymakers may also consider integrating positive psychology-based interventions into health strategies to address the needs of various socioeconomic groups and enhance happiness in older populations.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by Üsküdar University Non-interventional Researches Ethics Committee (Date:20.04.2024, Decision No: 61351342/2024-30).

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

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The effect of inflammatory scores on the prognosis of malignant mesothelioma

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ABSTRACT

Aims: Malignant mesothelioma (MM) is a rare cancer with a poor prognosis that is frequently detected late in the disease's progression. The purpose of our sudy was to contribute to the literature by investigating how inflammation indices such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), prognostic nutritional index (PNI), systemic inflammation response index (SIRI), and HALP scores affect disease progression and prognosis in patients with MM.

Methods: This study retrospectively examined 85 patients pathologically diagnosed with malignant pleural and peritoneal mesothelioma. NLR, PLR, LMR, PNI, SIRI, and HALP scores of the patients were calculated.

Results: The area under the curve (AUC) values obtained by ROC analysis are NLR (0.65), PLR (0.67), LMR (0.66), PNI (0.64), SIRI (0.66), and HALP (0.77). The cut-off values were as follows: NLR (3.2), PLR (168.5), PNI (35.2), LMR (2.5), SIRI (2.2) and HALP (22.8). In multivariate analysis, being inoperable was found to be associated with lower survival, while receiving chemotherapy and high PNI value were found to be associated with higher survival ($p<0.05$).

Conclusion: In our study, patients with high PNI had longer median survival time. This score can serve as a simple and useful scoring system for predicting the prognosis of malignant pleural mesothelioma in clinical practice.

Keywords: Inflammation indices, malignant mesothelioma, prognostic nutritional index

INTRODUCTION

Malignant mesothelioma (MM) is a cancer that develops in the thin layer of tissue that surrounds organs in the chest or abdomen. Pleural mesothelioma develops in the lining of the lung and accounts for around 75% of cases. People with this kind of cancer have the highest survival rate.[1]

Chronic inflammation is an important factor in determining the prognosis of various types of cancer, including MM. Relationships between survival and inflammation indices have been shown in various types of cancer, including neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), platelet distribution width (PDW)/platelet count ratio (PPR), prognostic nutritional index (PNI), lymphocyte/monocyte ratio (LMR), HALP score and systemic inflammation response index (SIRI), but studies on MM are limited. These parameters can be calculated simply by looking at the laboratory values of patients in daily practice.[2-4]

Systemic inflammatory diseases have emerged as a significant indicator of malignant tumors in recent years and are intimately linked to the development, spread, metastasis, and resistance to medication. Platelets, a crucial component of inflammation, are involved in both the development of cancer and inflammation. In order to promote tumor growth, blood vessel creation, and metastasis, tumor cells have the ability to trigger immune cell migration to tumor sites. Additional physiological roles of albumin as a gauge of the body's nutritional state include preserving plasma osmotic pressure, promoting tissue growth and repair, transferring endogenous and exogenous substances like different medications or nutrients, and controlling systemic inflammation. NLR, LMR and PLR are markers of systemic inflammatory response. There are studies in the literature in which high NLR, low LMR and high PLR predict shorter survival before treatment.[5,6]

The primary cells involved in the body's immunological response are lymphocytes. As a heterogeneous antigen, they can trigger the body to mount an immune response and generate a significant number of lymphocytes during the growth of malignancies. Tumor cells may express antigens that suppress immune cells when immune evasion occurs, which will cause immune cells to adhere to the tumor and undergo death. Patients with hypoalbuminemia are more likely to experience postoperative problems, tumor growth and migration, infection, and inflammation, all of which might

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decrease their prognosis. Since its introduction by Chen et al.[8] in 2015, the HALP score, which takes into account the patient's immunological and nutritional status, has been demonstrated to be an independent predictor of gastric cancer outcome. The prognosis of various cancer types has also been linked to the HALP score in recent years.[7,8]

PNI was first devised to assess perioperative immunonutritional status and surgical risk in patients undergoing gastrointestinal surgery. It is based on the total lymphocyte count in peripheral blood and the serum albumin concentration.[9] Emerging inflammatory markers SIRI, PNI, and HALP are good indicators of the body's nutritional condition and chronic inflammation.

The potential importance of certain inflammation indices in MM has not been thoroughly addressed, despite the fact that inflammation indices and their predictive usefulness have been examined in a variety of cancer types. The purpose of our study was to contribute to the literature by investigating how inflammation indices such as NLR, PLR, LMR, PNI, SIRI, and HALP scores affect disease progression and prognosis in patients with MM.

METHODS

The study included 85 patients over the age of 18 who were pathologically diagnosed with malignant pleural and peritoneal mesothelioma and did not have any secondary malignancy. It was designed as a single-center, cross-sectional, and retrospective study. The study was conducted with the permission of Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology SUAM Non-interventional Clinical Researches Ethics Committee (Date: 17.10.2024, Decision No: 2024-10/142). This research was conducted in conjunction with the Helsinki Declaration (revised in 2013).

NLR, PLR, LMR, PNI, SIRI, and HALP scores were calculated with the following formulas;

NLR: Neutrophil count (/μL)/lymphocyte count (/μL),

PLR: Platelet count (10^9/L)/lymphocyte count (/μL),

LMR: Lymphocyte count (/μL)/monocyte count (/μL),

PNI: 10×Serum albumin (g/dl)+0.005×lymphocyte count (/μL)]

SIRI: NLR×monocyte count (/μL),

HALP: Hemoglobin (g/dl)×serum albumin (g/L)xlymphocyte count (/μL)]/platelet count (/L).

Inclusion Criteria for the Study

- Patients over the age of 18,
- Patients whose demographic information, additional disease information, laboratory values, tomography results, pathology reports and 6-month prognosis information can be accessed from the hospital system or patient files will be included in the study.

Exclusion Criteria for the Study

- Patients whose researched criteria cannot be accessed from the patient file or computer environment,
- Patients with active infection,
- Patients using steroids,
- Patients with secondary malignancies will be excluded from the study.

Statistical Analysis

Descriptive statistics and statistical analyses of the study variables were performed using the SPSS 27.0 package program. In all statistical tests performed at a 95% confidence interval, a p value of <0.05 was considered statistically significant. ROC analysis was applied to determine the optimum NLR, PLR, PNI, LMR, SIRI and HALP cut-off values with high sensitivity and specificity. Patients were classified according to these values. Survival among categorized groups was evaluated using Log-rank curves and Kaplan-Meier tests. Multivariate analysis was performed on statistically significant data using Cox regression analysis. Analysis results were presented as median (25%-75% quartile range), mean, standard deviation and hazard ratio (HR). Clinically significant p<0.200 data were also included in the multivariate analysis.

RESULTS

A total of 85 patients were included in the study. 70.6% of the patients had pleural and 29.4% had peritoneal mesothelioma. The median age of the patients was 68 (59.50-76.50). 56.5% of the patients were male, 51.8% had asbestos exposure, and 32.9% were smokers. 43.5% of the patients were inoperable, while 31 patients (36.5%) had an ECOG value ≥2. The clinicopathological characteristics of the patients are shown in **Table 1**. The cut-off values were as follows: NLR (3.2), PLR (168.5), PNI (35.2), LMR (2.5), SIRI (2.2) and HALP (22.8). Parameters were grouped as low and high according to the cut-off values. While no significant difference was found in terms of survival time in NLR, PLR, LMR, HALP and SIRI values, high PNI value were found to be associated with higher survival (p<0.05).

Univariate and multivariate analyses were evaluated by Cox regression analysis. In multivariate analysis, being inoperable was found to be associated with lower survival, while receiving chemotherapy were found to be associated with higher survival (p<0.05). The results of univariate and multivariate analyses for survival are shown in **Table 2**.

The median survival time of operable patients was 14 months, while the median survival time of inoperable patients was 8 months. The difference was found to be statistically significant (p<0.05). The median survival time of patients who received chemotherapy was 12 months, while the median survival time of patients who did not receive chemotherapy was 4 months, and the difference was found to be statistically significant (p<0.05). Finally, the median survival time of patients with high PNI was 14 months, while the median survival time of

Table 1. Clinicopathological features and inflammatory markers of patients

	Median (25-75 CI)	
Age (year)	68.00 (59.50-76.50)	
Survival time (months)	12 (12-26)	
	Category	n (%)
Gender	Male	48 (56.5)
	Female	37 (43.5)
Tumor localization	Pleura	60 (70.6)
	Peritoneum	25 (29.4)
Asbestos exposure	Yes	44 (51.8)
	No	41 (48.2)
Smoke	Non smoker	57 (67.1)
	Smoker	28 (32.9)
Operation status	Operable	48 (56.5)
	Inoperable	37 (43.5)
ECOG PS	0-1	54 (63.5)
	≥2	31 (36.5)
Chemotherapy	Yes	76 (89.4)
	No	9 (10.6)
Radiotherapy	Yes	27 (31.8)
	No	58 (68.3)
Pathological diagnosis	Epitheloid	72 (84.7)
	Sarcomatoid	6 (7.1)
	Biphasic	7 (8.2)
NLR	≤3.2	34 (40.0)
	>3.2	51 (60.0)
PLR	≤168.5	34 (40.0)
	>168.5	51 (60.0)
LMR	≤2.5	48 (56.5)
	>2.5	36 (42.4)
PNI	≤35.2	56 (65.9)
	>35.2	29 (34.1)
SIRI	≤2.2	35 (41.2)
	>2.2	50 (58.8)
HALP	≤22.8	53 (62.4)
	>22.8	32 (37.6)

CI: Confidence interval, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio, PNI: Prognostic nutritional index, SIRI: Systemic inflammation response index, HALP: Hemoglobin*albumin*lymphocyte/platelet ratio

patients with low PNI was 10 months, and the difference was found to be statistically significant (p<0.05).

DISCUSSION

This study evaluated the prognostic significance of certain inflammation indices in MM including PNI, NLR, PLR, LMR, HALP and SIRI which which have previously been examined in other types of cancer. Several studies have previously been undertaken to evaluate prognostic variables in MM. Each study looked at different prognostic variables. The quest for a predictive biomarker has switched to inflammatory markers, owing to the long-standing concept that inflammation plays a role in the development of MM.[10] It has been postulated that inflammation may be a contributing factor to MM, and so inflammatory indicators may have a role in disease prognosis. Several studies have found that high PLR and NLR are poor prognostic variables in MM patients.[11,12]

Males often have a higher incidence of malignant pleural mesothelioma than females.[13] Due to relatively recent use restrictions and a 40-year lag between exposure and presentation, incidence is still rising in many countries. The usage of asbestos in developing nations is still on the rise.[14] Men are more likely than women to have the condition, and numerous studies have shown that women have higher survival rates than men. In our study, the median age of the patients was 68. 56.5% of the patients were male, 51.8% had asbestos exposure. The median age is 68, and when the literature was examined, it was seen to be higher compared to other studies conducted in Turkey.[15]

NLR was not identified as a prognostic factor at the time of MM diagnosis in a study by Tural et al.[16] or in a retrospective analysis of 274 patients. Disease queries with low NLR and PLR scores were not statistically significant, according to a different study examining the predictive significance of PLR scores in MM patients.[17] However, in our investigation, we found no significant association between NLR or PLR and OS. Perhaps our limited sample size and the varied NLR-PLR cut-off values are the cause of this insignificance.

Malnutrition contributes significantly to shorter OS, lower quality of life, and higher mortality from malignant cancers. Serum albumin levels are the most extensively used serological indicators of malnutrition. Several studies have found that blood albumin, a simple and objective measure of nutritional status, is an independent predictive factor for malignant pleural mesothelioma.[18] The prognostic role of PNI in MM was investigated in the study conducted by Zhou-Hong et al.[19] While the median OS and one-year survival rate in patients with PNI <44.6 were 18 months and 72.3%, these rates were 11 months and 45.5% in patients with PNI ≥44.6. Ebinç et al.[20] discovered that a high PNI value is a good prognostic factor for MM, but Mutlu et al.[2] found no significant association between high PNI value and OS. In our study, the median survival time for patients with high PNI was 14 months, whereas the median survival time for patients with low PNI was 10 months, and the difference was shown to be statistically significant (p<0,05). There were no research in the literature that examined the association between MM prognosis and HALP, SIRI, and LMR. However, in our investigation, there was no statistically significant relationship between these inflammatory indicators and the prognosis of MM. In our analyses, being inoperable was associated with lower survival, while receiving chemotherapy and a high PNI value were associated with higher survival.

