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Assessment of demographic characteristics and non-occupational exposures in occupational asthma: a single-center experience

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ABSTRACT

Aims: This study aimed to evaluate differences in demographic characteristics, occupational, and non-occupational exposures (NOE) between patients diagnosed with occupational asthma (OA) and non-occupational asthma (NOA).

Methods: A total of 114 patients with suspected work-related asthma were evaluated, and 82 asthma-diagnosed patients were included in the study.

Results: Among the 82 patients, 29 (35.4%) were diagnosed with OA. Seventy-two (87.8%) asthma patients were exposed to low molecular weight agents. The most common sector was ceramics (OA group n: 6 [7.3%]; NOA group n: 6 [7.3%]). The NOA group had a higher likelihood of being exposed to non-occupational agents that could trigger asthma. A higher frequency of pet bird ownership (OA group n: 4 [4.9%]; NOA group n: 12 [14.6%]) and current humidity or moisture exposure at home (OA group n: 3 [3.7%]; NOA group n: 7 [8.5%]) was observed in the NOA group. A negative correlation was found between the duration of asthma symptoms and both FEV1 and the FEV1/FVC ratio in OA patients with a history of COVID-19. Additionally, total IgE levels were significantly higher in immunological asthmatics with OA compared to those with NOA. Among OA patients exposed to NOE, FEV1 levels were 1.33 times higher in those without NOE.

Conclusion: NOE that may cause asthma can coexist with occupational exposures in OA cases. A comprehensive history, including environmental, indoor, and individual risk factors, as well as previous COVID-19 infection, is crucial for accurately identifying multiple asthma-causing agents and improving disease management by eliminating triggers.

Keywords: Non-occupational exposures, sector, occupational asthma, occupational exposures

INTRODUCTION

Occupational exposures are responsible for 15-25% of asthma cases in adults.[1] A detailed history of occupational exposure during patient examination is essential to prevent misdiagnosis of work-related asthma.[2] Work-related asthma is classified into two categories: occupational asthma (OA), which is directly caused by occupational exposures, and work-exacerbated asthma (WEA), which occurs when asthma, previously under control, is triggered by workplace-related exposures.[3,4] The prevalence of WEA in adults is 21.5%, while the prevalence of OA is 16%.[5,6]

OA-causing exposures are generally classified into agents of high molecular weight (HMW) and low molecular weight (LMW).[1,7,8] In 2018, a new OA-specific occupational exposure matrix (OAsJEM) was developed by Moual et al.[9,10] which added eight additional exposures to known irritants and sensitizers that directly cause OA. Specific irritants such as household cleaners, pesticides, endotoxins, aliphatic amines, acrylates, epoxy resins, persulfates/henna, and organic solvents were incorporated into subgroups in the updated OAsJEM.[10] Although certain agents known to cause asthma in the workplace have been identified, the effects of exposures such as humidity or animal proteins—known to trigger non-occupational asthma (NOA)—are not fully understood when they coexist with occupational exposures. The role of non-occupational exposures (NOE) in OA remains unclear, and research on this subject is limited.

In this study, our primary objective was to investigate whether there were differences in demographics, asthma symptom duration, smoking habits, occupational and NOE, exposure duration, total IgE levels, and pulmonary function test (PFT) results between patients diagnosed with OA and NOA. The secondary aim was to explore the coexistence of NOE agents with occupational exposures.

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METHODS

Ethics

The study protocol was approved by the Non-interventional Clinical Researches Ethics Committee of Eskişehir City Hospital (Date: 18.01.2023, Decision No: ESH/GOEK 2022/19SK). This study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Study Population

This retrospective descriptive cross-sectional study was conducted between January 2021 and January 2022. A total of 114 patients with suspected OA who were admitted or referred to the Occupational Diseases Clinic at Eskişehir City Hospital were evaluated. As a retrospective study, the research did not require direct informed consent from participants. Patient data was anonymized and handled in strict accordance with ethical guidelines to protect the privacy and confidentiality of all participants.

Evaluations included demographics, symptoms, duration of asthma symptoms, host history, occupational and NOE, duration of exposures, smoking habits, lung function test results, laboratory and radiological tests, reversibility tests, and peak expiratory flow (PEF) measurements.

Eighty two patients diagnosed with asthma were included in the study. Asthma patients were divided into OA and NOA groups (**Figure**).

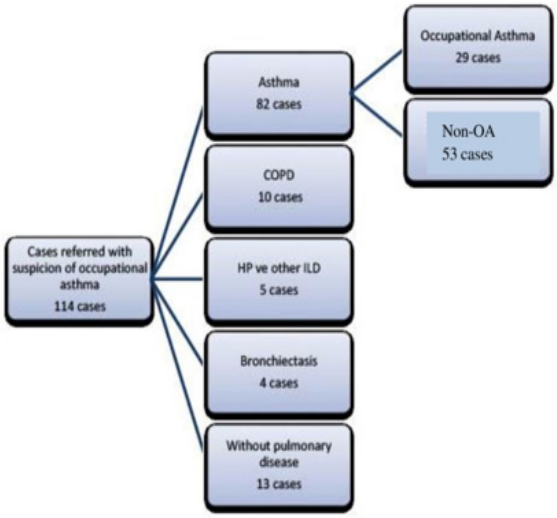

Figure. 114 cases with differential diagnosis
COPD: Chronic obstructive pulmonary disease, HP: *Helicobacter pylori*, OA: Occupational asthma

Diagnosis of Asthma

Asthma was diagnosed in patients with one or more respiratory symptoms, including shortness of breath related to work or non-work related factors, cough, wheezing, chest fullness, air hunger, and a positive reversibility on the PFT or a positive nonspecific bronchial provocation test (NSBPT). In cases where patients exhibited symptoms but negative early or late reversibility, a positive result from the PEF meter in follow-up testing, with a forced expiratory volume in the first second/forced vital capacity (FEV_1/FVC) ratio of less than 70%, was used to confirm asthma diagnosis.[11]

One patient underwent a specific bronchial provocation test (SBPT) at a outpatient university hospital. SBPT was performed when workers were suspected to have OA due to exposure to specific agents, mimicking actual workplace exposures under clinically monitored conditions. A positive SBPT was defined by a significant decrease in FEV1 after exposure, indicating an asthmatic response.[1,12]

Groups Definition

Occupational asthma: Diagnosed by a positive SBPT in patients who had no prior respiratory symptoms or known history of asthma, but developed work-related respiratory symptoms and/or signs after workplace exposure, or by positive variability of the PEF at work versus away from work.

Non-occupational asthma: Included patients with asthma who did not meet the criteria for OA.

Specific Bronchial Provocation Test (SBPT)

The SBPT aims to simulate workplace exposure to a suspected causative agent of asthma.[1,12] SBPT was performed on a patient exposed to isocyanates, which was later confirmed as OA with a positive SBPT result. Only one patient underwent SBPT at a university hospital.

PEF Meter Monitoring and Method

A PEF meter was used to monitor the variability of PEF. The test was considered positive if PEF variability was detected on more than two-thirds of the total measurement days, with at least four PEF measurements per day over a period of at least five weeks, including three weeks at work and two weeks without work interruption.[13,14] PEF measurements were made using a mini peak flow meter, known for its reliability and precision in asthma management. The formula for PEF variability calculation was as follows:

PEF variability %=(PEF-lowest PEF)/(2x[(PEF+lowest PEF)/2])x100. This formula was used to assess fluctuations in PEF over time.[13,14]

Non-Occupational Exposure (NOE)

The occupational history of lung disease, diagnosis, and follow-up form was used in the clinic to document both occupational and NOE. In this region, keeping pet birds (budgerigar, pigeon, canary, cockatoo-parrot), pigeon cultivation, and environmental asbestos exposure are common. Detailed records were kept regarding smoking habits, pet bird ownership, pigeon cultivation, and other NOE such as environmental mould, humidity, and hobbies related to asthma development (e.g., animal husbandry, farming, painting). Additionally, history of allergy, family allergy, and COVID-19 were also recorded. NOE was defined within this context.

Immunologic Occupational Asthma (Immunologic OA)

Cases with total IgE levels greater than 100 U/ml were classified as immunologic OA.[15]

Exclusion Criteria

Patients with respiratory symptoms and/or signs that did not meet asthma diagnostic criteria (e.g., chronic

obstructive pulmonary disease with irreversible airway obstruction on respiratory function tests), patients with asthma-related symptoms but radiologic findings consistent with hypersensitivity pneumonitis or other interstitial lung diseases, and patients without work-related complaints or abnormalities on pulmonary function or bronchial provocation tests were excluded from the study.

Statistical Analysis

Data analysis was conducted using the SPSS V22 software (SPSS Inc., Chicago, IL, USA). The frequencies and percentages of categorical variables and the mean, median, and standard deviation of numerical variables were calculated. The t-test was used for normally distributed numerical variables, while categorical variables were analyzed using the Chi-square test. Nonparametric tests were applied for variables without a normal distribution. The Pearson correlation test was used for correlation analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

OA was diagnosed in 29 patients (35.4%) among the 82 asthma patients evaluated. The average age of the participants was 40.8±7.5 years, with a predominance of male patients (75.6%, n=62). Dyspnea was the most common symptom (n=64). The mean duration of asthma symptoms was 3.6±3.8 years. More than half of the patients were smokers (54.9%, n=45), with an average of 5 pack-years (8.6±8.6 cigarette pack-years in total). No statistically significant differences were found in terms of demographic and clinical characteristics between OA and NOA patients, suggesting that differentiating between OA and NOA based solely on these factors is challenging (Table 1).

Occupational and Non-Occupational Exposures

When examining occupational exposures, several industries were associated with both OA and NOA. The ceramic industry had an equal distribution of OA and NOA cases, with 7.3% of both groups originating from this sector, totaling 14.6%. Similarly, food manufacturing and painting industries had relatively higher proportions of OA, each contributing 11.0% of the total cases. The metal industry also represented a significant portion of the cases, with metalworking comprising 9.8% and welding 8.5%.

In contrast, NOE played a significant role in the NOA group. The NOA patients had a notably higher frequency of exposure to NOA triggers. For example, 12 (14.6%) patients in the NOA group reported exposure to humidity or mould in their homes, compared to only 3 (3.7%) in the OA group. Additionally, 12 (14.6%) patients in the NOA group kept pet birds at home, while only 4 (4.9%) patients in the OA group had this exposure. This highlights the importance of environmental and domestic factors as potential triggers for asthma in the NOA group, which can overlap with occupational exposures in patients diagnosed with OA (Table 2).

Specific IgE positivity results have been added. RAST was performed in 33 cases. In the OA group, six cases had RAST positivity for latex, inhalant allergens (two cases), grass pollen mix, mold mix, and tree mix. In the NOA group, specific IgE positivity was detected for bee venom, *Aspergillus*, mold mix, weed mix, *Dermatophagoides*, inhalant allergens, and budgerigar dander.

Duration of Symptoms, Work Duration, and Immunological Findings

We found significant correlations between the duration of symptoms, work exposure duration, and levels of Total IgE with clinical factors. Specifically, there was a relationship between the duration of asthma symptoms and both FEV_1 and FEV_1/FVC ratios in patients with OA (p=0.05 and p=0.001), showing a decline in lung function as symptoms persisted over time. Furthermore, a longer duration of dyspnea was observed in patients with OA who had prolonged exposure to work-related allergens (p=0.007), indicating that work-related exposures might exacerbate asthma symptoms over time (Table 3).

Importantly, a positive relationship was found between the duration of symptoms and total IgE levels in both OA (p=0.012) and NOA (p=0.019) patients, emphasizing the role of immune responses in the progression of asthma. Moreover, the NOE were linked to higher IgE levels, further suggesting that these environmental factors contribute to asthma exacerbation in both OA and NOA patients (Table 3).

DISCUSSION

In our study, we observed that individuals diagnosed with OA, when exposed to NOE agents, experienced a significant decrease in FEV_1 levels compared to those diagnosed with NOA. A thorough evaluation of environmental exposures was conducted through detailed patient histories, environmental surveys, and tracking of exposures to both occupational and non-occupational agents. This comprehensive approach highlights the necessity of considering both environmental and occupational exposures when diagnosing asthma, even in patients with a history of occupational exposure. However, due to the limited sample size, our findings should be interpreted with caution, and further research with larger sample sizes is needed to clarify the complex relationships among environmental, occupational, and individual factors in asthma pathogenesis.

The importance of obtaining a detailed environmental exposure history was reinforced by our findings. Structured questionnaires that address both occupational and NOE should be utilized to improve diagnostic accuracy and treatment efficacy. These should include inquiries about home environments, hobbies, and lifestyle factors that could contribute to asthma-related exposures. Additionally, family history should be considered, particularly in relation to any environmental changes that coincide with symptom onset or worsening. Incorporating these detailed investigations into routine clinical evaluations can enhance diagnostic precision and improve the effectiveness of subsequent treatments, including those targeting removal from exposures in OA.[16,17]

The increasing diversity of non-occupational respiratory environmental agents complicates the establishment of a direct causal relationship between asthma and exposure in occupational diseases. The complex pathogenesis of asthma, variability in individual responses to allergens, and the

Table 1. Comparison of demographics, symptoms, exposures, smoking habits, allergy status, and pulmonary function test parameters in OA and NOA cases

Parameters	OA (n: 29)	NOA (n: 53)	Total (n: 82)	p
Age (mean±SD)	40.7±7.7	40.9±7.4	40.8±7.5	0.933
Gender (n, %)				
Male	21 (25.6)	41 (50.0)	62 (75.6)	0.404
Female	8 (9.8)	12 (14.6)	20 (24.4)	
Symptoms (n, %)				
Cough	6 (7.4)	7 (8.6)	13 (16.0)	0.602
Dyspnea	13 (16.0)	31 (38.3)	44 (54.3)	
Cough & dyspnea	8 (9.9)	12 (14.8)	20 (24.4)	
Duration of asthma symptoms (mean±SD)	3.7±4.4	3.4±3.6	3.6±3.8	0.762
Package-year (mean±SD)	8.7±8.4	8.5±8.7	8.6±8.6	0.765
Smoking habits (n, %)				
Nonsmoker	8 (9.8)	19 (23.2)	27 (32.9)	0.309
Current smoker	19 (23.2)	26 (31.7)	45 (54.9)	
Ex-smoker	2 (2.4)	8 (9.8)	10 (12.2)	
Non-occupational exposures and host history				
Present history of COVID-19 (n, %)	8 (9.8)	17 (20.7)	25 (30.5)	
Present COVID-19 vaccine (n, %)	24 (29.3)	43 (52.4)	67 (81.7)	0.758
Pet bird at home	4 (4.9)	12 (14.6)	16 (19.5)	0.323
Present history of humidity or moisture (n, %)	3 (3.7)	7 (8.5)	10 (12.2)	0.702
Present history of pet animal at home (n, %)	1 (1.2)	2 (2.4)	3 (3.7)	-
Present history of farming (n, %)	2 (2.4)	4 (4.9)	6 (7.3)	-
Present history of pneumonia	1 (1.2)	1 (1.2)	2 (2.4)	-
Hobbies (painting, pigeon cultivation and wood working) (n, %)	0	3 (3.7)	3 (3.7)	-
Present history of allergy (n, %)	5 (6.1)	8 (9.8)	13 (15.9)	0.800
Occupational exposures (n, %)				
HMW	2 (2.4)	7 (8.5)	9 (11.0)	0.283
LMW	26 (31.7)	46 (56.1)	72 (87.8)	
Mix	1 (1.2)	0 (0.0)	1 (1.2)	
Present peripheral eosinophilia	4 (4.9)	2 (2.4)	6 (7.4)	0.269
Present total IgE ≥100 U/ml (n, %)	7 (8.8)	18 (22.5)	25 (31.3)	0.329
Total IgE, U/ml, (mean±SD)	190.3±614.8	181.1±380.9	184±475.2	0.935
Present spesifik IgE positive (n: 33)	6 (18.2)	9 (27.3)	15 (45.5)	0.614
Pulmonary function test findings				
Present FEV_1/FVC<%70, (n, %)	12 (14.6)	21 (25.6)	33 (40.2)	0.877
FEV_1,L (mean±SD)	2.9±0.9	3.1±0.9	3.0±0.9	0.253
FEV_1% (mean±SD)	86.1±21.2	89.5±20.8	88.3±20.9	0.484
FEV1/FVC% (mean±SD)	75.9±7.9	74.9±8.7	75.3±8.4	0.623

OA: Occupational asthma, NOA: Non-occupational asthma, SD: Standard deviation, IU: International unit, L: Liters, HMW: High molecular weight, LMW: Low molecular weight, IgE: Immunoglobulin E, FEV_1: Forced expiratory volume in the first second, FVC: Forced vital capacity, statistical significance p<0.05

diversity of agents that trigger asthma make distinguishing OA challenging.[18,19] Factors such as clinicians' neglect of occupational exposure histories, failure to assess the relationship between symptoms and work, and the use of multiple diagnostic tests can delay the diagnosis of OA. A study at the Ontario Occupational Lung Disease Clinic found that the average time to diagnosis was over 3 years.[20] Similarly, our study found that the average diagnostic delay was 3.7 years. This underlines the importance of symptom screening questionnaires in workplaces to evaluate symptoms following exposure, which may facilitate earlier diagnosis of OA.

In our investigation, NOE, such as home humidity, mold, and the feeding of domestic birds, were also considered as potential contributors to asthma. While no significant differences in NOE were observed between OA and NOA patients, those with NOE were more likely to be diagnosed with asthma. A survey by Rollins et al.[21] demonstrated that home renovations

Table 2. Distribution of OA and NOA cases according to their respective work industries

Sectors or jobs	OA n (%)	NOA n (%)	Total n (%)
Duration of occupational exposure, year, (mean±SD)	7.9±6.1	10.4±8.8	9.5±8.0
Metal	2 (2.4)	6 (7.3)	8 (9.8)
Ceramic	6 (7.3)	6 (7.3)	12 (14.6)
Food	3 (3.7)	6 (7.3)	9 (11.0)
Non-domestic cleaners	3 (3.7)	5 (6.1)	8 (9.8)
Manufacture	2 (2.4)	3 (3.7)	5 (6.1)
Animal husbandry	0 (0.0)	1 (1.2)	1 (1.2)
Painter	5 (6.1)	4 (4.9)	9 (11.0)
Mining	2 (2.4)	4 (4.9)	6 (7.3)
Glass industry	0 (0.0)	1 (1.2)	1 (1.2)
Hairdresser	0 (0.0)	1 (1.2)	1 (1.2)
Welder	3 (3.7)	4 (4.9)	7 (8.5)
Foundry	0 (0)	4 (4.9)	4 (4.9)
Artificial marble	0 (0.0)	2 (2.4)	2 (2.4)
Other	2 (2.4)	4 (4.9)	6 (7.3)

This table shows how many cases of occupational asthma (OA) and non occupational asthma (NOA) are reported in industry sectors. OA cases are related to workplace exposures while NOA cases involve asthma diagnoses not connected to work conditions but are included for an industry overview. SD: Standard deviation

needed to investigate the effect of these exposures on asthma and OA specifically.

In terms of exposure to LMW and HMW agents, no significant differences in asthma development were noted in our study. However, a higher number of cases were exposed to LMW agents, likely due to the industrial focus of the region, including ceramics, casting, and metal industries. This finding may also reflect the higher prevalence of LMW agents in workplaces, especially in industrial settings.[7]

Post-COVID-19 disease has also been associated with asthma-like symptoms.[23,24] In our study, 20.7% of patients with a history of COVID-19 were diagnosed with NOA, indicating that patients with ongoing respiratory symptoms after COVID-19 should not solely be considered to have prolonged COVID symptoms but should also be evaluated for asthma.

Cigarette smoking is a well-known risk factor for chronic diseases, including coronary heart disease and chronic obstructive pulmonary disease. The relationship between smoking and OA remains controversial, with insufficient and contradictory findings regarding its role in increasing OA risk.[25] In our study, 54.9% of asthmatic patients were smokers, and no significant differences in smoking habits were found

Table 3. Correlation between duration of symptoms, duration of exposure, and total IgE levels with pulmonary function and IgE levels

Relationship type	Parameters	Group	Correlation type	p-value
Symptom duration vs. FEV_1 & FEV_1/FVC ratios	FEV1 & FEV1/FVC	NOA	Negative	0.05 & 0.001
Duration of exposure vs. duration of asthma symptoms	Dyspnea duration	OA	Positive	0.007
Symptom duration vs. total IgE levels	Total IgE levels	OA & NOA	Positive	0.012 & 0.019

Table 3 illustrates correlations and their significance (p-value) across groups, negative values indicate inverse relationships, positive values indicate direct relationships. FEV1: Forced expiratory volume in the first second, FVC: Forced vital capacity, IgE: Immunoglobulin E, OA: Occupational asthma, NOA: Non-occupational asthma, statistical significance $p<0.05$

and humidity, particularly related to work environments, can be risk factors for asthma symptoms. While occupational exposures are more prominent in OA, ongoing exposure to such environments, combined with the cessation of other non-occupational environmental exposures, indicates that controlling asthma is complex.

In the OA group, six cases had specific IgE positivity for specific allergens, including latex, inhalant allergens, grass pollen mix, mold mix, and tree mix. However, no significant differences were found between the occupational and NOA groups regarding household environmental factors such as mold exposure and bird keeping. This suggests that occupational exposure plays a key role in OA development, while individual sensitivities and environmental factors may contribute to asthma pathogenesis. Larger studies are needed to further evaluate these influences.

Our region is characterized by common household pet ownership, including parrots and budgerigars, as well as pigeon breeding. Although no significant differences between OA and NOA were found in relation to these exposures, it may be necessary to address non-occupational environmental agents in asthma management, as they are known to cause asthma and extrinsic allergic alveolitis.[22] Further studies are

between OA and NOA patients. Nevertheless, the higher degree of airway obstruction in smokers with OA suggests that both smoking and occupational exposures may have a compounded effect on airway function.

Although no significant differences in airway obstruction or FEV1 levels were observed between asthmatic patients, the lower FEV1 levels in OA patients exposed to non-occupational agents suggest that multiple exposure factors play a role. The combination of non-occupational environmental and occupational exposures may have a synergistic effect on the loss of airway function. These results remain hypothetical and should be confirmed through further studies. The positive correlation between the duration of symptoms and loss of function in OA supports the idea that prolonged exposure exacerbates airway limitation and can lead to permanent airway damage.[26]

CONCLUSION

The etiology of OA is complex, and the interaction between occupational and NOE requires further investigation. While our study's limited sample size and regional factors should be considered, our findings emphasize that asthma cannot be attributed to a single cause, and a comprehensive evaluation

of environmental, occupational, and personal factors is essential. Due to the small sample size, the results should be interpreted as preliminary and require validation through larger-scale studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the Non-interventional Clinical Researches Ethics Committee of Eskişehir City Hospital (Date: 18.01.2023, Decision No: ESH/GOEK 2022/19SK).

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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Importance and comparison of inflammatory biomarkers in COVID-19 patients follow-up in intensive care unit

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ABSTRACT

Aims: This study aimed to determine the power of laboratory parameters and biomarkers in predicting the prognosis of patients admitted to the intensive care units (ICU) with COVID-19 in a state hospital.

Methods: In this retrospective study, the hospital automation system of all patients admitted to Bolu İzzet Baysal State Hospital's ICUs because of COVID-19 between March 2020 and December 2021 were recorded and examined. Demographic data, blood tests, APACHE II score, and inflammatory biomarkers were also recorded. The results of patients who survived and did not survive were compared.

Results: The study included 452 patients and the mortality was 72.6%. Exitus patients had higher APACHE II scores and age. The mortality rate was significantly higher in patients with neurological disorders. For patients who did not survive, blood leukocyte, procalcitonin, LDH, and creatinine levels were higher, whereas blood lymphocyte and thrombocyte levels were lower. Based on the ROC analyses, the lymphocyte count AUC was 0.624, APACHE II score AUC was 0.618, serum procalcitonin level AUC was 0.584, and platelet count was 0.560. Age, APACHE II score, neutrophil-to-lymphocyte ratio, and lymphocyte count were associated with mortality according to a univariate logistic regression analysis. Age (OR (95 CI%)1.02 (1.00-1.04, p=0.018)), APACHE II (OR (95 CI%)1.05 (1.01-1.09, p=0.018)), and neutrophil to lymphocyte ratio (OR (95 CI%) 1.02 (1.01-1.03, p=0.003)) were associated with mortality according to multivariate logistic regression

Conclusion: For patients admitted to the ICU, laboratory parameters and inflammatory biomarkers can help in diagnosis, follow-up, and prognosis in COVID-19. We believe that combinations of hemogram parameters are effective in predicting clinical follow-up and prognosis.

Keywords: Intensive care unit, mortality, COVID-19, lymphocyte, neutrophil-to-lymphocyte ratio

INTRODUCTION

In December 2019, pneumonia causing acute respiratory failure was observed for the first time in Wuhan, China, which was named COVID-19 in February 2020.[1] The disease can exhibit varying clinical spectrum, from asymptomatic infection to viral pneumonia, which can result in death.[2]

Oxygen therapy, mechanical ventilation support, renal replacement therapy, and other mechanical support systems are required in intensive care units (ICU) for patients with severe respiratory failure.[3] Care is provided to critically ill patients in the ICU, and understanding the factors that affect the outcomes of intensive care patients is useful, in terms of both the effective use of ICU beds and their cost.

This study aimed to investigate the clinical and laboratory parameters affecting the outcomes of patients admitted to the ICU owing to COVID-19. Our secondary aim was to compare the effects of inflammatory biomarkers, such as red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), C-reactive protein-to-albumin ratio (CRP/Alb), and procalcitonin (PCT), on mortality.

METHODS

This retrospective study was conducted by examining the records in the hospital automation system of all patients admitted to Bolu İzzet Baysal State Hospital ICUs because of COVID-19 between March 2020 and December 2021. Patients >18 years of age with COVID-19 PCR results were included in this study. Patients with missing data, those <18 years of age and according to radiological imaging or blood tests, suspicious cases were excluded. Routine blood tests, comorbid conditions, age, sex, ICU length of stay (LoS), and Acute Physiology, Assessment, and Chronic Health Evaluation (APACHE) II values of patients included in the study were recorded when they were admitted to the ICU. The patients were divided into two groups, non-surviving and surviving, and the factors affecting mortality were compared. This study was approved by the Bolu Abant İzzet Baysal University

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Clinical Researches Ethics Committee (Date: 22.06.2021, Decision No: 2021/161). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

For descriptive statistics, the mean±SD was used with a normal distribution. Categorical variables are expressed as numbers and percentages. Shapiro–Wilk, Kolmogorov–Smirnov, and Anderson-Darling tests were performed. The Mann–Whitney U test was used to compare age, APACHE II score, ICU LoS, and laboratory parameters in terms of mortality between the two independent groups. Pearson's X^2 and Fisher's exact tests were used to compare the differences between categorical variables (sex and comorbidities) in terms of mortality. Univariate and multivariate logistic regression analyses were performed to analyze the factors affecting mortality. Cut-off values were determined using the Youden and Delong method for receiver operating characteristic (ROC) analysis of leukocytes, lymphocytes, and platelets; PCT; RDW; NLR; CRP/Alb; creatinine; and lactate dehydrogenase (LDH), which predict mortality. The area under the curve (AUC) and corresponding 95% confidence interval (CI) were calculated using the MedCalc Statistical Software Trial Version (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2015). For statistical analysis, the Jamovi project (2020), Jamovi, and JASP (JASP, Amsterdam, Holland; Version 0.16.0.0), were used. Statistical significance was set at p-value of 0.05.

RESULTS

The study group included 452 patients with an average age of 71.3±13.6 years. Two hundred and forty-eight (54.9%) patients were men. Hypertension (HT) and neurological disorders were the two most common comorbidities, observed in 34.7% and 26.8% of the patients, respectively. The median APACHE II score was 21. The demographic and clinical characteristics of the patients are presented in Table 1.

The mortality rate in the study group was 72.6% (328 patients). We observed significant differences in age, APACHE II scores, and proportion of neurological disorders between surviving and non-surviving patients (p<0.05) (Table 1). The non-surviving patients were significantly older than the survivors (72.3±13.3 years vs. 68.7±14.0 years, p=0.010). The number of men and women were similar between the groups (p=0.999). The non-survivor group had a higher proportion of patients with neurological disorders (30.5% vs. 16.9%, p=0.005) than the survivor group. Non-surviving patients had significantly higher APACHE II scores than survivors (22.0 vs. 19.0, p<0.001). Other characteristics of the surviving and non-surviving patients are presented in Table 1.

Table 2 presents the laboratory results of the study groups. Laboratory parameters differed between the groups (p<0.05).

Table 2. Laboratory investigations of the survived and non-survived patients

	Patient groups		p*
	Survived (n=124)	Non-survived (n=328)	
Leukocyte count ($\times10^9$/L)‡	10.6 [2.6-43.9]	12.7 [1.9-66.8]	0.019
Lymphocyte count ($\times10^9$/L)‡	0.5 [0.0-3.1]	0.4 [0.0-4.2]	<0.001
Platelet count ($\times10^9$/L)‡	224.0 [22.0-707.0]	208.0 [17.5-649.0]	0.047
Procalcitonin& (ng/ml)‡	0.3 [0.0-33.5]	0.4 [0.0-98.3]	0.006
Red cell distribution width (%) ‡	14.8 [12.6-24.7]	14.9 [12.3-29.0]	0.355
Neutrophil/ lymphocyte ratio‡	19.6 [3.2-146.5]	32.1 [1.0-235.0]	<0.001
C-reactive protein&&/ albumin ratio‡	38.5 [6.0-85.7]	40.0 [3.0-88.0]	0.126
Creatinine (mg/dl)‡	1.0 [0.5-6.1]	1.1 [0.4-12.0]	0.011
Lactate dehydrogenase (U/L)‡	445.5 [103.0-2142.0]	542.0 [156.0-2751.0]	<0.001

‡: Median [min-max], *: Mann-Whitney U test, &: ACCESS immunoassay systems, method comparison (0.07-95.412 ng/ml), &&: Beckman Coulter Unicell DXI, high sensitive (0.2-480 mg/L)

Table 1. Demographic and clinical characteristics of the groups

	Overall (n=452)	Patient groups		p
		Survived (n=124)	Non-survived (n=328)	
Age (year)†,‡	71.3±13.6	68.7±14.0	72.3±13.3	0.010*
	72.0 [24.0-98.0]	69.0 [37.0-91.0]	73.5 [24.0-98.0]	
Sex§				
Female	204 (45.1)	56 (45.2)	148 (45.1)	0.999*
Male	248 (54.9)	68 (54.8)	180 (54.9)	
Comorbidities§				
Hypertension	157 (34.7)	46 (37.1)	111 (33.8)	0.591*
Neurological disorders	121 (26.8)	21 (16.9)	100 (30.5)	0.005*
Diabetes mellitus	89 (19.7)	28 (22.6)	61 (18.6)	0.414*
Coronary artery disease	91 (20.1)	26 (21.0)	65 (19.8)	0.888*
Chronic obstructive pulmonary disease	64 (14.2)	21 (16.9)	43 (13.1)	0.374*
Chronic renal failure	51 (11.3)	12 (9.7)	39 (11.9)	0.619*
Cancer	15 (3.3)	3 (2.4)	12 (3.7)	0.769*
APACHE II score ‡	21.0 [6.0-37.0]	19.0 [6.0-37.0]	22.0 [7.0-37.0]	<0.001**
Length of stay (day) ‡	9.00 [1.00-81.00]	8.0 [2.0-46.0]	10.0 [1.0-81.0]	0.307**

†: mean±standard deviation, ‡: median [min-max], §: n (%), *: Pearson x^2, Fisher's Exact test , **: Mann-Whitney U test

The non-surviving patients had higher leukocyte counts and PCT, NLR, creatinine, and LDH levels than the survivors. (Table 2).The median NLR was 32.1 and 19.6 in the non-surviving and surviving groups, respectively, and was statistically significant (p<0.001) (Figure 1).

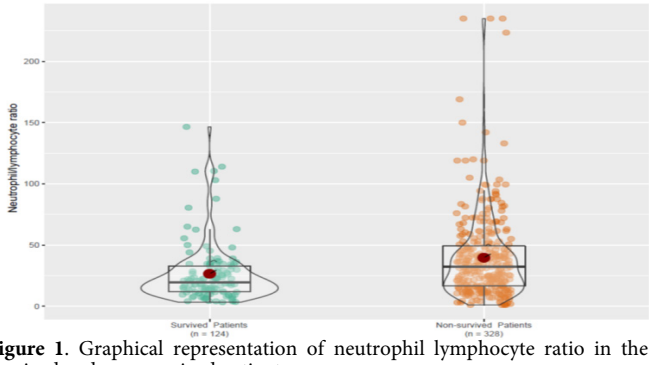

Figure 1. Graphical representation of neutrophil lymphocyte ratio in the survived and non-survived patients

In the study group, ROC curve analysis revealed significant laboratory parameter values and APACHE II scores (Table 3). The AUCs were 0.624 (95% CI: 0.577–0.669, p<0.001) for lymphocyte count, 0.618 (95% CI: 0.572–0.663, p<0.001) for APACHE II score, 0.617 (95% CI: 0.570–0.662, p<0.001) for LDH, 0.584 (95% CI: 0.537–0.630, p=0.005) for PCT, 0.572 (95% CI: 0.525–0.618, p=0.017) for leukocyte count, and 0.560 (95% CI: 0.513–0.607, p=0.037) for platelet count. The best cut-off point for lymphocyte count was ≤0.6 for predicting the mortality with a sensitivity and specificity of 78.05% and 41.94%, respectively (Figure 2).

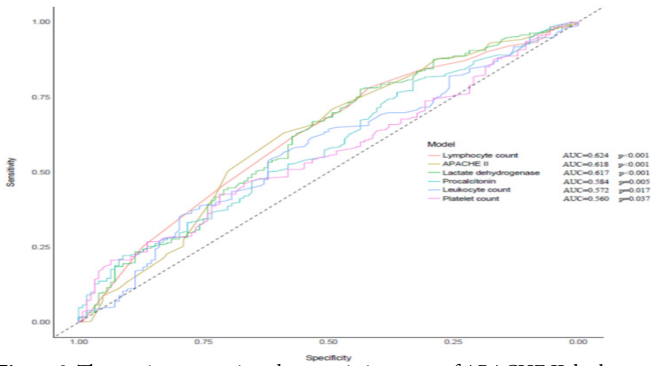

Figure 2. The receiver operating characteristic curves of APACHE II, leukocyte, lymphocyte, and platelet counts, procalcitonin, and lactate dehydrogenase
AUC: Area under the curve

Univariate logistic regression analysis revealed that age, APACHE II score, lymphocyte and platelet counts, PCT, NLR, creatinine, and LDH were significantly associated with mortality in patients with COVID-19 (Table 4). Multivariate logistic regression analysis revealed that age (OR=1.02, 95% CI: 1.000–1.0.4, p=0.018), APACHE II score (OR=1.01, 95% CI: 1.01–1.09, p=0.018), PCT (OR=1.05, 95% CI: 1.01–1.11, p=0.023), NLR (OR=1.02, 95% CI: 1.01–1.03, p=0.003), and LDH (OR=1.00, 95% CI: 1.00–1.00, p=0.0077) were the risk factors for prognosis in patients with COVID-19 (Figure 3).

Table 4. Logistic regression analysis of risk factors that impact on the development of mortality

	Univariate analysis	Multivariate analysis
	OR (95 CI%)	**OR** (95 CI%)
Age (year)	1.02 (1.00-1.03, p=0.013)	1.02 (1.00-1.04, p=0.018)
APACHE II score	1.07 (1.03-1.10, p=0.018)	1.05 (1.01-1.09, p=0.018)
Lymphocyte count	0.62 (0.43-0.89, p=0.009)	0.79 (0.52-1.24, p=0.295)
Platelet count	1.00 (1.00-1.00, p=0.022)	1.00 (1.00-1.00, p=0.287)
Procalcitonin	1.06 (1.02-1.12, p=0.014)	1.05 (1.01-1.11, p=0.023)
Neutrophil/ lymphocyte ratio	1.02 (1.01-1.03, p=0.003)	1.02 (1.01-1.03, p=0.003)
Creatinine (mg/dl)	1.20 (1.03-1.44, p=0.034)	1.07 (0.91-1.27, p=0.452)
Lactatedehydrogenase (U/L)	1.00 (1.00-1.00, p=0.003)	1.00 (1.00-1.00, p=0.007)

OR: Odds ratio, CI: confidence interval

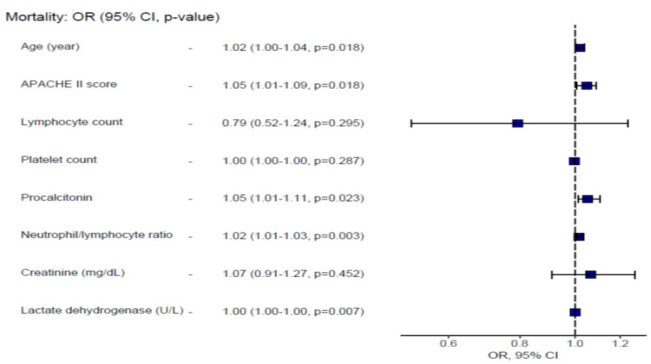

Figure 3. Multivariate logistic regression analysis of risk factors affecting mortality in COVID-19 patients
OR: Odds ratio, CI: confidence interval

Table 3. The area under curve analysis of the laboratory parameters and the APACHE II score in predicting the development of mortality

	AUC	Sensitivity	Specificity	Cut-off	95% CI	p
APACHE II	0.618	63.11	58.87	>20	0.572-0.663	<0.001
Leukocyte count	0.572	54.57	61.29	>11.9	0.525-0.618	0.017
Lymphocyte count	0.624	78.05	41.94	≤0.6	0.577-0.669	<0.001
Platelet count	0.560	42.68	71.77	≤194	0.513-0.607	0.037
Procalcitonin	0.584	22.26	91.13	>2.78	0.537-0.630	0.005
Red cell distribution width	0.528	47.87	66.13	>15	0.481-0.575	0.338
Neutrophil lymphocyte ratio	0.641	44.51	83.06	>36	0.595-0.686	0.641
CRP albumin ratio	0.547	29.88	79.03	>47	0.499-0.593	0.115
Creatinine	0.577	57.01	59.68	>1.01	0.530-0.623	0.577
Lactate dehydrogenase	0.617	77.74	43.55	>405	0.570-0.662	<0.001

AUC: Area under the curve, CI: confidence interval, CRP: C-reactive protein

DISCUSSION

Identifying high-risk patients with serious life-threatening diseases is important for predicting a poor clinical course, which contributes to the clinician's management of cases and hospital costs. In this study, the relationship between the demographic data recorded in the ICU of patients with COVID-19 and mortality was investigated. The power of inflammatory markers such as RDW, NLR, CRP/Alb, and PCT, measured as a result of COVID-19 infection, in predicting mortality was defined.

Although ICU mortality rates vary between 17% and 66.5% in patients with COVID-19,[4,5] different rates may be observed. Many studies have identified advanced age and high APACHE II scores as risk factors for mortality.[6,7] According to a study, men have a higher mortality risk than women.[8] The most common comorbidities upon ICU admission are HT, diabetes mellitus (DM), chronic obstructive pulmonary disease, heart disease, and chronic kidney disease (CKD), and their relationships with mortality have been shown.[1,3]

In our study, the 72.6% of our patients did not survive, and sex did not affect mortality. The increase in mortality with age observed in our study is consistent with that reported in the literature. The common comorbidities in patients admitted to the ICU because of COVID-19 were HT, neurological disorders, DM, and coronary artery disease. Furthermore, we found that neurological disorders, such as cerebrovascular and Alzheimer's diseases, were associated with mortality, and contrary to most of the literature, no relationship was observed between other comorbidities and mortality.

Considering laboratory parameters, previous studies have shown that increased D-dimer, CRP, urea, creatinine, RDW, LDH, and leukocyte count, as well as decreased albumin, lymphocyte counts, platelet counts, and arterial pH were detected in patients with COVID-19 and exitus patients.[1,3,7] Lee et al.[9] found a significant correlation between the depth of lymphopenia and mortality in a study conducted across the country and investigated the power of lymphopenia in predicting mortality. Similarly, Toori et al.[10] indicated a relationship between disease mortality, severity, and lymphopenia in their study.

In our study, we found that low lymphocyte and platelet counts and increased LDH, leukocyte, and creatinine levels were associated with mortality in terms of laboratory parameters.

Feng et al.[11] reported that high PCT levels were associated with both ICU demand and mortality in patients admitted to the ICU. Jackson et al.,[12] in their study investigating the relationship between PCT and the clinical course, found that high PCT levels indicate the severity of the disease; however, there was no relationship between hospital mortality and LoS in the hospital or ICU. In a multicenter study, Zattera et al.[13] reported that high PCT levels were not associated with mortality and that acute immunosuppression decreased PCT levels. In our study, a correlation was observed between increased PCT levels and increased mortality.

Many studies have investigated the relationship between the NLR and disease severity and mortality in different disease groups. In their study of patients with COVID-19, Imran et al.[14] found a relationship between the severity of COVID-19 pneumonia and NLR. King et al.[15] reported that a high NLR is associated with mortality and morbidity and is a guide for clinical follow-up and treatment. Moradi et al.[16] found a relationship between NLR and 30-day mortality. Yildiz et al.[17] found that an NLR value of 5.94 at admission to the hospital was associated with increased hospital mortality. In our study, a relationship was observed between increased NLR and mortality.

When we examined the roles of CRP/Alb and RDW in COVID-19, Lorente et al.[7] found a relationship between high RDW and 30-day mortality. Wang et al.[18] found that an increase in RDW levels showed the severity of the disease; however, they could not determine its effect on predicting hospital stay and mortality. Kalabin et al.[19] found that CRP/Alb was effective in determining the severity of COVID-19; however, they could not detect its effect on mortality. El-Shabrawy et al.[20] reported that CRP/Alb is a parameter that indicates disease severity and predicts mortality in patients with COVID-19. In our study, when patients who did not survive and those who survived were compared, both RDW and CRP/Alb were high. However, this difference was not statistically significant, and we could not detect the effects of either parameter on mortality recognition. We believe that the interleukin 6 blocker and high-dose steroids used in the treatment of COVID-19 may have affected the levels of some biomarkers and affected the results. Previous studies have shown that CRP can be affected by the attributed treatment leading to the difference in results between the literature and our study.[21]

In their study investigating the factors affecting mortality in patients with COVID-19, Vicka et al.[22] reported that APACHE II is a good scoring system. In a multicenter study, Ferrando et al.[23] found that the APACHE II score calculated upon admission was effective in predicting mortality. In our study, we found that the APACHE II score was effective in predicting mortality, which is consistent with the literature.

Limitations

Our study have some limitations, limitations of our study, the first is that it was retrospective in nature. Second, during the COVID-19 pandemic, it was difficult to reach the ICUs on busy days. During these periods, some treatments, such as tocilizumab and pulse steroids, were administered to patients in service patient rooms, and these treatments may have affected the levels of some laboratory parameters. At the same time, treatment modalities changed at the beginning and towards the end of the pandemic. This is also the case for oxygen support therapy, which may not have been standardized. In our study, we could not perform subgroup analyses of the patients who received these treatments. Finally, we could not determine secondary infections or the effects of these infections.

CONCLUSION

COVID-19 is a complex disease that can be diagnosed based on clinical presentation and laboratory parameters. The absence of specific and effective antiviral treatments can

lead to complications and superinfections. As in all patients followed up in the ICUs, both laboratory parameters and inflammatory biomarkers can help in the diagnosis, follow-up, and prognosis of COVID-19. Immunomodulators used in the treatment of COVID-19 can affect biomarker levels. This situation presents itself with different and even contradictory results in the literature. We believe that our study will contribute to the literature by predicting how similar situations can help clinicians treat COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Bolu Abant İzzet Baysal University Clinical Researches Ethics Committee (Date: 22.06.2021, Decision No: 2021/161).

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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Validation of the Emergency Department Assessment of Chest Pain Score and its accelerated diagnostic protocol in Turkish cohort

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ABSTRACT

Aims: The Emergency Department Assessment of Chest Pain Score (EDACS) and its accelerated diagnostic protocol (EDACS-ADP) are widely used for risk stratification of chest pain patients. This study evaluated their diagnostic performance in a Turkish cohort.

Methods: This retrospective cross-sectional study analyzed patients presenting with chest pain to a Turkish Emergency Department (ED). Major adverse cardiac event (MACE) occurrence was determined through clinical follow-up and medical record review. The diagnostic accuracy of EDACS and EDACS-ADP in predicting MACE was evaluated.

Results: A total of 744 patients were included, with 94 (12.6%) in the MACE group and 650 (87.4%) in the no-MACE group. The median EDACS score was higher in the MACE group (20 [IQR 14-24] vs. 15 [IQR 9.75-20], p<0.001). EDACS sensitivity was 71.3% (95% CI 61.0-80.1), while EDACS-ADP achieved 100% (95% CI 96.2-100.0). Specificity was similar (EDACS: 52.3% [95% CI 48.4-56.2]; EDACS-ADP: 52.2% [95% CI 48.2-56.1]). EDACS-ADP had a higher positive likelihood ratio (PLR) (2.09 [95% CI 1.93-2.26] vs. 1.49 [95% CI 1.28-1.73]) and a lower negative likelihood ratio (NLR) (0 vs. 0.55 [95% CI 0.4-0.76]). Positive predictive value (PPV) was higher for EDACS-ADP (23.2% [95% CI 21.8-24.7]) than for EDACS (17.8% [95% CI 15.7-20.1]), while negative predictive value (NPV) was 100% for EDACS-ADP and 92.6% (95% CI 90.1-94.6) for EDACS.

Conclusion: EDACS effectively identified high-risk patients, while EDACS-ADP achieved 100% sensitivity and NPV, making it a reliable tool for safely discharging low-risk patients in a Turkish ED cohort.

Keywords: Chest pain, scores, adverse cardiac events, diagnostic performance, emergency department

INTRODUCTION

Chest pain is the most common symptom of coronary artery disease (CAD).[1] Although only 5.1% of patients presenting to the emergency department (ED) with chest pain are diagnosed with acute coronary syndrome (ACS), over half of these cases are ultimately attributed to non-cardiac causes.[2] However, CAD affects more than 18.2 million adults in the United States and remains the leading cause of death for both men and women, with over 365.000 deaths annually.[3]

As a result, chest pain is a frequent reason for ED visits (accounting for 4.7% of visits in the U.S., with more than 6.5 million annual visits), yet only a small proportion of these patients experience life-threatening cardiac events or require hospitalization. ACS carries a one-month mortality rate of 5.9%, with more than half of these deaths occurring within the first hour of symptom onset.[4] Therefore, emergency physicians (EPs) must accurately, rapidly, and objectively distinguish patients with potentially serious cardiac conditions requiring immediate intervention from those who do not.[5] The aim is to prevent the unnecessary, costly, and potentially risky hospital admissions and comprehensive evaluations of non-critical patients, thereby optimizing the allocation of limited resources.

To achieve this balance, various diagnostic strategies and modalities have been developed in recent years, including chest pain units (CPUs), new cardiac biomarkers, risk scores, accelerated diagnostic protocols (ADPs), and noninvasive imaging of the myocardium and coronary arteries.[6,7] In this context, several risk stratification scoring systems have been developed in recent years to estimate the risk of major adverse cardiac events (MACE) due to their speed, simplicity, and cost-effectiveness.

One of the commonly used tools to predict MACE in patients with chest pain is the Emergency Department Assessment of Chest Pain Score (EDACS), which was developed using a two-phase process incorporating a statistical model and enhanced clinical practicality and usability.[8] Additionally, by integrating variables such as electrocardiography (ECG) and troponin data, classification systems like the history

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electrocardiogram age risk factor troponin (HEART) score and EDACS with its accelerated diagnostic pathway (EDACS-ADP) have been derived to identify low-risk cases that can be safely discharged from the ED with minimal observation.[9] These classifications aim to manage overcrowding and ensure that ED resources are effectively directed toward the appropriate population. However, there is limited recent evidence regarding the performance of these classifications across different populations and clinical settings.

The aim of our study is to evaluate and validate the performance of EDACS and EDACS-ADP in predicting MACE among patients presenting to our ED with chest pain and to assess the applicability of these tools within the Turkish population.

METHODS

Ethics

This study was conducted as a retrospective cross-sectional analysis at a tertiary ED. Patients presenting with chest discomfort to ED of Memorial Şişli Hospital between January 1, 2021, and January 1, 2024, were retrospectively identified from hospital electronic medical records. The study was approved by the Memorial Şişli Hospital Institutional Ethics Committee (Date: 26.12.2024, Decision No: 004), and patient data were anonymized before analysis. Because the study was designed retrospectively, no written informed consent form was obtained from patients. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

Patients aged ≥18 years who presented to the ED with chest pain or chest discomfort were included. Patients were identified using ICD-10 codes for general chest pain (R07.9, R07.1, R07.2, R07.89) and cardiac-related chest pain (I20.0, I20.1, I20.8, I20.9, I21.0-I21.4, I24.9). Patients with missing key data (troponin measurements, electrocardiograms [ECG], or EDACS scores) were excluded. Cases with ST-elevation myocardial infarction (STEMI), known alternative diagnoses requiring immediate intervention (e.g., aortic dissection, pulmonary embolism), were also excluded. Patients who were directly transferred to another facility were excluded only if follow-up data on MACE outcomes were unavailable. Transfers where complete clinical and outcome data could be obtained were retained in the analysis. Only first-time presentations to the ED were included in this study, with repeated visits for the same episode of chest discomfort excluded.

Data Collection

Demographic variables, clinical characteristics, comorbidities, and risk factors for cardiovascular disease were extracted from electronic health records. The EDACS score was calculated for all included patients, and the EDACS-ADP classification was determined based on clinical assessment, ECG findings, and serial high-sensitivity cardiac troponin (hs-cTn) measurements at 0 and 2 hours. hs-cTn assays were performed using the same manufacturer's kit and analyzed on the same device throughout the study period to ensure consistency.

MACE events were identified through electronic health record review, including hospital discharge summaries, procedure reports, and mortality data. Follow-up data for MACE outcomes were obtained from hospital records, national death registries, and outpatient visit documentation. Additionally, patients were contacted via phone calls for outcome verification. Cases were adjudicated by two independent emergency physicians, with discrepancies resolved by consensus.

ECGs were interpreted by emergency medicine specialists with at least six years of experience. Automated ECG readings were not used for classification. Cardiovascular risk factors, including hypertension, diabetes, dyslipidemia, smoking status, and family history of premature CAD, were self-reported by patients.

The primary outcome was the occurrence of MACE within 30 days, defined as a composite of cardiac death, myocardial infarction (MI), or coronary revascularization. Patients lost to follow-up were excluded from the final outcome analysis.

In this study, the EDACS was calculated by assigning specific point values to patient characteristics, including age, sex, cardiovascular risk factors, and symptom characteristics.[10] Age was categorized into predefined groups: 18–45 years (2 points), 46–50 years (4 points), 51–55 years (5 points), 56–60 years (8 points), 61–65 years (10 points), 66–70 years (12 points), 71–75 years (14 points), 76–80 years (16 points), 81–85 years (18 points), and 86 years or older (20 points). Male sex contributed an additional 6 points. Patients with a history of CAD or three or more cardiovascular risk factors—including hypertension, diabetes, dyslipidemia, smoking, or a family history of premature CAD—were assigned 4 additional points. Symptom characteristics modified the total score accordingly: the presence of diaphoresis added 3 points, pain radiating to the arm or shoulder added 5 points, pleuritic pain subtracted 4 points, and palpitation-related pain subtracted 6 points. If any variable required for EDACS calculation was missing, it was considered absent and assigned zero points. The total EDACS score was obtained by summing these variables, with a score of 16 or higher indicating high risk.

The EDACS-ADP was applied by incorporating electrocardiogram (ECG) findings and high-sensitivity cardiac troponin (hs-cTn) measurements at 0 and 2 hours. Patients were classified as low risk if they had an EDACS score below 16, no new ischemic changes on ECG, and negative hs-cTn results at both time points. If any of these criteria were not met, the patient was classified as intermediate or high risk. If an initial hs-cTn result was unavailable, a delayed troponin test was performed. EDACS and EDACS-ADP scores were retrospectively calculated by trained emergency physicians who were blinded to patient outcomes. Interobserver agreement was assessed in a random subset of cases to ensure consistency in scoring.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, version 30.0 (IBM Corp., Armonk, NY, USA). Continuous

variables were assessed for normality using the Kolmogorov-Smirnov test and histograms and presented as mean±standard deviation (SD) or median with interquartile range (IQR), as appropriate. Categorical variables were expressed as frequencies and percentages. Differences between groups were analyzed using the independent samples t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Categorical variables were compared using the Chi-square test or Fisher's exact test, as appropriate. The diagnostic performance of the EDACS and its EDACS-ADP was evaluated using sensitivity, specificity, PPV, negative predictive value (NPV), positive likelihood ratio (LR+), and negative likelihood ratio (LR–). A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 744 patients were included in the study and were categorized into two groups: the MACE group (n=94, 12.6%) and the No-MACE group (n=650, 87.4%) (Table 1). The mean age of patients in the MACE group was statistically significantly higher compared to the no-MACE group (60.3±14.3 years vs. 54.3±12.8 years, p<0.001, mean difference=6. The proportion of males was statistically significantly higher in the MACE group compared to the no-MACE group. Hypertension was more frequent in patients with MACE (p=0.005), whereas no statistically significant differences were observed for diabetes mellitus (p=0.177), history of CAD (p=0.128), and hyperlipidemia (p=0.141). Current smoking was statistically significantly more common in the MACE group (p=0.016). A positive family history of CAD was also statistically significantly more frequent in the MACE group (p=0.002). Pain exacerbated by inspiration was statistically significantly lower in the MACE group (p=0.002). No statistically significant differences were observed for pain radiating to the shoulder or arm (p=0.588), presence of diaphoresis (p=0.550), or pain reproducible by palpation (p=0.981).

Table 1. Baseline characteristics of patients stratified by the Emergency Department Assessment of Chest Pain Score and its accelerated diagnostic protocol

Characteristic	No MACE (n=650)	MACE (n=94)	p
Age (years), mean±SD	54.3±12.8	60.3±14.3	<0.001
Male sex, n (%)	332 (51.1)	60 (63.8)	0.021
Hypertension, n (%)	190 (29.2)	41 (43.6)	0.005
Diabetes mellitus, n (%)	127 (19.5)	24 (25.5)	0.177
History of coronary artery disease, n (%)	141 (21.7)	27 (28.7)	0.128
Hyperlipidemia, n (%)	130 (20.0)	25 (26.6)	0.141
Current smoker, n (%)	85 (13.1)	21 (22.3)	0.016
Family history of coronary artery disease, n (%)	19 (2.9)	9 (9.6)	0.002
Radiation of pain to shoulder/arm, n (%)	247 (38.0)	33 (35.1)	0.588
Presence of diaphoresis, n (%)	256 (39.4)	34 (36.2)	0.550
Pain exacerbated by inspiration, n (%)	207 (31.8)	15 (16.0)	0.002
Pain reproducible by palpation, n (%)	28 (4.3)	4 (4.3)	0.981

MACE: Major adverse cardiovascular events, SD: Standard deviation

Initial troponin positivity was statistically significantly higher in the MACE group compared to the No-MACE group (p<0.001). Similarly, 2-hour troponin positivity was statistically significantly higher in the MACE group (p<0.001). Ischemic ECG findings were more common in the MACE group (p<0.001) (Table 2).

Table 2. Laboratory findings and risk stratification using the emergency department assessment of chest pain score and its accelerated diagnostic protocol in predicting major adverse cardiovascular events

Category	Characteristic	No MACE (n=650)	MACE (n=94)	p
Laboratory finding	Positive initial troponin, n (%)	24 (3.7)	60 (63.8)	<0.001
	Positive 2-hour troponin, n (%)	31 (4.8)	89 (94.7)	<0.001
	Ischemic ECG findings, n (%)	22 (3.4)	64 (68.1)	<0.001
Risk assessment	EDACS score, median (IQR)	15 (9.75-20)	20 (14-24)	<0.001
	Low-risk EDACS, n (%)	340 (52.3)	27 (28.7)	<0.001
	High-risk EDACS, n (%)	310 (47.7)	67 (71.3)	-
	Low-risk EDACS-ADP, n (%)	339 (52.2)	0 (0.0)	<0.001
	High-risk EDACS-ADP, n (%)	311 (47.8)	94 (100.0)	-

MACE: Major adverse cardiovascular events, ECG: Electrocardiogram, EDACS: Emergency Department Assessment of Chest Pain Score, ADP: Accelerated diagnostic protocol

The median EDACS score was statistically significantly higher in the MACE group (20 vs. 15, p<0.001). Patients classified as low risk by EDACS were significantly lower in the MACE group (p<0.001), while the proportion of high-risk patients was higher. Similarly, patients classified as low-risk by EDACS-ADP were significantly lower in the MACE group (p<0.001), while all MACE cases fell into the high-risk category (100% vs. 47.8%). The sensitivity of EDACS was 71.3% (95% CI 61.0 - 80.1), whereas EDACS-ADP had a sensitivity of 100%. Specificity was similar for both scores (EDACS: 52.3%; EDACS-ADP: 52.2%) (Table 3). The PLR was higher for EDACS-ADP compared to EDACS (2.09 vs. 1.49), and the negative likelihood ratio was lower for EDACS-ADP (0 vs. 0.55). The PPV was higher for EDACS-ADP (23.2% compared to EDACS 17.8%), while the NPV was 100% for EDACS-ADP and 92.6% for EDACS.

Table 3. Validation of the Emergency Department Assessment of Chest Pain Score and its accelerated diagnostic protocol: sensitivity, specificity, and predictive values

Metric	EDACS	EDACS-ADP
Sensitivity (95% CI)	71.3% (61-80.1%)	100% (96.2-100%)
Specificity (95% CI)	52.3% (48.4-56.2%)	52.2% (48.2-56.1%)
Positive likelihood ratio	1.49 (1.28-1.73)	2.09 (1.93-2.26)
Negative likelihood ratio	0.55 (0.4-0.76)	0
Positive predictive value (95% CI)	17.8% (15.7-20.1%)	23.2% (21.8-24.7%)
Negative predictive value (95% CI)	92.6% (90.1-94.6)	100%

EDACS: Emergency Department Assessment of Chest Pain Score, ADP: Accelerated diagnostic protocol, CI: Confidence interval

DISCUSSION

In this study, the diagnostic performance of EDACS and EDACS-ADP in predicting MACE among Turkish patients presenting with chest pain to the ED was evaluated. Our findings demonstrated that EDACS-ADP, with its 96.2–100% sensitivity and 100% NPV, supports the safe early discharge of low-risk patients and thereby promotes efficient resource utilization. However, its specificity of 48.2–56.1% indicates a potential increase in unnecessary diagnostic tests and frequent false-positive results. As for EDACS, its sensitivity of 61.0–80.1% and NPV of 90.1–94.6% suggest limited performance in excluding high-risk patients. Moreover, its specificity of 48.4–56.2% and a negative likelihood ratio of 0.55 highlight the potential risk of false negatives, posing a threat to missing clinically critical cases. Based on these findings, while EDACS-ADP should be used alongside clinical judgment for optimal application in the Turkish population, EDACS may not be sufficient on its own for managing high-risk patients and should be supplemented with additional diagnostic methods.

The current goal of all strategies used to manage ED overcrowding is to ensure the rapid, early, and safe discharge of low-risk patients through accurate classification systems that identify those with low mortality and morbidity risks. Among the ED-based risk stratification tools for chest pain, commonly studied systems include the HEART score (The structure of the five elements with a 0, +1, and +2 scoring system (analogous to the Apgar score) helps to translate a long history and examination of a patient with chest pain into a comprehensible score of 0 to 10. parameters: history, age, risk factors, initial troponin[11]), Vancouver chest pain rule (Step-wise analysis of EKG, biomarker, history and physical exam; if all questions are answered "no," the patient is low-risk by the Vancouver chest pain rule. Parameters: Abnormal initial EKG, Positive troponin at 2 hours, Prior ACS or nitrate use, Does palpation reproduce pain?, Age 50 and above?, Does pain radiate to neck, jaw, or left arm?[12]), ADAPT (2-Hour EDACS-ADP to assess patients with chest pain symptoms using contemporary troponins as the only biomarker[13]), Marburg heart score (Rules out CAD in primary care patients with chest pain. parameters: gender, pain, history[14]), and Global Registry of Acute Coronary Events (*GRACE,* estimates admission to 6 month mortality for patients with ACS. Parameters: age, heart rate/pulse, systolic blood pressure, creatinine, cardiac arrest at admission, ST segment deviation on EKG, Abnormal cardiac enzymes, Killip class (signs/symptoms)[15]).[10] These scoring systems differ in the parameters they use, which results in variations in calculation time, observation duration in the ED, and their ability to predict MACE effectively.

EDACS classifies patients into low-risk and non-low-risk categories based on four key parameters: age, sex, known CAD (or the presence of three or more CAD risk factors), and symptoms.[16] hese four parameters can be assessed within seconds, making EDACS simple to apply and comparable in ease to current ED triage algorithms. Studies have shown that EDACS is more effective than standard ED triage systems in predicting MACE.[16] However, despite its speed and simplicity, EDACS lacks two critical components for chest pain evaluation: ECG and troponin testing. Consequently, shortly after EDACS was introduced, its accelerated version (EDACS-ADP) was developed by incorporating ECG and 2-hour troponin assessment. Although this modification requires more time for calculation and longer ED stays, our study confirmed its superior predictive accuracy.

The main limitation of EDACS-ADP in the ED is the time needed for troponin testing and the processing of follow-up troponin values. This is why, in its initial definition, EDACS-ADP was described as the 2-hour EDACS-ADP version of EDACS. In our study, we observed that troponin positivity at 2 hours was significantly higher in the MACE group compared to the initial troponin levels. However, in the No-MACE group, the highest rates of positivity were also associated with 0- and 2-hour troponin measurements. This highlights the importance of considering non-ACS causes of elevated troponin when interpreting these results. We found similar percentages for low-risk EDACS and low-risk EDACS-ADP among patients in the No-MACE group, indicating that both tools may have comparable utility in identifying low-risk patients.

A key question remains in current ED triage systems: should triage clinicians prioritize identifying high-risk (red) patients or low-risk (green) patients first? If the primary goal is to identify high-risk patients, EDACS-ADP is more suitable due to its superior sensitivity. However, if the goal is to rapidly identify low-risk patients without the need for extended observation, EDACS may be sufficient. Our study suggests that in situations of ED overcrowding, when patient volumes are high, EDACS can be effectively used to identify low-risk patients, saving the time otherwise needed for EDACS-ADP's 2-hour protocol. This advantage could allow emergency physicians to manage patient flow more efficiently while awaiting troponin results when necessary.

Although chest pain is a common reason for ED visits, it does not typically involve the simultaneous arrival of multiple patients, as seen in cases of mass casualties or physical trauma. However, the impact of climate change on CAD epidemiology, ACS management, and changes in ED visit volumes warrants further research to determine whether adjustments in the EDACS and EDACS-ADP thresholds for classification may be necessary.

When initially introduced, EDACS-ADP demonstrated 99–100% sensitivity in accurately identifying low-risk patients and classified approximately 45% of the cohort as low-risk.[10] Similarly, in our study, we observed comparable performance within the Turkish population.

Studies conducted in different populations have provided important evidence supporting the performance of the EDACS-ADP algorithm in classifying chest pain in EDs. In a Canadian study, the algorithm was shown to effectively identify high-risk patients while enabling the safe early discharge of those at low risk and a study conducted in a Turkish cohort found that EDACS-ADP was effective in distinguishing low-risk patients who were unlikely to require urgent intervention.[17,18] Furthermore, Wang and colleagues emphasized that EDACS-ADP can serve as a valuable clinical

tool for identifying low-risk individuals and supporting early discharge decisions in emergency settings.[19]

In summary, we evaluated the use of EDACS-ADP in Turkish EDs for the safe management of chest pain patients and observed that it could be successfully applied within this population. Our findings further highlight the potential for EDACS to be used effectively in specific situations of ED overcrowding, providing emergency physicians with additional flexibility and time management options.

Limitations

This study has several limitations. First, although the derivation of EDACS was originally based on a statistical model derived from prospectively collected data, this study did not modify the original criteria and was retrospective, keeping the diagnostic framework as designed. However, this may limit the exploration of potential adaptations that could improve its performance in specific subpopulations within the Turkish cohort. Future studies may explore the impact of customized adaptations on performance outcomes. Although we observed excellent inter-rater agreement for EDACS and EDACS-ADP in predicting MACE, the interrater reliability of individual clinical variables was not specifically tested. Thus, we cannot fully exclude minor variations in the application of these variables by different clinicians. The study was conducted in a single-center ED in Türkiye, which may limit the generalizability of the findings to different healthcare settings and populations. While our results are consistent with findings from international cohorts, validation in a broader, multicenter context is recommended to ensure wider applicability. Lastly, we used a p-value of <0.05 as the threshold for statistical significance in the multivariate analysis. Although this threshold is commonly used in clinical research, it may restrict the inclusion of additional variables that could further improve the prediction model's accuracy. Future studies may consider incorporating a broader range of variables to enhance diagnostic performance, provided that clinical simplicity is preserved.

CONCLUSION

In this study, the performance of EDACS and EDACS-ADP in predicting MACE among patients presenting with chest pain to the ED was evaluated in a Turkish Cohort. Our findings demonstrated that EDACS-ADP, with its 100% sensitivity and 100% NPV, is a highly reliable tool for identifying low-risk patients who can be safely discharged. Although both scoring systems exhibited similar specificity (EDACS: 52.3%, EDACS-ADP: 52.2%), the higher PLR and PPV of EDACS-ADP further emphasize its clinical utility in improving diagnostic accuracy and optimizing resource allocation.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Memorial Şişli Hospital Institutional Ethics Committee (Date: 26.12.2024, Decision No: 004).

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

MEDICINE PALLIATIVE CARE

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Evaluating the diagnostic accuracy of the 2022 ACR/EULAR classification criteria for giant cell arteritis in routine clinical practice

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ABSTRACT

Aims: The 2022 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria for giant cell arteritis (GCA) were developed to enhance diagnostic accuracy by incorporating advanced imaging modalities and addressing large vessel involvement. This study evaluates the performance of these criteria in routine clinical care.

Methods: This study was retrospective and single-center. The results included 25 GCA patients routinely followed at a tertiary rheumatology center from March 2017 to January 2024. The accuracy, sensitivity, specificity, positive and negative predictive values, and area under the receiver operating characteristic (ROC) curve (AUC) of the classification criteria were compared.

Results: The sensitivity (92.0%), specificity (92.9%), positive predictive value (92.0%), negative predictive value (92.9%), accuracy (92.4%) and AUC (0.979 (0.925-0.998)) of the 2022 ACR/EULAR classification criteria for GCA were higher than those of the 1990 ACR classification criteria for GCA (88.0%, 85.7%, 84.6%, 88.9% and 86.8%, respectively), and the difference in AUC was statistically significant (0.871 (0.770-0.973), p<0.001).

Conclusion: These findings indicate that the 2022 ACR/EULAR criteria significantly improve the sensitivity and maintain adequate specificity compared to the 1990 criteria, making them a valuable tool for diagnosing GCA in clinical practice. The new classification criteria will help to select the right patients and will reduce clinical errors.

Keywords: Giant cell arteritis, vasculitis, classification criteria

INTRODUCTION

Giant cell arteritis (GCA), a systemic inflammatory rheumatic disease, is one of the most common forms of systemic vasculitis. The pathogenesis of GCA is not fully understood. Clinical studies provide evidence for the importance of specific pathways in the pathogenesis of vascular inflammation. Immune system research shows inflammation of the arteries, primarily involving CD4+ T lymphocytes and macrophages, generally leading to a granulomatous reaction with the presence of giant cells. As a result of the inflammation, intimal hyperplasia and lumen occlusion can be seen in the arteries.[1] The disease is rarely seen in individuals under the age of 50; however, its incidence increases with age, most commonly affecting individuals in their seventh decade.[2] GCA is more common in people of Northern European descent and in women.[3] The first classification criteria for GCA were published by the American College of Rheumatology (ACR) in 1990.[4] These criteria are not intended to diagnose patients but rather to be used as classification criteria for clinical trials. Their low sensitivity in clinical studies has limited their use for diagnostic purposes in daily practice.[5] In the 1990s, due to the inadequacy of imaging techniques, attempts were made to establish classification criteria using clinical features, laboratory findings and invasive methods. With a better understanding of disease pathophysiology and the growing diagnostic value of imaging, techniques such as ultrasound (US), fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT), and magnetic resonance imaging (MRI) have been incorporated in double-blind, randomized controlled trials of newly developed drugs for the treatment of GCA.[6,7] The development of new classification criteria became essential due to the limited sensitivity and specificity of previous criteria and the emergence of advanced imaging modalities. In clinical practice, it is valuable in terms of differentiating it from other diseases included in the differential diagnosis with modern imaging methods, and it can also be considered

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to reduce the need for temporal artery biopsy, which is an invasive procedure.

In 2022, the European Alliance of Associations for Rheumatology (EULAR) and the ACR published newly classification criteria for GCA.[8] These new criteria include new clinical criteria that were not included in the previous criteria and modern imaging techniques that are increasingly used in routine practice.[4] Although the high sensitivity of the new classification criteria meets the need, concerns regarding potential limitations in specificity, as reported in some studies, may affect their broader applicability. Additionally, as with many autoimmune diseases, geographic variations in incidence and clinical presentation may influence the sensitivity and specificity of the criteria, which may affect the specificity and sensitivity results. Epidemiologic studies have reported that being Northern European ancestry is important predisposing factor for GCA. Female predominance in the GCA has been reported in many different cohorts, and this gender difference is more pronounced in the northern part of Europe.[9] Given these factors, we aimed to evaluate the classification performance of the 2022 ACR/EULAR criteria in a Turkish GCA cohort and to compare them with the 1990 ACR classification criteria.

METHODS

The study was conducted with the permission of the Non-Intervention Scientific Research Ethics Committee of the University of Health Sciences Gülhane Training and Research Hospital (Date: 05.12.2024, Decision No: 2024/89). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was designed as a retrospective study and carried out in a tertiary center. Medical records of patients diagnosed with GCA between March 2017 and January 2024 were reviewed. Clinical diagnoses were confirmed by two independent rheumatologists with a minimum of five years of experience. All valid medical records were manually reviewed before confirming the diagnosis. GCA was diagnosed based on clinical findings, imaging results, and temporal artery biopsy if available, in accordance with the 1990 ACR protocols. Twenty-eight patients over the age of 50 with elevated acute phase reactants and constitutional symptoms were included as the control group. The control group consisted of patients diagnosed with infections, malignancy, polymyalgia rheumatica, nonspecific headache, and fever of unknown origin.

All data specified in the 2022 ACR/EULAR GCA classification criteria were retrospectively collected from the hospital registry system and included: Demographic characteristics, clinical findings, laboratory parameters including C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), imaging modalities, temporal artery biopsy with evidence of vasculitis if present. Patients whose clinical, laboratory, or imaging data were unavailable in the hospital records were excluded from the study. During the diagnostic phase, imaging is requested from patients based on clinical suspicion. PET/CT was not routinely requested due to the duration of the procedure and radiation exposure risks. A patient was classified as having GCA if the total score from the imaging and clinical findings is six or more, after meeting the requirements of the GCA 2022 ACR/EULAR classification criteria.[8] To be classified as having GCA, a patient must meet three or more of the five criteria listed in the 1990 ACR classification criteria.[4] The clinical diagnosis was accepted as the reference standard for all patients. To investigate the performance of the new GCA criteria, all patients were classified according to the 1990 ACR classification criteria and the updated 2022 ACR/EULAR classification criteria for GCA. The features of the machines used in imaging methods are as follows. For large-vessel evaluation, US machines with 6–15 MHz transducers were used. The scan began with gray-scale US, followed by color doppler mode. All PET images were interpreted by experienced nuclear medicine physicians using the Discovery 690-GE Healthcare PET/CT scanner.

Statistical Analysis

The data analysis was conducted using SPSS version 28, which is compatible with Mac. The distribution of variables was tested with the Shapiro-Wilk test. Parametric variables that were not regularly distributed were presented as median interquartile range (IQR), normally distributed variables as mean±standard deviation (SD), and categorical variables as number (n) and percentage (%). The independent samples t-test was conducted for comparison of normally distributed data, and the Mann-Whitney test was used to test whether there was a difference between two groups when the data were non-normally distributed. The area under the curve (AUC) of the receiver operating characteristic (ROC) was calculated. Also, sensitivity, specificity, accuracy, positive predictive values, and negative predictive values were evaluated.

RESULTS

A total of 27 patients with GCA were identified, and two patients were excluded due to the incomplete data. Also, after exclusion of patients with incomplete data, 28 patients were included as a control group. Nineteen (67.9%) of the patients in the control group were female and the mean age was 66.4±3.7 years. Of the patients diagnosed with GCA, 17 (68%) were female and the mean age was 71.5±7.3 years. There was a statistically significant difference between the two groups in the comparison of clinical criteria ($p<0.001$). In the comparison of acute phase values, a statistically significant difference was found between the two groups ($p<0.001$). Temporal artery US comparison showed a statistically significant difference between the two groups ($p<0.001$). When evaluating the imaging findings between the two groups, temporal artery and bilateral axillary US were found to be statistically significant, but no significance was found for FDG-PET uptake in the aorta. Further details of the demographic, clinical and imaging results of the two groups are shown in **Table 1**.

The 2022 ACR/EULAR classification criteria for GCA had higher sensitivity (92.0%), specificity (92.9%), positive predictive value (92.0%), negative predictive value (92.9%), accuracy (92.4%), and AUC (0.979 (0.925-0.998)) compared to the 1990 ACR classification criteria for GCA (88.0%, 85.7%, 84.6%, 88.9%, and 0.86.8%, respectively). The difference in

Table 1. Comparison of general status and clinical features between giant cell arteritis and control groups

Variables	Giant cell arteritis (n=25)	Control group (n=28)	p
Age ≥50 years at time of diagnosis, n (%)	25 (100.0)	28 (100.0)	0.119
Clinical criteria, n (%)			
Morning stiffness in shoulders/neck	23 (92.0)	7 (25)	<0.001
Sudden visual loss	2 (8.0)	0 (0)	<0.001
Jaw or tongue claudication	12 (48)	0 (0)	<0.001
New temporal headache	22 (88)	1 (3.6)	<0.001
Scalp tenderness	16 (64)	1 (3.6)	<0.001
Abnormal examination of the temporal artery	20 (80)	0 (0)	<0.001
Laboratory, imaging, and biopsy criteria, n (%)			
Maximum ESR ≥50 mm/hour or maximum CRP ≥10 mg/liter	25 (100.0)	26 (92.8)	0.621
Positive temporal artery biopsy or halo sign on temporal artery ultrasound	13 (52.0)	0 (0)	<0.001
Bilateral axillary involvement	2 (8.0)	1 (3.6)	<0.001
FDG-PET activity throughout aorta	2 (8.0)	3 (10.7)	0.471

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein; FDG-PET: Fluorodeoxyglucose positron emission tomography

Table 2. Comparison of evaluation indices of different diagnostic/classification criteria

Classification criteria	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)	AUC (95%)
1990 ACR	88.0	85.7	84.6	88.9	86.8	0.871 (0.770-0.973)
2022 ACR/EULAR	92.0	92.9	92.0	92.9	92.4	0.979 (0.925-0.998)

AUC: Area under the curve, ACR: American College of Rheumatology, EULAR: European Alliance of Associations for Rheumatology

AUC was statistically significant (0.871 (0.770-0.973), p<0.001) (Table 2, Figure 1, 2).

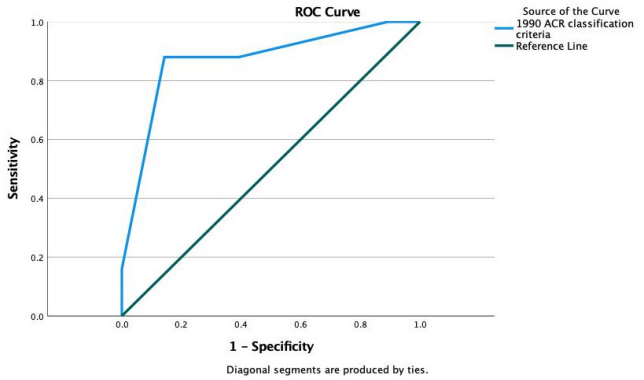

Figure 1. ROC curve according to 1990 ACR classification criteria
ROC: Receiver operating characteristic, ACR: American College of Rheumatology

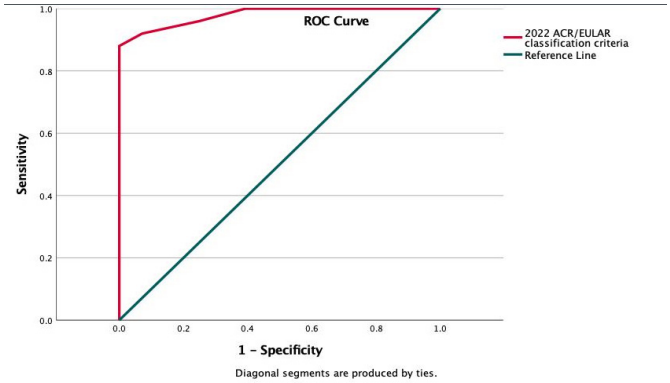

Figure 2. ROC curve according to 2022 ACR/EULAR classification criteria
ROC: Receiver operating characteristic, ACR: American College of Rheumatology, EULAR: European Alliance of Associations for Rheumatology

DISCUSSION

The 2022 ACR/EULAR criteria have shown comparable specificity and a significant increase in sensitivity in the diagnosis of GCA. The findings of the present study demonstrated a high level of diagnostic accuracy, as evidenced by an AUC value of 0.979, sensitivity of 92.0%, and specificity of 92.9%. In the study, AUC was shown to be 0.928, sensitivity was 92.6% and specificity was 71.8%.[10] Similar results were found in another study where the sensitivity was 87.3% and the specificity was 70.3%.[11] The new criteria demonstrate a significant improvement in sensitivity, with studies reporting values ranging from 87.0% to 98.0%. Specificity, however, varies more widely, with reported values between 57.5% and 94.8%.[10,12,15] The reasons for this difference in sensitivity and specificity between studies may be due to the different societies in which the criteria were applied, the differences in the diseases in the control group, and the differences in the imaging methods used. This information led to similar results in several patient subgroups, such as those with biopsy-proven GCA and isolated large-vessel GCA, where sensitivity was close to 100%.[11] The 1990 ACR criteria did not perform as well as the 2022 ACR/EULAR criteria. In our study, the AUC was 0.871, with sensitivity at 88.0% and specificity at 85.7%. In the study conducted by Molina-Collada et al.[10], the overall sensitivity of the 1990 ACR criteria was found to be 53.2% and the specificity was found to be 80.2%. Another study found a sensitivity of 66.1% and a specificity of 85.1%.[12] The significant contribution of advanced imaging modalities such as FDG-PET and US, which have improved the detection of GCA, particularly in individuals without traditional cranial symptoms, is responsible for this increase in diagnostic accuracy.[13,14] The inclusion of imaging modalities in the 2022

criteria allows for the identification of a broader range of GCA phenotypes, including cranial and extracranial large-vessel involvement.[8] This is particularly important for patients who may not exhibit classic cranial symptoms but have significant extracranial vasculitis, which can now be more accurately classified and treated.[11] The criteria's ability to classify patients with mixed GCA phenotypes further supports their utility in diverse clinical settings. Studies have shown that the use of US and FDG-PET significantly increases the likelihood of identifying GCA. FDG-PET activity in the aorta and its branches or the presence of a halo sign on US are important markers of GCA in research.[16,17] In the diagnosis of large-vessel GCA, where cranial symptoms are typically rare, this is an important consideration.[11] Once the 2022 criteria are routinely used, it will be possible to diagnose GCA more accurately and earlier than with the previous criteria. This is crucial for starting treatment early and avoiding consequences such as vision loss. However, the new standards have some drawbacks. For example, the weighting of abrupt vision loss and the inclusion of polymyalgia rheumatica (PMR) symptoms may lead to false-positive results in people with non-vasculitic ophthalmic disorders and PMR.[11] Although they provide significant improvements over the 1990 criteria, clinicians should consider the possibility of false-positive results and consider all clinical findings when making a diagnosis of GCA.

Limitations

The study has some limitations. The main limitation is that it is retrospective, which may lead to biases regarding patient selection and data collection. A fixed cut-off score of ≥6 for classification criteria may not be optimal for all patient populations. Although imaging techniques are useful for identifying large vessel involvement, they may not be interpreted in the same way in different medical settings. This can affect how accurate the results are and whether they can be used in the same way, especially in places with limited access to advanced imaging equipment. The number of patients is limited in terms of generalizability of the data to the population, but it should not be forgotten that this disease is also rare in the population.

To improve specificity and avoid false positives, future studies should focus on improving the criteria. This could include the inclusion of more diagnostic indicators or the inclusion and weighting of additional symptoms or imaging results in the criteria. To ensure accurate and reliable diagnosis, agreement on efficient imaging techniques and uniformity of clinical results are needed.[10]

CONCLUSION

The 2022 ACR/EULAR classification criteria for GCA represent a significant advancement in the field of rheumatology, offering healthcare professionals a more sophisticated instrument with which to diagnose GCA in routine clinical practice. Their integration of imaging techniques aligns with current clinical practices and enhances the ability to diagnose and manage various GCA phenotypes effectively. However, ongoing evaluation and potential adjustments are necessary to address the remaining challenges in specificity and atypical presentations. Further research is needed to improve the criteria and reduce false-positive results.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Non-Intervention Scientific Researches Ethics Committee of the University of Health Sciences Gülhane Training and Research Hospital (Date: 05.12.2024, Decision No: 2024/89).

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

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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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Left atrial appendage strain and P-wave dispersion: electro-mechanical markers of paroxysmal atrial fibrillation

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ABSTRACT

Aims: Paroxysmal atrial fibrillation (PAF) is a major clinical challenge due to its intermittent nature and the difficulty of early detection. Left atrial appendage (LAA) function plays a crucial role in atrial mechanics, while P-wave dispersion (PWD) reflects electrical inhomogeneity. We hypothesized that both parameters would independently and synergistically predict PAF and aimed to develop an integrative electro-mechanical model to enhance risk stratification.

Methods: We retrospectively analyzed 191 patients, including 91 with PAF and 100 in sinus rhythm (SR). LAA function was assessed using speckle-tracking echocardiography, and PWD was measured digitally from 12-lead electrocardiography. Multivariable logistic regression models were constructed: model 1 included clinical parameters, model 2 incorporated PWD, and Model 3 further added LAA strain reservoir (LAA-Sr)

Results: PAF patients exhibited significantly lower LAA-Sr (14.7 % [12.2-18.0] vs. 21.6% [19.1-25.3], p<0.001) and higher PWD (30.3 [27.6-34.5] ms vs. 20.9 [17.3-26.6] ms, p<0.001). In multivariable analysis, LAA-Sr (OR: 1.315, 95% confidence interval [CI]: 1.201-1.439, p<0.001) and PWD (OR: 1.128, 95% CI: 1.054-1.215, p=0.038) were independent PAF predictors. Model 3, which included both parameters, demonstrated the best predictive performance (AUC: 0.983, sensitivity: 92.8%, specificity: 79.4%) compared to model 1 (AUC: 0.890) and model 2 (AUC: 0.950).

Conclusion: Our study highlights LAA strain and PWD as robust, independent predictors of PAF. The combination of mechanical and electrophysiological markers enhances AF risk stratification and early detection. Future prospective, multi-center studies are warranted to validate these findings and optimize risk assessment strategies for PAF.

Keywords: Atrial fibrillation, left atrial appendage, transesophageal echocardiography, electrocardiography, prediction algorithms

INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and is associated with an increased risk of stroke, heart failure, and cardiovascular mortality.[1] Paroxysmal atrial fibrillation (PAF), a subtype of AF characterized by self-terminating episodes, poses a particular diagnostic challenge as many patients remain asymptomatic or experience only transient symptoms.[2] Identifying patients at risk of developing PAF is crucial for timely intervention and stroke prevention.

Left atrial appendage (LAA) function plays a central role in atrial mechanics and thrombogenesis. As an embryological remnant of the primitive left atrium, the LAA is the most common site of thrombus formation in AF and serves as a key marker of atrial mechanical dysfunction.[3] LAA morphology influences its mechanical function, with variations in size and shape potentially impacting contractile performance and predisposing to AF.[4] Beyond structural remodeling, speckle tracking echocardiography (STE)-derived LAA strain analysis has emerged as a novel method to assess LAA function, providing insights into atrial mechanics beyond conventional echocardiographic parameters.[5] A decline in LAA strain may reflect early atrial remodeling, potentially identifying patients at increased risk for AF development.[6]

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Similarly, P-wave dispersion (PWD), defined as the difference between the maximum and minimum P-wave durations on a surface electrocardiogram (ECG), is a marker of atrial conduction heterogeneity.[7] Increased PWD has been associated with atrial electrical remodeling and a higher risk of developing AF.[8] Despite their potential complementary roles, the predictive value of LAA strain and PWD in PAF detection remains largely unexplored.

We hypothesized that impaired LAA mechanical function and increased atrial electrical dispersion may independently predict PAF, and their combination could enhance diagnostic performance in at-risk individuals. To our knowledge, this is among the first studies to evaluate their combined role in PAF prediction.

METHODS

Ethics

The study was conducted in accordance with the Declaration of Helsinki and was initiated with the approval of the Clinical Researches Ethics Committee of Başakşehir Çam and Sakura City Hospital (Date: 27.04.2022, Decision No: 136). Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Study Population

This retrospective, observational study included patients diagnosed with PAF and a control group with sinus rhythm (SR). PAF was defined as AF episodes lasting less than seven days and terminating spontaneously or with medical intervention. Importantly, all patients in the PAF group were in SR at the time of evaluation. The control group consisted of individuals with persistent SR on standard 12-lead ECG at the time of enrollment, without a history of palpitations, documented arrhythmia, or known structural heart disease.

In the SR group, TEE was performed either to evaluate suspected interatrial septal abnormalities (e.g., to differentiate between patent foramen ovale [PFO] and atrial septal defect [ASD]) or due to inadequate transthoracic echocardiographic imaging. Patients with PFO, hemodynamically insignificant small ASD (<10 mm)[9], or suboptimal transthoracic views were included, provided they did not meet other exclusion criteria. LAA strain measurements were retrospectively evaluated in patients with optimal image quality.

Patients with structural heart disease, prior cardiac interventions involving the left atrium (including ASD or PFO closure), significant valvular heart disease (including prosthetic valves, moderate-to-severe mitral regurgitation, mitral stenosis, tricuspid regurgitation), severe atrial dilation >50 mm, left ventricular dysfunction (LVEF <50%), prior AF ablation, persistent or ongoing AF at enrollment, pacemaker history, QRS duration >120 ms, uncontrolled hypertension (systolic blood pressure >160 mmHg despite medical therapy), or obesity (BMI ≥35 kg/m²) were excluded. Additionally, patients with suboptimal LAA visualization on STE and those with ECGs showing unclear P-wave morphology or poor signal quality were excluded to ensure measurement accuracy.

All participants underwent a comprehensive echocardiographic evaluation and a standard 12-lead ECG at the time of enrollment. Clinical characteristics, including age, sex, cardiovascular risk factors, and medication history, were recorded.

Electrocardiographic Assessment of P-Wave Dispersion

P-wave dispersion was assessed using a digital electrocardiographic measurement software on standard 12-lead ECG recorded at a paper speed of 50 mm/s and an amplitude of 10 mm/mV. P-wave onset was defined as the first positive or negative deflection from the isoelectric line, while P-wave offset was marked as the return to baseline.

Measurements were performed manually with software assistance by two independent observers blinded to the clinical data. PWD was calculated as the difference between the longest and shortest P wave durations measured across the 12 leads. To minimize inter-observer variability, both observers independently repeated the measurements, and significant discrepancies (>5 ms) were resolved by consensus. Additionally, a subset of randomly selected ECGs was reanalyzed after two weeks by the same and different observers to evaluate intra-observer and inter-observer agreement.

Left Atrial Appendage Speckle Tracking Strain Echocardiography

This study retrospectively included patients who had undergone TEE for various clinical indications. TEE imaging was performed using a Philips EPIQ CxT system with an X8-2t transesophageal probe. TEE examinations were performed under conscious sedation and oropharyngeal anesthesia, following standard institutional protocols. Routine LAA functional parameters, including emptying velocity, end-diastolic volume, end-systolic volume, ejection fraction, and volume change, were assessed using two-dimensional TEE. LAA volumes were measured using the biplane area-length method in the long-axis view.

LAA function was further evaluated using speckle tracking echocardiography (STE), as illustrated in **Figure 1**. As no dedicated software currently exists for LAA strain analysis, we adopted a methodology similar to previous studies that adapted standard LV or LA strain software for this purpose.[6] LAA strain analysis was performed via offline post-processing using TomTec Imaging Systems (Unterschleissheim, Germany). LAA strain measurements were derived using an automated LA strain analysis software initially developed for LA strain evaluation. The region of interest (ROI) was manually repositioned to focus on the LAA myocardium, ensuring accurate contouring. The software automatically provided LAA reservoir strain (LAA-Sr), conduit strain (LAA-Scd), and contraction strain (LAA-Sct). These parameters reflect distinct aspects of LAA function: LAA-Sr represents reservoir function during atrial filling, LAA-Scd reflects passive emptying function, and LAA-Sct indicates active contraction capacity. **Figure 1A** demonstrates an example of strain tracking on the LAA, while **Figure 1B** displays the corresponding strain curve with numerical values. To ensure measurement reliability, strain curves with inadequate tracking quality were manually corrected, and poorly tracked segments were excluded from the analysis. The onset of the

QRS complex was used as a reference point for strain curve analysis.

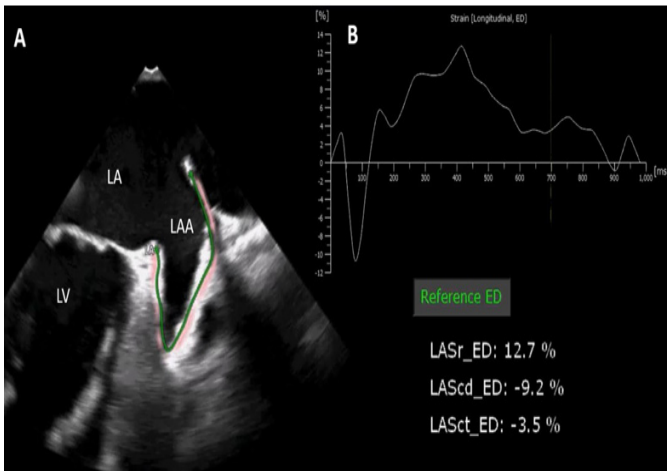

Figure 1. Left atrial appendage (LAA) strain analysis using speckle-tracking echocardiography (STE). (**A**) Mid-esophageal transesophageal echocardiographic (TEE) view at 90°, showing automated speckle-tracking of the LAA myocardium with manual contour adjustments. (**B**) Corresponding strain curve analysis displaying LAA reservoir strain (LAA-Sr), conduit strain (LAA-Scd), and contraction strain (LAA-Sct).

Spontaneous echocardiographic contrast (SEC) and thrombus assessment was performed by optimizing gain settings to enhance contrast resolution while minimizing noise and artifacts, reducing the risk of misinterpretation. SEC in the LA and LAA was evaluated based on echogenic swirling patterns and classified as grade 0 (absent), grade 1 (minimal), grade 2 (mild), grade 3 (moderate), or grade 4 (severe), as previously described.[10]

To assess intra-observer and inter-observer variability, a subset of randomly selected measurements was repeated by the same and different observers after a two-week interval.

Statistical Analysis

The study population was divided into two groups: SR and PAF, and all statistical comparisons were performed between these groups. The distribution of continuous variables was assessed using the Shapiro-Wilk test and visual inspection of histograms. Continuous variables were expressed as mean±standard deviation (SD) or median (interquartile range, IQR), depending on data distribution, and compared using the independent samples t-test or Mann-Whitney U test. Categorical variables were presented as counts and percentages [n (%)] and analyzed using the χ^2 test or Fisher's exact test, where appropriate.

To determine independent predictors of PAF, variables demonstrating statistical significance in univariate analyses ($p<0.05$) were incorporated into multivariable logistic regression models. Model performance was evaluated using Nagelkerke R^2 values, Akaike information criterion (AIC), and C-index analysis. The incremental predictive value of LAA strain parameters was assessed using integrated discrimination improvement (IDI) and net reclassification improvement (NRI) indices. Model accuracy was further assessed by receiver operating characteristic (ROC) curve analysis, and decision-making utility was evaluated using decision curve analysis (DCA). Model calibration was verified with calibration plots.

Post-hoc power analyses were performed to assess the adequacy of the sample size. Intra-observer and inter-observer variability for PWD and LAA strain measurements were assessed using intraclass correlation coefficients (ICCs). All statistical analyses were performed using IBM SPSS Statistics for Windows, version 30.0 (IBM Corp., Armonk, NY, USA) and R software (R Foundation for Statistical Computing, Vienna, Austria). A two-tailed p-value <0.05 was considered statistically significant.

RESULTS

A total of 191 patients were included, with 91 in the PAF group and 100 in the SR group. Patients with PAF had a higher burden of comorbidities, including hypertension and coronary artery disease (p=0.001 for both) (Table 1) and had significantly larger LA dimensions and volume index (LAVI) (p<0.001).

Echocardiographic assessments revealed that LAA function was significantly impaired in the PAF group. LAA ejection fraction was lower in PAF patients compared to the SR group. LAA end-diastolic and end-systolic volumes were also larger in the PAF group (p=0.005 and p<0.001, respectively). LAA-Sr was significantly lower in the PAF group (21.6 [19.1-25.3]% vs. 14.7 [12.2-18.0]%, p<0.001), indicating impaired LAA mechanics (Table 2). The optimal cut-off value for LAA-Sr to predict PAF was 19.21%, with a sensitivity of 74% and a specificity of 72%, yielding an AUC of 0.832 (95% confidence interval [CI]: 0.775–0.890).

PWD was significantly higher in the PAF group compared to the SR group (30.3 [27.6–34.5] ms vs. 20.9 [17.3–26.6] ms, p<0.001). The optimal cut-off value for PWD in predicting PAF was determined as 23.79 ms, with a sensitivity of 84% and a specificity of 69%, yielding an AUC of 0.829 (95% CI 0.767–0.891).

To identify predictors of PAF, multivariable logistic regression analysis was performed, incorporating variables that were significant in univariate analysis and clinically relevant (Table 3). Given the collinearity among LA parameters, only LA strain was included in the final models. Model 1 included general clinical parameters such as age, hypertension, coronary artery disease, CHA_2DS_2-VASc score, and LA strain. Model 2 extended model 1 by adding PWD. Model 3 further extended model 2 by incorporating LAA- Sr (Table 4). The predictive performance of the models, as assessed by ROC analysis, including AUC, sensitivity, and specificity values, is summarized in Figure 2. Model 3 demonstrated the highest AUC (0.983, 95% CI 0.970–0.996), with improved sensitivity (92.8%) and specificity (79.4%), indicating its superior predictive ability. Further comparisons of model indices confirmed the superiority of model 3. The final model exhibited the strongest predictive capability, as evidenced by a higher Nagelkerke R^2 (0.575), a lower AIC: (162.9), an improved C-index (0.890), and significant improvements in IDI (0.152). These findings are summarized in Figure 3. DCA demonstrated the highest net clinical benefit with

Table 1. Baseline clinical, demographic, and electrocardiographic characteristics compared between the sinus rhythm and PAF groups

Clinical parameters	Sinus rhythm, n=100	PAF, n=91	Total, n=191	p-value
Male, n (%)	45 (45%)	42 (46%)	87 (46%)	0.885
Age, years	49 (37-58)	59 (50-66)	54 (44-63)	<0.001
Hypertension, n (%)	15 (15%)	34 (37%)	49 (26%)	0.001
Coronary artery disease, n (%)	14 (14%)	48 (53%)	62 (32%)	0.001
Diabetes mellitus, n (%)	22 (22%)	32 (35%)	54 (28%)	0.076
Chronic kidney disease, n (%)	9 (9%)	11 (12%)	20 (10%)	0.638
Chronic obstructive pulmonary disease, n (%)	3 (3%)	7 (8%)	10 (5%)	0.202
History of stroke, n (%)	26 (26%)	10 (11%)	36 (19%)	0.009
BMI, kg/m²	25.9 (23.0-30.2)	26.6 (24.4- 29.7)	26.1 (23.8-30.0)	0.145
HR, bpm	71 (61-75)	79 (67-89)	73 (65-83)	<0.001
CHADS2-VASc score	2 (1-3)	3 (2-4)	3 (1-4)	0.001
Anticoagulation, n (%)				0.001
None, n (%)		11 (12%)	11 (6%)	
Apixaban, n (%)		16 (18%)	16 (8%)	
Rivaroxaban, n (%)		28 (31%)	28 (15%)	
Edoxaban, n (%)		22 (24%)	22 (12%)	
Dabigatran, n (%)		2 (2%)	2 (1%)	
Warfarin, n (%)		11 (12%)	11 (6%)	
Pmax, ms	90 (80-100)	100 (80-120)	92.5 (80-110)	0.266
Pmin, ms	40 (40-50)	50 (40-58.75)	45 (40-55)	0.002
P dispersion, ms	20.9 (17.3-26.6	30.3 (27.6-34.5)	26.9 (20.1-32.0)	<0.001

Data are presented as median (IQR) for continuous variables and n (%) for categorical variables. A p-value <0.05 was considered statistically significant. BMI: Body-mass index, CHADS2-VASc: Congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, sex, EDV: End-diastolic volume, EF: Ejection fraction, E/e': Mitral E-wave to early diastolic annular velocity, HR: Heart rate, LAA: Left atrial appendage, LAA EF: Left atrial appendage ejection fraction, LAA emptying velocity: Left atrial appendage emptying velocity, LAA volume ED: Left atrial appendage volume at end-diastole, LAA volume ES: Left atrial appendage volume at end-systole, LAA volume change: Left atrial appendage volume change, LA: Left atrium, LAAScd: Left atrial appendage strain conduit phase, LAASct: Left atrial appendage strain contraction phase, LAASr: Left atrial appendage strain reservoir phase, LAVI: Left atrial volume index, P dispersion: P-wave dispersion, Pmax: Maximum P-wave duration, Pmin: Minimum P-wave duration

model 3, and calibration analysis confirmed the reliability of predictions. These findings are summarized in **Figure 4**.

Post-hoc power analyses based on group differences in LAA-Sr and PWD demonstrated large effect sizes (Cohen's d≈1.55) and statistical power >0.99, confirming the adequacy of the sample size, which is also comparable to or larger than those reported in similar observational studies[6], in line with current STROBE recommendations for observational studies.[11] Intra-observer and inter-observer variability analyses showed good reproducibility for both PWD and LAA strain measurements. The ICC values were 0.92 and 0.89 for intra- and inter-observer agreement of PWD, respectively, and 0.91 and 0.87 for intra- and inter-observer agreement of LAA strain.

DISCUSSION

This study demonstrated that LAA- Sr and PWD are independent predictors of PAF. The addition of these parameters to a conventional clinical model significantly enhanced the ability to predict PAF, improving both model discrimination and classification performance. To the best of our knowledge, this is one of the first studies to evaluate the combined role of LAA-Sr and PWD in PAF prediction. These findings suggest that a combined assessment of LAA mechanical function and atrial conduction properties may provide additional value in identifying patients at risk for PAF.