MM is a rare malignant tumor with strong invasiveness and poor prognosis. In a study conducted in our nation with 55 MM patients, the median OS was 13 months. It climbed to 16 months in the pleural MM subgroup, but declined to 9 months in the peritoneal MM group.[2] The median OS in Dogan et al.'s[21] study of patients with pleural and peritoneal MM was 22 months, whereas in a large series of 910 patients analyzing just patients with pleural MM, the median OS was 10 months. However, the effect of induction chemotherapy and adjuvant high-dose hemithoracic radiation on outcome following extrapleural pneumonectomy for MPM is still debated, and further research is needed to identify the patient population most likely to benefit from this aggressive strategy. In our analysis, 43.5% of the patients were inoperable, with 31 (36.5%) having an ECOG score of ≥2. While 89.4% of the patients got platinum-based chemotherapy, 27 (31.8%)

Table 2. Results of univariate and multivariate analysis for survival

	Category	Median survival time (months)	Single analysis HR 95% CI	P	Multiple analysis HR 95% CI	p
Age	<65*	14				
	>65	12	1.20 (0.72-1.98)	0.471		
Gender	Male*	12				
	Female	12	1.32 (0.81-2.15)	0.262		
Tumor localization	Pleura*	12				
	Peritoneum	12	1.29 (0.76-2.19)	0.344		
Operation status	Operable*	14				
	Inoperable	8	1.82 (1.10-2.45)	**0.018**	1.94 (1.14-3.31)	**0.014**
ECOG PS	0-1*	12				
	>2	12	1.01 (0.62-1.66)	0.954		
Chemotherapy	Yes*	4				
	No	12	0.58 (0.27-1.22)	0.152	0.45 (0.21-0.98)	**0.047**
Radiotherapy	Yes*	10				
	No	18	0.87 (0.53-1.45)	0.610		
Pathological diagnosis	Epitheloid *	12				
	Sarcomatoid	2	1.80 (0.77-4.21)	0.174	2.07 (0.86-4.98)	0.101
	Biphasic	6	1.37 (0.54-3.45)	0.501	1.41 (0.54-3.70)	0.475
NLR	≤3.2*	12				
	>3.2	12	1.33 (0.79-2.24)	0.272		
PLR	≤168.5*	12				
	>168.5	12	1.37 (0.81-2.31)	0.228		
LMR	≤2.5*	12				
	>2.5	12	0.86 (0.52-1.44)	0.582		
PNI	≤35.2*	10				
	>35.2	14	0.37 (0.20-0.69)	**0.002**	0.35 (0.17-0.74)	**0.006**
SIRI	≤2.2*	12				
	>2.2	12	1.12 (0.67-1.87)	0.646		
HALP	≤22.8*	12				
	>22.8	12	0.61 (0.36-1.06)	0.084	0.95 (0.50-1.79)	0.880

*Reference category, HR: Hazard ratio, CI: Confidence interval, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, LMR: Lymphocyte/monocyte ratio, PNI: Prognostic nutritional index, SIRI: Systemic inflammation response index, HALP: Hemoglobin*albumin*lymphocyte/platelet ratio

required adjuvant radiotherapy. The better survival time of patients who received treatment was an expected result and was consistent with the literature.

Limitations

This study has some limitations. It was retrospective, and a prospective multicenter study would be much better in terms of evaluating the prognostic factors of MM. The study's reduced patient count and missing data may lead to bias in some conclusions.

CONCLUSION

In our study, patients with high PNI had longer median survival time. This score can serve as a simple and useful scoring system for predicting the prognosis of malignant pleural mesothelioma in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Health Sciences University Dr. Abdurrahman Yurtaslan Ankara Oncology SUAM Non-interventional Clinical Researches Ethics Committee (Date: 17.10.2024, Decision No: 2024-10/142).

Informed Consent

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

Referee Evaluation Process

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Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
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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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Evaluation of the long-term autonomic dysfunction after the recovery of COVID-19 disease

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ABSTRACT

Aims: Beyond the acute phase of the COVID-19 disease, many patients experience persistent symptoms, collectively termed "post-COVID syndrome," which includes autonomic dysfunction. Heart rate variability (HRV) is a well-established method to assess autonomic nervous system (ANS) function. This study aimed to investigate the long-term impact of COVID-19 on autonomic function through evaluating the changes in HRV.

Methods: This retrospective study included 225 participants divided into two groups: 117 post-COVID patients and 108 age and gender matched controls. HRV was assessed using 24-hour Holter monitoring. Time-domain and frequency-domain indices were analyzed, including standard deviation of normal-to-normal intervals (SDNN), root mean square of successive RR interval differences (RMSSD), and low frequency (LF)/high frequency (HF) ratio. Statistical comparisons were performed using independent t-tests, Mann-Whitney U tests, and correlation analyses.

Results: Post-COVID patients exhibited significantly lower HRV indices compared to controls. Time-domain metrics such as SDNN (135.7±39.5 ms vs 149.1±34.2 ms, p=0.007) and RMSSD (32.7±13.7 ms vs 37.5±14.7 ms, p=0.012) were reduced in the COVID-19 group. Frequency-domain indices, including total power (TP) and HF power, were also diminished. Correlation analysis revealed no significant association between the duration of time post-COVID (one-year follow-up) and most HRV parameters.

Conclusion: Post-COVID patients experience significant autonomic dysfunction, marked by reduced parasympathetic activity and increased cardiovascular risks, with some evidence of partial recovery during sleep. Routine HRV monitoring and targeted interventions, alongside further research with larger cohorts, are crucial for better understanding of the long-term effects and improving patient outcomes.

Keywords: Post-COVID syndrome, autonomic dysfunction, heart rate variability

INTRODUCTION

The novel coronavirus SARS-CoV-2, responsible for the 2019 coronavirus disease (COVID-19) global pandemic[1], resulted in significant morbidity and mortality.[2] This disease presents a wide spectrum of clinical manifestations, ranging from asymptomatic or mild symptoms, such as fever, headache, myalgia, sore throat, and anosmia, to severe viral pneumonia, which can progress to acute respiratory distress syndrome and multi-organ failure.[3]

While the acute manifestations of COVID-19 have been extensively studied, there is a growing concern about the long-term effects of the virus, often referred to as "long COVID" or "post-COVID syndrome".[4] This syndrome encompasses a variety of symptoms, including fatigue, cognitive disturbances, chest pain, and autonomic dysfunction, which persist for weeks or months after the initial infection has resolved.[5] The autonomic nervous system (ANS), which regulates involuntary physiological functions, appears to be particularly affected in these patients. Recent studies have demonstrated the neurotropism of SARS-CoV-2, with viral particles being detected in brain tissues and cerebrospinal fluid of COVID-19 patients. This neurotropism suggests a possible mechanism for the autonomic dysfunction observed in many patients during and after the acute phase of the disease.[6]

Heart rate variability (HRV) is a well-established, non-invasive method for assessing the ANS's function.[7] HRV reflects the heart's ability to respond to various physiological and environmental stimuli, and its indices can provide insight into the balance between sympathetic and parasympathetic activity.[8] Time-domain indices of HRV, such as the standard

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deviation of normal-to-normal intervals (SDNN) and the root mean square of successive RR interval differences (RMSSD), reflect parasympathetic activity.[9] Frequency-domain indices, including low frequency (LF) and high frequency (HF) bands, represent the contributions of sympathetic and parasympathetic nervous systems.[10] Abnormalities of these parameters indicates impaired HRV which is associated with poor cardiovascular prognosis.[11]

Limited research has been conducted on ANS status in recovered COVID-19 patients using HRV indices in the long term of the post-infection period. This study aimed to compare HRV indices in patients recovered from the COVID-19 disease (post-COVID) with individuals who have never contracted the virus. The study seeks to understand the long-term effects of COVID-19 on the ANS in order to obtain valuable insights into the persistent symptoms experienced by those patients and contribute to the development of therapeutic interventions to improve their quality of life.

METHODS

Ethics

The study was conducted following the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from Adıyaman University Non-interventional Clinical Researches Ethics Committee (Date: 21.06.2022, Decision No: 2022/6-4).

Study Population

This retrospective study evaluated 225 participants in two groups: 117 patients in the COVID-19 group and 108 control subjects. The patient group consisted of individuals diagnosed with COVID-19 disease but did not experience severe symptoms requiring hospitalization, this group was evaluated within 12 month after the recovery of the disease. The control group, matched by age and gender to the patient group, was selected from the non-COVID era database to prevent the unintentional inclusion of asymptomatic COVID-19 cases.

The exclusion criteria included the presence of any comorbidities known to influence autonomic function, such as cardiovascular diseases, obesity, diabetes, chronic renal disease, obstructive sleep apnea and depression. Those using medications that could affect HRV (like beta blockers, inhaled beta-mimetics, atropine, glycosides, selective serotonin reuptake inhibitors, angiotensin-converting enzyme inhibitors, etc.) were also excluded.

HRV Assessment

HRV was assessed using 24-hour ambulatory electrocardiography (ECG) recordings. The ECG data were collected using a DMS300-4A Holter ECG recorder and analyzed with CardioScan Premier 12 software. Time-domain indices of HRV including SDNN (standard deviation of all normal RR intervals in a 24-hour period), Standard deviation of the average normal-to-normal intervals (SDANN), SDNNi (the index of SDNN), RMSSD and pNN50 (percentage of successive RR intervals that differ by more than 50 ms) were calculated. Furthermore frequency-domain indices of HRV including LF (low frequency, representing both sympathetic and parasympathetic activity), HF (high frequency, representing parasympathetic activity) and LF/HF ratio (indicating the balance between sympathetic and parasympathetic activity) were also calculated.

Statistical Analysis

Statistical analysis was conducted using SPSS (Statistical Package for Social Sciences) version 20. Normality of the data was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics were presented as mean and standard deviation for numerical variables, and as counts and percentages for categorical variables. Comparative analyses between the study and control groups were performed using independent t-tests for normally distributed numerical data and the Mann-Whitney U test for non-normally distributed data. Categorical variables were compared using the Chi-square test. Pearson correlation analysis was used for variables that met normal distribution criteria, while Spearman correlation was used for non-normally distributed variables. A significance level of $p<0.05$ was considered statistically significant.

RESULTS

The mean age of the study group was 38.7±6.7 years, while the control group had a mean age of 41.3±13.7 years. The gender distribution was comparable between the groups, with 68.5% females in the study group and 58.1% females in the control group.

The HRV metrics for both groups, summarized in **Table**, reveal significant differences. In the time-domain indices, the control group had higher SDNN over 24 hours values than the study group (149.1±34.2 ms vs 135.7±39.5 ms, p=0.007). Similarly, SDANN over 24 hours was higher in the control group compared to the study group (134.7±34.1 ms vs 123.4±41.7 ms, p=0.027). SDNNi over 24 hours was also greater in the control group than the study group (64.2±17.1 ms vs 56.7±16.2 ms, p<0.001). RMSSD was higher in the control group than in the study group (37.5±14.7 ms vs 32.7±13.7 ms, p=0.012), and pNN50 was significantly higher in the control group compared to the study group (14.7±10.5 vs 10.8±9, p=0.003).

In the frequency-domain indices, total power (TP) was significantly higher in the control group compared to the study group (4.254±2.208 ms^2 vs 3.378±1.908 ms^2, p=0.002). LF power was also higher in the control group compared to the study group (992.2±421.6 ms^2 vs 736.5±412.1 ms^2, p<0.001). HF power was elevated in the control group compared to the study group (413.9±272.5 ms^2 vs 305.7±251.5 ms^2, p=0.023). However, the LF/HF ratio did not differ significantly between the two groups (3.05±1.6 vs 3.17±1.8, p=0.597). Similar results were observed during both sleep and waking periods, with the control group consistently showing higher values across most HRV metrics compared to the study group.