Several studies have explored LAA strain in AF, specifically focusing on its role in predicting stroke risk, arrhythmia occurrence and AF recurrence. Saberniak et al.[6] investigated LAA-Sr in stroke patients and found that lower LAA-Sr was associated with subclinical AF, with a cut-off of 22.2%. Similarly, studies assessing AF recurrence after catheter ablation reported even lower LAA-Sr values, with one study identifying a cut-off of 10.2%, indicating that LAA function deteriorates significantly in persistent AF or post-ablation settings.[12] Another study demonstrated that LAA-Sr is associated with thromboembolic risk, showing an inverse correlation between strain values and SEC or thrombus formation.[13] In a direct comparison of persistent vs. paroxysmal AF patients, LAA strain was significantly lower in persistent AF, reinforcing its role in AF progression.[14] Additionally, a study evaluating AF burden in non-valvular AF patients demonstrated that LAA strain was significantly reduced in those with higher arrhythmic burden, further supporting its predictive value.[15]

Our study differs from previous research on LAA strain in AF, particularly in patient selection and methodology. While prior studies mainly focused on persistent AF, stroke populations, or post-ablation recurrence, our cohort consisted of PAF patients evaluated in SR. This distinction is important, as AF itself impairs LAA contractility and remodeling, leading to lower strain values in persistent AF. Consequently, while previous studies reported LAA-Sr cut-offs as low as 10.2% in post-ablation settings and 22.2% in stroke patients, we identified a cut-off of 19.21% for PAF prediction. This

Table 2. Echocardiographic and strain parameters compared between the sinus rhythm and PAF groups

Parameters	Sinus rhythm, n=100	PAF, n=91	Total, n=191	p-value
EDV, ml	45 (41-47)	46 (43-50)	45 (43-49)	0.111
EF, %	60 (69-65)	61 (57-63)	60 (58-62)	0.060
E/e' ratio	12.8 (11.7-13.4)	13.3 (12- 14.8)	13.2 (11.7-14.6)	0.078
Mitral stenosis, n (%)				0.321
None	89 (89%)	84 (92%)	173 (91%)	
Mild	8 (8%)	3 (3%)	11 (6%)	
Mitral regurgitation, n (%)				0.001
None	17 (17%)	7 (8%)	24 (13%)	
Mild	83 (83%)	65 (71%)	148 (77%)	
Tricuspid regurgitation, n (%)				0.003
None	29 (29%)	25 (27%)	54 (28%)	
Mild	71 (71%)	54 (59%)	125 (65%)	
LAA spontaneous echo contrast, n (%)				0.008
Grade 0, n (%)	97 (97%)	77 (84%)	174 (91%)	
Grade 1, n (%)	3 (3%)	10 (10%)	13 (7%)	
Grade 2, n (%)	0	4 (4%)	4 (2%)	
LAA thrombus, n (%)	0	3 (3%)	3 (2%)	0.001
LA diameter, mm	35 (32-41.75)	40 (37-45)	39 (34-44)	<0.001
LAVI, ml/m²	32.1 (29.5-35.4)	42.6 (40.1-46.3)	37.0 (31.4-42.6)	<0.001
LAA emptying velocity, cm/s	73.6 (71.2-76.9)	74.6 (72.1-78.3)	74.2 (71.3-77.6)	0.124
LAA volume ED, ml	3.7 (2.7-5.7)	4.6 (3.6-6.1)	4.2 (2.9-5.6)	0.005
LAA volume ES, ml	0.8 (0.5-1.1)	1.5 (1.2-1.8)	1.2 (0.7-1.6	<0.001
LAA EF, %	78.3 (62.1-87.0)	66.9 (64.4-68.6)	68.2 (64.0-79.8)	<0.001
LAA volume change, ml	2.7 (1.6-4.4)	3.09 (2.33-4.21)	2.9 (1.9-4.3)	0.279
LA Sr, %	26.7 (24.3-30.0)	13.5 (11.0-17.2)	21.2 (13.9-27.0)	<0.001
LA Scd, %	-15.0 (-17.5--11.7)	-7.2 (-9.7--3.5)	-11.2 (-15.9--6.8)	<0.001
LA Sct, %	-12.1 (-14.6--8.8)	-5.2 (-7.7--1.5)	-8.6 (-13.0--4.3)	<0.001
LAA Sr, %	14.7 (12.2-18.0)	21.6 (19.1-25.3)	18.2 (13.8-22.6)	<0.001
LAA Scd, %	-10.1 (-12.5--6.8)	-13.3 (-15.8--9.6)	-11.3 (-14.8--8.1)	<0.001
LAA Sct, %	-6.9 (-9.4--4.0)	-9.3 (-11.8--5.6)	-7.8 (-10.8--4.7)	0.004

EDV: End-diastolic volume, EF: Ejection fraction, LAA: Left atrial appendage, LAA EF: Left atrial appendage ejection fraction, LAA emptying velocity: Left atrial appendage emptying velocity, LAA volume ED: Left atrial appendage volume at end-diastole, LAA volume ES: Left atrial appendage volume at end-systole, LAA volume change: Left atrial appendage volume change, LA: Left atrium, LAAScd: Left atrial appendage strain conduit phase, LAASct: Left atrial appendage strain contraction phase, LAASr: Left atrial appendage strain reservoir phase, LAVI: Left atrial volume index

Table 3. Univariate regression analysis for predictors of paroxysmal atrial fibrillation

Univariate regression	OR (95% CI)	p value
Age (years)	1.063 (1.038-1.091)	<0.001
HT	3.198 (1.617-6.57)	<0.001
DM	1.831 (0.967-3.515)	0.070
CAD	6.612 (3.349-13.742)	<0.001
CHA_2DS_2-VASc score (points)	1.611 (1.322-1.997)	<0.001
LA (mm)	1.121 (1.065-1.188)	<0.001
LAVI (ml/m²)	1.477 (1.342-1.659)	<0.001
LAA emptying velocity (cm/s)	1.034 (0.982-1.091)	0.210
LAA EF (%)	1.002 (0.997-1.008)	0.460
LA Sr (%)	0.612 (0.522-0.692)	<0.001
LAA Sr (%)	1.298 (1.208-1.411)	<0.001
P-wave dispersion (ms)	1.075 (1.042-1.116)	<0.001

Odds ratios (OR) with 95% confidence intervals (CI) are presented. A p-value <0.05 was considered statistically significant. CAD: Coronary artery disease, CHA_2DS_2-VASc score (points): Congestive heart failure, hypertension, age ≥75 (2 points), diabetes mellitus, stroke/TIA (2 points), vascular disease, age 65-74, DM: Diabetes mellitus, HT: Hypertension, LAA Sr (%): Left atrial appendage strain reservoir, LA Sr (%): Left atrial strain reservoir

difference likely reflects variations in study populations, as we excluded patients with prior LAA interventions, significant atrial fibrosis, or advanced structural disease, making our findings more relevant for early-stage AF detection.

Methodological differences may have also contributed to these discrepancies. Unlike prior studies that often used LV strain software, we utilized LA strain software, providing a more physiologically accurate assessment of reservoir, conduit, and contraction phases. Moreover, whereas most previous studies performed strain analysis using GE ultrasound systems with EchoPAC software, our study utilized Philips ultrasound systems with TomTec software. These vendor-related differences in imaging platforms and post-processing algorithms may have influenced contouring precision and strain quantification.

The role of PWD in AF prediction has also been extensively studied. Aytemir et al.[16] identified a PWD cut-off of 36 ms for PAF detection, with 77% sensitivity and 82% specificity.

Table 4. Multivariate regression analysis for predictors of paroxysmal atrial fibrillation across different models

	Model 1		Model 2		Model 3	
Parameter	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**
Age (years)	0.007	1.045 (1.012-1.078)	0.006	1.048 (1.014-1.084)	0.004	1.057 (1.018-1.098)
HT	0.170	0.257 (0.037-1.786)	0.769	0.649 (0.036-11.636)	0.137	2.262 (0.772 - 6.627)
CAD	<0.001	4.430 (1.871-10.491)	0.003	3.814 (1.562-9.315)	0.015	3.532 (1.276-9.772)
DM	0.117	0.300 (0.067-1.352)	0.188	0.218 (0.023-2.105)	0.448	1.505 (0.523-4.330)
CHA_2DS_2-VASc score	0.355	1.357 (0.710-2.594)	0.742	0.855 (0.335-2.179)	0.476	0.851 (0.546-1.326)
LA Sr (%)	<0.001	0.555 (0.451-0.683)	<0.001	0.465 (0.330-0.655)	0.027	0.685 (0.512-0.849)
P-wave dispersion (ms)	-	-	<0.001	1.174 (1.086-1.270)	0.038	1.128 (1.054-1.215)
LAA Sr (%)	-	-	-	-	<0.001	1.315 (1.201-1.439)

Odds ratios (OR) with 95% confidence intervals (CI) are presented for three models. A p-value <0.05 was considered statistically significant. CAD: Coronary artery disease, CHA_2DS_2-VASc score (points): Congestive heart failure, hypertension, age ≥75 (2 points), diabetes mellitus, stroke/TIA (2 points), vascular disease, age 65-74, DM: Diabetes mellitus, HT: Hypertension, LAA Sr (%): Left atrial appendage strain reservoir, LA Sr (%): Left atrial strain reservoir

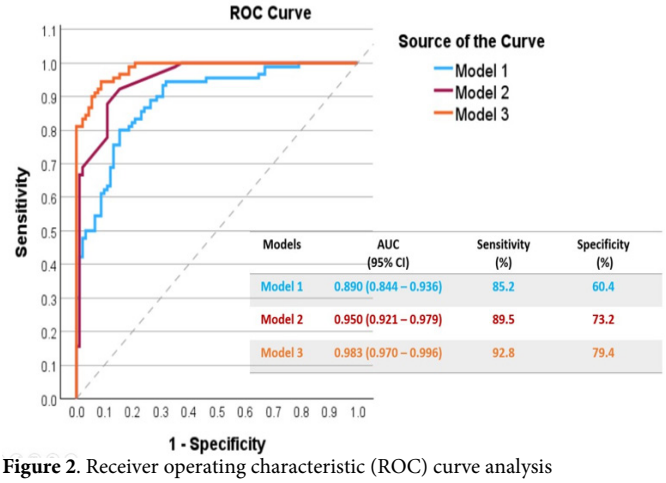

Figure 2. Receiver operating characteristic (ROC) curve analysis

The ROC curves illustrate the discriminatory performance of the three models. The table below presents the AUC, sensitivity, and specificity values for each model, highlighting the superior predictive accuracy of model 3

A meta-analysis further confirmed the association between PWD and AF risk, demonstrating significantly higher values in patients with recurrent AF. Additionally, increased PWD has been linked to greater AF burden, reinforcing its role in atrial conduction abnormalities.[17] However, many of these studies primarily included patients with persistent AF, stroke, or advanced atrial remodeling, which may account for differences in reported findings.[8]

In contrast, our study determined a PWD cut-off of 23.79 ms for PAF prediction. This discrepancy is likely due to differences in study populations, as our cohort consisted of PAF patients evaluated while in SR, making our findings particularly relevant for early-stage AF detection. Furthermore, we excluded patients with severe atrial fibrosis or structural disease, further distinguishing our cohort from prior studies. Methodological variations may have also contributed—while previous studies often relied on manual ECG measurements,

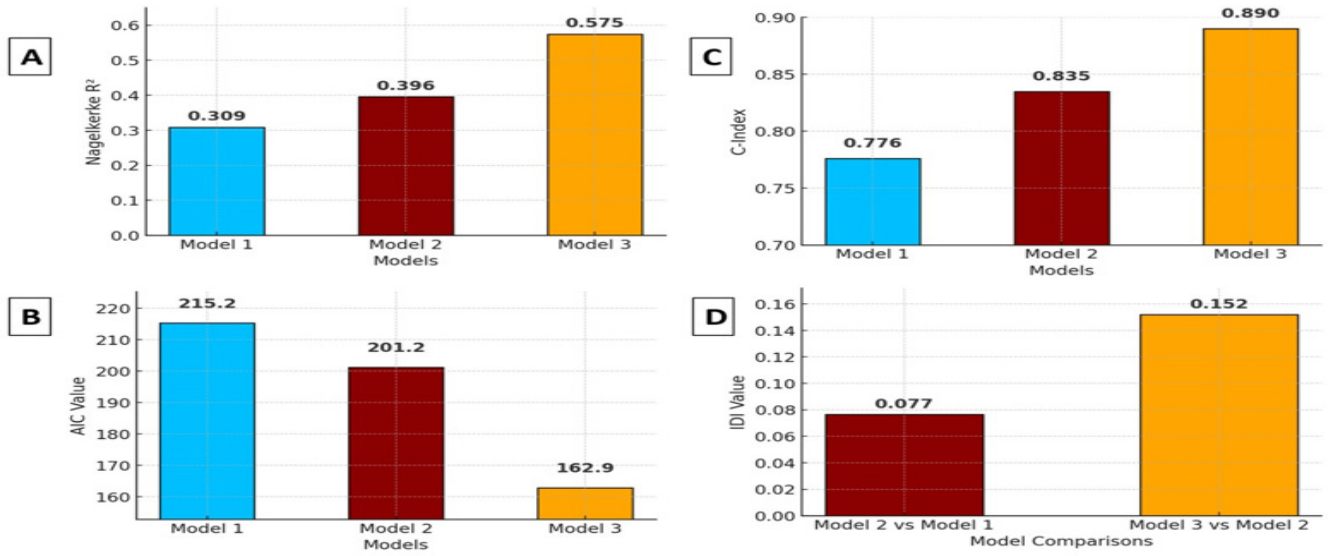

Figure 3. Model performance metrics. Panel (**A**) shows Nagelkerke R^2 values, demonstrating the improved explanatory power of model 3. Panel (**B**) presents Akaike information criterion (AIC) values, indicating better model fit with lower AIC. Panel (**C**) displays the C-index, highlighting the enhanced discriminative ability of model 3. Panel (**D**) illustrates the integrated discrimination improvement (IDI) values, confirming the incremental predictive value gained with each model refinement

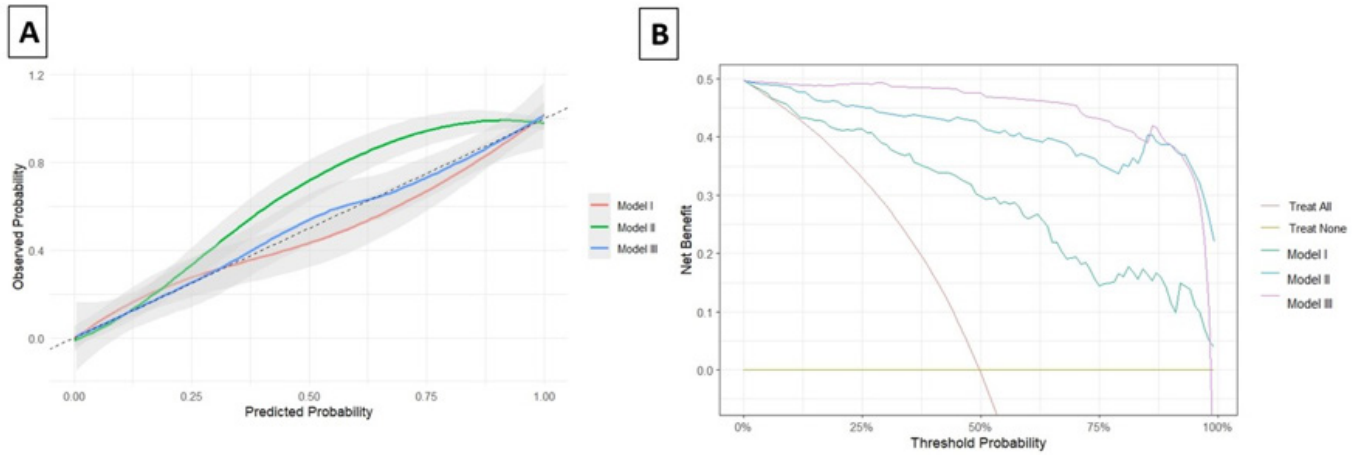

Figure 4. Model calibration and clinical utility**.** Panel (**A**) displays the calibration curves for the three models, illustrating the agreement between predicted and observed probabilities. Model 3 (blue) shows the best calibration. Panel (**B**) presents the decision curve analysis (DCA), demonstrating the net clinical benefit across different threshold probabilities, with model 3 providing the highest benefit

we employed automated digital ECG analysis, ensuring greater precision and reproducibility. These factors collectively highlight the importance of population-specific cut-off values and reinforce PWD's potential utility in PAF prediction.

AF accounts for 15–25% of all ischemic strokes and increases stroke risk by three to five times, highlighting the need for early detection and effective prevention strategies.[18] Given the episodic nature of PAF, its timely identification is crucial, as even short-lived AF episodes can contribute to thromboembolic risk.[19] In our cohort, LAA thrombus was detected in 3% of PAF patients, reinforcing that PAF is not a benign condition and that its early recognition may help prevent stroke-related complications.

In this context, the combined use of LAA strain and PWD offers a novel electro-mechanical approach to PAF prediction. While PWD reflects atrial conduction abnormalities, LAA strain provides insights into atrial mechanical dysfunction, making them complementary markers in AF risk assessment. Our findings suggest that incorporating both parameters improves PAF detection beyond traditional risk factors, potentially refining risk stratification and guiding early intervention strategies in clinical practice.

Limitations

Despite its strengths, our study has several limitations. First, the retrospective design may introduce selection bias. Second, this was a single-center study, which may limit the generalizability of our results to broader populations. Third, long-term follow-up data were not available, preventing an assessment of whether patients with impaired LAA strain and increased PWD eventually developed AF over time. Additionally, since continuous ECG monitoring (e.g., Holter) was not performed, subclinical AF episodes may have been missed, potentially affecting the predictive accuracy of our findings. Finally, we used Philips software for speckle-tracking analysis, and variations in strain values across different imaging vendors should be considered when comparing results across studies.

CONCLUSION

Our study demonstrates that LAA strain and PWD are independent and complementary predictors of PAF. The integration of mechanical and electrophysiological markers enhances AF risk stratification beyond conventional parameters, offering a novel electro-mechanical approach to early AF detection. The final predictive model, incorporating both parameters, exhibited the highest diagnostic performance, emphasizing the clinical relevance of this combined approach. Although not suitable for general screening, TEE-based LAA strain analysis may have clinical value in selected patients at high risk for paroxysmal AF. Future prospective, multi-center studies with long-term follow-up are needed to validate these findings and determine their impact on AF screening, risk stratification, and stroke prevention strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Clinical Researches Ethics Committee of Başakşehir Çam and Sakura City Hospital (Date: 27.04.2022, Decision No: 136).

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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Evaluation of hemogram parameters in the diagnosis of ectopic pregnancy, early pregnancy loss and threatened miscarriage

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ABSTRACT

Aims: In present study, it aimed to analyse the importance and potential use of inflammatory blood parameters in the prediction of threatened miscarriage (TM), early pregnancy loss (EPL) and ectopic pregnancy (EP).

Methods: Between October 2021 and 2023, the demographic data and obstetric histories of a total of 300 patients (n=100 for each group) diagnosed with TM, EPL, and EP at a single center, as well as 100 healthy women with a first-trimester intrauterine pregnancy, were analyzed. Complete blood count data obtained from these participants included. In statistical analyses, the significance level was set at $p<0.05$.

Results: Although there was no notable discrepancy between the groups with regard to age, gravidity, and gestational week, the EPL cohort exhibited a markedly elevated parity rate (p=0.003). Additionally, notable disparities in platelet-lymphocyte ratio (PLR) were observed between the EPL and TM groups (p=0.021) and between the EP and TM groups (p=0.030). Additionally, monocyte-lymphocyte ratio (MLR) and neutrophil-lymphocyte ratio (NLR) were found to be higher in the EP group compared to the TM and EPL groups (p=0.004 and p=0.001 for MLR; p=0.000 in both comparisons for NLR).

Conclusion: Inflammatory blood parameters namely PLR, MLR, and NLR appear to be significant biomarkers for the diagnosis and management of TM, EPL, and EP. These findings suggest that integrating PLR, MLR, and NLR into obstetric practice could facilitate the early diagnosis and treatment of these complications.

Keywords: Early pregnancy loss, ectopic pregnancy, hematologic markers, inflammation, threatened miscarriage

INTRODUCTION

Early pregnancy loss (EPL) is defined as the absence of an embryo or the lack of detectable heart activity in the gestational sac within the first three months of pregnancy, occurring in approximately 10% of all pregnancies.[1,2] The contributing factors include genetic, infectious, endocrinological, anatomical, and immunological implantation abnormalities; however, in some cases, the exact cause remains unknown.[3,4] Ectopic pregnancy (EP) is characterized by the implantation of a fertilized egg outside the uterine cavity, with 98% of cases occurring in the fallopian tubes. It is primarily associated with impaired tubal embryo transfer due to ciliary dysfunction resulting from microenvironmental changes.[5,6] The overall incidence of EP is estimated to be approximately 2% of reported pregnancies.[7] Threatened miscarriage (TM) is defined by painless vaginal bleeding in the presence of a viable intrauterine pregnancy and occurs in approximately 20% of pregnancies.[8,9] Among these cases, the rate of missed abortion (pregnancy loss) ranges from 5.5% to 17%.[10,11] The literature suggests that immunological, endocrinological, and hematological factors may contribute to TM.[12]

TM may present with symptoms similar to those of EPL and EP, making differential diagnosis challenging. The presence of severe pain and heavy bleeding further increases the risk of miscarriage.[13] Blood parameters have been widely utilized to assess the prognosis of inflammatory diseases.[14] Inflammatory conditions lead to an increase in neutrophils and a decrease in lymphocytes due to platelet activation and the release of arachidonic acid metabolites. Consequently, neutrophil-to-lymphocyte ratio (NLR) is considered a reliable marker of underlying inflammatory processes.[15] Recent research has demonstrated that platelets and platelet-derived substances play a crucial role in various biological processes.[16] Furthermore, in EP, specific inflammatory cytokines have been observed to increase both at the implantation site and in the systemic circulation.[17]

The diagnosis and management of EPL, EP, and TM require the development of rapid, reliable, and cost-effective methods. Hematological inflammatory parameters represent easily accessible and inexpensive tests that may aid in differentiating these conditions.

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This study aims to analyze hematological inflammatory markers, including platelet count (PLT), mean platelet volume (MPV), mean platelet volume-to-platelet ratio (MPV/PLT), NLR, monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR), by comparing their levels in EPL, EP, TM, and normal intrauterine pregnancies. These markers will be evaluated using routine hemogram parameters obtained during pregnancy. This analysis seeks to enhance the diagnostic process and explore the potential clinical applications of these markers in disease diagnosis and management.

METHODS

Ethics

This study was approved by the Non-interventional Ethics Committee of Niğde Ömer Halisdemir University Faculty of Medicine (Date: 22.12.2022, Decision No: 2022/109). The study was conducted in accordance with all versions of the Helsinki Declaration.

Study Design and Participant Groups

Between October 2021 and October 2023, a retrospective case analysis was performed on patients diagnosed with EP, EPL, and TM at the Department of Obstetrics and Gynecology, Niğde Ömer Halisdemir University Faculty of Medicine Research and Practice Hospital. Demographic data and obstetric histories of the patients were collected.

Diagnosis and Criteria

The diagnoses of EP, TM, and EPL were established based on clinical examination, transvaginal ultrasonography, and hCG testing, considering gestational age. The study groups were defined as follows:

- **Threatened miscarriage (TM) group**: Patients presenting with vaginal bleeding and cramping, a detected fetal heartbeat, but no cervical dilation.
- **Early pregnancy loss (EPL) group**: Patients who experienced spontaneous miscarriage after being diagnosed with TM.
- **Ectopic pregnancy (EP) group**: Patients diagnosed with EP requiring surgical intervention.
- **Control group**: Healthy pregnant women up to 20 weeks of gestation without any signs of TM, selected randomly.

Exclusion Criteria

Patients meeting any of the following criteria were excluded from the study:

- Multiple pregnancies
- Conception through in vitro fertilization (IVF)
- History of cervical insufficiency
- History of cervical loop electrosurgical excision procedure (LEEP) or conization
- Presence of uterine pathologies
- Diagnosed thrombophilia or use of oral/parenteral anticoagulants
- Pregnancy while using an intrauterine device (IUD)
- Presence of pregnancy-related complications

Hematologic Parameters

The study evaluated the following hematologic inflammatory markers:

- Platelet count (PLT)
- Mean platelet volume (MPV)
- MPV/PLT ratio
- Neutrophil-to-lymphocyte ratio (NLR)
- Platelet-to-lymphocyte ratio (PLR)
- Monocyte-to-lymphocyte ratio (MLR)

These parameters were compared among the EPL, EP, TM, and normal intrauterine pregnancy groups to assess their diagnostic utility in early pregnancy complications.

RESULTS

A total of 400 patients were included in the study and categorized into four groups: healthy intrauterine pregnancies, TM, EPL, and EP. The control group comprised 100 healthy intrauterine pregnancies, while the study group consisted of 100 patients with TM, 100 with EPL, and 100 with EP. Demographic and hemogram data of the study and control groups are presented in Table 1. No significant differences were observed between the groups in terms of age, gravidity, or gestational week (Table 1). However, parity was significantly higher in the EPL group compared to the control and TM groups (p=0.02, p=0.048, respectively) (Table 2, Table 3). Additionally, MPV, MPV/PLT, and PLT values did not differ significantly between the groups (p=0.909, p=0.557, and p=0.135, respectively) (Table 1).

A statistically significant difference in PLR values was observed between the EPL and EP groups compared to the control group (p=0.02, p=0.03, respectively) (Table 2). Furthermore, when comparing PLR values among the groups, significant differences were noted between EPL and TM, as well as between EP and TM (p=0.021, p=0.03, respectively) (Table 3).

The NLR value was significantly higher in the EP group compared to the control group (p<0.001) (Table 2). Additionally, NLR was significantly elevated in the EP group compared to the TM and EPL groups (p<0.001 for both) (Table 3).

Similarly, the MLR value was significantly higher in the EP group compared to the control group (p<0.001) (Table 2). Moreover, MLR was significantly elevated in the EP group compared to the TM and EPL groups, with statistically significant differences (p<0.001 for both) (Table 3).

Table 1. Distribution of blood parameters and demographic characteristics of the groups

	Control	Threatened miscarriage	Early pregnancy lose	Ectopic pregnancy	p-value
Age (years, mean±SD)	27.2±4.8	27.6±5.6	29±6.5	28±5.6	0.132
Gestational age (weeks, mean±SD)	10.1±2	10.9±3.4	9.8±3.6	8.9±1.8	0.145
Gravidity	2.3±1.1	2.6±1.6	3±1.5	2.6±1.1	0.09
Parity	1±0.9	1.1±1.1	1.5±1.1	1.3±0.9	0.03
PLT (103/µL) (mean±SD)	249.5±71.8	259.5±63.1	277.2±248.8	232.4±63.7	0.135
MPV/PLT (mean±SD)	428.7±182.9	499.6±531.4	452.5±441.6	437.9±244.5	0.557
PLR (mean±SD)	9408.1±4735.3	9996±5670	12444±5215.4	12348.1±7556.4	0.000
MLR (mean±SD)	2495.1±1324.6	2711.2±2751.1	2609.5±2094.8	3718.5±1932	0.000
NLR (mean±SD)	25465.9±13267.6	277719.5±1550	30927±32920.9	44631.1±28514.3	0.000
MPV (fl) (mean±SD)	99.5±28.6	96.9±26.9	97.3±27.3	97.1±30.8	0.909

* The mean difference is significant at the 0.05 level. NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte, MPV: Mean platelet volume, PLT: Platelet, MLR: Monocyte-lymphocyte ratio, Data are mean±SD. Statistically significant p values are shown in boldface. p-values were calculated with the One-Way ANOVA

Table 2. Comparison of demographic characteristics and blood parameters

Parameters	Groups		
	Control group-threatened miscarriage	Control group-early pregnancy lose	Control group-ectopic pregnancy
PLT (×10³/µL)	10 p=1.000	27.6 p=0.927	17.1 p=1.000
MPV/PLT	70.8 p=1.000	23.8 p=1.000	9.17 p=1.000
PLR	587.9 p=1.000	3035.9 p=0.02	2940 p=0.03
MLR	216.1 p=1.000	114.3 p=1.000	1223.4 p=<0.001
NLR	2253.6 p=1.000	5461.1 p=0.655	19165.2 p=0.<001
MPV (fL)	2.6 p=1.000	2.2 p=1.000	2.4 p=1.000
Parity	0.14 p=1.000	0.54 p=0.02	0.28 p=0.379

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte, MPV: Mean platelet volume, PLT: Platelet, MLR: Monocyte-lymphocyte ratio, †Bonferroni correction was made for post-hoc analyses.

Table 3. Comparison of demographic characteristics and blood parameters between groups

Parameters	Groups		
	Threatened miscarriage-early pregnancy lose	Threatened miscarriage-ectopic pregnancy	Early pregnancy lose-ectopic pregnancy
PLT (×10³/µL)	17.6 p=1.000	27.1 p=0.975	44.7 p=0.129
MPV/PLT	47 p=1.000	61.6 p=1.000	14.6 p=1.000
PLR	2448 p=0.021	2352.1 p=0.03	95.8 p=1.000
MLR	101.7 p=1.000	1007.2 p=0.004	1109 p=<0.001
NLR	3207.5 p=1.000	16911.6 p=<0.001	13704.1 p=0.<001
MPV (fL)	0.4 p=1.000	0.2 p=1.000	0.2 p=1.000
Parite	0.40 p=0.048	0.14 p=1.000	0.26 p=0.506

NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte, MPV: Mean platelet volume, PLT: Platelet, MLR: Monocyte-lymphocyte ratio, †Bonferroni correction was made for post-hoc analyses.

DISCUSSION

This study aimed to evaluate the role of inflammatory biomarkers in predicting EP, TM, and EPL. Our key findings indicate that NLR, PLR, and MLR were significantly higher in the EP group compared to the control group. Additionally, MLR and NLR levels were significantly higher in the EP group than in the EPL group. Furthermore, PLR values were significantly elevated in the EP group compared to the TM group.

These findings suggest that NLR, PLR, and MLR may serve as potential biomarkers for the diagnosis of EP and EPL. Therefore, integrating these parameters into the early diagnostic process could enhance clinical decision-making and facilitate patient management.

Lurie et al.[18] evaluated changes in leukocyte count and leukocyte differentials across trimesters in a large cohort of women with healthy and uncomplicated singleton pregnancies. Their study demonstrated that leukocyte and neutrophil counts increased gradually and significantly from the first to the third trimester, whereas lymphocyte counts decreased from the first to the second trimester. Overall, these findings suggest that neutrophil counts are relatively low, while lymphocyte counts are higher in the first trimester.

However, studies investigating the relationship between NLR and PLR and pregnancy loss have reported conflicting results. For instance, one study found no significant difference in NLR between women who experienced pregnancy loss and those who had a healthy birth in the first trimester.[19] In contrast, another study reported an association between low NLR and PLR values and EPL, whereas a different study found a link between high PLR and NLR values and EPL.[20,21]

Specifically, in cases of TM diagnosed in the first trimester, one study found that NLR values were significantly higher in women who experienced pregnancy loss compared to those whose pregnancies continued beyond the 24th week (p<0.001).[22] Similarly, Bas et al.[23] reported that NLR levels in women who experienced pregnancy loss during the first and second trimesters were significantly higher compared to those who had live births (p<0.0001). Additionally, Onat et al.[24] demonstrated that PLR values were significantly higher in the pregnancy loss group compared to the control group

(p=0.032). Furthermore, a study conducted in 2020 found that PLR was significantly higher in the EPL compared to both TM and healthy control groups (p<0.001).[25] Additionally, a study comparing hemogram parameters between 112 women with a healthy intrauterine pregnancy (6–8 weeks) and 97 women with EPL reported that NLR was significantly higher in the EPL group.[26]

Regarding EP, studies suggest that NLR and PLR may serve as important biomarkers. For instance, Yılmaz et al.[27] found that NLR levels were higher in ruptured EP cases compared to non-ruptured EP cases. Similarly, Dönmez et al.[28] reported significantly elevated NLR and PLR levels in patients with ruptured EP. These differences can be explained by the varying degrees of inflammation observed in ruptured and non-ruptured EP, as well as the progression and severity of the inflammatory response. Therefore, these findings suggest that inflammatory markers may play a crucial role in the diagnosis of EP and EPL.

Since platelets function as acute-phase reactants, an increase in PLT and changes in platelet-related markers may serve as indicators of inflammation.[29] MPV is a parameter that directly reflects platelet function, as larger platelets exhibit greater pro-inflammatory and pro-thrombotic activity. In pregnancy loss cases, it has been suggested that larger platelets migrate to the damaged site, leading to a decrease in MPV as part of the inflammatory response.[30]

On the other hand, some studies suggest that platelet indices, including MPV and platelet distribution width (PDW), differ between ectopic and intrauterine pregnancies due to inflammation at the implantation site and microenvironmental changes in the fallopian tube.[31] In this context, Ülkümen et al.[31] analyzed 153 EP cases and reported a significant decrease in MPV and an increase in PDW, particularly in ruptured EP cases. However, Turgut et al.[32] examined 138 EP cases and found an increase in MPV values. This discrepancy suggests that MPV may vary across different stages of inflammation. Additionally, some studies have shown that MPV decreases in mild inflammation but increases in severe inflammatory disorders.[33]

However, in our study, MPV, PLT, and MPV/PLT values did not show significant differences among the TM, EPL, and EP groups. Similarly, Kara et al.[34] compared spontaneous abortion cases with healthy pregnancies and found similar MPV values, but reported that PLTs were significantly higher in abortion cases. In contrast, Kaplanoğlu et al.[35] reported significantly lower MPV levels in the pregnancy loss group compared to the control group (p<0.001). These discrepancies may be attributed to variations in patient populations or methodological differences.

In recent years, there has been a growing number of studies evaluating hematological inflammatory markers in terms of diagnosis and prognosis in conditions such as EPL, TM, and tubal EP. For instance, Çallıoğlu et al.[36] reported elevated systemic immune-inflammation index (SII) and decreased platelet PDW in women experiencing EPL. Similarly, Huang et al.[37] emphasized significantly reduced lymphocyte levels in patients diagnosed with missed abortion. In cases of tubal EP, Dereli et al.[38] found that patients who responded to medical treatment had lower NLR and SII values, along with higher lymphocyte and PLTs. Erten and Soysal[39] reported a significantly lower MLR in cases of ruptured EP. Furthermore, in patients with TM, Topkara Sucu et al.[40] suggested that systemic and pan-immune-inflammation indices could serve as potential risk markers, while Yang et al.[41] demonstrated that NLR, MLR, and IL-1β levels may also be used as predictive indicators.

In line with these findings, a multicenter study conducted in Iran reported that women who experienced miscarriage had elevated levels of PLR, NLR, PDW, and lymphocytes, while their MPV was found to be decreased.[42] In a multicenter retrospective study conducted in Greece, mean NLR levels were not found to be associated with miscarriage; however, an NLR value greater than 5.8, observed only in the miscarriage group, was reported to be statistically significant.[19] On the other hand, a prospective study by Görkem et al.[43] found no significant differences in complete blood count parameters and serum kisspeptin levels among groups with healthy pregnancies, TM, and spontaneous miscarriage. Similarly, in a prospective study by Amedy et al.,[44] elevated NLR and decreased LMR were shown to be useful in distinguishing ectopic pregnancies from other types of gestation.

Nevertheless, the literature reveals inconsistencies in the findings related to inflammatory parameters. These discrepancies may be attributed to various factors, including heterogeneity in patient populations, variability in gestational age, individual differences in the inflammatory response, the timing of parameter measurement, and differences in laboratory methodologies. Despite these variations, inflammatory blood parameters are believed to have potential as supportive biomarkers in the diagnosis of early pregnancy complications and may contribute to the clinical decision-making process.

Limitations

In this context, certain methodological limitations of our study should be acknowledged. Its retrospective and single-center design may limit the generalizability of the findings. Therefore, future research should aim to overcome these limitations by incorporating a broader range of hematological and biochemical parameters and including long-term follow-up data. In particular, prospective, multicenter validation studies involving diverse populations are needed to enhance the reliability of current findings and to better clarify the clinical utility of inflammatory biomarkers.

CONCLUSION

As a result, the hematologic inflammatory markers PLR, MLR, and NLR were found to have clinical significance, particularly in the diagnosis of EP and EPL. These findings suggest that blood parameters could serve as valuable diagnostic tools for early pregnancy complications, enabling faster and more effective treatment approaches.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Ethics Committee of Niğde Ömer Halisdemir University Faculty of Medicine (Date: 22.12.2022, Decision No: 2022/109).

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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Retrospective evaluation of oral health-related quality of life in patients after dental implant treatment

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ABSTRACT

Aims: The study aimed to evaluate oral health-related quality of life in patients long after dental implant treatment.

Methods: The study was carried out on patients who underwent dental implant surgery and completed prosthetic treatment at Erciyes University Faculty of Dentistry between 2009 and 2013. Oral health-related quality of life was evaluated by applying the OHIP-14 scale to the patients. The data obtained from the patients was compared in terms of age, gender, educational status, and prosthesis type.

Results: After 10–14 years of follow-up, the dental implant survival rate was 96.3%. There was no statistically significant difference between OHIP-14 scores according to gender and educational status ($p>0.05$). It was determined that individuals between the ages of 18 and 50 were statistically more advantageous than individuals between the ages of 51 and 73 in terms of functional limitation and physical pain subcategories ($p<0.05$). Patients using implant-supported fixed prostheses were found to have higher satisfaction levels in terms of quality of life compared to patients using implant-supported removable prostheses ($p<0.05$). The type of removable prosthesis was determined to be responsible for 15% of the change in the total OHIP-14 score ($p<0.05$).

Conclusion: Among patients with a long-term follow-up, the survival rate of dental implants was 96.3%. Individuals aged 51-73 years may be more prone to physical pain and functional limitations compared to individuals aged 18-50 years after dental implant therapy. The oral health-related quality of life was shown to be higher in individuals with implant-supported fixed prostheses than in those with removable prostheses.

Keywords: Dental implant, OHIP-14, oral health, quality of life

INTRODUCTION

Dental implants have been used successfully and predictably for decades to restore function and aesthetics in partially or completely edentulous patients. However, some complications may occur with this treatment method. The loss of dental implants is one of these problems.[1-3] Dental implant loss is defined as the implant moving for a variety of reasons following osseointegration. In other words, the inability to start and continue osseointegration in the host tissue is dental implant loss and includes many clinical problems.[4-6] According to studies in the literature, between 90% and 98% of dental implants survive after a follow-up of 10 years.[7] The aforementioned factors include biological and physiological characteristics (aesthetics, phonation, and function), longevity and survival (natural teeth, restorations, and implants), psychological and social characteristics of patients (personal satisfaction, quality of life, perception of body image), and financial and economic aspects associated with the course of treatment. Although studies have focused primarily on the first two categories, psychosocial characteristics have drawn increasing attention from researchers recently.[8-11] Improving patients' quality of life is typically the goal of edentulism rehabilitation. When assessing the effectiveness of dental therapy, subjective perceptions of the patient's comfort, social standing, and psychosocial state should not be neglected.[12]

The term "quality of life" is a broad concept. The study of oral health-related quality of life (OHRQoL) focuses on how an individual's perception of function, level of physical and psychological discomfort, and general well-being are affected by their dental health. An assessment of OHRQoL is useful in the treatment of patients with complete or partial tooth loss. This is because tooth loss causes serious problems for patients' diet, social life, and daily life in general, which in turn causes functional, cosmetic, and psychological issue.[13-17] Clinical trials have long used the Oral Health Impact Profile Index (OHIP-14), a 14-question questionnaire, as a reliable method to measure OHRQoL.[14,18-21]

The literature includes various studies that evaluate the OHRQoL in patients following dental implant treatment. Nevertheless, the majority of these investigations focused

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on data provided shortly after treatment.[8,22,23] There isn't much research investigating OHRQoL in this scenario long after dental implant treatment.[13] The present study analyzed participants who were followed up at least 10 years after treatment to evaluate the long-term effects of dental implant treatment. The study aimed to evaluate the OHRQoL in patients long after dental implant treatment.

METHODS

The research protocol was approved by the Clinical Researches Ethics Committee at the Erciyes University (Date: 10.07.2024, Decision No: 2024/81). The Declaration of Helsinki Principles were followed in the conduct of the study. Patients with tooth loss in the upper or lower jaw who underwent dental implant surgery and completed prosthetic treatment at Erciyes University Faculty of Dentistry between 2009 and 2013 were the subjects of the study. The study included patients who did not use any medicine that affects bone metabolism, such as denasumab, glucocorticoids, bisphosphonates, or osteopetrosis, or who did not have any bone metabolism diseases, such as fibrous dysplasia, hyperparathyroidism, or Paget's disease. Patients who had previously received chemotherapy or radiation therapy, as well as those excluded from the study if they refused to complete the questionnaire.

Participants did not sign a written informed consent form because the study was designed retrospectively. Patients who had received dental implant treatment for a minimum of ten years were invited to the clinic for a routine follow-up visit. Each participant underwent an intraoral clinical examination and radiographic evaluation; outcomes were recorded in the patient files. These files included information about the demographic characteristics of the patients and the number of lost dental implants. The demographic characteristics of the participants include age, gender, educational status, and type of prosthesis. To evaluate their OHRQoL, all participants were requested to fill out the OHIP-14-TR quality of life questionnaire, which is the Turkish version of the OHIP-14 scale. In the study of Başol et al.,[24] it was found that OHIP-14-TR was reliable (Cronbach's Alpha: 0.74), reproducible (r: 0.932), valid, and understandable (96.2%) in Turkish translation. The Cronbach's alpha value of this study was calculated as 0.819. The 14 items that comprise the OHIP-14-TR are divided into seven domains, each with two questions: functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap. A 5-point Likert scale was used to rate the patients' survey responses: never (score 0), rarely (score 1), occasionally (score 2), rather often (score 3), and very often (score 4).[24] Inadequate OHRQoL is demonstrated by high OHIP-14 scores, whereas proper and satisfactory OHRQoL is represented by low OHIP-14 scores. All participant information was documented in the patient files and utilized in the present study. The data obtained from the patients were compared regarding age, gender, educational status, and prosthesis type.

Statistical Analysis

The data from the research were investigated with the SPSS 21.0 package (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to determine whether the study's numerical data were suitable for a normal distribution. Independent Sample T-test, One-Way Anova test, and regression analyses were performed on the data suitable for normal distribution. The significance level was determined at $p<0.05$, and the results were assessed at a 95% confidence range.

RESULTS

Of the 270 patients who met the study criteria, 141 were female, 129 were male, and the mean age was 49.59±10.29 years. Participants' educational backgrounds were 34.8% with a primary education, 22.6% with a high school education, and 42.6% with a university degree. 78.9% of the patients used implant-supported fixed prostheses, while 21.1% used implant-supported removable prostheses. The demographic data of the patients is demonstrated in Table 1. The 270 individuals in the research received a total of 891 dental implants. After 10–14 years of follow-up, the overall implant survival rate was 96.3%.

Table 1. Demographic characteristics of patients

Demographic characteristics	n	%
Mean age (x±SD)	49.59±10.29	
Gender		
Female	141	52.2
Male	129	47.8
Education level		
Primary education	94	34.8
High school	61	22.6
Undergraduate	115	42.6
Prosthesis type		
Fixed	213	78.9
Removable	57	21.1

SD: Standart deviation

The OHIP-14 scale questions and the percentage distribution of patients' answers to these questions are shown in Table 2. The mean total OHIP-14 scale score of the participants was 5.31±6.40. When the OHIP-14 sub-dimension total mean scores of the patients were examined, the highest score (1.68±1.99) was obtained from the psychological discomfort category and the lowest score (0.32±0.85) was obtained from the psychological disability category. The responses of the patients to the OHIP-14 scale are shown in Table 3.

The mean scores for the OHIP-14 sub-dimension and total were compared based on the patients' descriptive features. The OHIP-14 scores did not differ statistically significantly based on the patient's gender or level of education ($p>0.05$). Patients aged 18-50 and patients aged 51-73 differed statistically significantly in the functional limitation and physical pain subcategories, favoring the patients aged 18-50 ($p=0.000$ and $p=0.038$, respectively). This shows that patients aged 51-73 years were less satisfied with their quality of life in terms of functional limitations and physical pain than the patients aged 18-50 years. The mean OHIP-14 total score of patients using implant-supported fixed prostheses was statistically lower than that of patients using implant-supported removable prostheses ($p=0.014$). The mean scores on the OHIP-14 subscale were compared based on the patients' prosthesis type. The subcategories of functional limitation, physical pain, physical disability, and social disability were

Table 2. Oral Health Impact Profile (OHIP-14) –questionnaire and the percentage distribution of answers

		(%)	(%)	(%)	(%)	(%)	Mean±SD
Dimension	**Variables**	**0**	**1**	**2**	**3**	**4**	
Functional limitation	1-Have you had trouble pronouncing any words because of problems with your teeth, mouth, or dentures?	81.1	7.4	8.9	2.2	0.4	0.33±0.762
	2-Have you felt that your sense of taste has worsened because of problems with your teeth, mouth, or dentures?	84.1	10.4	3.3	0.7	1.5	0.26±0.715
Physical pain	3-Have you had painful aching in your mouth?	60.7	20.0	14.8	3.0	1.5	064±0.940
	4-Have you found it uncomfortable to eat any foods because of problems with your teeth, mouth, or dentures?	77.4	10.4	7.0	1.5	3.7	0.44±0.961
Psychological discomfort	5-Have you been self-conscious because of your teeth, mouth, or dentures?	54.1	10.7	9.3	15.9	10	1.17±1.474
	6-Have you felt tense because of problems with your teeth, mouth, or dentures?	71.9	10.7	13.3	2.2	1.9	0.51±0.936
Physical disability	7-Has your diet been unsatisfactory because of problems with your teeth, mouth, or dentures?	80.7	7.0	7.4	2.6	2.2	0.39±0.900
	8-Have you had to interrupt meals because of problems with your teeth, mouth, or dentures?	86.3	6.7	5.2	1.1	0.7	0.23±0663
Psychological disability	9-Have you found it difficult to relax because of problems with your teeth, mouth, or dentures?	77.4	9.6	7.8	1.9	3.3	0.44±0.957
	10-Have you been a bit embarrassed because of problems with your teeth, mouth, or dentures?	87.4	6.3	4.1	0.7	1.5	0.23±0.693
Social disability	11-Have you been a bit irritable with other people because of problems with your teeth, mouth, or dentures?	91.1	5.2	3.3	0.4	0	0.13±0.450
	12-Have you been a bit irritable with other people because of problems with your teeth, mouth, or dentures?	87.4	8.1	3.0	0.7	0.7	0.19±0591
Handicap	13-Have you felt that life in general was less satisfying because of problems with your teeth, mouth, or dentures?	86.3	8.1	3.7	1.5	0.4	0.21±0.614
	14-Have you been totally unable to function because of problems with your teeth, mouth, or dentures?	92.6	3.7	2.2	0.7	0.8	0.14±0.572

Never (=0), Hardly ever (=1), Occasionally (=2), Fairly often (=3) and Very often (=4)

SD: Standart deviation

Table 3. OHIP-14 total mean scores and OHIP-14 domains total mean scores

OHIP-14 domain	Mean±SD	Median (min-max)
Functional limitation	0.58±1.15	0.00 (0.00-7.00)
Physical pain	1.08±1.50	0.00 (0.00-8.00)
Psychological discomfort	1.68±1.99	1.00 (0.00-8.00)
Physical disability	0.61±1.30	0.00 (0.00-7.00)
Psychological disability	0.32±0.85	0.00 (0.00-6.00)
Social disability	0.66±1.33	0.00 (0.00-8.00)
Handicap	0.35±1.01	0.00 (0.00-8.00)
Total	5.31±6.40	0.00 (0.00-40.00)

OHIP-14: Oral Health Impact Profile, SD: Standard deviation, Min: Minimum, Max: Maximum

shown to have statistically significant differences in favor of fixed prosthesis users (p=0.017, p=0.000, p=0.001, p=0.000, respectively). This suggests that patients with fixed prostheses supported by implants are more satisfied with their quality of life than those with removable prostheses supported by implants (Table 4).

A linear regression analysis was performed for the type of prosthesis used by the patients and the mean total score of the OHIP-14 scale. A statistical significance was determined in the regression model ($p<0.05$; $R^2=0.023$). Based on the statistical analysis results, the prosthesis type proved to be the most effective factor for OHIP-14 ($\beta=0.150$, $p<0.05$). The type of prosthesis was found to be responsible for 15% of the change in the OHIP-14 total score (Table 5).

DISCUSSION

The present study assessed the long-term survival rate of dental implants and the OHRQoL in patients using the OHIP-14 scale. The study's results revealed that the patient's age and the type of prosthesis affect the quality of life related to oral health. Additionally, patients between the ages of 18 and 50 were less likely to experience physical jaw pain and limitations in function than patients between the ages of 51 and 73. The quality of life associated with oral health was higher for patients with implant-supported fixed prostheses than those with implant-supported removable prostheses.

For many years, dental implants have been utilized for treating complete or partial tooth loss with great success. However, in some cases, patients may experience complications, including the loss of dental implants.[1] Therefore, practitioners must have reliable information about the long-term complications and survival rates of dental implant treatment when informing patients about the therapy before the procedure.[25] Balshi et al.[2] reported that the survival rate of dental implants placed in the total or partially edentulous lower jaw and followed up for at least 10 years was 92.7%. According to Becker et al.,[7] 88.03% of dental implants survived during a long-term follow-up

Table 4. Comparison of OHIP-14 total and OHIP-14 domain mean scores according to the descriptive characteristics of the patients

Descriptive characteristics	Functional limitation mean±SD	Physical pain mean±SD	Psychological discomfort mean±SD	Physical disability mean±SD	Psychological disability mean±SD	Social disability mean±SD	Handicap mean±SD	OHIP total mean±SD
Gender								
Female	0.49±1.04	1.16±1.60	1.73±2.02	0.66±1.39	0.35±0.86	0.72±1.45	0.42±1.20	5.55±6.67
Male	0.68±1.25	0.98±1.39	1.64±1.97	0.57±1.22	0.29±0.84	0.61±1.19	0.27±0.77	5.07±6.15
p*	0.168	0.330	0.722	0.559	0.612	0.525	0.214	0.543
Age								
18-50	0.59±1.07	1.00±1.36	1.82±2.15	0.48±1.19	0.35±0.92	0.70±1.42	0.32±1.00	5.30±6.14
51-73	3.33±2.88	2.66±0.57	2.66±2.30	1.33±1.15	0.00±0.00	1.00±1.73	1.33±1.52	12.33±4.72
p*	0.000	0.038	0.508	0.226	0.507	0.725	0.093	0.052
Education level								
Primary education	0.68±1.32	1.37±1.75	1.54±1.92	0.68±1.38	0.39±0.93	0.80±1.40	0.32±0.92	5.80±6.70
High school	0.65±1.26	0.90±1.20	1.60±1.80	0.70±1.37	0.34±0.70	0.62±1.18	0.32±0.94	5.16±5.35
Undergraduate	0.47±0.91	0.93±1.40	1.85±2.14	0.52±1.20	0.25±0.85	0.57±1.35	0.35±1.01	5.00±6.69
p**	0.395	0.067	0.502	0.576	0.479	0.432	0.913	0.649
Prosthesis type								
Fixed	0.50±1.03	0.91±1.29	1.75±2.03	0.48±1.16	0.31±0.83	0.51±1.18	0.33±1.01	4.82±5.77
Removable	0.91±1.49	1.71±2.00	1.43±1.82	1.12±1.65	0.35±0.91	1.22±1.66	0.40±1.33	7.17±8.15
p*	0.017	0.000	0.286	0.001	0.775	0.000	0.666	0.014

OHIP-14: Oral Health Impact Profile, SD: Standard deviation

Table 5. The effect of some independent variables on OHIP-14 total score: multiple linear regression analysis

Independent variables	B †	SE †	β †	t	p	95% CI †
Prosthesis type	2.354	0.947	0.150	2.487	0.014*	0.490 to 4.217

†: B, non-standardised regression coefficient, SE: Standard error, β: Standardised regression coefficient, CI: Confidence interval, R^2=0.023 , t: Test statistic , * tested by linear regression analysis. A significance level was taken as p<0.05.

period of 12 to 23 years. In a study by Adler et al.[25] with a follow-up of 9-15 years, the dental implant survival rate was 82.6%, and in a study by Simonis et al.[26] with a follow-up of up to 16 years, this rate was 82.94%. According to meta-analysis research published in the literature, 96.4% of dental implants with a 10-year follow-up survived.[27] In the present study, the survival rate of dental implants followed up for 10–14 years was found to be 96.3%. In this sense, the findings of our study were found to be compatible with the results of similar studies in the literature.

Studies on dental implants have generally focused on their biological success or failure. However, there is a limited number of investigations in the literature evaluating treatment outcomes based on patient perceptions. Moreover, some researchers have argued that treatment success should be evaluated by individual patients instead of using traditional clinical evaluation methods. In this way, OHQoL assessments allow patients to assess the outcomes of dental treatments on an individual basis.[12,20] Bramanti et al.[8] investigated the physical and psychological influences of implant-supported fixed partial denture treatment on edentulous patients. For this purpose, they assessed oral health-related quality of life in patients before and after prosthetic implant therapy. At the end of the study, the authors concluded that dental implant treatment had a positive effect on OHRQoL.[8] A study by Yoo et al.[23] investigated the effect of dental implant treatment on OHRQoL in edentulous individuals with disabilities using the OHIP-14 questionnaire. The researchers reported that dental implant treatment contributed positively to the improvement of OHRQoL for disabled patients, and OHRQoL decreased with age for patients with similar levels of disability.[23] When participants' responses to the OHIP-14 scale were analyzed in the present research, it was discovered that patients aged 51-73 years had a lower oral health-related quality of life than patients aged 18-50 years.

Coltro et al.[13] evaluated the effect of implant-supported fixed prosthesis treatment on patients' OHRQoL in a prospective clinical study. At the end of the study, the researchers reported that dental implant treatment had a positive long-term effect on patients' OHRQoL.[13] Kuoppala et al.[19] assessed the OHRQoL of patients treated with implant-supported mandibular overdenture prostheses. Within the scope of the study, they investigated the relationships between OHIP-14 variables and the age and gender of the patients. They found that elderly patients using implant-supported mandibular overdenture prostheses were more satisfied with OHRQoL compared to younger patients.[19] However, contrary to the findings of Kuoppala et al.,[19] our study results revealed that the likelihood of patients experiencing functional limitation and physical pain in the jaws may increase with the increasing age of the participants.