Regarding the relationship between the length of the post-COVID period and HRV metrics. Most HRV indices did not show significant correlation with the duration of post-COVID symptoms with 12 months of follow up, except for the LF/HF ratio during sleep, which had a negative correlation (r=-0.23, p=0.02).

Table 1. Descriptive statistics of study variables and comparison between groups

Variable	Control group (n=117)	Study group (n=108)	p
Age (years)	38.7±6.7	41.3±13.7	0.068
Gender n(%)			
Female	68 (58.1%)	74 (68.5%)	0.106
Male	49 (41.9%)	34 (31.5%)	0.107
Post-COVID duration (months)	-	5.8±3.9	-
HRmin	46.7±6.8	49.1±8.6	0.021*
HRmax	145.7±17.9	139.3±28.2	0.041*
HRaverage	79.1±9.2	78.5±9.3	0.627
SDNN ms (24 hours)	149.1±34.2	135.7±39.5	0.007*
SDANN (24 hours)	134.7±34.1	123.4±41.7	0.027*
SDNNi (24 hours)	64.2±17.1	56.7±16.2	<0.001*
RMSSD (24 hours)	37.5±14.7	32.7±13.7	0.012*
pNN50 (24 hours)	14.7±10.5	10.8±9.1	0.003*
TP (24 hours)	4.254±2.208	3.378±1.908	0.002*
LF (24 hours)	992.2±421.6	736.5±412.1	<0.001*
HF (24 hours)	413.9±272.5	305.7±251.5	0.023*
LF/HF ratio (24 hours)	3.05±1.6	3.17±1.8	0.597
Awake SDNN	128.8±29.9	117.3±32.8	0.006*
Awake RMSSD	33.2±14.1	31.4±21.6	0.461
Awake pNN50	11.5±9.6	10.4±9.7	0.393
Awake TP	4.012±2.191	3.118±1.846	0.001*
Awake LF	962.1±415.3	707.6±434.7	<0.001*
Awake HF	360.5±375.9	241.4±193.1	0.004*
Awake LF/HF ratio	3.7±2.1	3.8±2.3	0.734
Sleep SDNN	120.4±35.2	108.4±38.3	0.015*
Sleep RMSSD	46.3±19.3	38.5±18.9	0.003*
Sleep pNN50	22.8±15.1	16.1±15.2	0.001*
Sleep TP	4.695±2.489	3.798±2.487	0.007*
Sleep LF	1046.3±484.1	720.4±450.9	<0.001*
Sleep HF	566.4±378.4	420.6±422.9	0.007*
Sleep LF/HF ratio	2.46±1.5	2.81±1.7	0.102

Abbreviations: HR: Heart rate, SDNN: Standard deviation of normal-to-normal intervals, SDANN: Standard deviation of the average normal-to-normal intervals, SDNNi: Index of the standard deviation of normal-to-normal intervals , RMSSD: Root mean square of successive RR interval differences, pNN50: Percentage of successive RR intervals that differ by more than 50 ms, TP: Total power , LF: Low frequency bands, HF: High frequency bands

DISCUSSION

The findings of this study provide significant insights into the autonomic dysfunction and HRV alterations in post-COVID-19 patients on the long term. This autonomic impairment, reflected in diminished HRV indices, suggests a persistent dysregulation of the ANS following SARS-CoV-2 infection.

The pathophysiological mechanisms underlying the autonomic dysfunction in post-COVID patients remain an area of active research.[12] The observed alterations in HRV among post-COVID-19 patients is likely multifactorial in origin.[13] SARS-CoV-2 is known to invade the central nervous system (CNS) via the olfactory nerve, with subsequent involvement of the hypothalamic-pituitary-adrenal (HPA) axis which is critical for autonomic regulation.[14] This neuroinvasion, combined with a systemic inflammatory response characterized by elevated levels of pro-inflammatory cytokines (e.g., IL-6, TNF-α), likely contributes to autonomic imbalance.[15] Furthermore, the cytokine storm associated with severe COVID-19 exacerbates oxidative stress and endothelial dysfunction, which are critical in mediating autonomic dysregulation leading to chronic dysautonomia.[16]

In comparison with the control group, the post-COVID-19 patients in our study exhibited significant reductions in key HRV parameters, such as the SDNN and the root mean square of successive differences (RMSSD). These reductions suggest a shift towards sympathetic dominance, a condition often associated with poor cardiovascular outcomes. The reduction in parasympathetic tone leads to an increased risk for cardiovascular morbidity, including arrhythmias and myocardial ischemia.[17,18] Furthermore, the persistence of autonomic dysfunction post-COVID-19 raises significant concerns regarding long-term cardiovascular health. These findings underscore the necessity for ongoing cardiovascular monitoring and proactive management strategies in this population.

Recent studies that have reported similar patterns of autonomic dysfunction in COVID-19 survivors.[19] A study conducted using 24-hour Holter monitoring, obtained 12 weeks after the diagnosis of the disease, revealed significant reductions in HRV among post-COVID-19 patients compared to healthy controls. Notably, time-domain indices like SDNN and rMSSD were substantially lower in the COVID-19 group, indicating diminished parasympathetic activity. This finding supports the hypothesis that SARS-CoV-2 infection leads to prolonged autonomic imbalance, which could predispose patients to future cardiovascular complications.[20] Another research tracking HRV in patients up to six months post-COVID-19 hospitalization demonstrated that autonomic dysfunction persists long after the acute phase of the infection.[21]

We evaluated HRV within 12 months after the recovery of the disease and our findings reinforce the concept of autonomic impairment as a sequela of COVID-19, highlighting its persistence over an extended follow-up periods. In addition, we explored the correlation between the duration since recovering from COVID-19 and the degree of autonomic dysfunction. Our results indicated that there is no statistically significant correlation between post-COVID duration and most markers of autonomic function (such as SDNN, RMSSD, and TP) in both awake and sleep states. These results suggest that the duration of time following the recovery of COVID-19 infection does not seem to be associated with a decrease in

autonomic dysfunction. However, one notable exception is the LF/HF ratio during sleep, which showed a statistically significant negative correlation. This suggests that as time passes, there may be a trend toward improved autonomic balance during sleep, characterized by a reduction in the LF/HF ratio, potentially reflecting a shift toward parasympathetic dominance during this period. Therefore, while there is some evidence that autonomic dysfunction may improve over time during sleep, it cannot be generalized across all autonomic parameters. From a clinical perspective, the incorporation of HRV monitoring into routine follow-up for post-COVID-19 patients could serve as a valuable tool for early detection of autonomic dysregulation and impending cardiovascular complications. Moreover, therapeutic interventions aimed at modulating autonomic function, such as exercise-based rehabilitation, biofeedback, and pharmacologic agents (e.g., beta-blockers, ACE inhibitors), can be considered as part of a comprehensive care strategy.

Limitations

This study has some limitations that need to be addressed in future research. The cross-sectional design and the relatively small sample size of the study may limit the generalizability of the findings. Furthermore, the exclusion of severe COVID-19 cases might result in an incomplete representation of the entire spectrum of post-COVID autonomic dysfunction. Future research should consist of longitudinal studies with larger cohorts and diverse populations to explain the course of autonomic recovery and identify potential predictors of persistent dysfunction. Additionally, exploring the impact of various therapeutic interventions on HRV recovery could inform clinical practice and improve patient outcomes.

CONCLUSION

This study provides insights into the autonomic dysfunction elicited by the decreased HRV indices observed in post-COVID patients, highlighting the need for continued research and targeted interventions to address the long-term cardiovascular effects of COVID-19. Understanding and managing these autonomic imbalances will be critical for improving the health and well-being of individuals recovering from COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval was obtained from Adıyaman University Non-interventional Clinical Researches Ethics Committee (Date: 21.06.2022, Decision No: 2022/6-4).

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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The impact of health workforce and health expenditures on life expectancy and infant mortality rates in Turkiye

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ABSTRACT

Aims: This study examines the impact of the number of health personnel and health expenditures on life expectancy and infant mortality rates in Turkiye. The study's primary purpose is to determine the effect of increased health personnel and health expenditures on quality of life and infant mortality rates. Therefore, the impact of health personnel and expenses on life expectancy and infant mortality rates was investigated. It was analyzed how these variables shape the effectiveness of health services and how they affect public health.

Methods: This study used multiple regression analysis to assess the effects of healthcare workforce and expenditures on health outcomes in Turkiye between 2001 and 2021. Life expectancy and infant mortality rate were dependent variables, while per capita healthcare expenditure, the number of doctors, and the number of nurses were used as independent variables. Data were obtained from the World Health Organization (WHO) and the Organization for Economic Cooperation and Development (OECD) databases and analyzed using the SPSS software.

Results: The findings indicate that per capita healthcare expenditures positively and significantly affect life expectancy (B=0.015, p=0.016), suggesting that increases in healthcare spending contribute to longer life expectancy. Conversely, the effects of the number of doctors (B=-1.580, p=0.138) and nurses (B=0.232, p=0.400) were not statistically significant, indicating that workforce numbers alone may not directly impact life expectancy. Regarding infant mortality rate, healthcare expenditure (B=-0.016, p=0.166) and doctor availability (B=-1.503, p=0.467) showed negative associations, while the number of nurses had a positive but non-significant association (B=0.407, p=0.457). Although these variables theoretically demonstrated the potential to reduce infant mortality rates, none of these effects reached statistical significance. The model explained 82.5% (R^2=0.825) of the variance in life expectancy and 88.7% (R^2=0.887) in infant mortality rate, underscoring the model's robustness in explaining variations in these health outcomes.

Conclusion: The study findings suggest that while healthcare expenditures positively affect life expectancy, the number of healthcare workers alone is insufficient, and factors such as service quality and efficiency also play a role. In developing health policies, strategies should focus on systematically improving the quality of services rather than merely increasing the number of personnel. Particularly in rural and low-income areas, the scope and quality of healthcare services should be enhanced to reduce disparities in health indicators.

Keywords: Health expenditures, life expectancy, infant mortality, regression analysis

INTRODUCTION

The effectiveness of health services is critical to public health, and the success of health systems depends mainly on the quality, distribution, and adequacy of the health workforce. The education, experience, geographic distribution, and workload of health workers directly affect the quality and accessibility of health services. The health workforce directly impacts health indicators and can make significant differences in key indicators, particularly infant and overall mortality.[1,2] These indicators are used to evaluate the effectiveness of health systems and develop policies to improve public health.[3]

Inadequate health workforce in low-income countries around the world results in negative health indicators.[4,5] This situation is directly related to the quality and distribution of the health workforce. It is known that in regions where the number of health workers is insufficient and their education levels are low, infant mortality rates are higher, and access to health services is limited.[6] The adequacy of the health workforce plays a critical role in improving the quality of health services. In particular, an increase in essential health workers, such as nurses and doctors, can positively affect the quality and accessibility of health services.[7]

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The COVID-19 pandemic has once again highlighted the importance of the healthcare workforce in healthcare systems. During the pandemic, healthcare workers have faced increased workloads, insufficient protective equipment, and intense psychological pressure.[8,9] In this process, the burnout syndrome and stress faced by healthcare professionals in many countries have negatively affected the overall effectiveness of healthcare services and led to deterioration in health indicators.[10,11] Especially in low- and middle-income countries, the inadequacy of the health workforce during the COVID-19 period has caused health indicators to deteriorate.[12]

The regional distribution of the health workforce is an essential factor determining its impact on health indicators. Even in developed countries, imbalances in health workers between rural and urban areas lead to significant differences in the quality of health services.[13] A study conducted in Turkiye revealed that health workforce indicators, especially the number of nurses and doctors, significantly impact infant mortality rates.[2] These studies have shown that inequalities in the distribution of the health workforce directly affect access to and quality of health services.[4]