Gecikli et al.[20] researched whether patients' quality of life was affected by overdenture prosthesis treatment supported by dental implants. To achieve this, they administered the UK oral health-related quality of life (OHQoL-UK) and the Turkish versions of OHIP-14 to the patients both before and

after treatment. They found significant decreases in the OHIP-14 scores of the patients at the end of therapy compared to the pretreatment scores. They discovered that for both the OHIP-14 and OHQoL-UK scores, the patient's gender was a non-significant pre-treatment variable. The authors reached the view that patients' quality of life significantly improved when implant-retained overdenture prostheses were rehabilitated in the mandible.[20] Değirmenci et al.[22] evaluated the effects of removable partial dentures (RPD) on the quality of life of patients. According to the authors, OHIP-14 scores were not influenced by the patient's gender, level of education, or oral hygiene practices. At the end of the study, they found that patients with RPD in both jaws were more likely to experience physical pain and functional limitation problems than patients with RPD in one jaw.[22] In our study, we determined that gender and educational status had no effect on patients' oral health-related quality of life. However, patients using implant-supported fixed prosthesis were found to be more advantageous than patients using implant-supported removable prosthesis in terms of functional limitation and physical pain.

Limitations

The study has some limitations. Firstly, due to the retrospective nature of the study, oral health-related quality of life could not be evaluated in patients before dental implant treatment. The second limitation is that the periodontal health status and oral hygiene motivation levels of the participants were not standardized. Finally, systemic diseases of the participants and their effects on dental implants were not assessed. Further randomized controlled clinical trials evaluating the participants according to their systemic diseases will provide more precise results.

CONCLUSION

As a result, the survival rate of dental implants was found to be 96.3% in patients with a long-term follow-up of 10–14 years. Patients aged 51-73 years may be more likely to experience functional limitations and physical pain in their jaws. Patients using implant-supported fixed prostheses had a higher oral health-related quality of life compared to patients using implant-supported removable prostheses. Pre-treatment assessment of the individuals' OHQoL assists the physician with creating therapy predictions and identifying the most efficient treatment strategy that fulfills the patient's expectations.

ETHICAL DECLARATIONS

Ethics Committee Approval

The research protocol was approved by the Clinical Researches Ethics Committee at the Erciyes University (Date: 10.07.2024, Decision No: 2024/81).

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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Pan-immune inflammation value as a determinant of coronary collateral circulation in patients with chronic coronary syndrome and chronic total occlusion

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ABSTRACT

Aims: This study aimed to investigate the association between coronary collateral circulation (CCC) pan-immune-inflammation value (PIV) in patients with chronic coronary syndrome (CCS) and chronic total occlusion (CTO).

Methods: The study included 297 patients with CCS who underwent coronary angiography and had CTO in at least one major coronary artery. Patients with CTO were categorized into two groups based on Rentrop grading: group 1 (grades 2–3, well-developed CCC) and group 2 (grades 0–1, poor CCC).

Results: Patients with poor CCC had higher WBC levels (p=0.04), neutrophil counts (p=0.001), platelet counts (p=0.023), and median PIV values (p=0.003) compared to patients with well-developed CCC. Logistic regression identified PIV (per hundred units) as an independent predictor of poor CCC (OR=1.10, 95% [CI=1.02–1.23], p=0.044). Receiver operating characteristic (ROC) analysis demonstrated that a cut-off value of 168 for PIV predicted poor CCC slightly better compared to other markers, with 94.6% sensitivity and 22.8% specificity (area under the curve=0.601, 95% CI=0.543–0.657, p=0.002).

Conclusion: These findings indicate that PIV may serve as an independent predictor of CCC development.

Keywords: Coronary collateral circulation, pan-immune-inflammation value, chronic coronary syndrome, chronic total occlusion

INTRODUCTION

Coronary artery disease (CAD) is characterized by the buildup of atherosclerotic plaques and is a leading cause of death and disability globally.[1] Coronary collateral circulation (CCC) refers to the small blood vessels that connect different coronary arteries or segments of the same artery. Under normal physiological conditions, these collateral vessels are typically very small and play a minimal role in coronary blood flow. However, in response to chronic or repeated myocardial ischemia, these collateral vessels gradually enlarge and develop into a functional network of collateral circulation.[2] The role of CCC is to function as an alternative blood vessel, thereby ensuring the area beyond the blocked segment of the coronary artery receives a sufficient blood supply. This may assist in mitigating myocardial ischemia. Research has indicated that the presence of well-developed CCC in patients with CTO can be associated with enhanced survival and improved overall prognosis.[3,4] However, it should be noted that CCC formation can vary significantly among patients. The current methods for assessing CCC formation, such as the collateral flow index and intracoronary electrocardiogram, are both costly and complex. Consequently, there is a need to identify a simple, cost-effective biomarker for evaluating CCC formation.

The precise mechanisms underlying CCC formation remain unclear. However, research has shown that inflammation can impede the growth of collateral formation by affecting the development of new blood vessels. Studies have indicated that inflammatory biomarkers derived from complete blood counts, such as the platelet-to-lymphocyte ratio (PLR) and the neutrophil-to-lymphocyte ratio (NLR), are linked to CCC formation and can be useful for evaluating it.[5,6]

There are very few studies in the literature that specifically examine the role of PIV in predicting CCC formation. Therefore, this study aims to examine the relationship between PIV and CCC formation in patients with CTO and to evaluate whether PIV is a more effective predictor of CCC formation compared to other inflammatory biomarkers.

METHODS

Ethics

The study was conducted with the permission of Başakşehir Çam and Sakura Hospital Scientific Researches Ethics Committee No. 1 (Date: 16.07.2024, Decision No: KAEK/10.07.2024.109). All procedures were carried out in

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accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

A total of 297 patients over 18 years of age, diagnosed with CCS according to the criteria recommended by the European Society of Cardiology and who had CTO in ≥1 major coronary artery and underwent coronary angiography (CAG) between March 2021 and January 2023, were included in this retrospective study conducted at the Cardiology Department of Başakşehir Çam and Sakura City Hospital. CTO were defined as lesions persisting for more than three months, characterized by either a complete interruption of antegrade blood flow on angiography or minimal contrast penetration through the lesion without opacification of the distal vessel.[7,8] CAG is mostly indicated because of typical chest pain or results of noninvasive stress tests suggesting myocardial ischemia (positive stress test result and/or ischemia on myocardial perfusion scintigraphy). Patients were excluded from the study if they had previous coronary artery bypass graft surgery, history of acute coronary syndrome within 3 months, presence of left main coronary stenosis of 50% or more, history of previous percutaneous coronary intervention, left ventricular ejection fraction (LVEF) <40%, severe valvular disease, hematologic disease, malignancy, severe renal (estimated glomerular filtration rate <30 ml/min/1.73 m^2 calculated using the modification of diet in renal disease formula) or hepatic disease, ongoing infection or chronic inflammatory disease, and autoimmune disease.

A detailed medical history was obtained from all patients, along with a physical examination, complete blood count, and serum biochemistry tests. Classical cardiovascular risk factors such as age, gender, diabetes mellitus (DM), hypertension (HT), dyslipidemia, and smoking were evaluated. All patients underwent a transthoracic echocardiographic examination. The definitions of DM, HT, and dyslipidemia followed established criteria.[9]

Laboratory Analysis

Venous blood samples were collected from the antecubital region of all patients into tripotassium EDTA-based anticoagulant tubes before CAG. Samples were collected in the morning after a 20-min rest period followed by a 12-h fasting period. Hemoglobin, platelet count, white blood cell (WBC) count, neutrophils, lymphocytes, glucose levels, lipid profile, and other routine biochemical tests were analyzed using an autoanalyzer (Roche Diagnostic Modular Systems). Tripotassium EDTA-based anticoagulant blood samples were stored at 4°C and analyzed with a Sysmex K-1000 autoanalyzer (Sysmex) within 30 min of collection.

PIV was calculated as neutrophil count multiplied by platelet count multiplied by monocyte count divided by lymphocyte count (or multiplying the monocyte count with SII).

Transthoracic Echocardiography (TTE)

Transthoracic echocardiography was performed for each patient before CAG. M-mode and 2D ECHO were performed in the left lateral decubitus position using a 3.25 probe from the Vivid 5 ECHO echocardiography device, according to the American Society of Echocardiography criteria.[10] Parasternal short-long axis images and apical 4 and 2 chamber views, which are standard echocardiography positions, were used for measurements. LVEF was calculated using the Modified Simpson method.[11]

Coronary Angiography Methods

CAG was performed using the standard Judkins technique using either the femoral or radial access, depending on the operator's preference. CAG image evaluations were performed by two experienced interventional cardiologists. CCC was assessed using the Rentrop classification: grade 0=no filling in any collateral vessels; grade 1=filling in the lateral branches of the artery supplying the epicardial segment; grade 2=partial filling of the epicardial artery via collateral vessels; and grade 3=complete filling of the epicardial artery by a collateral vessel.[12] Rentrop grade 0 was considered to indicate no CCC development. In addition, Rentrop grades 2 and 3 were classified as satisfactory CCC development (group 1), while Rentrop grades 0 and 1 were classified as poor CCC development (group 2). If more than one coronary collateral vessel was observed on CAG, classification was made according to the vessel with the highest Rentrop grade. Intra-observer and inter-observer variability for CCC assessment were found to be 2% and 3%, respectively.

Statistical Analysis

All data tests were conducted using the Statistical Package for the Social Sciences 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normality using the Kolmogorov-Smirnov or Shapiro-Wilk test. Data were presented as mean±standard deviation (SD) for normally distributed variables or median [interquartile range-IQR_{25-75}] for non-normally distributed variables. Categorical variables were expressed as frequencies and percentages.

Comparisons between the two groups (group 1: Rentrop 2–3; group 2: Rentrop 0–1) were conducted using the following tests; The independent samples t-test was applied for normally distributed continuous variables. The Mann-Whitney U test was used for non-normally distributed continuous variables. The Chi-square test was utilized for categorical variables. A receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive ability of PIV for the determination of poor CCC. The area under the curve (AUC) and corresponding 95% confidence interval (CI) were calculated. The optimal cutoff value for PIV (per hundred units) was determined based on Youden's index, and sensitivity and specificity values were reported. To identify independent predictors of poor CCC (Rentrop 0–1), logistic regression analysis was conducted. Variables with a p-value <0.05 in univariable analysis were included in the multivariable model. The Youden index was utilised in order to ascertain a cut-off point for PIV in the assessment of collateral circulation. Results were expressed as odds ratios (OR) with 95% CI. A p-value <0.05 was considered statistically significant for all analyses.

RESULTS

The demographic variables, including gender distribution, mean age, prevalence of HT, DM, and smoking status, were

comparable between well-developed and poor coronary circulation groups, with no statistically significant differences observed (Table 1). The mean age was 64.5±10.5 years in group 1 (well-developed) and 63.3±10.6 years in group 2 (poor). Similarly, the distribution of HT (p=0.686), DM (p=0.591), and smoking status (p=0.96) was balanced between both groups. Several laboratory parameters demonstrated significant differences between the two groups. WBC counts in group 2 had significantly higher WBC levels compared to group 1 (9.5±3.3 vs. 8.8±3.1, p=0.04). High-density lipoprotein cholesterol (HDL-C) levels were significantly lower in group 2 (38.8±8.4 mg/dl) compared to group 1 (42.0±11.7 mg/dl; p=0.007). The median PIV values were higher in group 2 (347.5 [260.3–666.9]) compared to group 1 (331.2 [175.4–491.1]; p=0.003). Neutrophil counts in group 2 exhibited a higher compared to group 1 (5.5 [4.6–6.9] vs. 4.9 [4.0–6.0]; p=0.001). Similarly, platelet counts in group 2 had higher (268.8±82.5 vs. 247.2±80.3; p=0.023). Table 1 details the clinical characteristics and laboratory results of the study population by CCC.

Multivariable logistic regression analysis was performed to determine independent predictors of poor CCC development. The results revealed that PIV (OR=1.10, 95% CI=1.02–1.23, p=0.044, per hundred units) and urea (OR=0.98, 95% CI=0.97-0.99, p=0.013) were a significant independent predictor (Table 2). The variable importance analysis, incorporating the parameters from the univariable analysis, indicated that PIV (per hundred units) was the variable with the most significant contribution to the model in determining poor CCC (Figure 1).

The predictive capacity of PIV for the determination of poor CCC was assessed using ROC analysis, which yielded an AUC of 0.601 (95% CI=0.543-0.657, p=0.002). A cut-off value of >168

Table 2. Multivariable logistic regression analysis of determinants of poor collateral circulation development

Variable	Odds ratio	95% confidence interval	p*
HDL-C	0.98	0.95-1.00	0.094
PIV (per hundred units)	1.10	1.02-1.23	0.044
Urea	0.98	0.97-0.99	0.013
LVEF (%)	0.98	0.96-1.01	0.122
Neutrophil	1.03	0.89-1.19	0.714
Platelet	1.00	0.99-1.01	0.648
Monocyte	1.51	0.48-4.77	0.486
Hyperlipidemia	1.41	0.86-2.31	0.171

HD-CL: High-density lipoprotein cholesterol, LVEF: Lefft ventricular ejection fraction, PIV: Pan-immune- inflammation value. *p value <0.05 was considered significant

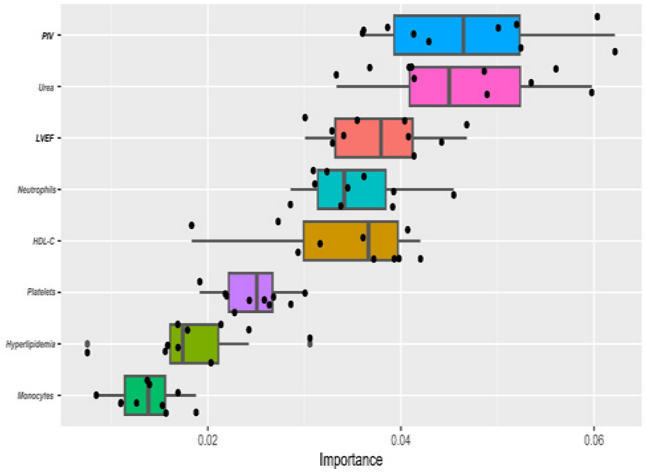

Figure 1. Variable importance plot

PIV: Pan-immune-inflammation value, LVEF: Left ventricular ejection fraction, HDL-C: High-density lipoprotein cholesterol

Table 1. Clinical and laboratory characteristics of the study population by coronary collateral circulation

		Coronary collateral circulation		
Characteristic	**Levels**	**Group 1 (n=149) (well-developed)**	**Group 2 (n=148) (poor)**	**p***
Gender	Male	111 (74.5%)	116 (78.4%)	0.515
Age, years	Mean (SD)	64.5 (10.5)	63.3 (10.6)	0.320
HT, n (%)	Yes	54 (36.2%)	58 (39.2%)	0.686
DM, n (%)	Yes	66 (44.3%)	60 (40.5%)	0.591
Smoking, n (%)	Yes	63 (42.3%)	64 (43.2%)	0.960
Hyperlipidemia, n (%)	Yes	75 (50.3)	63 (42.6)	0.180
LVEF (%)	Mean (SD)	55.5 (9.6)	53.4 (11.2)	0.078
Hgb (g/dl)	Mean (SD)	13.7 (1.9)	13.8 (2.2)	0.911
Plt (10^3/μL)	Mean (SD)	247.2 (80.3)	268.8 (82.5)	0.023
Monocyte (10^3/μL)	Median (IQR)	0.53 (0.41-0.70)	0.60 (0.50-0.79)	0.006
Lymphocytes (10^3/μL)	Median (IQR)	2.1 (1.7-2.7)	2.2 (1.7-2.9)	0.521
Urea (mg/dl)	Median (IQR)	36 (26-50)	33 (28-44)	0.209
HDL-C (mg/dl)	Mean (SD)	42.0 (11.7)	38.8 (8.4)	0.007
WBC (10^3/μL)	Mean (SD)	8.8 (3.1)	9.5 (3.3)	0.040
NEU (10^3/μL)	Median (IQR)	4.9 (4.0–6.0)	5.5 (4.6–6.9)	0.001
PIV	Median (IQR)	331.2 (175.4–491.1)	347.5 (260.3–666.9)	0.003

Values are n (%), median (interquartile range [IQR]), or mean±standard deviation. p value was calculated using an independent samples t-test or the Mann-Whitney U-test for continuous variables and a Chi-squared test or the Fisher's exact test for categorical variables, as appropriate. SD: Standard deviation, HT: Hypertension, DM: Diabetes mellitus; Hgb: Hemoglobin, HDL-C: High-density, LVEF: Lefft ventricular ejection fraction, Lipoprotein cholesterol, WBC: White blood cell count, NEU: Neutrophil count, Plt: Platelet count, IQR, Interquartile Range; PIV, Pan-immune-inflammation value, *p value <0.05 was considered significant.

was determined, with 94.6% sensitivity and 22.8% specificity, indicating a modest discriminatory ability (Figure 2).

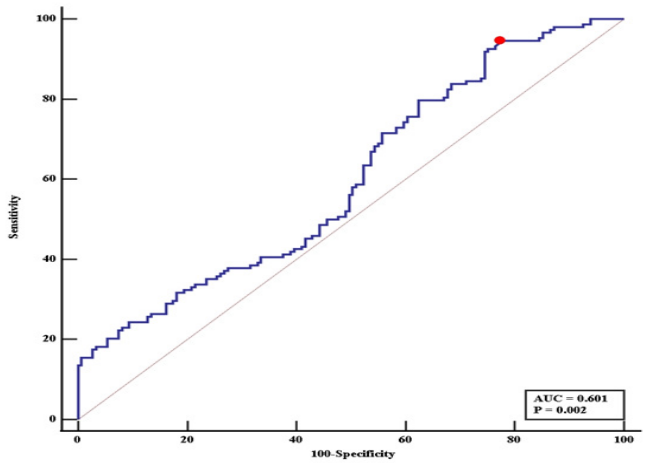

Figure 2. The analysis of receiver operating characteristic curves in determining the presence of poor collateral circulation

DISCUSSION

Our findings in this study highlight the significant association between high PIV and impaired collateral circulation in CCS patients with CTO, suggesting that systemic inflammation may play an important role in the development of coronary collaterals.

CCC serves as an important compensatory mechanism to maintain myocardial perfusion in the presence of CAD, particularly in the case of significant stenosis or occlusion. Well-developed CCC has been shown to enhance ventricular function and limit infarct size. Furthermore, it may reduce the incidence of cardiovascular events, lower mortality risk and improve the prognosis of patients with CTO.[13,14]

Chronic inflammation impairs the development of CCC by contributing to endothelial dysfunction, partly through the increased production of reactive oxygen species.[15] Platelets and various subtypes of leukocytes such as neutrophils, lymphocytes, and monocytes serve as key effector cells in the inflammatory response. Platelets, in particular, store both pro- and anti-angiogenic factors that regulate neovascularization in response to ischemia. Neutrophils contribute to vascular endothelial damage by releasing large amounts of reactive oxygen species, along with inflammatory mediators and proteolytic enzymes. Elevated neutrophil counts have been associated with impaired collateral vessel development. While monocytes are known to promote angiogenesis, it is primarily tissue-resident monocytes not circulating ones hat play a pivotal role in the process of arteriogenesis.[16] Monocytes also contribute to local ischemia and endothelial dysfunction. Evidence from previous studies indicates that patients with poorly developed CCC exhibit higher monocyte counts compared to those with well-developed CCC.[5] Lymphocyte counts tend to decline in response to systemic inflammation. This reduction may impair the formation of CCC by decreasing levels of vascular endothelial growth factor and other pro-angiogenic mediators, as well as by limiting vascular infiltration necessary for collateral development.[17]

Building on the previous findings, several inflammatory biomarkers derived from peripheral immune cells have been identified as potential diagnostic markers for CCC formation in patients with CTO. Among these, NLR and PLR have been shown to be associated with CCC formation and may serve as predictors for its development in CTO patients.[5,6]

However, PLR and NLR alone do not fully capture the complex immune and inflammatory landscape, as they only assess the counts of two types of immune-inflammatory cells. Recently, the PIV has emerged as a more comprehensive immunoinflammatory biomarker that better reflects the overall immune and inflammatory status. The PIV includes all types of blood inflammatory cells (e.g., neutrophils, lymphocytes, monocytes, and platelets). Recent research has demonstrated that PIV outperforms NLR and PLR in predicting the prognosis of STEMI patients.[18]

In the study conducted by Çetinkaya et al.[19] PIV was found to be significantly associated with higher Syntax and CAD severity in non-STEMI patients. In another study conducted by Keleşoğlu et al.[20] in 354 patients, they found that stable CAD and high CRP/albumin ratio could be an independent predictor of poor CCC. These two studies, similar to our study, showed that inflammatory markers increased in severe vascular occlusion and associated poor CCC.

Similar to our study, in a study conducted by Zhang et al.[21] on 1150 CTO patients, PIV was found to be associated with the development of CCC. In another study by Yilmaz et al.[22] including 663 patients with CCS, PIV was found to be an independent predictor of the development of CCC, similar to our study.

Consistent with previous studies, our findings demonstrated that patients with poor CCC exhibited significantly elevated levels of inflammatory markers, including WBC, neutrophil count, and PIV.[21,22] The PIV offers a more comprehensive evaluation of systemic inflammation by integrating the contributions of both platelet activity and immune cell activation. Notably, our analysis revealed that high PIV levels were independently associated with poor CCC, similar to the literature.

Wu et al.[23] demonstrated the relationship between PIV and long-term prognosis in patients with HT, indicating that the inflammatory markers incorporated in PIV could have broader clinical applications in predicting outcomes beyond cardiovascular disease. These findings further suggest that PIV could be a valuable tool in various disease settings.

Limitations

This study has several limitations. It was a single-center, retrospective study with a relatively small patient population. PIV was measured only at the time of hospitalization. The study results would have been stronger if inflammatory markers such as PLR, NLR, and systemic immune index were measured together with PIV. In addition, the cross-sectional study design prevents the establishment of causality between systemic inflammation and the development of CCC. Further prospective studies, especially multicenter studies, are needed to confirm these findings and to investigate the underlying

mechanisms by which inflammation affects collateral vessel formation.

CONCLUSION

Our study suggests that PIV could be a significant determinant of poor CCC among patients with CCS and CTO, underscoring the importance of systemic inflammation in collateral vessel development. The PIV may serve as a useful biomarker in identifying patients at risk for impaired collateral circulation and could guide therapeutic interventions aimed at improving myocardial perfusion in CAD patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Başakşehir Çam and Sakura Hospital Scientific Researches Ethics Committee No. 1 (Date: 16.07.2024, Decision No: KAEK/10.07.2024.109).

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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Exploring the evolution of artificial intelligence in pathology: a bibliometric and network analysis

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ABSTRACT

Aims: Artificial intelligence (AI) has emerged as a transformative force in pathology, significantly influencing diagnostic accuracy, workflow efficiency, and digital pathology integration. Despite the rapid growth in AI-related pathology research, a comprehensive analysis of publication trends, key contributors, and scientific impact remains limited. This study aims to provide a bibliometric and network analysis of AI applications in pathology, mapping research trends, citation networks, institutional collaborations, and emerging thematic clusters.

Methods: A bibliometric analysis was conducted using data from the Web of Science Core Collection, covering studies published between 2007 and 2024. Research trends, citation distributions, keyword co-occurrences, and collaboration networks were analyzed using VOSviewer. Descriptive statistics and network visualization techniques were applied to assess publication growth, author collaborations, and journal impact.

Results: The findings are consistent with other studies showing a more than proportionate increase in AI-based research in pathology since 2018, especially AI related pathology research is on a significant rise focusing on laboratory investigation, modern pathology and journal of pathology as the primary high impact journals. Important research centers like the University of Pittsburgh, Radboud Universiteit, and the Cleveland Clinic have made significant advancements in AI based pathology which have and will continue to make a significant impact within this area. The key words used most frequently were "AI", "digital pathology", "deep learning", and "machine learning" which corroborate the centrality of AI in pathology.

Conclusion: AI does have a major contribution towards transforming pathology by aiding in providing quick and efficient diagnosis. Nonetheless, issues around the standardization of data, the black box nature of algorithms, and the regulation of data raise serious challenges towards achieving successful clinical incorporation of AI. The focus of future work should center around standardization of validation protocols, inter-disciplinarity, and ethical issues in order to ensure the dependable implementation of AI enabled solutions in pathology.

Keywords: Artificial intelligence, digital pathology, deep learning, machine learning, bibliometric analysis

INTRODUCTION

Artificial intelligence (AI) is transforming virtually every facet of medicine, including pathology. The integration of AI in pathology stems from its ability to improve diagnostic accuracy, enable workflow efficiency, and increase the adoption of digital pathology systems.[1,2] These innovations have transformed clinical medicine and fundamentally altered the academic research landscape of the discipline. Even with the growing body of literature around AI and pathology, little is known regarding the research landscape, major works, and their scholarly influence.[3]

Tracing the articulation of AI in pathology is important as it allows the stakeholders to identify gaps in work as well as evaluate potential high-impact interventions for collaborative efforts. Today, deep learning and machine learning based approaches have led to significant automation of feature extraction, disease classification, and predictive modeling within histopathological image analysis.[4,5] As a result, there has been improved diagnostic accuracy, decreased interobserver variability, and more sophisticated decision support systems. On the other hand, the concepts of standardization of data, obscurity of algorithms, and embodying ethics still shape the issues on the adoption of AI in clinical practice.[6]

While AI is transforming technology in medicine and healthcare, its application areas seem to deepen by the minute. The application of computer vision in pathology has witnessed tremendous growth due to its capability of improving accuracy in diagnosis, improving workflow productivity, and smooth integration with digital pathology systems. These developments have equally transformed health care practice as much as they have influenced academic pursuit in the area.

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However, there does not appear to be an extensive analysis of the fusion of AI and pathology, and its research trends, major stakeholders, or academic contributions. The development of such analysis is fundamental in helping close pertinent research gaps, understanding the scope of high-impact publications, and enable cross-border collaborations.

This paper takes on the systematic investigation of the scientific landscape concerning AI applications in pathology with the use of bibliometric analysis. In doing so, the research tackles the mapping of publication activity, citation and indexing of articles, the collaborations of various authors, and the thematic clusters of research which in turn helps towards providing an evidence based analysis on the growth and academic impact of AI in pathology. The analysis further investigates the concentration of research productivity in the top journals, the leading institutions and countries in the field that help in identifying important contributions and new areas of research. Using bibliometric data extracted from Web of Science, this study applies quantitative methods to assess publication patterns and scholarly impact, facilitating a deeper understanding of how AI-driven innovations are shaping the field of pathology. The findings aim to serve as a valuable reference for researchers, clinicians, and policymakers, guiding future investigations and strategic decision-making in AI-based pathology research.

METHODS

Ethics

Since this research is a bibliometric study, it did not require ethics committee approval.

Data Collection

Data for this bibliometric analysis were obtained from the Web of Science (WoS) Core Collection, a comprehensive database containing high-quality, peer-reviewed scientific publications. The study focused on the topic of "AI" within the field of "pathology" and examined studies published between January 1, 2007, and December 31, 2024. The search query applied the keyword "AI" with the "topic" filter and restricted the results to the "pathology" category in WoS categories (Table 1).

Table 1. Data set creation and analysis process

Step	Description
1. Data collection	Data was retrieved from the Web of Science platform using the keyword 'artificial intelligence' with the 'topic' filter applied.
2. Category selection	The 'pathology' category was selected from the Web of Science Categories section.
3. Data analysis	A bibliometric analysis method was used to evaluate 959 articles.
4. Presentation of results	The analysis findings were reported with tables and graphics.

As a result of the initial search, 959 articles were identified. The titles, abstracts, and keywords of the articles were carefully examined, and duplicate records were removed. Only peer-reviewed articles that met the inclusion criteria were selected for analysis. The first 10 articles were independently reviewed by two researchers, and disagreements regarding selection were resolved through discussion and consensus.

Data collection was conducted between January and March 2024. For each article, the following bibliometric information was extracted:

- Article title
- Author names
- Publication year
- Journal name
- Journal impact factor
- Citation counts
- Country of affiliation of authors
- Institution names
- Frequently used keywords

The extracted data were verified by two independent observers, and inconsistencies were resolved through consensus.

Bibliometric Analysis

Bibliometric analysis was performed using VOSviewer (version 1.6.11, Leiden University, The Netherlands) to visualize research trends, keyword relationships, and collaboration networks. The primary areas of focus in the analysis included:

- **Annual publication trends:** Examination of publication growth over time.
- **Journal-specific publication trends:** Identification of the most frequently publishing journals in the field.
- **Citation analysis:** Assessment of highly cited authors, articles, journals, and publication years.
- **Keyword co-occurrence analysis:** Identification of commonly used terms and thematic clusters.
- **Institutional affiliations and inter-institutional collaborations:** Mapping research contributions by different institutions.
- **Country-level collaboration networks:** Visualization of international research collaborations.
- **Author collaboration networks:** Analysis of research partnerships among authors.

Statistical Analysis

Descriptive statistics (frequencies and percentages) were used to summarize publication numbers, citation distributions, and journal impact measures. Temporal trends in article output were analyzed using SPSS software to assess changes in research activity over time. Keyword co-occurrence networks were generated to reveal thematic clusters and conceptual relationships in the field.

Inter-institutional and international collaboration patterns were visualized using bibliometric mapping techniques. The density of collaborations was represented by the thickness

of the connection lines, revealing common research focuses across institutions and countries. Cluster coefficients and connection densities were calculated to measure the integrity and integration of research themes within the bibliometric landscape.

RESULTS

Analysis of the Distribution of Articles by Year

Figure 1 presents the distribution of studies over the years in the dataset compiled using Web of Science data.

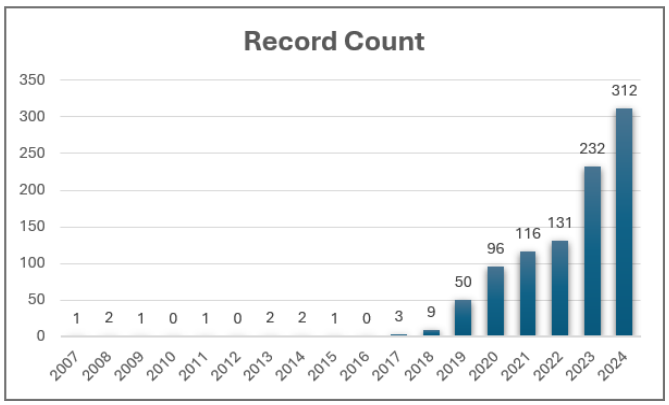

Figure 1. Distribution of articles by year

An analysis based on Web of Science data illustrates the distribution of studies published between 2007 and 2024 in the "AI" field within the "pathology" category.

In 2007, only one study was published. In the following years, a limited increase was observed. By 2018, the number of studies had reached 9, followed by a substantial increase in 2019, with 50 publications. A more pronounced growth trend began in 2020, with the number of studies reaching 232 in 2023 and peaking at 312 in 2024.

Overall, these findings indicate a notable rise in scientific research on AI in pathology, particularly in recent years. This trend highlights the increasing significance of AI applications in pathology and demonstrates the growing interest in the field, driven by technological advancements and innovative approaches.

Journals with the Highest Number of Publications on the Topic

The distribution of journals publishing the highest number of articles related to "AI" in the field of "pathology" in the Web of Science database is presented in Table 2.

The majority of 959 analyzed publications are concentrated in a few key journals. Laboratory Investigation leads with 168 articles (17.52%), followed by modern pathology (106, 11.05%), and Virchows Archiv (75, 7.82%).

While a significant portion of studies is published in a select group of journals, 364 articles (37.96%) are spread across various other journals, indicating both specialization and diversity in publication venues.

Table 2. Distribution of journals by number of publications and proportional shares

Publication titles	Record count	% of 959
Laboratory Investigation	168	17.52%
Modern Pathology	106	11.05%
Virchows Archiv	75	7.82%
Journal of Pathology	63	6.57%
American Journal of Clinical Pathology	36	3.75%
Histopathology	36	3.75%
American Journal of Pathology	32	3.34%
Toxicologic Pathology	28	2.92%
Expert Review of Molecular Diagnostics	27	2.82%
Cancer Cytopathology	24	2.50%
Others	364	37.96%

Comprehensive Analysis of the Most Cited Studies: Authors, Article Titles, Published Journals, Publication Years, and Citation Counts

Table 3 provides detailed information on the authors, article titles, publication journals, years, and citation counts of these highly cited studies.

The data in Table 3 highlights the most cited studies on AI in pathology. The most cited study, van Leenders et al. (2020), published in the American Journal of Surgical Pathology, received 366 citations, discussing the ISUP consensus on grading prostatic carcinoma.

Steiner et al. (2018) followed with 283 citations, examining deep learning-assisted diagnosis of metastatic breast cancer. Abels et al. (2019), with 238 citations, focused on best practices and regulations for digital pathology. Cui and Zhang (2021) explored AI's role in pathology (230 citations), while Baxi et al. (2022) assessed AI in clinical digital pathology (224 citations).

These highly cited studies underscore AI's growing impact on pathology, highlighting its critical role in diagnostics and academic research.

Statistical Evaluation of Publications from the Most Cited Institutions

The database Web of Science was examined to find the institutions with the largest citation impact within the scope of "AI" in "pathology." The Table 4 contains the records of each institution in regard to publication numbers and total citations received.

Table 4 indicates that the University of Pittsburgh have the largest number of publications (33) and citations (588), followed by Radboud Universiteit (20 publications, 539 citations), and Cleveland Clinic (21 publications, 524 citations).

However, after only 7 published articles, the private sector company PathAI has already made a tremendous academic impact with a staggering 485 citations. This shows the increasing penetration of Ai in the pathology scope of even the private sector driven research.

Table 3. Most cited studies on "artificial intelligence" in pathology

No	Author(s)	Article title	Journal name	Year of publication	Citation count
1	van Leenders Geert JLH et al.	The 2019 international society of urological pathology (ISUP) consensus conference on grading of prostatic carcinoma	American Journal of Surgical Pathology	2020	366
2	Steiner DF. et al.	Impact of deep learning assistance on the histopathologic review of lymph nodes for metastatic breast cancer	Merican Journal of Surgical Pathology	2018	283
3	Abels E. et al.	Computational pathology definitions, best practices, and recommendations for regulatory guidance: a white paper from the Digital Pathology Association	Journal of Pathology	2019	238
4	Cui M and Zhang DY	Artificial intelligence and computational pathology	Laboratory Investigation	2021	230
5	Baxi V et al.	Digital pathology and artificial intelligence in translational medicine and clinical practice	Modern Pathology	2022	224

Table 4. Most cited institutions and their publications (Web of Science Data)

Organization	Documents	Citations
University of Pittsburgh	33	588
Radboud Universiteit	20	539
Cleveland Clinic	21	524
Pathai	7	485
Ohio State University	31	475

In sum, these results imply that noted medical faculties and research institutions head the activities of AI in pathology, but at the same time, increasing industrial participation is also noted. These results reinforce the notion to a wide variety of research from academic and industry interest of focus in pathology in which AI is applicable.

Trends in Keyword Usage

The most frequently used keywords related to " AI " in the field of pathology, along with their associations, are illustrated in Figure 2.

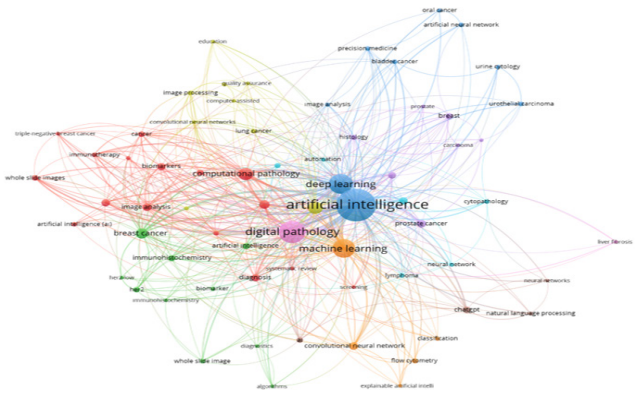

Figure 2. Keyword co-occurrence and frequency of use

VOSviewer software was used for the bimetrical analysis along with a set minimum of five occurrences for inclusion during keyword selection. This measure allowed for occurrence over five times without going to over-focusing on relevant and often used terms.

Despite the discovery of 1.639 varied keywords, only 68 were chosen to be significant and analyzed further. This type of analysis makes it clear how the study prioritized the chosen keywords and their assigned relations.

The analysis captured the previously mentioned keywords that were most frequently used in conjunction to the research field and their strongest overlaps. 8 other groups showed the presence of 533 linked keywords, creating a total of 9 clusters. These figures are illustrative of the presence of conglomerates for certain terms that aid in constructing boundaries for various evolving concepts that need to be investigated in the future. In figure 1, the link between AI and academic publications in pathology is represented through the arising prominent phrases and their relationships.

From the presented data sets, "AI" is the most common keyword used, recorded 355 times. This figure is accurate as “AI” plays an important role in pathology research. The second most common keyword “digital pathology” was found recorded 166 times which underlines the importance of digital activities in pathology. “deep learning” is recorded for the 128 times, while “machine learning” came to second at 114 times showing focus of sub AI fields in Pathology studies.

The notable keywords that were recorded less frequently but still captured the eye were “computational pathology”, flagged at 49 times & “pathology” at 48. Both indicate a growing interest of academic literature towards computational approaches and core pathology concepts.

These examples confirm that AI has impacted pathology research. The number of times keywords appear is one of the most important sign of ongoing research, whereas the repetition of certain words improves the comprehension of pathology aided by AI.

Analysis of Institutional Collaborations in Publications

Academic studies focusing on "AI" in the field of "pathology" were analyzed in terms of the institutions affiliated with researchers and their collaboration networks. The findings reveal the structure and intensity of institutional collaborations, with the results visually presented in Figure 3.

Collaboration analysis was performed using VOSviewer software, which uses colors to differentiate thematic or regional groups, while the links represent collaborative activities (or relations) of the institutions. The thickness of the connections

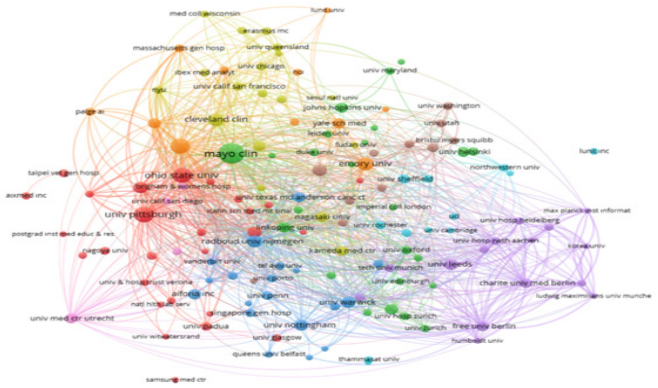

Figure 3. Visualization of institutional bibliometric networks

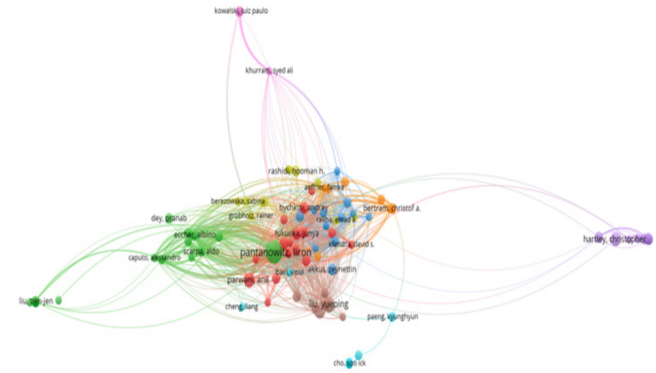

Figure 4. Academic collaboration network (larger circles represent prominent authors, and connecting lines indicate scientific collaborations.)

shows the less and more interactions among the institutions. This type of analysis protects against large intercontinental differences as it reveals important interactions and possible future collaboration covers in AI in pathology research.

The analysis reveals that academic collaboration in this area is limited to few institutions. For instance, the University of Michigan and Mayo Clinic have formed over 139 connections. These are some of the most central institutions, which capture their strong academic network and leadership in AI pathology research.

In the same manner, the University of Pittsburgh, and Ohio State University also has formed connections with 138 other institutions. Both are considered as another primary institutions that maintain active collaboration with a large number of scientists from multiple research centers and academic institutions. There have been other centers such as Radboud Universiteit and Emory University with 137 and 135 connections respectively, which are considered lesser but are also significant academic contributors to the research landscape.

Generally, the results show that the studies about AI and pathology are concentrated in certain universities and research centers. These analyses help in understanding academic interactions, assessing collaboration potential, and identifying new partnership opportunities in a strategic research framework.

Analysis of Author Collaborations

A comprehensive analysis of academic publications on AI in pathology within the Web of Science database was conducted, focusing on the collaboration networks among researchers. The results of this analysis reveal the structure of academic interactions and the dynamics of scientific collaborations, visually represented in Figure 4.

Figure 4 analyzes bibliometric connections among researchers who have published at least five articles in the field of AI in pathology. Out of 5.198 authors, only 106 researchers met the threshold for inclusion in the analysis. This selection criterion ensures that the study focuses on influential researchers with substantial contributions, enhancing the reliability and scientific value of the findings.

The visualization illustrates the collaborative networks and bibliometric connections among researchers in the field. Every author is represented as circles, where the size of their circle indicates their significance in terms of their contributions to the literature. The lines between circles show the intensity of collaborations as well as the strength of bibliometric relationships. Clusters distinguished by colors indicate groups of researchers working in themes or methodologically related areas.

- **Green cluster:** Pantanowitz Liron is a recognized central figure of the group, as he is one of the top scientists within this network. Scarpa Aldo and Eloy Catarina are also prominent figures in this network. This green cluser proves to have a higher interfiliatory interaction which is thematic in nature, forming a wide net of collaboration, as well as contributing greatly to the literature.
- **Orange cluster:** In this cluster, the strongest net is built up by Bertram Christof A. together with Klopfleisch Robert and Westerling-Bui Thomas, who are also active contributors. The theme of this cluster is single but well defined and it is one of the key themes in the realm.
- **Blue cluster:** In this group, Rajpoot Nasir is the key researcher, who works closely with Kather Jakob Nikolas and Snead David. In this literature cluster, there is a dense network of these researchers focusing on specific sub disciplines and making significant contributions to the field.
- **Purple cluster:** This group is led by Khurram Syed Ali and Kowalski Luiz Paulo. This cluster is less connected than others, which makes it focus on subtopics of great importance. Because of this, it contributes significantly to niche areas.

This sheds light on the particular movements of author collaborations and scientific social networks. The color coded clusters show the diversity of themes studied and their contribution to the body of literature. The analysis of these author relationships aids in forming one of the academic collaboration strategies to focus research efforts and improve innovation and collaborative efforts in AI in pathology as a branch of science.

Citation Distribution by Country

Using the Web of Science (WoS) database, the citation distribution for AI in pathology was examined comprehensively

at the national level. Results are shown below in Figure 5 for the citation distribution by country, as well as for the geographical distribution of citations, regional concentration, and the international scientific community partnership. This study shows an important consideration on the dynamics of research and scholarly activity across different countries.

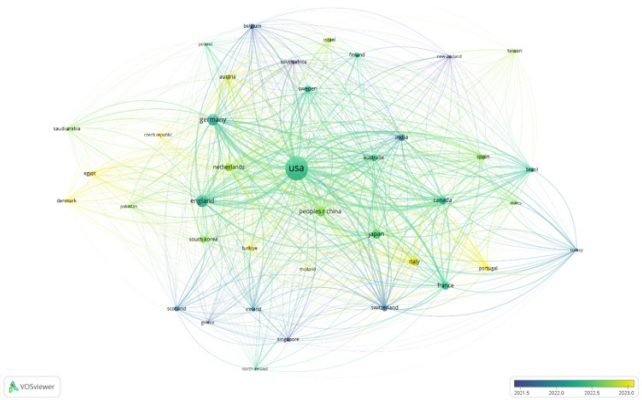

Figure 5. Analysis of citation distribution by country

In Figure 5, I depicted the concentration of citation counts from international studies conducted in Web of Science (WoS) and also charted the collaborative academic networks worldwide. This analysis covered 74 countries, but in the end only 39 countries qualified for the evaluation, as they published a minimum of five papers each. It clustered the participants into five distinct categories, each reflecting their primary area of interest or the collaboration network they belong to. This work is crucial for understanding not only the interactions between various countries, but also the overarching tendencies of AI-pathology research.

The circles which appear in figure 4 portray citation concentration regions in addition to international scientific collaboration networks. The mini-maps exhibit the interconnectedness between different countries depicting the degree of research collaboration, while the basic citation regions of IP and literature contribution bya are signified by size of the circles.

As such, the United States (US) is the first and the key node and therefore the most important country within the network which suggests that AI-related pathology research is most advanced there. The US is also collaborating with China, the United Kingdom, Canada, Germany, France and Japan, which points to the cooperation power of the USA.

Among European countries, Germany, the United Kingdom, France, Italy, and the Netherlands stand out, demonstrating both high citation impact and strong collaborative ties with each other.

In Asia, China and Japan are among the most prominent contributors. China shows strong connections with the US, while Japan has established a robust research network with both the US and European countries. India, Taiwan, and South Korea also contribute significantly, maintaining both regional and international collaborations.

Canada and Australia play key roles in their respective regions, forming strong research ties with the US. Brazil is noteworthy in South America, while Turkiye appears as a bridge between Europe and Asia, highlighting its regional research impact.

Countries with less dense collaboration networks include Sweden, Switzerland, Spain, Israel, and Portugal. These nations contribute to regional and thematic research collaborations, enriching the diversity of the literature.

DISCUSSION

The results of the research highlight the growing pace and reach of AI in pathology, which can be observed from the drastic increase in the number of research publications in the last twenty years. Based on previous studies, bibliometric evaluations reported that novel technologies powered by AI have significantly improved digital pathology by enhancing diagnostic accuracy, increasing efficiency of workflows, and improving decision-support systems. In addition to these general trends, it is important to highlight the key studies that have significantly contributed to the advancement of AI in pathology. For instance, van Leenders et al. (2020) discussed the ISUP consensus on grading prostatic carcinoma, contributing to standardized diagnostic criteria and receiving 366 citations. Steiner et al. (2018) demonstrated the role of deep learning-assisted diagnosis in metastatic breast cancer detection, showcasing AI's potential to enhance diagnostic sensitivity, with 283 citations. Abels et al. (2019) focused on establishing best practices and regulatory frameworks for digital pathology, a foundational step in clinical translation, cited 238 times. Cui and Zhang (2021) provided an extensive overview of AI applications in pathology, offering critical insights into emerging methods, cited 230 times. Finally, Baxi et al. (2022) examined the integration of AI into clinical digital pathology workflows, reflecting the shift from theoretical research to clinical utility, with 224 citations. Together, these influential studies highlight how AI has progressed from experimental innovations to practical applications in diagnostic pathology, improving accuracy, standardization, and operational efficiency.

This trajectory of growth is consistent with other scholarly studies such as those done by Shen et al.[7] and Zhao et al.,[8] which noted as well the increased and expanded thematic focus of AI-driven research in pathology. This work answers and builds on these studies by providing a comprehensive overview of the key research players, new development directions, and international collaboration networks.

Great attention must be paid to the exponential increase in AI-pathology publications, that began in 2018, predicting a peak in 2024, which is very noticeable. This surge can be attributed to the advancements in the deep learning architecture, increased adoption of whole-slide imaging, and the increased computational power available to perform large scale data analysis. Such phenomenon was also noted by Xiong et al.[9] in their examination of AI-based digital pathology research in relation to lung cancer where it was noted AI played a vital role in the Automated Image Analysis and AI-based high through put diagnostics and triaging bulk samples. These technologies and the collaboration among different

specialties have propelled the use of AI in pathology to active practice. However, despite the surge in publications, a review of previous literature suggests that there is publication bias towards primary subfoelds such as leepology and predictive deep learning, rather than the cross-branch applications of molecular pathology or predictive modeling, which are at best labeled as minimalistic in scope.[4,5] These unbalanced windows should be the center of focus for upcoming studies.

The citation and journal analysis reports indicate that the AI pathology works seem to be concentrated within high impact journals like Laboratory Investigation, Modern Pathology, and Journal of Pathology. This looks like AI is one of the main features within the scope of pathology research which correlates with the work of Moran-Sanchez et al.,[10] who said that "in diagnostic pathology, especially in the field of lymphoid neoplasms, innovative AI-based technologies are greatly changing the scope of the specialty. Furthermore, the institutional analysis indicates that other major medical and research institutions such as University of Pittsburgh, Radboud Universiteit, and Cleveland Clinic are leaders on the AI pathology research. This suggests a concentration of resources in technologically sophisticated and well funded research centers, supporting the work done by Zhang et al.,[11] who claimed that a disproportionate concentration of resources is needed so that instititons can be considered AI innovation leaders in pathology.

Co-occurrence of keywords and thematic analysis shows that the most used phrases are "AI," "digital pathology," "deep learning," and "machine learning," which highlights the primary focus of pathology research: AI. These results are consistent with previous bibliometric studies which noted an increasing dependence on deep learning and computational approaches to automated histopathological analysis.[4,5] A significant gap of this study was that few papers had been published focusing on the explainability of AI models. Although many strides have been made, the reality remains that AI is a "black-box" system that threatens any semblance of transparency and confidence in the clinical setting.[6] Subsequent researches should utilize AI technologies in pathology for better regulation and acceptance of the algorithms.

The analysis of institutional and authors' collaborations indicates that AI-pathology research is largely conducted by some leading research groups that have well-established collaborative networks between the US, Europe, and Asia. This corroborates the work of Xiong et al.,[9] who pointed out the disparity of AI lung cancer pathology research and the need for international collaboration. However, our work shows that these networks are unevenly distributed and concentrated among high and upper middle-income regions that have advanced research activity, while less developed countries remain underrepresented in AI based pathology research. This indicates that more efforts are needed to promote international pathology research programs and equity in funding for AI applications in diverse health care systems.

There is, however, a range of persistent challenges that remain prevalent regarding the integration of AI within the domain of pathology. As some literature suggests, these issues include, but are not limited to, data standardization, algorithmic opacity, and ethical issues that are recurrent in this field.[6,10] The diminishing of interobserver variability using AI models is one of the critical contentious issues. Research has shown that while some areas benefit from enhanced consistency AI provides, human and AI collaboration is crucial for sustaining trust in the diagnosis.[1] Furthermore, the proliferation of commercial AI models into pathology such as those provided by PathAI, for example, brings to light the question of data confidentiality and training bias regarding the proprietary data. The fair use of AI to solve problems in pathology requires greater responsiveness than this approach offers. There is a stronger case for using open-source AI and greater collaboration between institutions to achieve an ethical and fair use of AI in pathology.[12]

In addition, the citation impact of PathAI's work shows that there are significant contributions from the private sector, hinting the industry's impact on AI development is growing. This marks a shift towards transnational work on AI, where commercial AI systems are put to use as Baxi et al.[12] put it - integrated into the workflows. The combination of academic and industry sponsored AI Development requires continuous scrutiny to avoid unethical practices, biasing and clinically unverified applications.

Moreover, the thematic evolution of research over time provides additional insights into the development trajectory of AI in pathology. When evaluating the evolution of AI in pathology, a clear thematic shift over time becomes evident. In the early years (2007–2015), studies predominantly focused on developing image analysis algorithms for histopathological slides, using traditional machine learning methods such as support vector machines and random forests. These systems primarily aimed at automating simple tasks like nuclei detection and mitosis counting. However, with the advent of deep learning technologies post-2016, the research focus expanded towards more complex tasks, including whole-slide imaging analysis, automated cancer grading, and prediction of molecular alterations directly from pathology images. Systems such as convolutional neural networks (CNNs) and deep convolutional generative adversarial networks (DCGANs) became the most intensively studied technologies. In recent years (2020 onwards), attention has shifted towards explainable AI (XAI) models, multimodal data integration (combining pathology with genomics and clinical data), and regulatory frameworks for clinical implementation. This developmental trajectory illustrates the maturation of AI in pathology from isolated image analysis tools to sophisticated, clinically oriented diagnostic support systems.

Finally, the absence of common standardized evaluation criteria for various studies poses a significant barrier for AI research in pathology. As many AI studies apply different validation methods, comparison across studies becomes difficult.[13] There is a call for development of benchmarking criteria for designing AI systems in pathology to promote reliability and reproducibility of results, which is the focus of future studies.

Ultimately, this study sheds light on AI's pivotal role in transforming the pathology field. Despite the remarkable AI-facilitated progress in histopathological analysis, standardization, transparency, and clinical implementation still require essential attention. Achieving wider clinical utilization of AI applications in pathology will require intensified cross-border collaborations as well as legislative changes. In order to leverage AI's full potential in pathology, subsequent studies need to enhance AI model interpretability, resolve concerns regarding the unity of global research, and create universally validated benchmark standards. By focusing on these areas, AI pathology research will begin to tackle the gaps that can maximize patient benefits through ethical and valid clinical practices.

Limitations

One limitation of this study is its reliance on the Web of Science database, which, while comprehensive, may not include all relevant publications indexed in other databases such as PubMed or Scopus. Additionally, citation-based metrics may not fully capture the qualitative impact of studies, as citation practices can vary across disciplines. Furthermore, the study primarily focuses on English-language publications, potentially overlooking significant contributions in other languages. Despite these limitations, the bibliometric and network analysis provides valuable insights into the evolution of AI in pathology, offering a robust foundation for future research and interdisciplinary collaboration.

CONCLUSION

As a result, this research assesses the evolution of AI in pathology, especially in diagnostics, workflow management, and decision-support system enhancement. While AI-based research in pathology is booming, the field still faces considerable challenges such as a lack of standardization, opaque algorithms, and insufficient regulation. The study also underlines that interrelations between science and business must be considered as factors that foster development in the area and that future studies need to concern themselves with how to construct ethical and dependable universal validation frameworks for clinical AI. Through multidisciplinary cooperation, data standardization, and the establishment of regulatory structures, AI in pathology can become more effective and reliable.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since this research is a bibliometric study, it did not require ethics committee approval.

Informed Consent

Since this research is a bibliometric study, it did not require informed consent.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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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 relationship between anemia and health-related QoL in patients with chronic kidney disease receiving hemodialysis treatment

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ABSTRACT

Aims: Anemia is a frequent complication in hemodialysis patients and associated with a poor quality of life (QoL). Our goal was to examine the connection between anemia and health-related QoL (HR-QoL) in those with renal failure receiving hemodialysis treatment.

Methods: In this cross-sectional study, 128 subjects that underwent hemodialysis volunteered. Demographic, clinical, and laboratory parameters and QoL using SF-12 were assessed. Socio-demographic characteristics in patients with and without anemia according to hemoglobin value were compared. The scores obtained from the physical (PCS12) and mental subscales (MCS12) of the SF-health survey were compared with other variables (age, gender, education, smoking, marital status, co-morbidity, BMI, duration of hemodialysis, hemoglobin values). Regression analyses were conducted using PCS12 and MCS12 as the independent variables.

Results: There were 27 (21.1%) patients with Hb values between 10-11 and 38 (29.7%) patients with Hb values below 10. The findings of this study indicated that an early age (p=0.001) and higher education (p=0.009) were linked to improved QoL, while no association was found with anemia (p=0.228). Smoking was also found to be significant (p=0.01) for better scores. Univariate linear regression analysis was performed to evaluate the interaction or relationship between age and smoking. Smoking was found to be an effective risk factor in patients younger than 65 years, but not in patients older than 65 years. The comparison of socio-demographic characteristics between patients with and without anemia revealed that married patients exhibited statistically significant higher hemoglobin levels (p=0.001).

Conclusion: A notable association was identified between the physical aspect of the SF-12 survey and both younger age and higher educational level, whereas no such relationship was observed for the mental aspect. The findings indicated that younger individuals with higher education levels experienced an improved physical QoL. However, no link has been found between anemia and QoL.

Keywords: Chronic kidney disease, chronic renal failure, hemodialysis, anemia, health-related quality of life

INTRODUCTION

Chronic kidney disease (CKD) represents a significant global health issue. A meta-analysis suggests that around 13.4% of the global population is affected by CKD, with 79% of these individuals being in the advanced stages of the condition (stage 3-5).[1] The incidence of CKD is rising swiftly in both Western nations and Turkiye, which is driven by the aging population and the increasing rates of heart disease, metabolic syndrome, diabetes, and hypertension.[1,2]

Hemodialysis treatment is vital in patients with end-stage CKD, and is mostly used in people who have no chance of organ transplantation or who cannot receive peritoneal dialysis treatment. According to the statistics of the Turkish Society of Nephrology as of 2024, over 68.000 patients in our country are receiving dialysis treatment for end-stage renal failure. Of these patients, 64.300 were treated with hemodialysis, 3.250 were treated with peritoneal dialysis, and 1.300 were treated with home hemodialysis.[1,2]

Anemia frequently occurs in CKD and serves as a distinct risk factor that negatively impacts health-related quality of life (HR-QoL).[3] Anemia in CKD is mainly attributed to a relative lack of erythropoietin, a hormone primarily synthesized by the kidneys in adults. Additionally, factors such as reduced red blood cell lifespan and iron deficiency further exacerbate anemia associated with CKD.[4,5] Iron deficiency in CKD patients is categorized into absolute and functional iron deficiency. Absolute iron deficiency has significantly

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diminished or nonexistent iron reserves in the body. Functional iron deficiency, characterized by the presence of normal or elevated total iron stores that cannot be utilized for the production of erythroid precursors, is necessary for erythropoiesis. This condition primarily arises from elevated hepcidin, which hinder the mobilization of iron reserves for the process of erythropoiesis. Iron metabolism is regulated by hepcidin, which is a 25-amino acid peptide released by the liver, with subsequent filtration and degradation occurring in the kidney.[3,6] In CKD, hepcidin levels rise and inversely correlate with the glomerular filtration rate (GFR).[6]

Iron deficiency anemia frequently occurs in patients with CKD due to reduced iron absorption and heightened iron loss, regardless of whether they are undergoing dialysis therapy.[3,4,6] Anemia, a complication of chronic renal failure, is associated with decreased QoL[5], and increased mortality and morbidity.[7]

Current treatment strategies involve the use of oral/intravenous iron and erythropoiesis-stimulating agents (ESAs), with the recent addition of hypoxia-inducible factor prolyl hydroxylase inhibitors (HIF-PHIs), thereby expanding the range of therapeutic options available. Since it is treatable, we wanted to draw attention to the importance of anemia in hemodialysis patients. The goal of this report was to investigate the relationship for anemia and HR-QoL in CKD subjects undergoing hemodialysis.

METHODS

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Informed consents of all patients were obtained before administration of the QoL scale. The study was conducted with the permission of Ankara Etlik City Hospital Scientific Researches Evaluation Ethics Committee (Date: 31.01.2024 Decision No: AEŞH-BADEK-2024-054).

In this observational study of a cross-sectional and descriptive nature, the medical histories and examination documentation, along with the results of blood tests, were meticulously analyzed from the records of 128 patients who participated in the hemodialysis unit at a tertiary hospital and Ankara Hemodialysis Center during the period from February 1, 2024, to May 31, 2024.

Participants in the study were individuals aged 18 years and above who underwent two or three hemodialysis sessions weekly. Exclusions were made for patients with cognitive impairments, those on continuous tube feeding, individuals in the acute phase of illness, hospitalized patients, and those who had experienced a stroke. As this was a descriptive study, no sampling was conducted.

We evaluated the patients based on their demographics, marital status, level of education, and smoking status. Anthropometric measurements were taken, which included height in centimeters and weight in kilograms. BMI was determined by dividing weight (kg) by height squared (m2) and obesity was determined as BMI≥24.0 kg/m2.[8] Hemodialysis year and comorbidities were recorded. The laboratory data obtained from medical records included hemoglobin (Hb), mean corpuscular volume (MCV), ferritin, iron levels, total iron binding capacity (TIBC), transferrin saturation (TSAT), as well as B12, and folic acid. According to the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines, anemia of CKD is defined as Hb<13 mg/dl for men and <12 mg/dl for women.[9] Since the same guidelines generally recommend that erythropoiesis-stimulating agent (ESAs) should not be used to maintain an Hb concentration above 11.5 g/dl (115 g/L) in adult patients with CKD, anemia was defined as Hb<11.5 g/dl in this study. Anemic patients exhibiting serum ferritin below 50 ng/ml were classified as having "absolute iron deficiency anemia." In contrast, those with ferritin levels exceeding 50 ng/ml underwent evaluation of serum iron, TIBC, and TS. Anemic individuals presenting with normal serum iron levels (greater than 60 µ/dl), normal or reduced TIBC ranging from 250 to 450 µg/dl, and normal TS levels above sixteen percent were categorized as having "unknown anemia." Those exhibiting ferritin levels exceeding 100 ng/ml, along with reduced TS and reduced total iron-binding capacity, were classified as having "anemia of chronic disease".[10,11]

QoL was assessed using SF-12.[12] The validity and reliability assessment of this scale in Turkiye was carried out by Soylu and Küçük[13] from the Department of Psychology at Ege University, Faculty of Literature. This questionnaire serves as a standardized tool for assessing physical (PCS12) and mental (MCS12) health across eight distinct areas: physical function, limitations in roles due to physical health issues, pain, overall health, vitality (energy and fatigue), social function, limitations in roles due to emotional challenges, and mental health (psychological distress and well-being). The SF-12, which is a condensed version of the SF-36, comprises only 12 items. These items are divided into two categories—physical and mental—each containing six items. Quality of life (QoL) scores for these domains range from 0 to 100, with higher scores indicating better QoL.

A power analysis was performed to determine whether the sample size of 128 patients was sufficient to determine the effect size and the power of the study was 0.96. Since this value was greater than 0.80, it was concluded that the power of the study was sufficient.

Statistical Analysis

Statistics were conducted with SPSS v11.5 (SPSS Inc., USA). Descriptive statistics were presented as mean±standard deviation or median (minimum–maximum) for continuous variables, and frequency (percentage) for categorical variables. The Shapiro-Wilk test was used to assess the normality of distribution for the PCS12 and MCS12 component summary scores. Both PCS12 and MCS12 scores were found to deviate from normal distribution. Therefore, non-parametric comparisons between groups were performed using the Mann-Whitney U test. Categorical variables were compared using Chi-square or Fisher's exact tests as appropriate. Univariate and multivariate linear regression analyses were conducted to determine the association between independent variables and PCS12 or MCS12 scores. A two-tailed p-value <0.05 was considered statistically significant. In addition, a post-hoc power analysis was performed to evaluate whether the sample size (n=128) was adequate to detect a clinically meaningful

difference. Assuming a medium effect size (Cohen's d=0.5), an alpha level of 0.05, and using a two-tailed test, the calculated statistical power was 0.88. Since this exceeds the commonly accepted threshold of 0.80, the sample size was considered sufficient for detecting moderate effects in PCS12 and MCS12 scores.

RESULTS

The comparison of socio-demographic characteristics in patients with and without anemia according to Hb value is given in Table 1.

In the study, there were 27 (21.1%) patients with Hb values between 10-11, and 38 (29.7%) patients with Hb values below 10. In addition, there were 68 (87.2%) males with Hb less than 13 and 42 (84.0%) females with Hb less than 12.

When serum iron, TIBC and ferritin of 122 patients with anemia were examined, results were consistent with 'absolute iron deficiency' in three patients, 'anemia of unknown cause' in 10 patients and 'anemia of chronic disease' in the other 109 patients were obtained.

All parameters analyzed from these patients are shown in Table 2.

Table 2. Laboratory values recorded for the study sample

Variables	Total		
	n (%)	Mean±SD	Median (min.-max.)
Hb	128 (100.0)	10.83±1.75	10.95 (5.60-15.00)
MCV	128 (100.0)	94.06±6.77	94.80 (75.50-118.00)
Serum iron	122 (95.3)	49.02±23.29	46.00 (8.00-117.00)
SIBC	122 (95.3)	162.49±52.17	157.50 (60,00-315.00)
TSAT	122 (95.3)	33.98±20.35	30.10 (4.80-94.30)
Ferritin	123 (96.1)	550.77±280.80	612.00 (15.40-1209.00)
Vitamin B12	32 (25.0)	507.31±323.45	400.00 (155.00-1471.00)
Folic acid	116 (90.6)	9.71±38.89	5.55 (1.70-424.00)
Vitamin D	7 (5.5)	26.73±25.14	18.00 (6.34-76.00)

SD: Standard deviation, Hb: Hemoglobin, Min: Minimum, Max: Maximum, SIBC: Serum iron binding capacity, TSAT: Transferrin saturation, MCV: Mean corpuscular volume

In Table 3, the scores obtained from PCS12 and MCS12 of the SF-health survey were compared with other variables. Significant differences for age and smoking (p=0.004 and p=0.008) were found for PCS12. The PCS12 scores for patients less than 65 years of age were significantly higher than those aged 65 and older. The PCS12 score of smoking subjects was increased compared to non-smokers.

Table 1. Characteristics of the study sample according to hemoglobin level

Variables		Total	Hb <11.5	Hb ≥11.5	p value
		n (%)	n (%)	n (%)	
Age	<65	78 (60.9)	46 (60.5)	32 (61.5)	0.908[a]
	≥65	50 (39.1)	30 (39.5)	20 (38.5)	
Gender	Female	50 (39.1)	30 (39.5)	20 (38.5)	0.908[a]
	Male	78 (60.9)	46 (60.5)	32 (61.5)	
Smoking	No	104 (81.2)	59 (77.6)	45 (86.5)	0.205[a]
	Yes	24 (18.8)	17 (22.4)	7 (13.5)	
Marital status	Single	41 (32.0)	34 (44.7)	7 (13.5)	<0.001[a]
	Married	87 (68.0)	42 (55.3)	45 (86.5)	
Education	Illiterate	20 (15.6)	13 (17.1)	7 (13.5)	0.622[b]
	Literate	2 (1.6)	2 (2.6)	0 (0.0)	
	Primary school	41 (32.0)	22 (28.9)	19 (36.5)	
	Secondary school	12 (9.4)	9 (11.8)	3 (5.8)	
	High school	34 (26.6)	18 (23.7)	16 (30.7)	
	University	19 (14.8)	12 (15.9)	7 (13.5)	
BMI	<24	60 (46.9)	38 (50.0)	22 (42.3)	0.392[a]
	≥24	68 (53.1)	38 (50.0)	30 (57.7)	
Duration of hemodialysis	<5	72 (56.2)	45 (59.2)	27 (51.9)	0.414[a]
	≥5	56 (43.8)	31 (40.8)	25 (48.1)	
Comorbidity	No	44 (34.4)	23 (30.3)	21 (40.4)	0.236[a]
	Yes	84 (65.6)	53 (69.7)	31 (59.6)	
Hypertension	No	71 (55.5)	41 (53.9)	30 (57.7)	0.675[a]
	Yes	57 (44.5)	35 (46.1)	22 (42.3)	
Type II DM	No	111 (86.7)	64 (84.2)	47 (90.4)	0.312[a]
	Yes	17 (13.3)	12 (15.8)	5 (9.6)	

Hb: Hemoglobin, BMI: Body-mass index, DM: Diabetes mellitus, a: Chi-Square test, b:Fisher-exact test

Table 3. Characteristics of the study sample according to SF-12 subscales

Variables		SF12			
		PCS12		MCS12	
		Median (min-max)	p value	Median (min-max)	p value
Age	<65	37.17 (24.24-56.19)	0.004[a]	40.08 (21.71-53.93)	0.912[a]
	≥65	35.44 (16.37-51.95)		38.71 (28.37-53.97)	
Gender	Female	36.15 (24.24-47.20)	0.510[a]	39.24 (24.91-53.45)	0.942[a]
	Male	37.02 (16.37-56.19)		39.00 (21.71-53.97)	
Smoking	No	36.15 (16.37-56.19)	0.008[a]	39.30 (21.71-53.97)	0.716[a]
	Yes	38.94 (25.77-54.80)		38.53 (25.01-53.93)	
Marital status	Single	36.53 (25.77-56.19)	0.363[a]	38.40 (25.01-53.93)	0.314[a]
	Married	36.43 (16.37-53.48)		39.45 (21.71-53.97)	
Education	Illiterate	36.47 (16.37-47.05)	0.053[a]	39.09 (27.59-52.67)	0.431[a]
	Literate	29.27 (24.24-34.30)		41.80 (30.15-53.45)	
	Primary school	35.70 (25.77-53.48)		38.62 (21.71-53.93)	
	Secondary school	34.50 (29.60-56.19)		37.66 (24.91-50.47)	
	High school	37.44 (26.53-54.80)		41.30 (29.62-53.97)	
	University	39.21 (30.25-52.42)		37.24 (30.60-48.25)	
BMI	<24	36.38 (24.24-54.80)	0.357[a]	37.15 (21.71-53.97)	0.082[a]
	≥24	36.63 (16.37-56.19)		40.38 (27.59-52.67)	
Duration of hemodialysis	<5	36.15 (24.24-56.19)	0.770[a]	38.95 (21.71-53.45)	0.781[a]
	≥5	37.16 (16.37-52.87)		39.45 (25.47-53.97)	
Comorbidity	No	37.60 (25.77-53.48)	0.162[a]	40.28 (25.47-50.47)	0.710[a]
	Yes	36.08 (16.37-56.19)		38.68 (21.71-53.97)	
Hb	<11.5	36.83 (24.24-56.19)	0.304[a]	38.50 (25.01-53.97)	0.509[a]
	≥11.5	36.29 (16.37-52.87)		40.27 (21.71-51.97)	

PCS12: Scores obtained from the physical, MCS12: Mental subscales, Min: Minimum, Max: Maximum, Hb: Hemoglobin, BMI: Body-mass index, a: Mann-Whitney U test

Predictor variables for PCS12 were analyzed in Table 4. Age, smoking and educational status were significant (p=0.001, p=0.010 and p=0.009). The PCS12 score for those less than 65 years of age was 3.704 points more compared to patients aged 65 and over. Age alone explained 7.8% of the change in PCS12 score. The PCS12 score of smokers was 3.767 points higher than that of non-smokers. Smoking alone explained 5.2% of the change in PCS12 score. Univariate linear regression analysis was performed to evaluate the effect of smoking in patients younger and older than 65 years of age. While smoking was found to be an effective risk factor in patients younger than 65 years of age, smoking was not found to be an effective risk factor in patients older than 65 years of age.

For each improvement in educational status, the PCS12 score increased by 0.928 units. In particular, PCS12 of literate subjects was 0.928 more than illiterate patients. The PCS12 score of primary school graduates was 0.928 points higher than that of literate patients. Education alone explained 5.3% of the variation in PCS12 score.

In Table 5; A multivariate linear regression model was constructed to evaluate the independent effects of age, smoking status, and educational level on PCS12 scores. The model demonstrated an R^2 value of 0.135, indicating that approximately 13.5% of the variance in physical QoL could be explained by these three variables. Being under the age of 65 was associated with a 2.90-point increase in PCS12 scores (p=0.008; 95% CI: -5.08 to -0.72), while current smoking was associated with a 2.80-point increase (p=0.045; 95% CI: 0.05 to 5.55). Additionally, each incremental increase in educational attainment was linked to a 0.75-point improvement in PCS12 scores (p=0.018; 95% CI: 0.10 to 1.40). These findings suggest that younger age, smoking status, and higher education levels

Table 4. Predictors of PCS12 using univariate regression analysis

Variables	β	SE	R^2	p value	95% CI for β	
					Lower bound	Upper bound
Age	-3.704	1.134	0.078	0.001	-5.948	-1.461
Gender	1.274	1.175	0.009	0.280	-1.052	3.600
Smoking	3.767	1.437	0.052	0.010	0.922	6.611
Marital status	-1.502	1.227	0.012	0.223	-3.931	0.927
Education	0.928	0.349	0.053	0.009	0.238	1.619
BMI	1.088	1.150	0.007	0.346	-1.188	3.365
Duration of hemodialysis	-0.395	1.161	0.001	0.734	-2.692	1.902
Comorbidity	-2.072	1.199	0.023	0.086	-4.444	0.301
Hb	-1.387	1.146	0.011	0.228	-3.654	0.880

PCS12: Scores obtained from the physical, SE: Standard error, CI: Confidence interval, Hb: Hemoglobin, BMI: Body-mass index

are independent predictors of better physical QoL among hemodialysis patients.

Table 5. Multivariate regression analysis for PCS12

Variables	β	SE	R^2	p value	95% CI (lower)	95% CI (upper)
Constant	35.1	1.3	0.135	<0.001	32.5	37.7
Age (<65)	-2.9	1.1		0.008	-5.08	-0.72
Smoking (yes)	2.8	1.4		0.045	0.05	5.55
Education (↑ each level)	0.75	0.33		0.018	0.1	1.4

PCS12: Scores obtained from the physical, SE: Standard error, CI: Confidence interval

In Table 6, the predictor variables for MCS12 were analyzed and none of the variables were statistically significant. Therefore, MLR analysis could not be performed.

Table 6. Predictors of MCS12 using univariate regression analysis

Variables	β	SE	R^2	p value	95% CI for β	
					Lower bound	Upper bound
Age	0.164	1.235	0.001	0.894	-2.281	2.609
Gender	-0.225	1.235	0.001	0.856	-2.669	2.220
Smoking	-0.608	1.543	0.001	0.694	-3.663	2.446
Marital status	1.335	1.286	0.008	0.301	-1.211	3.881
Education	0.242	0.375	0.003	0.520	-0.499	0.983
BMI	1.932	1.196	0.020	0.109	-0.434	4.299
Hemodialysis	0.575	1.214	0.002	0.637	-1.828	2.978
Comorbidity	-0.100	1.269	0.001	0.938	-2.611	2.412
Hb	0.341	1.205	0.001	0.777	-2.044	2.727

MCS12: Mental subscales, SE: Standard error, CI: Confidence interval, BMI: Body-mass index, Hb: Hemoglobin

DISCUSSION

The SF-12 instrument was employed to evaluate the influence of anemia on the QoL among patients undergoing hemodialysis. The findings indicated that younger age and greater educational achievement correlated with improved QoL, while anemia itself did not show a significant association. A review of existing literature reveals that hemodialysis patients with higher educational backgrounds tend to experience enhanced health-related QoL.[14-16] Another study showed that a higher level of education positively affects not only physical health quality but also mental health quality.[17] In a study conducted in Greece, similar to our results, it was shown that younger patients and patients of higher educational status presented better QoL scores.[18]

International guidelines for managing anemia associated with CKD recommend maintaining target Hb levels at or below 11.5 g/dl, while also allowing for personalized adjustments to slightly higher Hb targets to enhance QoL.[9] Since the publication of the 2012 KDIGO; anemia guideline which provided recommendations for the diagnosis and treatment of anemia related to CKD, new therapies for the treatment of anemia have emerged; therefore, a reevaluation of the 2012 KDIGO guideline was required. Following conferences starting in 2019 and continuing in December 2021, KDIGO reported in 2023 on the new evidence and its potential impact on anemia management in clinical practice.[19]

A recent meta-analysis of randomized trials indicates that erythropoietin-stimulating agent therapy aimed at achieving higher Hb levels does not lead to a significant enhancement in QoL.[20] Here, we found no association between anemia and QoL. Similar to the results of our study, there are studies showing no significant positive correlation between Hb values and QoL.[21] Conversely, there is a study showing that lower Hb values are associated with worse QoL scores.[22] When the patient socio-demographics for those with anemia and those without were compared, only married status was found to be statistically significant. The Hb values of the married patients statistically significantly higher and were on the non-anemic side. Since we could not find a study with similar characteristics in the literature, we could not make a comparison.

Since patients receiving hemodialysis treatment due to CKD are under constant doctor control and follow-up, Hb values can fluctuate very rapidly due to immediate intervention in case of anemia. This could be a contributing factor to the absence of a positive correlation between anemia and QoL.

A significant correlation was identified for smoking status of hemodialysis patients and their QoL. However, contrary to the results of a similar study in the literature, this relationship was in favor of smoking, that is, QoL scores were higher in smokers in our study. Research indicates that smoking is potentially linked to kidney failure, and individuals who smoke heavily tend to report markedly lower QoL scores.[23] We hypothesize that the findings in this study may be attributed to the observation that younger hemodialysis patients in better physical condition were also smokers. The findings of multivariate regression analysis for PCS12 suggest that younger age, smoking status, and higher education levels are independent predictors of better physical QoL among hemodialysis patients. These findings support our hypothesis.

The QoL of adult patients with CKD receiving hemodialysis was compared to a control group without comorbidities using the WHOQOL-BREF scale in a study conducted in Brazil. It was found that smoking negatively affected the perception of QoL of both groups.[24] In this study, it was shown that hemodialysis patients' perception of QoL was positively influenced by marital status-having a spouse-. In our study, Hb values were statistically significantly higher in married patients.

In another study, the 5-level EuroQol-5 Dimension (EQ-5D-5L) tool was applied to 887 CKD patients to measure HR-QoL.[25] In this study it was shown that older age, female sex, former and current smoking status were associated with lower mean EQ-5D-5L utility score.

Limitations

This study has limitations including a small patient population. A larger patient dataset would have enhanced the reliability of the findings. Additionally, the cross-sectional design precludes any causal inferences. Potential biases, such as reporting bias, may have influenced the results, particularly as QoL scores

were elevated among smokers. Another potential selection bias is that the study was conducted in a single-center dialysis unit and excluded patients with cognitive disabilities, which may limit generalizability. Another notable limitation is that SF-12 does not capture dialysis-specific QoL issues such as fatigue, vascular access pain, or post-dialysis recovery, which could have influenced the findings. The use of a dialysis-specific QoL instrument, such as the KDQOL-36, could provide a more comprehensive assessment. Although the regression models identified statistically significant predictors of PCS12 scores, the explained variance (R^2 values) in both models was relatively low (R^2=0.135). This indicates that the included variables account for only a small portion of the total variability in physical QoL scores. However, it is important to note that a low R^2 does not preclude statistical significance of individual predictors. In regression analysis, statistically significant p-values can still be observed for independent variables that show consistent effects, especially when the sample size is adequate. Therefore, while age, smoking, and educational status were found to be significant contributors to PCS12, the modest R^2 values suggest that additional factors—such as nutritional status, depression, physical activity, and dialysis-related clinical parameters—may also influence QoL and should be considered in future models to enhance explanatory power. However, it is considered to be valuable since one of the few similar studies conducted in our country.

CONCLUSION

In this report, our goal was to determine the link between QoL and anemia in CKD patients receiving hemodialysis treatment. A significant relationship as found between the physical domain of the SF-12 survey and younger age and higher education level, but not for mental domain. It was shown that early age and a higher level of education attainment were linked to improved physical QoL. No significant relationship was found between anemia and QoL. In the presence of a higher number of patients, we think it is necessary to evaluate the effect of anemia after adjustments according to age and gender. In multicenter and prospective studies, recording and following up on treatments received by hemodialysis patients related to anemia may provide more reliable data to determine the cause-and-effect relationship.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of Ankara Etlik City Hospital Scientific Researches Evaluation Ethics Committee (Date: 31.01.2024 Decision No: AEŞH-BADEK-2024-054).

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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Examination of the behaviors of physically active adults in obtaining and confirming health information in digital environments in the case of illness

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ABSTRACT

Aims: This study aimed to examine the behaviors of adults who engage in physical activity to obtain and confirm health information in the digital environment when faced with illness. It aimed to understand how widespread access to digital health information and the ability to access accurate information shape and influence health behaviors.

Methods: This research is a quantitative study utilizing a relational screening model. The study's research group consisted of 1052 individuals aged 45 years and over who are engaged in physical activity and have a working life. Data were collected using a personal information form that included variables such as gender, marital status, sector of employment, place of residence, educational status, perceived socio-economic status, medication use, presence of a serious health problem, social media follow-up status for health, weekly physical activity status, and the Scale of Health Information Acquisition and Confirmation Behaviors in Digital Media in Infodemia developed by Çömlekçi and Bozkanat (2021).

Results: The findings revealed significant differences in the behaviors of obtaining and confirming health information in the digital environment across the variables of gender, marital status, educational status, socioeconomic status, medication use, social media health information following, and weekly physical activity level. It was concluded that women, married individuals, highly educated persons, public sector employees, those with high socio-economic status, individuals who do not use medication, those who have not experienced serious health problems, and those who follow health-related social media have higher health information acquisition behaviors in the digital environment.

Conclusion: The study suggests notable differences in digital health information acquisition behaviors based on various demographic factors. The findings highlight the importance of improving digital literacy training for health professionals and digital health information providers and the development of public health policies to accelerate the adoption of healthier behaviors across society.

Keywords: Physical activity, adult individuals, obtaining health information, digital media

INTRODUCTION

Physical activity is of great importance for individuals to maintain a healthy life and support their physical and mental well-being.[1,2] Today, many individuals resort to digital resources to access the most up-to-date information while doing sports or planning exercise.[3,4] Especially physically active individuals need reliable health information to improve their performance, reduce the risk of injury, and maintain healthy lifestyles.[5,6]

Technological developments and widespread use of the internet have led to radical changes in the way individuals access health information.[1,5] Today, many adults primarily search in digital environments to obtain information about exercise programs or to assess their health status.[3,4] According to the World Health Organization (WHO), approximately 70% of internet users globally search for health-related information from online sources.[7] However, the ease of access to digital health information brings with it the risk of information pollution and misdirection.[8,9]

How individuals evaluate the health information they obtain from the internet and how this information affects their decisions to apply to health institutions is an important research topic in terms of public health.[10,11] Especially during the COVID-19 pandemic, individuals have turned to digital resources to evaluate their symptoms and learn

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about treatment options.[12,13] However, problems with the reliability of digital health information may cause individuals to make wrong decisions and undermine their trust in health systems.[14,15] At this point, the ability to access reliable information and trust in health professionals directly affects individuals' health decisions.[16,17] According to WHO reports, inaccurate health information creates an additional burden on health systems by leading to unnecessary concerns, incorrect treatment methods, and delayed hospital admission behaviors.[18] Therefore, increasing the ability to assess the accuracy of digital health resources is of great importance for public health policies.[19,20]

From the perspective of individuals engaged in physical activity, access to accurate health information and reliable evaluation of this information play a vital role in exercise planning and prevention of sports injuries. In this context, training programs and awareness-raising activities to improve digital health literacy support individuals' healthy life processes and minimize the risks that may be posed by false information sources.[21]

This study aims to examine the behaviors of adults who engage in physical activity in obtaining and confirming health information in the digital environment. Within the scope of the study, individuals' digital health literacy levels, their ability to distinguish reliable information sources, and the effect of the information they obtain from the internet on their health service seeking will be evaluated. It is expected that the findings obtained will provide recommendations to better understand the health behaviors of individuals and to make access to health services more conscious.

METHODS

Ethics

This study was carried out with the permission of Kırıkkale University Social and Human Sciences Researches Ethics Committe (Date: 17.03.2025, Decision No: 3/25). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Research Model

This research is a quantitative study conducted to examine the health information acquisition and confirmation behaviors of adult individuals engaged in physical activity in a digital environment. It was planned in the relational screening model, one of the general screening models. The relational survey model is among the studies aiming to determine the existence or degree of change between two or more variables.[22]

Research Group

The study group of this research consists of adult individuals aged 45 and over who are engaged in physical activity and are in working workforce. The number of participants is n=1052. Participants were determined voluntarily basis and consisted of individuals with various demographic characteristics that may affect their behaviors of obtaining and confirming health information in the digital environment.

Data Collection

In this study, a personal information form including variables such as gender, marital status, sector of employment, place of residence, educational status, perceived socio-economic status, medication use, whether there is a serious health problem, social media follow-up status for health, weekly physical activity status, and the 'Scale of Health Information Acquisition and Confirmation Behaviors in Digital Media in Infodemia' developed by Çömlekçi and Bozkanat[23] was used. In the study, it was aimed to measure the tendency of adult individuals who are engaged in physical activity and working life to obtain and verify health information through digital platforms. The scale consists of 10 items and 3 sub-dimensions. The sub-dimensions are 'obtaining health information,' 'obtaining digital health information,' and 'digital confirmation.' It is graded on a 5-point Likert scale. Participants responded to each item with options ranging from 'Strongly Disagree' (1) to 'Strongly Agree' (5). The internal consistency value of the scale is 0.758.

Statistical Analysis

Cronbach's alpha analysis was performed to determine the reliability of the study. The data were found to be normally distributed, which indicates that they fulfill the prerequisites for parametric tests. Therefore, an independent samples t-test was used for pairwise group comparisons, and an ANOVA test was used for comparisons of three or more groups. In case of a significant difference, Tukey's post hoc test was applied to determine which groups the difference was between. Data were analyzed using SPSS 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The data obtained shows the demographic characteristics and physical activity levels of 1052 participants. Among the participants, 51.5% were female, 62.0% were single, 51.9% worked in the private sector, 50.5% lived in urban areas, 46.6% had a bachelor's degree, 66.3% had a medium perceived socio-economic status, 72.4% did not use medication, 56.5% had no previous serious health problems, 58.0% followed social media for health, and 50.4% did physical activity 1-2 days a week (**Table 1**).

Shows that there is a significant difference in 'health information,' 'digital health information,' and 'health information in total digital environment' of the scale according to the variables of gender, marital status, and place of residence according to the scale of health information acquisition and confirmation levels in the digital environment of adult individuals engaged in physical activity. In terms of the sector they work in, it was seen that there was a statistically significant difference in all sub-dimensions in favor of adults working in the public sector (**Table 2**).

Shows that there is a statistically significant difference in the sub-dimensions of 'health information,' 'digital health information,' 'digital confirmation,' and 'health information in total digital environment' of the scale according to the

Table 1. Demographic characteristics and physical activity profile of the participants

Variables		n=1052	%
Gender	Male	510	48.5
	Woman	542	51.5
Marital status	Married	400	38.0
	Single	652	62.0
Sector he/she works in	Public	506	48.1
	Special	546	51.9
Where he lives	Urban	531	50.5
	Rural	521	49.5
Education status	Secondary education	108	10.3
	High school	300	28.5
	Associate's degree	154	14.6
	Bachelor's degree and above	490	46.6
Perceived socio-economic status	Low	213	20.2
	Middle	698	66.4
	High	141	13.4
Using medication	Yes	290	27.6
	No	762	72.4
Previous serious health problem	Yes	458	43.5
	No	594	56.5
Social media monitoring for health	Yes	610	58.0
	No	442	42.0
Weekly physical activity level	1-2	530	50.4
	3-4	312	29.7
	5+ days	210	19.9

level of obtaining and confirming health information in the digital environment and the educational status variable of adult individuals engaged in physical activity ($p<0.001$). This significant difference shows that adult individuals with higher education levels have the highest scores, in favor of adult individuals with higher education levels (Table 3).

Shows that there is a statistically significant difference in the sub-dimensions of 'health information,' 'digital health information,' 'digital confirmation,' and 'health information in total digital environment' of the scale according to the levels of obtaining and confirming health information in a digital environment and the perceived socio-economic status variable of adult individuals engaged in physical activity ($p<0.001$). It shows that this significant difference is in favor of adult individuals with higher perceived socio-economic levels (Table 4).

Shows significant differences in the digital health information acquisition and confirmation scale (DHIACS) based on medication use, serious health problems, and social media monitoring for health (Table 5).

Shows that there is a statistically significant difference in the sub-dimensions of 'health information,' 'digital health information,' 'digital confirmation,' and 'health information in total digital environment' of adult individuals who perform physical activity according to the level of weekly physical activity ($p<0.001$). This difference shows that the scores are highly in favor of those who do 5 or more weekly physical activities (Table 6).

Table 2. Comparison of adult individuals engaged in physical activity according to gender, marital status, sector of employment and place of residence with digital health information acquisition and confirmation scale (DHIACS)

Variables			t	p	Cohen's d	Descriptor
Gender	**Female (n=510)**	**Male (n=542)**				
Health information	8.13±2.6	7.54±2.8	2.661	0.005 *	0.22	Small
Digital health information	7.54± 3.2	6.13± 3.0	3.050	0.001*	0.45	Middle
Digital confirmation	11.39± 3.9	11.26± 4.0	0.539	0.590	0.03	Small
DHIACS	27.42±7.5	25.23± 7.1	2.371	0.005*	0.30	Small
Marital status	**Married (n=400)**	**Single (n=642)**				
Health information	8.42±2.9	7.69±2.5	0.820	0.005*	0.27	Small
Digital health information	7.72± 2.6	6.77± 2.5	-5.942	0.001*	0.37	Middle
Digital confirmation	11.52± 4.2	11.20± 3.8	1.217	0.224	0.08	Small
DHIACS	27.67± 8.1	25.14± 6.9	-1.096	0.001*	0.34	Middle
Sector he/she works in	**Public (n=506)**	**Private (n=546)**				
Health information	8.02±2.6	7.50±2.8	3.148	0.005*	0.19	Small
Digital health information	7.66± 2.7	6.39± 2.4	1.942	0.001*	0.50	Middle
Digital confirmation	11.93± 3.9	10.77± 4.1	4.737	0.001*	0.29	Small
DHIACS	27.12±7.1	25.51± 7.4	4.465	0.001*	0.22	Small
Where he lives	**Urban (n=531)**	**Rural (n=521)**				
Health Information	7.91±2.7	7.14±2.6	-0.599	0.005*	0.29	Small
Digital health information	7.69± 2.1	6.33± 2.4	-0.421	0.001*	0.60	Big
Digital confirmation	11.88± 3.6	11.10± 4.1	0.315	0.753	0.20	Small
DHIACS	27.73±7.4	25.34± 7.2	-0.198	0.001*	0.33	Middle

*p< 0.001, *p< 0.005

Table 3. Comparison of adults engaged in physical activity according to educational status based on DHIACS

Variables	Secondary education[1] (n=108)	High school[2] (n=300)	Associate degree[3] (n=154)	Licence and above [4] (n=490)	F	p	Tukey
Health information	6.18±2.5	7.56±2.8	7.97±2.9	8.50±2.5	18.639	0.001*	1<2<3<4
Digital health information	4.6±2.1	6.10±2.5	6.90±2.6	7.14±2.6	25.408	0.001*	1<2<3=4
Digital confirmation	9.4±3.9	11.1±4.5	11.6±4.1	12.12±3.6	11.908	0.001*	1<2=3<4
DHIACS	20.3±7.0	24.7±7.8	26.3±6.5	27.72±7.3	28.180	0.001*	1<2<3<4

DHIACS: Digital health information acquisition and confirmation scale, *p<0.001

Table 4. Comparison of adults engaged in physical activity according to perceived socio-economic status based on DHIACS

Variables						
Economic situation	**Low[1]**	**Medium[2]**	**High[3]**	**F**	**p**	**Tukey**
Health information	6.61±2.6	7.87±2.5	8.87±3.1	33.408	0.001*	1<2<3
Digital health information	5.59±2.5	6.50±2.6	7.26±3.1	22.271	0.001*	1<2<3
Digital confirmation	9.93±3.9	11.36±3.8	13.2±4.5	29.968	0.001*	1<2<3
DHIACS	22.05±7.3	25.73±6.6	29.4±8.6	47.072	0.001*	1<2<3

DHIACS: Digital health information acquisition and confirmation scale, *p<0.001

Table 5. Comparison of adults engaged in physical activity according to medication use, serious health problems, and social media monitoring for health based on DHIACS

Variables						
Using medication	Yes (n=290)	No (n=762)	t	p	Cohen's d	Descriptor
Health information	7.12±2.5	8.17±2.7	-3.124	0.001*	0.40	Middle
Digital health information	6.34±2.6	7.60±2.6	-1.553	0.001*	0.48	Middle
Digital confirmation	11.14±3.9	11.81±4.0	-2,420	0.184	0.17	Small
DHIACS	25.24±7.6	27.10±6.6	-3.039	0.001*	0.26	Small
Serious health problem	Yes (n=458)	No (n=594)				
Health information	7.36±2.7	8.06±2.6	-4.166	0.001*	0.26	Small
Digital health information	5.98±2.6	6.81±2.7	-4,506	0.001*	0.31	Middle
Digital confirmation	10.72±4.1	11.79±3.9	-4.297	0.001*	0.27	Small
DHIACS	24.10±7.6	26.56±6.9	-5.491	0.001*	0.34	Middle
Social media monitoring for health	Yes (n=610)	No (n=442)				
Health information	9.12±2.1	8.11±2.2	-2.421	0.001*	0.47	Middle
Digital health information	8.70±2.3	7.10±2.1	-1,531	0.001*	0.73	A lot big
Digital confirmation	10.61±3.4	9.13±3.3	-1.235	0.001*	0.44	Middle
DHIACS	27.73±7.2	25.17±7.2	-1.657	0.001*	0.36	Middle

DHIACS: Digital health information acquisition and confirmation scale, *p<0.001

Table 6. Comparison of adults engaged in physical activity according to weekly physical activity status based on DHIACS

Variables						
Weekly physical activity	**1-2 days[1] (n=530)**	**3-4 days[2] (n=312)**	**5 to the power [of 3] (n=210)**	**F**	**p**	**Tukey**
Health information	6.62 ± 2.1	7.40 ± 2.2	10.88 ± 2.3	1,865	0.001*	1<2<3
Digital health information	7.23 ± 2.4	8.2 ± 2.3	8.5 ± 2.2	1,940	0.001*	1<2=3
Digital confirmation	9.10 ± 3.1	10.9 ± 3.6	11.0 ± 3.1	2,420	0.001*	1<2=3
DHIACS	24.1 ± 2.7	27.1 ± 2.2	29.6 ± 2.6	2,326	0.001*	1<2<3

DHIACS: Digital health information acquisition and confirmation scale, *p<0.001

DISCUSSION

The aim of this study is to examine the behaviors of adults who engage in physical activity in obtaining and confirming health information in a digital environment. According to the findings obtained from the levels of obtaining and confirming health information in the digital environment of adult individuals engaged in physical activity according to gender, marital status, and place of residence variables,

it was determined that there was a significant difference in the sub-dimensions of "obtaining health information," "obtaining digital health information," and total obtaining health information in the digital environment" of the scale, and this difference was determined by the fact that the scores were high and the effect sizes were small in favor of women, married people, and those living in urban areas. In terms of the sector of employment, it was observed that adults engaged in physical activity working in the public sector had higher scores in all sub-dimensions than adults engaged in physical activity working in the private sector. As a result, women scored higher in obtaining digital health information than men. In addition, married individuals scored higher on acquiring health information than single individuals. These results indicate that gender and marital status may affect individuals' health information acquisition habits. It can be thought that women are more likely to acquire health information than men and that married individuals make more effort in terms of health literacy both for themselves and for other members of the family. It is observed in the study that individuals living in urban areas are luckier than those living in rural areas in terms of accessing information and that they use this opportunity well. It was concluded that living in cities, working in the public sector, being married, and being a woman are associated with high health literacy. When the literature is examined, it is seen that women's behaviors of obtaining and confirming digital health information are higher than men's.[24-26] Akgün and Toker[25] stated in their study that the digital health information acquisition and confirmation behaviors of married people were higher than those of single people. This study is similar to other studies. Balcı et al.[27] stated that men had higher levels of obtaining health information in digital environments compared to women.

It was observed that there was a significant difference in the levels of obtaining and confirming health information in a digital environment and in the sub-dimensions of "obtaining health information," "obtaining digital health information," "digital confirmation," and total obtaining health information in a digital environment" of the scale. This significant difference was found to be high in individuals with bachelor's degrees and above and low in secondary education. As a result, as the level of education increases, the awareness of obtaining health information also increases, which means that higher education levels can increase digital literacy, and individuals can evaluate health information more accurately. Temel and Güzel[26] stated in their study that the scores of individuals with associate, undergraduate, and graduate education levels on the scale of obtaining and confirming health information in a digital environment were higher than those of individuals with primary, secondary, and high school education levels.

According to the perceived socio-economic status variable, it was observed that there was a difference in the levels of obtaining and confirming health information in the digital environment and the sub-dimensions of "obtaining health information," "obtaining digital health information," "digital confirmation," and total health information in the digital environment" of the perceived scale, and this difference was seen in that the scores of adult individuals with high perceived socio-economic status in all sub-dimensions of the scale were higher than those with low perceived socio-economic status. As a result, it has been observed that adults with high economic status have better health awareness than adults with low economic status and that they use and confirm digital means to access the necessaryhealth information. This shows that inequalities in access to health information can negatively affect individuals' health decision-making processes. Individuals with higher socioeconomic status are better equipped to access and verify more information. In Temel and Güzel's[26] and Jung's[28] studies, it was stated that the behaviors of individuals with high perceived socioeconomic status to obtain and verify digital health information were higher than those of individuals with low socioeconomic status. It is similar to the research.

According to the variables of medication use status, history of serious health problems, and following social media for health, there is a significant difference in all sub-dimensions of the scale with the level of obtaining and confirming health information in the digital environment of adult individuals who engage in physical activity, and the scores in all sub-dimensions of the scale are high in favor of those who do not use medication. According to the variable of having a serious health problem, it was seen that the scores were high in all sub-dimensions of the scale in favor of those who said that they did not have a serious health problem, and according to the variable of following social media for health, it was seen that the scores of obtaining health information in a digital environment were high in all sub-dimensions of the scale in favor of those who said, Yes, I follow social media for health. The effect of social media follow-up on digital health information acquisition was found to be large and excellent. It is thought that the high scores of individuals who are in the working environment, who do physical activity, and those who say that they do not use medication; those who say that they do not have serious health problems; and those who say that they follow social media for health have such good scores because they have gained health literacy and have developed awareness about health. Aydemir and Yaşar[29] stated in their study in 2023 that as health literacy increases, the behavior of obtaining health information in digital environments also tends to increase. Akgün and Toker[25] stated in 2023 that those who said yes to having a serious health problem before had high scores for "obtaining health information" and "obtaining digital health information," while those who said no had high scores for "digital confirmation." Akgün and Toker[25] stated that those who said yes to following a social media page about health in 2023 had high scores in all sub-dimensions of obtaining health information in a digital environment.

It was concluded that there was a significant difference in the levels of obtaining and confirming health information in the digital environment and in the sub-dimensions of "obtaining health information," "obtaining digital health information," "digital confirmation," and total obtaining health information in the digital environment" of the scale according to the weekly physical activity level variable. This difference was found to be high in favor of those who did physical activity

for 5 or more weeks. As a result, it was determined that as the level of physical activity increases, the habits of obtaining and confirming digital health information also increase. It is thought that individuals who engage in physical activity in some way in social life have adopted a healthy life on their own behalf, create awareness in order to stay healthy, and reach the information that physical activity has important effects on staying healthy.

CONCLUSION

As a result, this study highlights the significant role of various demographic and socio-economic factors in shaping individuals' behaviors regarding obtaining and confirming health information in a digital environment. Factors such as gender, marital status, employment sector, education level, perceived socio-economic status, health status, social media engagement, and physical activity level all play crucial roles in influencing digital health literacy. Women, married individuals, those with higher education, and those with higher socio-economic status were found to have better health information acquisition and confirmation behaviors. These findings underline the importance of promoting equitable access to digital health information, particularly for underrepresented groups, and suggest that targeted public health policies and educational programs should be developed to improve digital health literacy for all individuals, ensuring they can make informed decisions regarding their health. Such initiatives could potentially reduce disparities in health outcomes and minimize unnecessary healthcare usage.

RECOMMENDATIONS

In order to make the processes of confirming digital health information healthier and more reliable, training programs should be organized to increase the digital health literacy of individuals. The reliability of health information sources should be improved, and awareness about verification methods on social media platforms should be raised. In addition, health institutions should collaborate with digital platforms to disseminate accurate information, and awareness-raising activities should be initiated in society. Access to health services should be facilitated for individuals with low socio-economic status. Technological infrastructure should be strengthened to make access to digital health information more understandable and accessible, and the quality and safety of digital health services should be enhanced through legal regulations.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was carried out with the permission of Kırıkkale University Social and Human Sciences Researches Ethics Committe (Date: 17.03.2025, Decision No: 3/25).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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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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Comparison of the marginal fit of soft-machined monolithic zirconia crowns*

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ABSTRACT

Aims: The aim of this study was to compare the marginal fit of five different soft machined monolithic zirconia materials.

Methods: A mandibular right first molar on an acrylic model was prepared with standardized dimensions using diamond burs. Fifty metal duplicates were fabricated via laser sintering with Co-Cr alloy and divided into five groups (n=10). All duplicates were scanned using a CAD/CAM system, and zirconia crowns with a 1.5mm occlusal thickness and 20μm cement space were produced. Following sintering, marginal gaps were measured using the silicone replica technique. The obtained silicone replicas were sectioned into four parts mesiodistally and buccolingually using a scalpel. The marginal gaps of the samples were examined using a stereomicroscope under 10×magnification. Marginal gap measurements were performed at four specific points where the crown margin was closest to the cemento-enamel junction: mesial, distal, buccal, and lingual. For each crown, the measurements were repeated three times, and the mean value was recorded. A total of 600 measurements were performed for 50 crowns. Statistical analysis was conducted using one-way ANOVA and Tukey's HSD test ($p<0.05$).

Results: Significant differences were found among the zirconia groups ($p<0.001$). Zenostar exhibited the highest marginal gap (92±22μm), followed by Katana (81±18μm) and Incoris TZI (66±20μm). The lowest values were recorded in the Bruxzir (46±9μm) and Prettau (48±23μm) groups. Zenostar and Katana showed significantly larger marginal gaps compared to Prettau and Bruxzir ($p<0.05$), while Incoris TZI presented intermediate values without significant differences.

Conclusion: All tested monolithic zirconia materials demonstrated clinically acceptable marginal fit. However, notable differences were observed among materials, with Bruxzir and Prettau showing superior marginal fit compared to Zenostar and Katana.

Keywords: Yttria stabilized tetragonal zirconia, dental marginal adaptation, dental crown

*It was presented as an oral presentation at the European Prosthodontic Association Congress held on September 28–30, 2017.

INTRODUCTION

In recent years, all ceramic restorations have gained increasing importance in fixed prosthodontic treatments due to their superior aesthetic properties.[1] Among these materials, yttria-stabilized tetragonal zirconia polycrystals (Y-TZP) have become one of the most commonly used options, owing to their high flexural strength[2], low plaque accumulation[3], and exceptional resistance to fracture.[4] The development of monolithic zirconia restorations has eliminated the need for porcelain veneering, thereby reducing complications such as chipping and delamination seen in bilayered systems and further enhancing the clinical performance of zirconia.[5]

In dentistry, there are two main milling techniques used in the production of zirconia for the fabrication of dental crowns and fixed partial dentures: soft machining and hard machining. In the soft machining technique, partially sintered zirconia blocks with lower density are milled, followed by a final sintering process to achieve full densification. In contrast, the hard machining technique involves milling fully sintered, high-density zirconia blocks.[6,7] Due to the high hardness and density of fully sintered blocks, hard machining is associated with increased tool wear, longer processing times, and the potential formation of microcracks during fabrication.[8] Soft machining, on the other hand, overcomes these challenges by offering a more efficient and cost-effective manufacturing process. Moreover, the approximate 20% shrinkage that occurs during sintering is digitally compensated during the design stage, ensuring dimensional accuracy of the final product.[9] For these reasons, soft machining has become the preferred method in the fabrication of monolithic zirconia restorations.