The mental health of the healthcare workforce can directly impact the quality of care. Especially during pandemics and times of crisis, the stress, burnout, and work-life balance issues faced by healthcare professionals can negatively affect the quality of healthcare services.[14,15] Studies conducted during the COVID-19 pandemic show that the psychological well-being of healthcare workers affects general health indicators.[9,16] Therefore, supporting the mental health of healthcare professionals and balancing their workload is strategically essential in improving healthcare services' quality.[10,11]

The level of education and continuing professional development of the health workforce are other important factors determining the quality of health services. Highly educated and specialized health professionals can provide more effective interventions in complex emergencies and improve health outcomes.[4] This becomes especially evident during times of crisis; for example, during the COVID-19 pandemic, trained healthcare professionals were seen to improve health indicators by providing rapid and effective interventions.[13,17] Continuous professional development of healthcare professionals is a sustainable solution to improve public health.[18]

During the pandemic, challenges faced by healthcare professionals have negatively affected healthcare services' overall performance. Factors such as workload, mental health, and work-life balance of healthcare professionals have a significant impact on health indicators such as infant mortality rate and overall mortality.[7,19] This situation reveals the need to support and strengthen the health workforce.[8] Reducing the workload of healthcare professionals, increasing training, and improving working conditions is a strategic priority for the sustainability of healthcare systems.[10,14]

Ecological studies conducted in Turkiye have examined the effects of socioeconomic factors and health service indicators on the infant mortality rate.[2,12] These studies have revealed that socioeconomic level determines the relationship between health service indicators and infant mortality rate.[2,12] Similarly, the impact of variables such as income level and education level on health indicators are critical elements to be considered in developing health policies.[9]

A balanced distribution of the health workforce is an important strategy to improve the performance of health systems and reduce health inequalities. Increasing the number of health workers, especially in rural and disadvantaged areas, can improve access to health services and achieve positive health indicators results.[4,5] The qualification and training of the health workforce provide sustainable solutions to improve public health.[18] Therefore, health policies must be planned to increase and develop the health workforce, especially in low-income and rural areas.[13]

As a result, the health workforce's quality, distribution, and workload are among the main factors that directly affect the overall effectiveness of health systems and public health. Improving health indicators will be possible by strengthening and supporting the health workforce. In this context, increasing the education of health workers, protecting their mental health, and improving their working conditions are strategic requirements to ensure the sustainability of health systems.[9,14]

METHODS

Type and Model of the Study

Since secondary data is used in the study, ethics committee approval is not required. This study used multiple regression analysis to evaluate the impact of health resources on significant health outcomes in Türkiye from 2001-2021. Regression models were structured to assess the health expenditure per capita, number of doctors per 10,000 people, and number of nurses per 10,000 people as independent variables, and life expectancy and infant mortality rate as dependent variables.

Statistical Analysis

Data were obtained from the World Health Organization (WHO) and the Organization for Economic Co-operation and Development (OECD) databases, and consistency and comparability were ensured throughout the period examined. Multiple regression analysis was performed to analyze how health expenditure and personnel distribution changes affected the selected health outcomes. The significance level was taken as 5% in each model. The analyses were performed in the SPSS Package program. Data sources are shown in **Table 1**.

After the data is obtained, the analysis includes variables such as life expectancy, infant mortality rate, health expenditures, and number of doctors and nurses. The variables used in the study are defined below.

- **Dependent Variables:**

Life Expectancy (Years): Indicates life expectancy in Turkiye.

Infant Mortality Rate (per 1000 Live Births): Indicates the proportion of babies who die within one year after birth.

Table 1. Sources of data for variables

Variables	Data source
Number of doctors per 10000 people	https://data.who.int/indicators/i/CCCEBB2/217795A?m49=792
Number of nurses per 10,000 people	https://data.who.int/indicators/i/B54EB15/5C8435F?m49=792
Health expenditure per capita	https://www.oecd.org/en/data/indicators/health-spending.html?oecdcontrol-38c744bfa4-var1=TUR&oecdcontrol-00b22b2429-var3=2001
Life expectancy	https://www.oecd.org/en/data/indicators/life-expectancy-at-birth.html?oecdcontrol-0ad85c6bab-var1=TUR&oecdcontrol-f42fb73652-var3=2001
Infant mortality rate per 1000 live births	https://platform.who.int/data/maternal-newborn-child-adolescent-ageing/indicator-explorer-new/MCA/infant-mortality-rate-(per-1000-live-births)

• Independent Variables:

Number of Doctors (Per Capita): Shows the number of doctors available per 1000 people.

Number of Nurses (Per Capita): Shows the number of nurses available per 1000 people.

Health Expenditure Per Capita (USD): The amount of spending on health services per person.

• The following steps were followed for data analysis:

1. **Descriptive Statistics:** Basic descriptive statistics were calculated to reveal the general characteristics of the data.
2. **Assumption Analysis:** Assumptions were tested and analyzed for multiple regression analysis. As a result of the study, necessary corrections were made to meet the assumptions.
3. **Regression Analysis:** Multiple regression analyses examined the relationships between dependent and independent variables. Two separate models were developed, the first of which evaluated the effects of independent variables on life expectancy and the second on infant mortality rate. The analysis was performed as a multiple regression analysis in the SPSS package program.

Assumption Tests and Corrections

A multicollinearity problem was detected in the analyses due to the high correlation between the independent variables. This problem was resolved using Principal Component Analysis (PCA). Although PCA is generally used for dimension reduction, it was preferred in this study to eliminate multicollinearity. Using only one component (PC1) from PCA means benefiting from a single combined effect rather than directly seeing the interaction of these variables.

As a result of PCA, the first principal component (PC1) was obtained, which explains 98.8% of the variance of the independent variables. PC1 consists of the following independent variables:

- Healthcare spending per capita (the variable contributing the highest weight),
- Number of doctors per 10,000 people,
- Number of nurses per 10,000 people.

The weight of each variable in PC1 is based on its capacity to represent the total variance of these variables. Multiple regression analyses were performed using this component.

To accurately evaluate the effects of independent variables, regression analysis assumptions were tested, and necessary corrections were made. Heteroskedasticity (non-constant variance) and autocorrelation (dependence of error terms on each other) problems were detected in error terms. These problems were resolved by using Newey-West standard errors. In addition, to better evaluate the effects of corrections, error terms, and model accuracy were checked in more detail in terms of repeatability. Regression analyses were applied using the OLS (Ordinary Least Squares) method, and care was taken to verify the assumptions.

The linearity assumption was tested by examining the relationships between the independent variables and the error terms, and it was determined that this assumption was met in both models. The normal distribution of the error terms was examined with the help of Q-Q plots. Although slight deviations were seen in the infant mortality rate model, the assumption was generally met. Heteroskedasticity problems were tested using the Breusch-Pagan test. It was determined that this problem existed for the life expectancy model, which was corrected using Newey-West standard errors. Autocorrelation problems were determined with the Durbin-Watson test, and autocorrelation was observed in both models. Newey-West standard errors also corrected these problems and provided reliable results. While making these corrections, the maximum lag length was taken as 1, and the HAC (Heteroskedasticity and Autocorrelation Consistent) matrix was used to minimize the autocorrelation and heteroskedasticity effects of the error terms. Multiple linearity problems were eliminated using PCA, and PC1 represented the common effects of the independent variables.

Q-Q plots examining the normal distribution of error terms are shown in **Figure 1** and **Figure 2**.

RESULTS

In the study, the data shown in **Table 2** were obtained using WHO and OECD databases.

According to **Figure 3**, life expectancy in Türkiye has generally shown a steady increase between 2001 and 2021. While the average life expectancy in 2001 was 71.5 years, this value increased to 77.5 years in 2021. This increase in life

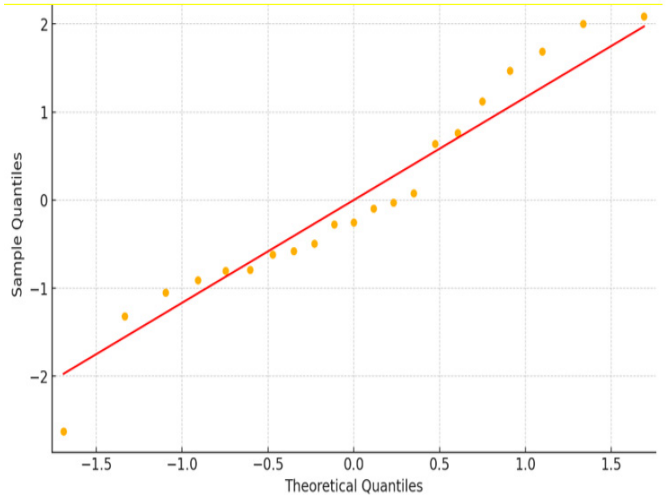

Figure 1. Quality of life Q-Q chart

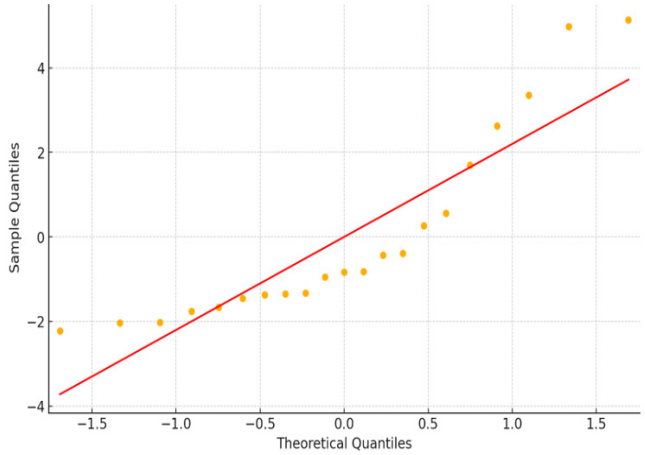

Figure 2. Infant mortality rate Q-Q chart

expectancy may reflect the improvements in Turkiye's health system and the positive effects of policies aimed at improving access to health services and public health. However, the slight decline in 2020 and 2021 also reveals the pressure of the COVID-19 pandemic on health systems and the effects of the pandemic on public health.

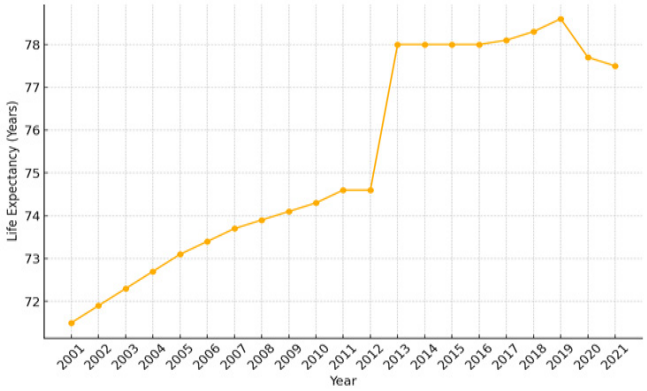

Figure 3. Change in life expectancy over the years

According to **Figure 4**, the infant mortality rate in Turkiye, which was 28.71 per 1,000 live births in 2001, has decreased to 8.62 in 2021. This decrease reflects the impact of improvements in Turkiye's infant health services, the expansion of prenatal care programs, and awareness-raising efforts for infant health. This decrease in infant mortality rates indicates the successful implementation of general health infrastructure and child health programs. This trend reveals that health standards in the country are rising and positively affect public health.

According to **Figure 5**, health expenditure per capita in Türkiye has shown a significant increase between 2001 and 2021. Health expenditure, which was 472.84 USD in 2001, increased

Tablo 2. Changes in variables over the years

Year	Life expectancy (years)	Infant mortality rate (per 1000 live births)	Health expenditure per capita (USD)	Number of doctors (per 10,000 people)	Number of nurses (per 10,000 people)
2001	71.5	28.71	472.84	13.8	17.6
2002	71.9	26.79	519.98	13.9	17.3
2003	72.3	24.99	509.73	14.1	17.4
2004	72.7	23.28	558.59	14.3	17.6
2005	73.1	21.70	588.13	14.7	17.7
2006	73.4	20.22	678.16	15.0	18.3
2007	73.7	18.86	733.36	15.4	20.1
2008	73.9	17.58	807.05	15.9	20.7
2009	74.1	16.42	815.07	16.4	21.4
2010	74.3	15.37	843.63	16.9	22.6
2011	74.6	14.43	888.31	17.0	23.8
2012	74.6	13.56	894.74	17.2	25.0
2013	78.0	12.78	947.74	17.5	25.2
2014	78.0	12.09	1006.77	17.4	25.0
2015	78.0	11.46	1040.11	17.7	25.9
2016	78.0	10.89	1128.75	17.9	25.4
2017	78.1	10.37	1175.66	18.3	26.8
2018	78.3	9.89	1205.31	18.5	29.8
2019	78.6	9.44	1231.63	19.3	30.4
2020	77.7	9.02	1304.71	20.4	34.0
2021	77.5	8.62	1559.54	21.7	34.2

Using these data, graphs showing the changes in the variables over the years will be obtained and interpreted.

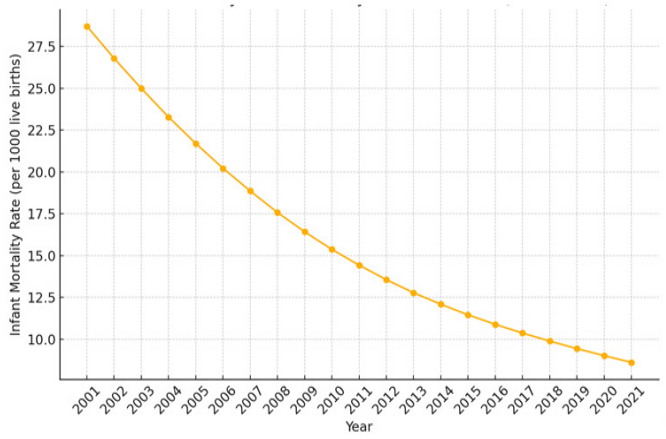

Figure 4. Change in infant mortality rate over the years

to 1559.54 USD in 2021. This increase indicates that public and private investments in health services have increased, and the health budget per capita has expanded. These increased health expenditures may also suggest improved access to and quality health services. In addition, the acceleration of the rise in health expenditures in 2020 and 2021 during the COVID-19 pandemic can be considered a reflection of efforts to strengthen the health system against the pandemic.

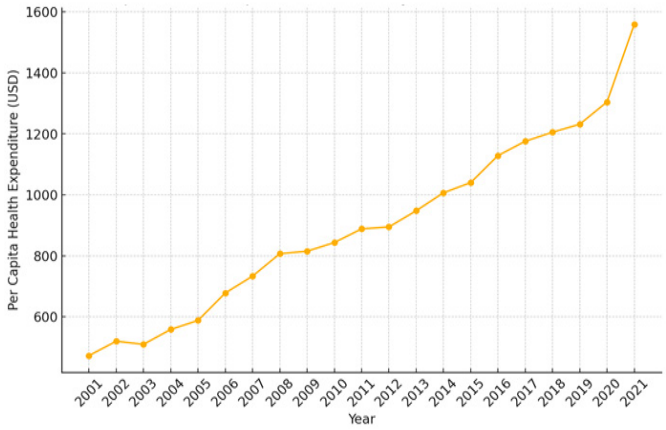

Figure 5. Change in health expenditure per capita over the years (USD)

According to **Figure 6**, there has been a continuous increase in the number of doctors and nurses per capita in Turkiye between 2001 and 2021. While the number of doctors was 13.8 per capita in 2001, it increased to 21.7 in 2021. The number of nurses, 17.6 per capita in 2001, reached 34.2 in 2021. These increases indicate Turkiye's strategic investments to increase its health workforce and support for medical education. The increase in the number of health workers has contributed to the expansion of access to health services, the increase in the quality of health services, and the reduction of the number of health workers per patient. The continuation of this increase during the pandemic supports the sustainability of Turkiye's long-term goals to strengthen its health system.

Table 3 above shows the multiple regression analysis results. The analyses revealed that the independent variables exhibited significant effects in both models. In particular, the increasing impact of PC1 on life expectancy shows that this component has a favorable structure originating from health expenditures and the number of doctors and nurses. The life expectancy

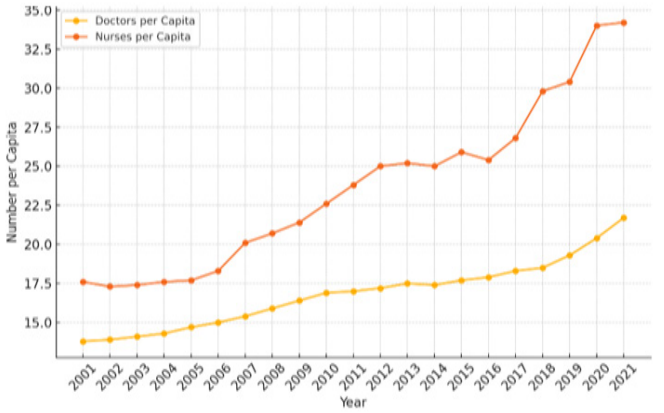

Figure 6. Change in the number of physicians and nurses per 10,000 people over the years

model is a strong model with an explanatory power of 77.3%, and the coefficient of PC1 was calculated at 1.25. This indicates that each unit increase in PC1 increases life expectancy by an average of 1.25 years.

The infant mortality rate model is even more impressive, with an explanatory power of 86.8%. The PC1 coefficient in this model was calculated as -3.28, which reveals that infant mortality rates decrease significantly with the increase in PC1.

These results suggest that increasing health expenditures and the number of health personnel alone may not be sufficient to reduce infant mortality. More comprehensive and systematic approaches, such as improving the quality of health services, strengthening health infrastructure, and improving access to health services, may be more effective in reducing infant mortality rates. In this context, it is considered necessary that health policies focus on increasing the system's overall efficiency, not just the number of personnel.

DISCUSSION

This study evaluated the effects of health expenditures and the distribution of health personnel on life expectancy and infant mortality rates in Turkiye. The findings reveal that health expenditures and various health personnel have a significant positive effect on life expectancy. The increase in the number of health personnel and increasing health expenditures contribute to the increase in life expectancy by improving the quality and accessibility of general health services. For example, Nixon and Ulmann state that health expenditures positively contribute to life expectancy, increasing access to treatment and improving service quality, thus affecting life expectancy.[20]

The effect of the number of health personnel on life expectancy in Turkiye is significant. However, increasing the number of health workers alone is not enough; the quality of service must also be improved. Studies by Anand and Bärnighausen[21] have indicated that health indicator improvements can be achieved by increasing the number of personnel and improving their professional competencies and education levels. This finding suggests that more investment should be made in training and development programs for healthcare professionals in Turkiye. Advanced training and development programs can positively

Table 3. Multiple regression analysis results

Model	R^2	PC1	PC1 std. error	t	p
Life expectancy	0.773	1.2488	0.217	5.752	0.000015
Infant mortality rate	0.868	-3.2758	0.499	-6.567	0.000003

affect health indicators by enabling healthcare professionals to intervene more effectively in complex situations.[22]

When evaluated regarding the infant mortality rate, it was concluded that health expenditure per capita and the number of health personnel could reduce it. In addition to health expenditure, socioeconomic conditions, access to health services, and infrastructure also play an essential role in infant mortality rates. Speybroeck and colleagues[23] stated that financial investments and the comprehensiveness of health services are critical in reducing the infant mortality rate. In this regard, Turkiye's health policies must focus on increasing access to health services in rural areas and strengthening the health infrastructure.

The COVID-19 pandemic has significantly increased the workload of healthcare professionals, which has negatively affected the effectiveness of healthcare services. The increased workload of healthcare professionals and increased psychological stress during the pandemic have led to a decrease in the quality of healthcare services and negative results in health indicators. Studies show that high workload and stress negatively affect the performance of healthcare professionals and lead to burnout syndrome.[24,25] Supporting the mental health of healthcare professionals during pandemic conditions is of strategic importance for both the sustainability of healthcare services and the improvement of health indicators in the long term.[12]

However, in addition to increasing the number of health workers, improving their qualifications is essential. The WHO report published in 2006 emphasized that health personnel should be strengthened not only in terms of numbers but also in terms of educational and professional skills.[26] Studies conducted in various countries have shown that trained health workers positively affect health outcomes. Khamisa et al.[25] stated that health workers' general health and job satisfaction increase health services' effectiveness and improve patient outcomes. Therefore, taking strategic steps towards training healthcare professionals in Turkiye may effectively improve health indicators.

Finally, balancing the workload of healthcare workers, protecting their mental health, and ensuring work-life balance are of great importance to ensure the sustainability of healthcare systems. The fact that healthcare workers constantly work under high workloads increases the turnover rate and leads to instability in healthcare services. Joshi and colleagues[16] argue that telehealth applications effectively alleviate this burden during the pandemic and can play an essential role in reducing the burden on healthcare workers in the future.

CONCLUSION

In conclusion, considering the positive impact of health expenditures and the number of health personnel on life expectancy and infant mortality rate in Turkiye, it can be said that efforts to increase financial resources of health policies can have positive results on public health. While it is necessary to increase the number of personnel to reduce infant mortality rates, it is also necessary to increase the quality of service, facilitate access to health services in rural areas and improve health infrastructure. Improving the qualifications of health workers and balancing their workload can also provide sustainable improvements in the health system.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since secondary data is used in the study, ethics committee approval is not required.

Informed Consent

Written authorisation is not required as the study was not performed on 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

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ANATOLIAN CURRENT MEDICAL

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Evaluation of prenatal-postnatal outcomes and risk factors in fetal jejunoileal atresia

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ABSTRACT

Aims: The aim of the current study is to reveal ultrasonographic and clinical features, evaluation of prenatal-postnatal outcomes and risk factors of fetal jejunoileal atresia.

Methods: This retrospective study evaluated all cases of fetal jejunoileal atresia identified between 2018 and 2024 at a tertiary centre of maternal-fetal medicine. In all cases, the pediatric surgery team confirmed the definitive diagnosis of jejunoileal atresia during the postnatal period. The cohort was divided into two groups, the "poor outcome" and "good outcome", in order to compare and evaluate risk factors determining the outcome.

Results: During the study period, a total of 18 cases were recorded. All cases in the cohort managed to reach live birth. 15 (83.3%) neonates survived after the surgical procedure, whereas 3 (16.7%) neonates were deceased during the post-operative period. Short bowel syndrome was diagnosed in 2 (11.1%) living cases during postoperative follow-ups. ≤80 cm intact bowel length predicts poor outcome with 80% sensitivity and 92.3% specificity (p<0,015). The distance of the most proximal point of atresia to Treitz ≤40 cm predicts poor outcome with 80% sensitivity and 69.2% specificity (p<0,025).

Conclusion: Fetal jejunoileal atresia still has high mortality and morbidity rates despite improved technology, surgical techniques and advanced postoperative care. Therefore, it is very important that the delivery and particularly surgical procedure should be performed by an experienced surgical team in well-equipped centers.

Keywords: Fetal jejunoileal atresia, prenatal diagnosis, outcome, risk factors

INTRODUCTION

Jejunoileal atresia is an extremely rare condition, with a prevalance of between 0.3 and 1.1 per 10.000 live births in Europe.[1] A significant portion of affected infants are born prematurely.[2,3] Commonly associated anomalies include cardiac and abdominal wall defects, and cystic fibrosis. The initial surgical intervention typically involves either primary anastomosis (with or without resection) or the creation of an ostomy. The outcomes for children with this condition can vary; some may thrive, while others may experience significant complications, including difficulties with feeding, short bowel syndrome, or liver failure.[4,5]

The prenatal identification of fetal gastrointestinal disorders plays a crucial role in the management following birth. By facilitating a pre-arranged approach to these conditions, it is possible to recommend delivery at a facility equipped with a pediatric surgical team at the appropriate gestational age, thereby reducing the long-term outcomes of the anomaly.[6]

Inaccurate prenatal counseling can adversely affect the psychological well-being of parents and diminish the overall quality of the pregnancy experience. The sensitivity of prenatal ultrasound in detecting small bowel atresia (SBA) has been noted to vary significantly, primarily influenced by the level of the obstruction. The diagnostic accuracy for jejunal and ileal atresia has been reported to range from 25% to 50%.[7]

The presence of bowel dilation and polyhydramnios during the third trimester of pregnancy are recognized as major findings of jejunal and ileal atresia; however, their sensitivity and specificity are limited. This is due to the fact that other conditions, including meconium ileus, colonic atresia, Hirschsprung's disease, and imperforate anus, may mimic comparable ultrasound characteristics.[8]

The aim of the current study is to reveal ultrasonographic and clinical features, evaluation of prenatal-postnatal outcomes and risk factors of fetal jejunoileal atresia.