The clinical success and overall quality of restorations are largely determined by their fit to the prepared tooth, with

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marginal fit being one of the most critical factors affecting the long-term success of fixed prosthetic restorations.[4] The marginal gap was defined as the vertical or horizontal space between the finish line of the prepared tooth and the edge of the restoration. Inadequate marginal fit can compromise the integrity of the restoration by leading to microleakage, cement dissolution[10], bacterial infiltration[11], secondary caries[12], and periodontal inflammation.[13] According to the literature, marginal gaps up to 120µm were considered clinically acceptable; however, minimizing this gap is always preferable.[14]

The physical properties of zirconia materials can vary depending on factors such as their chemical composition[15], grain size[16], sintering protocol[17], translucency level and additive content.[18] These variations can affect the material's adaptation behavior to the prepared tooth surface. Therefore, comparing the marginal fit of different zirconia types is of great importance for clinical material selection.

Although various measurement methods have been used by researchers to evaluate marginal fit, the silicone replica technique is widely preferred due to its ease of application and high reproducibility. This method uses low- and high-viscosity silicone materials to create a negative mold of the gap between the crown and the prepared tooth.[19] This allows for indirect but highly precise measurements of marginal fit without damaging the restoration, making it an ideal technique for both in vitro and clinical studies.[20]

The aim of this in vitro study was to compare the marginal fit of five different soft machined monolithic zirconia materials Bruxzir, Katana, Prettau, Zenostar, and InCoris TZI. The null hypothesis of the study was that there would be no significant difference in the marginal fit among the different zirconia materials.

METHODS

This study did not require ethical approval as it did not involve any human subjects or animal experiments. The research was carried out in accordance with the ethical standards applicable to in vitro studies. In this study, the preparation of the mandibular right first molar on an acrylic jaw model (Ivoclar-Vivadent, Schaan, Liechtenstein) was performed using diamond burs (229-014XC Torpedo, Romidan, Kiryat-Ono, Israel) with a rotary instrument. The occlusal surface was reduced by 2 mm, and all other surfaces by 1.5 mm. The prepared tooth had a chamfer finish line with a thickness of 1mm, a 6°taper, a height of 4 mm, a mesiodistal dimension of 8mm, and a buccolingual dimension of 6 mm. Based on the prepared acrylic tooth, a total of 50 duplicates were fabricated via laser sintering using a Co-Cr alloy (Dentorium, New York, USA), with ten specimens produced for each experimental group. The metal duplicates were scanned using a CAD/CAM system (Yenamak D40, Yenadent, İstanbul, Turkiye), and zirconia crowns with a 1.5 mm occlusal thickness and a cement space of 20 µm were fabricated. Subsequently, all crowns underwent a sintering process. The compositions of the zirconia materials used in the study and the sintering temperatures applied were presented in **Table 1**. The marginal gap measurements were evaluated using the silicone replica technique. A low-viscosity silicone impression material (Elite HD+, Zhermack, Italy) was applied to the internal surface of each crown, which was then seated onto the prepared tooth under standardized manual pressure for five minutes. After setting, the crowns containing the light-body material were carefully removed, and a high-viscosity silicone material (Elite HD+, Zhermack, Italy) was poured into the crown to support the thin replica layer. The obtained silicone replicas were sectioned into four parts mesiodistally and buccolingually using a scalpel. The marginal gaps of the samples were examined using a stereomicroscope (ZEISS Stemi 2000-C, Oberkochen, Germany) under 10×magnification. Marginal gap measurements were performed at four specific points where the crown margin was closest to the cemento-enamel junction: mesial, distal, buccal, and lingual. For each crown, the measurements were repeated three times, and the mean value was recorded. A total of 600 measurements were performed for 50 crowns. The marginal gap of all crowns, with 10 crowns in each group, was evaluated by the same operator. The analyses were conducted using the commercial software IBM SPSS Statistics version 19 (IBM Inc., Somers NY, USA). One-way ANOVA followed by Tukey's HSD post hoc test was used for statistical analysis. All data were presented as mean±standard deviation (SD). A p-value of <0.05 was considered statistically significant.

RESULTS

The mean marginal gap values of the tested monolithic zirconia groups were presented in **Table 2**. Statistically significant differences were observed among the groups ($p<0.001$). The Zenostar group showed the highest mean marginal gap value (92±22 µm), followed by Katana (81±18 µm) and Incoris TZI (66±20 µm). The lowest values were observed in the Bruxzir (46±9 µm) and Prettau (48±23 µm) groups. According to the results of the Tukey HSD post hoc test, the marginal gap values of Katana and Zenostar were significantly higher than those of Prettau and Bruxzir ($p<0.05$). While Incoris TZI did not show a statistically significant difference compared to the other groups, Prettau differed significantly from Katana and Zenostar. However, there was no statistically significant difference between Prettau and BruxZir, or between Katana and Zenostar. Despite these statistical differences, all tested zirconia materials showed marginal gaps below the clinically acceptable threshold of 120µm.

DISCUSSION

Monolithic zirconia restorations have gained increasing popularity in fixed prosthodontics due to their enhanced mechanical strength, high fracture resistance, and reduced risk of chipping compared to veneered zirconia systems.[21,22] In addition to their structural advantages, their monolithic nature allows for simplified fabrication workflows and the elimination of layering ceramics, which are typically associated with technical complications. Furthermore, their low surface roughness and favorable biocompatibility make them a viable option for long-term clinical success.[3]

In addition to high fracture resistance, low surface roughness, and favorable biocompatibility, marginal fit plays a crucial role among the key parameters influencing the clinical longevity

Table 1. The materials used with brand name, manufacturer, material composition, sintering temperature and grain size

Brand name	Manufacturer	Material composition	Sintering temperature (°C)	Dwell time	Grain size
Incoris TZI	Sirona	-ZrO_2+HfO_2+Y_2O_3:≥99.0% -Y_2O_3: 5.6% (Σ Y_2O_3+Er_2O_3) -Al_2O_3:≤0.35% -Other oxides (excluding Er_2O_3):≤0.2%	1510°C	2h	0.4µm
Prettau anterior	Zirkonzahn	-ZrO2+Y_2O_3+HfO_2 ≥ 99.0% -Y_2O_3>4.5 to≤6.0, HfO_2≤5% -Al_2O ≤ 0.5% -Other oxides≤0.5%.	1600°C	2h	0.58µm
Katana UTML	Kuraray noritake	-ZrO_2+HfO_2+Y_2O_3>99.0% -Yttrium oxide (Y_2O_3)>4.5 -Hafnium oxide (HfO_2)≤6.0% -Other oxides≤5.0% -Fully stabilized zirconia≤1.0%	1550°C	2h	Unknown
Zenostar translucent	Ivoclar	-ZrO_2 Y_2O_3: 4–6% -Al_2O_3<1% -SiO_2<0.02% -Fe_2O_3<0.01% -Na_2O<0.04%	1450°C	2h	0.3µm
Bruxzir zirconia	Glidewell	-ZrO_2 Yttria	1580°C	2h	0.3–0.7µm

Table 2. Mean and SD of marginal gaps between the zirconia crowns

Groups	n	Marginal gap (µm)
		Mean±SD
Incoris TZI	10	66±20 (ab)
Prettau	10	48±23 (b)
Katana	10	81±18 (a)
Zenostar	10	92±22 (a)
Bruxzir	10	46±9 (b)
		p<0.001

SD: Standard deviation, *Different letters indicate statistically significant difference between groups (p<0.05)

of fixed prosthetic restorations. An insufficient marginal fit may lead to complications such as microleakage, cement dissolution, secondary caries, and periodontal inflammation, potentially compromising both the restoration and the supporting tooth structure.[23,24] Thus, evaluating the marginal fit of zirconia materials remains a relevant and valuable pursuit in prosthetic dentistry.

This study aimed to provide evidence-based guidance for clinicians in optimizing restoration fit and longevity by simultaneously evaluating the marginal fit of five popular soft machined monolithic zirconia brands.

In the present in vitro study, the marginal fit of monolithic zirconia materials was evaluated using the silicone replica technique. Statistical analysis showed a significant difference between the groups. In our study, the marginal gap measurements of monolithic zirconia crowns were determined as follows: 46±9 µm for BruxZir, 48±23 µm for Prettau, 66±20 µm for InCoris TZI, 81±18 µm for Katana, and 92±22 µm for Zenostar. This indicates that the type of zirconia material can influence marginal fit. Therefore, the null hypothesis of the study was rejected.

McLean and von Fraunhofer evaluated the marginal fit of 1000 fixed prosthetic restorations over a five-year period and reported that marginal discrepancies less than 80 µm are difficult to detect under clinical conditions.[14] Therefore, they proposed a clinically acceptable marginal gap threshold of 120 µm. Although statistically significant differences were observed among the materials, all values obtained in the present study were below 120 µm, demonstrating marginal fit within the clinically acceptable limits defined by McLean and von Fraunhofer.[14]

Ceramic manufacturers produce zirconia ceramics with different sintering temperatures and grain sizes (**Table 1**). To obtain aesthetically acceptable monolithic restorations from the highly white Y-TZP, certain modifications in its optical properties have been necessary. These include adjustments made during the manufacturing process, such as reducing crystal size, increasing sintering temperature, and altering yttrium content to enhance translucency and better replicate the natural tooth color.[25] Additionally, the color of zirconia can be adjusted by adding other oxides.[18] It has been shown that the material composition of zirconia affects the quality of the crown margin and, consequently, the marginal fit.[15] To promote the transformation from the tetragonal to the monoclinic phase for crack arrest and fracture toughness, while preventing undesirable phase transformation, a grain size between 0.2–1.0 µm is recommended for 3Y-TZP.[26] The grain sizes of all materials in the present study fall within this range. The polycrystalline density affects the strength of zirconia.[27] Stawarczyk et al.[7] reported that the grain size of zirconia increases with rising sintering temperatures. A decrease in the sintering temperature results in smaller grain sizes, which may lead to insufficient phase transformation and inadequate material density.[25] The desired sintering temperature for 3Y-TZP should be between 1350–1550°C. In the present study, although the sintering temperatures of the zirconia materials used were within the ideal range, Prettau and BruxZir, which had the highest sintering temperatures, exhibited the lowest

marginal gap values. Katana, which had the lowest sintering temperature, was found to have the highest marginal gap. Further studies are needed to investigate the correlation between grain size and sintering temperature. However, this may be attributed to the complex production processes involved in soft machining. During sintering, approximately 20% shrinkage occurs, which must be accurately anticipated and compensated for.[28] To accommodate this shrinkage, soft-machined zirconia frameworks are over-milled prior to sintering. However, this compensation may not always be precisely predictable, potentially leading to variations in marginal fit. Therefore, the findings of our study suggest that dimensional changes due to sintering in the soft-machining process can have an impact on the marginal fit. Additionally, Schwiver et al.[15] reported that marginal defects occurred in crowns as a result of the soft machining procedure, and these defects are likely to negatively affect marginal fit. Since the ceramics evaluated in this study differ in terms of composition, sintering temperature, and grain size, it was not possible to clearly determine which specific factor influenced the marginal fit.

When examining previous studies on the marginal fit of zirconia, Shembesh et al.[29] evaluated the effect of four different impression techniques on marginal gap values and reported that Zenostar zirconia crowns exhibited marginal gaps ranging from 26.6 µm to 81.4 µm. In another study by Ji et al.,[30] the marginal fit of Prettau and Zenostar zirconia crowns produced using different CAD/CAM systems was assessed, with reported marginal gaps of 109 µm for Prettau and 84.7 µm for Zenostar. Kale et al.[31] investigated the influence of different cement space settings on the marginal fit of monolithic zirconia crowns, finding values between 53 µm and 85 µm. Kocaağaoğlu et al.[32] measured the marginal gap of monolithic zirconia crowns using three different digital scanning methods, reporting results ranging from 47.7 µm to 85.6 µm. The mean cement gap in the present study ranged from 46 µm to 92 µm, and these values were consistent with the marginal gap measurements reported in the previous studies.

Sachs and colleagues stated that the accuracy of marginal gap measurements in zirconia was also influenced by the scanning method, restoration design, milling, and sintering procedures.[33] Upon reviewing the literature, it was observed that there was no standardization for the measurement of marginal gaps. The marginal measurement methods used in the studies[34-42], the applied ceramic production techniques (e.g., CAD/CAM or casting)[34,36,39,43-45], the type of finishing line of the dental preparation[34,46,47], and variables such as the number of measurements taken per sample[45,48,49] are observed. Due to differences in the monolithic zirconia materials used, the finish line design of the preparations, marginal gap measurement methods, cement space settings, manufacturing systems, and the number of measurements taken per specimen, it is not possible to make a direct comparison with previous studies. Nevertheless, all marginal gap values obtained in the present study were found to be within the clinically acceptable range of 120 µm.

Limitations

This study has several limitations that should be acknowledged. Firstly, the investigation was limited to soft-machined monolithic zirconia crowns; fully sintered (hard-machined) zirconia restorations were not included in the comparison. Secondly, all marginal gap evaluations were conducted using a fixed cement space of 20 µm, which may not reflect the variations encountered in clinical practice. Additionally, the marginal gaps were assessed using the silicone replica technique, which, while widely used, could be complemented or validated by more advanced methods such as micro-computed tomography. Furthermore, only a single CAD/CAM system was employed; the influence of different scanning and milling systems on marginal fit remains to be explored. Lastly, the measurements were performed prior to cementation. Since the cementation process can affect the final fit of restorations, future studies should include post-cementation evaluations for a more comprehensive analysis.

CONCLUSION

All tested monolithic zirconia materials demonstrated clinically acceptable marginal fit. However, notable differences were observed among materials, with Bruxzir and Prettau showing superior marginal fit compared to Zenostar and Katana.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study did not require ethical approval as it did not involve any human subjects or animal experiments.

Informed Consent

Because the study has no study with human and human participants, no written informed consent form was obtained.

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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Accelerated recovery protocol in total knee replacement patients: reducing pain and opioid consumption with adductor canal block

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ABSTRACT

Aims: This study aims to evaluate the effects of ultrasound-guided adductor canal block (ACB) on postoperative pain control, opioid consumption, and discharge time in total knee arthroplasty (TKA) operations performed in accordance with enhanced recovery after surgery (ERAS) protocols.

Methods: This prospective randomized controlled trial was conducted at Pamukkale University Hospital after obtaining ethical approval. A total of 60 patients who underwent TKA under spinal anesthesia were randomly assigned into two groups. Group I received only local infiltration analgesia (LIA), while group II received both LIA and an ACB. The groups were compared in terms of postoperative Visual Analog Scale (VAS) score at rest and during first ambulation, comparison of tramadol use, dosage, and side effects, time to first ambulation, ambulation distance, quadriceps muscle strength scores, and patient satisfaction and hospital discharge times.

Results: Group II showed consistently lower VAS scores compared with group I at all time points, including rest, walking, and sleep ($p<0.05$). Opioid consumption was significantly higher in group I ($p=0.027$), and readiness for discharge was delayed in group I compared with group II ($p<0.05$).

Conclusion: In patients undergoing TKA, the combination of LIA and ACB appears to be an effective option in multimodal analgesia practices during the postoperative period and may provide potential benefits in accelerating recovery and reducing opioid-related side effects.

Keywords: Adductor canal block, functional recovery, knee arthroplasty, opioid consumption, postoperative pain, regional anesthesia

INTRODUCTION

Prof. Dr. Henrik Kehlet pioneered the development of enhanced recovery after surgery (ERAS) protocols in the 1990s, which aim to accelerate the recovery process after surgery. These protocols include a comprehensive approach, starting from the preoperative preparation period, through the patient's discharge and recovery at home.[1] In 2019, the ERAS Association published a consensus report that includes recommendations for the implementation of these protocols in total knee and hip replacement surgeries, including patient education, development of anesthesia practices, and the use of multimodal analgesia methods.[2]

Effective pain management after total knee arthroplasty (TKA) is critical to patient recovery. A multimodal analgesia approach is recommended for pain control after TKA, and peripheral nerve blocks (PNBs) are essential to this strategy.[3] PNBs may offer several advantages compared to central blocks, especially in patients with comorbidities such as dementia and opioid addiction.[4] Opioid use in multimodal analgesia can lead to complications, such as nausea, vomiting, and decreased intestinal motility, resulting in prolonged hospital stays.[5] Adductor canal block (ACB) is considered a method that provides analgesia like femoral nerve blocks. ACB is especially preferred in lower limb surgeries such as total knee replacement, anterior cruciate ligament reconstruction, and meniscus repair because it provides effective pain control without causing loss of quadriceps muscle strength.[6]

The hypothesis of our study is that ACB will provide effective analgesia, alleviate postoperative pain, reduce opioid requirements, and shorten the hospital stay of patients. Accordingly, this study aimed to evaluate the effects of ultrasound-guided ACB on postoperative pain control, opioid consumption, and discharge time in TKA operations performed in accordance with ERAS protocols.

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METHODS

This prospective randomized controlled trial was conducted at Pamukkale University Hospital between January 8 and October 30, 2020, following ethical approval obtained from the Non-interventional Clinical Researches Ethics Committee of Pamukkale University (Date: 08.01.2020, Decision No: E.1710). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients aged 18 to 40 years who underwent elective TKA under spinal anesthesia with Local infiltration analgesia (LIA) and had American Society of Anesthesiologists (ASA) classification I-III were included in this study. Patients with any of the following conditions were excluded: had already undergone TKA surgery, had coagulopathies or drug allergies, were addicted to drugs or alcohol, had infections or anatomical structural problems at the injection site, had severe liver or kidney failure, uncontrolled diabetes, neuropathy, severe heart or lung disease, were pregnant or lactation period, or were morbidly obese.

Patients were informed about the methods to be used, and their written consent were obtained for the study. Patients who refused to participate in the study or whose data were missing during follow-up were excluded from the study.

Patient selection was made using the sealed envelope randomization method and the patients were divided into two groups: group i without ACB and group II with ACB.

All patients received preemptive analgesia with oral acetaminophen 500 mg three times a day for three days preoperatively. Midazolam (0.03mg/kg/IV) was administered to patients for preoperative sedation; granisetron (3 mg/IV) was administered to patients at risk of nausea and vomiting; antibiotic prophylaxis was provided. Upon arrival in the operating theater, vital signs were monitored noninvasively following ASA standards. Intravenous access was established, and supplemental oxygen was provided via nasal cannula. The same anesthetist used 10 mg of 0.5% hyperbaric bupivacaine to perform spinal anesthesia in the lateral decubitus position. Once sensory and motor block were achieved, patients were moved to the supine position, surgery commenced, and they were recorded as group I.

In group II, following spinal anesthesia, patients were positioned supine once sensory and motor block were achieved. Then, under ultrasound guidance (GE LOGIQ-E, USA), the linear probe was used to the medial of the patella and thigh fold, and the depth was adjusted to 4 cm. The adductor canal, bounded by the femoral artery vastus medialis and sartorius muscles, is shown along the short axis and needle with an in-plane technique. For the ACB, a 10 cm Stimuplex (B. Braun R) needle was carefully inserted approximately 2.5 cm into the canal. Initially, the patient was administered 2 ml of a test dose from a 20 ml mixture containing 15 ml of 0.5% bupivacaine, 4 ml saline, and 1 ml epinephrine. Upon successful verification of the needle placement, the remaining anesthetic mixture was given to complete the block.

The Ranawat Orthopaedic Center (ROC) Cocktail (0.5% bupivacaine hydrochloride 20 ml, 50 µg fentanyl, 1 g cefazolin sodium, 0.3 ml 1:1000 epinephrine, and 50 mL %0,9 saline solution) for LIA around the knee of each patient before and after the implant was put in place by the same surgeon.

Following surgery, patients received acetaminophen intravenously at a dose of 10 mg/kg every 6 hours, not exceeding a total daily dose of 4 grams and 75 mg of intramuscular diclofenac sodium every 12 hours. Rescue analgesia, 1 mg/kg of tramadol intravenously, was provided if the Visual Analog Scale (VAS) score was above three with a maximum total daily dose of 400 mg.

The sensory block in the ACB group was evaluated by cold stimulation in the area covering the dermatome where ACB was administered. The severity of pain was measured with the VAS score both before and after surgery. VAS scores were checked hourly for the first four hours, then at 6, 12, and 24 hours, and at the time of the first ambulation. Adverse effects, the timing and distance of the first ambulation, and rescue analgesic requirements were recorded. Quadriceps muscle strength was assessed using a manual muscle test, scored from 0 to 5 before and 24 hours after surgery.

The Post-Anesthesia Discharge Scoring System (PADSS), which rates criteria such as vital signs, ambulation, postoperative nausea/vomiting, pain, and surgical site bleeding, assesses patients within the first 24 hours following ambulation. Scores ranged from 0 to 2. Patients with a PADSS score of 9 and above were eligible for discharge. A ten-point rating scale following the first ambulation was used to measure patient satisfaction (1: dissatisfied; 10: completely satisfied).

The primary outcome measure of the study was determined as VAS scores measured at rest and during the first ambulation within 24 hours postoperatively. Secondary outcome measures were determined as postoperative tramadol use, dosage, and side effects related to opioid use; first ambulation time in terms of functional recovery, ambulation distance, and patient satisfaction with quadriceps muscle strength at the 24th hour postoperatively and time to be ready for discharge.

Statistical Analysis

The sample size was calculated based on the study by Kastelik et al.[7] A substantial effect size (d=0.7) was used for power analysis, and it was estimated that when at least 26 participants were present for each group, 95% confidence and 80% power would be achieved. SPSS version 25.0 was used to analyze the data. Continuous variables were presented as mean±standard deviation, while categorical variables were reported as counts and percentages. Between-group comparisons were conducted using independent T-tests and Mann-Whitney U tests, and within-group changes were analyzed using the Friedman test. Categorical data were evaluated using Pearson's Chi-square test. A p-value of <0.05 was considered statistically significant.

RESULTS

We successfully enrolled 100 patients during the study period. However, 37 patients who met the exclusion criteria, which

included [specific exclusion criteria], were excluded. Initially, our study included 63 patients scheduled for TKA, allocated in two groups. Three randomized patients were excluded from the study because of failed spinal anesthesia. We included 60 patients in the analysis (Figure).

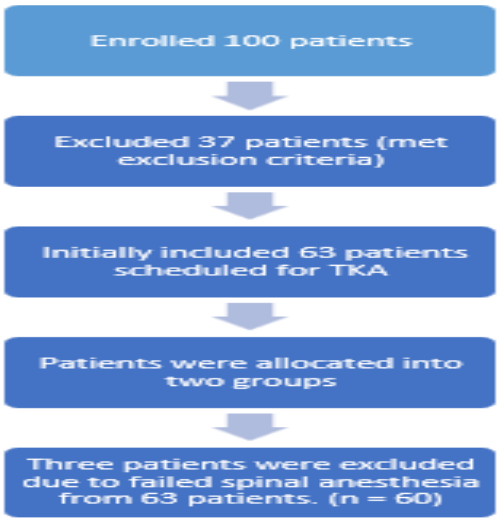

Figure. Study flowchart

The study groups were comparable in age, body-mass index (BMI), and preoperative VAS scores. Gender differences were not statistically observed between the groups; the distribution of genders was 20% male and 80% female. Educational status was examined in the groups. While there was one patient in the illiterate group I, three patients in group II were illiterate. Two patients were who were university graduates in group II, and none in group I, and the number of primary school graduates in both groups was equal. Eleven patients (18.3%) were classified as ASA 1, 48 patients (80%) as ASA 2, and 1 patient (1.7%) as ASA 3. The groups' ASA classifications were found to be similar. Three patients (10%) in group II reported having allergies to penicillin-class medications (Table 1).

Table 1. Demographic data

	Group I (mean±SD) (n=30)	Group II (mean±SD) (n=30)	p-value
Age (years)	66.87±6.72	65.80±6.53	0.525*
BMI (kg/m²)	30.51±5.85	31.06±4.16	0.677*
Sex, n (%)			
Female	25 (83.3%)	23 (76.7%)	0.374†
Male	5 (16.7%)	7 (23.3%)	0.374†
Preoperative VAS	7.07±1.11	7.10±1.06	0.906*
ASA physical status, n (%)			
I	7 (23.3%)	4 (13.3%)	0.386† - -
II	23 (76.7%)	25 (83.3%)	
III	0 (0%)	1 (3.3%)	
Drug allergy, n (%)			
Yes	0 (0%)	3 (10%)	0.119† -
No	30 (100%)	27 (90%)	

SD: Standard deviation, p< 0.05 statistically significant difference; *: Independent T-test, †: Chi-square analysis, BMI: Body-mass index, VAS: Visual Analog Scale, ASA: American Society of Anesthesiologists

In the first 4 postoperative hours, group I had significantly higher VAS scores at rest than group II (p<0.05). After the 4th hour, VAS scores were comparable among the study groups at each time interval. Group I first ambulation VAS (5.40±1.16) was significantly higher than group II (3.90±1.09) (p<0.001) (Table 2).

Table 2. Postoperative VAS score at rest and during first ambulation

Time (hour)	Group I (mean±SD)	Group II (mean±SD)	p-value
1st	2.03±0.47	0.7±0.17	0.002*
2nd	4.43±0.77	1.77±0.27	0.000*
3rd	3.63±0.27	2.7±0.33	0.023*
4th	4.27±0.33	3.33±0.31	0.023*
6th	3.1±0.07	3.07±0.07	0.934*
8th	3.6±0.47	3.47±0.31	0.763*
10th	4.2±0.31	3.1±0.17	0.055*
12th	3.17±0.13	2.13±0.13	0.927*
24th	2.8±0.27	2.27±0.27	0.048*
First ambulation	5.40±1.16	3.90±1.09	0.000*

SD: Standard deviation, p<0.05 indicates a statistically significant difference; *: Mann Whitney U analysis of variance, VAS: Visual Analogue Scale

With a mean duration of 18.2 hours, patients in the ACB group maintained sensory blocks in the L3-L4 dermatomal distribution, indicating ACB's sustained analgesic efficacy. In group II, 13 (43.3%) patients required opioid (tramadol 1 mg/IV) rescue therapy. In group I, 18 patients received rescue therapy once, 11 patients received it twice, and 1 patient received tramadol three times. Maintenance-dose opioid (tramadol 0.5 mg/IV infusion, up to 400 mg/day) analgesia was administered to 3 patients in group I and 7 patients in group II. More opioids were used in group I, and fewer side effects were seen in group II (Table 3).

Table 3. Comparison of tramadol use, dosage, and side effects

	Number of doses	Group I (n=30)	Group II (n=30)	p-value
Tramadol use	0	0	17 (56.7)	p=0.027*
	1	18 (60%)	13 (43.3%)	
	2	11 (36.7)	0	
	3	1 (3.3%)	0	
Tramadol dose (1 mg/kg)	1.	27 (90%)	6 (20%)	p<0.05
	2.	12 (40%)	0	
	3.	1 (3.3%)	0	
Tramadol dose (0.5 mg/kg)	1.	3 (10%)	7 (23.3%)	
Side effects				
Hypotension		4 (13.3%)	0	
Nausea and vomiting		23 (76.6%)	12 (40%)	

p<0.05 indicates a statistically significant difference, *: Chi-square analysis

The time to first ambulation and ambulation distance were comparable between the groups (p>0.05). Group I had higher postoperative quadriceps strength at the 24th hour (4.33±0.61) compared to group II (3.97±0.32) (p=0.05) (Table 4).

Table 4. Time to first ambulation, ambulation distance, and quadriceps muscle strength scores

	Group I (mean±SD) (n=30)	Group II (mean±SD) (n=30)	p-value
First ambulation time (hours)	4.95±1.50	5.0±1.82	0.908
Ambulation distance (minutes)	305.0±151.06	393.33±201.60	0.060
Preoperative quadriceps strength	2.83±0.59	3.03±0.49	0.160
Postoperative quadriceps strength	4.33±0.61	3.97±0.32	0.005

SD: Standard deviation, p<0.05 indicates a statistically significant difference, *: Independent T-test

Patient satisfaction at discharge was significantly higher in group II (8.57±0.90) than in group I (7.53±0.63) (p<0.001). Group II time to hospital discharge was significantly shorter compared to group I (23.15±3.28 vs 30.25±3.77, respectively) (p<0.001) (Table 5).

Table 5. Patient satisfaction and hospital discharge times

	Group I (mean±SD) (n=30)	Group II (mean±SD) (n=30)	p-value
Patient satisfaction at discharge	7.53±0.63	8.57±0.90	<0.000*
Time to hospital discharge (hours)	30.25±3.77	23.15±3.28	<0.000*

p<0.05 statistically significant difference, *: Mann-Whitney U analysis of variance, Patient satisfaction (1 not at all satisfied-10 completely satisfied), SD: Standard deviation

DISCUSSION

In this study, we tested the hypothesis that the ACB, performed under ultrasound guidance in TKA procedures conducted in accordance with ERAS protocols, would provide effective analgesia, reduce postoperative pain, decrease opioid requirements, and shorten hospital stay. We found that in patients who received ACB, VAS scores measured at rest, during ambulation, and during sleep within the first 24 hours postoperatively were significantly lower. Additionally, opioid consumption was lower, the incidence of side effects was reduced, patient satisfaction was higher, and the time to discharge readiness was shorter in the ACB group.

In post-TKA patient populations, Agarwala et al.[9] and Deiter et al.[8] reported mean ages of 64.86 and 67 years, respectively, while our study reported a mean age of 66.33 years. In terms of gender distribution, 80% of our patients were female and 20% male, consistent with literature reporting higher joint problem rates in women in both Western (50.3%–83.7%) and Asian (62.9%–69.7%) populations.[10] Regarding ASA classification, Deiter et al.[8] applied ACB mostly in ASA III patients, while Frassanito et al.[11] reported 31 ASA I, 116 ASA II, and 60 ASA III patients. In our sample, 80% of patients were ASA II and only one was ASA III. The lower ASA scores of our patients might be because patients suitable for the ERAS protocol generally have lower ASA scores.

Goytizolo and others[12] found the preoperative numerical rating scale (NRS) scores at rest between 2.7 and 3.4 and during flexion between 5.7 and 6.3. Sawhney and others[13] reported an average preoperative VAS score of 5.4 among 159 patients across the ACB, LIA, and LIA+ACB groups. Henshaw et al.[14] reported that preoperative VAS scores during movement for patients who were planned for knee arthroscopy were between 7.2 and 7.5. Similarly, in our study, the preoperative VAS average was 7.07 in group I and 7.10 in group II, with a similarity between the groups.

Time-dependent evaluations of postoperative VAS scores demonstrated that ACB+LIA provided superior pain management during walking on the first day, akin to LIA at rest. At the same time, ACB alone showed higher pain levels.[13,15] Studies by Gudmundsdottir et al.[18] confirmed that ACB combined with LIA enhances pain control. Similarly, Hussain et al.[17] demonstrated that while both single-shot and continuous ACB were effective for analgesia, continuous ACB was associated with a higher risk of complications.

In our study, group II consistently demonstrated lower VAS scores than group I at all time points, indicating superior pain management, especially by the 24th hour (p<0.05). The AKB+LIA combination was notably more effective than either treatment alone in managing pain during rest, walking, and sleep, consistent with findings by Sawhney et al.[13] Gudmundsdottir et al.[18] noted similar results for rest pain but reduced movement pain with AKB+LIA. Early postoperative pain control was comparable between AKB and iPACK, but their combined use resulted in higher pain scores after 72 hours.[19] Similarly, Mingdeng's[16] meta-analysis underscored enhanced resting analgesia with AKB+LIA during the first 24 to 48 hours post-operation. Our data also revealed higher first-day pain levels in group I, with VAS scores at rest and during ambulation of 2.60 and 5.40, respectively (p<0.05). Furthermore, nausea and vomiting were more prevalent in group I (76.6%) compared to group II (40%), and opioid usage was significantly lower in group II (p<0.05). These findings align with multimodal analgesia strategies aimed at minimizing opioid use and side effects. Research by Muñoz et al.[21] showed that non-opioid regimens did not enhance outcomes in opioid consumption or pain relief. At the same time, Xing et al.[22] reported that AKB+LIA significantly reduced morphine usage and decreased nausea and vomiting rates. Similarly, Hanson et al.[23] found that AKB effectively lowered pain scores and opioid use in meniscus surgery.

In a randomized controlled trial by Zhou et al.,[24] the combination of AKB+LIA significantly reduced use of tramadol 48 hours after the procedure compared to LIA alone. Li et al.[25] also performed postoperative 6 of AKB + LIA and 24. They found that it significantly reduced morphine consumption during the hours. AKB made with bupivacaine and magnesium increases overall patient satisfaction by reducing pain scores and opioid consumption after TKA without increasing the incidence of nausea.[26] Also, a 2022 study by Ahmad et al.[27] showed that AKB provides adequate pain control after TKA and reduces the need for opioids. In our study, the combination of AKB+LIA required the use of tramadol and other analgesic drugs less compared to group I. It resulted in fewer side effects and better pain control in group II. Our findings are consistent with the data in the literature and show that the combination of AKB and LIA offers a practical solution in postoperative pain management.

AKB+LIA facilitated earlier ambulation, according to a meta-analysis by Ma et al.[28] In a similar study, Biswas et al.[29] assessed functional recovery and ambulation distances among three groups and found no significant differences. In their study comparing three different anesthesia methods for TKA, Perlas et al.[30] discovered that the LIA+AKB group walked a longer distance on the first postoperative day than the other groups. Incorporating interspace between the knee capsule and the popliteal artery into continuous AKB has shown that it enhances postoperative pain control and reduces the need for nalbuphine. However, after the first day, no discernible ambulation or motor power changes were seen.[31] Although the AKB+LIA group showed a longer ambulation distance in our study, this difference was not statistically significant ($p>0.05$).

Gudmundsdottir and Franklin[18] found that adding AKB to a single dose of LIA did not provide additional benefits for pain and ambulation. Still, AKB offered advantages over the femoral nerve block (FSB) in preserving motor functions. Based on the neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) following TKA, a recent study by Domagalska et al.[32] demonstrated that the combination of iPACK and AKB significantly improves pain management, functional recovery and reduces stress responses. Kampitak et al.[33] (X) have stated that AKB+LIA does not negatively affect quadriceps strength and facilitates ambulation. Grevstad et al.[34] compared the effects of FSB and AKB on quadriceps muscle strength. They observed a 16% strength loss in the FSB group, which was not seen in the AKB group, attributing this to AKB reducing centrally mediated inhibition and lacking peripheral motor inhibition caused by FSB. LIA provides adequate pain control without affecting the strength of the quadriceps muscle and offers pain scores similar to FSB and shorter stay durations. At the same time, Gudmundsdottir et al.[18] have noted that LIA provides good analgesia post-TKA but increases the risk of falls by affecting quadriceps muscle strength. A study by Zhou et al.[24] has shown that AKB does not harm quadriceps muscle strength, and correct anatomical placement and appropriate block volume do not spread to the femoral nerve. In our study, the quadriceps strength test results for patients in group II increased from a preoperative average of 3.03 to a postoperative average of 3.97, which can be attributed to adequate analgesia provided by AKB+LIA and improved joint function post-TKA—in their study comparing AKB, LIA, and AKB+LIA groups, Zhou et al.[24] observed higher patient satisfaction in the AKB and AKB+LIA groups during the fourth and eighth postoperative hours. However, Kastelik et al.[7] did not find a significant difference in patient satisfaction in their studies involving LIA and AKB infusions. In our study, higher patient satisfaction was observed in the AKB+LIA group.

Goytizolo et al.[12] found no difference in discharge time between the LIA and AKB+LIA groups. However, Perlas et al.[30] showed that the LIA+AKB group had shorter hospital stays and more discharges than other groups. In our study, the hospital stay duration was 23.15 hours for group II and 30.25 hours for group I, indicating that adding AKB to analgesia positively influenced functional recovery.

Limitations

The limited sample size of our study, its execution at a single center, and the restricted diversity of participants potentially limit the generalizability of our findings. The applicability of our results across broader patient populations and various clinical settings will enable us to obtain more detailed and definitive information about long-term outcomes.

CONCLUSION

We found that in patients who received ACB, VAS scores measured at rest, during ambulation, and during sleep within the first 24 hours postoperatively were significantly lower. Additionally, opioid consumption was lower, the incidence of side effects was reduced, patient satisfaction was higher, and the time to discharge readiness was shorter in the ACB group. In patients undergoing TKA, the combination of LIA and ACB appears to be an effective option in multimodal analgesia practices during the postoperative period and may provide potential benefits in accelerating recovery and reducing opioid-related side effects.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval obtained from the Non-interventional Clinical Researches Ethics Committee of Pamukkale University (Date: 08.01.2020, Decision No: E.1710).

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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Association of serum HIF-1α levels with mortality and ICU admission in hospitalized patients with SARS-CoV-2 infection: a prospective cohort study

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ABSTRACT

Aims: SARS-CoV-2 infection can trigger a dysregulated immune response, including cytokine storm syndrome (CSS), which exacerbates respiratory failure through heightened pro-inflammatory mediators and hypoxemia. Hypoxia-inducible factor-1α (HIF-1α) orchestrates cellular adaptation to hypoxia by shifting metabolism toward glycolysis. Prior studies present varying evidence regarding HIF-1α's role in acute inflammatory states. The purpose of this study was to investigate the role of hypoxia-inducible factor 1a (HIF-1a) in predicting mortality, ward and intensive care unit (ICU) admission requirements.

Methods: The study was performed as a single center prospective study in a tertiary center. Hospitalized patients with at least one positive nasopharyngeal COVID-19 reverse transcription-polymerase chain reaction test were included in the study. White blood cell count, thrombocyte count, lactate levels, fibrinogen, D-dimer, brain natriuretic peptide (BNP), C-reactive protein (CRP), procalcitonin, ferritin, interleukin 6 (IL-6) troponin, partial oxygen, and partial carbon dioxide pressure from arterial blood gas sampling were recorded.

Results: Of 127 screened, 80 participants completed the study (mean age 66.1±17.2 years; 54% male). Thirty-day mortality was 21.3% (n=17). Median BNP (529 vs. 1,957 pg/ml), ferritin (256 vs. 598.5 ng/ml), and IL-6 (14 vs. 101 pg/ml) were significantly higher in non-survivors (p=0.043, 0.003, and 0.001, respectively). Survivors exhibited lower median HIF-1α (0.85 vs. 1.20 ng/ml), but this difference was not statistically significant (p>0.05). Subgroup analyses by CURB-65 and ICU status similarly revealed no significant HIF-1α differences. HIF-1α did not correlate with any inflammatory markers. HIF-1α levels at admission did not significantly predict ICU care or mortality. This may reflect HIF-1α's pro- and anti-inflammatory roles and variability in sampling timing relative to disease onset. Current literature suggests both protective and detrimental HIF-1α effects, complicating its prognostic utility.

Conclusion: Admission HIF-1α alone does not predict clinical outcomes in hospitalized COVID-19. Studies incorporating serial measurements and baseline controls are warranted to evaluate HIF-1α's involvement in COVID-19 pathophysiology.

Keywords: Critical care, coronavirus, hypoxia, mortality

INTRODUCTION

SARS-CoV-2 belongs to the family of coronaviruses, which are responsible for infections in both humans and a wide range of animal species, and is the causative agent of Coronavirus Disease 2019 (COVID-19). As seen in the COVID-19 situation, cross-species infection can lead to a pandemic. At the time of this study, vaccination and prevention appeared to be the only viable approaches, with no specific treatments in sight. Currently, many drugs have been repurposed to treat COVID-19, including antiviral therapies for human immunodeficiency virus, monoclonal antibodies, and immunosuppressive regimens.[1,2]

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The mortality and morbidity of COVID-19 are often caused by respiratory system infections and associated complications. This is further exaggerated by the presence of cytokine storm syndrome (CSS) in certain patients, which causes an unprecedented increase in pro-inflammatory markers, including tumor necrosis factor-alpha (TNF-a) and interleukin-1 beta (IL-1b).[3] From a clinical perspective, CSS presents with fever, organ failure, and tachypnea, with respiratory failure and hypoxemia being the most severe symptoms.[4,5] A shift in favor of alternative pathways for ATP production in hypoxia is necessary in patients with CSS, and hypoxia-inducible factor 1α (HIF-1α) plays a role in this transition to a hypoxic state. HIF-1α contributes to the shift in energy production to alternative pathways, causing increased activity of the glycolytic pathway and glucose-carrying mechanisms to compensate for the overall reduction in ATP production in hypox conditions.[6,7]

Hypoxemia in itself has been an important aspect of patient management, regardless of an underlying cause. While clear approaches and treatment modalities have been established, depending on the cause, the degree of tissue damage caused by hypoxia or any parameters that may predict this damage remains a topic that requires further study. Definitions of hypoxia and hypoxemia are often used interchangeably and often present together, albeit that may not be necessary in all cases.[8,9] Hypoxemia is defined as a condition with partial oxygen in arterial blood below normal values, while hypoxia is the failure of oxygenation at the cellular level. Hypoxemia often leads to hypoxia; however, in cases where the patient is compensated for low delivery of oxygen, this may not be observed. In cases of COVID-19, both respiratory and cardiac functions may be affected; as such, hypoxemia and hypoxia may be present in different stages.[10]

The role of HIF-1a in regulating hypoxemia is a subject of investigation, with more than 100 reported genes upon which HIF-1 has a regulatory effect.[11] The degree of this modification in acute cases, such as COVID-19 infection, requires clarification, as current studies report varying results. Some studies suggest a protective role for HIF-1α activation, while others indicate a correlation with other inflammatory markers, such as IL-6.[12-14] The study hypothesized that an elevation in HIF-1 levels predicts an increased inflammatory system burden and reflects the severity of respiratory failure. Our study investigated the association between HIF-1 levels and clinical outcomes, such as mortality and intensive care unit (ICU) admission, among patients infected with COVID-19.

METHODS

This study was conducted as a single-center prospective study in a tertiary care hospital and approved by the Clinical Researches Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 17.05.2021, Decision No: 111/08). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was received in writing and orally from all patients who participated in the study. This was witnessed by at least one additional medical doctor and one relative who did not participate in the study. Mortality and survival were evaluated from the national COVID-19 database after a follow-up period of one month.

The study group consisted of patients admitted to a tertiary care hospital with COVID-19 infection between June 1, 2021, and September 1, 2021. Baseline characteristics and clinical outcomes were recorded from initial admission evaluation and the hospital patient system. The patient admissions between the mentioned dates continued until the required patient count was reached.

Blood sampling for HIF-1 serum levels was performed in addition to routine blood tests for initial COVID-19 evaluation. The sampling was performed after confirmation of COVID-19 positivity and was done within the first day of hospital admission. These samplings were collected early in the morning after a minimum of 10 hours of fasting, immediately centrifuged for 15 minutes at 1000×g, and the serum was stored at -80 °C in aliquots until the day of analysis. Serum HIF-1A level was measured using a quantitative enzyme-linked immunoassay technique (ELISA), according to manufacturer's indications (Bioassay Technology Laboratory, Zhejiang, China).

Patients aged ≥18 years, reverse transcription polymerase chain reaction test positive, and admitted through the emergency department were accepted as the study population. Those with former hospitalization histories and/or diagnosed with COVID-19 at another ward were not accepted as candidates.

Other exclusion criteria included refusal to participate, treatment with immunosuppressive agents (regardless of the disease origin), and a history of supplementary vitamin use (due to a possible anti-inflammatory effect). Overall, these additional treatment and support regimens could have affected HIF-1a levels and thus had to be excluded. Patients with known comorbidities that might have caused an increase in HIF-1a levels were also excluded from the study, including those with a history of coronary heart disease, renal failure (regardless of dialysis status), and chronic obstructive pulmonary disease.

White blood cell count, thrombocyte count, lactate levels, fibrinogen, d-dimer, brain natriuretic peptide (BNP), C-reactive protein (CRP), procalcitonin, ferritin, interleukin 6 (IL-6) troponin, partial oxygen, and partial carbon dioxide pressure from arterial blood gas sampling were recorded from routine blood tests in the hospital system and medical records.

ICU admission and mortality at day 30 were accepted as primary outcome parameters. The aforementioned inflammatory markers (CRP, lactate levels, IL-6, ferritin, and procalcitonin) were used along with CURB-65 pneumonia severity scoring to validate the need for ICU admission and mortality. Patients with ICU admission requirements were evaluated by a responsible emergency medicine specialist, according to clinical status, at the emergency ward and were transported to the ICU unit if accepted.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to evaluate the distribution of the parameters. For categorical variables,

Chi-square and Fisher-Exact tests were used. For continuous parameters, depending on the distribution, independent samples T-tests or Mann-Whitney U test were used. Subgroup analysis was planned if a statistically significant parameter was observed in the overall group evaluation. A p-value less than 0.05 was to be accepted as statistically significant. International Business Machines (IBM) Statistical Product and Service Solutions (SPSS) Edition 30 was used as the statistical analysis program. The power analysis for the study was performed to estimate the patient requirement, in which to distinguish a difference between means of two independent groups, with a power of 0.8, type 1 error of 0.5% and effect size of 0.6, at least 72 patients were required. The effect size was chosen as to represent a moderate effect of HIF-1a, and evaluate if such an effect was present.

Considering at least 10% patient loss in the evaluation with inadequate data or later refusal to participate, a total patient count of 80 was planned with an upper limit of 90 patients were being deemed acceptable due to varying mortality rates. A subgroup analysis regarding comorbidities and age was not planned, due to exclusion criteria and the assumption of average age being at least 65 years.

RESULTS

Ninety patients (n=90) were enrolled during the first month. To reach this number, a total of 127 patients were evaluated. The remaining 37 (29%) patients were excluded from the study due to an unknown history of supplementary vitamin usage, improper blood sampling techniques, severe medical conditions unsuitable for informed consent, and refusal to participate. An additional ten patients (11%) were later excluded from the study due to missing data and/or their requests to be removed, resulting in a total sample of 80 participants.

The average age of the patients was 66.1 (±17.2) years. 37 (46%) of the sample group were female, and the rest, 43 (54%), were male. One-month mortality was observed in 17 (21.3%) of the patients. Less than half of the patients (n=36, 45%) had been diagnosed with hypertension, followed by asthma (n=10, 12.5%) and malignancy (n=6, 7.5%) as the second and third most commonly observed comorbidity. Neurologic (n=4, 5%) comorbidities were limited, and two patients (2.5%) had atrial fibrillation. Half of the patients were vaccinated for COVID-19. Regarding admission evaluation, mean arterial pressure (MAP), pulse rate, and body temperature were within normal ranges (a mean of 93.70 mmHg, 92.12 bpm, and 36.77 °C, respectively), while desaturation was present in both groups in terms of mortality (a mean of 86.53% at room air). The respiration rate was slightly elevated in both groups (a mean of 21.57 per minute). Mortality did not vary according to comorbidities and admission vitals (**Table 1**).

Regarding laboratory evaluation, WBC, PLT, and arterial blood gas sampling results, which included lactate, pH, PO_2, and PCO_2, did not differ between groups in terms of mortality. Similarly, while elevated at a mean of 527.8 (±116.56) mg/dl, fibrinogen levels were similar between groups. Other inflammatory parameters and cardiac markers were found to have non-parametric distribution. Median values of BNP (529 to 1957 pg/ml), ferritin (256 to 598.5 ng/ml), and IL-6 (14 to 101 pg/ml) were higher in the mortality group compared to the survivors (p values of 0.043, 0.003, and 0.001 respectively). Other markers, including high-sensitivity cardiac troponin (hs-ctn), D-dimer, procalcitonin, and CRP, while higher in the mortality group, did not show a statistically significant difference. HIF-1α was lower in the survivor group compared to the mortality group (1.2 to 0.85 ng/ml), but the difference was statistically insignificant (**Table 2**).

Regarding admission evaluation, the CURB-65 score was observed to be a statistically relevant parameter in mortality, with a cutoff of 2 being statistically significant in evaluating patients with mortality (p value of 0.027). Admission localization was in favor of ICU among patients in the mortality group (p-value of 0.001), while tomography findings did not differ between groups (p-value of 0.682) (**Table 3**).

Parameters were then evaluated according to the distribution among patients with a CURB-65 score of 2 or higher, to those with a score lower than 2. In this analysis; BNP, Troponin and procalcitonin were observed to be lower among CURB-65 score <2 group (p value of 0.007, 0.001 and 0.002 respectively). The same analysis was performed regarding admission localization, and BNP, procalcitonin, CRP, and ferritin were observed to be higher in the group requiring ICU admission (P value of 0.005, 0.038, 0.037, and 0.021 respectively). In both analyses, HIF-1a levels did not vary between groups (**Table 4**).

Correlation between inflammatory markers were performed to investigate any additional role of HIF-1a, however, no correlation between HIF-1a and other parameters were observed, while additional correlations between inflammatory markers were present, with BNP being correlated with troponin and D-dimer (r=0.559 and 0.464, p:0.001 for both values), troponin being corelated with D-dimer and procalcitonin (r=of 0.411, 0.307 and p value of 0.001, 0.007 respectively), procalcitonin being correlated with D-dimer, CRP and ferritin (r=0.342, 0.469 and 0.278 and p=0.003, 0.001 and 0.018 respectively) and ferritin being correlated with IL-6 (r=0.294 and p value of 0.013) (**Table 5**).