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METHODS

The study was conducted with the permission of the Clinical Researches Ethics Committee of Zeynep Kamil Women's and Children's Diseases Training and Research Hospital (Date: 20.12.2023, Decision No: 170). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study evaluated all cases of fetal jejunoileal atresia identified between 2018 and 2024 at a tertiary centre of maternal-fetal medicine.

Patients with fetuses suspected of having jejunoileal atresia underwent weekly or biweekly ultrasound evaluations to monitor several key parameters. These assessments included the amniotic fluid index, indicators of fetal growth restriction (FGR), the presence of hyperechogenic bowel, and examinations of the stomach, gallbladder, small intestines, colon, anal target sign, as well as the detection of pseudocysts or intra-abdominal calcifications. Additionally, evaluations were conducted to assess for fetal anemia, ascites, intestinal peristalsis, and any associated anomalies. The volume of amniotic fluid was assessed using the amniotic fluid index, with values below 50 mm classified as oligohydramnios and those exceeding 250 mm categorized as polyhydramnios. A dilated intestinal loop is characterized as a hypoechoic, fluid-filled segment of the intestine that measures greater than 7 mm in diameter at its widest point. FGR was identified when the abdominal circumference was below the 3rd percentile in biometric assessments. Intestinal structures that appeared isoechoic in relation to adjacent bony elements were classified as hyperechogenic bowel. A lack of intestinal peristalsis observed for a minimum of 15 minutes during the ultrasonographic evaluation was characterized as decreased intestinal peristalsis. The diagnosis of fetal anemia was made when the peak systolic velocity of the middle cerebral artery exceeded 1.5 multiples of the median (MoM).

Genetic counseling was provided to all patients, and fetal karyotyping was offered. For those patients who did not have karyotyping conducted during the prenatal period, both karyotyping and cystic fibrosis mutation analysis were carried out after birth.

In each case, the pediatric surgery team confirmed the definitive diagnosis of jejunoileal atresia during the postnatal period. Details about the intraoperative findings were gathered from the surgical records and the surgical team.

The latest information regarding the cases was obtained through assessments carried out by specialists in paediatrics and paediatric gastroenterology, in addition to direct discussions with the parents concerned.

The cohort was divided into two separate groups: "poor outcome" and the other as "good outcome." This classification was intended to enable a comparison of outcomes and to evaluate the factors affecting these results. The two groups were compared in terms of demographic data, clinical characteristics, ultrasonographic findings, and postnatal outcomes.

All examinations were performed by experienced maternal-fetal medicine specialists utilizing a 5 MHz convex abdominal transducer (VOLUSON E6, GE).

Descriptive data are presented as median/25-75% interquartile range or numbers and %.

Statistical Analysis

Statistical analyses were performed using the Mann-Whitney U test for continuous data and the Fisher's exact test for proportions. To assess the performance of distance of atresia to Treitz and remaining intact bowel length in predicting poor and good outcome, receiver operating characteristic (ROC) analysis was performed. In all statistical analyzes the significance level (p-value) was determined at 0.05. The study data were analyzed using IBM SPSS statistics version 22.0 (IBM Corporation, Armonk, New York, United States) and MedCalc statistical software version 19.2.

RESULTS

From 2018 to 2024, our perinatology center monitored a total of 18 cases of fetal jejunoileal atresia, all of which were confirmed through postnatal pediatric surgical intervention. The median age of the cohort was 28 years old and the median gestational age for the first admission was 29.5 weeks. The most common reason for referral to our centre was dilated intestinal loops in 13 cases (72%). Hyperechogenic bowel in 2 cases (11%), FGR in 1 case (5.6%), fetal hydrops in 1 case (5.6%) and multiple structural anomaly in 1 case (5.6%) were the other reasons respectively. Clinical characteristics and prenatal-postnatal outcomes of the cohort were summerized in **Table 1**.

Throughout the prenatal monitoring, 4 cases showed no indications of intestinal obstruction. In one of these cases, there were no ultrasonographic findings at all. In the remaining three cases, the only ultrasonographic observation was a hyperechogenic bowel. Jejunoileal atresia was suspected in 14 cases based on ultrasonographic evaluations. Among these 14 cases, the median gestational age at which the diagnosis was suspected was 33 weeks, with the earliest gestational age of suspected jejunoileal atresia being 26 weeks (**Table 1**).

All patients except one received genetic counseling and were offered genetic diagnostic tests but prenatal genetic analysis was performed in only 2 patients via amniocentesis. Trisomy 18 was identified in one of these cases with jejunal atresia in addition to hypoplastic left heart syndrome and omphalocele. No karyotype abnormalities were detected in the other case that underwent amniocentesis and in the remaining 16 patients underwent postnatal genetic analysis (**Table 1**).

Ultrasonographic findings suggestive of fetal jejunoileal atresia were summarized in **Table 1**. Associated structural anomalies (hypoplastic left heart syndrome and omphalocele) were detected in 2 cases: hypoplastic left heart syndrome and omphalocele in 1 case and left isomerism in the other case. In 1 case (5.6%), FGR was detected before 32 weeks of gestation which were considered as early-onset FGR with umbilical artery end-diastolic flow loss.

Table 1. Demographic, clinical and ultrasonographic characteristics and prenatal-postnatal outcomes of the cohort (n=18)

Age, years (median/range)	28 (19-38)
Parity (median/range)	2 (1-4)
Consanguineous marriage (n,%)	5 (27.8)
GA at prenatal diagnosis, weeks (median/range)	33 (26-37)
Karyotype result	
Normal (n,%)	17 (94.4)
Trisomy 18 (n,%)	1 (5.6)
Ultrasonographic features	
FGR (n,%)	5 (27.8)
Polyhydramnios (n,%)	6 (33.3)
Oligohydramnios (n,%)	1 (5.6)
Dilated stomach (n,%)	3 (16.7)
Hyperechogenic intestines (n,%)	5 (27.8)
Dilated intestinal loops (n,%)	14 (77.8)
Ascites (n,%)	1 (5.6)
Decreased intestinal peristalsis (n,%)	4 (22.2)
Meconium pseudocyst (n,%)	1 (5.6)
Associated anomaly (n,%)	2 (11.1)
Prenatal diagnosis	
Jejunoileal atresia (n,%)	14 (77.8)
No diagnosis (n,%)	4 (22.2)
Mode of delivery	
Vaginal (n,%)	4 (22.2)
Cesarean (n,%)	14 (77.8)
GA at delivery, weeks (median/range)	37 (30-40)
Birthweight, gram (mean±SD)	2381±879
Postnatal surgery	18 (100)
Delivery to surgery, days (median/range)	2 (1-73)
Long term outcomes of live birth	
Neonatal death (n,%)	2 (11.1)
İnfant death 2-4 months (n,%)	1 (5.6)
Short gut syndrome (n,%)	2 (11.1)
Normal (n,%)	13 (72.2)
Cystic fibrosis (n,%)	2 (11.1)

Abbreviations: GA: Gestational age, FGR: Fetal growth restriction, SD: Standard deviation

All cases in the cohort managed to reach live birth. In the postnatal period, 8 of the neonates who were evaluated as intestinal obstruction were operated within the first 24 hours. Ten neonates were operated on after postnatal day 1, at the latest on day 73. Intraoperative features of the cases were summarized in **Table 2**. Accordingly, the median distance from Treitz ligament to the atresia was 45 cm (IQR 22.25-82.5) and the median length of intact bowel was 102.5 (IQR 78.25-122.5) cm in the cohort. During the postnatal period, cystic fibrosis was identified in two cases following the diagnosis of jejunoileal atresia. In six cases, thickened meconium was observed during surgical procedures; however, only one of these cases was subsequently confirmed to have cystic fibrosis after.

15 neonates survived after the surgical procedure, whereas 3 neonates were deceased during the post-operative period. Short bowel syndrome was diagnosed in 2 living cases during postoperative follow-ups. According to these findings, 5 cases including 3 deceased cases and 2 cases with short bowel syndrome were categorized as the "poor outcome" group, as 13 cases who had totally normal findings in postoperative period were categorized as the "good outcome" group to evaluate risk factors.

To evaluate prenatal and postnatal risk factors leading to poor outcome; demographic and clinical characteristics, ultrasonographic and surgical findings of both groups were analyzed. It was determined that there were no significant differences between two groups. On the other hand, receiver-operating characteristic (ROC) analysis was performed to determine a cut off value for the distance of the atresia to Treitz and intact bowel length (**Figure**). Accordingly, ≤80 cm intact bowel length predicts poor outcome with 80% sensitivity and 92.3 % specificity (p<0,015). The distance of the most proximal point of atresia to Treitz ≤40 cm predicts poor outcome with 80% sensitivity and 69.2% specificity (p<0,025).

DISCUSSION

Jejunoileal atresia frequently leads to neonatal intestinal obstruction, often resulting from intrauterine mesenteric vascular incidents. Recent developments in surgical methods, enhanced perinatal and postoperative care, along with the provision of artificial nutrition, have contributed to a decline in the overall mortality rate to 11-16% over the past few decades.[9] In more recent studies, mortality rates have been reported between 4% and 9%.[3,10,11] Mortality rate in our cohort was 16.6% as in line with the literature. Strategies aimed at

Table 2. Types of atresia, intraoperative findings, surgery type and complications

	Type 1	Type 2	Type 3a	Type 3b	Type 4
n, %	6 (33.3)	2 (11.1)	6 (33.3)	2 (11.1)	2 (11.1)
Segment with atresia					
Jejunal (n)	3	0	1	0	0
Ileal (n)	2	1	1	1	0
Jejunoileal (n)	1	1	4	1	2
Findings					
Malrotation (n)	4	0	1	2	1
Perforation (n)	1	0	2	0	0
Thick meconium (n)	2	1	1	1	1
Surgery type					
Resection+PA (n)	6	1 (ji)	6	2	1
Resection+stoma (n)	0	1 (i)	0	0	1
Complications					
Anastomosis leakage (n)	0	1	1	0	0
Adhesive obstruction (n)	2	0	0	1	0
Short bowel syndrome (n)	0	1 (ji)	0	0	1
Mortality (n)	1 (ji)	0	2 (1 j, 1 ji)	0	0