DISCUSSION

HIF-1a levels were observed to not statistically differ according to mortality, ward or ICU admission, albeit lower in the survival group. BNP, ferritin, and IL-6 levels had a significant difference regarding mortality. However, a correlation between these parameters and HIF-1a levels were not observed. Similarly, a correlation between additional inflammatory markers that had varied regarding ICU admission, CRP, and procalcitonin did not correlate with HIF-1a. Despite an acceptable patient distribution and expected pattern of other inflammatory markers regarding their role in ICU admission and mortality, no correlation or difference in HIF-1a was observed. Currently available studies regarding the evaluation of other acute inflammatory statuses do support similar predictive roles of inflammatory markers; however, due to the varying conditions, investigation of HIF-1a remains a limited aspect of investigation.[15,16]

In human peripheral blood cell studies, it was hypothesized that HIF-1a acted as an inducer of the pro-inflammatory

Table 1. Demographic parameters, comorbidities, and admission vitals

Parameters (n, %)		Survivor (n=63)	Non-survivor (n=17)	Total (n=80)	p value
Gender	Male	33 (52.4)	10 (58.8)	43 (53.8)	0.636
	Female	30 (47.6)	7 (41.2)	37 (46.2)	
Age (mean, SD, years)		64.61 (18.42)	71.64 (13.95)	66.11 (17.72)	0.096
Hypertension	Present	28 (44.4)	8 (47.1)	36 (45)	0.848
	Absent	35 (55.6)	9 (52.9)	44 (55)	
Asthma[1]	Present	8 (12.7)	2 (11.8)	10 (12.5)	0.642
	Absent	55 (87.3)	15 (88.2)	70 (87.5)	
Malignancy[1]	Present	4 (6.3)	2 (11.8)	6 (7.5)	0.602
	Absent	59 (93.7)	15 (88.2)	74 (92.5)	
Neurological comorbidities[1]	Present	3 (4.8)	1 (5.9)	4 (5)	0.623
	Absent	60 (95.2)	16 (94.1)	76 (95)	
Atrial fibrillation[1]	Present	2 (3.2)	0 (0)	2 (2.5)	0.618
	Absent	61 (96.8)	100 (100)	78 (97.5)	
COVID-19 vaccination (%)	No	31 (49.2)	9 (52.9)	40 (50)	0.785
	Vaccinated	32 (50.8)	8 (47.1)	40 (50)	
Mental status (%)	Normal	53 (84.1)	12 (70.6)	65 (81.2)	0.204
	Altered	10 (15.9)	5 (29.4)	15 (18.8)	
Mean arterial pressure (mmHg)		94.57 (15.10)	90.53 (13.78)	93.70 (14.83)	0.303
Pulse rate (bpm)		92.33 (15.22)	91.35 (12.40)	92.12 (14.60)	0.808
Body temperature (°C)		36.76 (0.75)	36.78 (0.61)	36.77 (0.71)	0.965
Oxygen saturation (%)		86.73 (10.4)	85.76 (8.82)	86.53 (9.75)	0.717
Respiration rate (/min)		21.65 (2.80)	21.29 (1.72)	21.57 (2.60)	0.62

SD: Standard deviation, 1Fisher Exact Test was used for comparison

Table 2. Comparison of laboratory parameters between survivor and non-survivor groups

Parameters (mean, SD)[1]	Survivor (n=63)	Non-survivor (n=17)	Total (n=80)	p value
WBC (10^9/L)	8.72 (3.92)	10.93 (5.13)	9.20 (4.27)	0.069
PLT (10^9/L)	222.30 (85.20)	254.52 (138.98)	229.24 (99.08)	0.374
Lactate (mmol/L)	2.14 (1.08)	2.26 (0.61)	2.16 (1.01)	0.665
pH	7.37 (0.09)	7.36 (0.08)	7.37 (0.09)	0.607
PO_2 (mmHg)	78.68 (12.41)	74.8 (10.27)	77.91 (12.06)	0.266
PCO_2 (mmHg)	40.96 (11.04)	41.16 (12.44)	41.00 (11.26)	0.951
Fibrinogen (mg/dl)	516.40 (114.78)	574.13 (116.01)	527.8 (116.56)	0.086
Parameters (median, 25-75th percentile)[2]				
BNP (pg/ml)	529 (91-1490.5)	1957 (570-4930)	714 (103.4-2097)	0.043
Hs-cTn (ng/ml)	16.42 (5.98-32.03)	20.9 (9.03-61.64)	17.53 (6.28-34.45)	0.198
D-dimer (mcg/ml)	0.97 (0.47-1.89)	1.05 (0.47-2.40)	0.97 (0.47-1.89)	0.466
Procalcitonin (ng/ml)	0.08 (0.06-0.23)	0.24 (0.07-0.39)	0.1 (0.06-0.28)	0.067
CRP (mg/dl)	73.43 (37.44-139.65)	91.95 (59.6-124.29)	76.88 (43.01-139.65)	0.249
Ferritin (ng/ml)	256 (102-520)	598.5 (339.5-767)	310 (136-564)	0.003
IL-6 (pg/ml)	14 (7.5-25)	101 (66.3-145)	17.1 (9-51)	0.001
HIF-1a (ng/ml)	1.2 (0.38-1.97)	0.85 (0.41-1.30)	1.17 (0.39-1.72)	0.129

SD: Standard deviation, WBC: White blood cell, PLT: Platelet, BNP: Brain natriuretic peptide, Hs-Ctn: High sensitivity cardiac troponin, CRP: C-reactive protein, IL-6: Interleukin-6, HIF-1a: Hypoxia-inducible factor 1-alpha; Lactate, Ph, PO_2 and PCO_2 were recorded from arterial blood gas sampling. [1]Independent samples T test was used for comparison between groups. [2] Mann-Whitney U test was used for comparison between groups

Table 3. Radiological imaging, pneumonia scoring, and admission localization

Parameters (n, %)		**Survivor** (n=63)	**Non-survivor** (n=17)	**Total** (n=80)	p value
Tomography findings consistent with COVID-19	None	12 (19)	4 (23.5)	16 (20)	0.682
	Present	51 (81)	13 (76.5)	64 (80)	
CURB-65 score	<2	41 (65.1)	6 (35.3)	47 (58.8)	0.027
	≥2	22 (34.9)	11 (64.7)	33 (41.3)	
Admission localization	Ward	49 (77.8)	4 (23.5)	53 (66.3)	0.001
	ICU	14 (22.2)	13 (76.5)	27 (33.8)	

ICU: Intensive care unit

Table 4. Cardiac and inflammatory markers comparison according to CURB-65 and admission localization

CURB-65 score		**Mean rank**	**Z score**	**p value**
Brain natriuretic peptide	<2	32.46	2.698	0.007
	≥2	46.32		
Troponin	<2	28.12	5.463	0.001
	≥2	56.76		
D-dimer	<2	33.8	1.501	0.133
	≥2	41.34		
Procalcitonin	<2	32.44	3.055	0.002
	≥2	48.22		
CRP	<2	38.18	0.147	0.883
	≥2	38.94		
Ferritin	<2	37.08	0.449	0.654
	≥2	39.38		
Interleukin-6	<2	36.09	0.703	0.482
	≥2	39.69		
HIF-1a	<2	41.59	-0.726	0.468
	≥2	37.79		
Admission localization				
Brain natriuretic peptide	Ward	32.95	2.838	0.005
	ICU	48.1		
Troponin	Ward	38.65	0.466	0.641
	ICU	41.19		
D-dimer	Ward	35.22	1.057	0.29
	ICU	40.87		
Procalcitonin	Ward	35.24	2.072	0.038
	ICU	46.28		
C-reactive protein	Ward	35.02	2.087	0.037
	ICU	46.52		
Ferritin	Ward	34.02	2.306	0.021
	ICU	46.46		
Interleukin-6	Ward	34.36	1.869	0.062
	ICU	44.46		
HIF-1a	Ward	42.08	-1.158	0.247
	ICU	35.73		

Statistical analysis between groups was made by Mann Whitney U Test due to nonparametric distribution. CRP: C-reactive protein, HIF-1a: Hypoxia-inducible factor 1-alpha, ICU: Intensive care unit, Z score: Standardized test statistic

system, as was discussed earlier.[17] However, as stated in Palazon et al.'s[18] study, HIF-1a also has regulatory roles depending on the cell being under hypoxia that may reduce a TNF-a-related inflammatory response. As such both pro and anti-inflammatory roles of HIF-1a has been reported. Early dysregulation of HIF-1a has been suggested as a trigger for inflammatory response.[13,14,18] However, HIF-1a elevation has also been reported to decrease Angiotensin-converting enzyme (ACE) receptors.[19] This effect may limit the possibility of preemptive HIF-1α inhibition in patients with COVID-19, as it would prevent the reduction of ACE receptors, thereby providing the virus with more accessible entry routes. Overall, these pathways and differing roles of HIF-1a in both pro and anti-inflammatory roles may contribute to the lack of correlation between HIF-1a and other inflammatory markers in the study, as despite standardized sampling time, an exact time of HIF-1a sampling at the start of every patient's inflammatory process could not be made.

Our study, despite not being statistically significant, had stated lower HIF-1a levels among survivors. This could have been attributed to a possible type II error, patient sample size limitation or related to the time of sampling. Indeed, sampling time compared to the initial infection might have played a role in the predominance of either pro-inflammatory or anti-inflammatory processes of HIF-1a.

A study made by Tian et al.[17] supports the aggravating role of HIF-1a among COVID-19 patients, especially among the elderly population. Another study made by Deveci et al,[20] while reporting similar results, also supports the assumption that patients with a low HIF-1a may be actually caused due to inadequate increase in HIF-1a as a sign of systemic and clinical collapse. Thus lower HIF-1a could have also been accepted as a risk factor. Conflicting results of these studies may arise from the study population, the severity of the disease upon sampling, and the sampling time. This dual nature of the HIF-1a is further affected by the genetic background of the patients, as seen in Ljujic et al.[21] study, in which HIF-1a gene polymorphism was reported to affect thrombocytopenia in COVID-19 patients.

A protective role of HIF-1a had been reported in the study of Devaux and Raoult,[22] in which altitude and HIF signaling pathway were investigated. Altogether, we may state that, similar to what we found in our study, HIF-1a may have both protective and detrimental effects on COVID-19 patients, and

Table 5. Correlation between HIF-1a and inflammatory parameters

Parameters		HIF-1a	BNP	Troponin	D-dimer	PRC	CRP	Ferritin	IL-6
HIF-1a	CC		-0.054	-0.062	0.006	0.211	0.119	-0.038	-0.161
	p value		0.647	0.594	0.959	0.067	0.310	0.748	0.173
BNP	CC	-0.054		0.559	0.464	0.067	0.060	0.143	0.138
	p value	0.647		0.001	0.001	0.577	0.621	0.238	0.258
Troponin	CC	-0.062	0.559		0.411	0.307	0.112	0.045	0.163
	p value	0.594	0.001		0.001	0.007	0.341	0.707	0.170
D-dimer	CC	0.006	0.464	0.411		0.342	0.123	0.115	-0.024
	p value	0.959	0.001	0.001		0.003	0.308	0.350	0.847
PRC	CC	0.211	0.067	0.307	0.342		0.469	0.278	0.045
	p value	0.067	0.577	0.007	0.003		0.001	0.018	0.708
CRP	CC	0.119	0.060	0.112	0.123	0.469		0.29	0.170
	p value	0.310	0.621	0.341	0.308	0.001		0.013	0.150
Ferritin	CC	-0.038	0.143	0.045	0.115	0.278	0.29		0.294
	p value	0.748	0.238	0.707	0.350	0.018	0.013		0.013
IL-6	CC	-0.161	0.138	0.163	-0.024	0.045	0.170	0.294	
	p value	0.173	0.258	0.170	0.847	0.708	0.150	0.013	

The correlation analysis between parameters was done using Spearman Rho correlation. CC: Correlation coefficient, HIF-1a: Hypoxia-inducible factor 1-alpha, BNP: Brain natriuretic peptide, PRC: Procalcitonin, CRP: C-reactive protein, IL-6: Interleukin-6

establishing an exact cut-off may be difficult even with further studies due to the sampling time and other contributing factors.

Limitations

The study's main limitation was the lack of an initial HIF-1a level in patients before COVID-19 history. Such a limitation is not expected to be overcome easily. As in optimal conditions, a population would have been studied with basal inflammatory markers, and during the follow-up period, those who had the requirement for COVID-19-related hospital admission would be re-evaluated. This limitation was also present, in another form, regarding a lack of repeated testing, which was another possible approach to evaluate the dynamic roles of HIF-1a, especially regarding the time of pro or anti-inflammatory role.

In a similar approach, this study was limited to patients who required hospital admission after an initial emergency department evaluation. It is possible that patients whose evaluation was performed on an out-clinic basis could have provided us with different results.

The main bias in this study was related to selection. The patients in the study had hospitalization requirements, hence limiting the study population to those whose condition warranted emergency care. This limitation could not be reduced per the study design, as the investigation was to be performed on those evaluated in an emergency care setting.

CONCLUSION

Further studies with more extended follow-up periods and participants are required to evaluate the role of HIF-1a in COVID-19 patients. Studies that include a rapid testing of inflammatory markers and repeated HIF-1a testing might illuminate the exact role and time of effect regarding HIF-1a's regulatory functions. In addition to repeated testing, sampling of HIF-1a in tissue expression might have also provided a different outlook to its possible roles. While HIF-1a could not be utilized as an independent marker in our study, its utilization with other inflammatory markers, such as BNP or IL6 may be a topic of interest in future investigations.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approved by the Clinical Researches Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital (Date: 17.05.2021, Decision No: 111/08).

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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The impact of thyroid dysfunction on domain-specific cognitive performance: a cross-sectional study*

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ABSTRACT

Aims: While thyroid dysfunction has been implicated in cognitive impairment, its domain-specific effects remain unclear. This study investigates the relationship between thyroid status and performance across distinct cognitive domains in older adults.

Methods: We analyzed 166 participants (32 controls, 48 mild cognitive impairment, 86 Alzheimer's disease) aged 50-80 years without pre-existing thyroid conditions. Participants underwent comprehensive assessment including Mini-Mental State Exam (MMSE) and Clinical Dementia Rating (CDR). Thyroid status was classified by TSH levels: low (<0.55 μIU/ml), normal (0.55-4.78 μIU/ml), and high (>4.78 μIU/ml). Data normality was evaluated using the Shapiro-Wilk test, and non-parametric methods were applied due to non-normal distributions. Spearman's correlation and Kruskal-Wallis tests were used for bivariate analyses. Chi-square tests assessed associations between thyroid status and categorical variables. A multinomial logistic regression model was employed to identify predictors of thyroid status, with the low TSH group as the reference category. To address class imbalance, the SMOTE technique was applied, and multicollinearity was examined using the variance inflation factor (VIF).

Results: Among the MMSE subdomains, recall, orientation, and attention and calculation were significantly associated with thyroid status. Recall was a strong predictor for both normal and high TSH levels. Orientation scores positively predicted normal TSH and negatively predicted high TSH. Attention and calculation was significantly associated only with normal TSH. Additionally, higher CDR scores were significantly linked to high TSH status.

Conclusion: These findings suggest that rather than evaluating global cognition, domain-specific cognitive assessment may provide more meaningful insights into the cognitive effects of thyroid dysfunction.

Keywords: Thyroid dysfunction, cognitive domains, Mini-Mental State Exam, dementia, TSH, cognitive impairment

*Our study has been accepted for presentation as a poster at the European Academy of Neurology Congress 2025, which will take place on June 21–24.

INTRODUCTION

Cognitive decline is a growing global concern, particularly as aging populations expand and life expectancy increases. The World Health Organization estimates that over 55 million people worldwide live with dementia, a number expected to triple by 2050, highlighting the urgent need for preventive strategies and effective interventions to address this public health challenge.[1] Cognitive decline can result from a combination of factors, including aging, neurodegenerative diseases like Alzheimer's, vascular conditions, chronic stress, and lifestyle factors such as poor diet, physical inactivity, and lack of mental stimulation. Additionally, underlying medical conditions like thyroid dysfunction, diabetes, and depression, as well as genetic predispositions, can significantly contribute to the deterioration of cognitive function. Screening for thyroid dysfunction in patients with cognitive disorders is recommended by clinical guidelines.[2]

The hypothalamic-pituitary-thyroid axis regulates the thyroid gland, which primarily produces, stores, and releases approximately thyroxine (T4) and triiodothyronine (T3). The majority of thyroid hormones (THs) (99.8%) are reversibly bound to plasma proteins, with only the free forms of T3 and T4 being biologically active. The synthesis and release of thyroid hormones (THs) are stimulated by thyroid-stimulating hormone (TSH), which is regulated by the hypothalamus-pituitary axis. Dysfunction in the hypothalamus or pituitary can disrupt thyroid activity by altering TSH levels. THs exert negative feedback on the anterior pituitary, suppressing TSH secretion when T3/T4 levels are high and promoting it when T3/T4 levels are low.[3] Insufficiency of the levels of thyroid hormone leads to impaired neurogenesis, behavioral alterations, and cognitive deficits.[4]

Optimal central nervous system function depends on maintaining precise thyroid hormone balance in the brain, as

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even slight disturbances in cerebral hormone concentrations may lead to significant cognitive and behavioral deficits.[5]

The Mini-Mental State Exam (MMSE) is the most extensively utilized screening instrument for assessing cognitive function in older adults and is commonly employed as an outcome measure in clinical studies. The test evaluates various cognitive domains, such as orientation to time and place, immediate and delayed recall, visuospatial skills, and language abilities.[6] The Clinical Dementia Rating (CDR) is a standardized tool used to assess the severity of dementia in individuals. It evaluates cognitive and functional performance across six domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. Each domain is rated on a scale from 0 (no impairment) to 3 (severe impairment), and an overall CDR score is calculated to classify dementia stages as 0 (none), 0.5 (questionable), 1 (mild), 2 (moderate), or 3 (severe). The CDR is widely used in clinical and research settings to track disease progression and guide treatment decisions.[7]

To date, the relationship between thyroid function and cognitive decline has been extensively studied, yet a definitive association remains unclear. The aim of our study is to evaluate whether thyroid function impacts specific core cognitive domains that constitute the cognitive assessment tests, even if it does not alter the total scores. We seek to determine whether thyroid function influences individual subtests, potentially revealing subtle differences that are not reflected in the overall scoring.

METHODS

The study was initiated with the approval of the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 12.03.2025, Decision No: TABED 1-25-1083). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 166 participants were enrolled in the study, comprising 32 cognitively normal controls, 48 patients with mild cognitive impairment (MCI), and 86 patients with Alzheimer's disease (AD) (**Table 1**). While the control group was not matched to the patient groups in terms of age and gender, no statistically significant differences were observed between the groups. Participants were recruited from individuals who visited the Dementia Outpatient Clinic at Ankara Bilkent City Hospital between January and December 2024, and eligibility was determined based on inclusion and exclusion criteria. Inclusion criteria required participants to be aged between 50 and 80 years, with no history of diagnosed or treated thyroid disease. Exclusion criteria encompassed a history of insulin-dependent diabetes, uncorrected adrenal cortical insufficiency, chronic liver or kidney failure, malignancy, cerebrovascular events, head trauma, or psychiatric disorders associated with significant cognitive impairment. Additionally, individuals those with a history of treatments that could influence thyroid hormone levels, and those with recent alcohol abuse were excluded.

Table 1. Characteristics of the study population

Feature/ gender	AD (n=86)	MCI (n=48)	NC (n=32)	Total (n=166)	p-value
Gender: female (n)	36 (49.3%)	18 (37.5%)	19 (59.4%)	73	
Gender: male (n)	50 (50.7%)	30 (62.5%)	13 (40.6%)	93	
Age (mean±SD)	74.1±8.4	75.7±7.0	67.9±10.9		0.0034
fT3 (mean±SD)	3.0±0.4	3.0±0.2	3.1±0.3		0.4043
fT4 (mean±SD)	1.1±0.1	1.1±0.1	1.4±1.9		0.6258
TSH (mean±SD)	2.5±3.1	1.6±1.2	2.3±1.5		0.1114
Education (years±SD)	6.6±5.0	6.7±4.8	7.1±3.6		0.8114
Orientation (mean±SD)	4.5±2.2	6.7±1.9	9.8±0.3		0.0000
Memory (mean±SD)	2.7±0.5	2.9±0.1	3.0±0.0		0.0006
Attention & calculation (mean±SD)	1.9±1.6	3.6±1.5	4.5±0.6		0.0000
Recall (mean±SD)	0.4±0.7	0.8±0.8	2.3±0.7		0.0000
Language (mean±SD)	6.4±1.5	7.3±1.2	8.9±0.2		0.0000
Total MMSE (mean±SD)	16.1±4.2	21.4±2.9	28.6±0.9		0.0000
CDR (mean±SD)	1.9±0.8	0.5±0.0	0.0		0.0000

AD: Alzheimer disease, MCI: Mild cognitive impairment, NC: Normal control, fT3: Free T3, fT4: Free T4, MMSE: Mini-Mental State Exam, CDR: Clinical Dementia Rating, SD: Standard deviation, p-value: Indicates whether the variable is statistically significant p<0.05 is considered significant

Statistical Analysis

This study aimed to examine the relationship between patients' thyroid status and the sub-scores of the MMSE, specifically orientation, memory, attention and calculation, recall, and language. To evaluate these associations, correlation analyses and multiple logistic regression were conducted.

Prior to these analyses, the Shapiro-Wilk test was applied to assess the normality of the data. As the p-values for all variables were ≤0.05, the null hypothesis of normal distribution was rejected. Consequently, the data were considered not normally distributed at the 5% significance level. Since the data did not follow a normal distribution, Spearman's rank correlation coefficient was used for the analysis of continuous numerical variables.

In this study, a new categorical variable titled "thyroid status" was created based on the TSH values present in the dataset. Participants were classified into three groups according to their TSH levels: low thyroid (TSH <0.55 μIU/ml, shown as thyroid status=0), normal thyroid (TSH between 0.55 μIU/ml and 4.78 μIU/ml, shown as thyroid status=1), and high thyroid (TSH >4.78 μIU/ml, shown as thyroid status=2). To evaluate whether there were statistically significant differences among

these thyroid status groups, the Kruskal-Wallis test was applied, as the data did not meet the assumptions of normality required for parametric tests.

To examine the associations between gender, cognitive status, and thyroid status, separate Chi-square tests of independence were conducted. These analyses aimed to determine whether thyroid status is statistically independent from gender and cognitive status.

Following the correlation analyses, a regression analysis was performed to further examine the association between thyroid status and the independent variables, as well as to evaluate their predictive power. Given that the dependent variable (thyroid status) is categorical with more than two levels, a multinomial logistic regression model was employed. This method allowed for assessing the influence of multiple predictors on the likelihood of belonging to different thyroid status categories. Prior to modeling, multicollinearity was assessed using the variance inflation factor (VIF), which quantifies how much the variance of an estimated regression coefficient increases due to collinearity. Based on the VIF results, the Total MMSE score was excluded to avoid multicollinearity. As the thyroid status categories were imbalanced, the Synthetic Minority Over-sampling Technique (SMOTE) was applied to synthetically increase the number of samples in minority classes and prevent model bias. All categorical variables were encoded numerically, and features were standardized before building the final model.

RESULTS

According to the results, among the MMSE sub-scores, only the recall subdomain showed a statistically significant positive correlation with TSH levels (r=0.21). A strong negative correlation was observed between orientation and CDR (r=-0.76). Additionally, there were moderate negative correlations between CDR and memory (r=-0.35), CDR and attention & calculation (r=-0.61), CDR and recall (r=-0.61), and CDR and language (r=-0.58). A moderate positive correlation was also found between attention & calculation and language (r=0.41). All results were statistically significant at the 95% confidence level (**Table 2**).

The differences between thyroid status categories were assessed using the Kruskal-Wallis test. According to the results, there were no statistically significant differences among the thyroid status groups in any of the variables at the 95% confidence level. Additionally, effect sizes were found to be very small across all comparisons, indicating that thyroid status does not have a meaningful impact on these variables (**Table 3**).

According to the results, the Chi-square value for the relationship between gender and thyroid status was 5.1651, with a p-value of 0.0756. Since the p-value is greater than 0.05, it was concluded that there is no statistically significant association between gender and thyroid status. Similarly, the Chi-square value for the relationship between cognitive status and thyroid status was 4.0886, with a p-value of 0.3941. This also exceeds the 0.05 significance threshold, indicating that cognitive status and thyroid status are statistically independent of each other.

A multinomial logistic regression analysis was conducted to investigate the association between thyroid status (categorized as low TSH=0, normal TSH=1, and high TSH=2) and cognitive performance based on MMSE subdomains (**Table 4**). The reference category was defined as low TSH (0). Significant associations were found between several MMSE subdomains and thyroid status.

Orientation scores were significantly associated with normal thyroid function (OR=14.792, 95% CI: 1.729–126.572, p=0.014), indicating that higher orientation performance was associated with approximately 15-fold increased odds of being in the normal TSH group compared to the low TSH group. Additionally, Orientation was negatively associated with high TSH status (OR=0.067, 95% CI: 0.005–0.921, p=0.043), suggesting that lower orientation scores were predictive of higher TSH levels.

Attention and calculation performance was significantly associated with normal TSH status (OR=7.322, 95% CI: 2.058–26.05, p=0.002). Participants with better attention and calculation scores were more likely to have normal thyroid function compared to those with low TSH. However, this relationship was not statistically significant for high TSH (p=0.384).

Recall was a strong predictor for both normal (OR=37.639, 95% CI: 9.882–143.360, p<0.001) and high thyroid status (OR=66.890, 95% CI: 13.666–327.413, p<0.001), implying that improved recall performance was robustly associated with normal or high TSH states.

Memory was not significantly associated with normal thyroid status (p=0.332), but showed a significant positive association with high TSH levels (OR=30.860, 95% CI: 2.439–390.582, p=0.008), indicating that patients with better memory scores were more likely to be in the high TSH group.

Language did not show statistically significant associations with either thyroid category (p=0.281 and p=0.812, respectively).

CDR score was positively associated with both normal and high TSH statuses. However, statistical significance was reached only for the high TSH group (OR=54.820, 95% CI: 5.848–513.885, p<0.001), whereas the association with normal TSH did not reach significance (OR=5.028, p=0.093). This indicates that individuals with higher levels of cognitive impairment, as indicated by elevated CDR scores, were substantially more likely to be in the high TSH group relative to the low TSH group.

Cognitive Status was found to be a highly significant predictor of thyroid classification. Individuals with cognitive disease (MCI or AD) had significantly higher odds of belonging to the normal TSH group compared to those in the low TSH group (OR=162.440, 95% CI: 31.344–841.83, p<0.001).

These findings suggest that specific cognitive domains particularly recall, orientation, and attention and calculation along with clinical indicators such as CDR and cognitive status, are significantly related to thyroid hormone patterns. Notably, recall emerged as a consistent predictor for both normal and

Table 2. Spearman's rank correlation

Variable	Age	fT3	fT4	TSH	Education	Orientation	Memory	Attention and calculation	Recall	Language	CDR	Thyroid status
Age	-											
fT3	r=-0.096 p=0.2197	-										
fT4	r=0.088 p=0.2595	r=0.14 p=0.0676	-									
TSH	r=-0.057 p=0.4671	r=-0.014 p=0.8530	r=-0.064 p=0.4114	-								
Education	r=0.025 p=0.7487	r=-0.051 p=0.5105	r=0.019 p=0.8039	r=0.11 p=0.1667	-							
Orientation	r=-0.23 p=0.0027	r=0.023 p=0.7656	r=-0.08 p=0.3052	r=0.057 p=0.4621	r=0.27 p=0.0004	-						
Memory	r=-0.036 p=0.6435	r=0.03 p=0.7022	r=-0.063 p=0.4181	r=0.0038 p=0.9613	r=0.11 p=0.1777	r=0.38 p=0.0000	-					
Attention and calculation	r=0.0068 p=0.9312	r=-0.066 p=0.3991	r=-0.096 p=0.2190	r=0.016 p=0.8383	r=0.15 p=0.0528	r=0.51 p=0.0000	r=0.35 p=0.0000	-				
Recall	r=-0.21 p=0.0073	r=0.039 p=0.6147	r=-0.096 p=0.2185	r=0.21 p=0.0061	r=0.098 p=0.2095	r=0.52 p=0.0000	r=0.2 p=0.0084	r=0.33 p=0.0000	-			
Language	r=-0.1 p=0.1878	r=0.05 p=0.5253	r=0.01 p=0.8983	r=-0.029 p=0.7115	r=0.1 p=0.1896	r=0.54 p=0.0000	r=0.38 p=0.0000	r=0.41 p=0.0000	r=0.41 p=0.0000	-		
CDR	r=0.14 p=0.0664	r=-0.015 p=0.8500	r=0.034 p=0.6623	r=-0.032 p=0.6844	r=-0.062 p=0.4276	r=-0.76 p=0.0000	r=-0.35 p=0.0000	r=-0.61 p=0.0000	r=-0.61 p=0.0000	r=-0.58 p=0.0000	-	
Thyroid status	r=-0.14 p=0.0675	r=0.017 p=0.8310	r=-0.098 p=0.2097	r=0.68 p=0.0000	r=0.054 p=0.4902	r=-0.039 p=0.6186	r=0.019 p=0.8042	r=-0.043 p=0.5860	r=0.14 p=0.0783	r=-0.034 p=0.4902	r=0.045 p=0.5618	-

r: Spearman's rank correlation coefficient, p: p-value, indicates whether the variable is statistically significant p<0.05 is considered significant, CDR: Clinical Dementia Rating, fT3: Free T3, fT4: Free T4

Table 3. Kruskal Wallis test for tyroid status

	H-value	p-value	Effect size
Age	3.53	0.171	0.0094
fT3	3.14	0.2076	0.007
fT4	5.11	0.0775	0.0191
Education	2.94	0.2298	0.0058
Orientation	0.25	0.8814	0.0107
Memory	0.16	0.9242	0
Attention and calculation	0.9	0.6369	0
Recall	4.12	0.1276	0.013
Language	0.63	0.729	0
CDR	0.34	0.8416	0
Cognitive status	0.17	0.9162	0
Sex	5.13	0.0768	0.0192

fT3: Free T3, fT4: Free T4, MMSE: Mini-Mental State Exam, CDR: Clinical Dementia Rating, p-value: Indicates whether the variable is statistically significant p<0.05 is considered significant

high TSH status, while orientation, CDR score, and cognitive status provided additional insight into how cognitive function and clinical context relate to thyroid classification.

DISCUSSION

TSH levels have been widely studied in relation to cognitive function, with both hypothyroidism and hyperthyroidism being associated with cognitive impairments. THs play a critical role in brain development and function, influencing neurogenesis, synaptic plasticity, and the maintenance of cognitive processes such as memory, attention, and executive function.[8] Even subtle alterations in thyroid function, as reflected by abnormal TSH levels, can have significant effects on cognitive performance.

Numerous systematic reviews have investigated the association between thyroid dysfunction and cognitive impairment. In a review conducted by Akintola et al.,[9] out of the 15 observational studies examined, only two small cross-sectional studies found significant associations between subclinical hypothyroidism and cognitive decline, specifically affecting global cognition (as assessed by the MMSE) and memory. The other studies consistently reported no meaningful associations.

In the Danish National Patient Register (DNPR) cohort, hypothyroidism was initially linked to an increased risk of dementia, but this association diminished after adjusting for comorbidities such as cardiovascular disease and diabetes. A higher risk remained in individuals under 56, with no significant association in older adults—suggesting that younger hypothyroid patients may be more vulnerable, possibly due to the greater impact of TSH fluctuations on developing neuronal circuits.[10] A 2021 study conducted in Belgium among older adults found no significant association between thyroid dysfunction and cognitive performance, including executive function, memory, or risk of dementia.[11] Our study did not reveal any significant relationship between age and cognitive performance among patients with thyroid dysfunction.

Moreover, a Ukrainian study conducted in 2012, which included only female participants, reported a strong positive correlation between cognitive impairment and fT4 levels, along with a significant inverse correlation between MMSE

Table 4. OR results of multinominal regression model

	OR (thyroid status=1)	95% CI (thyroid status=1)	p-value (thyroid status=1)	OR (thyroid status=2)	95% CI (thyroid status=2)	p-value (thyroid status=2)
Age	0.164	0.0002208 - 1.2160	0.077	0.035	0.004-0.362	0.005
fT3	504.675	37.6815- 6759.19	0.000	42.470	2.123-849.670	0.014
fT4	10614.309	0.0000022-5.043E+13	0.415	0.000	2.731E+42-2.245E-15	0.000
Education	0.434	0.1370- 1.372	0.155	160.200	39.416-650.925	0.000
Orientation	14.792	1.729 - 126.572	0.014	0.067	0.005-0.921	0.043
Memory	0.345	0.0402-2.96	0.332	30.860	2.439-390.582	0.008
Attention and calculation	7.322	2.058-26.05	0.002	0.488	0.097-2.448	0.384
Recall	37.639	9.882-143.360	0.000	66.890	13.666-327.413	0.000
Language	3.007	0.407-22.201	0.281	0.135	0.058-9.292	0.812
CDR	5.028	0.762-33.160	0.093	54.820	5.848-513.885	0.000
Disease status	162.440	31.344-841.83	0.000	0.364	0.666-1.996	0.245
Sex	0.721	0.40 - 1.31	0.283	0.178	0.086-0.370	0.00

OR: Odds ratio, CI: Confidence interval, p-value: Indicates whether the variable is statistically significant p<0.05 is considered significant, CDR: Clinical Dementia Rating, fT3: Free T3, fT4: Free T4, Thyroid status=1: normal thyroid (TSH between 0.55 µIU/ml and 4.78 µIU/ml) thyroid status=2: high thyroid (TSH >4.78 µIU/ml)

scores and TSH levels.[12] In our study, no difference was observed between genders regarding TSH levels and total MMSE scores.

In our study, we observed that patients with low TSH levels exhibited more pronounced impairments in recall and memory subscores compared to those with normal and high TSH levels. Our findings also indicate that attention and calculation abilities tend to be more impaired in individuals with low TSH levels. This finding aligns with previous research suggesting that hyperthyroidism (low TSH levels) can lead to deficits in memory and attention, potentially due to the overstimulation of neural circuits and accelerated metabolic activity in the brain.[13] Conversely, patients with hypothyroidism (high TSH levels) showed greater impairment in orientation which may reflect the slowing of cognitive processes and reduced metabolic activity associated with thyroid hormone deficiency.[14,15] Recent research demonstrates that elevated thyroid hormone levels worsen cognitive dysfunction and accelerate β-amyloid plaque deposition in mice models through RIPK3/MLKL-mediated necroptosis and heightened neuroinflammatory responses.[16]

Our findings also revealed that CDR scores were higher in patients with low TSH levels.[17,18] Some studies propose a nonlinear association between thyroid function and cognition: both high and low TSH levels are linked to impairment, while mildly suppressed TSH (0.1–0.4 mIU/L) may correlate with optimal cognitive performance.[19]

In this study, disease status was found to be a strong predictor of thyroid classification; however, normal TSH levels were observed across all cognitive groups, including patients with AD, MCI, and cognitively healthy controls. This suggests that, although thyroid function is statistically associated with disease classification in the model, it does not appear to reliably distinguish between cognitive diagnostic categories within the studied sample. Consistent with previous findings in the literature, our results indicate that thyroid hormone levels alone may not adequately explain cognitive status, especially in clinically heterogeneous patient populations.[20,21]

The lack of a statistically significant relationship between total MMSE scores and TSH levels in our study is consistent with findings from several other studies.[22-24] This suggests that while global cognitive measures like the MMSE may not be sensitive enough to detect subtle thyroid-related cognitive changes, This highlights the assessment of cognitive function in thyroid disorders necessitates detailed neuropsychological testing beyond simple screening tools to reliably detect subtle cognitive deficits.[25,26] Despite limitations such as sample size and the lack of advanced cognitive testing, our statistically significant results may guide future studies on thyroid-related cognitive dysfunction.

CONCLUSION

As a result, our findings underscore the complex relationship between TSH levels and cognitive function. Both low and high TSH levels appear to affect specific cognitive domains, with recall and orientation being particularly vulnerable. Future studies should explore the mechanisms underlying these associations and investigate whether optimizing thyroid function can improve cognitive outcomes in affected individuals.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Ankara Bilkent City Hospital Clinical Researches Ethics Committee (Date: 12.03.2025, Decision No: TABED 1-25-1083).

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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Clinical accuracy of the posterior fat pad sign for detecting elbow fractures in children

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ABSTRACT

Aims: To assess the diagnostic accuracy of the posterior fat pad sign (PFPS) on lateral elbow radiographs in identifying fractures in pediatric patients with acute elbow trauma, and to evaluate whether angle measurement of PFPS enhances diagnostic performance.

Methods: This retrospective study included patients under 18 years who presented with elbow trauma to a tertiary emergency department between January 2022 and January 2025. All patients underwent lateral elbow radiography followed by computed tomography (CT), which served as the reference standard. The presence of PFPS and the angle between the posterior fat pad and humeral shaft were independently assessed by two emergency physicians blinded to CT findings. Diagnostic metrics—including sensitivity, specificity, likelihood ratios, and misclassification rates—were calculated for both visual PFPS presence and angle-based assessment.

Results: Of the 213 patients included, 65.3% had CT-confirmed elbow fractures. PFPS was present in 66.2% of cases and demonstrated a sensitivity of 62.2% and specificity of 81.3% for predicting fractures. The optimal PFPS angle cutoff was 16.5°, which yielded a sensitivity of 81.3% and specificity of 62.2%.

Conclusion: PFPS is a reliable radiographic indicator of pediatric elbow fractures. Quantitative angle measurement improves diagnostic accuracy and may support more consistent decision-making in emergency settings where radiographic findings are ambiguous.

Keywords: Posterior fat pad sign, pediatric elbow fracture, diagnostic accuracy

INTRODUCTION

Elbow trauma is a common cause of emergency department visits among children, often resulting from low-energy falls or sports-related injuries. While many of these injuries are minor, a significant proportion involves occult or radiographically subtle fractures, especially in younger children whose epiphyseal anatomy is still developing. Supracondylar and radial neck fractures, in particular, may not be visible on initial X-rays, making clinical and radiologic correlation essential for timely diagnosis and appropriate management.[1-3]

The posterior fat pad sign (PFPS) is a widely recognized indirect radiographic indicator of intra-articular effusion, often suggesting the presence of an occult fracture when no cortical disruption is visible. In pediatric elbow injuries, PFPS has been associated with both supracondylar and radial head fractures, and its diagnostic value continues to be the subject of clinical scrutiny. Recent investigations have emphasized the importance of observer reliability and imaging quality in interpreting the PFPS, with varying reports of its sensitivity and specificity depending on methodology and patient selection.[4-7] In addition, studies have explored the use of adjunct modalities such as ultrasonography and digital tomosynthesis to complement traditional radiography, particularly in ambiguous cases.[8-10]

This study aims to evaluate the diagnostic accuracy of the PFPS in identifying elbow fractures confirmed by computed tomography (CT) in children with acute elbow trauma.

METHODS

This retrospective diagnostic accuracy study was conducted in the emergency department of a tertiary care hospital. The study included patients under the age of 18 who presented with acute elbow trauma between January 1, 2022, and January 1, 2025. Approval was obtained from the Ethics Committee of İstanbul Yeni Yüzyıl University (Date: 07.05.2025, Decision No: 2025/05-1541), and all procedures were performed in accordance with the Declaration of Helsinki.

Patients were eligible if they were younger than 18 years, presented to the emergency department with blunt elbow

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trauma, underwent lateral elbow radiography at the time of admission, and subsequently received a CT scan for diagnostic confirmation. Patients were excluded if initial imaging was unavailable, if there was evidence of open fractures or dislocations on presentation, or if CT was not performed within 24 hours of admission.

Radiographs were retrospectively reviewed by two emergency physicians blinded to CT findings. The presence or absence of a PFPS was recorded for each case. As part of the radiographic assessment protocol, the presence of the PFPS was visually identified on lateral elbow radiographs. A representative image from the study cohort is provided to illustrate the diagnostic criteria used (Figure 1). Lateral X-ray of the left elbow demonstrating the "anterior fat pad sign" and "PFPS." The anterior fat pad, normally visible and seen here elevated and displaced anteriorly, suggests joint effusion. The posterior fat pad, which is not typically visualized on normal radiographs, is visible and displaced posteriorly, indicating an occult intra-articular fracture—most commonly a supracondylar fracture in pediatric patients or a radial head fracture in adults. For patients with a visible PFPS, the angle between the humeral shaft and the posterior fat pad was measured using standardized DICOM viewing software. CT images were independently evaluated by a board-certified radiologist to confirm the presence or absence of elbow fractures, which served as the reference standard. The primary outcome of the study was the diagnostic performance of PFPS—presence versus absence—in predicting CT-confirmed elbow fractures.

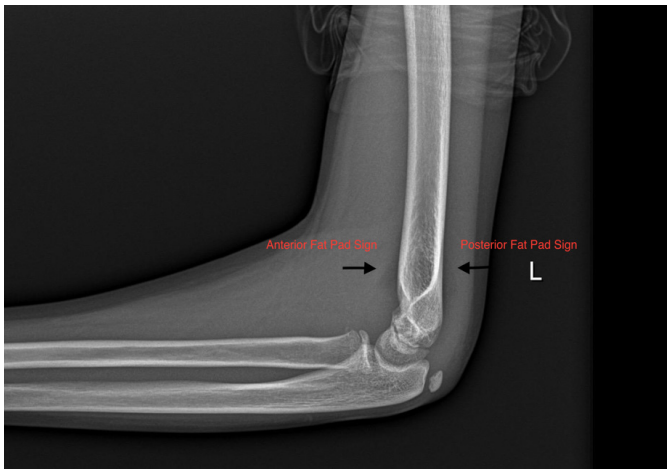

Figure 1. Lateral elbow radiograph illustrating elevated anterior and visible posterior fat pad signs, indicative of joint effusion and possible occult fracture

Statistical Analysis

The data analyses were performed using R version 4.4.2. Descriptive statistics were presented as frequencies and percentages for categorical variables and as median [interquartile range (IQR)] for non-normally distributed continuous variables. Normality was assessed visually using histograms and Q–Q plots, and numerically with the Shapiro–Wilk test and skewness statistics. Diagnostic performance metrics of PFPS presence for predicting elbow fractures confirmed by CT were calculated, including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (+LR), negative likelihood ratio (–LR), and the Youden index. A 95% confidence interval (CI) was reported for all estimates, where applicable, using the Wilson method. Receiver operating characteristic (ROC) curve analysis was performed for PFPS angle, with the area under the curve (AUC) and 95% CI calculated using the DeLong method. The optimal PFPS angle cutoff was determined by maximizing the Youden index. Diagnostic metrics at this cutoff, including sensitivity, specificity, +LR, and –LR, were also calculated, with 95% CIs derived using the Katz method for likelihood ratios. False discovery rate (FDR) and false omission rate (FOR) were calculated both at the observed prevalence and modeled across a range of hypothetical disease prevalence levels (5% to 95%) to provide a clinical misclassification profile of PFPS. FDR and FOR curves were plotted accordingly. All statistical tests were two-sided, and p-values <0.05 were considered statistically significant.

RESULTS

A total of 213 patients with elbow trauma were included in the study (Figure 2). The median age of the cohort was 10 years [interquartile range (IQR) 7–12], and 45.1% were male. Right-sided injuries were more common (55.9%), and the dominant arm was involved in 48.8% of cases. The most frequent mechanism of injury was fall from standing height (37.6%), followed by fall from height (25.4%). Swelling, tenderness, and limited range of motion were observed in 81.7%, 79.8%, and 78.9% of the patients, respectively. PFPS was present in 66.2% of cases (Table 1).

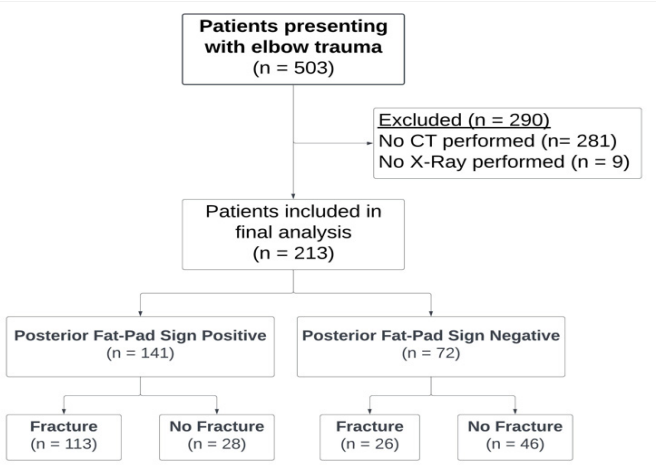

Figure 2. Patient flowchart

CT confirmed elbow fracture in 139 patients (65.3%), with supracondylar fractures being the most prevalent subtype (33.8%). Among those with fractures, 40.4% had displaced fractures (≥2 mm). Metaphyseal and intra-articular locations were the most frequent fracture sites. The majority of CT scans were performed due to clinical suspicion (45.1%) or protocol-based indications (28.6%). Hospital admission was required in 28.2% of the cohort, and 21.1% underwent surgical intervention (Table 2).

In the diagnostic performance analysis, PFPS presence demonstrated a sensitivity of 0.622 (95% CI: 0.501–0.732) and a specificity of 0.813 (95% CI: 0.738–0.874) for predicting

Table 1. Baseline demographic and clinical characteristics of included patients

Variable	Subcategory	(n=213)	%/[IQR]
Age (years), median [IQR]		10	[7–12]
Sex	Male	96	45.1%
Side of injury	Left	94	44.1%
	Right	119	55.9%
Dominant arm involved	Yes	104	48.8%
Mechanism of injury	Fall from standing height	80	37.6%
	Fall from height	54	25.4%
	Direct blow	8	3.8%
	Sports injury	23	10.8%
	Motor vehicle accident	14	6.6%
	Other	34	16.0%
Swelling	Yes	174	81.7%
Tenderness	Yes	170	79.8%
Limited range of motion	Yes	168	78.9%
Pain score (VAS), median [IQR]		7	[6–8]
BMI (kg/m²), median [IQR]		18.1	[15.5–20.9]
PFPS present		141	66.2%

BMI: Body-mass index, IQR: Interquartile range, PFPS: Posterior fat pad sign, VAS: Visual Analog Scale

Table 2. CT findings, management, and outcomes of included patients

Variable	Subcategory	(n=213)	%/[IQR]
Fracture on CT		139	65.3%
Displaced fracture (≥2 mm)		86	40.4%
Fracture type	No fracture	74	34.7%
	Supracondylar	72	33.8%
	Radial head	29	13.6%
	Olecranon	6	2.8%
	Capitellum	10	4.7%
	Coronoid process	8	3.8%
	Monteggia variant	7	3.3%
	Other	7	3.3%
Fracture location	No fracture	74	34.7%
	Metaphyseal	47	22.1%
	Intra-articular	77	36.2%
	Other	15	7%
Reason for CT	Clinical suspicion	96	45.1%
	Protocol-based	61	28.6%
	Inconclusive X-ray	39	18.3%
	Other	17	8%
Hospital admission		60	28.2%
Surgical intervention		45	21.1%
Days until pain resolution, median [IQR]		12	[6–15]

CT: Computed tomography, IQR: Interquartile range

CT-confirmed elbow fractures. The PPV was 0.639 (95% CI: 0.517–0.749), and the NPV was 0.801 (95% CI: 0.726–0.864). The +LR was 3.323 (95% CI: 2.251–4.906), and the –LR was 0.465 (95% CI: 0.344–0.630). The Youden index was calculated as 0.435 (Table 3).

Table 3. Diagnostic performance of posterior fat pad sign for predicting elbow fractures confirmed by computed tomography

Metric	Value	95% CI
Sensitivity	0.622	0.501-0.732
Specificity	0.813	0.738-0.874
Positive predictive value	0.639	0.517-0.749
Negative predictive value	0.801	0.726-0.864
Positive likelihood ratio	3.323	2.251-4.906
Negative likelihood ratio	0.465	0.344-0.630
Youden index	0.435	-

CI: Confidence interval

Analysis of PFPS angle yielded an AUC of 0.698 (95% CI: 0.621–0.775) (Figure 3). The optimal cutoff point was determined as 16.5°, providing a sensitivity of 0.813 and a specificity of 0.622 at this threshold. The corresponding +LR and –LR were 2.149 (95% CI: 1.587–2.908) and 0.301 (95% CI: 0.204–0.444), respectively (Table 4).

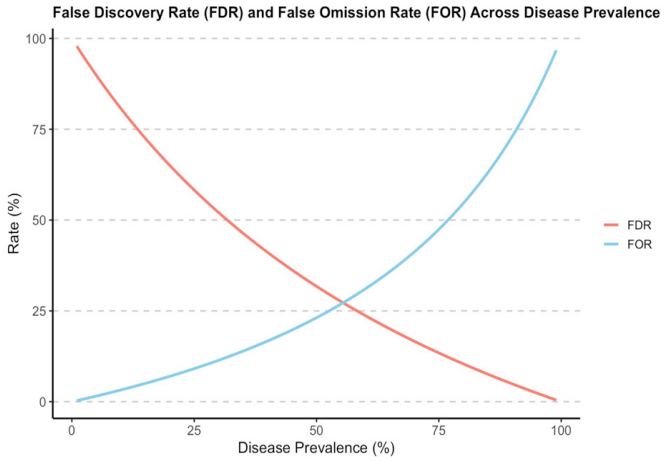

Figure 3. Receiver operating characteristic curve of posterior fat pad sign angle for predicting elbow fractures confirmed by computed tomography

Table 4. Diagnostic performance of posterior fat pad sign angle for predicting elbow fractures confirmed by computed tomography

Metric	Value	95% CI
Area under the curve	0.698	0.621-0.775
Optimal PFPS angle cutoff (°)	16.5	-
Sensitivity at cutoff	0.813	-
Specificity at cutoff	0.622	-
Positive likelihood ratio	2.149	1.587-2.908
Negative likelihood ratio	0.301	0.204-0.444

The optimal cutoff was determined using the Youden index. Data are presented as point estimate and 95% confidence interval where applicable. CI: Confidence interval, PFPS: Posterior fat pad sign

Beyond conventional diagnostic performance metrics, FDR and FOR were analyzed across varying disease prevalence levels to assess the clinical misclassification profile of PFPS.

At a disease prevalence of 10%, FDR was 80.7%, decreasing progressively to 4.9% at 90% prevalence. Conversely, FOR increased from 3.2% at 10% prevalence to 73.0% at 90% prevalence (Table 5, Figure 4).

Table 5. False discovery and omission rates of posterior fat pad sign at varying disease prevalence levels for predicting elbow fractures confirmed by computed tomography

Disease prevalence	FDR	FOR
10%	80.7%	3.2%
20%	65.1%	7.0%
30%	52.1%	11.4%
40%	41.1%	16.7%
50%	31.8%	23.1%
60%	23.7%	31.1%
70%	16.6%	41.2%
80%	10.4%	54.6%
90%	4.9%	73.0%

FDR: False discovery rate, FOR: False omission rate

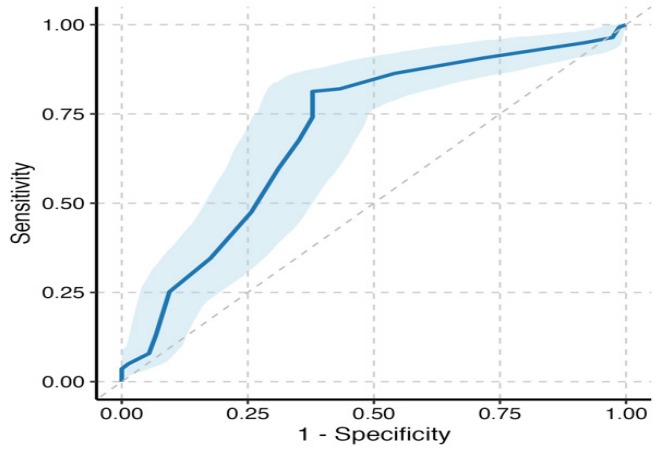

Figure 4. False discovery rate and false omission rate curves of posterior fat pad sign across varying disease prevalence for predicting elbow fractures confirmed by computed tomography

DISCUSSION

This study demonstrates that the PFPS has substantial diagnostic value in detecting elbow fractures in children, especially when confirmed by CT. The presence of PFPS on initial radiographs was significantly associated with CT-confirmed fractures, and its diagnostic accuracy improved further when the posterior fat pad angle was taken into account.

Pediatric elbow fractures represent a significant portion of orthopedic trauma cases in children and are associated with both immediate and long-term functional consequences. Supracondylar and lateral condyle fractures, in particular, can lead to growth disturbances, neurovascular injury, and joint stiffness if not promptly diagnosed and appropriately managed.[11] As such, early recognition is essential not only to prevent complications but also to optimize surgical outcomes and rehabilitation potential. Recent data also suggest that simulation-based training in the management of pediatric elbow fractures improves procedural accuracy and reduces complication rates among orthopedic trainees.[12] Furthermore, postoperative pain control and opioid-sparing strategies, such as brachial plexus block, have been explored to improve perioperative safety in this population.[13]

Conventional radiography is the primary imaging modality used in the evaluation of pediatric elbow injuries due to its rapid availability and low radiation exposure. However, plain X-rays may miss subtle or occult fractures, particularly when bone displacement is minimal or absent. In such cases, CT provides superior sensitivity and can confirm intra-articular involvement, although concerns about radiation dose limit its routine use in children.[14] The PFPS, visible on lateral radiographs, serves as an important indirect indicator of intra-articular effusion and potential fracture. Several studies have emphasized that the presence of PFPS—especially in the absence of visible cortical disruption—should prompt further evaluation or follow-up imaging.[15] The introduction of quantitative approaches, such as measuring the angle between the posterior fat pad and the humeral shaft, may reduce subjective variability and improve diagnostic precision.[16]

Our findings confirm the diagnostic value of the PFPS in pediatric elbow trauma, especially when assessed with angular measurement. The observed association between PFPS angle and fracture presence is consistent with prior literature emphasizing the limitations of plain radiographs in detecting subtle injuries. Afacan et al.[17] reported improved diagnostic performance when PFPS was considered alongside conventional imaging, supporting its role in guiding further evaluation or treatment decisions. The structured use of PFPS angle in our study also aligns with recommendations by Poppelaars et al.,[18] who proposed objective definitions to improve interobserver consistency. Their findings indicate that visible posterior fat pads should not be dismissed, even when no overt fracture is identified on X-ray. Similarly, Burnier et al.[19] observed that PFPS often coincides with occult fractures, reinforcing the clinical relevance of this radiographic marker in early diagnosis.

Limitations

This study has several limitations. As a retrospective, single-center analysis, its findings may not be generalizable to other clinical settings or populations. The sample consisted exclusively of patients who underwent CT imaging, which may have introduced a selection bias toward more severe or ambiguous cases. Additionally, interpretation of the PFPS may be subject to interobserver variability, although efforts were made to standardize angle measurement. The absence of follow-up data also precludes assessment of long-term clinical outcomes.

CONCLUSION

The PFPS remains a valuable radiographic finding in the evaluation of pediatric elbow trauma. Its presence was strongly associated with CT-confirmed fractures, and the addition of quantitative angle measurement significantly enhanced diagnostic accuracy. These findings support the integration of both visual and angle-based assessment of

PFPS into emergency radiographic evaluation protocols for children with suspected elbow fractures.

ETHICAL DECLARATIONS

Ethics Committee Approval

Approval was obtained from the Ethics Committee of İstanbul Yeni Yüzyıl University (Date: 07.05.2025, Decision No: 2025/05-1541).

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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Scientific output on dyspepsia in internal medicine: a quantitative and visual bibliometric approach

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ABSTRACT

Aims: Dyspepsia is a prevalent and multifaceted gastrointestinal disorder that imposes a significant global health burden. Despite its widespread occurrence and complex clinical presentation, there has been no comprehensive bibliometric analysis addressing the scientific output on dyspepsia within the domain of general internal medicine. This study aims to quantitatively and visually evaluate global scientific trends, key contributors, thematic structures, and collaborative networks in dyspepsia research published under the category of internal medicine over the last two decades.

Methods: A total of 984 articles published between 2005 and 2024 were retrieved from the Web of Science Core Collection. Bibliometric indicators such as publication trends, top journals, highly cited articles, influential institutions, keyword co-occurrences, and collaboration patterns at the institutional and international levels were analyzed using VOSviewer and SPSS.

Results: The number of publications on dyspepsia has steadily increased, with the highest output observed in 2022. The most frequently used keywords included dyspepsia, *Helicobacter pylori*, and functional dyspepsia, which clustered with terms such as anxiety, depression, and endoscopy. Cureus Journal of Medical Science emerged as the top publishing journal, while the University of Bologna was the most cited institution. Collaboration network visualizations showed strong partnerships primarily among East Asian and North American institutions.

Conclusion: Dyspepsia research within internal medicine has gained momentum, especially in relation to functional dyspepsia and its psychosomatic dimensions. Despite the growing volume of publications, fragmentation across journals and disciplines remains. This study provides a strategic overview of the literature and highlights key areas for future research and policy development.

Keywords: Dyspepsia, functional dyspepsia, bibliometric analysis, internal medicine, *Helicobacter pylori*

INTRODUCTION

Dyspepsia is a common gastrointestinal disorder characterized by symptoms such as upper abdominal discomfort, bloating, early satiety, and epigastric pain, significantly affecting patients' quality of life and increasing healthcare costs globally.[1,2] While organic causes can sometimes be identified, the majority of cases fall under functional dyspepsia (FD), which is defined by the absence of detectable structural abnormalities. The pathophysiology of FD involves a complex interplay of factors such as altered gastric motility, visceral hypersensitivity, gut microbiota dysbiosis, and psychological comorbidities like anxiety and depression.[3,4] This multifactorial nature has made FD a subject of increasing research interest across various medical disciplines, including internal medicine, psychiatry, and gastroenterology.

In recent years, the scientific literature on dyspepsia has grown considerably, reflecting heightened academic and clinical interest in understanding its mechanisms and management strategies.[5,6] Bibliometric analysis has emerged as a valuable method to quantitatively assess research trends and developments within specific topics. Previous studies have explored selected aspects of FD, such as its association with mental health,[4] alternative treatments like acupuncture,[6] or broader motility disorders including gastroparesis.[7] However, there is currently no comprehensive bibliometric analysis that specifically examines dyspepsia-related publications within the field of internal medicine.

Given the ongoing global burden of dyspepsia, along with evolving clinical approaches to its diagnosis and treatment, identifying trends and gaps in the literature has become increasingly important. Despite rising research activity, no study to date has mapped the bibliometric landscape of dyspepsia within the general internal medicine literature. This study aims to fill that gap by analyzing key publication patterns, major contributors, and collaborative networks over the past two decades. The results are intended to inform

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clinicians, researchers, funding bodies, and journal editors by highlighting critical areas of focus and emerging themes.

Using data from the Web of Science Core Collection between January 1, 2005, and December 31, 2024, this bibliometric study focuses on dyspepsia publications classified under general internal medicine. It examines temporal publication trends, leading journals and institutions, prolific authors, citation metrics, keyword frequencies, and co-authorship networks. Ultimately, the study aims to evaluate how scientific interest in dyspepsia has evolved and to provide a clearer picture of its position within internal medicine research.

METHODS

Ethics

This study relies solely on open-access bibliometric information, thus ethical committee approval was not needed. Because there are no biomedical applications or direct interventions with human subjects, no ethical restrictions pertain to the research conducted.

Database and Scope

The primary source of this bibliometric study's data is the WoS Core Collection, which is a reputable academic database that consists of high-quality peer-reviewed scholarly publications. Due to its deep coverage and high reliability, this database is one of the first choices for bibliometric studies.

The analysis was restricted to publications that featured the word "dyspepsia" in their title, abstract, or keyword (the so-called "topic" filter) and within the "medicine general internal" category in WoS. This category was selected because it encompasses core clinical journals that publish research relevant to adult internal medicine, thereby providing a representative view of dyspepsia research from a generalist medical perspective. However, this focus may exclude relevant articles from subspecialties such as gastroenterology or psychiatry, and this limitation should be acknowledged. The timeframe for publication was set for between January 1, 2005, and December 31, 2024. Only records which were labeled "article" were included in the dataset. Reviews, editorials, conference papers, letters, and book chapters were excluded (Table 1).

Table 1. Data set construction and analysis process

Step	Description
1. Data collection	Data were retrieved from the Web of Science platform using the keyword 'dyspepsia' with the 'topic' filter applied.
2. Category selection	Only publications classified under the 'medicine general internal' category in the Web of Science Categories section were included.
3. Document type limitation	Only records categorised as "article" were selected for analysis.
4. Data analysis	A total of 984 articles were examined using the bibliographic analysis method.
5. Presentation of findings	The results of the analysis were presented in detail through tables and graphical illustrations.

Data Collection Process

Following the application of inclusion and exclusion criteria, a total of 984 articles were retained for final analysis. Completion of data collection was scheduled from January to March 2024. Initially, relevant articles underwent a review process wherein the titles, abstracts, and keywords of all retrieved articles were checked for relevance and duplicates were removed.

The following bibliometric data was carefully collected for each article:

- Title of the article
- Author(s)
- Article publication date
- Name of the journal
- Journal impact factor (if applicable)
- Citation count
- Affiliated institution(s) of the authors
- Corresponding author's country
- Keywords that seem to be used often

All data was checked and confirmed independently by two researchers. Any inconsistency was settled through discussions until a consensus was reached.

Survey Methodology

VOSviewer software (v. 1.6.11, Leiden University, The Netherlands) was used to conduct bibliometric analysis. For all visualizations, the layout algorithm was set to "LinLog/modularity", and "Association Strength" was selected as the normalization method. A minimum cluster size was determined automatically by the software. It creates and visualizes bibliometric networks which was the underlying focus of this study. Key areas of focus included:

- **Citations by year:** Analysis of the yearly frequency of published documents.
- **Journal mapping:** Determine which journals have published most articles on dyspepsia.
- **Citation analysis:** Study citation counts of the most popular authors, articles, institutions, and years of publications.
- **Keyword co-occurrence analysis:** Creation of visual representations of words along with other words from different contexts.
- **Research collaborations:** Showcase collaboration between different institutions on a single-research basis.
- **Country collaborations:** Study scientific collaborations with other countries.
- **Creator network analysis:** Analyze coauthorship to identify networks and graph the relationships between independant collaboratively involved writers.

For the purpose of term co-occurrence analysis, a minimum threshold of 5 occurrences per keyword was established. This

limit ensured that no conceptual patterns were ignored by focusing only on terms which were meaningfully used.

Statistical and Visual Analysis

Publication and citation metrics were summarized with descriptive statistics which included publication counts, journal distributions, and citations frequencies and percentages. Trends over time in scientific output were assessed with SPSS version 25.0 (IBM Corp.).

The following analytic and visual methods were employed:

- Annual publication trends were analyzed with line and bar graphs.
- Proportional tables were employed to represent journal and institutional output.
- Collaboration structures were illustrated with network maps generated using VOSviewer.
- Thematic or regional publication intensity were represented with density visualizations.
- Authors and keywords were grouped by thematic or regional proximity using clustering techniques.

The intensity of collaboration between the institutions and countries was illustrated by line thickness on the visual maps. In addition, cluster coefficients and link strengths were calculated to evaluate the cohesiveness and the density of research collaboration on the dyspepsia literature.

RESULTS

Analysis of Annual Publication Trends

Figure 1 illustrates the chronological distribution of studies included in the dataset retrieved from the Web of Science database.

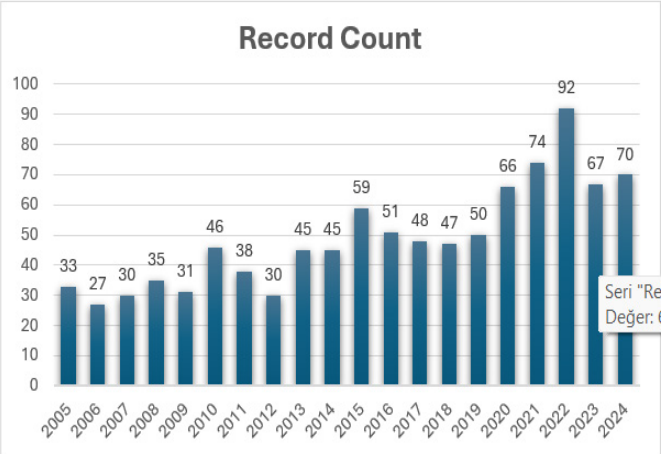

Figure 1. Annual distribution of articles

Figure 1 presents the annual distribution of articles published with the keyword "dyspepsia" between the years 2005 and 2024. The trend began in 2005 with 33 publications. Although fluctuations were observed in the initial years, an upward trend became evident starting from 2010. The number of publications reached 46 in 2010, increased to 59 in 2015, and reached 66 by 2020. The highest number of publications was recorded in 2022, with a total of 92 articles. This increase clearly reflects the growing academic interest in the topic of dyspepsia, particularly in the last decade.

In 2021, a total of 74 articles were published, followed by 67 in 2023 and 70 in 2024, indicating that research activities on the topic remain at a consistently high level. The overall increase in annual publication numbers underscores the rising medical and clinical significance of dyspepsia and suggests that the topic has secured a lasting position in the scientific literature.

Journals Contributing Most to the Field Literature

Based on data obtained from the Web of Science database, the distribution of journals that have published the highest number of articles on the topic of "dyspepsia" within the "medicine general internal" category is presented in Table 2.

Table 2. Journals of publication, number of articles, and proportional distributions

Publication titles	Record count	% of 959
Cureus Journal of Medical Science	69	7.01%
Medicine	44	4.47%
Journal of Clinical and Diagnostic Research	32	3.25%
Journal of Evolution of Medical and Dental Sciences Jemds	31	3.15%
Internal Medicine	27	2.74%
Terapevticheskii Arkhiv	25	2.54%
Journal of Clinical Medicine	22	2.24%
Bmj Open	19	1.93%
Current Medical Research and Opinion	14	1.42%
International Journal of Clinical Practice	14	1.42%
Others	687	69.82%

Table 2 presents the number and percentage distribution of 984 articles on "dyspepsia" published under the "medicine general internal" category. The journal with the highest number of publications is Cureus Journal of Medical Science, which accounts for 69 articles (7.01%). This is followed by Medicine (44 articles, 4.47%), Journal of Clinical and Diagnostic Research (32 articles, 3.25%), and Journal of Evolution of Medical and Dental Sciences *(JEMDS)* (31 articles, 3.15%). These four journals play a central role in the scientific dissemination of dyspepsia-related studies.

The top ten journals collectively published 297 articles, representing 30.18% of the entire dataset. The remaining 687 articles (69.82%) fall under the "others" category, indicating that they are distributed across a wide range of different journals. This distribution suggests that research on dyspepsia is not limited to a few core journals but is rather dispersed throughout a broad spectrum of academic publications. This variety reflects the interdisciplinary nature of the subject and its tendency to be addressed in diverse scholarly platforms.

Detailed Bibliometric Analysis of Highly Cited Publications: Authors, Titles, Journals, Years, and Citation Metrics

In the Web of Science database, the most highly cited studies related to the topic of "dyspepsia" within the "medicine

general internal" category are presented in detail in Table 3, including author information, journal names, publication years, and citation counts.

The data presented in Table 3 comprehensively highlights the most highly cited publications within the "medicine general internal" category on the topic of dyspepsia. According to the data, the most cited article is by Galiè et al. (2005), published in the New England Journal of Medicine, which focuses on sildenafil citrate therapy for pulmonary arterial hypertension and has received 1.849 citations. Although this study is not directly related to dyspepsia, it appears in the analysis due to category-based inclusion criteria and represents the top-cited publication within the selected scope.

The second most cited article is by Noble et al. (2011), published in The Lancet, which presents a randomized controlled trial on pirfenidone use in patients with idiopathic pulmonary fibrosis. This article has received 1.616 citations.

In third place is a study by McColl (2010), published in the New England Journal of Medicine, which directly addresses *Helicobacter pylori* infection. This article has garnered 565 citations and is considered a key reference in the literature regarding the etiology of dyspepsia.

The fourth article, authored by Simonneau et al. (2008), evaluates the addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension. Published in the Annals of Internal Medicine, it has received 510 citations.

Finally, in fifth place, Webster et al. (2005) published a meta-analysis comparing tacrolimus and ciclosporin as primary immunosuppression in kidney transplant recipients, in the British Medical Journal (BMJ). This study has accumulated 413 citations.

These findings demonstrate that while some of the most cited articles are not exclusively focused on dyspepsia, their inclusion within the "medicine general internal" category contributes to the broader scientific landscape in which dyspepsia research is situated.

Analytical Evaluation of Publications by Institutions with the Highest Citation Counts

In the Web of Science database, institutions affiliated with authors who published studies on "dyspepsia" within the "medicine general internal" category were analyzed in terms of the number of documents and the total citations received. This information is presented in detail in Table 4.

Table 4. Top cited institutions and distribution of their publications according to web of science data

Organization	Documents	Citations
University of Bologna	9	3101
The University of Sydney	5	804
The University of Adelaide	9	691
Mayo Clinic	8	506
Kawasaki Medical School	9	389

The data in Table 4 reveal the institutions that have made the most significant academic impact in the field of dyspepsia within the "medicine general internal" category, as measured by citation counts. The University of Bologna stands out as the top-performing institution, with 9 publications garnering a total of 3.101 citations, reflecting its substantial influence and leading contributions in dyspepsia research.

The University of Sydney ranks second with 5 publications and 804 citations, indicating that despite a lower publication count, its research output has had a high scientific impact. Similarly, The University of Adelaide has achieved 691 citations from 9 publications, reflecting a strong academic contribution.

Trends in Keyword Usage

The most frequently used keywords related to the topic of "dyspepsia" in the Web of Science database and their interrelationships are visualized in Figure 2.

The bibliometric analysis was conducted using VOSviewer software, and a minimum threshold of 5 occurrences was applied to the selection of keywords. This criterion ensured that only keywords appearing at least five times were included in the analysis, allowing the evaluation to focus on more meaningful, widely used, and representative terms.

Although a total of 2.103 unique keywords were identified, only 90 met the threshold for inclusion. This methodological approach indicates the study's focus on in-depth analysis of conceptual structures and relationships based on high-frequency terms.

Table 3. Author information, journal titles, publication years, and citation counts of the most cited articles on the topic of "dyspepsia"

No	Author(s)	Article title	Journal name	Year of publication	Number of citations
1	Galiè N, et al.	Sildenafil citrate therapy for pulmonary arterial hypertension	New England Journal of Medicine	2005	1849
2	Noble PW, et al.	Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials	Lancet	2011	1616
3	McColl KEL.	*Helicobacter pylori* Infection	New England Journal of Medicine	2010	565
4	Simonneau G, et al.	Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension a randomized trial	Annals of Internal Medicine	2008	510
5	Webster AC et al.	Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data	Bmj-British Medical Journal	2005	413

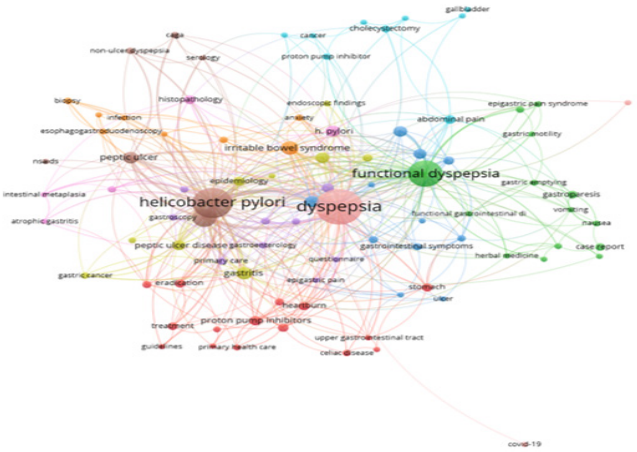

Figure 2. Co-occurring keywords and their usage frequencies

The analysis revealed the most frequently used keywords and the strongest relational ties among them. In total, 460 keyword connections were identified, and the keywords were grouped into 10 distinct clusters. These findings help map terminological patterns and conceptual proximities in the field and contribute to identifying key concepts for future research.

Figure 2 visualizes the most frequently used keywords in academic publications on dyspepsia within the "Medicine General Internal" category and the relationships among these terms. This analysis highlights conceptual focal points in the dyspepsia literature and illustrates the main thematic concentrations.

According to the data, the most frequently used keyword is "dyspepsia", with a total of 213 occurrences. This indicates that the topic of focus holds a central position in the literature and is widely examined. The second most frequent term is "*Helicobacter pylori*" with 154 occurrences, reflecting its role as one of the most common etiological factors in dyspepsia. This relationship emphasizes the microbiological dimension of the disorder.

"FD", with 116 occurrences, ranks third and indicates the prominence of studies addressing dyspepsia cases without identifiable organic causes. This term has gained increasing attention in recent years due to the growth in functional gastroenterological research.

Other less frequent but clinically significant keywords include "endoscopy" (54 times), "peptic ulcer" (23 times), and "gastritis" (27 times). These concepts represent diagnostic methods and comorbid conditions commonly evaluated alongside dyspepsia. Endoscopy, in particular, stands out as a fundamental diagnostic tool in differentiating dyspepsia, while peptic ulcer and gastritis are often considered concurrent pathologies.

In general, the results of the keyword analysis suggest that publications on dyspepsia focus predominantly on diagnosis, etiology, and clinical subtypes. The frequency of keyword usage serves as an important indicator of both current trends in the literature and priority concepts for future investigations.

Institutional-Level Academic Collaboration: Analytical Evaluation

The structure of scientific collaboration among institutions affiliated with researchers publishing on dyspepsia has been examined in detail. The density and network of inter-institutional partnerships reflect the academic interaction at the organizational level. The results of this analysis are visualized in Figure 3.

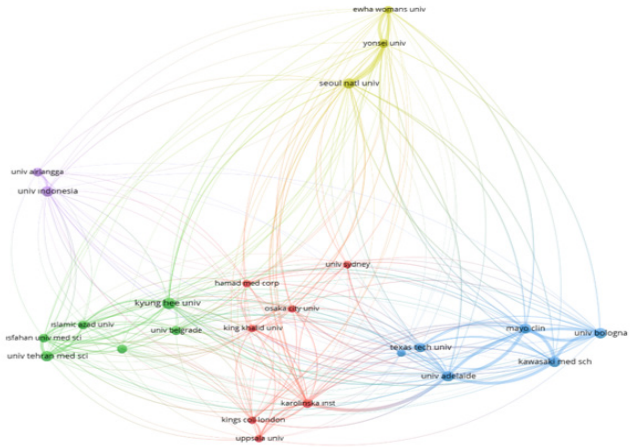

Figure 3. Bibliometric network visualization of inter-institutional collaborations

The collaboration analysis was conducted using VOSviewer software. In the resulting map, different colors represent institutions grouped by thematic proximity or geographical clustering. The lines connecting institutions indicate academic collaborations, and the thickness of the lines reflects the intensity and continuity of these interactions. This visualization helps uncover the institutional distribution of dyspepsia-related academic output and offers strategic insight for identifying existing strong partnerships and potential future collaborations.

The analysis shows that institutional collaborations in dyspepsia research are particularly concentrated among a few universities. Notably, Seoul National University and Karolinska Institutet stand out with 23 connections each. This highlights their central role in both scientific productivity and international cooperation in dyspepsia studies.

Mayo Clinic and The University of Sydney also demonstrate strong academic networks, each with 22 connections, indicating their active participation in multicenter studies. Additionally, Texas Tech University and Kyung Hee University, each with 21 connections, are also among the prominent institutions with high collaborative capacity both regionally and globally.

Overall, the findings indicate that scientific output on dyspepsia is not limited to individual researchers but is often based on robust institutional networks. These analyses make the structural characteristics of current collaborations visible and provide strategic data for developing new research partnerships.

Researcher-Level Academic Collaboration Analysis

Based on publications retrieved from the Web of Science, collaborative networks among researchers working in the field of dyspepsia were analyzed in detail. The results reveal the intensity, structure, and clustering patterns of academic interactions between authors and provide key insights into how much scientific production is based on collaboration. The results are visualized in Figure 4.

Figure 4. Collaboration map showing academic partnerships (larger circles represent prominent researchers, while lines indicate co-authored studies.)

Figure 4 visualizes bibliographic connections among researchers who have published at least five articles on dyspepsia. Although a total of 5,053 authors were evaluated, only 11 authors met the inclusion threshold and were included in the analysis. This threshold ensures the inclusion of researchers who have made significant academic contributions, thereby increasing the reliability and scientific value of the findings.

Each researcher is represented as a circle in the map. The size of the circle indicates the author's contribution to the literature, and the lines between circles represent co-authorship and collaborative efforts. Clusters are distinguished by color and represent researcher groups formed based on thematic or geographical proximity.

In the red cluster, Ha, Nayoon and Kim, Jisung are notable for their central positions and multiple connections. These two authors have established strong collaborative ties, particularly in Asia-centered dyspepsia research. Miwa, Hiroto and Haruma, Ken, who are also part of this cluster, play key roles in both intra- and inter-cluster collaborations. Ahmet Cumhur Dülger is also part of this group and displays an internationally collaborative profile.

In the green cluster, Watanabe, Toshio stands out as the most connected author. Alongside Fujiwara, Yasuhiro, Tanigawa, Tetsuya, and Tominaga, Kazunari, this group forms a strong thematic network, particularly in Japan-based studies. Their close collaboration and high output make this cluster a prominent example of regional academic synergy.

Country-Level Citation Distribution

Citations to publications on dyspepsia were analyzed on a country-by-country basis using data from the Web of Science database. This analysis highlights how citation distributions vary at national and regional levels and reveals the intensity of academic collaboration between countries. The findings identify the countries that shape the global literature on dyspepsia and are visualized in Figure 5.

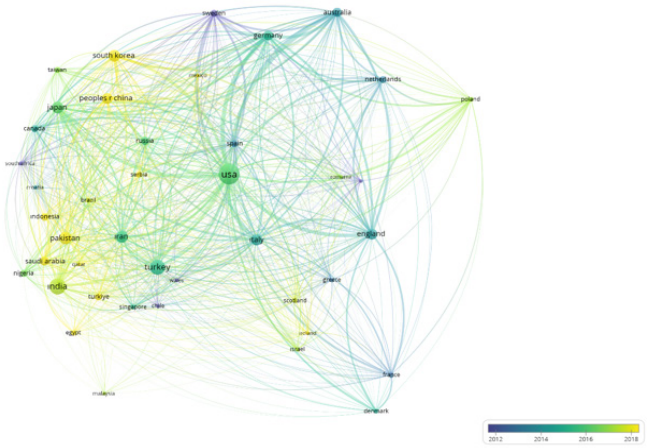

Figure 5. Visualization of the geographic distribution of academic citations by country

Figure 5 presents a detailed visualization of the geographical distribution of citations and inter-country academic collaboration structures based on publications in the Web of Science (WoS). Only countries with at least five publications were included in the analysis. Out of 89 countries, 42 met the inclusion criteria. These countries were grouped into five clusters, based on similar research trends or collaborative networks.

This mapping contributes to understanding global research dynamics and provides a valuable foundation for assessing international research contributions and trends in dyspepsia literature.

The connections between countries represent academic collaborations, with line thickness indicating the strength of partnerships. The size of each country's node reflects its level of contribution to the literature. A color scale indicates the temporal distribution of publication activity, highlighting the evolution of research trends over time.

The United States appears as the central node and the most significant contributor to dyspepsia literature, with the broadest international collaboration network. The U.S. has particularly strong ties with countries such as the United Kingdom, China, Germany, Italy, Canada, Japan, and France, reflecting its global leadership in the field.

Among European countries, Germany, the United Kingdom, France, Italy, Spain, and the Netherlands are notable for both high citation counts and dense inter-country collaborations, forming a robust Europe-centered academic network.

In Asia, China, India, Japan, and South Korea stand out. China, with strong connections to the U.S., plays a significant role in the global research network. Japan, with well-balanced collaborations with both American and European countries, demonstrates its strong presence in the international research arena. India and South Korea also contribute significantly through both regional and global partnerships.

Turkiye, with a moderate number of collaborations, acts as a regional bridge, particularly through its academic relationships with Iran, Pakistan, and European countries. Canada, Australia, and Brazil have also established distinct regional collaboration networks and maintain strong ties with major contributors like the United States.

Countries with more limited but focused collaborations include Sweden, Switzerland, Greece, Israel, and Denmark, contributing to the literature through specialized thematic partnerships.

Mayo Clinic, with 8 publications and 506 citations, ranks fourth, followed by Kawasaki Medical School, which published 9 articles and received 389 citations, placing it in fifth position. These institutions have clearly served as key centers of knowledge production in the field of dyspepsia.

Overall, the findings indicate that the most highly cited institutions are primarily medical schools and clinically focused research universities. This suggests that dyspepsia is being addressed both theoretically and clinically, and that research activities in this field are strongly supported at the institutional level. Additionally, the observation that some institutions achieve high citation counts with relatively few publications highlights the importance of research quality and scientific impact over sheer publication volume.

DISCUSSION

This bibliometric analysis shows that the number of publications related to dyspepsia in the internal medicine field has steadily and sharply increased over the last twenty years. This increase is in the annual publication numbers is in line with Wang et al.'s[5] findings, which indicated a rising global research focus on FD. Their analysis of the literature from 2001 to 2021 identified a shift in 2010 in the growth rate of literature on FD, mainly driven by the growing fascination with the gut-brain axis and psychosomatic approaches. Our keyword co-occurrence analysis supports this finding. In our analysis, the highest number of publications was recorded in 2022 and remained at a high level in the following years of 2023–2024, illustrating sustained momentum in scholarly activity. Huang et al.[4] further noted the growing focus of publications integrating the psychiatric angle of anxiety and depression alongside FD. We also found that those keywords, alongside 'anxiety' and 'depression', with 'FD', were tightly clustered in the VOSviewer co-occurrence map, indicating that these fields of research are increasingly collaborating across disciplines, suggesting the emergence of a research theme that combines gastroenterology and psychiatry.

The thematic distribution of journals identified in the data set follows trends established in previous bibliometric studies. Wang et al.[5] identified Neurogastroenterology & Motility and World Journal of Gastroenterology as FD focus area leaders, but we found that Cureus, Medicine, and the Journal of Clinical and Diagnostic Research had the highest publication counts under the general internal medicine category. This difference may indicate that our analysis, which takes a generalist approach to medicine rather than a gastroenterology-focused approach, is more diffuse and less specialized. Nevertheless, the two studies' findings regarding the preeminent clinically relevant, open-access publishing avenues suggest that researchers tend to prefer such venues for dissemination when working on dyspepsia because it is a significant public health issue.

For dyspepsia, citation analysis brought to light articles that were peripheral to the topic, but fell within the same WoS category. This partly reflects the challenge faced in Wei et al.,[6] where bibliometric studies on acupuncture and FD had to be purged of broad Chinese medicine publications not focused on the condition. Most importantly, the other McColl[11] and Ford et al.[8,9] Overlapping roles and risks focuses on IBS-dyspepsia were among the most cited works in our dataset. It remains important that the shared, multi-cited patho-physiological interest in gastrointestinal diseases is relevant. Ford et al.[8] showed that as many as 30% of patients with dyspepsia meet the IBS criteria which accounts for the prevalent co-occurrence of keywords like "IBS", "functional bowel disorders" and "visceral hyper-sensitivity" that we found in the network visualization of our study. In addition, some of the keywords used included "post infection", "motility", and "GI inflammation" which, together with Futagami et al.[10] meta-analysis on post-infectious FD, illustrate the cluster analysis results interlinked with dyspepsia, inflection, and systemic triggers—incorporated these connections indirectly evidenced through the clustering results.

Based on national and institutional collaboration, our research highlights Japan, South Korea, China, and the United States as the forefront participants. This was already documented by Huang et al.[4] and Li et al.[7] in their analyses of FD and gastroparesis. While primarily focusing on North America's research dominance, Li et al.[7] also noted Eastern Asian institutions' increasing contributions to pathophysiology research. In the case of motility disorder research as well as in our collaboration network maps, there are notable hubs of activity around Seoul National University and Mayo Clinic and Kyung Hee University: a further testament to the East–West academic partnership in dyspepsia research. Wei et al.[3] remarked on the Chinese and Korean contribution to acupuncture-based FD studies which coincide with the presence of complementary medicine clusters from our co-occurrence analysis.

Most strikingly, our observation that more than two-thirds of articles were dispersed over numerous journals aligns with earlier bibliometric notes on fragmentation in functional GI literature.[4,5] This scattering could illustrate the interdisciplinary aspect of dyspepsia but it also indicates a need for greater consolidation and collaboration across disciplines. In the keyword clustering performed in our work, besides capturing dominant terms like 'FD' and '*Helicobacter pylori*', 'gastritis', and 'endoscopy', there was also capture of pioneering

terms such as microbiome, low-grade inflammation, and psychosocial stress in line with newer mechanistic theories in FD pathophysiology. Focusing on these themes and fostering international academic collaborations aimed at developing stronger multicenter resources could shift future research agendas towards these issues.

CONCLUSION

This investigation offers a dyspepsia research evaluation within internal medicine on the bases of publications over the past 20 years. Its bibliometric review shows an interdisciplinary focus surge alongside an overarching increase in publication output. Keywords such as FD, *Helicobacter pylori*, and comorbid psychological disorders underline the developing viewpoint that dyspepsia is a multifaceted disorder with biological and psychosocial dimensions. Unlike previous studies that focused on ancillary issues like acupuncture or anxiety, this study provides a more comprehensive assessment of scientific output by mapping major scientific centers, their productive institutions, prominent journals, and international collaboration patterns demonstrating the scope of cooperation across borders. Although there is increased output, it remains scattered and fragmented across numerous journals and geographic locations and does not consolidate around a few high-impact multicenter studies, which slows advancement. These results offer a starting point for strategic research planning important for clinicians and policy strategists aimed towards more effective dyspepsia management, ultimately enabling advanced understanding of the disease.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since this research is a bibliometric study, it did not require ethics committee approval.

Informed Consent

Since this research is a bibliometric study, it did not require informed consent.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare. T he 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

MEDICINE PALLIATIVE CARE

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Evaluation of the relationship between the RDW/albumin ratio and coronary artery ectasia

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ABSTRACT

Aims: Coronary artery ectasia (CAE) is a vascular abnormality associated with inflammation and adverse cardiovascular outcomes. The red blood cell distribution width-to-albumin ratio (RAR) has emerged as a novel biomarker reflecting systemic inflammation and nutritional status. This study aimed to evaluate the relationship between RAR and the presence of CAE.

Methods: In this retrospective study, 80 patients diagnosed with CAE via coronary angiography and 80 age-and sex-matched healthy controls were included. Laboratory parameters, including RDW, serum albumin, and RAR, were analyzed. The Mann-Whitney U test was used for group comparisons, and significance was set at $p<0.05$. Patients with active infection, severe organ failure, or malignancy were excluded.

Results: Demographic and clinical variables were similar between groups ($p>0.05$). Median (IQR) serum albumin levels were significantly lower in the CAE group compared to controls [41.0 (39.0–43.9) g/L vs. 43.9 (42.0–45.7) g/L; $p<0.001$]. Although RDW alone did not differ significantly between groups ($p=0.448$), the RAR was significantly higher in CAE patients [0.375 (0.338–0.410)] than in controls [0.355 (0.330–0.390)] ($p=0.036$). Additional findings included reduced lymphocyte and platelet counts and elevated monocyte counts and mean platelet volume (MPV) in the patient group, indicating a pro-inflammatory state.

Conclusion: The RDW/albumin ratio was significantly elevated in patients with CAE, suggesting that it may serve as a simple, inexpensive, and effective inflammatory biomarker in this population. While RDW and albumin are routinely available in clinical practice, their combined interpretation via RAR may provide additional insight into the inflammatory status of patients with CAE. Further prospective, large-scale studies are warranted to confirm these findings and clarify the prognostic value of RAR in CAE.

Keywords: Coronary artery ectasia, RDW/albumin ratio, inflammation, red blood cell

INTRODUCTION

Coronary artery ectasia (CAE) is a vascular anomaly characterized by segmental or diffuse dilation of a coronary artery, with the affected segment exhibiting a diameter at least 1.5 times greater than that of an adjacent normal coronary segment.[1] The prevalence of CAE varies between 0.3% and 5% across different populations.[2] Although often identified incidentally, its clinical relevance has gained attention due to its potential association with adverse cardiovascular outcomes.[3]

The most common method of diagnosis is invasive coronary angiography. Quantitative measurements improve the evaluation's impartiality and make it possible to determine luminal dilatation more precisely, especially when it comes to vascular diameter increase. Ectasia is categorized as little (less than 5 mm), moderate (5 to 8 mm), and large/"giant" (more than 8 mm) in the literature.[1]

The pathogenesis of CAE is multifactorial. While atherosclerosis remains the most common underlying cause accounting for more than half of all cases other etiologies, including congenital anomalies, vasculitis, connective tissue disorders, and infections, have also been reported.[1-4] Recent evidence underscores the role of inflammatory and immune-mediated processes, as demonstrated by elevated levels of matrix metalloproteinases (particularly MMP-9), tumor necrosis factor-alpha (TNF-α), and interleukins such as IL-1β and IL-6. These mediators contribute to extracellular matrix degradation and vascular remodeling. Additionally, lipid profile disturbances such as elevated low-density lipoprotein cholesterol (LDL-C) and reduced high-density lipoprotein cholesterol (HDL-C) have been implicated in the pathophysiology of CAE.[5]

Clinically, CAE presents across a wide spectrum—from asymptomatic cases to those manifesting with stable angina,

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acute coronary syndromes (ACS), or myocardial infarction. These manifestations are believed to result from disturbed coronary hemodynamics, leading to turbulent blood flow, endothelial dysfunction, and thrombus formation within the dilated segments.[1-5] The diagnosis is primarily established via coronary angiography, which remains the gold standard for assessing the morphology and extent of ectasia.[1] Nevertheless, non-invasive modalities such as coronary computed tomography angiography (CCTA) and magnetic resonance angiography (MRA) have gained prominence, offering high-resolution, three-dimensional imaging of the coronary anatomy, supporting both diagnosis and longitudinal monitoring.[4] Importantly, patients with CAE face an increased risk of distal embolization and recurrent myocardial infarction, even in the absence of significant obstructive coronary artery disease.[6]

Management of CAE remains challenging due to the lack of universally accepted treatment guidelines. Therapeutic approaches are often tailored to the individual, focusing on the use of antiplatelet agents, anticoagulation in selected cases, and rigorous control of modifiable cardiovascular risk factors. Invasive interventions, such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), are typically reserved for patients with significant stenosis or ischemia-inducing lesions.[7]

In conclusion, CAE represents a complex and frequently underrecognized clinical entity with diverse implications. Given its heterogeneous etiology, variable clinical presentation, and inconsistent therapeutic response, further research is necessary to elucidate its pathophysiology, refine diagnostic criteria, and establish evidence-based management strategies.

The utilization of biomarkers in the diagnosis and prognosis of cardiovascular diseases has significantly increased in recent years. Within this context, erythrocyte distribution width (RDW) and serum albumin levels have emerged as important parameters that reflect systemic inflammation and overall physiological status. RDW indicates the degree of variation in erythrocyte volume, and its elevation has been associated with inflammation, oxidative stress, and malnutrition.[8] Conversely, reduced serum albumin levels have been linked to chronic inflammation, malnutrition, and cardiovascular events.[9]

More recently, the RDW/albumin ratio (RAR) has been proposed as a novel biomarker that reflects the combined effect of these two parameters. RAR is believed to hold prognostic value, particularly in conditions such as stroke. Moreover, RAR has been associated with increased morbidity and mortality across various cardiovascular diseases.[10]

However, the association between RAR and more specific cardiovascular conditions such as CAE has not been thoroughly explored. Accordingly, investigating the clinical significance and potential prognostic value of RAR in CAE patients represents an important area of study. Recent research suggests that hematological parameters may contribute to the pathophysiology of CAE. Therefore, this study aimed to assess the relationship between the RDW/Albumin ratio and the presence of CAE, with the hypothesis that inflammation may play a contributing role.

METHODS

The study was conducted with the permission of Bolu İzzet Baysal University Non-interventional Clinical Researches Ethics Committee (Date: 06.05.2025, Decision No: 2025/208). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this retrospective study, laboratory blood results recorded in the hospital automation system were analyzed for patients diagnosed with CAE who underwent coronary angiography at İzzet Baysal Training and Research Hospital, along with data from a healthy control group. Blood RDW, albumin levels, RDW/Albumin ratio, and several additional hematological parameters were compared between CAE patients and controls. Data were evaluated from 80 patients with CAE and 80 control individuals. Blood samples were processed using an automated hematology analyzer. Group comparisons were conducted using the Mann-Whitney U test ($p<0.05$), and correlation analyses were performed to assess associations with CAE severity.

Exclusion criteria included patients with severe valvular disease, advanced heart failure (EF<30%), severe acute or chronic liver and/or kidney failure, recent coronary intervention within the past 3 months, advanced chronic lung disease, age below 18 years, pregnancy, history of thrombolytic therapy, severe inflammation, hematological or oncological malignancies, and severe anemia.

Statistical Analysis

The data analysis was conducted using SPSS software (SPSS 22.0 for Windows, IBM Corp., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate normality of distribution. For normally distributed variables, comparisons were made using the t-test and results were expressed as mean±standard deviation. For variables with non-normal distribution, the Mann-Whitney U test was used, and results were presented as median and interquartile range (IQR, 1st-3rd quartile values). Categorical variables were compared using the Chi-square test.

RESULTS

A total of 160 participants were included in the study, with 80 individuals in the patient group and 80 in the control group. **Table 1** outlines the baseline demographic and clinical characteristics of the study population. The median (IQR) age was higher in the patient group [63 (51.75–69) years] than in the control group [59 (52.75–66) years]; however, this difference was not statistically significant ($p = 0.097$). Sex distribution was identical between groups, with 40 females (50%) and 40 males (50%) in each group, indicating no sex-based imbalance ($p>0.999$).

With regard to lifestyle factors and comorbidities, smoking prevalence was nearly the same between groups (28.75% in patients vs. 27.5% in controls), with no statistically significant difference ($p=0.860$). Similarly, diabetes mellitus was present

Table 1. Demographic and clinical characteristics of patients and controls

		Control	Patient	p value
Age, years		59 (52.75-66)	63 (51.75-69)	0.097
Sex	Female	40 (50%)	40 (50%)	>0.999
	Male	40 (50%)	40 (50%)	
Smoking	Absent	58 (72.5%)	57 (71.25%)	0.860
	Present	22 (27.5%)	23 (28.75%)	
Diabetes mellitus	Absent	53 (66.25%)	52 (65.0%)	0.868
	Present	27 (33.75%)	28 (35.0%)	
Hypertension	Absent	40 (50%)	32 (40%)	0.204
	Present	40 (50%)	48 (60%)	

Descriptive statistics were presented as median (1st–3rd quartile) for continuous variables or number (percentage) for categorical variables. Comparisons were performed using the Mann–Whitney U test or the Pearson Chi-square test, as appropriate

in 35.0% of patients and 33.75% of controls (p=0.868). The prevalence of hypertension was slightly higher in the patient group (60%) than in the control group (50%), though this difference was not statistically significant (p=0.204). These findings indicate that both groups were well-matched demographically and clinically, thereby reducing the risk of confounding (Table 1).

Laboratory parameters are presented in Table 2. Several hematological indices demonstrated statistically significant differences. Lymphocyte counts were significantly lower in the patient group [2.03 (1.58–2.50)×10^9/L] compared to the control group [2.50 (1.92–3.01)×10^9/L] (p<0.001). Monocyte levels were significantly elevated in patients [0.55 (0.42–0.70)×10^9/L] relative to controls [0.47 (0.36–0.57)×10^9/L] (p=0.004). Neutrophil counts did not significantly differ between the two groups [4.06 (3.44–5.16) vs. 3.96 (3.42–4.93)×10^9/L, p=0.416].

Hemoglobin (HGB) levels were significantly lower in patients (13.5±5.5 g/dl) than in controls (14.0±5.1 g/dl) (p=0.040). Platelet (PLT) counts were also significantly reduced in the patient group [230.5 (194.8–267.5)×10^9/L] compared to controls [253.5 (212.8–298.8)×10^9/L] (p=0.028). Mean platelet volume (MPV) was significantly elevated in patients [8.45 (7.55–9.45) fL] versus controls [7.93 (7.52–8.67) fL] (p=0.029). Hematocrit (HCT) values showed a slight, non-significant decrease in patients [41.2 (37.65–45.08)%] relative to controls [42.25 (40.00–45.2)%] (p=0.071).

Serum albumin levels were significantly lower in the patient group [41.0 (39.0–43.9) g/L] compared to the control group [43.9 (42.0–45.7) g/L] (p<0.001). RDW did not significantly differ between groups [15.3 (14.40–16.43)% in patients vs. 15.45 (14.8–16.3)% in controls, p=0.448]. However, the RDW/albumin ratio was significantly higher in patients [0.375 (0.338–0.410)] than in controls [0.355 (0.330–0.390)] (p=0.036), suggesting that this ratio may serve as a more sensitive marker than RDW alone (Table 2).

To further illustrate the distribution of key variables, violin plots were generated (Figure). These plots depict the distributions of albumin, RDW, and RDW/albumin ratio across both groups. Figure 1a shows a clear leftward shift in albumin values in the patient group, indicating lower levels. Figure 1b displays RDW distributions, which appear similar between groups, consistent with the non-significant p-value. Figure 1c highlights a higher RDW/albumin ratio in patients, confirming the statistical findings. The violin plots, through kernel density estimation, visually emphasize central tendency and variability, supporting the numerical results.

DISCUSSION

This study investigated the association between RAR and the presence of CAE. Our findings demonstrate that elevated RAR levels are significantly associated with CAE, suggesting that RAR may function as a novel inflammatory biomarker in this clinical context.

The pathophysiology of CAE is multifaceted and not yet fully elucidated; however, inflammation is recognized as a critical contributor to its development. Previous studies have shown that patients with CAE exhibit higher levels of inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6), compared to individuals with normal coronary arteries.[11] RDW, which reflects the variability in red blood cell size, has been identified as an independent predictor of various cardiovascular diseases and is thought to mirror underlying inflammatory activity.[8] Similarly, hypoalbuminemia has been associated with poor nutritional status and systemic

Table 2. Laboratory parameters of patients and controls

	Control	Patient	p value
White blood cell (WBC), ×10^9/L	7.23 (6.25-8.68)	7.33 (6.01-8.30)	0.700
Lymphocyte, ×10^9/L	2.50 (1.92-3.01)	2.03 (1.58-2.50)	<0.001
Monocyte, ×10^9/L	0.47 (0.36-0.57)	0.55 (0.42-0.70)	0.004
Neutrophil, ×10^9/L	3.96 (3.42-4.93)	4.06 (3.44-5.16)	0.416
Hematocrit (HCT), %	42.25 (40.00-45.2)	41.2 (37.65-45.08)	0.071
Hemoglobin (HGB), g/dL	14.0±5.1	13.5±5.5	0.040
Platelet count (PLT), ×10^9/L	253.5 (212.8-298.8)	230.5 (194.8-267.5)	0.028
Mean platelet volume (MPV), fL	7.93 (7.52-8.67)	8.45 (7.55-9.45)	0.029
Red cell distribution width (RDW), %	15.45 (14.8-16.3)	15.3 (14.40-16.43)	0.448
Albumin, g/L	43.9 (42.0-45.7)	41.0 (39.0-43.9)	<0.001
RDW/albumin ratio	0.355 (0.330-0.390)	0.375 (0.338-0.410)	0.036

Descriptive statistics were presented as mean±standard deviation or median (1st–3rd quartile), and comparisons were made using Student's t-test or the Mann–Whitney U test, as appropriate

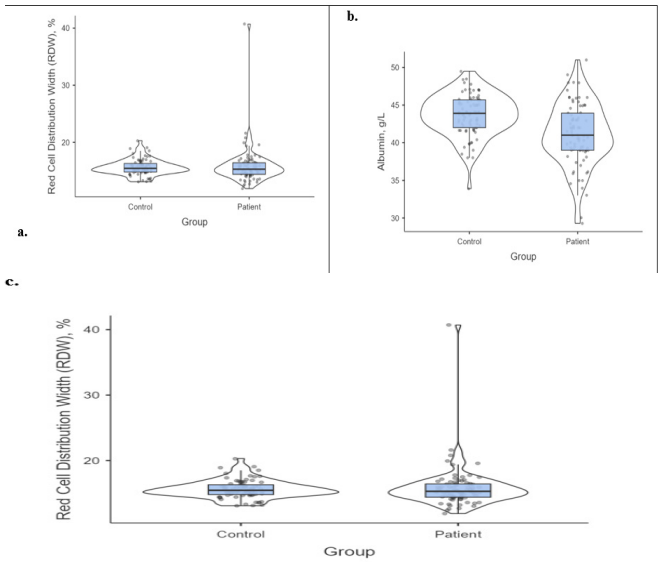

Figure. Violin plots comparing albumin (**a**), red cell distribution width (RDW) (**b**), and RDW/albumin ratio (**c**) between control and patient groups. In each plot, the central box represents the interquartile range (25^{th}–75^{th} percentile), the horizontal line within the box indicates the median, and the thin vertical lines ("whiskers") extend to 1.5 times the interquartile range. Individual data points are shown as dots, and the width of the violin reflects the kernel density estimation, indicating the distribution of values

inflammation, both of which correlate with unfavorable cardiovascular outcomes.[12]

Emerging research highlights the involvement of systemic inflammation and oxidative stress in the vascular remodeling observed in CAE, as demonstrated by elevated levels of CRP, IL-6, and TNF-α.[13] Given these associations, composite biomarkers such as the RDW/albumin ratio (RAR) may also hold relevance in this disease process. This retrospective cohort study evaluated the prognostic utility of RAR in critically ill patients diagnosed with both coronary heart disease (CHD) and diabetes mellitus (DM). The results demonstrated that elevated RAR values were significantly associated with increased in-hospital mortality. These findings underscore the potential of composite indices, such as RAR, to capture multidimensional physiological disturbances and enhance risk stratification in complex cardiovascular conditions.[14]

The integration of RDW and albumin into a single ratio the RAR provides a more holistic assessment of a patient's inflammatory and nutritional state. Recent studies have highlighted the prognostic value of RAR in several cardiovascular conditions, including acute myocardial infarction and heart failure.[15] However, to the best of our knowledge, this is the first study to examine the relationship between RAR and CAE.

Our findings align with the results of Li et al.,[16] who reported that elevated RDW levels are associated with the presence of CAE. Additionally, the inverse relationship between serum albumin and inflammation has been well established in atherosclerotic diseases, further supporting the biological plausibility of our results.[9] Cai et al.[17] focused on developing a predictive model for MACE in patients with CAE and found that certain clinical and angiographic features are associated with an increased risk of adverse cardiovascular events. The authors emphasized the importance of early risk stratification in these patients.

In a comprehensive cohort study involving 12.765 participants, Liu et al.[18] identified a non-linear, positive association between elevated RAR levels and increased risks of cardiovascular disease (CVD), all-cause mortality, and cardiovascular mortality. Notably, glycated hemoglobin (HbA1c) partially mediated the relationship between RAR and CVD, suggesting a link between glycemic control and inflammatory status in cardiovascular outcomes.

Similarly, Li et al.[19] demonstrated that higher RAR values independently predicted one-year mortality in intensive care unit (ICU) patients with heart failure. The study also highlighted RAR's potential to enhance prognostic accuracy when integrated with established scoring systems like SOFA and APACHE II.

In a meta-analysis conducted in 2025, RAR was identified as a novel and independent prognostic marker that is significantly associated with increased all-cause mortality in patients with cardiovascular disease.[20]

The clinical implications of these findings are substantial. RAR is a simple, inexpensive, and routinely accessible laboratory parameter that can be derived from standard blood tests. Its potential utility as a biomarker for CAE could facilitate earlier diagnosis and improved risk stratification, thereby enhancing clinical decision-making and patient outcomes.

Limitations

Nonetheless, our study has certain limitations. The cross-sectional nature of the design restricts the ability to draw causal inferences between elevated RAR and the presence of CAE. Moreover, the relatively small sample size necessitates further large-scale, prospective studies to confirm our findings and to evaluate the clinical utility of RAR in routine practice. Detailed information on patients' history of prior coronary interventions was not consistently available, which might have had a minimal or indirect effect on the findings.

CONCLUSION

In this study, we analyzed hematological and biochemical parameters in patients with CAE, focusing on albumin, RDW, and particularly the RDW/albumin ratio. While RDW alone did not differ significantly between groups, the RDW/albumin ratio was notably higher in patients, indicating its potential as a more sensitive marker of systemic inflammation or subclinical disease. The CAE group also exhibited lower albumin, reduced lymphocyte and platelet counts, and higher monocyte levels and MPV, collectively reflecting an underlying inflammatory or cardiovascular risk profile. These findings support the use of integrated indices like the RDW/albumin ratio over isolated values in clinical assessment. Given its ease of access and routine availability, this ratio may enhance clinical insight into CAE-related inflammation, though larger prospective studies are needed to confirm its prognostic relevance.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Bolu Abant İzzet Baysal University Non-interventional Clinical Researches Ethics Committee (Date: 06.05.2025, Decision No: 2025/208).

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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Erratum to "The frequency of structural causes (PALM) according to FIGO PALM-COEIN classification in patients undergoing hysterectomy for abnormal uterine bleeding"

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In the original article, the ORCID of one of the co-authors, Enes Akdan, was incorrectly reported by the corresponding author. At the request of the authors, the ORCID has been corrected to reflect the accurate information. This correction does not affect the content or conclusions of the article. The authors apologize for this oversight.

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