Abbreviations: i: ileal, j: jejunal, ji: jejunoileal

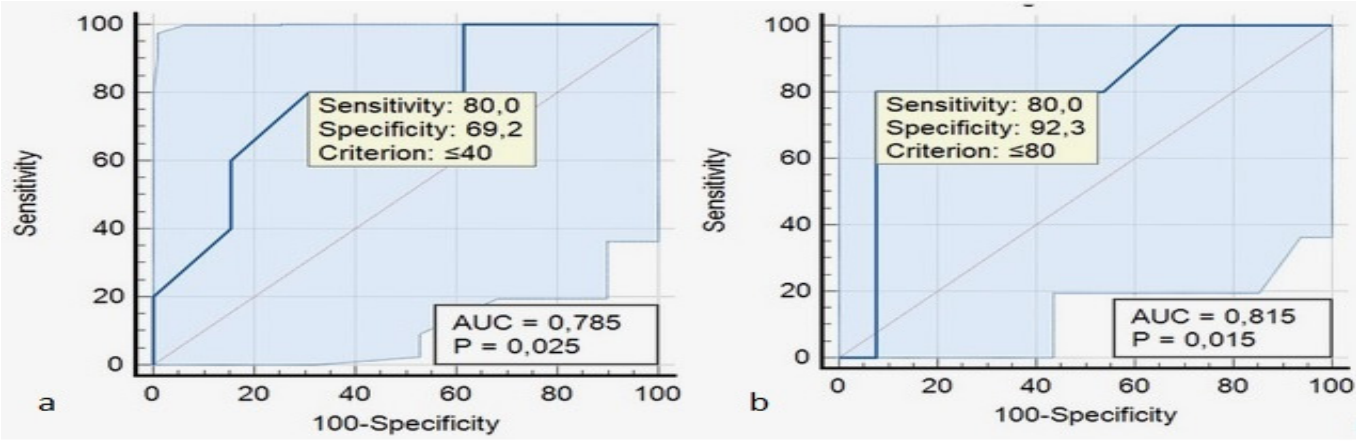

Figure. Receiver-operating characteristics analysis determined a cut-off for a) distance of the most proximal point of atresia to Treitz and b) remaining intact bowel

preserving bowel length and function have an impact on the length of time patients require total parenteral nutrition (TPN), with this duration being inversely related to the length of the remaining small bowel.[12] Extended reliance on artificial nutritional support increases the risk of complications, such as sepsis,[13] which was the cause of death in three cases within our cohort. It has been reported that associated anomalies can impact the outcome.[2] In our study, we observed that associated anomalies influenced two cases (11.1%): the first case involved hypoplastic left heart syndrome and omphalocele associated with trisomy 18, while the second case presented with left isomerism. As in the first case associated anomalies significantly contributed to the death of the newborn, in the second case did not affect the outcome. As previously reported in the literature, chromosomal abnormalities are observed at very low rates in jejunoileal atresia.[14] In our study, aneuploidy was detected in 1 case (5.5%) which is in line with the literature. Cystic fibrosis (CF) is estimated to impact between 5% and 24% of cases diagnosed with JIA.[3,15] In alignment with the findings of the current study, CF was identified in two of our cases, representing 11.1%, as determined through postnatal genetic analysis. JIA, particularly types IIIb and IV, along with associated complications such as volvulus, complicated meconium ileus, and meconium peritonitis, can lead to considerable intestinal loss, resulting in short bowel syndrome.[11] It is estimated that this occurs in 43% of cases.[16] In current study, during the long-term follow-up, two patients (11.1%) were identified as having short bowel syndrome and required nutritional support at home. One patient was born at term and underwent resection anastomosis due to type 2 atresia; however, a second surgical intervention was necessary 38 days later due to an anastomotic leakage, leading to another resection. The other patient was born at 35 weeks and received resection anastomosis for type 4 atresia, with a subsequent diagnosis of cystic fibrosis confirmed through genetic testing.

The prenatal ultrasound findings indicative of JIA including hyperechoic bowel, dilated fetal loops, and polyhydramnios, were commonly observed in our study. However, these findings did not influence the outcomes when compared between poor outcome and good outcome groups. There were also no differences in demographic and clinical characteristics, ultrasonographic and surgical findings between two groups.

CONCLUSION

In summary, it is well established that bowel loss and the resulting prolonged reliance on artificial nutrition are significant contributors to morbidity and mortality in patients with JIA, ultimately affecting their long-term prognosis and quality of life. Jejunoileal atresia still has high mortality and morbidity rates despite improved technology, surgical techniques and advanced postoperative care. Therefore, it is very important that the delivery and particularly surgical procedure should be performed by an experienced surgical team in well-equipped centers.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Clinical Researches Ethics Committee of Zeynep Kamil Women's and Children's Diseases Training and Research Hospital (Date: 20.12.2023, Decision No: 170).

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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Review

ANATOLIAN CURRENT MEDICAL

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Current approaches in the diagnosis and treatment of organizing pneumonia

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ABSTRACT

Organizing pneumonia (OP), is a rare yet well-defined form of interstitial lung disease. The condition can be idiopathic, termed cryptogenic organizing pneumonia (COP), or secondary to various causes, including infections, connective tissue diseases, medications, and malignancies. OP typically presents with nonspecific symptoms such as cough, dyspnea, fever, and weight loss, often mimicking other respiratory conditions like pneumonia or interstitial lung diseases. Radiological findings are varied but commonly include bilateral, patchy consolidations or ground-glass opacities with preserved lung volumes. Diagnosis often requires high-resolution computed tomography (HRCT) and may be confirmed by lung biopsy when clinical and imaging findings are inconclusive. Laboratory studies and bronchoalveolar lavage can aid in excluding alternative diagnoses. Glucocorticoids remain the mainstay of treatment, with most patients responding well to therapy. This review explores current advances in the diagnosis, differential diagnosis, and management of OP, emphasizing the importance of a multidisciplinary approach to optimize patient outcomes.

Keywords: Organizing pneumonia, cryptogenic organizing pneumonia, interstitial lung disease, glucocorticoid therapy

INTRODUCTION

Organizing pneumonia (OP) is a rare yet highly distinctive form of interstitial lung disease. Previously known as bronchiolitis obliterans organizing pneumonia (BOOP), this condition was reclassified as OP in the guidelines updated by the American Thoracic Society/European Respiratory Society (ATS/ERS) on the classification of idiopathic interstitial pneumonias. When no underlying cause is identified, it is referred to as "idiopathic/cryptogenic" organizing pneumonia (COP). If it develops secondary to connective tissue diseases, various medications, malignancies, or other interstitial pneumonias, it is termed secondary OP. The causes of Secondary OP are listed in **Table 1**. It is an interstitial lung disease that typically involves recurrent involvement of the peripheral areas of the lung, resulting from destruction of the alveolar wall, and is characterized by a good response to systemic glucocorticoid therapy.

Table 1. Causes of secondary organizing pneumonia

Systemic diseases	Conditions such as *Crohn's disease, ulcerative colitis, Behçet's disease, systemic lupus erythematosus, scleroderma, myelodysplastic syndromes, leukemia,* and malignancies.
Collagen tissue diseases	*Rheumatoid arthritis, Sjögren's syndrome, Wegener's granulomatosis.*
Infectious agents	*Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionella pneumophila, Pseudomonas aeruginosa, Streptococcus pneumoniae,* viruses (*Herpes, HIV, Influenza, Parainfluenza*), *Pneumocystis jirovecii,* and others.
Drugs	Medications such as *aminosalicylic acid, amiodarone, bleomycin, cocaine, sulfasalazine, mesalazine, gold salts, phenytoin, ticlopidine,* among others.
Radiotherapy	

EPIDEMIOLOGY

While OP can affect individuals of any age, it is more commonly observed in the fifth and sixth decades of life. The disease occurs with similar frequency in both men and women.[1] Precise data on its incidence are not available; however, it is recognized as a rare condition.

PATHOGENESIS

The exact pathogenesis of cryptogenic organizing pneumonia (COP) remains unclear. Following acute damage to the alveolar epithelium, plasma proteins and fibroblasts accumulate within the alveolar lumen, leading to fibrin deposition. This

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is followed by a reversible inflammatory and fibroproliferative process, characterized by fibroinflammatory buds (Masson bodies) that do not disrupt the lung's architecture.

Some studies suggest that COP may be associated with the abnormal regulation of vascular endothelial growth factor and matrix metalloproteinases.[2,3] Additionally, publications propose a relationship between microaspiration caused by gastroesophageal reflux and COP.[4] Environmental factors have also been reported to play a role in its development.[5]

CLINICAL FEATURES

The clinical presentation is highly characteristic. The most common symptoms include non-productive cough, dyspnea, weight loss, fever, and fatigue, often accompanied by a viral infection-like syndrome that began a few weeks earlier. These symptoms are frequently observed in patients with unresolved or recurrent pulmonary infiltrates, mimicking infectious pneumonia. As a result, it is often initially evaluated as community-acquired pneumonia but should be considered when there is insufficient response to empirical antibiotic therapy. Similar to interstitial lung diseases (ILDs), symptoms or history suggestive of connective tissue diseases-such as arthralgias, dry eyes, dry mouth, or muscle weakness-may also be present. A history of medication use, therapeutic radiation, or exposure to smoke or dust should be investigated, especially in cases of secondary OP. Additionally, a recent study evaluated the seasonal characteristics of COP and reported that the highest rates of diagnosis and hospitalization occurred during the spring season.[6]

PHYSICAL EXAMINATION FINDINGS

Inspiratory crackles are heard in approximately 60% of patients with COP. Fewer than 5% of cases present with finger clubbing. Additionally, systemic examination findings such as alopecia, Gottron's papules, or heliotrope rash should be noted, particularly given the associations with dermatomyositis, polymyositis, and scleroderma.

RADIOLOGICAL FINDINGS

The radiological findings of COP are variable and are presented in **Table 2**. Typically, bilateral, diffuse, patchy consolidation or ground-glass opacities are observed, with no changes in lung volumes. Consolidations may also exhibit recurrent and migratory characteristics.

Table 2. Radiological findings of cryptogenic organizing pneumonia[7]

- Bilateral, diffuse, patchy consolidation or ground-glass opacities with unchanged lung volumes
- Opacities often localized to peripheral lung fields, similar to chronic eosinophilic pneumonia
-Recurrent or shifting lung opacities
-Unilateral consolidation or ground-glass opacities
-Nodular opacities
-Minimal and usually unilateral pleural effusion (5%)

LABORATORY FINDINGS

There are no specific laboratory findings for COP.[8] Patients frequently present with clinical features resembling pneumonia; therefore, routine laboratory tests should include complete blood count, blood urea nitrogen, creatinine, and hepatic function tests. Leukocytosis is present in approximately 50% of patients.[9] While not routinely utilized, elevated erythrocyte sedimentation rate (ESR; often ≥100 mm/hr) and C-reactive protein are found in 70-80% of patients. For patients hospitalized with suspected community-acquired pneumonia, additional tests may be performed to identify pathogens, such as sputum Gram staining and culture, or testing for pneumococcal and Legionella antigens.

COP patients may develop mild to moderate restrictive pulmonary function abnormalities. Most patients exhibit reduced carbon monoxide diffusion capacity. Mild hypoxemia, either at rest or during exercise, is a common finding observed in approximately 80% of cases.

HISTOPATHOLOGICAL FINDINGS

In COP, histopathological examination reveals granulation tissue buds (Masson bodies) composed of fibroblasts, collagen, and fibrinous exudates within alveolar ducts and alveoli. Two main criteria must be met to establish the histopathological diagnosis of COP:

1.The sample must exhibit the characteristic histopathological features of OP.

2.There should be no histopathological features indicative of other processes, such as:

- Granulomas suggestive of hypersensitivity pneumonitis.
- Prominent eosinophilia suggestive of chronic eosinophilic pneumonia.
- Temporal heterogeneity of lesions or fibroblast foci characteristic of usual interstitial pneumonia.

To ensure adequate tissue is obtained for diagnosis and to exclude other processes like nonspecific or usual interstitial pneumonia, transthoracic biopsy under CT guidance or video-assisted thoracoscopic surgery (VATS) is recommended instead of transbronchial biopsy.

DIAGNOSIS

Patients with COP often present with symptoms suggestive of community-acquired pneumonia. Less commonly, they may present with clinical and radiographic features similar to other interstitial lung diseases (ILDs). The hallmark features in these patients include subacute cough and dyspnea, with peripheral, irregularly defined ground-glass infiltrations or consolidations that do not respond to antibiotic treatment.

High-resolution computed tomography (HRCT) is used to evaluate the extent of lung involvement and differentiate COP from other ILDs.

Spirometry is used to evaluate diffusion capacity, determine disease severity, and monitor disease.

OP may present as an initial clinical manifestation of dermatomyositis and polymyositis. Less frequently, it may be associated with rheumatoid arthritis, systemic lupus erythematosus, or scleroderma. In patients without overt symptoms of rheumatologic diseases, it is recommended to test for antinuclear antibody, rheumatoid factor, creatine

kinase, antitopoisomerase (anti-Scl70), anticentromere antibody, anti-double-stranded DNA, and anti-JO1.

Bronchoalveolar lavage (BAL) typically demonstrates a mixed pattern, with lymphocytes (20-50%) being predominant, and neutrophils (5-10%) and eosinophils (5-25%) also elevated.[10] While BAL is not diagnostic for OP, it is essential for ruling out alternative diagnoses.

In cases where COP diagnosis remains uncertain or to exclude other potential diagnoses, transthoracic lung biopsy under CT guidance is recommended. If the disease does not regress as expected with treatment, larger tissue samples should be obtained through video-assisted thoracoscopic surgery (VATS) or thoracotomy. In most cases, the differential diagnosis includes atypical infections, eosinophilic pneumonia, alveolar hemorrhage, or lymphangitic malignancy.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of COP includes a wide range of diseases with similar clinical, radiological, and histopathological features:

Pneumonia

The onset of symptoms and radiographic appearance often mimic community-acquired pneumonia; however, COP is differentiated by the prolonged duration of symptoms and lack of response to antibiotic therapy.

Chronic Eosinophilic Pneumonia (CEP)

CEP can present with clinical features similar to COP. Both diseases show subpleural patchy consolidation areas. Peripheral eosinophilia and eosinophil counts exceeding 25% in bronchoalveolar lavage (BAL) favor CEP. Response to treatment is typically slower in COP, while CEP often shows a rapid response to corticosteroids within a few days.

Hypersensitivity Pneumonitis (HP)

The clinical presentation of COP (e.g., cough, dyspnea, fatigue, weakness, loss of appetite, and weight loss) is similar to subacute HP. However, subacute HP is distinguished by its radiographic findings (e.g., widespread micronodules and ground-glass appearance) and a history of exposure to an etiological agent. Additionally, BAL findings in HP typically reveal a higher percentage of lymphocytes, which supports the diagnosis of HP.

Pulmonary Lymphoma

The radiological appearance of pulmonary lymphoma, including areas of consolidation and air bronchograms, can resemble COP. However, in lymphoma, consolidation is typically unilateral, focal, and not widespread.

Pulmonary Lymphomatoid Granulomatosis (PLG)

PLG is a type of lymphoproliferative disease that can mimic multifocal COP. On CT imaging, PLG often presents with multiple irregularly defined nodules. Lung biopsy reveals polymorphic lymphoid infiltrates, transmural infiltration of arteries and veins by lymphoid cells (angiitis), and focal necrotic areas within the lymphoid infiltrates.

Diffuse Alveolar Damage (DAD)

Diffuse alveolar damage is the most common finding in patients with acute respiratory distress syndrome (ARDS). It represents a nonspecific histopathological reaction to lung injury. Rarely, some cases of COP may exhibit a fulminant onset and rapidly progress to respiratory failure.[11]

TREATMENT

The treatment of COP has not been extensively studied in randomized trials. Consequently, treatment decisions are based on observations from case series and clinical experience.[12] The decision to initiate treatment and the choice of the initial therapy depend on factors such as the severity of symptoms, baseline lung function, the extent of radiographic involvement, and the rate of disease progression.[11]

Patients with Minimal Radiological Findings and Symptoms

For patients with mild symptoms and minimal radiological involvement, follow-up without treatment is recommended unless symptoms or lung function show any signs of worsening. Regular follow-up every 8-12 weeks is advised to monitor symptoms and pulmonary function. Spontaneous remission is rare (<10%) but can occur in mild cases.

In patients with mild radiological findings but significant symptoms, macrolides may be considered if glucocorticoids cannot be administered. The benefits of macrolide therapy are likely linked to their anti-inflammatory effects. If symptoms do not improve despite radiological stability during macrolide treatment, the therapy duration can be extended.[13]

Case reports have described favorable responses to macrolide antibiotics in patients with mild symptoms, such as:

- **Clarithromycin:** 250–500 mg twice daily.
- **Azithromycin:** 250 mg daily or 500 mg three times per week.[14]

These treatments often require a prolonged duration of 3-6 months. Reducing the macrolide dose to once daily has been successful in some patients but has also been associated with recurrences in others.

Patients with Symptoms but Without Severe Respiratory Failure

Most patients with COP have progressive symptoms and pulmonary function test abnormalities with widespread radiographic changes. Treatment with oral glucocorticoids is recommended in these patients. In general, it is recommended to start with prednisone at a dose of 0.5-1 mg/kg/day, depending on ideal body weight, and increase to a maximum of 60 mg/day. In patients with relative contraindications to glucocorticoid therapy, azathioprine or mycophenolate mofetil is recommended, preferably in combination with a lower dose of prednisone. Many patients begin to show a clinical response within the first few days of glucocorticoid therapy, but significant response is usually seen after a few weeks. Radiological findings usually resolve within 3-4 months.

If there is a response after four to six weeks from the start of treatment, the dose should be gradually reduced to 0.25 mg/kg/day over 2 to 4 weeks. It is recommended to continue at this dose for 4 to 6 months. After four to six months of oral prednisone, if the patient remains stable or improves, it should be tapered off gradually over the next six weeks. In patients who respond rapidly to systemic glucocorticoids, the dose should be increased to 0.25 mg/kg and then tapered off gradually over three to four months.[15]

Pneumocystis jirovecii prophylaxis is recommended for all patients receiving prednisone doses greater than 20 mg/day. PFTs are recommended with clinical and radiological follow-up at three-month intervals for 1 year after discontinuation of glucocorticoids.

Patients with Severe Respiratory Failure

For patients with rapidly progressive and widespread disease, treatment should be tailored based on the need for mechanical ventilation:

If mechanical ventilation is not required: For these patients, it is recommended to start treatment with intravenous (IV) glucocorticoids. They can be given in divided doses or as a single dose (125-250 mg methylprednisolone every 6 hours or 750-1000 mg/day pulse steroid for 3-5 days).[11] When the patient's oxygen requirement decreases, it is recommended to switch to oral prednisone at a dose of 0.5-1 mg/kg (maximum 60 mg/day).

If mechanical ventilation is required: It is recommended to start treatment with intravenous (IV) glucocorticoids. They can be given in divided doses or as a single dose (250 mg methylprednisolone every 6 hours or 1000 mg/day pulse steroid for 3-5 days).[11] If there is no response within 72 hours, a second agent should be added. Cyclophosphamide is often used (500-750 mg/m^2) because of its rapid effect. However, the choice of treatment in this regard is based on clinical experience.

Treatment for Patients Not Responding to Glucocorticoids

In cases where disease progression is not observed but the response to glucocorticoid therapy is inadequate, alternative diagnoses must be excluded. Once the diagnosis is confirmed, treatment should continue with oral prednisone while initiating a cytotoxic agent. Although there are no definitive recommendations, azathioprine is commonly used. In patients with normal renal function, the dose is started at 50 mg per day. It is recommended to increase the maximum dose (1-2 mg/kg) within 2-4 weeks.

Treatment of Relapses During Glucocorticoid Tapering

Relapses are common during the tapering of glucocorticoid therapy. Therefore, in addition to clinical evaluation, routine follow-up with chest radiographs and pulmonary function tests every 2-3 months is recommended during systemic glucocorticoid treatment. Relapse usually occurs when the glucocorticoid dose is reduced to 15 mg. If there is any evidence of worsening or recurrence of the disease, it is recommended to restart the last and well-tolerated glucocorticoid dose. Relapse is more common in cases of delayed diagnosis and treatment, severe disease with widespread involvement, severe hypoxemia, and lung fibrosis.[16,17]

Long-term treatment with prednisone is recommended for patients with persistent or frequent (more than three) relapses. Azathioprine is recommended for patients who respond to glucocorticoids but require high doses to control disease or who cannot use glucocorticoids because of side effects.

PROGNOSIS

The prognosis for COP is better than for fibrotic lung diseases. Complete recovery occurs in approximately two-thirds of patients treated with glucocorticoids. Symptomatic improvement is sometimes dramatic, occurring within one to two weeks. However, many patients have a slower clinical course, extending from several weeks to several months.

CONCLUSION

Organizing pneumonia (OP) is a rare yet distinct type of interstitial lung disease with a multifaceted clinical presentation and a variety of underlying causes. Its nonspecific symptoms and overlapping radiological findings with other pulmonary conditions pose diagnostic challenges, necessitating a multidisciplinary approach that integrates clinical, radiological, and histopathological evaluations. Glucocorticoids remain the primary treatment modality, offering significant clinical and radiological improvement in most cases, although relapses are common, particularly during dose tapering. Recent advances in understanding the pathophysiology and management of OP underscore the importance of timely and accurate diagnosis to improve patient outcomes while minimizing unnecessary interventions. Future research should prioritize the identification of biomarkers predictive of treatment response and relapse, as well as the development of alternative therapies for cases resistant to glucocorticoids.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The author has no conflicts of interest to declare.

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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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Letter to the Editor

ANATOLIAN CURRENT MEDICAL

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Insights on the relationship between essential tremor and carpal tunnel syndrome: a letter to the editor

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Dear Editor,

I read with great interest your article titled "Is essential tremor a risk factor for carpal tunnel syndrome? A prospective study excluding the most common comorbid conditions" by Kocatürk İ., published in Anatolian Current Medical, 2024;6(4):325-330.[1]

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy of the upper extremity, resulting from compression of the median nerve as it passes through the carpal tunnel.[2] CTS is commonly associated with risk factors such as repetitive hand movements, wrist injuries, obesity, and conditions like diabetes mellitus, hypothyroidism, and rheumatoid arthritis. These factors contribute to the compression of the median nerve within the carpal tunnel, leading to characteristic symptoms.

Kocatürk İ. examined whether essential tremor is a risk factor for CTS in the article. In this study, the most common risk factors for CTS were excluded, and the presence of CTS in this patient group was evaluated using electromyography (EMG), with tremor severity assessed via the Fahn-Tolosa-Marin Clinical Tremor Rating Scale (FTM TRS). Although the study was well planned, there are a few ambiguities we would want to address.

First, in this study, CTS classification was conducted using only distal latency and amplitude assessments to differentiate normal, mild, and moderate cases. However, in mild CTS cases, sensory distal latency prolongation and/or reduction in sensory conduction velocity are typically observed, while moderate CTS cases are characterized by these findings along with prolongation of the median nerve distal motor latency and/or reduction in motor conduction velocity. In the literature, including studies investigating the association between tremor and CTS, distal latency measurements are supplemented with sensory conduction velocity for mild CTS and motor conduction velocity for moderate CTS.[3,4] The pathophysiology of CTS is associated with demyelination, where compression of the median nerve within the carpal tunnel results in slowed conduction velocity and prolonged distal latency, both markers of demyelination. In the study by Kocatürk İ., however, the omission of conduction velocity measurements may have led to the lack of a significant association between tremor and EMG findings, potentially leading to the detection of fewer CTS cases overall.

Secondly, the analysis of occupational groups in this study reveals a methodological limitation. The authors reported the distribution of occupational categories; retiring, homemaker, worker, civil servant and student-but only performed a statistical comparison between the homemaker and "others" categories. The exclusion of other occupational groups from the analysis may have influenced the results. Given that CTS is recognized as a common occupational disease often associated with job-related factors, studies have shown higher prevalence rates among office workers and civil servant.[5,6] A comprehensive comparison among the included occupational groups could have highlighted significant differences in CTS distribution.

Finally, we believe that the issues mentioned in our letter may be beneficial to comment on the results of the current study. We are aware of the challenges in performing experimental research studies and congratulate the authors for their valuable study.

Sincerely.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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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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Dear Editor,

1. In this study, patients with only sensory findings were defined as mild carpal tunnel syndrome (CTS), and patients with sensory and motor findings (distal latency prolongation or speed decrease) were defined as moderate CTS. In other words, median motor speed was also taken into account when defining moderate CTS.[1] Although the referenced study stated motor involvement in addition to sensory findings for moderate CTS, as stated in the method section of this study, prolongation of median motor distal latency has been accepted as a sufficient and sensitive method for defining moderate CTS in many studies.[2,3] In addition, prolongation of median motor latency is also an expected finding in patients with decreased median motor speed.[2]

2. Since this study population was relatively small, it would be difficult to evaluate 4 or 5 groups statistically, and therefore patients were divided into two groups as housewives and others.

Thank you for your valuable contributions.

Best regards.

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